JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy #    00420
Original Effective Date: 04/23/2014
Current Effective Date: 01/01/2023

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 patients 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 10⁹/L greater than 3 months.

PMF is suspected in individuals with leukocytosis ≥11 x 10⁹/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 patients 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.**
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 patients with myeloproliferative neoplasms (MPNs); or
- Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms (MPNs)

Policy Guidelines
Testing strategy
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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
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

<table>
<thead>
<tr>
<th>Major Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased hemoglobin level (&gt;16.5 g/dL in men or &gt;16.0 g/dL in women); or</td>
</tr>
<tr>
<td>• Increased hematocrit (&gt;49% in men or &gt;48% in women); or</td>
</tr>
<tr>
<td>• Other evidence of increased red cell volume (increased red cell mass &gt; 25% above mean normal predicted value)</td>
</tr>
<tr>
<td>• 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)</td>
</tr>
<tr>
<td>• JAK2 V617F or JAK2 exon 12 variant detected</td>
</tr>
</tbody>
</table>

Minor Criterion
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- 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 \( \geq 450 \times 10^9/L \) (\( \geq 450,000/\mu\text{L} \))
- 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 $>\text{grade }1$, 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.
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- 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 patients who present with pre-PMF have different patterns of clinical presentation, survival, and disease progression.

**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.

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 amorphologic 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.
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Molecular Genetics of Ph-Negative Myeloproliferative Neoplasms

JAK2 Gene
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 transcript (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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<table>
<thead>
<tr>
<th>Study</th>
<th>Variant Detection Method</th>
<th>PV</th>
<th>ET</th>
<th>PMF</th>
<th>Normals</th>
<th>Secondary Erythrocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter et al (2005)</td>
<td>DNA sequencing, PCR</td>
<td>71/73 (97)</td>
<td>29/51 (57)</td>
<td>8/16 (50)</td>
<td>0/90 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>Jones et al (2005)</td>
<td>PCR testing</td>
<td>58/72 (81)</td>
<td>24/59 (41)</td>
<td>15/35 (43)</td>
<td>0/160 (0)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>Levine et al (2005)</td>
<td>DNA sequencing</td>
<td>121/164 (74)</td>
<td>37/115 (32)</td>
<td>16/46 (35)</td>
<td>0/269 (0)</td>
<td>NR</td>
</tr>
<tr>
<td>James et al (2005)</td>
<td>DNA sequencing</td>
<td>40/45 (88)</td>
<td>9/21 (43)</td>
<td>3/7 (43)</td>
<td>0/15 (0)</td>
<td>0/35 (0)</td>
</tr>
<tr>
<td>Kralovics et al (2005)</td>
<td>DNA sequencing</td>
<td>83/128 (65)</td>
<td>21/94 (23)</td>
<td>13/23 (56)</td>
<td>0/142 (0)</td>
<td>0/11 (0)</td>
</tr>
<tr>
<td>Tefferi et al (2005)</td>
<td>PCR testing</td>
<td>36/38 (95)</td>
<td>12/46 (55)</td>
<td>3/10 (30)</td>
<td>NR</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>Zhao et al (2005)</td>
<td>DNA sequencing</td>
<td>20/24 (83)</td>
<td>NR</td>
<td>NR</td>
<td>0/12 (0)</td>
<td>NR</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Value</th>
<th>414/776 (53)</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell et al (2005)</td>
<td>PCR testing</td>
<td>NR</td>
<td>73/150 (49)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Wolanskyj et al (2005)</td>
<td>PCR testing</td>
<td>NR</td>
<td>73/150 (49)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Campbell et al (2006)</td>
<td>PCR testing</td>
<td>NR</td>
<td>83/152 (55)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Tefferi et al (2005)</td>
<td>PCR testing</td>
<td>NR</td>
<td>80/157 (51)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

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, CALR, and MPL Somatic Variants in Ph-Negative MPNs

<table>
<thead>
<tr>
<th>Ph-Negative MPNs</th>
<th>JAK2 Somatic Variant Detected, % of Patients</th>
<th>CALR Somatic Variant Detected, % of Patients</th>
<th>MPL Somatic Variant Detected, % of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia vera</td>
<td>• JAK2 V617F, 95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Adapted from Cazzola et al (2014).

<table>
<thead>
<tr>
<th></th>
<th>JAK2 exon 12 variants, 5</th>
<th>CALR exon 9 indels, 20-25</th>
<th>MPL exon 10 variants, 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential thrombocythemia</td>
<td>JAK2 V617F, 60-65</td>
<td>CALR exon 9 indels, 20-25</td>
<td>MPL exon 10 variants, 5</td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
<td>JAK2 V617F, 60-65</td>
<td>CALR exon 9 indels, 20-25</td>
<td>MPL exon 10 variants, 5</td>
</tr>
</tbody>
</table>

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**

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.
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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.

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 (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 World Health Organization (2016) classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocytosis 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 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 ET and PMF. In individuals with suspected MPN, a positive genetic test for MPL satisfies a major criterion for the World Health Organization (2016) classification for ET and PMF and eliminates secondary or reactive causes of thrombocytosis 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 a meaningful improvement in the net health outcome.
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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 causes of thrombocytemia 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 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 thrombocytemia: "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]."

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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.”

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 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

References


JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420
Original Effective Date: 04/23/2014
Current Effective Date: 01/01/2023

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420
Original Effective Date: 04/23/2014
Current Effective Date: 01/01/2023


Policy History
Original Effective Date: 04/23/2014
Current Effective Date: 01/01/2023
04/03/2014 Medical Policy Committee review
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.
JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Policy # 00420
Original Effective Date: 04/23/2014
Current Effective Date: 01/01/2023

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
10/03/2019 Medical Policy Committee review
10/09/2019 Medical Policy Implementation Committee approval. No change to coverage.
10/01/2020 Medical Policy Committee review
12/11/2020 Coding update
08/05/2021 Medical Policy Committee review
08/11/2021 Medical Policy Implementation Committee approval. WHO criteria revised
10/07/2021 Medical Policy Committee review
11/03/2022 Medical Policy Committee review

Next Scheduled Review Date: 11/2023

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 2021

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

<table>
<thead>
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<th>Code Type</th>
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<tr>
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<td>0017U, 0027U, 81219, 81270, 81279, 81338, 81339</td>
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<td></td>
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<td>Delete codes effective 01/01/2023: 81402, 81403</td>
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<tr>
<td>HCPCS</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>C92.10-C92.12, C96.2, D45, D47.1, D47.3</td>
</tr>
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</table>

*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.

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