JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420
Original Effective Date: 04/23/2014
Current Effective Date: 12/11/2023

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

Note:
See Policy Guidelines for 2017 WHO diagnostic criteria for PV, ET, PMF.

PV is suspected when hemoglobin is > 16.5 g/dL in men, > 16.0 g/dL in women, or hematocrit is > 49% in men, > 48% in women on two separate occasions, or increased red cell mass is > 25% above mean normal predicted value, and no other known causes of erythrocytosis.

ET is suspected when platelet count is ≥450 x 10^9/L greater than 3 months.

PMF is suspected in individuals with leukocytosis ≥11 x 10^9/L (>11,000/microL) on two separate occasions in the absence of other conditions that can cause leukocytosis or enlarged spleen.

Based on review of available data, the Company may consider MPL and CALR testing in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis when genetic testing would impact medical management to be **eligible for coverage.****

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Note:
For laboratories performing single gene technologies, a sequential genetic testing approach is expected; once a positive result is obtained and the appropriate diagnosis is established, testing should stop. Reflex testing to the next gene will be reasonable if the following sequence of genetic tests produce a negative result:

1. *BCR-ABL negative results, progress to #2*
2. *JAK2 V617F (common variant) negative results, progress to #3 or #4*
3. *JAK, exon 12 only when PV is suspected*
4. *CALR/ MPL only when either ET or PMF is suspected- if negative results progress to #5*
5. *ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2, and SF3B1 only when either ET or PMF is suspected (see Policy Guidelines section), and JAK2, CALR, and MPL analyses were negative.*

For the laboratories performing next generation sequencing (NGS) or using 'hotspot' testing platforms, molecular testing for BCR-ABL, JAK2 V617F, JAK exon 12, CALR, MPL, and above noted PMF/ET prognostic genes by NGS can be considered for the identification of myeloproliferative disorders. In this situation and when criteria are met, testing 5 or more genes on the same platform, such as multi-gene NGS panel, should be reported with a single CPT code 81450.

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

Policy Guidelines

Testing strategy

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Individuals 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.

Individuals 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
Based on the World Health Organization (WHO) major and minor criteria (see Table PG1), documentation of serum erythropoietin level below the reference range for normal meets a minor criterion for polycythemia vera.

Based on 2017 WHO diagnostic criteria for polycythemia vera, diagnosis requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion.

Table PG1. WHO Diagnostic Criteria for Polycythemia Vera

Major Criteria
• Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women); or • Increased hematocrit (>49% in men or >48% in women); or • Other evidence of increased red cell volume (increased red cell mass > 25% above mean normal predicted value)
• Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
• *JAK2* V617F or *JAK2* exon 12 variant detected
Minor Criterion

- Subnormal serum erythropoietin (EPO) level

Adapted from Arber et al (2016).
WHO: World Health Organization.

CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA TESTING

Diagnosis of essential thrombocythemia (ET) by the 2017 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 ≥450 x 10^9/L (≥450,000/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

- Presence 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.

CRITERIA FOR PRIMARY MYELOFIBROSIS TESTING
Diagnosis of overt primary myelofibrosis (PMF) by the 2017 WHO criteria requires all three of the following major criteria and at least one minor criterion:

Major criteria:

- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
- WHO criteria for polycythemia vera (PV), essential thrombocythemia (ET), BCR-ABL1+ chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), or other myeloid neoplasm not met.
- Demonstration of a *JAK2*, *CALR*, or *MPL* mutation **or** in the absence of these mutations, presence of another clonal marker (*ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2*, or *SR3B1* mutation) **or** absence of reactive fibrosis (eg, infection, autoimmune disorder, chronic inflammatory disorder, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or chronic toxic myelopathy).

Minor criteria (must be confirmed in two consecutive measurements):

- Anemia not attributable to a comorbid condition
- Leukocytosis $\geq 11 \times 10^9$/L (>11,000/microL)
- Palpable splenomegaly
- LDH above the upper limit of normal
- Leukoerythroblastosis

The diagnosis of early prefibrotic PMF (pre-PMF) can be challenging as the presentation can mimic that of ET. WHO criteria require all three of the following major criteria and at least one minor criterion:

Major criteria:

- Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted bone marrow cellularity, granulocyte proliferation, and often decreased erythropoiesis. Grade 1 myelofibrosis is a loose network of reticulin with many intersections, especially in perivascular areas.
- WHO criteria for PV, ET, CML, MDS, or other myeloid neoplasm not met.

- Demonstration of a *JAK2*, *CALR*, or *MPL* mutation **or** in the absence of these mutations, presence of another clonal marker (*ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, or *SR3B1* mutation) **or** absence of minor reactive BM reticulin fibrosis (e.g., secondary to infection, autoimmune disorder, chronic inflammatory disorder, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or chronic toxic myelopathy).

Minor criteria (must be confirmed in two consecutive measurements):

- Anemia not attributable to a comorbid condition
- Leukocytosis ≥11 x 10^9/L (>11,000/microL)
- Palpable splenomegaly
- LDH above the upper limit of normal

Distinction of pre-PMF from overt PMF is important because individuals who present with pre-PMF have different patterns of clinical presentation, survival, and disease progression.

Background/Overview

Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are rare overlapping blood diseases characterized by the production of 1 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 in 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. Rarely, individuals 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*.

Diagnosis and monitoring of individuals 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.In 2022, both the World Health Organization 5th edition and an International Consensus Classification were published. Applying these criteria has been challenging because they involve complex diagnostic algorithms, rely on a 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
Philadelphia Chromosome-Negative Myeloproliferative Neoplasms
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), rarely, individuals 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 Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

***JAK2* Gene**

The *JAK2* gene, located on chromosome 9, contains the genetic code for making the Janus kinase 2 (JAK2) protein, a nonreceptor tyrosine kinase. The JAK2 protein is part of the JAK/ signal transducer and activator of transcription (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 individuals 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 individuals 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 individuals with classic *BCR-ABL*-negative (ie, Ph-negative) MPNs including 65% to 97% of individuals 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 individuals 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 Individuals With Classic Philadelphia Chromosome-Negative Myeloproliferative Neoplasm From Case Series

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
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; MPN: myeloproliferative neoplasm; 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 individuals without the *JAK2* V617F variant. Individuals 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 individuals with PV and individuals with idiopathic erythrocytosis. Based on these findings, it has been concluded that the identification of *JAK2* exon 12 variants provides a diagnostic test for *JAK2* V617F-negative individuals 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 Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Philadelphia chromosome-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 Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Ph-Negative MPNs	*JAK2* Somatic Variant Detected, % of Individuals	*CALR* Somatic Variant Detected, % of Individuals	*MPL* Somatic Variant Detected, % of Individuals
PV	• *JAK2* V617F, 95 • *JAK2* exon 12 variants, 5	•	
ET	*JAK2* V617F, 60 to 65	*CALR* exon 9 indels, 20 to 25	*MPL* exon 10 variants, 5
PMF	*JAK2* V617F, 60 to 65	*CALR* exon 9 indels, 20 to 25	*MPL* exon 10 variants, 5

Adapted from Cazzola et al (2014).
ET: essential thrombocythemia; indels: insertions and deletions; MPN: myeloproliferative neoplasm; Ph: Philadelphia chromosome; PMF: primary myelofibrosis; PV: polycythemia vera.

A more recent retrospective study of individuals observed at the National Research Center for Hematology (Moscow, Russia) from October 2016 to November 2020 assessed the frequency of detection of *JAK2* V617F, *CALR,* and *MPL* mutations in a Russian cohort of individuals with *BCR::ABL* rearrangement negative (ie, Ph-negative) MPNs. Individuals (N=1958) with a diagnosis of ET, PV, PMF, or MPN-unclassified were examined. Table 3 summarizes the driver genes and somatic variants associated with specific Ph-negative MPNs.

Table 3. Frequency of *JAK2*, *CAL4*, and *MPL* Genes in Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Ph-Negative MPNs	*JAK2* Somatic Variant Detected, % of Individuals	*CALR* Somatic Variant Detected, % of Individuals	*MPL* Somatic Variant Detected, % of Individuals
PV	• *JAK2* V617F, 91.1% • *JAK2* exon 12 variants, 8.9%	0%	0%
ET	*JAK2* V617F, 53.9%	*CALR* exon 9 indels, 40.3%	*MPL* W515L/K, 1.5%
PMF	*JAK2* V617F, 60.5%	*CALR* exon 9 indels, 36.9%	*MPL* W515L/K, 3.4%
MPN-unclassified	*JAK2* V617F, 61.9%	19.8%	1.9%

ET: essential thrombocythemia; indels: insertions and deletions; MPN: myeloproliferative neoplasm; Ph: Philadelphia chromosome; PMF: primary myelofibrosis; PV: polycythemia vera.

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

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.

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 (MPN). This evidence review addresses the use of genetic testing for *JAK2*, *MPL*, and *CALR* genes for diagnosis, prognosis, and treatment selection of individuals with MPN.

Summary of Evidence

For individuals with a suspected myeloproliferative neoplasm (MPN) who receive genetic testing for *JAK2*, the evidence includes case series, retrospective studies, meta-analyses, and randomized controlled trials. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. For individuals with suspected Ph-negative MPN, *JAK2* variants are found in nearly 100% of those with polycythemia vera (PV), 60% to 65% of those with essential thrombocythemia (ET), and 60% to 65% of those with primary myelofibrosis (PMF). In individuals with suspected MPN, a positive genetic test for *JAK2* satisfies a major criterion for the International Consensus Classification (2022) and World Health Organization (WHO) 2022 (5th edition) 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 second-line therapy. The evidence is sufficient to determine that the technology results in an 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 are OS, disease-specific survival, test accuracy and validity, and resource utilization. For individuals with suspected Ph-negative MPN, *MPL* variants are found in approximately 5% of those with ET and PMF. In individuals with suspected MPN, a positive genetic test for *MPL* satisfies a major criterion for

the International Consensus Classification (2022) and WHO (2022, 5th edition) 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, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in an 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 are OS, disease-specific survival, test accuracy and validity, and resource utilization. For individuals 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 International Consensus Classification (2022) and WHO (2022, 5th edition) 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 *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, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information

Given that genetic testing for *MPL and CALR* variants is included in the WHO (2022, 5th edition) and International Consensus Classification (2022) major criteria and the National Comprehensive Cancer Network guidelines (2023) for MPNs, *MPL,* and *CALR* testing may be consistent with clinical practice in the diagnosis of individuals with clinical, laboratory, or pathological findings suggesting ET and PMF.

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Supplemental Information

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.

World Health Organization
The 2022 (5th edition) World Health Organization (WHO) major criteria for myeloproliferative neoplasms (MPNs) are unchanged from the 2016 (4th edition) criteria and are as follows:

- Polycythemia vera (PV): " Presence of *JAK2*, V617F, or *JAK2* exon 12 mutation"
- Essential thrombocythemia (ET): " Presence of *JAK2*, *CALR*, or *MPL* mutation"
- Primary myelofibrosis (PMF): " Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis."

International Consensus Classification
In 2022, an international clinical advisory committee endorsed by the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP) published a new classification schema for myeloid neoplasms and acute leukemias. Many of the clinical advisory committee authors were authors on the 2016 (4th edition) of the WHO criteria, but the International Consensus Classification was developed independently of the WHO. The gene-related major criteria for MPNs are as follows:

- PV: "Presence of *JAK2* V617F or *JAK2* exon 12 mutation"
- ET: "JAK2, CALR, or MPL mutation"
- PMF: "JAK2, CALR, or MPL mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis"

For PV, it is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level, <1%); in negative cases, searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15 can be considered. For ET and MPF, it is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level, <1%) and *CALR* and *MPL* (sensitivity level, 1% to 3%); in

negative cases, a search for noncanonical *JAK2* and *MPL* mutations can be considered. Other clonal markers that can be assessed in MPF include mutations associated with myeloid neoplasms (eg, *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2*, and *TET2* mutations).

National Comprehensive Cancer Network
The National Comprehensive Cancer Network published guidelines (v.1.2023) on the workup, diagnosis, and treatment of suspected MPNs. For individuals with suspicion of MPNs, the guidelines recommend "molecular testing (blood or bone marrow) for *JAK2* V617F mutation; if negative, test for *CALR* and *MPL* mutations (for individuals with ET and MF) and *JAK2* Exon 12 mutations (for individuals with PV) or molecular testing using multigene NGS [next-generation sequencing] panel that includes *JAK2*, *CALR*, and *MPL*. Once an MPN diagnosis is confirmed, NGS is recommended for mutational prognostication."

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 June 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

Original Effective Date: 04/23/2014
Current Effective Date: 12/11/2023

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 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

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420
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08/11/2021	Medical Policy Implementation Committee approval. WHO criteria revised
10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. Policy guideless updated.
11/03/2022	Medical Policy Committee review
11/09/2022	Medical Policy Implementation Committee approval. Criteria revised due to Senate bill update.
11/02/2023	Medical Policy Committee review
11/08/2023	Medical Policy Implementation Committee approval. No change to coverage. The word Patients was changed to individuals.

Next Scheduled Review Date: 11/2024

Coding

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JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420
Original Effective Date: 04/23/2014
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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, 81120, 81121, 81175, 81176, 81219, 81270, 81279, 81338, 81339, 81347, 81348, 81450 Delete codes effective 01/01/2023: 81402, 81403
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:
    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.

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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.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.