Genetic Testing for Alzheimer’s Disease

Policy # 00204
Original Effective Date: 05/17/2006
Current Effective Date: 11/15/2017

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider targeted genetic testing for a known familial variant in the presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease (AD) in an asymptomatic individual to determine future risk of disease to be eligible for coverage when the following criteria are met:

Patient Selection Criteria
Coverage eligibility will be considered when all of the following criteria are met:

- The individual has a close relative (ie, first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease (AD) AND
- Results of testing will inform reproductive decision making.

Based on review of available data, the Company may consider genetic testing for variants in presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant Alzheimer disease (AD) in an asymptomatic individual to determine future risk of disease to be eligible for coverage when the following criteria are met:

Patient Selection Criteria
Coverage eligibility will be considered when all of the following criteria are met:

- The individual has a family history of dementia consistent with autosomal dominant Alzheimer disease (AD) for whom the genetic status of the affected family members is unavailable AND
- Results of testing will inform reproductive decision making.

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

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Based on review of available data, the Company considers genetic testing for the diagnosis of Alzheimer's disease or for the risk assessment of Alzheimer disease (AD) in asymptomatic individuals in all other situations to be investigational.* Genetic testing includes, but is not limited to, testing for the apolipoprotein E ε4 allele (APOE) or triggering receptor expressed on myeloid cells 2 (TREM2.)

Policy Guidelines
Genetic testing for AD may be offered along with analysis of 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 (Worcester, MA).

TESTING STRATEGY
The 2011 guidelines from the American College of Medical Genetics and Genomics (ACMG) 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 have been recommended. Consultation of the Alzheimer Disease & Frontotemporal Dementia Mutation Database has also recommended before disclosure of genetic test results.

A family history of autosomal dominant AD is suggested by 3 affected members in 2 generations. In individuals at risk of early-onset, autosomal dominant AD, ideally an affected family member should 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
Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

ACMG and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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 PG2 shows the recommended standard terminology—

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“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. 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</td>
<td>Disease-associated variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG2. 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>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

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

Background/Overview
ALZHEIMER DISEASE
AD is commonly associated with a family history; 40% of patients with AD have a 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.
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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 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. A variety of variants within these genes has 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 have been investigated as an aid in diagnosis of patients presenting with symptoms suggestive of AD, or as a technique for risk assessment in asymptomatic patients with a family history of AD. Pathogenic 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 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 variants. 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.

Recent studies have identified rs75932628-T, a rare functional substitution for R47H on the triggering receptor expressed on myeloid cells 2 (TREM2), as a heterozygous risk variant for late-onset AD. On chromosome 6p21.1, at position 47 (R47H), the T allele of rs75932628 encodes a histidine substitute for arginine in the gene that encodes TREM2.
TREM2 is highly expressed in the brain and is known to have a role in regulating inflammation and phagocytosis. TREM2 may serve a protective role in the brain by suppressing inflammation and clearing it of cell debris, amyloids, and toxic products. A decrease in the function of TREM2 would allow inflammation in the brain to increase and may be a factor in the development of AD. The effect size of the TREM2 variant confers a risk of AD that is similar to the APOE*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
A diagnosis of possible AD dementia is made when the patient meets most of the AD criteria, but has an atypical course or an etiologically mixed presentation. This may consist of an atypical onset (e.g., sudden onset) or atypical progression. A diagnosis of possible AD is also made when there is another potentially causative systemic or neurologic disorder that is not thought to be the primary etiology of dementia.

Mild cognitive impairment (MCI) is a precursor of AD in many instances. MCI may be diagnosed when there is a change in cognition, but not sufficient impairment for the diagnosis of dementia. Features of MCI are evidence of impairment in 1 or more cognitive domains and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. Other diagnostic tests for AD include cerebrospinal fluid (CSF) levels of tau protein or APP, as well as positron emission tomography (PET) amyloid imaging. PET amyloid imaging is considered in evidence review 6.01.55 (β-amyloid imaging with PET for AD).

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Lab tests listed in Tables 1 and 3 are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

**Centers for Medicare and Medicaid Services (CMS)**
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left
GENETIC TESTING FOR LATE-ONSET ALZHEIMER DISEASE
Clinical Context and Test Purpose
The purpose of genetic testing in patients who are asymptomatic and at risk for developing late-onset AD is potentially to inform management decisions such as early treatment or behavioral changes. Asymptomatic patients at risk of late-onset AD are not generally treated with medical therapy but may choose to make behavioral changes associated with reduced risk of AD.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals who are asymptomatic and at risk for developing late-onset AD? The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is adults who are asymptomatic and at risk for developing late-onset AD due to family history of AD or dementia.

Interventions
Genetic testing can be performed on a number of candidate genes, individually or collectively. Lists of genes associated with AD and testing laboratories in the United States are provided on the Genetic Testing Registry website of the National Center for Biotechnology Information. Table 1 lists examples of commercially available genetic panels for AD.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>No. of Genes Tested</th>
<th>Testing Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fulgent Genetics</td>
<td>Parkinson-Alzheimer-</td>
<td>37</td>
<td>NGS</td>
</tr>
<tr>
<td></td>
<td>Dementia NGS Panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knight Diagnostic</td>
<td>Dementia</td>
<td>21</td>
<td>Sequence analysis of the entire coding region</td>
</tr>
</tbody>
</table>
Comparators
The comparator of interest is standard clinical management without genetic testing.

Outcomes
The general outcomes of interest are change in disease status, health status measures, and quality of life (QOL). Specific outcomes in each of these categories are listed in Table 2.

The potential beneficial outcomes of primary interest would be change in disease status if changes in management or behavior in asymptomatic patients at risk of AD are initiated that prevent or slow progression of cognitive decline. Improvement in health status measures is also important.

Potential harmful outcomes are those resulting from a true or false positive test result. Patients might suffer from psychological harm or anxiety after receiving positive test results.

Table 2. Outcomes of Interest for Individuals With Symptomatic Late-Onset AD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in disease status</td>
<td>Incidence or time to AD 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</td>
</tr>
<tr>
<td></td>
<td>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>

AD: Alzheimer disease.

Time
Trials of genetic testing in this population were sparse and generally included short-term outcomes of distress and anxiety measured within a year. Trials of prevention strategies in AD typically span many years to a decade to detect differences in conversion to AD in asymptomatic, at-risk individuals.
Setting
Asymptomatic patients are likely to be managed in primary care. Genetic testing for variants associated with late-onset AD is complex. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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

Clinical Validity
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. In a sample of 6852 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 8 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. In 1030 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 between the APOE*E4 allele and 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.

Associations between late-onset AD and more than 20 non-APOE genes has been suggested. Examples of large studies and meta-analyses on these non-APOE genes are discussed below.

In 2014, Naj et al published a genome-wide association study (GWAS) of multiple genetic loci in late-onset AD. Genetic data from 9162 white participants with AD from the Alzheimer Disease Genetics Consortium were assessed for variants at 10 loci significantly associated with risk of late-onset AD. Analysis confirmed the association between APOE and early onset, and found significant associations for CR1, BIN1, and PICALM. APOE contributed 3.7% of the variation in age of onset and the other 9 loci combined contributed 2.2% of the variation. Each additional copy of the APOE*E4 allele reduced age of onset by 2.45 years.
Lambert et al (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. 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.

Jonsson et al (2013) evaluated 3550 subjects with AD and found a genome-wide association for only 1 marker, the T allele of rs75932628 (excluding the APOE locus and the APP11 A673T variant). The frequency of rs75932628 (TREM2) was then tested in a general population of 110,050 Icelanders of all ages and found to confer a risk of developing AD of 0.63% (odds ratio [OR], 2.26; 95% CI, 1.71 to 2.98; p=1.13 x 10−8). In the control population of 8888 patients 85 years of age or older without a diagnosis of AD, TREM2 frequency was 0.46% (OR=2.92; 95% CI, 2.09 to 4.09; p=3.42 x 10−10). In 1236 cognitively intact controls age 85 or older, the frequency of TREM2 decreased to 0.31% (OR=4.66; 95% CI, 2.38 to 9.14; p=7.39 x 10−6). The decrease in TREM2 frequency in cognitively intact elderly patients supports findings associating TREM2 with increasing risk of AD. Guerriero et al (2013) also found a strong association of the TREM2 R47H variant with AD (p=0.001). Using 3 imputed data sets of GWAS, meta-analysis found a significant association between the variant and AD (p=0.002). The authors further reported direct genotyping of R47H in 1994 AD patients and 4062 controls, which detected a highly significant association between the variant and AD (OR=5.05; 95% CI, 2.77 to 9.16; p=9.0 x 10−9).

Clinical Utility
The Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study was designed to examine the consequences of AD risk assessment by APOE genotyping. Of 289 eligible participants, 162 were randomized (mean age, 52.8 years; 73% female) to risk assessment based on APOE testing plus family history (n=111) or family history alone (n=51). During a 1-year follow-up, those undergoing APOE testing with a high-risk genotype were more likely than low-risk or untested individuals to take more vitamins (40% vs 24% and 30%), change diet (20% vs 11% and 7%), or change exercise behaviors (8% vs 4% and 5%), all respectively. There is insufficient evidence to conclude that these short-term behavioral changes would alter clinical outcomes. Green et al (2009) examined anxiety, depression, and test-related distress at 6 weeks, 6 months, and 1 year in the 162 participants randomized in REVEAL. 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*E4 allele. However, the e4 negative participants had significantly lower test-related distress than e4 positive participants (p=0.01).
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Christensen et al (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. 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 disease-associated variant carriers can delay or mitigate future disease. There are many actions patients may take following knowledge of a disease-associated variant. Changes in lifestyle factors (eg, diet, exercise) and/or incorporation of “brain training” exercises can be made, but there is no evidence that these interventions impact clinical disease.

Section Summary: Genetic Testing for Late-Onset Alzheimer Disease
The APOE*E4 allele is strongly associated with the incidence of and age at onset of AD; many other genes have shown statistical associations with AD incidence and onset, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of the APOE*E4 allele is poor, and there is a lack of evidence on the clinical sensitivity and specificity of other genes.

We did not identify any studies that addressed how the use of the APOE or other AD-associated genetic variants might be incorporated into clinical practice. It is unclear how change in the management of asymptomatic patients with these genes would improve 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 AD WITH AND WITHOUT A KNOWN FAMILIAL VARIANT

Clinical Context and Test Purpose
The purpose of genetic testing in patients who are asymptomatic and at risk for developing early-onset AD is to inform management decisions such as initiation of AD therapy and to inform reproductive decision making. Asymptomatic patients at risk for early-onset AD are not generally treated with medical therapy.

The question addressed in this evidence review is: Does genetic testing improve health outcomes in individuals who are asymptomatic, at risk for developing early-onset AD, and have a known or unknown familial variant?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is adults who are asymptomatic and at risk for developing early-onset AD due to family history of early-onset AD, specifically those with autosomal dominant AD.

Interventions
Adults with a family history of early-onset AD caused by a known pathogenic APP, PSEN1, or PSEN2 variant would undergo targeted testing for the specific familial variant. In adults with a family history consistent with autosomal dominant AD but for whom the familial variant is unknown, genetic testing can be performed on the 3 genes (APP, PSEN1, PSEN2) individually or collectively. Multiple variants in these genes can cause early-onset AD so sequencing the entire coding regions is necessary to comprehensively assess risk when the familial variant is unknown. Table 3 provides examples of commercially available genetic panels that include the early-onset, autosomal dominant variants.

Table 3. Commercially Available Genetic Panels for Early-Onset Alzheimer Disease

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Panel Name</th>
<th>No. of 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 NGS Panel</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 coding region</td>
</tr>
<tr>
<td>PreventionGenetics</td>
<td>Alzheimer’s Disease, Familial via the</td>
<td>1 each test</td>
<td>Deletion/duplication</td>
</tr>
</tbody>
</table>

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Outcomes
The general outcomes of interest are change in disease status, health status measures, QOL, and changes in reproductive decision making. The potential beneficial outcome of primary interest would be change in reproductive decision making. Changes in management in asymptomatic patients at risk of AD might be initiated with the intent to prevent or slow progression of cognitive decline leading to changes in disease status. Improvement in health status measures is also important. Potential harmful outcomes are those resulting from a true- or a false-positive test result. Patients might suffer from psychological harm or anxiety after receiving positive test results.

Time
Outcomes of reproductive decision making are relevant during child-bearing years for asymptomatic adults at risk.

Setting
Asymptomatic patients are likely to be managed in primary care. Reproductive decision making is a complex psychological process. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes. The American College of Medical Genetics and Genomics and the National Society of Genetic Counselors guidelines have 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 also been recommended.

Analytic Validity
There is a lack of published evidence on the analytic validity of genetic testing for early-onset familial AD. Analytic validity is expected to be high when current methods of sequencing are performed (ie, Sanger sequencing and/or NGS).
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 PSEN1 is estimated to detect disease-causing variants in 30% to 60% of individuals with familial early-onset AD, 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 APP and PSEN2 genes account for another 10% to 20% of cases.

The Human Genome Variation Society maintains a catalog of identified pathogenic variants called the Alzheimer Disease & Frontotemporal Dementia Mutation Database. A pathogenic association (clinical validity) between variants and disease has been demonstrated for identified variants through the presence in related probands with nearly complete penetrance. Most of the PSEN1, PSEN2, and APP variants reported in the database (>200) are identified as pathogenic over half by multiple studies.

Clinical expressivity is variable, ie, 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.

Clinical Utility

The potential clinical utility of testing is 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. Alternatively, clinical utility could be demonstrated if knowledge of variant status leads to beneficial changes in psychological outcomes.

A systematic review of 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.
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and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings.

There is no evidence that early intervention for asymptomatic pathogenic 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 (eg, diet, exercise) and incorporation of “brain training” exercises; but there is no evidence that these interventions impact clinical disease.

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. For purposes of informing family planning, 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: Genetic Testing for Early-Onset AD
The clinical validity for autosomal dominant, early-onset AD will be nearly certain when a pathogenic variant has previously been identified in a family pedigree or in the variant database.

For those from families with early-onset, familial AD, when a pathogenic familial variant is known or when the family pedigree is consistent with autosomal dominant AD but the affected family members have not been tested to determine the familial variant, 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.

SUMMARY OF EVIDENCE
For individuals who are asymptomatic and at risk for developing late-onset 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 APOE, CR1, BIN1, PICALM, and TREM2, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will
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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 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 for genetic testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are asymptomatic, at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing for a known familial variant, 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 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.

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 PSEN1, 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 reasonably certain when a variant found in the database of pathogenic PSEN1, PSEN2, and APP variants is 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.
References


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05/03/2006 Medical Director review
06/21/2006 Medical Policy Committee approval
11/05/2008 Medical Director review
11/18/2008 Medical Policy Committee approval. No change to coverage eligibility.
11/04/2010 Medical Policy Committee review
11/03/2011 Medical Policy Committee review
11/01/2012 Medical Policy Committee review
11/07/2013 Medical Policy Committee review
11/20/2013 Medical Policy Implementation Committee approval. TREM2 added to investigational policy statement.
11/06/2014 Medical Policy Committee review
11/21/2014 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015 Coding Update
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015 Medical Policy Committee review
11/16/2015 Medical Policy Implementation Committee approval. No change to coverage.

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11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
11/02/2017 Medical Policy Committee review

Next Scheduled Review Date: 11/2018

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