Targeted genetic testing for a known familial variant in the presenilin genes (PSEN1, PSEN2) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease may be considered medically necessary in an asymptomatic or minimally symptomatic individual to determine future risk of disease when 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.

Genetic testing for variants in presenilin genes (PSEN1, PSEN2) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant Alzheimer disease may be considered medically necessary in an asymptomatic or minimally symptomatic individual to determine future risk of disease when 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.

Genetic testing for the risk assessment of Alzheimer disease in asymptomatic individuals is considered investigational in all other situations. Investigational testing includes, but is not limited to, testing for the apolipoprotein E ε4 allele (APOE) or triggering receptor expressed on myeloid cells 2 (TREM2).

**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 three affected members in two 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 three 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—"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 variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

### Table PG2. American College of Medical Genetics and Genomics-Association for Molecular Pathology 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.

### Coding

The following CPT coding is used to report APOE, PSEN, and APP testing:

CPT code **81401** includes:
- APOE (apolipoprotein E) (e.g., hyperlipoproteinemia type III, cardiovascular disease, Alzheimer disease), common variants (e.g., *2, *3, *4)

CPT code **81405** includes:
- PSEN1 (presenilin 1) (e.g., Alzheimer disease), full gene sequence

CPT code **81406** includes:
- APP (amyloid beta [A4] precursor protein) (e.g., Alzheimer disease), full gene sequence
- PSEN2 (presenilin 2 [Alzheimer disease 4]) (e.g., Alzheimer disease), full gene sequence

There following is a HCPCS code specific to APOE ε4 allele testing:
- **S3852**: DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer’s disease

### Description

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

- β-Amyloid Imaging With Positron Emission Tomography for Alzheimer Disease
- Biochemical Markers of Alzheimer Disease

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

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. Food and Drug Administration has chosen not to require any regulatory review of this test.

**Rationale**

**Background Alzheimer Disease**

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

**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: the amyloid-beta precursor protein (APP) gene, presenilin 1 (PSEN1) gene, and presenilin 2 (PSEN2) gene. APP and PSEN1 variants have 100% penetrance absent death from other causes, while PSEN2 has 95% penetrance. 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 a ε4 allele. However, not all patients with the allele develop AD. The ε4 allele represents a risk factor for AD rather than a disease-associated variant. In the absence of APOE testing, first-degree relatives of an individual with sporadic or familial AD are estimated to have a 2- to 4-fold greater risk of developing AD than the general population. There is evidence of possible interactions between ε4 alleles, other risk factors for AD (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.

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:
2.04.13  Genetic Testing for Alzheimer Disease
Page 5 of 19

- 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 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. The CSF tests are considered separately in evidence review 2.04.14. PET amyloid imaging is considered in evidence review 6.01.55 (β-amyloid imaging with PET for Alzheimer disease).

Literature Review
The most recent update was performed through February 23, 2017. The review was initially informed by a 1999 TEC Assessment. This review also addresses genetic testing category 3 on testing an asymptomatic individual to determine future risk of disease (see Appendix Table 1 for genetic testing categories).

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (i.e., a demonstration that the diagnostic information can be used to improve patient health outcomes).

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 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-Dementia NGS Panel</td>
<td>37</td>
<td>NGS</td>
</tr>
<tr>
<td>Knight Diagnostic Laboratories</td>
<td>Dementia</td>
<td>21</td>
<td>Sequence analysis of the entire coding region</td>
</tr>
<tr>
<td>PreventionGenetics</td>
<td>Dementia Sequencing Panel</td>
<td>13</td>
<td>Deletion/duplication analysis; sequence analysis of entire coding region; targeted variant analysis</td>
</tr>
</tbody>
</table>

NGS: next-generation sequencing.

**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>
<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 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 Alzheimer disease (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 (triggering receptor expressed on myeloid cells 2 [TREM2]) was then tested in a general population of 110,050 Icelanders of all ages and found to confer a risk of developing AD of 0.63% (odds ratio [OR], 2.26; 95% CI, 1.71 to 2.98; p=1.13 × 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 × 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 × 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
2.04.13  Genetic Testing for Alzheimer Disease
Page 8 of 19

detected a highly significant association between the variant and AD (OR=5.05; 95% CI, 2.77 to 9.16; p=9.0×10⁻⁹).

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%), 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 ε4 negative participants had significantly lower test-related distress than ε4 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 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 (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 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 Alzheimer Disease 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>AIDmark® Early Onset Alzheimer’s Evaluation</td>
<td>3</td>
<td>Bidirectional Sanger sequence analysis</td>
</tr>
<tr>
<td>Fulgent Genetics</td>
<td>Early Onset Familial Alzheimer Disease NGS Panel</td>
<td>3</td>
<td>Deletion/duplication analysis; sequence analysis of entire coding region</td>
</tr>
<tr>
<td>PreventionGenetics</td>
<td>Alzheimer's Disease, Familial via the APP Gene, Exons 16 and 17; Familial via the PSEN1 Gene; Familial via the PSEN2 Gene</td>
<td>1 each test</td>
<td>Deletion/duplication analysis; sequence analysis of entire coding region; targeted variant analysis</td>
</tr>
</tbody>
</table>

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

**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 (i.e., 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 presenilin 1 (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 amyloid-beta precursor protein (APP) and presenilin 2 (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, i.e., 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 and retrospective designs, and the research was conducted in different countries, which may limit the generalizability of the findings.23

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, 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 Alzheimer Disease
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 Alzheimer disease (AD) who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Relevant outcomes are test accuracy and validity, change in disease status, health status measures, and quality of life. Many genes, including apolipoprotein E (APOE), CR1, BIN1, PICALM, and TREM2, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing 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, 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 presenilin 1 and 2...
(PSEN1 and PSEN2) 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 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.

Supplemental Information
Practice Guidelines and Position Statements

American College of Medical Genetics and Genomics et al
The American College of Medical Genetics and Genomics (ACMG) has listed genetic testing for apolipoprotein E (APOE) alleles as 1 of 5 recommendations in the Choosing Wisely initiative.24 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 Alzheimer disease (AD), the most common cause of dementia: “The presence of a 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.”

In 2011, ACMG and the National Society of Genetic Counselors issued the following joint practice guidelines:

- 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.

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history of additional relatives may prove useful, especially in small families or those with a preponderance of early death that may mask a history of dementia.

- A risk assessment should be performed by pedigree analysis to determine whether the family history is consistent with EOAD [early-onset AD] or LOAD [late-onset AD] and with autosomal dominant (with or without complete penetrance), familial, or sporadic inheritance.
- Patients should be informed that currently there are no proven pharmacologic or lifestyle choices that reduce the risk of developing AD or stop its progression.
- The following potential genetic contributions to AD should be reviewed:
  - The lifetime risk of AD in the general population is approximately 10–12% in a 75–80 year lifespan
  - The effect(s) of ethnicity on risk is still unclear
  - Although some genes are known, there are very likely others (susceptibility, deterministic, and protective) whose presence and effects are currently unknown

For families in which an autosomal dominant AD gene mutation is a possibility:

- Discuss the risk of inheriting a mutation from a parent affected with autosomal dominant AD is 50%. In the absence of identifying a mutation in apparent autosomal dominant families, risk to offspring could be as high as 50% but may be less.
- Testing for genes associated with early onset autosomal dominant AD should be offered in the following situations:
  - A symptomatic individual with EOAD in the setting of a family history of dementia or in the setting of an unknown family history (e.g., adoption)
  - Autosomal dominant family history of dementia with one or more cases of EOAD
  - A relative with a mutation consistent with EOAD (currently PSEN1/2 or APP)
- The Alzheimer Disease & Frontotemporal Dementia Mutation Database should be consulted (available online at: www.molgen.ua.ac.be/ADMutations/) before disclosure of genetic test results, and specific genotypes should not be used to predict the phenotype in diagnostic or predictive testing:
  - Discuss the likelihood of identifying a mutation in PSEN1, PSEN2, or APP, noting that current experience indicates that this likelihood decreases with lower proportions of affected family members and/or older ages of onset.
  - Ideally, an affected family member should be tested first. If no affected family member is available for testing and an asymptomatic individual remains interested in testing despite counseling about the low likelihood of an informative result (a positive result for a pathogenic mutation), he/she should be counseled according to the recommended protocol. If the affected relative, or their next of kin, is uninterested in pursuing testing, the option of DNA banking should be discussed.

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

- Routine use of APOE genotyping in patients with suspected AD is not recommended at this time (Guideline)
- There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline)
- These guidelines are currently being updated as of March 2017

European Federation of Neurological Sciences
In 2010, the European Federation of Neurological Sciences made the following recommendations:

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

- Routine Apo E genotyping is not recommended

### Canadian Consensus Conference on Diagnosis and Treatment of Dementia

#### Fourth Canadian Consensus Conference

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

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

“Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI [mild cognitive impairment] criteria, or at-risk individuals (e.g., gene mutation carriers, family history of AD, APOE epsilon 4) should be restricted to research.”

### Third Canadian Consensus

The CCCDTD recommended the following:

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.

7. 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**)

8. Genetic testing with APOE genotype is not recommended for the purpose of diagnosing AD because the positive and negative predictive values are low. (Grade E, Level 2**)

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

### U.S. Preventive Services Task Force Recommendations

Not applicable.
Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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>National Cell Repository for Alzheimer's Disease (NCRAD)</td>
<td>3000</td>
<td>Jul 2021</td>
</tr>
<tr>
<td></td>
<td>A Phase II/III Randomized, Double-Blind, Placebo-Controlled Multi-Center Study of 2 Potential Disease Modifying Therapies in Individuals at Risk for and With Dominantly Inherited Alzheimer's Disease</td>
<td>210</td>
<td>Dec 2019</td>
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<tr>
<td>Ongoing</td>
<td>National Cell Repository for Alzheimer's Disease (NCRAD)</td>
<td>3000</td>
<td>Jul 2021</td>
</tr>
<tr>
<td></td>
<td>Alzheimer's Prevention Registry GeneMatch Program</td>
<td>500,000</td>
<td>Dec 2030</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Apoe Impact Study on Brain Structure and Function, in a Population 45 to 75 Years Old</td>
<td>575</td>
<td>Sep 2015 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.13

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual's germline to benefit the individual</td>
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</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
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<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

References


2.04.13  Genetic Testing for Alzheimer Disease
Page 17 of 19


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):
- History and physical and/or consultation notes including:
  - Diagnosis
  - Family history
  - Genetic counseling notes
  - How test result will impact clinical decision making
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
- Lab results documenting both partners carrier status or genetic disorder
- Physician order for genetic test
- Name and description of genetic test
- CPT codes billed for the particular genetic test

**Post Service**
- Laboratory report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
</tr>
<tr>
<td></td>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
</tbody>
</table>
### 2.04.13 Genetic Testing for Alzheimer Disease

#### Type | Code | Description
---|---|---
| Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
| 81406 |

#### HCPCS | S3852 | DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease

<table>
<thead>
<tr>
<th>ICD-10 Procedure</th>
<th>None</th>
</tr>
</thead>
</table>

| ICD-10 Diagnosis | All Diagnoses |

#### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
</table>
| 04/02/2010 | New policy Policies combined:  
- Apolipoprotein E Epsilon (apoE) 4 Allele and Alzheimer's Disease: Role for Genetic Testing for Diagnosis and Risk Management  
- Cerebrospinal Fluid and Urinary Assays of Neuronal (Neural) Thread Protein in the Diagnosis of Alzheimer's Dementia | Medical Policy Committee |
| 04/19/2012 | Added documentation required for clinical review | Administrative Review |
| 02/22/2013 | Coding Update | Administrative Review |
| 02/27/2015 | Policy title change from Alzheimer's Disease - Genetic and Biochemical Testing Policy revision without position change | Medical Policy Committee |
| 09/01/2016 | Policy title change from Genetic Testing for Familial Alzheimer's Disease Policy revision without position change | Medical Policy Committee |
| 11/01/2017 | Policy revision with position change | Medical Policy Committee |

#### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions,
but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.