KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 03/08/2021

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 KRAS variant analysis for patients with metastatic colorectal cancer (mCRC) to predict nonresponse prior to planned therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab to be **eligible for coverage.****

Based on review of available data, the Company may consider NRAS variant analysis for patients with mCRC to predict nonresponse prior to planned therapy with anti-EGFR monoclonal antibodies cetuximab or panitumumab to be **eligible for coverage.****

Based on review of available data, the Company considers BRAF variant analysis for patients with mCRC who are found to be wild-type on KRAS and NRAS variant analysis to guide management decisions 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.

Based on review of available data, the Company considers KRAS, NRAS, and BRAF variant analysis using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer to be **investigational.***

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Based on review of available data, the Company considers KRAS, NRAS, and BRAF variant analysis for all other indications to be **investigational.***

Policy Guidelines

There is support from the evidence and clinical input to use *BRAF* V600 variant testing for prognostic stratification.

It is uncertain whether the presence of a *BRAF* V600 variant in patients with metastatic colorectal cancer who are wild-type on *KRAS* and *NRAS* variant analysis is predictive of response to anti-epidermal growth factor receptor therapy. Furthermore, there is mixed opinion in clinical guidelines and clinical input on the use of *BRAF* variant analysis to predict response to treatment.

Background/Overview

Cetuximab (Erbitux; ImClone Systems) and panitumumab (Vectibix; Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neovascularization.

The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. The Ras proteins are G proteins that cycle between active (RAS guanosine triphosphate) and inactive (RAS guanosine diphosphate) forms in response to stimulation from a cell surface receptor, such as EGFR, and they act as a binary switch between the cell surface EGFR and downstream signaling pathways. The *KRAS* gene can harbor oncogenic variants that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. Approximately 40% of colorectal cancers (CRCs) have *KRAS* variants in codons 12 and 13 in exon 2. Another proto-oncogene that acts downstream from *KRAS-NRAS* harbors oncogenic variants in codons 12, 13, or 61 that result in constitutive activation of the EGFR-mediated pathway. These variants are less common compared with *KRAS*, detected in 2% to 7% of CRC specimens. It is unclear whether *NRAS* variants predict poor response due to anti-EGFR monoclonal antibody therapy or are prognostic of poor CRC outcome in general. A third proto-oncogene, *BRAF*, encodes a protein kinase and is involved in intracellular signaling and cell growth; *BRAF* is also a principal downstream effector of *KRAS*. *BRAF* variants occur in fewer than 10% to 15% of CRCs and appear to be a marker of poor prognosis. *KRAS* and *BRAF* variants are considered to be mutually exclusive.

Cetuximab and panitumumab have marketing approval from the U.S. Food and Drug Administration (FDA) for the treatment of metastatic CRC in the refractory disease setting. The FDA approval for panitumumab indicates that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* variant-positive disease in combination with oxaliplatin-based chemotherapy.

Detecting ctDNA and Circulating Tumor Cells

Typically, the evaluation of RAS mutation status requires tissue biopsy. Circulating tumor DNA (ctDNA) testing is proposed as a non-invasive alternative.

Detection of ctDNA is challenging because ctDNA is diluted by nonmalignant circulating DNA and usually represents a small fraction (<1%) of total cfDNA. Therefore, more sensitive methods than the standard sequencing approaches (eg, Sanger sequencing) are needed.

Highly sensitive and specific methods have been developed to detect ctDNA, for both single nucleotide variants (eg BEAMing [which combines emulsion polymerase chain reaction with magnetic beads and flow cytometry] and digital polymerase chain reaction) and copy-number variants. Digital genomic technologies allow for enumeration of rare variants in complex mixtures of DNA.

Approaches to detecting ctDNA can be considered targeted, which includes the analysis of known genetic mutations from the primary tumor in a small set of frequently occurring driver mutations, which can impact therapy decisions or untargeted without knowledge of specific variants present in the primary tumor, and include array comparative genomic hybridization, next-generation sequencing, and whole exome and genome sequencing.

CTC assays usually start with an enrichment step that increases the concentration of CTCs, either by biologic properties (expression of protein markers) or physical properties (size, density, electric charge). CTCs can then be detected using immunologic, molecular, or functional assays.

A number of liquid biopsy tests related to targeted treatment of metastatic colorectal cancer have been developed (Table 1).

Table 1. Examples of Liquid Biopsy Tests Related to Targeted Treatment of Metastatic Colorectal Cancer

Manufacturer	Test	Type of Liquid Biopsy
Biocept	Target SElector ctDNA EGFR Kit	ctDNA
CellMax Life	CellMax-CRC Colorectal Cancer Early Detection Test	CTC
Cynvenio	ClearID Solid Tumor Panel	ctDNA and CTC
Foundation Medicine	FoundationOne Liquid (Previously FoundationAct)	ctDNA
Guardant Health	Guardant360®	ctD
IV DIagnostics	Velox™	CTC
Pathway Genomics	CancerIntercept® Detect	ctD
Personal Genome Diagnostics	PlasmaSELECT	ctD
Sysmex Inostics	OncoBEAM	ctD
Circulogene	Theranostics	ctD

CTC: circulating tumor cell; ctDNA: circulating tumor DNA.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Approved Companion Diagnostic Tests for* KRAS *Variant Analysis to Select Cetuximab and Panitumumab in Metastatic Colorectal Cancer

Companion diagnostic tests for the selection of cetuximab and panitumumab have been approved by the FDA through the premarket approval process (Table 2):

Table 2. Companion Diagnostic Tests for the Selection of Cetuximab and Panitumumab for Metastatic Colorectal Cancer

Diagnostic Name.	**PMA/510(k)/HDE**	**Description**	**Approval Date**	**Diagnostic Manufacturer**
FoundationOne CDx	P170019	Next Generation Sequencing Oncology Panel, Somatic Or Germline Variant Detection System	11/30/2017	Foundation Medicine, Inc.
Praxis Extended RAS Panel	P160038	Next Generation Sequencing Oncology Panel, Somatic Or Germline Variant Detection System	06/29/2017	Illumina, Inc.
cobas KRAS Mutation Test	P140023	Somatic Gene Mutation Detection System		Roche Molecular Systems, Inc
therascreen KRAS RGQ PCR Kit	P110030P110027	Somatic Gene Mutation Detection System	5/23/2014	Qiagen Manchester, Ltd.
Dake EGFR pharmDx Kit	P030044/S002	Immunohistochemistry Assay, Antibody, Epidermal Growth Factor Receptor	9/27/2006	Dako North America, Inc.

Source: U.S. Food and Drug Administration (2019)

Laboratory-Developed Tests for* KRAS, NRAS, *and* BRAF *Variant Analysis

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. *KRAS*, *NRAS*, and *BRAF* variant analyses using polymerase chain reaction methodology are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Liquid Biopsy
No liquid biopsy test is currently FDA approved to select treatment for patients with metastatic colorectal cancer.

Rationale/Source

Description
The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy combined with monoclonal antibodies cetuximab and panitumumab has shown a clear survival benefit in patients with metastatic CRC. However, this benefit depends on a lack of variants in certain genes in the signaling pathway downstream from the EGFR. It has been hypothesized that knowledge of tumor cell *KRAS, NRAS,* and *BRAF* variant status might be used to predict nonresponse to anti-EGFR monoclonal antibody therapy. Typically, the evaluation of *RAS* mutation status requires tissue biopsy. Circulating tumor DNA or circulating tumor cell testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.

Summary of Evidence
For individuals with metastatic CRC who receive *KRAS* variant testing to guide treatment, the evidence includes multiple systematic reviews including a TEC Assessment. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Variant testing of tumor tissue performed in prospective and retrospective analyses of randomized controlled trials has consistently shown that the presence of a *KRAS* variant predicts nonresponse to cetuximab and panitumumab, either as monotherapy or in combination with other treatment regimens and supports the use of *KRAS* variant analysis of tumor DNA before considering a treatment regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with metastatic CRC who receive *NRAS* variant testing to guide treatment, the evidence includes prospective-retrospective analyses of randomized controlled trials and retrospective cohort studies. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. Pooled analyses have shown that *NRAS* variants (beyond the common *KRAS* exon 2 variants) predict nonresponse to cetuximab and panitumumab, and support the use of *NRAS* variant analysis of tumor DNA before considering a treatment regimen. In addition, there is strong support from the National

Comprehensive Cancer Network and the American Society of Clinical Oncology for *NRAS* and *KRAS* testing in patients with metastatic CRC. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with metastatic CRC who receive *BRAF* variant testing to guide treatment, the evidence includes 2 meta-analyses of prospective and retrospective analyses of randomized controlled trials. Relevant outcomes are OS, disease-specific survival, change in disease status, medication use, resource utilization, and treatment-related morbidity. The meta-analyses have shown that anti-EGFR monoclonal antibody therapy did not improve survival in patients with *RAS* wild-type or *BRAF*-mutated tumors; however, the individual studies have been small, and the results have been inconsistent. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2017 supports that the following indication provides a clinically meaningful improvement in net health outcome and is consistent with generally accepted medical practice.

- Use of *BRAF* V600E variant analysis in individuals with metastatic CRC who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions.

Thus, the above indication may be considered medically necessary considering the suggestive evidence and clinical input support.

For individuals with metastatic CRC who receive circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment, the evidence includes observational studies. Relevant outcomes are OS, disease-specific survival, test validity, morbid events, and medication use. Given the breadth of methodologies available to assess circulating tumor DNA and circulating tumor cells, the clinical validity of each commercially available test must be established independently. The clinical validity of the OncoBEAM RAS CRC Assay has been studied in multiple observational studies. When compared to tissue biopsy, sensitivity ranged from 70% (51% to 84%) to 96% (95% confidence interval 87% to 100%) and specificity ranged from 83% (95% confidence interval 71% to 92%) to 94% (82% to 98%). FoundationOne Liquid has been compared to tissue biopsy with the FoundationACT assay in one observational study; positive percent agreement was 80% overall and 90% when tissue and liquid biopsy were collected less than 270 days apart. Clinical validity studies

were limited by unclear reporting of blinding, use of convenience rather than consecutive samples, and variation in the timing of sample collection. There are no published studies reporting clinical outcomes or clinical utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2017 Input

In response to requests, clinical input on use of *BRAF* V600E variant analysis in individuals with metastatic colorectal cancer who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions was received from 11 respondents, including 2 specialty society-level response, 1 physician from the academic center, and 6 physicians from 2 health systems, while this policy was under review in 2017.

Based on the evidence and independent clinical input, the clinical input supports that the following indication provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice:

- Use of *BRAF* V600E variant analysis in individuals with metastatic colorectal cancer who are found to be wild-type on *KRAS* and *NRAS* variant analysis to guide management decisions.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines on the treatment of colon cancer (v.4.2020) recommend that tumor tissue should be genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* variants, individually or as part of a next-generation sequencing panel, for all patients with metastatic

colon cancer. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* muation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab. *BRAF* V600E mutation makes response to panitumamab or cetuximab highly unlikely unless given with a *BRAF* inhibitor.

American College of Medical Genetics and Genomics

In 2013, an evidence review published by the American College of Medical Genetics and Genomics has stated that evidence is insufficient to support the clinical validity or utility of testing colorectal cancer specimens for *NRAS* variants to guide patient management. That same review further found no guidelines on *NRAS* testing from any other U.S. group.

American Society of Clinical Oncology et al

In 2017, the American Society of Clinical Oncology along with American Society for Clinical Pathology, College of American Pathologists, and Association for Molecular Pathology published guidelines on molecular biomarkers for the evaluation of colorectal cancer. Table 3 summarizes the relevant guidelines.

Table 3. Summary of Recommendations

Guidelines	Type	SOE	QOE
Colorectal carcinoma patients being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12, 13 of exon 2; 59, 61 of exon 3; and 117 and 146 of exon 4 ("expanded" or "extended" RAS)	Recommendation	Convincing/ adequate, benefits outweigh harms	High/intermediate

Guidelines	Type	SOE	QOE
BRAF p.V600 (BRAF c. 1799 (p.V600) mutational analysis should be performed in colorectal cancer tissue in patients with colorectal carcinoma for prognostic stratification	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
BRAF p.V600 mutational analysis should be performed in deficient MMR tumors with loss of MLH1 to evaluate for Lynch Syndrome risk. Presence of a BRAF mutation strongly favors sporadic pathogenesis. The absence of BRAF mutation does not exclude risk of Lynch syndrome	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low
Clinicians should order mismatch repair status testing in patients with colorectal cancers for the identification of patients at high-risk	Recommendation	Adequate/inadequate, balance of benefits and harms	Intermediate/low

Guidelines	Type	SOE	QOE
for Lynch syndrome and/or prognostic stratification			
There is insufficient evidence to recommend BRAF c.1799 p.V600 mutational status as a predictive molecular biomarker for response to anti-EGFR inhibitors	No recommendation	Insufficient, benefits/harms balance unknown	Insufficient

EGFR: epidermal growth factor receptor; QOE: quality of evidence; SOE: strength of evidence.

In 2015, the American Society of Clinical Oncology updated its provisional clinical opinion on extended *RAS* variant testing in metastatic colorectal cancer to predict response to anti-EGFR monoclonal antibody therapy. The opinion was based on evidence from 13 articles on *KRAS* variants (11 systematic reviews, 2 health technology assessments) and 2 articles on *NRAS* testing. The opinion stated that subgroup analyses of patients with any of the less common *RAS* variants were small, and there was inadequate evidence to provide a definitive opinion on the lack of benefit for the use of anti-epidermal growth factor receptor antibodies for patients whose cancer harbors any specific *RAS* variant other than the exon 2 *KRAS* variant. The Society considered the less common *RAS* variants as a group, and a pooled analysis suggested the same lack of benefit with anti-epidermal growth factor receptor therapy as seen with the more common variants in exon 2 of *KRAS*.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
A March 2018 decision memo from the Centers for Medicare & Medicaid Services addressed next-generation sequencing for Medicare beneficiaries with advanced cancer. The memo states:

The Centers for Medicare & Medicaid Services has determined that Next Generation Sequencing (NGS) as a diagnostic laboratory test is reasonable and necessary and covered nationally when performed in a CLIA-certified laboratory, when ordered by a treating physician and when all of the following requirements are met:

1. Patient has:
    1.
        1.
        a. either recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer; and
        b. either not been previously tested using the same NGS test for the same primary diagnosis of cancer or repeat testing using the same NGS test only when a new primary cancer diagnosis is made by the treating physician; and
        c. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

2. The diagnostic laboratory test using NGS must have:
    1.
        a. FDA [U.S. Food and Drug Administration] approval or clearance as a companion in vitro diagnostic; and
        b. an FDA [U.S. Food and Drug Administration] approved or cleared indication for use in that patient's cancer; and
        c. results provided to the treating physician for management of the patient using a report template to specify treatment options.

Regarding liquid biopsies, the memo states, "The NCD does not limit coverage to how to prepare a sample for performing a diagnostic laboratory test using NGS. Commenters submitted published articles on liquid biopsies (also referred to as circulating tumor DNA (ctDNA) or plasma cell-free DNA (cfDNA) tests). We reviewed and included in the evidence and analysis of 4 studies on liquid biopsies. At this time, liquid-based multi-gene sequencing panel tests are left to contractor discretion if certain patient criteria are met."

Ongoing and Unpublished Clinical Trials
Currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Ongoing Trials

NCT No.	Trial Name	NCT No.	Trial Name
Ongoing		***Ongoing***	
NCT03038217	Investigation of the Value of ctDNA Analysis in the Diagnosis, Treatment, and Surveillance of Patients With Surgically Resectable Colorectal Cancer	NCT03038217	Investigation of the Value of ctDNA Analysis in the Diagnosis, Treatment, and Surveillance of Patients With Surgically Resectable Colorectal Cancer
NCT04425239	Intermittent or Continuous Panitumumab Plus FOLFIRI for First-line Treatment of Patients With RAS/B-RAF Wild-type Metastatic Colorectal Cancer: a Randomized Phase 2 Trial	NCT04425239	Intermittent or Continuous Panitumumab Plus FOLFIRI for First-line Treatment of Patients With RAS/B-RAF Wild-type Metastatic Colorectal Cancer: a Randomized Phase 2 Trial

NCT: national clinical trial.

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Policy History

Original Effective Date: 12/17/2008
Current Effective Date: 03/08/2021

12/03/2008	Medical Director review
12/17/2008	Medical Policy Committee approval. New policy.
12/04/2008	Medical Director review
12/16/2008	Medical Policy Committee approval. No change to coverage.
12/01/2010	Medical Policy Committee review
12/15/2010	Medical Policy Implementation Committee approval. No change to coverage.
12/08/2011	Medical Policy Committee review
12/21/2011	Medical Policy Implementation Committee approval. Title changed to indicate inclusion of BRAF testing to the policy. BRAF testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.
12/06/2012	Medical Policy Committee review
12/19/2012	Medical Policy Implementation Committee approval. No change to coverage.
03/04/2013	Coding revised
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2015	Coding Update
04/02/2015	Medical Policy Committee review
04/20/2015	Medical Policy Implementation Committee approval. Title changed to indicate inclusion of NRAS testing to the policy. NRAS testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/01/2016	Coding update
04/07/2016	Medical Policy Committee review
04/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/30/2016	Medical Policy Committee review
07/20/2016	Medical Policy Implementation Committee approval. Policy statement revised to indicate that NRAS testing policy statement added as medically necessary to predict

	nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
02/01/2018	Medical Policy Committee review
02/21/2018	Medical Policy Implementation Committee approval. Title changed from "KRAS, NRAS, and BRAF Mutant Analysis in Metastatic Colorectal Cancer" to "KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer". BRAF variant analysis changed from investigational to eligible for coverage. Policy revised with updated genetic nomenclature.
02/07/2019	Medical Policy Committee review
02/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/06/2019	Coding update
02/06/2020	Medical Policy Committee review
02/12/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Title changed from "KRAS, NRAS and BRAF Variant Analysis in Metastatic Colorectal Cancer" to "KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer". Investigational statement added for "using circulating tumor DNA or circulating tumor cell testing (liquid biopsy) to guide treatment for patients with metastatic colorectal cancer".
02/04/2021	Medical Policy Committee review
02/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 02/2022

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 2020 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	0037U, 0069U, 0111U, 81210, 81275, 81276, 81311, 81403, 81404, 81445, 81450, 81455, 88363
HCPCS	No codes
ICD-10 Diagnosis	C18.0-C18.9, C19, C20, C21.0-C21.2, C21.8

*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.