Genetic Testing of CADASIL Syndrome

Policy # 00319
Original Effective Date: 10/19/2011
Current Effective Date: 12/21/2016

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

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

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

Based on review of available data, the Company may consider genetic testing to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome to be eligible for coverage under the following conditions:

- Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pre-test probability of CADSIL is at least in the moderate to high range; and
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including magnetic resonance imaging (MRI) and skin biopsy.

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

Based on review of available data, the Company considers genetic testing for CADASIL syndrome in all other situations, including but not limited to testing of asymptomatic patients who have a first- or second-degree relative with CADASIL to be investigational.*

Background/Overview
Mutations in the NOTCH3 gene have been causally associated with CADASIL. Genetic testing is available to determine if pathogenic mutations exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.

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

The clinical presentation of CADASIL is variable and may be confused with multiple sclerosis, Alzheimer dementia, andBinswanger disease. The specific clinical signs and symptoms, along with family history and brain MRI findings, are extremely important in determining the diagnosis of CADASIL. When the differential diagnosis includes CADASIL, various other tests are available for diagnosis:
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- 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 NOTCH3 protein in the walls of small blood vessels. Lesnick Oberstein et al. (2003) estimated sensitivity and specificity at 85-90% and 95-100%, respectively, for 2 observers of the test results in a population of patients and controls correlated with clinical, genetic and MRI 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. Granular osmiophilic material 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%.

- Genetic testing, by direct sequencing of selected exons or of exons 2-24 of the NOTCH3 gene (see Rationale).

- Examination of brain tissue for the presence of GOM. Granular osmiophilic material was originally described as limited to brain vessels. Examination of brain biopsy or autopsy after death was an early gold standard for diagnosis. In some cases, peripheral staining for GOM has been absent even though positive results were seen in brain vessels.

**NOTCH3 Mutations**

Mutations in NOTCH3 have been identified as the underlying cause of CADASIL. In almost all cases, the mutations lead to loss or gain of a cysteine residue that could 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 2,321 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.

Mutations in the NOTCH3 gene have been differentiated into those that are causative of the CADASIL syndrome and those that are of uncertain significance. Causative mutations affect conserved cysteine residues within 34 EGF-like repeat domains in the extracellular portion of the NOTCH3 protein. More than 150 causative mutations have been reported in at least 500 pedigrees. NOTCH3 has 33 exons, but all CADASIL mutations reported to date have occurred in exons 2-24, which encode the 34 EGF-like repeats, with strong clustering in exons 3 and 4, which encode epidermal growth factor receptor, or EGFR 2–5 (>40% of mutations in >70% of families occur in these exons). Some studies indicate that the clinical variability in CADASIL presentation, particularly with regard to the development of white matter hyperintensities on MRI, may be related to genetic modifiers outside the NOTCH3 locus, but the specific role of these modifiers is not well-delineated.
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The probability that CADASIL is present is an individualized assessment, depending on numerous factors such as family history, symptoms, imaging results, and other specialized testing such as skin biopsy. In 2012, Pescini et al published a study that attempted to identify clinical factors that increase the likelihood of a pathologic mutation being present, with increasing likelihood with the presence of one or several factors, including 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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). NOTCH3 mutation testing is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no National Coverage Determination (NCD).

Rationale/Source
This evidence review was created in 2011 and has been updated periodically with literature review. The most recent review covers the period through September 18, 2015

Literature that describes the analytic validity, clinical validity, and clinical utility of NOTCH3 testing was sought.

Analytic Validity
Limited relevant primary data on analytic validity were identified. The test is generally done by gene sequencing analysis, which is expected to have high analytic validity when performed under optimal conditions.

Fernandez et al described the development of a next-generation sequencing (NGS) protocol for NOTCH3 and HTRA1 genes in 70 patients referred for clinical suspicion of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), all of whom had previously undergone Sanger sequencing of exons 3 and 4 of the NOTCH3 gene. NOTCH3 mutations were detected in 6 patients on NGS, including 2 mutations previously detected with Sanger sequencing and 4 mutations in exons 6, 11, and 19.

Clinical Validity
Several retrospective and prospective studies have examined the association between NOTCH3 genes and CADASIL, as shown in Table 1. These have been divided into 2 categories: Part 1, diagnostic studies, in which the patients enrolled were suspected but not confirmed to have CADASIL; and Part 2, clinical validity
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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 demonstrate that a NOTCH3 mutation 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 is from testing small numbers of healthy controls, and no false positive NOTCH3 mutations have been reported in these populations. The diagnostic yield studies report a variable diagnostic yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders.

Table 1. Association of NOTCH3 with CADASIL Diagnosis: Results of Published Studies Supporting NOTCH3 Genotyping Test Claims

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>NOTCH3 Exons Evaluated</th>
<th>Diagnostic Yield</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td><strong>Part 1: Diagnostic studies</strong></td>
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<tr>
<td>Mosca et al (2011)</td>
<td>Patients: 140 patients with clinical suspicion of CADASIL (Italian, Chinese)</td>
<td>Direct sequencing of exons 2-8, 10, 14, 19-20, and 22</td>
<td>Patients: 14 patients with causative mutations located in 10 different exons. 126 patients free of pathogenic mutations</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Patient selection: History of premature strokes; migraine with aura; vascular dementia; suggestive MRI findings; a consistent family history; or a combination of the previous criteria</td>
<td></td>
<td>Family members: Analysis of 15 additional family members identified 11 of the same causative mutations</td>
<td></td>
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</tbody>
</table>
| | Lee et al (2009) | Patients: 39 patients with suspected CADASIL (Chinese); 100 healthy elderly controls ≥80 y | Direct sequencing of exons 2-23 | Patients: 9 different point mutations identified in 21/39 patients | 100%
| | Patient selection: Suggestive MRI findings and at least 1 of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history | | Family members: No data for additional family members | No mutations in 100 healthy elderly controls |
| | Markus et al (2002) | Patients: 83 patients with suspected CADASIL (U.K.) | Direct sequencing of exons 3-4; SSCP of exons 2, 5-23 | Patients: 15 different point mutations identified in 48 families with a total of 116 symptomatic patients, 73% in exon 4, 8% in exon 3, 6% in exons 5 and 6 | NR |
| | Patient selection: Patients were <60 y with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but | | Family members: No data for additional family members | |
### Study Design and Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>NOTCH3 Exons Evaluated</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Choi et al (2013)</strong></td>
<td><strong>Patients</strong>: 151 consecutive patients (Korean) with acute ischemic stroke</td>
<td><strong>Patient selection</strong>: History of acute ischemic stroke, neurologic exam, cranial computed tomography, or MRI</td>
<td><strong>Patients</strong>: 6 patients (4%) were found with the identical NOTCH3 mutation (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 was higher in patients with mutations. <strong>Family members</strong>: No data for additional family members.</td>
</tr>
<tr>
<td><strong>Yin et al (2015)</strong></td>
<td><strong>Patients</strong>: 47 subjects from 34 families (Chinese) diagnosed with suspected CADASIL</td>
<td><strong>Patient diagnosis/selection</strong>: MRI abnormalities and presence of &gt;1 typical symptom (eg, migraine, stroke, cognitive deficits, psychiatric symptoms) or presence of atypical symptoms with positive family history</td>
<td><strong>Patients</strong>: 6 known mutations were identified in 8 families and 2 novel mutations were identified in 2 families (exons 3 and 4), and 1 VOUS was identified in 1 family (exon 2). Overall NOTCH3 mutation prevalence: 29.4%.</td>
</tr>
<tr>
<td><strong>Abramycheva et al (2015)</strong></td>
<td><strong>Patients</strong>: 30 unrelated patients with suspected CADASIL</td>
<td><strong>Direct sequencing of exons 2-23 via PCR</strong></td>
<td><strong>Patients</strong>: 16 point mutations were identified in 18 unrelated patients, 12 of which had been previously described and 4 were novel (C194G, V252M, C338F, C484G).</td>
</tr>
<tr>
<td><strong>Part 2: Clinical validity studies</strong></td>
<td><strong>Patients</strong>: 125 unrelated patients diagnosed with CADASIL</td>
<td><strong>Bidirectional sequencing of all exons</strong></td>
<td><strong>Sensitivity</strong>: 96% <strong>Patients</strong>: 54 distinct mutations in 120 (96.0%) of the 125 patients. In 5 patients (4.0%), no mutation identified. <strong>Family members</strong>: No data for additional family</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Evaluated</th>
<th>NOTCH3 Exons Evaluated</th>
<th>Results</th>
</tr>
</thead>
</table>
| Tikka et al (2009)     | **Patients**: 131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, French) | Direct sequencing of exons 2-24 | **Sensitivity**: 100%  
**Patients**: 131 CADASIL patients were mutation-positive  
**Family members**: No data for additional family patients  
• No mutation reported per family or per unrelated individual  
• 100%  
• No mutations in the 26 negative controls |
| Dotti et al (2005)     | **Patients**: 28 unrelated, consecutively diagnosed patients with CADASIL (Italian) | DHPLC, followed by confirmatory sequencing of identified mutations | **Sensitivity**: 100%  
**Patients**: All 28 patients had mutations  
NR |
| Joutel et al (1997)    | **Patients**: 50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls | SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified mutations | **Sensitivity**: 90%  
**Patients**: 45/50 CADASIL patients had mutations  
• 100%  
• No mutations in 100 healthy controls |

DHPLC: denaturing high-performance liquid chromatography; EM: electron microscope; MRI: magnetic resonance imaging; SSCP: single-stranded conformational polymorphism; VOUS: variant of uncertain significance.

Clinical Utility
Genetic testing may have clinical utility in several situations. The clinical situations addressed herein are:

- Confirmation of a clinical diagnosis of CADASIL in an individual with signs and symptoms of the disease;
- Predictive testing for at-risk individuals with a family history of CADASIL;

Other situations in which genetic testing may be considered are preimplantation testing and/or prenatal (in utero) testing when a pathologic NOTCH3 mutation is present in a parent.
Functional Testing of CADASIL Syndrome

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Confirmation of a CADASIL Diagnosis

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 90-100% for patients with a clinical diagnosis of CADASIL. This indicates that a negative test reduces the likelihood that CADASIL is present. However, since 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 pre-test likelihood that CADASIL is present.

Pescini et al. published a study that attempted to identify clinical factors that increase the likelihood of a pathologic mutation 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 were associated with a positive genetic test. Evidence was identified from 15 clinical series of patients with CADASIL. Table 2 summarizes the pooled frequency of clinical and radiologic features:

Table 2: Clinical and Radiologic Features in Patients with NOTCH3 Mutations

<table>
<thead>
<tr>
<th>Features</th>
<th>No. With NOTCH3 Mutation</th>
<th>Percent With NOTCH3 Mutation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>239/463</td>
<td>52%</td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>65/85</td>
<td>76%</td>
</tr>
<tr>
<td>Transient ischemic attack/stroke</td>
<td>380/526</td>
<td>72%</td>
</tr>
<tr>
<td>Psychiatric disturbance</td>
<td>106/380</td>
<td>28%</td>
</tr>
<tr>
<td>Cognitive decline</td>
<td>188/434</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Radiologic features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LE</td>
<td>277/277</td>
<td>100%</td>
</tr>
<tr>
<td>LE extended to temporal pole</td>
<td>174/235</td>
<td>74%</td>
</tr>
<tr>
<td>LE extended to external capsule</td>
<td>228/303</td>
<td>75%</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>210/254</td>
<td>83%</td>
</tr>
<tr>
<td>LE: leukoencephalopathy</td>
<td></td>
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</tbody>
</table>

Using these frequencies, a preliminary scoring system was developed and tested in 61 patients with NOTCH3 mutations, and in 54 patients with phenotypic features of CADASIL but who were NOTCH3-negative. With the addition of family history, and age at onset of TIA/stroke (transient ischemic attack), a scoring system was developed with the following point values: migraine; migraine with aura; TIA/stroke; TIA/stroke ≤50 years-old; psychiatric disturbance; cognitive decline; LE; LE extended to temporal pole; LE extended to external capsule; subcortical infarcts; family history, one generation; family history, 2 generations or more. The authors recommended that a total score of 14 be used to select patients for testing, as this score resulted in a high sensitivity (96.7%) and a moderately high specificity (74.2%).

Currently, there is no specific clinical treatment for CADASIL that 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.

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A double-blind, placebo controlled trial that evaluated the efficacy and safety of donepezil hydrochloride (HCl) in individuals with CADASIL was conducted. The study resulted in donepezil HCl having no effect on the primary cognitive endpoint, the Vascular Dementia Assessment Scale cognitive subscale (V-ADAS-cog) score in patients with CADASIL who had cognitive impairment.

Another study evaluated the efficacy and tolerance of a 24-week treatment with 250 mg/d acetazolamide (ACZ), which could be chronically implemented to improve cerebral hemodynamics in CADASIL patients (n=16). Treatment with ACZ resulted in a significant increase of mean blood flow velocity (MFV) in the middle cerebral artery (MCA) compared with MFV in the MCA at rest before treatment (57.68±12.7 cm/s versus 67.12±9.4 cm/s; p=0.001). During the treatment period, none of the subjects developed new neurologic symptoms, and the original symptoms in these patients, such as headaches and dizziness, were relieved.

A third study evaluated the use of 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase-inhibitors (statins) in 24 CADASIL subjects treated with atorvastatin for 8 weeks. Treatment was started with 40 mg, followed by a dosage increase to 80 mg after 4 weeks. Transcranial Doppler sonography measuring MFV in the MCA was performed at baseline and at the end of the treatment period. There was no significant treatment effect on MFV (p=0.5) or cerebral vasoreactivity, as assessed by hypercapnia (p=0.5) and 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 reported the results of a randomized, double-blinded trial of sapropterin compared with placebo for adults with CADASIL. Sapropterin is a synthetic analog 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 vasodilatation in CADASIL patients. Endothelial dysfunction was assessed by the reactive hyperemia index by peripheral arterial tonometry (RH-PAT) response, which has previously been demonstrated to be impaired in patients with CADASIL syndrome. Peripheral arterial tonometry (PAT) is a noninvasive, quantitative test that measures changes in digital pulse volume during reactive hyperemia (RH) and evaluates the endothelial function of resistance arteries and nitric oxide-mediated changes in microvascular response. The study randomized 61 subjects from 38 families, 32 to sapropterin and 29 to placebo. In intention-to-treat analysis, there was no significant difference in change in RH-PAT response (mean difference in RH-PAT change, 0.19: 95% confidence interval, -0.18 to 0.56). Both groups demonstrated improvements in RH-PAT values over the course of the study, but after results were adjusted for age, sex, and clinical characteristics, the improvement was not associated with treatment.

Predictive testing of at-risk family members
It has been suggested that asymptomatic family members follow the guidelines for presymptomatic testing for Huntington’s disease. Genetic counseling is recommended to discuss the impact of positive or negative test results, followed by molecular testing if desired. For an asymptomatic individual, knowledge of mutation
status will not generally lead to any management changes that can prevent or delay the onset of the disorder. Avoiding tobacco use may be one factor that delays onset of disease, but this is a general recommendation that is not altered by genetic testing. Genetic testing may assist decision making in such areas as employment choices and reproductive decision making, but the impact of these decisions on health outcomes is uncertain.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in September 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Clinical Input Received 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, input was received from 1 physician specialty society and 3 academic medical centers in 2013.

Most reviewers disagreed with statement that genetic testing was investigational to confirm the diagnosis of CADASIL. All reviewers expressed support for testing to confirm the diagnosis in selected patients, particularly when the diagnosis of CADASIL is inconclusive following other diagnostic testing, and when the pretest likelihood of CADASIL being present is moderate to high. In addition to consensus among the reviewers, contextual factors in support of medical necessity are present for this indication, ie, there is a highly suggestive indirect 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 second-degree relative, when there is a known pathologic mutation in the family. For this indication, contextual factors in support of medical necessity were not present. High-quality trials are unlikely to be performed, but other contextual criteria were lacking.

Summary
The evidence for the use of genetic testing for mutations associated with CADASIL syndrome in individuals with suspected CADASIL syndrome includes retrospective and prospective studies evaluating the clinical validity and yield of NOTCH3 mutation testing. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, changes in reproductive decision making, change in disease status, and morbid events. The clinical validity studies demonstrate that a NOTCH3 mutation 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 is from testing small numbers of healthy controls, and no false-positive NOTCH3 mutations have been reported in these populations. The diagnostic yield studies report a variable diagnostic yield, ranging from 10% to 54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders. There may be potential clinical utility
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for genetic testing to diagnose CADASIL in patients whose diagnosis cannot be confirmed by other methods (clinical presentation, magnetic resonance imaging [MRI] findings, skin biopsy). However, no direct evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. A strong chain of indirect evidence was identified demonstrating outcome improvements associated with genetic testing for CADASIL. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of genetic testing for mutations associated with CADASIL syndrome in individuals who are asymptomatic with family members with CADASIL syndrome is limited. Relevant outcomes are overall survival, test accuracy and validity, other test performance measures, 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 pathologic mutation may lead to changes in lifestyle decisions for the affected individual (eg, 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 the onset of disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

References

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10/06/2011 Medical Policy Committee review
11/01/2012 Medical Policy Committee review
02/19/2013 Coding updated
12/12/2013 Medical Policy Committee review
12/18/2013 Medical Policy Implementation Committee approval. Coverage changed from investigational to eligible for coverage for certain indications. Title changed.
12/04/2014 Medical Policy Committee review
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016 Medical Policy Committee review
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
Next Scheduled Review Date: 12/2017

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td>81406</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
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Original Effective Date: 10/19/2011
Current Effective Date: 12/21/2016

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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