Title: Genetic Testing for Alzheimer’s Disease

Description/Background

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

AD is commonly associated with a family history; 40% of patients with AD have a least one 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 (i.e., 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: amyloid-beta precursor protein gene (APP), presenilin 1 (PSEN1) gene, and the 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 up to 70% or more of these patients. Identifiable genetic variants are, therefore, rare causes of AD.

Testing for the APOE 4 allele among patients with late-onset AD and for APP, PSEN1, or PSEN2 variants in the rare patient with early onset AD has 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. 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 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 (e.g., 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 of *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* epsilon 4 allele, although it occurs less frequently.

**Diagnosis**

The diagnosis of AD is divided into three categories: possible, probable, and definite AD. A diagnosis of definite AD requires postmortem confirmation of AD pathology, documenting the presence of extracellular beta amyloid plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. As a result, a diagnosis of definite AD cannot be made during life, and the diagnosis of probable or possible AD is made on clinical grounds. 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 two 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 (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 one or more cognitive domains, and preservation of independence in functional abilities. In some patients, MCI may be a predementia phase of AD. Patients with MCI may undergo ancillary testing (e.g., neuroimaging, laboratory studies, and neuropsychological assessment) to rule out vascular, traumatic, and medical causes of cognitive decline and to evaluate genetic factors.

Biomarker evidence has been integrated into the diagnostic criteria for probable and possible AD for use in research settings. Other diagnostic tests for AD include cerebrospinal (CSF) fluid levels of tau protein or beta-amyloid precursor protein, as well as positron emission tomography (PET) amyloid imaging. The CSF tests are considered separately in the policy “Biochemical Markers for Alzheimer’s disease.”

**Regulatory Status:**

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. The U.S. Food and Drug Administration (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).

---

**Medical Policy Statement**

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 in an asymptomatic individual to determine future risk of disease is considered established only for those individuals meeting patient selection criteria and who are seeking preconception genetic counseling.

Genetic testing for variants in presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant Alzheimer disease in an asymptomatic individual to determine future risk of disease is established for individuals who meet patient selection criteria and who are seeking preconception genetic counseling.

Genetic testing for confirming a diagnosis of Alzheimer’s disease or determining the risk assessment of developing AD when family planning is not an issue is considered experimental/investigational.

---

**Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)**

**Inclusions:**
- Targeted genetic testing for known familial variant in the presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease is established when all the following criteria are met:
  - The individual has a close relative (i.e., first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease AND
  - Results of testing will inform reproductive decision making.
- Genetic testing for variants in presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease is established in an asymptomatic individual to determine future risk of disease when the following criteria are met:
  - The individual has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable AND
  - Results of testing will inform reproductive decision making

Genetic counseling by appropriately trained individuals is strongly encouraged to be done in conjunction with the genetic testing for Alzheimer’s disease when the above criteria are met.
Exclusions:
Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered experimental/investigational in all other situations. 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).

CPT/HCPCS Level II Codes (Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)

Established codes (for preconception testing purposes only):
- 81401
- 81405
- 81406

Other codes (investigational, not medically necessary, etc.):
- S3852

Rationale
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

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 Alzheimer disease (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 PICOs 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.6

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.

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 late-onset 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 1. 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</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>

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for Alzheimer disease, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.
Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer either to predicting a future condition or to predicting a response to therapy.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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 have 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 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 polymorphisms at 10 loci significantly associated with risk of late-onset AD. Analysis confirmed the association of APOE with an earlier age of onset and found significant associations for CR1, BIN1, and PICALM. APOE contributed 3.7% of the variation in age of onset and the other 9 loci combined contributed 2.2% of the variation. Each additional copy of the APOE*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 with only 1 marker, the T allele of rs75932628 (excluding the APOE locus and the A673T variant in APP11). The frequency of rs75932628 (triggering receptor expressed on myeloid cells 2 [TREM2]) was then tested in a general population of 110,050 Icelanders of all ages and 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 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=3.42x10^{-10}). In 1236 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=7.39 x10^{-6}). The decrease in TREM2 frequency in elderly patients who are cognitively intact supports the findings associating TREM2 with increasing risk of AD. Guerriero et al (2013) also found a strong association of the R47H TREM2 variant with AD (p=0.001). Using 3 imputed data sets of genome-wide association AD studies, a meta-analysis found a significant association with the variant and disease (p=0.002). The authors further reported direct genotyping of R47H in 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}).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There are no randomized controlled trials comparing outcomes of asymptomatic adults at risk for developing late-onset AD managed with and without genetic testing for AD.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study was designed to examine consequences of AD risk assessment by APOE genotyping. Of 289 eligible participants 162 were randomized (mean age, 52.8 years; 73% female; average education, 16.7 years) to either risk assessment based on APOE testing and family history (n=111) or family history alone (n=51). During a 1-year follow-up, those undergoing APOE testing with a high-risk genotype were more likely than low-risk or ungenotyped individuals to take more vitamins (40% vs. 24% and 30%, respectively), change diet (20% vs. 11% and 7%, respectively), or change exercise behaviors (8% vs. 4% and 5%, respectively). 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).

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 e4 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. There are many actions patients may take following knowledge of a disease-associated variant. Changes in lifestyle factors (e.g., 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, thus demonstrating some degree of clinical validity. However, the clinical sensitivity and specificity of APOE*E4 is poor, and there is a lack of evidence on the clinical sensitivity and specificity of other genes.

Literature searches did not identify any that addressed how the use of the APOE or TREM2 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 e4 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 e4 carriers. Therefore, clinical utility has not been demonstrated for these tests.

Genetic Testing for Early Onset Familial 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 **PICOs** 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.

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 the explanation of the 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.

**Comparators**

The following practice is currently being used: targeted familial variant testing for those with a known familial variant and genetic testing for those without a known familial variant.

**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.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and
unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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 30–60% of individuals with familial early-onset AD. A number of variants scattered throughout the presenilin 1 (*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 *PSEN2* genes account for another 10% to 20% of cases.

Genetic yields may vary by population. Giau et al (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. 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, i.e., the presence of *PSEN1*, *PSEN2*, or *APP* variants is not useful in predicting age of onset (although it is usually similar to age of onset in affected family members), severity, type of symptoms, or rate of progression in asymptomatic individuals.

A study by Cochran et al (2019) confirmed a high diagnostic yield in early-onset or atypical dementia. 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 6 had one or more variants with moderate penetrance. The authors noted this supports a potential oligogenic model for early-onset dementia.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.
Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There are no randomized controlled trials comparing outcomes of asymptomatic adults at risk for developing early-onset AD managed with and without genetic testing for AD.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about 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 will 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, reported by Rahman et al (2012), which assess 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.21

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 (e.g., 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, the 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, clinical utility for the purposes of reproductive decision making has not 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. 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>Ongoing</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>90</td>
<td>Mar 2021</td>
</tr>
<tr>
<td>NCT03634007</td>
<td>Gene Therapy for APOE4 Homozygote of Alzheimer's Disease</td>
<td>15</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT01998841a</td>
<td>A Double-Blind, Placebo-Controlled Parallel-Group Study in Preclinical PSEN1 E280A Mutation Carriers Randomized to Crenezumab or Placebo, and in Non-Randomized, Placebo-Treated Non-Carriers From the Same Kindred, to Evaluate the Efficacy and Safety of Crenezumab in the Treatment of Autosomal-Dominant Alzheimer's Disease</td>
<td>252</td>
<td>Feb 2022</td>
</tr>
<tr>
<td>NCT03977584a</td>
<td>Tau PET Longitudinal Substudy Associated With: A Double-Blind, Placebo-Controlled Parallel-Group Study in Preclinical PSEN1 E280A Mutation Carriers Randomized to Crenezumab or Placebo, and in Nonrandomized, Placebo-treated Non-carriers From the Same Kindred, to Evaluate the Efficacy and Safety of Crenezumab in the Treatment of Autosomal-Dominant Alzheimer's Disease</td>
<td>150</td>
<td>Feb 2022</td>
</tr>
<tr>
<td>NCT00869817</td>
<td>Dominantly Inherited Alzheimer Network (DIAN)</td>
<td>700</td>
<td>Jul 2024</td>
</tr>
<tr>
<td>NCT03657732</td>
<td>A Multi-center Longitudinal Cohort Study of Familial Alzheimer's Disease in China</td>
<td>10,000</td>
<td>Jan 2028</td>
</tr>
</tbody>
</table>

NCT: national clinical trial
a Denotes industry-sponsored or cosponsored trial

SUMMARY OF EVIDENCE
For individuals who are asymptomatic and at risk for developing late-onset Alzheimer disease (AD) who receive genetic testing the evidence for genetic testing in individuals who are asymptomatic and at risk for developing AD includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy, test validity, change in disease status, and health status measures. 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 for indicating 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 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 and at risk for developing early-onset, autosomal dominant AD with a known familial variant who receive targeted genetic testing for a known familial variant the evidence includes studies on gene associations and test accuracy. Variants in the presenilin 1/2 (PSEN1/2) and amyloid-beta precursor protein (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 been previously identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions regarding the benefit 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 and at risk for developing early-onset, autosomal dominant AD whose familial variant is unknown who receive genetic testing the evidence includes studies on gene associations and test accuracy. Variants in the presenilin 1/2 (PSEN1/2) and amyloid-beta precursor protein (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 variant database of pathogenic PSEN1/2 and APP variants is identified. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions regarding the benefit 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.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Medical Genetics and Genomics
The American College of Medical Genetics and Genomics lists genetic testing for APOE alleles as one of 5 recommendations in the Choosing Wisely initiative.22 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.”

The College, jointly with the National Society of Genetic Counselors, issued the following practice guidelines (2011)16:

- “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 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 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 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 \( \text{PSEN1} \), \( \text{PSEN2} \), or \( \text{APP} \), 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.

In 2019, ACMG reaffirmed its position in the original document. However, an addendum was issued clarifying 2 points:

- Use of the phrase "pathogenic variant" should be adopted rather than the word "mutation" in discussing pathogenic variants related to autosomal dominant EOAD.
- Because the original document no longer meets the criteria for an evidence-based practice guideline by either the ACMG or National Society of Genetic Counselors, both societies have since reclassified it as a Practice Resource.

**American Academy of Neurology**

In 2001, the American Academy of Neurology made the following recommendations:

- Routine use of \( \text{APOE} \) genotyping in patients with suspected AD is not recommended at this time (Guideline).
- There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline).
- This guideline is currently being updated as of February 2018. As of February 2019, none has been issued.

**European Federation of Neurological Sciences (EFNS)**

- Recommendations: genetic testing (level of evidence not reported)
- Screening for known pathogenic mutations can be undertaken in patients with appropriate phenotype or a family history of an autosomal dominant dementia.
- Testing of patients with familial dementia and of unaffected at-risk-relatives should be accompanied by neurogenetic counseling and undertaken only after full consent and by specialist centers. Presymptomatic testing may be performed in at-risk members of family-carrying mutation. It is recommended that the Huntington’s disease protocol be followed for pre-symptomatic testing.
- Routine Apo E genotyping is not recommended.

**Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD)**

The Fourth Canadian Consensus Conference on Diagnosis and Treatment of Dementia (CCCDTD4), held in 2012, updated guidelines from the third consensus, referenced next. Previous recommendations were endorsed if there were no changes in the literature. Full articles written by the CCCDTD workgroups providing complete background information for the consensus conference are available online.
A summary of consensus recommendations from the CCCDTD4 was published by Gauthier and colleagues in 2012. It is noted in the summary that: "Despite a large number of important advances, the CCCDTD4 concluded that fundamental changes in dementia diagnosis and management have not yet arrived." The 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 (e.g., gene mutation carriers, family history of AD, ApoE epsilon 4) should be restricted to research."

**Third Canadian Consensus:** The CCCDTD conference recommended the following:

"Predictive genetic testing for asymptomatic “at risk” individuals with an apparent autosomal dominant inheritance and a family-specific mutation has been identified:

1. With appropriate pre- and post-testing counseling, predictive genetic testing (PGT) can be offered to "at-risk" individuals (Grade B, Level 2). Examples:
   a. First-degree relatives of an affected individual with the mutation (e.g., 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 (e.g., in early onset AD, one might test for the most common mutations in PS1, APP). (Grade B, Level 2**) If a mutation is identified, it would have direct implications for offspring of the individual (if a de novo mutation is assumed). Conversely, it would also be important to test other family members such as parents and siblings for possible non-penetrance of a mutation.

Genetic screening with APOE genotype in asymptomatic individuals in the general population is not recommended because of the low specificity and sensitivity. (Grade E, Level 2**) Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2**)

**CCCDTD Evidence Ratings**

Grade (B) There is fair evidence to support this maneuver.
Grade (E) There is good evidence to recommend against this procedure.
Level 2: (1) Evidence obtained from well-designed controlled trial without randomization, or (2) Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center, or (3) Evidence obtained from comparisons between times or places with or without intervention. Dramatic results in uncontrolled experiments are included in this category.

---

**Government Regulations**
**National/Local:**
There is no national or local coverage determination on this topic. In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

**Related Policies**

Biochemical Markers of Alzheimer's Disease

**References**


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February 2021, the date the research was completed.
<table>
<thead>
<tr>
<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/21/03</td>
<td>7/21/03</td>
<td>7/7/03</td>
<td>Joint policy for Biochemical Markers of Alzheimer’s Disease established</td>
</tr>
<tr>
<td>10/6/03</td>
<td>10/6/03</td>
<td>10/14/03</td>
<td>Joint policy for Genetic Testing for Familial Alzheimer’s Disease established</td>
</tr>
<tr>
<td>2/26/05</td>
<td>2/26/05</td>
<td>1/14/05</td>
<td>Routine maintenance for Genetic Testing for Alzheimer’s Disease (changed title from Genetic Testing for Familial Alzheimer’s Disease)</td>
</tr>
<tr>
<td>2/27/05</td>
<td>2/27/05</td>
<td>1/14/05</td>
<td>Routine maintenance for Biochemical Markers of Alzheimer’s Disease policy</td>
</tr>
<tr>
<td>1/1/07</td>
<td>1/18/07</td>
<td>10/20/06</td>
<td>Biochemical Markers of Alzheimer’s Disease and Genetic Testing for Alzheimer’s Disease combined into one policy, Genetic Testing and Biochemical Markers for Alzheimer’s Disease.</td>
</tr>
<tr>
<td>9/1/07</td>
<td>7/3/07</td>
<td>8/29/07</td>
<td>Routine maintenance of combined policy</td>
</tr>
<tr>
<td>1/1/09</td>
<td>10/13/08</td>
<td>12/30/08</td>
<td>Routine maintenance of combined policy; policy retired.</td>
</tr>
<tr>
<td>5/1/12</td>
<td>2/21/12</td>
<td>2/21/12</td>
<td>Combined policy pulled out of retirement to clarify coverage guidelines; references updated. Policy enhanced to mirror BCBSA policy. Added codes 83520 and 83912 to policy for coding urinary and CSF biomarker testing.</td>
</tr>
<tr>
<td>11/1/13</td>
<td>8/22/13</td>
<td>8/27/13</td>
<td>Combined policy split out into two policies to mirror the BCBSA policies Biochemical Markers of Alzheimer’s Disease and Genetic Testing for Familial Alzheimer’s Disease. This policy speaks to genetic testing only.</td>
</tr>
</tbody>
</table>

Next Review Date: The combined policy, Genetic Testing and Biochemical Markers for Alzheimer's Disease will no longer be reviewed. Please reference individual policies.
 Joint BCBSM/BCN Medical Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Date</th>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/14</td>
<td>10/17/13</td>
<td>10/25/13</td>
<td>Separate policy, “Genetic Testing for Familial Alzheimer’s Disease” established.</td>
</tr>
<tr>
<td>7/1/16</td>
<td>4/19/16</td>
<td>4/19/16</td>
<td>Routine policy maintenance.</td>
</tr>
<tr>
<td>7/1/18</td>
<td>4/17/18</td>
<td>4/17/18</td>
<td>Routine policy maintenance. No change in policy status.</td>
</tr>
<tr>
<td>7/1/19</td>
<td>4/16/19</td>
<td></td>
<td>Routine policy maintenance, no change in policy status.</td>
</tr>
<tr>
<td>7/1/20</td>
<td>4/14/20</td>
<td></td>
<td>Routine policy maintenance. No change in policy status.</td>
</tr>
</tbody>
</table>

Next Review Date: 2nd Qtr. 2022

 Pre-Consolidation Medical Policy History for Genetic Testing for Alzheimer Disease

<table>
<thead>
<tr>
<th>Original Policy Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCN: N/A</td>
<td>Revised: N/A</td>
</tr>
<tr>
<td>BCBSM: 7/16/99</td>
<td>Revised: N/A</td>
</tr>
</tbody>
</table>
BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR ALZHEIMER DISEASE

I. Coverage Determination:

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Coverage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial HMO (includes Self-Funded groups unless otherwise specified)</td>
<td>Genetic testing for AD is covered for preconception family planning purposes only. All other uses are experimental/investigational.</td>
</tr>
<tr>
<td>BCNA (Medicare Advantage)</td>
<td>See government section.</td>
</tr>
<tr>
<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
</tr>
</tbody>
</table>

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.