



Genetic Testing of CADASIL Syndrome

Policy # 00319

Original Effective Date: 10/19/2011

Current Effective Date: 08/14/2023

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 for NOTCH3 variant to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome in an individual to be **eligible for coverage**** under the following conditions:

- Clinical signs, symptoms, 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); **AND**
- The diagnosis of CADASIL is inconclusive following alternative methods of testing, including magnetic resonance imaging.

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 for individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome to be **eligible for coverage**** under **EITHER** of the following conditions:

- Targeted genetic testing of the known NOTCH3 familial variant if there is a family member (first- and second-degree relative) with a known variant; **OR**
- Genetic testing of NOTCH3 if the family member's genetic status is unknown (see Policy Guidelines section).

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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 a NOTCH3 variant to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome in all other situations to be **investigational**.*

Policy Guidelines

Genetic testing for NOTCH3 comprises targeted sequencing of specific exons (eg, exon 4 only, exons 2-6), general sequencing of NOTCH3 exons (eg, exons 2-24 or all 33 exons), or targeted testing for known NOTCH3 pathogenic variants. Skin biopsy should be reserved for individuals where NOTCH3 genetic testing is inconclusive (e.g. variants of uncertain significance).

The probability that cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (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.

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 individuals 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

Features	No. With <i>NOTCH3</i> Variant	Percent With <i>NOTCH3</i> Variant	Points
<i>Clinical</i>			
Migraine	239/463	52%	1
Migraine with aura	65/85	76%	3

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Transient ischemic attack/stroke	380/526	72%	1 (2 if <50 y)
Psychiatric disturbance	106/380	28%	1
Cognitive decline	188/434	43%	3
<i>Radiologic</i>			
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; No: number.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology 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.

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Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

Experts recommend formal genetic counseling for individuals 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 individuals; 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.

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Background/Overview

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 (Table 1).

Table 1. Differential Diagnosis of CADASIL

Acquired Disorders	Inherited Disorders
<ul style="list-style-type: none">• Sporadic SVD with or without hypertension as the main risk factor• Multiple sclerosis• Primary angiitis of the central nervous system	<ul style="list-style-type: none">• Fabry disease• Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy• Familial SVD caused by heterozygous variants in the <i>HTRA1</i> gene• Some forms of leukodystrophy

CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; 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.

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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 (eg, 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 individuals and controls correlated with clinical, genetic, and magnetic resonance imaging parameters.
- Detection of granular osmiophilic material in the same skin biopsy sample by electron microscopy. The major component of granular osmiophilic material 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, granular osmiophilic material 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 granular osmiophilic material 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 granular osmiophilic material 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

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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 (eg, 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 1 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.

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

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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

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. 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 individuals 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 individuals 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 to exclude other conditions in a differential diagnosis. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision

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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 (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 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 an 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. 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 (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 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 an improvement in the net health outcome.

Additional Information

2013 Input

Given the high clinical sensitivity of genetic testing for CADASIL and the severity of the condition but no direct evidence on improvements in outcomes, clinical input was obtained in 2013. Input provided strong consensus that genetic testing for CADASIL syndrome is medically necessary when the diagnosis cannot be made by clinical presentation, magnetic resonance imaging, and skin biopsy results. In these cases, NOTCH3 testing can confirm the diagnosis of CADASIL with a high degree

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of certainty. Input also provided strong consensus that testing is medically necessary for a first- or a second-degree relative when there is a known pathogenic variant in the family. In these cases, NOTCH3 testing can predict the future development of CADASIL to permit earlier initiation of surveillance for symptoms and determine the likelihood of an affected offspring.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

2013 Input

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 while this policy was under review 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 individuals, particularly when the diagnosis of CADASIL is inconclusive, 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, ie, 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 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.

2020 Input

Clinical consultation was obtained in 2020 indicating that skin biopsy prior to NOTCH3 testing is not necessary; skin biopsy should be reserved for individuals where NOTCH3 genetic testing is inconclusive (e.g. variants of uncertain significance).

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Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or position statements with US representation or that were informed by a systematic review were identified.

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

One currently ongoing trial that might influence this review is listed in Table 2.

Table 2.

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04310098	Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Registry Study	1000	Mar 2049

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10/06/2011	Medical Policy Committee review
10/19/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. The policy is revised with updated genetics nomenclature. "Mutations" changed to "variants" in policy statements. Added "Notch 3" to all policy statements. Eligible for coverage statement added for testing in asymptomatic and pre-symptomatic family members of individuals with CADASIL. Investigational statement intent remains unchanged, altered for clarification. Policy Guidelines section added to the policy.
12/06/2018	Medical Policy Committee review

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Genetic Testing of CADASIL Syndrome

Policy # 00319

Original Effective Date: 10/19/2011

Current Effective Date: 08/14/2023

12/19/2018 Medical Policy Implementation Committee approval. Editorial change to coverage section to use “variant” terminology. Coverage eligibility unchanged.

12/05/2019 Medical Policy Committee review

12/11/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/02/2020 Medical Policy Committee review

07/08/2020 Medical Policy Implementation Committee approval. Removed skin biopsy from the first and second Patient Selection Criteria bullets for genetic testing for NOTCH3 variant to confirm the diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) syndrome. For individuals who are asymptomatic with a family member diagnosed with CADASIL syndrome, added “(first- and second-degree relative)” to specify degree of family members to the first bullet of the Patient Selection Criteria.

07/01/2021 Medical Policy Committee review

07/14/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/07/2022 Medical Policy Committee review

07/13/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

07/06/2023 Medical Policy Committee review

07/12/2023 Medical Policy Implementation Committee approval. Replaced “patients” with individuals” in the coverage section. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2024

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 2022 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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CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	81406
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*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:

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1. Consultation with 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;
- 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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