BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 09/14/2020

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.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon is addressed separately in medical policy 00190.

Note: Molecular Analysis for Targeted Therapy of Non-Small -Cell Lung Cancer is addressed separately in medical policy 00452.

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 testing for BRAF V600 variants in tumor tissue of patients with unresectable or metastatic melanoma to select patients for treatment with Food and Drug Administration (FDA) approved BRAF or MEK inhibitors to be **eligible for coverage.****

Based on review of available data, the Company may consider testing for testing for BRAF V600 variants in tumor tissue of patients with resected stage III melanoma to select patients for treatment with Food and Drug Administration (FDA) approved BRAF or MEK inhibitors to be **eligible for coverage.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

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Based on review of available data, the Company considers testing for BRAF V600 variants for all other patients with melanoma to be **investigational.***

Based on review of available data, the Company considers testing for BRAF V600 variants in patients with glioma to select patients for targeted treatment to be **investigational.***

Policy Guidelines

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 is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, 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 PG2 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

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 PG2. 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.

Background/Overview

Melanoma

Overall incidence rates for melanoma have been increasing for at least 30 years; in 2017, there were more than 87100 new cases. In advanced (stage IV) melanoma, the disease has spread beyond the original area of skin and nearby lymph nodes. Although only a small proportion of cases are stage IV at diagnosis, the prognosis is extremely poor; 5-year survival is 15% to 20%.

Treatment

Unresectable or Metastatic Melanoma

For several decades after its approval in 1975, cytotoxic chemotherapy with dacarbazine was considered the standard systemic therapy but has provided disappointingly low response rates of only 15% to 25% and median response duration of 5 to 6 months; less than 5% of responses are complete. Temozolomide has similar efficacy and, unlike dacarbazine, has much better efficacy with central nervous system tumors. Recently immunotherapy with ipilimumab or with checkpoint inhibitors such as pembrolizumab and nivolumab has demonstrated superior efficacy to chemotherapy regardless of *BRAF* status and is now recommended as a potential first-line treatment of metastatic or unresectable melanoma.

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Variants in the *BRAF* kinase gene are common in tumors of patients with advanced melanoma and result in constitutive activation of a key signaling pathway (RAF-MEK-ERK pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a *BRAF* variant; of these, 80% are positive for the *BRAF* V600E variant, and 16% are positive for *BRAF* V600K. Thus, 45% to 60% of advanced melanoma patients may respond to a BRAF inhibitor targeted to this mutated kinase.

Two BRAF inhibitors (vemurafenib, dabrafenib) and two MEK inhibitors (trametinib, cobimetinib) have been developed for use in patients with advanced melanoma. Vemurafenib (also known as PLX4032 and RO5185426) was developed using a fragment-based, structure-guided approach that allowed the synthesis of a compound with high potency to inhibit the *BRAF* V600E mutated kinase and with significantly lower potency to inhibit most of many other kinases tested.[8,] Preclinical studies have demonstrated that vemurafenib selectively blocked the RAF-MEK-ERK pathway in *BRAF* mutant cells and caused regression of *BRAF* mutant human melanoma xenografts in murine models. Paradoxically, preclinical studies also showed that melanoma tumors with the *BRAF* wild-type gene sequence could respond to mutant BRAF-specific inhibitors with accelerated growth, suggesting that it may be harmful to administer BRAF inhibitors to patients with *BRAF* wild-type melanoma tumors. Potentiated growth in *BRAF* wild-type tumors has not yet been confirmed in melanoma patients, because the supportive clinical trials were enrichment trials, enrolling only patients with tumors positive for the *BRAF* V600E variant.

Dabrafenib (also known as GSK2118436 or SB-590885) inhibits several kinases, including mutated forms of the BRAF kinase, with the greatest activity against V600E-mutated *BRAF*. In vitro and in vivo studies have demonstrated dabrafenib's ability to inhibit the growth of *BRAF* V600-variant melanoma cells.

Trametinib is an inhibitor of mitogen-activated extracellular signal-regulated kinase 1 (MEK1) and MEK2. MEK kinases regulate the extracellular signal-related kinase, which promotes cellular proliferation. *BRAF* V600E and V600K variants result in constitutive activation of MEK1 and MEK2. Trametinib inhibits the growth of *BRAF* V600 variant-positive melanoma cells in vitro and in vivo.

Cobimetinib is a MEK1 and MEK2 inhibitor. Coadministration of cobimetinib and vemurafenib has resulted in increased apoptosis and reduced tumor growth of *BRAF* V600E tumor cells in vitro, and cobimetinib has prevented the vemurafenib-mediated growth of wild-type *BRAF* tumor cells in vivo.

Resected Stage III Melanoma
Wide local excision is the definitive surgical treatment of melanoma. Following surgery, patients with American Joint Committee on Cancer stage III melanoma may receive adjuvant therapy. Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4, has been shown to prolong recurrence-free survival by approximately 25% compared with placebo at a median of 5.3 years in patients who had resected stage III disease. Nivolumab, a programmed cell death protein 1 blocking antibody has been shown to further prolong survival compared with ipilimumab by approximately 35% at 18 months. Before the development of checkpoint inhibitor immunotherapy and targeted therapy, high-dose interferon alfa was an option for adjuvant treatment of stage III melanoma. Interferon alfa has demonstrated an improvement in overall survival but with numerous serious side effects.

Glioma
More than 79000 new cases of primary malignant and nonmalignant brain and other central nervous system tumors are expected to be diagnosed in the U. S. in 2017, the majority of which are gliomas. Gliomas encompass a heterogeneous group of tumors and classification of gliomas has changed over time. In 2016, the World Health Organization (WHO) updated its classification of gliomas based on both histopathologic appearance and molecular parameters. The classification ranges from grade I to IV, corresponding to the degree of malignancy (aggressiveness), with WHO grade I being least aggressive and grade IV being most aggressive.

Treatment
Low-grade gliomas are classified as WHO grade I or II and include pilocytic astrocytoma, diffuse astrocytoma, and oligodendroglioma. Surgical resection of the tumor is generally performed, although additional therapy with radiotherapy and chemotherapy following surgery is usually required, except for pilocytic astrocytoma. The optimal timing of additional therapies is unclear. Many patients will recur following initial treatment, with a clinical course similar to high-grade glioma.

High-grade gliomas (WHO grade III/IV) include anaplastic gliomas and glioblastoma. Maximal surgical resection is the initial treatment followed by combined adjuvant chemoradiotherapy. Temozolomide, an oral alkylating agent, is considered standard systemic chemotherapy for malignant gliomas. The prognosis for patients with high-grade gliomas is poor; the 1-year survival in U.S. patients with anaplastic astrocytoma is about 63% and with glioblastoma is about 38%.

There is a high frequency of *BRAF* V600E variants in several types of gliomas. For example, *BRAF* V600E variants have been found in 5% to 10% of pediatric diffusely infiltrating gliomas, 10% to 15% of pilocytic astrocytoma, 20% of ganglioglioma, and more than 50% of pleomorphic xanthoastrocytoma. However, it may be rare in adult glioblastoma.

There is considerable interest in targeted therapies that inhibit the RAF-MEK-ERK pathway, particularly in patients with high-grade and low-grade gliomas whose tumors are in locations that prevent full resection. Evidence from early-phase trials in patients with *BRAF* variant-positive melanoma with brain metastases have suggested some efficacy for brain tumor response with vemurafenib and dabrafenib. indicating that these agents might be potential therapies for primary brain tumors.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Table 1 summarizes the targeted treatments approved by the U.S. FDA for patients with melanoma along with the concurrently approved diagnostic tests. The combination agent encorafenib and binimetinib (Array BioPharma) is under review for the treatment of *BRAF* variant advanced, unresectable, or metastatic melanoma with a target action date of June 30, 2018. The combination agent of dabrafenib and trametinib (GlaxoSmithKline) was approved in May 2018 for adjuvant treatment of *BRAF* variant, resected, stage III melanoma; the agent had both breakthrough therapy and priority review designations.

Table 1. FDA-Approved Targeted Treatments for Melanoma and Approved Companion Diagnostic Tests

Treatment	Indication	FDA Approval of Companion Diagnostic Test
Vemurafenib (Zelboraf®‡; Roche/Genentech and Plexxikon)	•2011: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600variants	•2011: cobas®‡ 4800 BRAF V600 Mutation Test (Roche) •2017: FoundationOne CDx™‡ (Foundation Medicine)
Dabrafenib (Tafinlar®‡; GlaxoSmithKline)	•2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E variants •2014: Used in combination with trametinib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants •2018: Used in combination with trametinib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants	•2013: THxID™‡ BRAF kit (bioMérieux) •2017: FoundationOne CDx™‡ (Foundation Medicine)
Trametinib (Mekinist™‡; GlaxoSmithKline)	•2013: treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants •2014: Used in combination with dabrafenib to treat patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K variants	•2013: THxID™‡ BRAF kit (bioMérieux) •2017: FoundationOne CDx™‡ (Foundation Medicine)

	•2018: Used in combination with dabrafenib for adjuvant treatment of patients with resected stage III melanoma with *BRAF* V600E or V600K variants	
Cobimetinib (Cotellic®‡; Genentech)	•2015: Used in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K variants	•2017: FoundationOne CDx™‡ (Foundation Medicine)
Binimetinib (Mektovi®‡; Array BioPharma)	• 2018: Used in combination with encorafenib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	• 2013: THxID™‡ BRAF kit (bioMérieux)
Encorafenib (Bravtovi®‡; Array BioPharma)	• 2018: Used in combination with binimetinib to treat patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	• 2013: THxID™‡ BRAF kit (bioMérieux)

FDA: Food and Drug Administration.
FDA product code: OWD.

Rationale/Source

Summary

BRAF and MEK inhibitors are drugs designed to target a somatic variant in the *BRAF* gene. The inhibitors were originally developed for patients with advanced melanoma. *BRAF* encodes a kinase component in the RAF-MEK-ERK signal transduction phosphorylation cascade. Mutated *BRAF* causes constitutive kinase activity, which is believed to promote oncogenic proliferation. Direct and specific inhibition of the mutated kinase has been shown to retard tumor growth significantly and may improve patient survival.

For individuals who have unresectable or metastatic melanoma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitor combination therapy, the evidence includes randomized trials. The relevant outcomes are overall survival (OS), disease-specific

survival, and test accuracy. Randomized phase 3 trials of BRAF inhibitor therapy in patients selected on the basis of*BRAF* variant testing have shown improvements in OS and progression-free survival. Single-agent BRAF inhibitor treatment compared with nontargeted treatments have shown superior outcomes for most endpoints. Combination BRAF and MEK inhibitor treatment with vemurafenib plus cobimetinib or dabrafenib plus trametinib have shown superior OS compared with vemurafenib or dabrafenib alone. Data showing treatment effects in patients without *BRAF* variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have resected stage III melanoma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes randomized trials. The relevant outcomes are OS, disease-specific survival, and test accuracy. One randomized phase 3 trial of BRAF and MEK combination therapy with dabrafenib plus trametinib in patients selected by *BRAF* variant testing has shown improvements in recurrence-free survival and OS compared with placebo. One randomized phase 3 trial of vemurafenib monotherapy did not find statistically significant differences in disease-free survival in patients with stage IIIC disease. In patients with stage IIC, IIIA, or IIIB disease, median disease-free survival was prolonged with vemurafenib, but this result was considered exploratory. Data showing treatment effects in patients without *BRAF* variants do not exist; therefore, *BRAF* variant testing is required to identify patients to whom these trial results apply. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have glioma who receive *BRAF* gene variant testing to select a treatment with BRAF or MEK inhibitors, the evidence includes small, prospective, uncontrolled studies and case reports. The relevant outcomes are OS, disease-specific survival, and test accuracy. Studies assessing the use of sorafenib in patients with newly diagnosed and recurrent gliomas combined with various other treatments have not shown benefit, although most did not report *BRAF* V600 variant status. Evaluation of the BRAF and MEK inhibitors vemurafenib, dabrafenib, and trametinib in patients with gliomas has been limited to a phase 2 "basket" study, including eight patients with glioma, as well as case reports and small case series. Early reports have suggested clinical benefit, but confirmatory randomized controlled trials are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements

The National Comprehensive Cancer Network Guidelines for melanoma (v.2.2018) recommends *BRAF* variant status should be tested "using an FDA-approved test or by a facility approved by CLIA [Clinical Laboratory Improvement Amendments] facility." Combination dabrafenib plus trametinib and combination vemurafenib plus cobimetinib therapies have a category 1 recommendation as a preferred regimen for advanced or metastatic melanoma. Vemurafenib and dabrafenib also have category 1 recommendations for advanced or metastatic melanoma. The National Comprehensive Cancer Network also recommends dabrafenib plus trametinib combination therapy as an option for patients with stage III melanoma who have a *BRAF* V600-activating variant and sentinel lymph node metastasis greater than 1 mm (category 1).

The National Comprehensive Cancer Network (2019) updated the melanoma guidelines to be specific to cutaneous melanoma (v.2.2019). The guidelines state, “for patients with cutaneous melanoma who are without evidence of disease,” a mutational analysis of the primary lesion for BRAF is not recommended, “unless required to guide adjuvant or other systemic therapy or consideration of clinical trials.” However, for patients who are symptomatic and/or have quickly progressing melanoma, testing for BRAF V600 could be indicated; BRAF/MEK inhibitors have shorter response time compared with checkpoint immunotherapies and may be the preferred treatment.

Network guidelines for central nervous system cancers (v.1.2018) indicate the following on the use of BRAF molecular markers to guide treatment decisions for primary brain cancers: "BRAF V600E tumors may respond to BRAF inhibitors such as vemurafenib, but comprehensive clinical trials are still ongoing." The 2019 update (v.1.2019) includes no new recommendations regarding the use of BRAF gene variant testing.

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
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
Melanoma			
NCT01909453	A 2-part Phase III Randomized, Open-Label, Multicenter Study of LGX818 Plus MEK162 Versus Vemurafenib and LGX818 Monotherapy in Patients With Unresectable or Metastatic *BRAF* V600 Mutant Melanoma (COLUMBUS)	921	Jan 2024
NCT01667419[a]	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients With Surgically Resected, Cutaneous *BRAF* Mutant Melanoma at High Risk for Recurrence	475	Oct 2020
NCT02224781	A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients With Advanced *BRAF*V600 Mutant Melanoma	300	Oct 2022
NCT01682083[a]	COMBI-AD: A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBInation With Trametinib (GSK1120212) Versus Two Placebos in the ADjuvant Treatment of High-risk *BRAF* V600 Mutation-positive Melanoma After Surgical Resection	852	Mar 2023

Glioma			
NCT01089101	A Phase 1 and Phase II and Re-Treatment Study of AZD6244 for Recurrent or Refractory Pediatric Low Grade Glioma	180	Dec 2020
NCT01748149[a]	PNOC-002: Safety, Phase 0, and Pilot Efficacy Study of Vemurafenib, an Oral Inhibitor of *BRAF*V600E, in Children and Young Adults With Recurrent/Refractory *BRAF*V600E- or *BRAF* Ins T Mutant Brain Tumors	54	Jun 2019
NCT01677741[a]	Phase I/IIa, 2-Part, Multi-Center, Single-Arm, Open-Label Study to Determine the Safety, Tolerability and Pharmacokinetics of Oral Dabrafenib in Children and Adolescent Subjects With Advanced *BRAF* V600-Mutation Positive Solid Tumors	86	Sep 2019
NCT02285439	Phase I Study of MEK162 for Children With Progressive or Recurrent Cancer and a Phase II Study for Children With Low-Grade Gliomas and Other Ras/Raf/MAP Pathway Activated Tumors	80	Jun 2020
NCT02034110[a]	A Phase II, Open-label, Study in Subjects With *BRAF* V600E-Mutated Rare Cancers With Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib	225	Aug 2020
NCT02465060	Molecular Analysis for Therapy Choice (MATCH)	6452	Jun 2022
NCT02684058	Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib in Combination With Trametinib in Children and Adolescent Patients With *BRAF* V600 Mutation PositiveLow Grade	142	Sep 2024

	Glioma (LGG) or Relapsed or Refractory High Grade Glioma (HGG)		
NCT02684058[a]	Phase II Open-label Global Study to Evaluate the Effect of Dabrafenib Treatment in Children and Adolescent Patients With *BRAF* V600 Mutation Positive Relapsed or Refractory High Grade Glioma (HGG)	142	Sep 2024
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	1500	Sep 2027

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Policy History

Original Effective Date: 11/16/2011
Current Effective Date: 09/14/2020

11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
11/28/2012	Medical Policy Implementation Committee approval. “Targeted” added to the title. Eligible for coverage statement modified to read “FDA-approved BRAF inhibitors” in place of “vemurafenib” .
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

Policy # 00320
Original Effective Date: 11/16/2011
Current Effective Date: 09/14/2020

01/01/2015	Coding Update
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. New policy.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
10/05/2017	Medical Policy Committee review
10/18/2017	Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature. Policy statements regarding BRAF testing in melanoma unchanged. Information about FDA-approved MEK inhibitor (cobimetinib) added. New policy statement stating BRAF testing in glioma is investigational was added. Policy title changed to "BRAF Gene Mutation Testing to Select Melanoma or Glioma Patients for Targeted Therapy".
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. New policy statement added stating BRAF testing in resected, stage III melanoma is eligible for coverage. "Mutation" changed to "variant" in policy title.
08/01/2019	Medical Policy Committee review
08/14/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020	Medical Policy Committee review
08/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2021

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 2019 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.

BRAF Gene Variant Testing to Select Melanoma or Glioma Patients for Targeted Therapy

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

Code Type	Code
CPT	81210
HCPCS	No codes
ICD-10 Diagnosis	C43.0-C43.9, D03.0-D03.9

*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);
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.