Medical Policy

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Title: Genetic Testing - JAK2, MPL and CALR Testing for Myeloproliferative Neoplasms

Description/Background

Myeloproliferative Neoplasms

Myeloproliferative neoplasms (MPNs) are rare overlapping blood diseases characterized by the production of one or more blood cell lines. The most common forms of MPNs include polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and chronic myeloid leukemia. A common finding in many MPNs is clonality, and a central pathogenic feature is 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 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 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] In 2022, both the World Health Organization 5th edition and an International Consensus Classification were published.[7,8,] Applying these criteria has been challenging because they involve complex diagnostic algorithms, rely on a morphologic assessment of uncertain consistency, and require tests that are not well-standardized or widely available, such as endogenous erythroid colony formation. An important component of the diagnostic process is a clinical and laboratory assessment to rule out reactive or secondary causes of disease.

CHRONIC MYELOID LEUKEMIA AND PHILADELPHIA CHROMOSOME

Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Classic Myeloproliferative Neoplasms

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

As noted, some diagnostic methods (eg, bone marrow microscopy) are not well-standardized,[9,10,11] and others (eg, endogenous erythroid colony formation) are neither standardized nor widely available.

Nonclassic Forms of Myeloproliferative Neoplasms

Although the most common Ph-negative MPNs include what is commonly referred to as classic forms of this disorder (PV, ET, PMF). Rare patients may show unusual manifestations of nonclassic forms of MPNs, such as chronic myelomonocytic leukemia, hypereosinophilic syndrome, systemic mastocytosis, chronic neutrophilic leukemia, or others. Reports have identified *JAK2* V617F variants in some of these cases.[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.[12]

JAK2 V617F Variant

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

The *JAK2* V617F variant was present in blood and bone marrow from a variable portion of patients with classic *BCR-ABL*-negative (ie, Ph-negative) MPNs including 65% to 97% of patients with PV, 23% to 57% with ET, and 35% to 56% with PMF (Table 1). The variant was initially reported to be absent in all normal subjects and patients with secondary erythrocytosis,[1,11-21] although very low levels of cells carrying the variant have been reported in a small subset of healthy individuals.[22,23]

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

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

Study	Variant Detection Method	PV	ET	PMF	Normals	Secondary Erythrocytosis
Baxter et al (2005) [11]	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) [13]	DNA sequencing	121/164 (74)	37/115 (32)	16/46 (35)	0/269 (0)	NR
James et al (2005) [14]	DNA sequencing	40/45 (88)	9/21 (43)	3/7 (43)	0/15 (0)	0/35 (0)
Kralovics et al (2005) [15]	DNA sequencing	83/128 (65)	21/94 (23)	13/23 (56)	0/142 (0)	0/11 (0)
Tefferi et al (2005) [16]	PCR testing	36/38 (95)	12/46 (55)	3/10 (30)	NR	0/19 (0)
Zhao et al (2005) [17]	DNA sequencing	20/24 (83)	NR	NR	0/12 (0)	NR
Campbell et al (2005) [18]	PCR testing	NR	414/776 (53)	NR	NR	NR
Wolanskyj et al (2005) [19]	PCR testing	NR	73/150 (49)	NR	NR	NR
Campbell et al (2006) [20]	PCR testing	NR	NR	83/152 (55)	NR	NR
Tefferi et al (2005) [21]	PCR testing	NR	NR	80/157 (51)	NR	NR

Values are n/N (%).
ET: essential thrombocythemia; MPN: myeloproliferative neoplasm; NR: not reported; PCR: polymerase chain reaction; PMF: primary myelofibrosis; PV: polycythemia vera.
In vivo, mice irradiated and then given transplanted bone marrow cells infected with a retrovirus containing the variant developed a myeloproliferative syndrome.[14]

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.[24] 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.[25,26] Based on these findings, it was 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.[24]

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.[27]

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

Ph-Negative MPNs	*JAK2* Somatic Variant Detected, % of Patients	*CALR* Somatic Variant Detected, % of Patients	*MPL* Somatic Variant Detected, % of Patients
Polycythemia vera	• *JAK2* V617F, 95 • *JAK2* exon12 variants, 5		
Essential thrombocythemia	*JAK2* V617F, 60-65	*CALR* exon 9 indels, 20-25	*MPL* exon 10 variants, 5
Primary myelofibrosis	*JAK2* V617F, 60-65	*CALR* exon 9 indels, 20-25	*MPL* exon 10 variants, 5

Adapted from Cazzola et al (2014).[27]
indels: insertions and deletions; MPN: myeloproliferative neoplasm; Ph: Philadelphia chromosome.

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::ABL* rearrangement negative (ie, Ph-negative) MPNs.[28] 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 Philadelphia Chromosome -Negative Myeloproliferative Neoplasms

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.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *JAK2, CALR*, and *MPL* testing under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

JAK2 testing is **established**. It may be considered a useful diagnostic option for individuals presenting with clinical, laboratory or pathologic findings suggesting polycythemia vera, essential thrombocythemia, or primary myelofibrosis.

MPL and *CALR* testing are **established**. They may be considered useful diagnostic options for individuals presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis.

The use of a genomic panel for hematolymphoid neoplasms may be considered appropriate for the diagnosis and for selecting the therapy of a myeloproliferative disorder or myelodysplastic syndrome.

The peer reviewed medical literature has not yet demonstrated the clinical utility for *JAK2, MPL* and *CALR* testing in other circumstances. Therefore, these services are considered **experimental/investigational**.

Inclusionary and Exclusionary Guidelines

Inclusions:

JAK2 testing as a diagnostic option for individuals presenting with clinical, laboratory or pathologic findings suggesting polycythemia vera, essential thrombocythemia, or primary myelofibrosis.

MPL and *CALR* testing as diagnostic options for individuals presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis.

The use of a genomic panel for hematolymphoid neoplasms may be considered appropriate for the diagnosis and for selecting the therapy of a myeloproliferative disorder or myelodysplastic syndrome.

Exclusions:

JAK2, MPL and *CALR* testing in other circumstances including, but not limited to, the following:

- Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs)
- Molecular phenotyping of individuals with MPNs

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81219	81270	81279	81338	81339
81450	81455			
0017U*	0027U			

* Effective August 1, 2017, there is a code specific to the University of Iowa's JAK2 mutation 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

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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 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.[29] 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; 2022, 5th edition) criteria and the International Consensus Classification (2022) 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 and MPF.[6,7,8]

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 (2022, 5th edition) and the International Consensus Classification (2022) diagnostic criteria incorporated the *JAK2* V617F variants for PV, ET, and PMF and *JAK2* exon 12 variants for PV and MPF.

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 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.[30] 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.[31,32,33] 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.[34]

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 pos-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]).[35] 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).[36] 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 overall survival 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.[37] 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 of 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 overall survival, 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 overall survival 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 study drug developed urinary tract infections and herpes zoster, although the incidence of these infections did not increase with 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: Clinical 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 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
See information under the first indication.

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.[29] 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 (2022, 5th edition) and International Consensus Classification (2022) 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.[6,7,8]

Section Summary: Clinically Valid

Evidence of the clinical validity of *MPL* exon 10 variant testing 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 (2022, 5th edition) and International Consensus Classification (2022) 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, more effective therapy, or avoid unnecessary therapy or 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 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: Clinical Useful

Direct evidence for the clinical utility of *MPL* testing is lacking. While, *MPL* exon 10 testing has potential clinical utility in diagnosing ET and PMF using the WHO (2022, 5th edition) and International Consensus Classification (2022) 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 *MPL* is included in the WHO (2022, 5th edition) and International Consensus Classification (2022) major criteria and the National Comprehensive Cancer Network guidelines (2024) for MPNs, *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 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 decision 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

See information under the first indication.

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.[29] 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 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 (2022, 5th edition) and International Consensus Classification (2022) 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 (2022, 5th edition) and International Consensus Classification (2022) major criteria and the National Comprehensive Cancer Network guidelines (2024) for MPNs, *CALR* testing maybe 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 myeloproliferative neoplasm (MPN) who receive genetic testing for *JAK2*, the evidence includes case series, retrospective studies, meta-analyses, and randomized controlled trials. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *JAK2* variants are found in nearly 100% of those with polycythemia vera (PV), 60% to 65% of those with essential thrombocythemia (ET), and 60% to 65% of those with primary

myelofibrosis (PMF). In individuals with suspected MPN, a positive genetic test for *JAK2* satisfies a major criterion for the International Consensus Classification (2022) and World Health Organization (WHO) 2022 (5th edition) classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocythemia from the differential diagnosis. The presence of a documented *JAK2* variant may aid in the selection of ruxolitinib, a *JAK2* inhibitor; ruxolitinib, however, is classified as second-line therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *MPL*, the evidence includes case series and retrospective studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. For 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 International Consensus Classification (2022) and WHO (2022, 5th edition) classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *MPL* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *MPL* genetic testing does not in and of itself result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *CALR*, the evidence includes case series and retrospective studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and resource utilization. For 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 International Consensus Classification (2022) and WHO (2022, 5th edition) classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *CALR* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *CALR* genetic testing does not result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Given that genetic testing for *MPL and CALR* variants is included in the WHO (2022, 5th edition) and International Consensus Classification (2022) major criteria and the National Comprehensive Cancer Network guideline (2024) for MPNs, *MPL,* and *CALR* testing may be consistent with clinical practice in the diagnosis of patients with clinical, laboratory, or pathological findings suggesting ET and PMF.

SUPPLEMENTAL INFORMATION

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 2022 (5th edition) World Health Organization (WHO) major criteria for myeloproliferative neoplasms (MPNs) are unchanged from the 2016 (4th edition) criteria and are as follows[6,7]

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

International Consensus Classification

In 2022, an international clinical advisory committee endorsed by the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP) published a new classification schema for myeloid neoplasms and acute leukemias.[8.] Many of the clinical advisory committee authors were authors on the 2016 (4th edition) of the WHO criteria, but the International Consensus Classification was developed independently of the WHO. The gene-related major criteria for MPNs are as follows:

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

For PV, it is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level , <1%); in negative cases, searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15 can be considered. For ET and MPF, it is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level , <1%) and *CALR* and *MPL* (sensitivity level, 1% to 3%); in negative cases, a search for noncanonical *JAK2* and *MPL* mutations can be considered. Other clonal markers that can be assessed in MPF include mutations associated with myeloid neoplasms (eg, *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2*, and *TET2* mutations).

National Comprehensive Cancer Network
The National Comprehensive Cancer Network published guidelines (v.2.2024) on the workup, diagnosis, and treatment of suspected myeloproliferative neoplasms.[38] For patients with suspicion of MPNs, the guidelines recommend "molecular testing (blood or bone marrow) for *JAK2* V617F mutation; if negative, test for *CALR* and *MPL* mutations (for patients with ET and MF) and *JAK2* Exon 12 mutations (for patients with PV) or molecular testing using multigene NGS [next-generation sequencing] panel that includes *JAK2, CALR, and MPL*.Once an MPN diagnosis is confirmed, NGS is recommended for mutational prognostication."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
There is no national coverage determination (NCD) for *JAK2, MPL* or *CALR* testing for myeloproliferative neoplasms. In the absence of an NCD, coverage decisions are left to the discretion of the local Medicare carriers.

Local:
Wisconsin Physicians Service Insurance Corporation [08202]
Local Coverage Determination (LCD): MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease (L36815)
Original Effective Date 02/16/2017; Revision Effective Date 07/06/2023

Coverage Guidance
Coverage Indications, Limitations, and/or Medical Necessity

This policy provides coverage for multi-gene non-next generation sequencing (NGS) panel testing and NGS testing for the diagnostic workup for myeloproliferative disease (MPD), also known as myeloproliferative neoplasms (MPNs), and limited coverage for single-gene testing of patients with BCR-ABL negative MPD. BCR-ABL negative MPD includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

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

1. BCR-ABL negative test results, progress to #2
2. JAK 2, cv negative test results, progress to #3 or #4
3. JAK, exon 12 (JAK2 exon 12 is only done when PV is suspected)
4. Calreticulin (CALR)/MPL (CALR/MPL is only done when either ET or PMF is suspected; testing for CALR/MPL does NOT require a negative JAK2 exon 12, just a negative JAK2 V617F result)

Genetic testing of the JAK2 V617F mutation is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet World Health Organization's (WHO) diagnostic criteria for myeloproliferative disease (i.e., PV, ET, PMF) **if** JAK2 V617F were identified.

Genetic testing of JAK2 exon 12, performed to identify PV, is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet WHO's diagnostic criteria for PV, if JAK2 exon 12 testing were positive; **and**
- JAK2 V617F mutation analysis was previously completed and was negative.

Genetic testing of the CALR gene (only found in ET and PMF) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet WHO's diagnostic criteria for MPD (i.e. ET, PMF) if a clonal marker were identified.

Genetic testing of the MPL gene is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet WHO's diagnostic criteria for MPD (i.e., ET, PMF) if a clonal marker were identified.

Note: In a single-gene sequential approach (not mandated by this policy), CALR would be a higher priority single gene test than MPL because:

- CALR mutations is more prevalent than MPL mutations in ET/PMF patients; and
- CALR mutations are reported to predict a more indolent disease course than that of patients with JAK2 mutations.

For laboratories performing NGS or "hotspot" testing platforms: Molecular testing for BCR-ABL, JAK 2, JAK, exon 12, and CALR/MPL genes by NGS is covered as medically necessary for the identification of myeloproliferative disorders.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Genetic Testing and Counseling
- Genetic Testing - BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
- Genetic Testing – NGS Multiple Genes (Panel) for Solid and Hematolymphoid Malignant Conditions

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 9/20/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/15	6/16/15	7/16/15	Joint policy established
9/1/16	6/21/16	6/21/16	Routine maintenance Added “Genetic Testing” to policy title Updated local Medicare coverage determination
9/1/17	6/20/17	6/20/17	Routine maintenance Added 2016 WHO criteria Updated Medicare information
11/1/17	1/12/18	1/16/18	Added CALR testing to policy Criteria and policy statements revised References and rationale updated Title changed to “Genetic Testing - JAK2, MPL and CALR Testing for Myeloproliferative Neoplasms” Previous title: “Genetic Testing - JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms” Updated Medicare LCD
11/1/18	8/21/18	8/21/18	Routine maintenance
11/1/19	8/20/19		Routine maintenance Medicaid section deleted
11/1/20	9/30/20		Routine maintenance Added 81450 to policy; added statement to MPS and to inclusions
5/1/21	2/16/21		Routine maintenance. Code update: 81279, 81338, 81339 added. Deleted: 81402, 81403
3/1/22	12/14/21		Routine maintenance. Ref 26 added
3/1/23	12/20/22		Routine maintenance (jf) Added code 81455 updated, inclusions and exclusions were updated. Removed Policy Guidelines/testing strategy from inclusion criteria and WHO criteria.

			We removed “targeted” from the medical policy statement and inclusion criteria in reference to genomic panel testing.
3/1/24	12/19/23		Routine maintenance (jf) Vendor Managed: NA Replaced patients to individuals in the policy. Added Ref: 7,8 -2024 CPT Code Update-81450 and 81455 Revised nomenclature to reflect current practice in genomic sequencing technology for somatic mutation and cancer treatment. - Code update recommended to revise nomenclature on code 81403, code was deleted from policy in 2021.
3/1/25	12/17/24		Routine maintenance (jf) Vendor Managed: NA Added code 0027U as EST MPS-Removal of “The safety and effectiveness of”

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: JAK2, MPL AND CALR TESTING FOR MYELOPROLIFERATIVE NEOPLASMS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. See Inclusionary and Exclusionary Guidelines
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.