



Louisiana

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420

Original Effective Date: 04/23/2014

Current Effective Date: 09/13/2021

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 Janus kinase 2 (*JAK2*) testing in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) to be **eligible for coverage**.**

Note: Based on criteria from the World Health Organization, documentation of a serum erythropoietin level below the reference range for normal is recommended before JAK2 testing.

Based on review of available data, the Company may consider MPL and CALR testing in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis 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 Janus kinase 2 (*JAK2*), MPL, and CALR testing to be **investigational*** in all other circumstances including, but not limited to, the following situations:

- **Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs); or**

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- Molecular phenotyping of patients with myeloproliferative neoplasms (MPNs); or
- Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms (MPNs)

Policy Guidelines

Testing strategy

Patients suspected to have polycythemia vera should first be tested for the most common finding, *JAK2* V617F. If the testing is negative, further testing to detect other *JAK2* tyrosine kinase variants (eg, in exon 12) is warranted.

Patients suspected to have essential thrombocythemia or primary myelofibrosis should first be tested for *JAK2* variants, as noted. If testing is negative, further testing to detect *MPL* and *CALR* variants is warranted.

CRITERIA FOR POLYCYTHEMIA TESTING

Diagnosis of essential thrombocythemia (ET) by the 2016 World Health Organization (WHO) criteria requires all four of the following major criteria or the first three major criteria plus the minor criterion:

Major criteria

- Platelet count $\geq 450 \times 10^9/L$ ($\geq 450,000/\text{microL}$)
- Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.
- WHO criteria for *BCR-ABL1*-positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, myelodysplastic syndrome, or other myeloid neoplasm not met
- Demonstration of a *JAK2*, *CALR*, or *MPL* mutation

Minor criterion

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- Demonstration of another clonal marker (*ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, or *SR3B1* mutation) **or** no identifiable cause of thrombocytosis (eg, infection, inflammation, iron deficiency anemia)

Reactive thrombocytosis — A variety of medical and surgical conditions can result in reactive thrombocytosis. These include iron deficiency anemia, surgical or functional asplenia, metastatic cancer, trauma (surgical or otherwise), acute bleeding or hemolysis, and a variety of infectious or inflammatory processes. Unlike in ET, reactive thrombocytosis is not driven by a clonal process.

When a cause for reactive thrombocytosis is not readily apparent, the demonstration of elevated acute-phase reactants (C-reactive protein [CRP], fibrinogen, erythrocyte sedimentation rate, ferritin) may be used as evidence for the presence of an occult inflammatory process.

Background/Overview

Myeloproliferative Neoplasms

MPNs are rare overlapping blood diseases characterized by the production of one or more blood cell lines. The most common forms of MPNs include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), and chronic myeloid leukemia. A common finding in many MPNs is clonality and a central pathogenic feature the detection of a somatic (acquired) pathogenic variant in disease-associated genes. Pathogenic variants in disease-associated genes result in constitutively activated tyrosine kinase enzyme or cell surface receptor.

The paradigm for the use of molecular genetics to revolutionize patient management is chronic myeloid leukemia. A unique chromosomal translocation t(9;22), the Philadelphia chromosome (Ph), leads to a unique gene rearrangement (*BCR-ABL*) creating a fusion gene that encodes for a constitutively active Bcr-abl fusion protein. These findings led to the development of targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions. Rare patients may show unusual manifestations of nonclassic forms of MPNs, such as chronic myelomonocytic leukemia, hypereosinophilic syndrome, systemic mastocytosis, chronic neutrophilic leukemia, or others. Reports have identified *JAK2* V617F variants in some of these cases. The remainder of this evidence review focuses only on the non-Ph or Ph-negative MPNs and genetic testing for *JAK2*, *CALR*, and *MPL*.

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Louisiana

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Diagnosis and monitoring of patients with Ph-negative MPNs have been challenging because many of the laboratory and clinical features of the classic forms of these diseases can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis, or myeloid fibrosis. Additionally, these entities can be difficult to distinguish on morphologic bone marrow exam, and diagnosis can be complicated by changing disease patterns: PV and ET can evolve into PMF or undergo a leukemic transformation. A complex set of clinical, pathologic, and biologic criteria was first introduced by the Polycythemia Vera Study Group in 1996 and by the World Health Organization as a benchmark for diagnosis in 2002 and updated in 2008 and 2016. Applying these criteria has been challenging because they involve complex diagnostic algorithms, rely on morphologic assessment of uncertain consistency, and require tests that are not well-standardized or widely available, such as endogenous erythroid colony formation. An important component of the diagnostic process is a clinical and laboratory assessment to rule out reactive or secondary causes of disease.

Chronic Myeloid Leukemia and Philadelphia Chromosome

Ph-Negative MPNs

Classic Myeloproliferative Neoplasms

Varying combinations of these criteria are used to determine whether a patient has PV, ET, or PMF, ie, MPNs that are Ph-negative. An important component of the diagnostic process is a clinical and laboratory assessment to rule out reactive or secondary causes of disease.

As noted, some diagnostic methods (eg, bone marrow microscopy) are not well-standardized, and others (eg, endogenous erythroid colony formation) are neither standardized nor widely available.

Nonclassic Forms of Myeloproliferative Neoplasms

Although the most common Ph-negative MPNs include what is commonly referred to as classic forms of this disorder (PV, ET, PMF). Rare patients may show unusual manifestations of nonclassic forms of MPNs, such as chronic myelomonocytic leukemia, hypereosinophilic syndrome, systemic mastocytosis, chronic neutrophilic leukemia, or others. Reports have identified *JAK2* V617F variants in some of these cases.

Molecular Genetics of Ph-Negative Myeloproliferative Neoplasms

JAK2 Gene

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Louisiana

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The *JAK2* gene, located on chromosome 9, contains the genetic code for making the Janus kinase 2 protein, a nonreceptor tyrosine kinase. The Janus kinase 2 (JAK2) protein is part of the JAK/signal transduction pathway and activators of transcription factor (STAT) proteins that are important for the controlled production of blood cells from hematopoietic cells. Somatic (acquired) variants in the *JAK2* gene are found in patients with PV, ET, and PMF.

JAK2 V617F Variant

In 2005, 4 separate groups using different modes of discovery and different measurement techniques reported on the presence of a novel somatic (acquired) single nucleotide variant in the conserved autoinhibitory pseudokinase domain of the gene encoding JAK2 protein in patients with classic MPNs. The single nucleotide variant caused a valine-to-phenylalanine substitution at amino acid position 617 (*JAK2 V617F*) leading to a novel somatic gain-of-function single nucleotide variant that resulted in the loss of autoinhibition of the JAK2 tyrosine kinase. *JAK2 V617F* is a constitutively activated kinase that recruits and phosphorylates substrate molecules including STAT proteins (so-called JAK-STAT signaling). The result is cell proliferation independent of normal growth factor control.

The *JAK2 V617F* variant was present in blood and bone marrow from a variable portion of patients with classic *BCR-ABL*-negative (ie, Ph-negative) MPNs including 65% to 97% of patients with PV, 23% to 57% with ET, and 35% to 56% with PMF (see Table 1). The variant was initially reported to be absent in all normal subjects and patients with secondary erythrocytosis, although very low levels of cells carrying the variant have been reported in a small subset of healthy individuals.

Although almost all studies were retrospective case series and/or cross-sectional studies, and although both the analytic and clinical performances appeared dependent on the laboratory method used to detect the variant, there has been consistency across studies in demonstrating that the *JAK2 V617F* variant is a highly specific marker for clonal evidence of an MPN.

Table 1. Frequency of the *JAK2 V617F* Variant in Patients With Classic Philadelphia Chromosome-Negative Myeloproliferative Neoplasm From Case Series

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Louisiana

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Policy # 00420

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Study	Variant Detection Method	PV	ET	PMF	Normals	Secondary Erythrocytosis
Baxter et al (2005)	DNA sequencing, PCR	71/73 (97)	29/51 (57)	8/16 (50)	0/90 (0)	NR
Jones et al (2005)	PCR testing	58/72 (81)	24/59 (41)	15/35 (43)	0/160 (0)	0/4 (0)
Levine et al (2005)	DNA sequencing	121/164 (74)	37/115 (32)	16/46 (35)	0/269 (0)	NR
James et al (2005)	DNA sequencing	40/45 (88)	9/21 (43)	3/7 (43)	0/15 (0)	0/35 (0)
Kralovics et al (2005)	DNA sequencing	83/128 (65)	21/94 (23)	13/23 (56)	0/142 (0)	0/11 (0)
Tefferi et al (2005)	PCR testing	36/38 (95)	12/46 (55)	3/10 (30)	NR	0/19 (0)
Zhao et al (2005)	DNA sequencing	20/24 (83)	NR	NR	0/12 (0)	NR

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Current Effective Date: 09/13/2021

Campbell et al (2005)	PCR testing	NR	414/776 (53)	NR	NR	NR
Wolanskyj et al (2005)	PCR testing	NR	73/150 (49)	NR	NR	NR
Campbell et al (2006)	PCR testing	NR	NR	83/152 (55)	NR	NR
Tefferi et al (2005)	PCR testing	NR	NR	80/157 (51)	NR	NR

Values are n/N (%).

ET: essential thrombocythemia; NR: not reported; PCR: polymerase chain reaction; PMF: primary myelofibrosis; PV: polycythemia vera.

In vivo, mice irradiated and then given transplanted bone marrow cells infected with a retrovirus containing the variant developed a myeloproliferative syndrome.

JAK2 Exon 12 Variants

Scott et al (2007) identified 4 somatic gain-of-function variants in *JAK2* exon 12 in 10 of 11 PV patients without the *JAK2* V617F variant. Patients with a *JAK2* exon 12 variant differed from those with the *JAK2* V617F variant, presenting at a younger age with higher hemoglobin levels and lower platelet and white cell counts. Erythroid colonies could be grown from their blood samples in the absence of exogenous erythropoietin, and mice treated with transfected bone marrow transplants developed a myeloproliferative syndrome.

Findings have been confirmed by a number of investigators who identified additional variants with similar functional consequences in patients with PV and patients with idiopathic erythrocytosis. Based on these findings, it has been concluded that the identification of *JAK2* exon

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12 variants provides a diagnostic test for *JAK2* V617F-negative patients who present with erythrocytosis. Of note, different variants in the same gene appear to have different effects on signaling, resulting in distinct clinical phenotypes.

MPL Gene

The *MPL* gene, located on chromosome 1, contains the genetic code for making the thrombopoietin receptor, a cell surface protein that stimulates the JAK/STAT signal transduction pathway. The thrombopoietin receptor is critical for the cell growth and division of megakaryocytes, which produce platelets involved in blood clotting. Somatic variants in the *MPL* gene are associated with ET and PMF.

CALR Gene

The *CALR* gene, located on chromosome 19, contains the genetic code for making the calreticulin protein, a multifunctional protein located in the endoplasmic reticulum, cytoplasm, and cell surface. The calreticulin protein is thought to play a role in cell growth and division and regulation of gene activity. Somatic variants in the *CALR* gene are associated with ET and PMF.

Frequency of JAK2, CALR, and MPL Somatic Variants in Ph-Negative Myeloproliferative Neoplasms

Ph-negative MPNs are characterized by their molecular genetic alterations. Table 2 summarizes the driver genes and somatic variants associated with specific Ph-negative MPNs.

Table 2. Frequency of *JAK2*, *CAL4*, and *MPL* Somatic Variants in Ph-Negative MPNs

Ph-Negative MPNs	<i>JAK2</i> Somatic Variant Detected, % of Patients	<i>CALR</i> Somatic Variant Detected, % of Patients	<i>MPL</i> Somatic Variant Detected, % of Patients
Polycythemia vera	<ul style="list-style-type: none"> <i>JAK2</i> V617F, 95 		

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	<ul style="list-style-type: none"> <i>JAK2</i> exon 12 variants, 5 		
Essential thrombocythemia	<i>JAK2</i> V617F, 60-65	<i>CALR</i> exon 9 indels, 20-25	<i>MPL</i> exon 10 variants, 5
Primary myelofibrosis	<i>JAK2</i> V617F, 60-65	<i>CALR</i> exon 9 indels, 20-25	<i>MPL</i> exon 10 variants, 5

Adapted from Cazzola et al (2014).

indels: insertions and deletions; MPN: myeloproliferative neoplasm; Ph: Philadelphia chromosome.

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. More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *JAK2*, *CALR*, and *MPL* testing under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

Somatic (acquired) genetic variants in *JAK2*, *MPL*, and *CALR* genes have been implicated as the underlying molecular genetic drivers for the pathogenesis of myeloproliferative neoplasms (MPNs). This policy addresses the use of genetic testing of *JAK2* and *CALR* genes for the diagnosis, prognosis, and treatment selection of patients with MPNs.

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For individuals with a suspected MPN who receive genetic testing for *JAK2*, the evidence includes case series, retrospective studies, meta-analyses, and randomized controlled trials. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Philadelphia chromosome-negative (Ph-negative) MPN, *JAK2* variants are found in nearly 100% of those with polycythemia vera, 60% to 65% of those with essential thrombocythemia, and 60% to 65% of those with primary myelofibrosis. In individuals with suspected MPN, a positive genetic test for *JAK2* satisfies a major criterion for the 2016 World Health Organization classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocythemia from the differential diagnosis. The presence of a documented *JAK2* variant may aid in the selection of ruxolitinib, a *JAK2* inhibitor; ruxolitinib, however, is classified as a second-line therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *MPL*, the evidence includes case series and retrospective studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *MPL* variants are found in approximately 5% of those with essential thrombocythemia (ET) and primary myelofibrosis cases (PMF). In individuals with suspected MPN, a positive genetic test for *MPL* satisfies a major criterion for the 2016 World Health Organization classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *MPL* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *MPL* genetic testing does not in and of itself result in changes in management that would be expected to improve the net health outcome. Thus, clinical utility has not been established. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *CALR*, the evidence includes case series and retrospective studies. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *CALR* variants are found in approximately 20% to 25% of those with ET and PMF. For individuals with suspected MPN, a positive genetic test for *CALR* satisfies a major criterion for the World Health Organization classification for ET and PMF and eliminates secondary or reactive

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Louisiana

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Policy # 00420

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causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *CALR* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *CALR* genetic testing does not result in changes in management that would be expected to improve the net health outcome. Thus, clinical utility has not been established. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Additional Information

Given that genetic testing for MPL and CALR variants is included in the WHO (2016) major criteria and the National Comprehensive Cancer Network guidelines (2020) for myeloproliferative neoplasms, MPL and CALR testing may be consistent with clinical practice in the diagnosis of patients with clinical, laboratory, or pathological findings suggesting ET and PMF.

Supplemental Information

Practice Guidelines and Position Statements

The 2016 World Health Organization major criteria for myeloproliferative neoplasms are as follows:

- Polycythemia vera: "Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation"
- Essential thrombocythemia: "Demonstration of JAK2 V617F or other clonal markers, or in the absence of a clonal marker, no evidence for reactive thrombocytosis"
- Primary myelofibrosis: "Demonstration of JAK2 V617F or other clonal markers (eg, MPL W515K/L), or, in the absence of a clonal marker, no evidence of bone marrow fibrosis [due to underlying inflammatory or other neoplastic disease]."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network published guidelines (v.1.2020) on the workup, diagnosis, and treatment of suspected myeloproliferative neoplasms. For patients with suspicion of myeloproliferative neoplasms, the guidelines recommend "molecular testing (blood) for JAK2 V617F mutation; if negative, test for CALR and MPL mutations (for patients with ET and MF) and JAK2 Exon 12 mutations (for patients with PV) or molecular testing using multigene NGS panel that includes JAK2, CALR, and MPL."

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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

A search of ClinicalTrials.gov in July 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

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Louisiana

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420

Original Effective Date: 04/23/2014

Current Effective Date: 09/13/2021

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Policy History

Original Effective Date: 04/23/2014

Current Effective Date: 09/13/2021

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|------------|---|
| 04/03/2014 | Medical Policy Committee review |
| 04/23/2014 | Medical Policy Implementation Committee approval. New policy. |
| 06/25/2015 | Medical Policy Committee review |
| 07/15/2015 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 06/30/2016 | Medical Policy Committee review |
| 07/20/2016 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 07/06/2017 | Medical Policy Committee review |
| 07/19/2017 | Medical Policy Implementation Committee approval. Coverage eligibility unchanged. |
| 10/05/2017 | Medical Policy Committee review |
| 10/18/2017 | Medical Policy Implementation Committee approval. CALR testing added to the policy. Policy revised with updated genetics nomenclature. Policy statements updated to clarify that JAK2 testing is medically necessary for PV, ET and PMF |

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and added recommendation for documentation of serum erythropoietin levels prior to JAK2 testing, MPL testing is medically necessary for ET and PMF, and new medical necessity statement added for CALR testing in ET and PMF. Title changed to “JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms”.

- 04/01/2018 Coding update
 - 10/04/2018 Medical Policy Committee review
 - 10/17/2018 Medical Policy Implementation Committee approval. Policy guidelines updated.
 - 10/03/2019 Medical Policy Committee review
 - 10/09/2019 Medical Policy Implementation Committee approval. No change to coverage.
 - 10/01/2020 Medical Policy Committee review
 - 10/07/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
 - 12/11/2020 Coding update
 - 08/05/2021 Medical Policy Committee review
 - 08/11/2021 Medical Policy Implementation Committee approval. WHO criteria revised.
- Next Scheduled Review Date: 08/2022

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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	0017U, 0027U, 81219, 81270, 81402, 81403 Code added eff 1/1/2021: 81279, 81338, 81339
HCPCS	No codes
ICD-10 Diagnosis	C92.10-C92.12, C96.2, D45, D47.1, D47.3

*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.

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****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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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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