Policy Statement

Janus kinase 2 (JAK2) testing may be considered medically necessary in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF).

Myeloproliferative leukemia (MPL) and calreticulin (CALR) testing may be considered medically necessary in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis.

JAK2, MPL, and CALR testing is considered investigational in all other circumstances including, but not limited to, the following situations:

- Diagnosis of non-classic forms of myeloproliferative neoplasms (MPNs)
- Molecular phenotyping of patients with myeloproliferative neoplasms
- Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms
- When ordered as a large panel of genes not otherwise allowed by another policy

Policy Guidelines

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for JAK2 and MPL analysis testing. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests. Variable analytical and clinical performance has been reported, suggesting that the nucleic acid amplification methodologies are more sensitive than mutation sequence analysis. It appears that there can be considerable interassay and interlaboratory variability in the generation of testing results.

Claims for JAK2 and MPL analysis testing should clearly identify the test type and the indications for testing. Appropriate CPT/HCPCS codes or CPT code modifiers should be utilized when available.

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 (e.g., 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. Serum erythropoietin testing may be done in place of JAK2 testing when the first four major criteria are met.

Diagnosis of PV: all major criteria, or first 4 major criteria plus 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)</td>
</tr>
<tr>
<td>• Increased hematocrit (&gt;49% in men or &gt;48% in women)</td>
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<tr>
<td>• Other evidence of increased red cell volume</td>
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<tr>
<td>• Bone marrow biopsy showing hypercellularity for age with trilineage maturation, 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>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serum erythropoietin level below the reference range for normal</td>
</tr>
</tbody>
</table>

Adapted from Arber et al (2016).

WHO: World Health Organization.

Genetics Nomenclature Update

The Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics (ACMG) and Genomics and the Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "variant of uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>Variant</td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

There is a specific CPT code for JAK2 V617F testing:
- **81270**: JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

If further JAK2 testing is performed, the following code might be reported:
- **81403**: Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR [polymerase chain reaction] in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) - which includes:
  - JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed

There is a code specific to the University of Iowa’s JAK2 variant test:
- **0017U**: Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected

The following CPT code is available for MPL testing:
- **81402**: Molecular pathology procedure, Level 3 (e.g., >10 SNPs [single-nucleotide polymorphism], 2-10 methylated variants, or 2-10 somatic variants [typically using nonsequencing target variant analysis], immunoglobulin and T cell receptor gene rearrangements, duplication/deletion variants 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) - which includes:
  - MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor TPOR) (e.g., myeloproliferative disorder), common variants (e.g., W515A, W515K, W515L, W515R).

There is a specific CPT code for CALR testing:
- **81219**: CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9

### Description

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 patients with MPN.

### Related Policies

- **N/A**

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.


### Regulatory Status

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

#### Background

**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 thrombocytosis (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.1, [10] 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 19962,3 and by the World Health Organization as a benchmark for diagnosis in 20024 and updated in 2008 and 2016.5,6 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 Ph-Negative MPNs**

**Classic MPNs**

Varying combinations of these criteria are used to determine whether a patient has PV, ET, or PMF, i.e., 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 (e.g., bone marrow microscopy) are not well-standardized,\textsuperscript{7,8,9} and others (e.g., endogenous erythroid colony formation) are neither standardized nor widely available.

**Nonclassic Forms of MPNs**

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.\textsuperscript{1}

**Molecular Genetics of Ph-Negative MPNs**

**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.\textsuperscript{10}

**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 (i.e., 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,\textsuperscript{9,11-19} although very low levels of cells carrying the variant have been reported in a small subset of healthy individuals.\textsuperscript{20,21}

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>
<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)\textsuperscript{9}</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)\textsuperscript{1}</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)\textsuperscript{11}</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)\textsuperscript{12}</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)\textsuperscript{13}</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)\textsuperscript{14}</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)\textsuperscript{15}</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>
In vivo, mice irradiated and then given transplanted bone marrow cells infected with a retrovirus containing the variant developed a myeloproliferative syndrome.12

**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.22 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.23,24 Based on these findings, it has been concluded that the identification of JAK2 exon 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.22

**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 MPNs 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.25

<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>CALR exon 9 indels, 20-25</td>
<td>MPL exon 10 variants, 5</td>
</tr>
<tr>
<td></td>
<td>JAK2 exon 12 variants, 5</td>
<td></td>
<td></td>
</tr>
<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>

Adapted from Cazzola et al (2014).25

indels: insertions and deletions; MPN: myeloproliferative neoplasm; Ph: Philadelphia chromosome.
Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

JAK2 Testing for a Suspected Myeloproliferative Neoplasm
Clinical Context and Test Purpose
The purpose of JAK2 testing of individuals with a suspected MPN is to establish a molecular genetic diagnosis of MPN to inform management decisions.

The question addressed in this evidence review is: In individuals with a suspected MPN, does the use of JAK2 testing improve the net health outcome?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals with a suspected MPN.

Patients with suspected MPN are actively managed by hematologists and oncologists.

Interventions
The test being considered is genetic testing for JAK2.

Comparators
The following practice is currently being used to make decisions about individuals with a suspected MPN: standard clinical management without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest include establishing a molecular genetic diagnosis of polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) to inform management decisions when test results are provided.

The time frame for outcomes measures varies from several months for the improvement of symptoms to long-term survival as a result of disease-related complications.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Mejia-Ochoa et al (2019) conducted a systematic review and meta-analysis of the frequency of JAK2, CALR, and MPL in Philadelphia chromosome (Ph)-negative chronic MPNs. Twenty studies reported the frequency of JAK2V617F in PV, ET, and PMF. The studies were heterogeneous with regard to the diagnostic techniques used and their results. The proportion of patients with
JAK2V617F ranged from 46.7% to 100% in patients with PV, from 31.3% to 72.1% in patients with ET, and from 25.0% to 85.7% in those with PMF.

The World Health Organization (WHO; 2016) criteria specifically recommended testing for JAK2 exon 12 variants in patients with suspected PV (presumably in patients who are JAK2 V617F-negative). The criteria suggested testing for JAK2 V617F in patients with ET.6

Section Summary: Clinically Valid
Evidence of the clinical validity of JAK2 V617F and exon 12 variant testing includes prospective studies and case series and a systematic review of these studies. In PV patients, the proportion of patients with JAK2V617F ranged from 46.7% to 100% in patients with PV, from 31.3% to 72.1% in patients with ET, and from 25.0% to 85.7% in those with PMF. Additionally, the WHO 2016 diagnostic criteria incorporated the JAK2 V617F variants for PV, ET, and PMF and JAK2 exon 12 variants for PV.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

Testing for JAK2 V617F or JAK2 exon 12 variants have potential clinical utility in several different clinical scenarios:
1. Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic MPNs (PV, ET, or PMF);
2. Phenotyping of disease subtypes in patients with MPNs to establish disease prognosis;

Treatment With JAK2 Inhibitors
Due to the strong epidemiologic and biologic literature linking JAK2 pathway variants to the occurrence of MPNs, there has been considerable recent attention on using JAK2 as a molecular target for drug discovery. In preclinical and early clinical studies, a number of promising JAK2 inhibitors have been identified, and reports have suggested that some are useful in symptom relief.26 Many patients with these diseases have good responses to cytotoxic drugs, and the natural course of the disease, particularly for PV and ET, can be quite indolent. Considerable study will be required to sort through the safety and efficacy of these new treatments before they enter routine clinical use. Several early-phase and preliminary treatment trials evaluating the safety and efficacy of tyrosine kinase inhibitors in patients with JAK2 V617F-positive MPNs have been reported.27,28,29 It also has been noted that benefits from tyrosine kinase therapy may not be specific for JAK2 V617F-positive MPNs but may be observed in wild-type disease as well.30

In 2011, ruxolitinib (a JAK kinase inhibitor) was approved by the U.S. Food and Drug Administration for the treatment of intermediate- and high-risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, and postessential thrombocytopenia myelofibrosis) based on results from 2 RCTs. One, a double-blind RCT by Verstovsek et al (2012) assessing patients with intermediate- to high-risk myelofibrosis, randomized participants to twice-daily oral ruxolitinib (n=155) or to placebo (n=154) and followed them for 76 weeks (Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment [COMFORT-I]).31 The primary outcome (a ≥35% reduction in spleen volume at or after 24 weeks) was observed in 41.9% of patients treated with ruxolitinib compared with 0.7% in the placebo group (p < 0.001). At the prospectively defined
data cutoff of 32 weeks, there were 10 (6.5%) deaths in the ruxolitinib group and 14 (9.1%) deaths in the placebo group (Kaplan-Meier method, p=0.33). With 4 additional months of follow-up (median, 51 weeks total follow-up), there were 13 (8.4%) total deaths in the ruxolitinib group and 24 (15.6%) total deaths in the placebo group (Kaplan-Meier method, p=0.04). Myelofibrosis symptom score at 24 weeks improved 45.9% from baseline in patients who received ruxolitinib and 5.3% in placebo patients. Discontinuations due to adverse events were similar in the ruxolitinib (11%) and placebo (10.6%) groups. In a post hoc subgroup analysis of patients with the JAK2 V617F variant, mean changes in spleen volume at 24 weeks were -34.6% in the ruxolitinib group and +8.1% in the placebo group; in patients without the variant, mean changes in spleen volume were -23.8% and +8.4%, respectively. Changes in total symptom score at 24 weeks in patients with the JAK2 V617F variant were -52.6% in the ruxolitinib group and +42.8% in the placebo group (higher scores indicate more severe symptoms); in patients without the variant, changes in total symptom score were -28.1% and +37.2%, respectively.

A second trial by Harrison et al (2012) reached similar conclusions (COMFORT-II).32, Patients with intermediate- or high-risk primary myelofibrosis, postpolycythemia vera myelofibrosis, or postessential thrombocythemia myelofibrosis, or postJAK2 V617F myelofibrosis were randomized to oral ruxolitinib (n=146) or best available therapy (n=73). No differences in overall survival (OS) were observed between the 2 groups at 48 weeks. Twenty-eight percent of patients in the ruxolitinib group had at least a 35% reduction in spleen volume at 48 weeks compared with 0% in the control group (p<0.001). In the JAK2 V617F-positive subgroup, the incidence of spleen reduction was 33% in the ruxolitinib group and 0% in the control group; in the JAK2 V617F-negative subgroup, the incidence of spleen reduction was 14% in the ruxolitinib group and 0% in controls. In the ruxolitinib group, patients had an improved overall quality of life and a reduction in myelofibrosis symptoms compared with no benefit to the control group. Serious adverse events were similar between groups: anemia occurred in 5% of patients in the ruxolitinib group and 4% of the control group, pneumonia occurred in 1% of the ruxolitinib group and 5% in controls. In the ruxolitinib group, patients had an improved overall quality of life and a reduction in myelofibrosis symptoms compared with no benefit to the control group. Serious adverse events were similar between groups: anemia occurred in 5% of patients in the ruxolitinib group and 4% of the control group, pneumonia occurred in 1% of the ruxolitinib group and 5% of the control group, and 8% of patients in the ruxolitinib group and 5% in the control group discontinued treatment.

A follow-up to the COMFORT-I trial, published by Verstovsek et al (2015), provided data on a median 3-year follow-up.33, At a median of 149 weeks (range, 19-175 weeks), 77 (49.7%) of the 155 patients originally randomized to ruxolitinib were still receiving therapy. One hundred eleven of 154 patients who originally received placebo crossed over to receive ruxolitinib, and, of these, 57 (51.4%) were still receiving the drug. Of the patients originally randomized to therapy, discontinuation rates were 21% at 1 year, 35% at 2 years, and 51% at year 3. Reasons for discontinuing ruxolitinib were disease progress (23.1%), adverse events (19.2%), death (19.2%), and withdrawal of consent (15.4%). The initial primary outcome measure of this study was a reduction in spleen volume, and, in this follow-up study, reductions in spleen size were durable with longer-term treatment. Mean percentage change from baseline was -31.6% at week 24 and -34.1% at week 144. Of patients initially randomized to ruxolitinib, 91 (59%) of 155 of patients achieved a 35% or more reduction in spleen volume at any time during study follow-up. The probability of maintaining the same reduction for at least 132 weeks was 0.53, and more than 80% of patients maintained a reduction of at least 10%. Regarding OS, 42 patients randomized to ruxolitinib died while 54 in the placebo group died. With a median follow-up of 149 weeks for both the ruxolitinib and placebo groups, the hazard ratio for (OS) favored patients in the ruxolitinib arm (hazard ratio, 0.69; 95% confidence interval, 0.46 to 1.03; p=0.067). Anemia and thrombocytopenia were the most common adverse hematologic events and were highest during the first six months of therapy, both of which subsequently increased to a new steady state. The most common nonhematologic adverse events, which occurred more commonly in the ruxolitinib group, were ecchymosis (18.7%), dizziness (14.8%), and headache (14.8%). Additionally, more patients treated with study drug developed urinary tract infections and herpes zoster, although the incidence of these infections did not increase with the length of therapy. All herpes zoster infections were grade 1 or 2, and no other opportunistic infections were identified during follow-up. Four new cases of acute myeloid leukemia were reported since the first analysis published in 2012, 2 in patients originally randomized to ruxolitinib and 2 in the placebo arm, for a total of 8 cases since the study began. The rate of leukemic transformation
per person-year of ruxolitinib exposure was 0.0121 per person-year and 0.0233 per person-year in patients originally randomized to ruxolitinib or placebo, respectively.

Although identification of a drug, producing long-term remission (like imatinib in chronic myeloid leukemia) is the ultimate goal, discovery likely will be complicated by the complexity of molecular processes occurring in patients with these other MPNs and the fact that JAK2 V617F alone does not appear to be a unique or absolutely necessary event in many patients with these diseases. The role of the JAK2 V617F variant in selecting or monitoring patients for new treatments or residual neoplasia remains undefined.

Section Summary: Clinically Useful
Evidence for the clinical utility of JAK2 testing includes meta-analyses, retrospective studies, and RCTs. Evidence for JAK2 testing for phenotyping and monitoring provides conflicting results. However, the presence of JAK2 V617F or JAK2 exon 12 variants is considered a major criterion for the diagnosis of PV, ET, and PMF. JAK2 V617F and JAK2 exon 12 testing allow secondary or reactive erythrocytosis or thrombocytosis to be differentiated from PV, ET, and PMF.

MPL Testing for a Suspected Myeloproliferative Neoplasm
Clinical Context and Test Purpose
The purpose of MPL testing of individuals with a suspected MPN is to establish a molecular genetic diagnosis of MPN to inform management decisions.

The question addressed in this evidence review is: In individuals with a suspected MPN, does the use of MPL testing result in improvement in the net health outcome?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals with a suspected MPN.

Patients with suspected MPN are actively managed by hematologists and oncologists.

Interventions
The test being considered is genetic testing for MPL.

Comparators
The following practice is currently being used to make decisions about treating individuals with a suspected MPN: standard clinical management without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest include establishing a molecular genetic diagnosis of ET or PMF to inform management decisions when test results are positive. The time frame for outcomes measures varies from several months for the improvement of symptoms to long-term survival as a result of disease-related complications.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
Mejia-Ochoa et al (2019) conducted a systematic review and meta-analysis of the frequency of JAK2, CALR, and MPL in Ph-negative chronic MPNs. Across 14 studies, the frequency of the MPL variant ranged from 0% in PV, from 0.9% to 12.5% in ET, and from 0% to 17.1% in PMF. The studies were heterogeneous with regard to the diagnostic techniques used and their results.

The WHO (2016) criteria specifically cited testing MPL exon 10 variants in patients with ET and PMF. The criteria included testing for MPL exon 10 variants in patients with ET and PMF.

**Section Summary: Clinically Valid**
Evidence of the clinical validity of MPL exon 10 variants includes case series. The frequency of the MPL variant ranged from 0% in PV, from 0.9% to 12.5% in ET, and from 0% to 17.1% in PMF. In ET and PMF patients, the WHO (2016) incorporated MPL exon 10 variants as a major criterion for the diagnosis of ET and PMF.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

**Direct Evidence**
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Testing for MPL exon 10 variants has potential clinical utility in several different clinical scenarios:
1. Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic ET or PMF;

No RCTs were identified that used the results of MPL exon 10 variant testing to guide treatment and management decisions. Additionally, there is no change in management that would be expected to improve the net health outcome.

**Section Summary: Clinically Useful**
Direct evidence for the clinical utility of MPL testing is lacking. While MPL exon 10 testing has potential utility in diagnosing ET and PMF using the WHO (2016) major criteria for MPNs and excluding reactive or secondary causes of thrombocytosis, there is no change in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. Given that genetic testing for CALR is included in the WHO (2016) major criteria and the National Comprehensive Cancer Network guidelines (2019) for myeloproliferative neoplasms, MPL testing may be consistent with clinical practice in the diagnosis of patients with clinical, laboratory, or pathological findings suggesting ET and PMF.

**CALR Testing for a Suspected Myeloproliferative Neoplasm**
**Clinical Context and Test Purpose**
The purpose of CALR testing of individuals with a suspected MPN is to establish a molecular genetic diagnosis of MPN to inform management decisions.

The question addressed in this evidence review is: In individuals with a suspected MPN, does the use of CALR testing result in improvement in health outcomes?

The following PICOs were used to select literature to inform this review.
**Patients**
The relevant population of interest includes individuals with a suspected MPN. Patients with suspected MPN are actively managed by hematologists and oncologists.

**Interventions**
The test being considered is genetic testing for CALR.

**Comparators**
The following practice is currently being used to make decisions about individuals with a suspected MPN: standard clinical management without genetic testing.

**Outcomes**
The potential beneficial outcomes of primary interest include establishing a molecular genetic diagnosis of ET or PMF to inform management decision when test results are positive. The timeframe for outcomes measures varies from several months for the improvement of symptoms to long-term survival as a result of disease-related complications.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires a review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Mejia-Ochoa et al (2019) conducted a systematic review and meta-analysis of the frequency of JAK2, CALR, and MPL in Ph-negative chronic MPNs.34, Thirteen studies reported the frequency of the CALR variant in PV, ET, and PMF. The studies were heterogeneous with regard to the diagnostic techniques used and their results. The frequency of the CALR variant was 0% in patients with PV, 12.6% to 50.0% in ET, and 10% to 100% in PMF.

**Section Summary: Clinically Valid**
Evidence of the clinical validity CALR variants includes retrospective studies, case series, and a systematic review of these studies. The frequency of the CALR variant was 0% in patients with PV, 12.6% to 50.0% in ET, and 10% to 100% in PMF.

**Clinically Useful**
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Testing for CALR exon 9 variants has potential clinical utility in several different clinical scenarios:
1. Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic ET or PMF;

However, establishing the diagnosis through CALR genetic testing does not result in changes in management that would be expected to improve net health outcome.
The goals of treatment and management for ET are to alleviate symptoms and minimize complications of the disease such as thrombotic events and bleeding, though establishing the diagnosis does not lead to preventive management. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on alleviation of symptoms.

**Section Summary: Clinically Useful**

Direct evidence for the clinical utility of CALR testing is lacking. While CALR exon 9 testing has potential clinical utility in diagnosing ET and PMF using the WHO (2016) major criteria for MPNs and excluding reactive or secondary causes of thrombocytosis, there is no change in management that would be expected to improve net health outcome. Thus, the clinical utility has not been established.

**Summary of Evidence**

For individuals with a suspected MPN who receive genetic testing for JAK2, the evidence includes case series, retrospective studies, meta-analyses, and RCTs. The relevant outcomes include OS, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, JAK2 variants are found in nearly 100% of those with PV, 60% to 65% of those with ET, and 60% to 65% of those with 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. The relevant outcomes include OS, 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.

For individuals with a suspected MPN who receive genetic testing for CALR, the evidence includes case series and retrospective studies. The relevant outcomes include OS, 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 thrombocytosis 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.
Supplemental Information

Practice Guidelines and Position Statements

World Health Organization (2016) 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 (e.g., 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.2.2018) 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)."

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.

References


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):
- Prescribing MD's history and physical and/or Hematology Consultation Notes including:
  - Clinical findings suggestive of myeloproliferative neoplastic disease
  - Specific tests requested
- Laboratory and/or Pathologic findings suggestive of myeloproliferative neoplastic disease

**Post Service**
- Results/reports of tests performed

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.
Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.