Genetic Testing of CADASIL Syndrome

Policy # 00319
Original Effective Date: 10/19/2011
Current Effective Date: 12/18/2013

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 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.
- The diagnosis of CADASIL is inconclusive following alternate methods of testing, including 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 (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Genetic testing is available to determine if pathogenic mutations exist in the NOTCH3 gene for patients with suspected CADASIL and their family members.

CADASIL 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 magnetic resonance imaging (MRI) findings, are extremely important in determining the diagnosis of CADASIL. When the differential diagnosis includes CADASIL, various other tests are available for diagnosis:

- 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
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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. 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%.
- 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. GOM 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-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 epidermal growth factor (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 EGFR 2–5 (>40% of mutations in >70% of families occur in these exons).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
As of August 2012, there are no manufactured test kits for detecting NOTCH3 gene mutations; therefore, this testing has not been reviewed by the U.S. FDA. Rather, NOTCH3 gene sequencing is a laboratory-developed test (LDT), offered by clinical laboratories licensed under Clinical Laboratory improvement Act (CLIA) for high-complexity testing.
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Centers for Medicare and Medicaid Services (CMS)
None

Rationale/Source
This policy was created in September 2011 and updated periodically with literature review. The most recent update covers the period of July 2012 through September 2013.

Literature that describes the analytic validity, clinical validity, and clinical utility of NOTCH3 testing was sought. No 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.

Clinical validity
Several retrospective and prospective studies have examined the association between NOTCH3 genes and CADASIL, as shown in the following table. 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 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.

Table. Studies of the 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>Results</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Diagnostic Yield</td>
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<tr>
<td>Part 1 Diagnostic Studies</td>
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<tr>
<td>Mosca et al. 2011</td>
<td>Patients: 140 patients with clinical suspicion of CADASIL (Italian and 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. Family Members: Analysis of 15 additional family members identified 11 of the same causative mutations.</td>
</tr>
<tr>
<td>Lee et</td>
<td>Patients: 39 patients with</td>
<td>Direct</td>
<td>Patients: 9 different point</td>
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#### Part 1 Clinical Validity Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Patient Selection</th>
<th>Methodology</th>
<th>Mutations Identified</th>
<th>Family Members</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi et al. 2011</td>
<td>151 consecutive Korean patients with acute ischemic stroke.</td>
<td>History of acute ischemic stroke, neurologic exam, cranial computed tomography or MRI.</td>
<td>Bidirectional sequencing of exons 3, 4, 6, 11 and 18.</td>
<td>6 patients (4%) were found with the identical NOTCH3 mutation (R544C; exon 11). Of these, all had pre-existing lacunar infarction, 5 (83.3%) had grade 2-3 white-matter hyperintensity lesions, and a history of hypertension; a history of stroke and dementia was higher in patients with mutations.</td>
<td>No data for additional family members.</td>
</tr>
<tr>
<td>Markus et al. 2002</td>
<td>83 patients with suspected CADASIL (UK).</td>
<td>Patients were younger than 60 years of age with recurrent lacunar stroke with leukoaraiosis on neuroimaging. Migraine, psychiatric disorders, or dementia could occur but were not essential.</td>
<td>Direct sequencing of exons 3-4; SSCP of exons 2, 5-23.</td>
<td>Patients: 15 different point mutations identified in 48 families with a total of 116 symptomatic patients, 73% in exon 4, 8% in exon 3, and 6% in exons 5 and 6.</td>
<td>No data for additional family members.</td>
</tr>
<tr>
<td>al. 2009</td>
<td>suspected CADASIL (China). 100 healthy elderly controls 80 years or older.</td>
<td>Patient Selection: Suggestive MRI findings and at least one of the following: young age at onset, cognitive decline, psychiatric disorders, or consistent family history.</td>
<td>Sequencing of exons 2-23.</td>
<td>Mutations identified in 21/39 patients.</td>
<td>No data for additional family members.</td>
</tr>
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</table>

#### Part 2 Clinical Validity Studies

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients:</th>
<th>Diagnosis/Selection:</th>
<th>Sensitivity:</th>
<th>Patients:</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al. 2005</td>
<td>125 unrelated patients diagnosed with CADASIL.</td>
<td>Skin biopsy-proven CADASIL pts referred between 1994 and 2003 (German).</td>
<td>Bidirectional sequencing of all exons.</td>
<td>96%</td>
<td>54 distinct mutations in 120 (96.0%) of the 125 patients. In 5 patients (4.0%), no mutation was identified.</td>
</tr>
<tr>
<td>Tikka et al. 2009</td>
<td>131 patients from 28 families diagnosed with CADASIL (Finnish, Swedish, and French).</td>
<td>EM examination of skin biopsy was performed; 26 asymptomatic controls from CADASIL families.</td>
<td>Direct sequencing of exons 2-24.</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Dotti et al. 2005</td>
<td>28 unrelated, consecutively diagnosed patients with CADASIL (Italian).</td>
<td>Patients were diagnosed via clinical and MRI.</td>
<td>DHPLC, followed by confirmatory sequencing of identified mutations.</td>
<td>100%</td>
<td>NR</td>
</tr>
<tr>
<td>Joutel et al. 1997</td>
<td>50 unrelated patients with a clinical suspicion of CADASIL and 100 healthy controls.</td>
<td>History of recurrent strokes, migraine with aura, vascular dementia, or a combination; brain MRI with suggestive findings; and a consistent</td>
<td>SSCP or heteroduplex analysis of all exons, followed by confirmatory sequencing of identified mutations.</td>
<td>90%</td>
<td>45 of 50 CADASIL patients had mutations.</td>
</tr>
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</table>
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familial history.

MRI, magnetic resonance imaging; SSCP, single-stranded conformational polymorphism; EM, electron microscope; DHPLC, denaturing high-performance liquid chromatography

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 90-100%. 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 10-54%. These lower numbers likely reflect testing in heterogeneous populations that include patients with other disorders.

Clinical utility
There are several situations in which genetic testing may have clinical utility. The clinical situations addressed in this policy 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. Preimplantation testing is addressed in a separate MPRM policy.

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 in 2013 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. The following table summarizes the pooled frequency of clinical and radiologic features:
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<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Number with NOTCH3 mutation</th>
<th>Percent with NOTCH3 mutation</th>
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<tbody>
<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>TIA/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>
</tbody>
</table>

<table>
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<tr>
<th>Radiologic features</th>
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<tbody>
<tr>
<td>Leukoencephalopathy (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>
</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
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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. Three studies were found that addressed treatment efficacy in CADASIL as follows:

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 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 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.

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 Clinical Trials
An updated search in August 2012 found no ongoing clinical trials at the online site: Clinicaltrials.gov (search strategy = CADASIL) relating to genetic testing for diagnosis.
Clinical Input Received through 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 one physician specialty society and 3 academic medical centers while this policy was under review in 2013.

The majority of the 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 pre-test 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, i.e. 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

Pathologic NOTCH mutations are found to be the cause of CADASIL in the majority of patients with the syndrome. The diagnostic accuracy of genetic testing cannot be determined with certainty due to the lack of a true gold standard for diagnosis of CADASIL. However, a high percentage of patients in whom CADASIL is diagnosed by clinical methods will have a pathologic mutation on genetic testing. Conversely, pathologic NOTCH mutations are not commonly found in unaffected individuals.

Genetic testing has clinical utility for a subset of patients with clinical signs and symptoms of CADASIL, but in whom the diagnosis cannot be made by other methods. The diagnosis of CADASIL can usually be confirmed by a combination of clinical presentation, MRI findings, and skin biopsy findings. In such cases, NOTCH3 testing is not necessary for diagnosis. In other cases, the diagnosis cannot be made on the basis of clinical presentation, MRI, and skin biopsy results. In these cases, NOTCH3 testing can confirm the diagnosis of CADASIL with a high degree of certainty. Based on the available evidence and results of clinical vetting, genetic testing may be considered medically necessary to confirm the diagnosis of CADASIL when there is uncertainty in the diagnosis following alternate testing methods, and there is at least a moderate to high likelihood that CADASIL is present based on clinical and imaging results.

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, for example in the areas of reproduction and 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. Therefore, genetic testing of asymptomatic relatives is considered investigational.
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References

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2012 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
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<tr>
<th>Code Type</th>
<th>Code</th>
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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-9 Diagnosis</td>
<td>All diagnoses</td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>No codes</td>
</tr>
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Policy History

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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.

Next Scheduled Review Date: 12/2014

*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. Food and Drug Administration (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); or

2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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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;

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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