MEDICAL POLICY – 12.04.13
Genetic Testing for Alzheimer Disease

BCBSA Ref. Policy: 2.04.13
Effective Date: July 1, 2018
Last Revised: June 22, 2018
Replaces: 2.04.13

SELECT A HYPERLINK BELOW TO BE DIREC TED TO THAT SECTION.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Alzheimer disease is the most common cause of dementia in older adults. It’s a progressive disease, which means it gets worse over time. In Alzheimer disease, damage occurs to brain cells, leading to brain shrinkage. There are two basic types of Alzheimer disease recognized now: early-onset and late-onset. Early-onset Alzheimer disease usually affects the brain between the ages of 30 and mid-60s. Only about 10 percent of Alzheimer cases are early-onset. In late onset, symptoms start in the mid-60s or later. We do not completely understand all of the factors that influence the development of Alzheimer disease. It’s believed that lifestyle may play a role, although it appears that genetics may play a role in less than five percent of cases. This policy discusses when genetic testing for Alzheimer disease is considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria
### Purpose

<table>
<thead>
<tr>
<th>Targeted genetic testing for familial early onset Alzheimer disease (AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Necessity</strong></td>
</tr>
<tr>
<td>Testing is considered medically necessary to determine future risk of disease under the following conditions:</td>
</tr>
<tr>
<td>- The individual has no symptoms</td>
</tr>
<tr>
<td>AND</td>
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<tr>
<td>- The information will be used to inform reproductive decision making</td>
</tr>
<tr>
<td><strong>AND either of the following are present:</strong></td>
</tr>
<tr>
<td>- The individual has a close relative (first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease (presenilin (PSEN) genes or amyloid-beta precursor protein (APP) gene)</td>
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<tr>
<td><strong>OR</strong></td>
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<tr>
<td>- The individual has a family history of dementia consistent with autosomal dominant Alzheimer disease</td>
</tr>
<tr>
<td>AND</td>
</tr>
<tr>
<td>o The affected family member(s) is not available for testing</td>
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<tr>
<td>AND</td>
</tr>
<tr>
<td>o Testing is for variants in the presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene</td>
</tr>
</tbody>
</table>

*Note:* Early-onset familial AD (before age 65 years but as early as 30 years)

**Note:** A family history of autosomal dominant AD is suggested by 3 affected family members in 2 generations

### Investigational

<table>
<thead>
<tr>
<th>Genetic testing for the risk assessment of Alzheimer disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational</td>
</tr>
<tr>
<td><strong>Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered investigational in all other situations.</strong></td>
</tr>
<tr>
<td>- Genetic testing includes, but is not limited to, testing for the apolipoprotein E ε 4 allele (APOE) or triggering receptor expressed on myeloid cells 2 (TREM2), or any other genes.</td>
</tr>
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</table>

### Coding
<table>
<thead>
<tr>
<th>Code</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>HCPCS</td>
<td></td>
</tr>
<tr>
<td>S3852</td>
<td>DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

Genetic testing for Alzheimer disease (AD) may be offered along with analysis of cerebral spinal fluid (CSF) levels of the tau protein and amyloid-β peptide 1-42. This group of tests may be collectively referred to as the ADmark™ Profile, offered by Athena Diagnostics.

**Testing Strategy**

The 2011 guidelines from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors recommended that genetic testing for early-onset, autosomal dominant AD should only occur in the context of genetic counseling with support by someone expert in the area. In asymptomatic patients, a testing protocol based on the 1994 International Huntington Association and World Federation of Neurology Research Group on Huntington's Chorea guidelines has been recommended. Consultation of the Alzheimer Disease & Frontotemporal Dementia Mutation Database has also been recommended before disclosure of genetic test results.

A family history of autosomal dominant AD is suggested by having 3 affected members in 2 generations. In individuals at risk of early-onset, autosomal dominant AD, ideally, an affected family member should ideally be tested first to identify the familial variant. If no affected family member is available for testing and an asymptomatic individual remains interested in testing to
inform reproductive decision making, then in-depth sequencing of the 3 genes (APP, PSEN1, PSEN2) associated with autosomal dominant AD may be indicated.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant found in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</tbody>
</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>
Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Table 3. Outcomes of Interest for Individuals With Symptomatic Late-Onset Alzheimer Disease

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Incidence or time to Alzheimer disease onset; changes in cognitive test scores</td>
</tr>
<tr>
<td>Health status measures</td>
<td>Activities of daily living or functional scales such as the 36-Item Short-Form Health Survey, Alzheimer Disease Cooperative Study Activities of Daily Living scale, or Disability Assessment for Dementia</td>
</tr>
<tr>
<td>Quality of life</td>
<td>EuroQoL EQ-5D; measures of anxiety or depression</td>
</tr>
</tbody>
</table>

Table 4. Examples of Commercially Available Genetic Panels for Early-Onset Alzheimer Disease

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>Genes Tested</th>
<th>Testing Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>PreventionGenetics</td>
<td>Alzheimer Disease, Familial, Sequencing Panel</td>
<td>3</td>
<td>CGH, NGS, bidirectional Sanger sequence analysis</td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>ADmark® Early Onset Alzheimer’s Evaluation</td>
<td>3</td>
<td>Bidirectional Sanger sequence analysis</td>
</tr>
<tr>
<td>Fulgent Genetics</td>
<td>Early Onset Familial Alzheimer Disease NGS Panel</td>
<td>3</td>
<td>Deletion/duplication analysis; sequence analysis of entire</td>
</tr>
<tr>
<td>Laboratory</td>
<td>Panel Name</td>
<td>Genes Tested</td>
<td>Testing Method</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>PreventionGenetics</td>
<td>Alzheimer’s Disease, Familial via the APP Gene, Exons 16 and 17; Familial via the PSEN1 Gene; Familial via the PSEN2 Gene</td>
<td>1 each test</td>
<td>Deletion/duplication analysis; sequence analysis of entire coding region; targeted variant analysis</td>
</tr>
</tbody>
</table>

CGH: comparative genomic hybridization; NGS: next-generation sequencing.

**Evidence Review**

**Description**

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

**Background**

**Alzheimer Disease**

Alzheimer disease (AD) is commonly associated with a family history; 40% of patients with AD have at least 1 other afflicted first-degree relative. Numerous genes have been associated with late-onset AD, while variants in chromosomes 1, 14, and 21 have been associated with early-onset familial AD.¹

**Genetic Variants**

Individuals with early-onset familial AD (ie, before age 65 years but as early as 30 years) form a small subset of AD patients. AD within families of these patients may show an autosomal dominant pattern of inheritance. Pathogenic variants in 3 genes have been identified in affected families: the amyloid-beta precursor protein (APP) gene, presenilin 1 (PSEN1) gene, and
presenilin 2 (PSEN2) gene. APP and PSEN1 variants have 100% penetrance absent death from other causes, while PSEN2 has 95% penetrance. Variants within these genes have been associated with AD; variants in PSEN1 appear to be the most common. While only 3% to 5% of all patients with AD have early-onset disease, pathogenic variants have been identified in 70% or more of these patients. Identifiable genetic variants are, therefore, rare causes of AD.

Testing for the apolipoprotein ε4 allele (APOE*E4) among patients with late-onset AD and for APP, PSEN1, or PSEN2 pathogenic variants in the rare patient with early-onset AD has been investigated as an aid in diagnosis of patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD. Pathogenic variants in PSEN1 and PSEN2 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 APOE lipoprotein is a carrier of cholesterol produced in the liver and brain glial cells. The APOE gene has 3 alleles—ε2, 3, and 4—with the ε3 allele being the most common. Individuals carry 2 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. Among those homozygous for epsilon 4 (>2% of the population), the risk of AD is higher than for those heterozygous for ε4. Mean age of onset of AD is about age 68 years for ε4 homozygotes, about 77 years for heterozygotes, and about 85 years for those with no ε4 alleles. About half of the 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-associated variant. In the absence of APOE testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a 2- to 4-fold greater risk of developing AD than the general population. There is evidence of possible interactions between ε4 alleles, other risk factors for AD (eg, risk factors for cerebrovascular disease such as smoking, hypertension, hypercholesterolemia, diabetes), and a higher risk of developing AD. However, it is not clear that all risk factors have been taken into account in such studies, including the presence of variants in other genes that may increase the risk of AD.

Studies have also identified rs75932628-T, a rare functional substitution for R47H on the triggering receptor expressed on myeloid cells 2 gene (TREM2), as a heterozygous risk variant for late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628 encodes a histidine substitute for arginine in the gene that encodes TREM2.

TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. TREM2 may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids, and toxic products. A decrease in the function of TREM2 would allow inflammation in the brain to increase and may be a factor in the development of
AD. The effect size of the TREM2 variant confers a risk of AD that is similar to the APOE*E4 allele, although it occurs less frequently.

**Diagnosis**

The diagnosis of AD is divided into 3 categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular β-amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. As a result, a diagnosis of definite AD cannot be made during life, and the diagnosis of probable or possible AD is made on clinical grounds. Probable AD dementia is diagnosed clinically when the patient meets core clinical criteria for dementia and has a typical clinical course for AD. Criteria for diagnosis of probable AD have been developed by the National Institute on Aging and the Alzheimer’s Association. These criteria require evidence of a specific pattern of cognitive impairment, a typical clinical course, and exclusion of other potential etiologies, as follows:

**Cognitive impairment**

- Cognitive impairment established by history from patient and a knowledgeable informant, plus objective assessment by bedside mental status examination or neuropsychological testing

- Cognitive impairment involving a minimum of 2 of the following domains:
  - Impaired ability to acquire and remember new information
  - Impaired reasoning and handling of complex tasks, poor judgment
  - Impaired visuospatial abilities
  - Impaired language functions
  - Changes in personality, behavior, or comportment

- Initial and most prominent cognitive deficits are one of the following:
  - Amnestic presentation
  - Nonamnestic presentations, either a language presentation with prominent word-finding deficits; a visuospatial presentation with visual cognitive defects; or a dysexecutive
presentation with prominent impairment of reasoning, judgment, and/or problem solving.

**Clinical Course**

- Insidious onset
- Clear-cut history of worsening over time
- Interference with ability to function at work or usual activities
- Decline from previous level of functioning and performing

**Exclusion of Other Disorders**

- Cognitive decline not explained by delirium or major psychiatric disorder
- No evidence of other active neurologic disease, including substantial cerebrovascular disease or dementia with Lewy bodies
- Lack of prominent features of variant frontotemporal dementia or primary progressive aphasia
- No medication use with substantial effects on cognition

A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria, but has an atypical course or an etiologically mixed presentation. This may consist of an atypical onset (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 insufficient impairment for the diagnosis of dementia. Features of MCI are evidence of impairment in 1 or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (eg, neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.
Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. Other diagnostic tests for AD include cerebrospinal fluid levels of tau protein or APP, as well as positron emission tomography (PET) amyloid imaging. PET amyloid imaging is not addressed in this policy.

Summary of Evidence

For individuals who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including apolipoprotein E (APOE), CR1, BIN1, PICALM, and TREM2, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing to predict which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD that was made clinically. The current lack of effective methods to prevent the onset of AD or to target AD treatments based on genetic characteristics limits the clinical benefit of genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes. Therefore testing in this population is considered not medically necessary.

For individuals who are asymptomatic, and at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing, the evidence includes studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision-making, health status measures, and quality of life. Variants in the PSEN1 and PSEN2 and APP genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be nearly certain when a familial pathogenic variant has previously been identified. Outside the reproductive setting and when used only for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, clinical utility for the purposes of reproductive decision-making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have no known familial variant who receive genetic testing, the evidence includes
studies on gene associations and test accuracy. Relevant outcomes are test accuracy and validity, change in disease status, change in reproductive decision-making, health status measures, and quality of life. Variants in the \textit{PSEN1}, \textit{PSEN2}, and \textit{APP} genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. The clinical validity for autosomal dominant early-onset AD will be reasonably certain when a variant found and in the database of pathogenic \textit{PSEN1}, \textit{PSEN2}, and \textit{APP} variants are identified. 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. Testing a prospective parent, when performed in conjunction with genetic counseling, provides more accurate information to guide reproductive planning than family history alone. Therefore, clinical utility for the purposes of reproductive decision-making has been demonstrated for these tests. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 5.

**Table 5. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00064870</td>
<td>National Cell Repository for Alzheimer’s Disease (NCRAD)</td>
<td>3000</td>
<td>Jul 2021</td>
</tr>
<tr>
<td>NCT02564692</td>
<td>Alzheimer’s Prevention Registry GeneMatch Program</td>
<td>500,000</td>
<td>Dec 2030</td>
</tr>
<tr>
<td>NCT01760005</td>
<td>A Phase II/III Randomized, Double-Blind, Placebo-Controlled Multi-Center Study of 2 Potential Disease Modifying Therapies in Individuals at Risk for and With Dominantly Inherited Alzheimer’s Disease</td>
<td>210</td>
<td>Dec 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
The American College of Medical Genetics and Genomics has listed genetic testing for apolipoprotein E (APOE) alleles as 1 of 5 recommendations in the Choosing Wisely initiative. 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 late-onset Alzheimer disease (AD), the most common cause of dementia. “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.”

The College, jointly with the National Society of Genetic Counselors, issued the following joint practice guidelines (2011):

- “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 [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 that 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, the 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 PSEN1, PSEN2, or APP, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.

- Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol.
If the affected relative, or their next of kin, is uninterested in pursuing testing, the option of DNA banking should be discussed.”

**American Academy of Neurology**

The American Academy of Neurology made the following recommendations:

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

These guidelines are being updated as of February 2018.

**European Federation of Neurological Sciences**

In 2010, the European Federation of Neurological Sciences made the following recommendations for 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. Pre-symptomatic 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.”
Canadian Consensus Conference on Diagnosis and Treatment of Dementia

Fourth Canadian Consensus Conference

The Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4), held in 2012, updated guidelines from the third consensus conference, referenced next. Previous recommendations were endorsed if there were no changes in the literature.

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

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 (eg, gene mutation carriers, family history of AD, ApoE epsilon 4) should be restricted to research.

Third Canadian Consensus

The CCCDTD recommended the following:

“Predictive genetic testing for asymptomatic ‘at-risk’ individuals with an apparent autosomal dominant inheritance and a family-specific mutation that 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 include:

   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.

3. 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)

4. 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 used the following evidence ratings for the Third Canadian Consensus: grade (B) is fair evidence to support this maneuver; grade (E) is good evidence to recommend against this procedure; level 2 evidence is that obtained from: (1) well-designed controlled trial without randomization or (2) well-designed cohort or case control analytic studies, preferably from more than one center or (3) comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments are included in this category.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/08/08</td>
<td>Replace policy - Policy updated with literature search; no change in policy statement; reference added.</td>
</tr>
<tr>
<td>02/10/09</td>
<td>Replace policy - Policy updated with literature search; no change to policy statement. Rational section extensively revised. Code and references added.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Replace policy - Policy updated with literature search; no change to policy statement.</td>
</tr>
<tr>
<td>09/14/10</td>
<td>Cross References Updated - No other changes.</td>
</tr>
<tr>
<td>08/09/11</td>
<td>Replace policy – Policy updated with literature search; no change in policy statement; reference added.</td>
</tr>
<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.13 (previously 2.04.13) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>11/27/12</td>
<td>Replace policy - Policy updated with literature review. References 2-6, 15, 17, 19 added. No change to policy statement. Add Related Policy 6.01.55. CPT codes 81200 – 81479 added effective 1/1/13; code range 83891 – 83912 deleted effective 12/31/12.</td>
</tr>
<tr>
<td>01/10/13</td>
<td>Coding update. CPT code 81599, effective 1/1/13, added to policy.</td>
</tr>
<tr>
<td>05/18/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>12/04/13</td>
<td>Replace Policy. Policy updated with literature review through July 2013. References 4-5 and 22 added. TREM2 added to investigational policy statement. CPT codes 81405 and 81406 added; 81599 and 83914 removed as they are not specific to this policy; 83891 – 83912 removed, as they are now deleted.</td>
</tr>
<tr>
<td>07/20/15</td>
<td>Update Related Policies. Remove reference to archived policy in the policy guidelines section.</td>
</tr>
<tr>
<td>09/01/16</td>
<td>Update Related Policies. Remove 2.04.14 as it was archived.</td>
</tr>
<tr>
<td>07/01/18</td>
<td>Annual review, approved June 22, 2018. Policy updated with literature review through February 2018; no references added. “Early-onset” added to the second policy</td>
</tr>
</tbody>
</table>
**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at
https://ocrportal.hhs.gov/ocr/portal/lobby.jsf

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

يجب أن يحتوي هذا الإشعار على معلومات هامة، حيث يجب أن يحتوي على معلومات مفيدة كهذا الإشعار على شكل صورة بألوان طيفية أو متعددة الأشكال الملونة. يشمل هذا الإشعار معلومات مهمة كهذا الإشعار على شكل صورة بألوان طيفية أو متعددة الأشكال الملونة. يشمل هذا الإشعار معلومات مهمة كهذا الإشعار على شكل صورة بألوان طيفية أو متعددة الأشكال الملونة.

Arabic (Qur'an):

يجب على هذا الإشعار أن يحتوي على معلومات هامة، حيث يجب أن يحتوي على معلومات مفيدة كهذا الإشعار على شكل صورة بألوان طيفية أو متعددة الأشكال الملونة. يشمل هذا الإشعار معلومات مهمة كهذا الإشعار على شكل صورة بألوان طيفية أو متعددة الأشكال الملونة.

Chinese (Chinese):

本通知有重要的讯息。本通知可能有关於您透过 Premera Blue Cross 提交的申请或保险的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前采取行动，以保留您的健康保险或费用补贴。您有权利免费以您的母语得到本讯息和帮助。请拨电话 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):


This notification may contain important information. This notification may contain important information about your claim or coverage for Premera Blue Cross. In this notification, we may be required to provide you with certain key dates for maintaining your health insurance or assistance. Please take note of the important dates listed in this notification. For more information, please contact us at 800-722-1471 (TTY: 800-842-5357) or visit our website at www.premerablue.com.

Premera Blue Cross: 800-722-1471 (TTY: 800-842-5357)