Genetic testing for a NOTCH3 variant to confirm the diagnosis of CADASIL syndrome in a patient may be considered medially necessary when both of the following criteria are met:

- Clinical signs, symptoms, skin biopsy, and imaging results are consistent with CADASIL, indicating that the pretest probability of CADASIL is at least in the moderate-to-high range (see the Policy Guidelines section).
- The diagnosis of CADASIL is inconclusive following alternative methods of testing, including skin biopsy and magnetic resonance imaging.

For individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome:

- If there is a family member (first- and second-degree relative) with a known variant, targeted genetic testing of the known NOTCH3 familial variant may be considered medially necessary.
- If the family member's genetic status is unknown, genetic testing of NOTCH3 (see Policy Guidelines section) may be considered medially necessary.

Genetic testing for a NOTCH3 variant to confirm the diagnosis of CADASIL syndrome in all other situations is considered investigational.

### Policy Guidelines

Genetic testing for NOTCH3 comprises targeted sequencing of specific exons (e.g., exon 4 only, exons 2-6), general sequencing of NOTCH3 exons (e.g., exons 2-24 or all 33 exons), or targeted testing for known NOTCH3 pathogenic variants.

The probability that CADASIL is present in an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy.

First degree relatives are defined as a blood relative with whom the individual shares approximately 50% of his/her genes, including parents, full-siblings, and children on both maternal and paternal sides.

Second degree relatives are defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including grandparents, grandchildren, uncles, aunts, nieces, nephews, and half-siblings.

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present. Table PG1 summarizes the pooled frequency of clinical and radiologic features, and the points assigned for each finding. The authors recommended that a total score of 14 be used to select patients for testing, because this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

### Table PG1. Pooled Frequency of Clinical and Radiologic Features

<table>
<thead>
<tr>
<th>Features</th>
<th>No. With NOTCH3 Variant</th>
<th>Percent With NOTCH3 Variant</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>239/463</td>
<td>52%</td>
<td>1</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>65/85</td>
<td>76%</td>
<td>3</td>
</tr>
</tbody>
</table>

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Features | No. With NOTCH3 Variant | Percent With NOTCH3 Variant | Points
---|---|---|---
Transient ischemic attack/stroke | 380/526 | 72% | 1 (2 if <50 y)
Psychiatric disturbance | 106/380 | 28% | 1
Cognitive decline | 188/434 | 43% | 3
Radiologic
LE | 277/277 | 100% | 3
LE extended to temporal pole | 174/235 | 74% | 1
LE extended to external capsule | 228/303 | 75% | 5
Subcortical infarcts | 210/254 | 83% | 2

Adapted from Pescini et al (2012).
LE: leukoencephalopathy.

**Genetics Nomenclature Update**
The 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 PG2). HGVS nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

**Table PG2. 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 PG3. ACMG-AMP Standards and Guidelines for Variant Classification**

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

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

**Genetic Counseling**
Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Coding
There is CPT coding to report NOTCH3 genetic testing. Code **81406** includes:
NOTCH3 (notch 3) (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), targeted sequence analysis (e.g., exons 1-23).

Description
Variants in the NOTCH3 gene have been causally associated with CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Genetic testing is available to determine if pathogenic variants exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.

Related Policies
- Preimplantation Genetic Testing

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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing of NOTCH3 is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale
Background
CADASIL
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an uncommon, autosomal dominant disease, though it is the most common cause of hereditary stroke and hereditary vascular dementia in adults. CADASIL syndrome is an adult-onset, disabling systemic condition, characterized by a migraine with aura, recurrent lacunar strokes, progressive cognitive impairment, and psychiatric disorders. The overall prevalence of the disease is unknown in the general population.

Diagnosis
The differential diagnosis of CADASIL includes the following conditions (see Table 1).
Table 1. Differential Diagnosis of CADASIL

<table>
<thead>
<tr>
<th>Acquired Disorders</th>
<th>Inherited Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sporadic SVD with or without hypertension as the main risk factor</td>
<td>• Fabry disease</td>
</tr>
<tr>
<td>• Multiple sclerosis</td>
<td>• Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy</td>
</tr>
<tr>
<td>• Primary angiitis of the central nervous system</td>
<td>• Familial SVD caused by heterozygous variants in the HTRA1 gene</td>
</tr>
<tr>
<td>• Some forms of leukodystrophy</td>
<td>• Some forms of leukodystrophy</td>
</tr>
</tbody>
</table>

SVD: small vessel disease.

Since the clinical presentation of CADASIL varies, the condition may be confused with multiple sclerosis, Alzheimer dementia, and Binswanger disease. The specific clinical signs and symptoms, along with family history and brain magnetic resonance imaging findings, are extremely important in diagnosing CADASIL. The clinical features and mode of inheritance (autosomal dominant vs autosomal recessive) help to distinguish CADASIL from other inherited disorders in a differential diagnosis.

When the differential diagnosis includes CADASIL, various diagnostic tests are available:

- Genetic testing, by direct sequencing of select exons or of exons 2 through 24 of the NOTCH3 gene (see the Rationale section). Identification of a NOTCH3 pathogenic variant definitively establishes a diagnosis of CADASIL without the need for additional diagnostic testing (e.g., skin biopsy)
- Immunohistochemistry assay of a skin biopsy sample, using a monoclonal antibody with reactivity against the extracellular domain of the NOTCH3 receptor. Positive immunostaining reveals the accumulation of the NOTCH3 protein in the walls of small blood vessels. Lesnick Oberstein et al (2003) estimated the sensitivity and specificity at 85% to 90% and 95% to 100%, respectively, for 2 observers of the test results in a population of patients and controls correlated with clinical, genetic, and magnetic resonance imaging parameters.
- Detection of granular osmiophilic material (GOM) in the same skin biopsy sample by electron microscopy. The major component of GOM is the ectodomain of the NOTCH3 gene product. GOM accumulates directly in vascular smooth muscle cells and, when present, is considered a hallmark of the disease. However, GOM may not be present in all biopsy samples. Sensitivity has been reported as low as 45% and 57% but specificity is generally near or at 100%.
- Examination of brain tissue for the presence of GOM was originally described as limited to brain blood vessels. Examination of brain biopsy or autopsy after death was an early criterion standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain blood vessels

**NOTCH3 Variants**

Variants in NOTCH3 have been identified as the underlying cause of CADASIL. In almost all cases, the pathogenic variants lead to loss or gain of a cysteine residue that can lead to increased reactivity of the NOTCH3 protein, resulting in ligand-binding and toxic effects.

The NOTCH3 gene is found on chromosome 19p13.2-p13.1 and encodes the third discovered human homologue of the *Drosophila melanogaster* type I membrane protein NOTCH. The NOTCH3 protein consists of 2321 amino acids, primarily expressed in vascular smooth muscle cells, and plays an important role in the control of vascular transduction. It has an extracellular ligand-binding domain of 34 epidermal growth factor (EGF)-like repeats, traverses the membrane once, and has an intracellular domain required for signal transduction.

Variants in the NOTCH3 gene have been differentiated into those causative of the CADASIL syndrome (pathogenic variants) and those of uncertain significance. Pathogenic variants affect conserved cysteine residues within 34 EGF-like repeat domains in the extracellular portion of the NOTCH3 protein. More than 150 pathogenic variants have been reported in at least 500
pedigrees. NOTCH3 has 33 exons but all CADASIL variants reported to date have occurred in exons 2 to 24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode EGF receptors 2 to 5 (>40% of variants in >70% of families occur in these exons). Some studies have indicated that the clinical variability in CADASIL presentation, particularly about the development of white-matter hyperintensities on magnetic resonance imaging, may be related to genetic modifiers outside the NOTCH3 locus but the specific role of these modifiers is not well-delineated.

The probability that CADASIL is present in an individualized assessment depends on numerous factors such as family history, symptoms, imaging results, and other specialized testing (e.g., skin biopsy). Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present, with increasing likelihood with the presence of one or several factors, including a migraine, migraine with aura, transient ischemic attack/stroke, psychiatric disturbance, cognitive decline, leukoencephalopathy (with greater risk for leukoencephalopathy extending to the temporal pole or external capsule), and subcortical infarcts.

**Literature Review**
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 of 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.

**Testing Individuals with Suspected CADASIL Syndrome**

**Clinical Context and Test Purpose**
The purposes of genetic testing of symptomatic individuals with suspected cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome are to establish the diagnosis of CADASIL without skin biopsy or other invasive testing and to aid in reproductive planning when the diagnosis cannot be made clinically.

The questions addressed in this evidence review are: In individuals with suspected CADASIL, does the use of genetic testing result in changes in management or outcome improvements, including eliminating the need for skin biopsy to confirm diagnosis of CADASIL, aid in preimplantation genetic testing to determine likelihood of an affected offspring, or alter reproductive planning decisions?

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

**Patients**
The relevant population of interest are individuals with suspected CADASIL.

**Interventions**
The test being considered is genetic testing for NOTCH3 variants.

**Comparators**
The following practice is currently being used: standard clinical management without genetic testing.
Outcomes
The potential beneficial outcome of primary interest would be changes in management associated with improved outcomes initiated based on confirming a genetic diagnosis of CADASIL. Reductions in skin biopsies or other invasive tests to confirm the diagnosis of CADASIL are also potentially beneficial outcomes.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to the inappropriate initiation of treatments or psychological harm after receiving positive test results. False-negative test results can lead to lack of medical or neurologic treatments or surveillance.

Timing
The time frame for outcome measures varies from the short-term development of symptoms to long-term changes in disease status and outcomes.

Setting
Patients suspected of CADASIL are actively managed by neurologists or psychiatrists due to ischemic episodes, cognitive deficits, migraines with aura, or psychiatric disturbances. Genetic testing is used to confirm a diagnosis of CADASIL. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Simplifying Test Terms
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:
- Technically reliable
- Clinically valid
- Clinically useful

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

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 both to predicting a future condition or 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).
Several retrospective and prospective studies have examined the association between NOTCH3 variants and CADASIL, as shown in Table 2. Studies have been divided into two categories: Part 1: Diagnostic studies, in which patients enrolled were suspected but not confirmed to have CADASIL; and Part 2: Clinical validity studies, in which the patients had already been diagnosed with the disease by some method other than genetic testing. The diagnostic studies are more likely to represent the target population in which the test would be used.

The results of the clinical validity studies demonstrated that a NOTCH3 pathogenic variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity ranging from 90% to 100%. Limited data on specificity derive from testing small numbers of healthy controls, and no false-positive NOTCH3 variants have been reported in these populations. The diagnostic yield studies have reported a variable yield (range, 10%-54%). These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders.

**Testing Strategy**

Identification of a NOTCH3 pathogenic variant establishes a diagnosis of CADASIL. For individuals suspected of CADASIL:

- Perform targeted sequencing and analysis of specific NOTCH3 exons (e.g., exon 4 only, exons 2-6) OR
- Perform general testing of NOTCH3 exons (e.g., exons 2-24 or all 33 exons)
- If no NOTCH3 pathogenic variant is identified, a skin biopsy is warranted for immunohistochemical staining for NOTCH3 protein and/or electron microscopy for granular osmiophilic material
### Table 2. Association Between NOTCH3 and CADASIL Diagnosis: Results From Studies Supporting NOTCH3 Genotyping Test Claims

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>NOTCH3 Exons Sequenced</th>
<th>Diagnostic Yield</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Part 1: Diagnostic studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosca et al (2011)⁹</td>
<td>Patients: 140 with clinical suspicion of CADASIL (Italian, Chinese)</td>
<td>Direct sequencing of exons 2-8, 10, 14, 19-20, 22</td>
<td>Patients: 14 with pathogenic variants located in 10 exons. 126 patients free of pathogenic variants</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Selection: History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; consistent family history or combination of previous criteria</td>
<td></td>
<td>Family members: Analysis of 15 additional family members identified 11 of the same pathogenic variants</td>
<td></td>
</tr>
<tr>
<td>Lee et al (2009)¹⁵</td>
<td>Patients: 39 with suspected CADASIL (Chinese); 100 healthy elderly controls ≥80 y</td>
<td>Direct sequencing of exons 2-23</td>
<td>Patients: 9 different SNVs identified in 21/39 patients</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Selection: Suggestive MRI findings and at least 1 of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history</td>
<td></td>
<td>Family members: No data</td>
<td>No variants in 100 healthy elderly controls</td>
</tr>
<tr>
<td>Markus et al (2002)⁷</td>
<td>Patients: 83 with suspected CADASIL (U.K.)</td>
<td>Direct sequencing of exons 3-4; SSCP of exons 2, 5-23</td>
<td>Patients: 15 SNVs identified in 48 families with 116 symptomatic patients, 73% in exon 4, 8% in exon 3, 6% in exons 5 and 6</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Selection: Patients were &lt;60 y with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but were not essential</td>
<td></td>
<td>Family members: No data</td>
<td></td>
</tr>
<tr>
<td>Choi et al (2013)⁸</td>
<td>Patients: 151 consecutive patients (Korean)</td>
<td>Bidirectional sequencing of exons 3, 4, 6, 11, 18</td>
<td>Patients: 6 (4%) found with identical NOTCH3 variant (R544C; exon 11). Of these, all had preexisting lacunar infarction, 5 (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; history of stroke and dementia higher in patients with variants</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Selection: History of acute ischemic stroke, neurologic exam, cranial computed tomography, or MRI</td>
<td></td>
<td>Family members: No data</td>
<td></td>
</tr>
<tr>
<td>Yin et al (2015)¹⁶</td>
<td>Patients: 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL</td>
<td>Testing method per Joutel et al (1997)¹⁷: exons 3 and 4 screened first; if no variants detected, remaining exons analyzed</td>
<td>Patients: 6 known familial variants identified in 8 families and 2 novel pathogenic variants identified in 2 families (exons 3 and 4), and 1 VUS identified in 1 family (exon 2). Overall NOTCH3 pathogenic variant prevalence: 29.4%</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Diagnosis/selection: MRI abnormalities and presence of &gt;1 typical symptom (e.g., migraine, stroke, cognitive deficits, psychiatric symptoms) or presence of atypical symptoms with positive family history</td>
<td></td>
<td>Family members: No data</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Patients Evaluated</td>
<td>NOTCH3 Exons Sequenced</td>
<td>Results</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------------------------------------</td>
<td>------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Abramycheva et al (2015)18.</td>
<td>Patients: 30 unrelated patients with suspected CADASIL</td>
<td>Direct sequencing of exons 2-23 via PCR</td>
<td>Patients: 16 SNVs identified in 18 unrelated patients, 12 of which had been previously described and 4 were novel (C194G, V252M, C338F, C484G)</td>
<td></td>
</tr>
<tr>
<td>Maksemous et al (2016)19.</td>
<td>Patients: 44 with suspected clinical diagnosis of CADASIL previously screened for standard Sanger sequencing exons (3, 4) and/or (2, 11, 18, 19) and classified as negative for known pathogenic variants</td>
<td>Custom NGS panel</td>
<td>Patients: 6 typical CADASIL pathogenic variants identified in 7/44 patients</td>
<td></td>
</tr>
</tbody>
</table>

**Part 2: Clinical validity studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>NOTCH3 Exons Sequenced</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis/selection: Skin biopsy-proven CADASIL patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis/selection: EM examination of skin biopsy was performed; 26 asymptomatic controls from CADASIL families</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dotti et al (2005)22.</td>
<td>Patients: 28 unrelated, consecutively diagnosed patients with CADASIL (Italian)</td>
<td>DHPLC, followed by confirmatory sequencing of identified pathogenic variants</td>
<td>Sensitivity: 100% Protection: 100% Family members: No data</td>
</tr>
<tr>
<td></td>
<td>Diagnosis/selection: Patients diagnosed via clinical and MRI criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joutel et al (1997)17.</td>
<td>Patients: 50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls</td>
<td>SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified variants</td>
<td>Sensitivity: 90% Protection: 100% Family members: No variants in 100 healthy controls</td>
</tr>
</tbody>
</table>

DHPLC: denaturing high-performance liquid chromatography; EM: electron microscope; MRI: magnetic resonance imaging; NGS: next-generation sequencing; NR: not reported; PCR: polymerase chain reaction; SNV: single nucleotide variant; SSCP: single-stranded conformational polymorphism; VUS: variant of uncertain significance.
Section Summary: Clinically Valid
The clinical sensitivity of genetic testing is high given that NOTCH3 is the only gene for which pathogenic variants are known to cause CADASIL. In clinical situations where the diagnosis of CADASIL cannot be confirmed by other methods (clinical presentation, MRI findings, skin biopsy), identification of a pathogenic variant in NOTCH3 establishes a diagnosis of CADASIL.

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.

The clinical specificity of genetic testing for CADASIL is high, and false-positive results have not been reported in studies of clinical validity. Therefore, a positive genetic test in a patient with clinical signs and symptoms of CADASIL is sufficient to confirm the diagnosis with a high degree of certainty. The clinical sensitivity is also relatively high, in the range of 90% to 100% for patients with a clinical diagnosis of CADASIL. This indicates that a negative test reduces the likelihood that CADASIL is present. However, because false-negative tests do occur, a negative test is less definitive in ruling out CADASIL. Whether a negative test is sufficient to rule out CADASIL depends on the pretest likelihood that CADASIL is present.

Pescini et al (2012) attempted to identify clinical factors that increase the likelihood of a pathogenic variant being present and therefore might be helpful in selecting patients for testing. The authors first performed a systematic review to determine the frequency with which clinical and radiologic factors are associated with a positive genetic test. Evidence was identified from 15 clinical series of patients with CADASIL. Table 3 summarizes the pooled frequency of clinical and radiologic features.

Table 3. Clinical and Radiologic Features in Patients with NOTCH3 Variants

<table>
<thead>
<tr>
<th>Features</th>
<th>No. With NOTCH3 Variant</th>
<th>Percent With NOTCH3 Variant</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>239/463</td>
<td>52</td>
<td>1</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>65/85</td>
<td>76</td>
<td>3</td>
</tr>
<tr>
<td>Transient ischemic attack/stroke</td>
<td>380/526</td>
<td>72</td>
<td>1 (2 if &lt;50y)</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>106/380</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>188/434</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td><strong>Radiologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LE</td>
<td>277/277</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>LE extended to temporal pole</td>
<td>174/235</td>
<td>74</td>
<td>1</td>
</tr>
<tr>
<td>LE extended to external capsule</td>
<td>228/303</td>
<td>75</td>
<td>5</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>210/254</td>
<td>83</td>
<td>2</td>
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</table>

Adapted from Pescini et al (2012).
LE: leukoencephalopathy.

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with NOTCH3 pathogenic variants, and in 54 patients with phenotypic features of CADASIL who were NOTCH3-negative. With the addition of family history and age at onset of transient ischemic attack or stroke, a scoring system was developed, as provided in Table 3. The authors recommended that a total score of 14 be used to select patients for testing because this score resulted in a high sensitivity (96.7%) and moderately high specificity (74.2%).
Currently, no specific clinical treatment for CADASIL has established efficacy. Supportive care in the form of practical help, emotional support, and counseling are appropriate for affected individuals and their families. Four studies were found that addressed the efficacy of potential treatments for CADASIL.

A double-blind, placebo-controlled trial by Dichgans et al (2008) evaluated the efficacy and safety of donepezil hydrochloride in individuals with CADASIL. The trial showed donepezil hydrochloride had no effect on the primary cognitive endpoint, the cognitive subscale of the Vascular AD Assessment Scale score in patients with CADASIL and cognitive impairment.

Another study, by Huang et al (2010), assessed the efficacy and tolerance of a 24-week therapy with acetazolamide 250 mg/d to improve cerebral hemodynamics in CADASIL patients. Treatment with acetazolamide resulted in a significant increase of blood mean flow velocity (MFV) in the middle cerebral artery (57.68 cm/s) compared with MFV in the middle cerebral artery at rest before treatment (67.12 cm/s; p=0.001). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients (e.g., headaches, dizziness) were relieved.

A third study, by Peters et al (2007), evaluated the use of 3-hydroxy-3-methylglutaryl-coenzyme A-reductase inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for 8 weeks. Treatment was started at 40 mg, followed by a dosage increase to 80 mg after 4 weeks. Transcranial Doppler sonography measuring MFV in the middle cerebral artery was performed at baseline and the end of treatment. There was no significant treatment effect on MFV (p=0.5) or cerebral vasoreactivity, as assessed by hypercapnia (p=0.5) or intravenous L-arginine (p=0.4) in the overall cohort. However, an inverse correlation was found between vasoreactivity at baseline and changes of both CO₂- and L-arginine-induced vasomotor response (both p<0.05). Short-term treatment with atorvastatin resulted in no significant improvement of hemodynamic parameters in the overall cohort of CADASIL subjects.

De Maria et al (2014) reported on the results of a randomized, double-blinded trial comparing sapropterin with placebo for adults with CADASIL. Sapropterin is a synthetic analogue of tetrahydrobiopterin, which is an essential cofactor in nitric oxide synthesis in endothelial cells. Given nitric oxide’s role in cerebrovascular function, the authors hypothesized that sapropterin supplementation would improve cerebral endothelium-dependent vasodilation in CADASIL patients. Endothelial dysfunction was assessed using the reactive hyperemia peripheral arterial tonometry response, which has been shown to be impaired in patients with CADASIL syndrome. Peripheral arterial tonometry is a noninvasive, quantitative test that measures changes in digital pulse volume during reactive hyperemia and evaluates the endothelial function of resistance arteries and nitric oxide-mediated changes in microvascular response. The trial randomized 61 subjects from 38 families, 32 to sapropterin and 29 to placebo. In the intention-to-treat analysis, there was no significant difference in change in reactive hyperemia peripheral arterial tonometry response (mean difference, 0.19; 95% confidence interval, -0.18 to 0.56). Both groups demonstrated improvements in reactive hyperemia peripheral arterial tonometry levels during the study, but, after results were adjusted for age, sex, and clinical characteristics, the improvement was not associated with treatment.

**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.

Genetic testing of individuals with suspected CADASIL may have clinical utility by:

- Establishing a diagnosis of CADASIL in an individual with signs and symptoms of the disease, particularly when other disorders are being considered, without the need for a skin biopsy
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when
a NOTCH3 pathogenic variant is present in a parent. Preimplantation testing is addressed elsewhere (Blue Shield of California Medical Policy: Preimplantation Genetic Testing).

**Section Summary: Clinically Useful**
Direct evidence for the clinical utility of genetic testing of individuals with suspected CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence for the clinical validity of NOTCH3 pathogenic variants in establishing a diagnosis of CADASIL leading to initiation of supportive care in the form of practical help, emotional support, and counseling may provide a chain of evidence for potential clinical utility.

**Targeted Familial Variant Testing in Asymptomatic Patients with Relatives who have CADASIL Syndrome**

**Clinical Context and Test Purpose**
The purposes of targeted familial variant testing of asymptomatic individuals with family members who have CADASIL are to screen at-risk individuals and predict the development of disease, to determine the need for surveillance, and to aid in reproductive planning.

The questions addressed in this evidence review are: In an asymptomatic patient with relatives who have CADASIL syndrome, does use of targeted genetic testing for a known familial variant lead to improved outcomes, including changes in surveillance, preimplantation genetic testing to determine the likelihood of an affected offspring, or alter reproductive planning decisions?

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

**Patients**
The relevant population of interest are asymptomatic patients with relatives who have CADASIL syndrome.

**Interventions**
The following test is currently being used: targeted familial variant testing of NOTCH3.

**Comparators**
The following practice is currently being used: standard clinical management without genetic testing.

**Outcomes**
The potential beneficial outcomes of primary interest would be confirming or excluding the need for surveillance or changes in reproductive decision making. A negative genetic test result would eliminate the need for surveillance to detect the development of symptoms and disease. A positive genetic test result would confirm a need for active surveillance and inform the reproductive decision process.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary medical or neurologic surveillance of asymptomatic individuals. False-negative test results can lead to lack of medical or neurologic surveillance.

**Timing**
The time frame for outcome measures varies from short-term surveillance of asymptomatic individuals for the development of signs or symptoms of CADASIL to long-term development of the disease.
Setting
Asymptomatic individuals with family members with CADASIL may be referred to a medical geneticist for investigation of genetic status for carrying a known familial variant. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

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).

See the clinical validity discussion in the Testing Individuals With Suspected CADASIL section.

Testing Strategy
Identification of a NOTCH3 pathogenic variant establishes a diagnosis of CADASIL in both symptomatic and asymptomatic individuals. For testing in asymptomatic individuals with family members who have CADASIL:
- When the proband’s NOTCH3 pathogenic variant is known, conduct targeted familial variant testing to determine genetic status

The testing strategy described is a general approach for targeted genetic testing for a known pathogenic variant previously identified in a family member (familial variant) with CADASIL.

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.

No randomized trials were identified addressing outcomes managed with CADASIL testing.

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.

Genetic testing of asymptomatic individuals with family members who have CADASIL may have clinical utility by:
- Confirming or excluding the need for surveillance based on the presence or absence of a known familial variant
- Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known NOTCH3 familial variant is present in a parent. Preimplantation testing is addressed elsewhere (Blue Shield of California Medical Policy: Preimplantation Genetic Testing)
Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired. At present, for an asymptomatic individual, knowledge of familial variant status will generally not lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use can be a factor that delays the onset of disease but this is a general recommendation that is not altered by genetic testing. However, a negative test may preclude the need for surveillance for complications. Genetic testing may also assist reproductive decision making.

A chain of evidence can be constructed to demonstrate that identification of a NOTCH3 pathogenic variant predicts future development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of symptoms, aids in reproductive planning, and helps determine the likelihood of an affected offspring.

**Section Summary: Clinically Useful**
Direct evidence for the clinical utility of genetic testing of asymptomatic relatives of patients with CADASIL is lacking. No specific clinical treatment for CADASIL has established efficacy. However, a chain of evidence can be developed for potential clinical utility, particularly for reproductive decision-making process for preimplantation and/or prenatal testing.

**Genetic Testing of NOTCH3 in Asymptomatic Patients with Relatives who have CADASIL and Unknown Genetic Status**

**Clinical Context and Test Purpose**
The purposes of genetic testing of NOTCH3 in asymptomatic individuals with family members with CADASIL whose genetic status is unknown are to screen at-risk individuals and to predict the development of disease, determine the need for surveillance, and aid in reproductive planning.

The questions addressed in this evidence review are: In an asymptomatic patient with relatives who have CADASIL and whose genetic status is unknown, does use of NOTCH3 genetic testing lead to improved outcomes, including changes in surveillance, preimplantation genetic testing to determine the likelihood of an affected offspring, or alter reproductive planning decisions?

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

**Patients**
The relevant population of interest are asymptomatic patients with relatives who have CADASIL and whose genetic status is unknown.

**Interventions**
The test being considered is genetic testing of NOTCH3 variants.

**Comparators**
The following practice is currently being used: standard clinical management without genetic testing.

**Outcomes**
The potentially beneficial outcomes of primary interest would be confirming or excluding the need for surveillance or changes in reproductive decision making. A negative genetic test result would eliminate the need for surveillance to detect the development of symptoms and disease. A positive genetic test result would confirm a need for active surveillance and also inform the reproductive decision-making process.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary medical or neurologic surveillance of
asymptomatic individuals. False-negative test results can lead to lack of medical or neurologic surveillance.

**Timing**
The time frame for outcome measures varies from short-term surveillance of asymptomatic individuals for the development of signs or symptoms of CADASIL to long-term development of the disease.

**Setting**
Asymptomatic individuals with family members who have CADASIL may be referred to a medical geneticist for investigation of genetic status for carrying a known familial variant. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**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).

See the clinical validity discussion in the Testing Individuals With Suspected CADASIL section.

**Testing Strategy**
For testing in asymptomatic individuals with family members who have CADASIL whose genetic status is unknown:

- Perform targeted sequencing and analysis of specific NOTCH3 exons (e.g., exon 4 only, exons 2-6) OR
- Perform general testing of NOTCH3 exons (e.g., exons 2-24 or all 33 exons)

This testing strategy to perform sequence analysis of multiple NOTCH3 exons to identify pathogenic variants is a general approach for genetic testing for NOTCH3.

**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.

No randomized trials were identified addressing outcomes managed with CADASIL testing.

**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. Genetic testing of asymptomatic individuals with family members who have CADASIL may have clinical utility by:

- Confirming or excluding the need for surveillance based on the presence or absence of a NOTCH3 pathogenic variant
Informing the reproductive decision-making process in preimplantation testing, prenatal (in utero) testing, or altering reproductive planning decisions when a known NOTCH3 pathogenic variant is present in a parent. Preimplantation testing is addressed elsewhere (Blue Shield of California Medical Policy: Preimplantation Genetic Testing)

**Section Summary: Clinically Useful**

Similar to the case where there is a known family variant associated with CADASIL, direct evidence for the clinical utility of genetic testing of asymptomatic relatives of patients with CADASIL is lacking. However, a chain of evidence can be developed to support the clinical utility of testing, as outlined above.

**Summary of Evidence**

For individuals with suspected CADASIL syndrome who receive NOTCH3 genetic testing, the evidence includes case reports, case series, and genotype-phenotype correlation studies evaluating the clinical validity and genetic testing yield for NOTCH3. The relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. The clinical validity studies have demonstrated that a NOTCH3 pathogenic variant is found in a high percentage of patients with a clinical diagnosis of CADASIL, with studies reporting a clinical sensitivity of 90% to 100%. Limited data on specificity derives from testing small numbers of healthy controls, and no false-positive NOTCH3 pathogenic variants have been reported in these populations. The diagnostic yield studies have reported a variable yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. No direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. However, a chain of evidence can be constructed to demonstrate that identification of a NOTCH3 pathogenic variant establishes the diagnosis of CADASIL without the need for a skin biopsy and reduces the need for other diagnostic tests used in the exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome who receive targeted genetic testing for a known NOTCH3 familial variant, the evidence is limited. The relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For asymptomatic family members of an individual with known CADASIL, knowledge of the presence of a familial variant may lead to changes in lifestyle decisions for the affected individual (e.g., reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent disease onset. A chain of evidence can be constructed to demonstrate that identification of a NOTCH3 familial variant predicts future development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning, and helps determine the likelihood of an affected offspring. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with family members who have CADASIL syndrome whose genetic status is unknown who receive NOTCH3 genetic testing, the evidence is limited. The relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. For asymptomatic family members of an individual with known CADASIL whose genetic status is unknown, knowledge of the presence of a NOTCH3 pathogenic variant may lead to changes in lifestyle decisions for the affected individual (e.g., reproduction, employment). However, the impact of these lifestyle decisions on health outcomes is uncertain, and there are no interventions for asymptomatic individuals that are known to delay or prevent disease onset. A chain of evidence can be constructed to demonstrate that identification of a NOTCH3 pathogenic variant predicts future
development of CADASIL in an asymptomatic individual, eliminates the need for additional diagnostic testing, allows for earlier monitoring for development of systems, aids in reproductive planning, and helps determine the likelihood of an affected offspring. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 3 academic medical centers in 2013. Most reviewers disagreed with the statement that genetic testing to confirm the diagnosis of CADASIL was investigational. All reviewers expressed support for testing to confirm the diagnosis in select patients, particularly when the diagnosis of CADASIL is inconclusive following other diagnostic testing, and when the pretest likelihood of CADASIL is moderate to high. In addition to consensus among reviewers, contextual factors in support of medical necessity are present for this indication, i.e., there is a highly suggestive chain of evidence; high-quality trials are unlikely to be performed, and there is a potential for reducing harms by avoiding additional testing and avoiding anticoagulants and antiplatelet agents when the disease is present.

Reviewers also agreed with the recommendation that testing is medically necessary for a first- or a second-degree relative when there is a known pathogenic variant (familial variant) in the family. For this indication, contextual factors in support of medical necessity were not present. High-quality trials are unlikely to be performed.

Practice Guidelines and Position Statements

The European Federation of Neurological Societies’ (2010) guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias noted that most NOTCH3 pathogenic variants occur within exons 3 and 4 and suggested direct sequencing of these 2 exons if clinical suspicion is high.27.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in March 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

References


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Specific clinical signs and symptoms
  - Family history for CADASIL, including Family relationship(s): (maternal or paternal), (family member [e.g., sibling, aunt, grandparent]), (living or deceased) (if applicable)
  - Imaging results (e.g., MRI)
  - Reason for Request
  - Laboratory testing/other specialized testing (e.g., skin biopsy)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes 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.

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**Policy History**

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