2.04.60	JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms		
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Section:	2.0 Medicine	**Page:**	Page 1 of 21

Policy Statement

Note: Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

I. *Janus kinase 2 (JAK2)* testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) such as a serum erythropoietin level below the reference range for normal.

II. *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.

III. *JAK2*, *MPL*, and *CALR* testing is considered **investigational** in all other circumstances including, but not limited to, the following situations:
   A. Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs)
   B. Molecular phenotyping of individuals with myeloproliferative neoplasms
   C. Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms
   D. Part of a large panel of genes (not otherwise allowed by another policy) instead of individual gene testing

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 (PV) 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 Vera 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

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
• Bone marrow biopsy showing hypercellularity for age with trilineage maturation, including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
• *JAK2* V617F or *JAK2* exon 12 variant detected
Minor Criterion
• Serum erythropoietin level below the reference range for normal

Adapted from Arber et al (2016).
PV: polycythemia vera; WHO: World Health Organization.

Coding

There is a specific CPT code for *CALR* testing:

- **81219***: CALR* (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9

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

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 Tier 1 code was created to specifically identify the *JAK2* gene:

- **81279**: *JAK2* (Janus kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13)

The following Tier 1 codes were created to specifically identify the *MPL* gene.

- **81338**: *MPL* (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; common variants (e.g., W515A, W515K, W515L, W515R)
- **81339**: *MPL* (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10

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

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, 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,] 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[2,3,] and by the World Health Organization as a benchmark for diagnosis in 2002[4,] 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

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 (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,[7,8,9,] and others (e.g., 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, 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,]

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 patients with PV, ET, and PMF.[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,[9,1,11,12,13,14,15,16,17,18,19,] although very low levels of cells carrying the variant have been reported in a small subset of healthy individuals.[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 1. Frequency of the *JAK2* V617F Variant in Patients With Classic Ph-Negative MPN From Case Series

Study	Variant Detection Method	PV	ET	PMF	Normals	Secondary Erythrocytosis
Baxter et al (2005)[9,]	DNA sequencing, PCR	71/73 (97)	29/51 (57)	8/16 (50)	0/90 (0)	NR
Jones et al (2005)[1,]	PCR testing	58/72 (81)	24/59 (41)	15/35 (43)	0/160 (0)	0/4 (0)
Levine et al (2005)[11,]	DNA sequencing	121/164 (74)	37/115 (32)	16/46 (35)	0/269 (0)	NR
James et al (2005)[12,]	DNA sequencing	40/45 (88)	9/21 (43)	3/7 (43)	0/15 (0)	0/35 (0)
Kralovics et al (2005)[13,]	DNA sequencing	83/128 (65)	21/94 (23)	13/23 (56)	0/142 (0)	0/11 (0)
Tefferi et al (2005)[14,]	PCR testing	36/38 (95)	12/46 (55)	3/10 (30)	NR	0/19 (0)
Zhao et al (2005)[15,]	DNA sequencing	20/24 (83)	NR	NR	0/12 (0)	NR
Campbell et al (2005)[16,]	PCR testing	NR	414/776 (53)	NR	NR	NR
Wolanskyj et al (2005)[17,]	PCR testing	NR	73/150 (49)	NR	NR	NR
Campbell et al (2006)[18,]	PCR testing	NR	NR	83/152 (55)	NR	NR
Tefferi et al (2005)[19,]	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; Ph: Philadelphia chromosome; 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.[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 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.[25,]

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

Ph-Negative MPNs	*JAK2* Somatic Variant Detected, % of Patients	*CALR* Somatic Variant Detected, % of Patients	*MPL* Somatic Variant Detected, % of Patients
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).[25,]
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 patients 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 patients with *BCR/ABL1* rearrangement negative (i.e., Ph-negative) MPNs.[26,] Patients (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 Ph-Negative MPNs

Ph-Negative MPNs	*JAK2* Somatic Variant Detected, % of Patients	*CALR* Somatic Variant Detected, % of Patients	*MPL* Somatic Variant Detected, % of Patients
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.

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 myeloproliferative neoplasm (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 PICO was used to select literature to inform this review.

Populations

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

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 general outcomes of interest are overall survival (OS), disease-specific survival, test accuracy, test validity, and resource utilization. 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.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for *JAK2*, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence

Systematic Review

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.[27,]Twenty studies

reported the frequency of *JAK2* V617F in PV, ET, and PMF. The studies were heterogeneous with regard to the diagnostic techniques used and their results. The proportion of patients with JAK2 V617F 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* V617 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 *JAK2* V617F 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, more effective therapy, 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 has potential clinical utility in several different clinical scenarios:

- Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic MPNs (PV, ET, or PMF);
- Phenotyping of disease subtypes in patients with MPNs to establish disease prognosis;
- Identification, selection, and monitoring of treatment.

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.[28,] 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 studies 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.[29,30,31,] 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.[32,]

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 PMF, post-PV myelofibrosis, and post-ET 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]).[33,] 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<.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=.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=.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).[34,] Patients with intermediate- or high-risk PMF, post-PV myelofibrosis, or post-ET myelofibrosis received oral ruxolitinib (n=146) or best available therapy (n=73). No differences in 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<.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% 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.[35,] At a median of 149 weeks (range, 19 to 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. The 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 patients achieved a 35% or more reduction in spleen volume at any time during study follow-up. The probability of maintaining this 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=.067). Anemia and thrombocytopenia were the most common adverse hematologic events and were highest during the first 6 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 the 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 PICO was used to select literature to inform this review.

Populations

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

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 general outcomes of interest are OS, disease-specific survival, test accuracy, test validity, and resource utilization. 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.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for *MPL*, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence

Systematic Review

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.[27,] Across 14 studies, the frequency of the *MPL* variant was 0% in PV, and ranged 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.[6,]

Section Summary: Clinically Valid

Evidence of the clinical validity of *MPL* exon 10 variant testing includes case series. The frequency of the *MPL* variant was 0% in PV, and ranged 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:

- Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic ET or PMF;
- Phenotyping of disease subtypes in patients with ET and PMF to establish disease prognosis.

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 *MPL* is included in the WHO (2016) major criteria and the National Comprehensive Cancer Network guidelines for MPNs (2022), *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 PICO was used to select literature to inform this review.

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

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 general outcomes of interest are OS, disease-specific survival, test accuracy, test validity, and resource utilization. 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.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for *CALR*, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

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).

Review of Evidence
Systematic Review
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.[27,] 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 of *CALR* variant testing 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

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:

- Diagnosis of patients with clinical, laboratory, or pathologic findings suggesting classic ET or PMF;
- Phenotyping of disease subtypes in patients with ET and PMF to establish disease prognosis.

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. Given that genetic testing for *CALR* is included in the WHO (2016) major criteria and the National Comprehensive Cancer Network guidelines (2022) for MPNs, *CALR* testing may be consistent with clinical practice in the diagnosis of patients with clinical, laboratory, or pathological findings suggesting ET and PMF.

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 randomized controlled trials. Relevant outcomes are 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 WHO 2016 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 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 WHO (2016) 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 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 WHO 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 2016 World Health Organization major criteria for myeloproliferative neoplasms (MPNs) are as follows[6,]:

- Polycythemia vera (PV): "Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation"
- Essential thrombocythemia (ET): "Demonstration of *JAK2* V617F or other clonal markers, or in the absence of a clonal marker, no evidence for reactive thrombocytosis"
- Primary myelofibrosis (PMF): "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 (v2.2022) on the workup, diagnosis, and treatment of suspected MPNs.[36,] For patients with suspicion of MPNs, 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 June 2022 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Jones AV, Kreil S, Zoi K, et al. Widespread occurrence of the JAK2 V617F mutation in chronic myeloproliferative disorders. Blood. Sep 15 2005; 106(6): 2162-8. PMID 15920007
2. Murphy S, Peterson P, Iland H, et al. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. Semin Hematol. Jan 1997; 34(1): 29-39. PMID 9025160
3. Pearson TC, Messinezy M. The diagnostic criteria of polycythaemia rubra vera. Leuk Lymphoma. Sep 1996; 22 Suppl 1: 87-93. PMID 8951778
4. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. Oct 01 2002; 100(7): 2292-302. PMID 12239137
5. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. Jul 30 2009; 114(5): 937-51. PMID 19357394
6. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. May 19 2016; 127(20): 2391-405. PMID 27069254
7. Tefferi A, Strand JJ, Lasho TL, et al. Bone marrow JAK2V617F allele burden and clinical correlates in polycythemia vera. Leukemia. Sep 2007; 21(9): 2074-5. PMID 17476276
8. Wilkins BS, Erber WN, Bareford D, et al. Bone marrow pathology in essential thrombocythemia: interobserver reliability and utility for identifying disease subtypes. Blood. Jan 01 2008; 111(1): 60-70. PMID 17885079
9. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. Mar 2005; 365(9464): 1054-61. PMID 15781101
10. NIH Genetics Home Reference. JAK2 gene: Janus kinase 2. 2014. Updated August 18, 2020; https://ghr.nlm.nih.gov/gene/JAK2. Accessed June 14, 2022.
11. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell. Apr 2005; 7(4): 387-97. PMID 15837627
12. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature. Apr 28 2005; 434(7037): 1144-8. PMID 15793561
13. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. Apr 28 2005; 352(17): 1779-90. PMID 15858187
14. Tefferi A, Sirhan S, Lasho TL, et al. Concomitant neutrophil JAK2 mutation screening and PRV-1 expression analysis in myeloproliferative disorders and secondary polycythaemia. Br J Haematol. Oct 2005; 131(2): 166-71. PMID 16197445
15. Zhao R, Xing S, Li Z, et al. Identification of an acquired JAK2 mutation in polycythemia vera. J Biol Chem. Jun 17 2005; 280(24): 22788-92. PMID 15863514
16. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet. Dec 03 2005; 366(9501): 1945-53. PMID 16325696
17. Wolanskyj AP, Lasho TL, Schwager SM, et al. JAK2 mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. Br J Haematol. Oct 2005; 131(2): 208-13. PMID 16197451
18. Campbell PJ, Griesshammer M, Dohner K, et al. V617F mutation in JAK2 is associated with poorer survival in idiopathic myelofibrosis. Blood. Mar 01 2006; 107(5): 2098-100. PMID 16293597

19. Tefferi A, Lasho TL, Schwager SM, et al. The JAK2(V617F) tyrosine kinase mutation in myelofibrosis with myeloid metaplasia: lineage specificity and clinical correlates. Br J Haematol. Nov 2005; 131(3): 320-8. PMID 16225651
20. Xu X, Zhang Q, Luo J, et al. JAK2(V617F): Prevalence in a large Chinese hospital population. Blood. Jan 01 2007; 109(1): 339-42. PMID 16946305
21. Sidon P, El Housni H, Dessars B, et al. The JAK2V617F mutation is detectable at very low level in peripheral blood of healthy donors. Leukemia. Sep 2006; 20(9): 1622. PMID 16775613
22. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med. Feb 01 2007; 356(5): 459-68. PMID 17267906
23. Pardanani A, Lasho TL, Finke C, et al. Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. Leukemia. Sep 2007; 21(9): 1960-3. PMID 17597810
24. Siemiatkowska A, Bieniaszewska M, Hellmann A, et al. JAK2 and MPL gene mutations in V617F-negative myeloproliferative neoplasms. Leuk Res. Mar 2010; 34(3): 387-9. PMID 19643476
25. Cazzola M, Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood. Jun 12 2014; 123(24): 3714-9. PMID 24786775
26. Makarik TV, Abdullaev AO, Nikulina EE, et al. Low JAK2 V617F Allele Burden in Ph-Negative Chronic Myeloproliferative Neoplasms Is Associated with Additional CALR or MPL Gene Mutations. Genes (Basel). Apr 12 2021; 12(4). PMID 33921387
27. Mejia-Ochoa M, Acevedo Toro PA, Cardona-Arias JA. Systematization of analytical studies of polycythemia vera, essential thrombocythemia and primary myelofibrosis, and a meta-analysis of the frequency of JAK2, CALR and MPL mutations: 2000-2018. BMC Cancer. Jun 17 2019; 19(1): 590. PMID 31208359
28. Kumar C, Purandare AV, Lee FY, et al. Kinase drug discovery approaches in chronic myeloproliferative disorders. Oncogene. Jun 18 2009; 28(24): 2305-13. PMID 19421140
29. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med. Sep 16 2010; 363(12): 1117-27. PMID 20843246
30. Rambaldi A, Dellacasa CM, Finazzi G, et al. A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. Br J Haematol. Aug 2010; 150(4): 446-55. PMID 20560970
31. Santos FP, Kantarjian HM, Jain N, et al. Phase 2 study of CEP-701, an orally available JAK2 inhibitor, in patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis. Blood. Feb 11 2010; 115(6): 1131-6. PMID 20008298
32. Quintas-Cardama A, Verstovsek S. Spleen deflation and beyond: the pros and cons of Janus kinase 2 inhibitor therapy for patients with myeloproliferative neoplasms. Cancer. Feb 15 2012; 118(4): 870-7. PMID 21766300
33. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. Mar 01 2012; 366(9): 799-807. PMID 22375971
34. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. Mar 01 2012; 366(9): 787-98. PMID 22375970
35. Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica. Apr 2015; 100(4): 479-88. PMID 25616577
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative neoplasms. Version.2.2022. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf Accessed June 14, 2022.

Documentation for Clinical Review

Please provide the following documentation:

- 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 (e.g., serum erythropoietin level)

Post Service (in addition to the above, please include the following):

- 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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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
	0027U	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
	81219	CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9
	81270	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81279	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13)
	81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; common variants (e.g., W515A, W515K, W515L, W515R)
	81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10
HCPCS	None	

Policy History

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

Effective Date	Action
07/06/2012	BCBSA Medical Policy adoption
02/22/2013	Coding update
06/30/2015	Coding update. Policy revision without position change.
09/30/2015	Coding update
09/01/2017	Policy title change from JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms.

Effective Date	Action
	Policy revision without position change.
05/01/2018	Coding update
09/01/2018	Policy revision without position change
10/01/2019	Policy revision without position change
10/01/2020	Annual review. Policy statement, guidelines and literature updated.
12/01/2020	Administrative update. Policy statement updated.
01/01/2021	Coding update
10/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.
05/01/2022	Administrative update.
10/01/2022	Annual review. Policy statement and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

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 and Feedback (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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms 2.04.60 **Policy Statement:** **Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). *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) such as a serum erythropoietin level below the reference range for normal. *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: I. Diagnosis of non-classic forms of myeloproliferative neoplasms (MPNs) II. Molecular phenotyping of patients with myeloproliferative neoplasms III. Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms IV. Part of a large panel of genes (not otherwise allowed by another policy) instead of individual gene testing	**JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms 2.04.60** **Policy Statement:** **Note:** Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). I. *Janus kinase 2 (JAK2)* testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) such as a serum erythropoietin level below the reference range for normal. II. *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. III. *JAK2*, *MPL*, and *CALR* testing is considered **investigational** in all other circumstances including, but not limited to, the following situations: A. Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs) B. Molecular phenotyping of individuals with myeloproliferative neoplasms C. Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
	D. Part of a large panel of genes (not otherwise allowed by another policy) instead of individual gene testing