MEDICAL POLICY

POLICY TITLE	JAK2, MPL, AND CALR TESTING FOR MYELOPROLIFERATIVE NEOPLASMS
POLICY NUMBER	MP 2.281

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

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I. POLICY

JAK2 testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera, essential thrombocythemia, or primary myelofibrosis. Based on criteria from the World Health Organization and the International Consensus Classification for diagnosis of PV, documentation of a serum erythropoietin level below the reference range for normal is recommended before *JAK2* testing (See Policy Guidelines).

MPL and *CALR* testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis.

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

- Diagnosis of non-classic forms of myeloproliferative neoplasms (MPNs)
- Molecular phenotyping of patients with MPNs
- Monitoring, management, or selecting treatment in patients with MPNs.

Policy Guidelines

Testing strategy

Individuals suspected to have polycythemia vera (PV) should first be tested for the most common finding, *JAK2* V617F (located on exon 14). If the testing is negative, further testing to detect other *JAK2* tyrosine kinase variants (e.g., in exon 12) is warranted.

Individuals suspected to have essential thrombocythemia or primary myelofibrosis should first be tested for *JAK2* variants, as noted above. If testing is negative, further testing to detect *MPL* and *CALR* variants is warranted.

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CRITERIA FOR POLYCYTHEMIA TESTING

Based on the World Health Organization (WHO) major and minor criteria (see Table PG1), documentation of serum erythropoietin level below the reference range for normal meets a minor criterion for PV. Therefore, serum erythropoietin testing is recommended before JAK2 testing.

Table PG1. WHO Diagnostic Criteria for PV

Major Criteria
□ Increased hemoglobin level (greater than 16.5 g/dL in men or greater than 16.0 g/dL in women); **or** □ Increased hematocrit (greater than 49% in men or greater than 48% in women); or
□ 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
The diagnosis of PV requires the presence of all 3 major criteria **or** the presence of the first two major criteria and the minor criterion†

† Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin levels >18.5 g/dL in men (hematocrit, 55.5%) or >16.5 g/dL in women (hematocrit, 49.5%) if major criterion number 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).

Genetics Nomenclature Update

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

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

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in the DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

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

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

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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 (CML). A common finding in many MPNs is clonality and a central pathogenic feature the detection of a somatic (acquired) pathogenic variant in disease-associated genes. Pathogenic variants in disease-associated genes result in constitutively activated tyrosine kinase enzyme or cell surface receptor.

The paradigm for the use of molecular genetics to revolutionize patient management is chronic myeloid leukemia. A unique chromosomal translocation t (9;22), the Philadelphia chromosome (Ph), leads to a unique gene rearrangement (BCR-ABL) creating a fusion gene that encodes for a constitutively active BCR-ABL fusion protein. These findings led to the development of targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions. Rarely, patients may show unusual manifestations of non-classic 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. Per World Health Organization criteria, presence of a specific variant is not needed for diagnosis of CML. The remainder of this evidence review focuses only on the non-Ph or Ph-negative MPNs and genetic testing for JAK2, CALR, and MPL.

Diagnosis and monitoring of patients with Ph-negative MPNs have been challenging because many of the laboratory and clinical features of the classic forms of these diseases can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis, or myeloid fibrosis. Additionally, these entities can be difficult to distinguish on morphologic bone marrow exam, and diagnosis can be complicated by changing disease patterns: PV and ET can evolve into PMF or undergo a leukemic transformation. A complex set of clinical, pathologic, and biologic criteria was first introduced by the Polycythemia Vera Study Group in 1996 and by the World Health Organization as a benchmark for diagnosis in 2002 and updated in 2008 and 2016. Applying these criteria has been challenging because they involve complex diagnostic algorithms, rely on amorphologic assessment of uncertain consistency, and require tests that are not well-standardized or widely available, such as endogenous erythroid colony formation. An important component of the diagnostic process is a clinical and laboratory assessment to rule out reactive or secondary causes of disease.

Chronic Myeloid Leukemia and Philadelphia Chromosome

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 and others (e.g., endogenous erythroid colony formation) are neither standardized nor widely available.

Non-classic Forms of MPNs

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

Molecular Genetics of Philadelphia Chromosome-Negative MPNs

JAK2 Gene

The *JAK2* gene, located on chromosome 9, contains the genetic code for making the Janus kinase 2 (JAK) protein, a nonreceptor tyrosine kinase. The JAK2 protein is part of the JAK/signal transduction pathway and activators of transcript (STAT) proteins that are important for the controlled production of blood cells from hematopoietic cells. Somatic (acquired) variants in the *JAK2* gene are found in patients with PV, ET, and PMF.

JAK2 V617F Variant

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

The *JAK2* V617F variant was present in blood and bone marrow from a variable portion of patients with classic *BCR-ABL*-negative (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, although very low levels of cells carrying the variant have been reported in a small subset of healthy individuals.

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

Table 1. Frequency of the *JAK2* V617FVariant 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)	DNA sequencing, PCR	71/73 (97)	29/51 (57)	8/16 (50)	0/90 (0)	NR
Jones et al (2005)	PCR testing	58/72 (81)	24/59 (41)	15/35 (43)	0/160 (0)	0/4 (0)
Levine et al (2005)	DNA sequencing,	121/164 (74)	37/115 (32)	16/46 (35)	0/269 (0)	NR
James et al (2005)	DNA sequencing	40/45 (88)	9/21 (43)	3/7 (43)	0/15 (0)	0/35 (0)
Kralovics et al (2005)	DNA sequencing	83/128 (65)	21/94 (23)	13/23 (56)	0/142 (0)	0/11 (0)
Tefferi et al (2005)	PCR testing	36/38 (95)	12/46 (55)	3/10 (30)	NR	0/19 (0)
Zhao et al (2005)	DNA sequencing	20/24 (83)	NR	NR	0/12 (0)	NR
Campbell et al (2005)	PCR testing	NR	414/776 (53)	NR	NR	NR
Wolanskyj et al (2005)	PCR testing	NR	73/150 (49)	NR	NR	NR
Campbell et al (2006)	PCR testing	NR	NR	83/152 (55)	NR	NR
Tefferi et al (2005)	PCR testing	NR	NR	80/157 (51)	NR	NR

JAK2 Exon 12 Variants

Scott et al (2007) identified 4 somatic gain-of-function variants in *JAK2* exon 12 in 10 of 11 PV patients without the *JAK2* V617F variant. Patients with a *JAK2* exon 12 variant differed from those with the *JAK2* V617F variant, presenting at a younger age with higher hemoglobin levels and lower platelet and white cell counts. Erythroid colonies could be grown from their blood samples in the absence of exogenous erythropoietin, and mice treated with transfected bone marrow transplants developed a myeloproliferative syndrome.

Findings have been confirmed by a number of investigators who identified additional variants with similar functional consequences in patients with PV and patients with idiopathic erythrocytosis. Based on these findings, it has been concluded that the identification of *JAK2* exon 12 variants provides a diagnostic test for *JAK2* V617F-negative patients who present with erythrocytosis. Of note, different variants in the same gene appear to have different effects on signaling, resulting in distinct clinical phenotypes.

MPL Gene

The *MPL* gene, located on chromosome 1, contains the genetic code for making the thrombopoietin receptor, a cell surface protein that stimulates the JAK/STAT signal transduction pathway. The thrombopoietin receptor is critical for the cell growth and division of megakaryocytes, which produce platelets involved in blood clotting. Somatic variants in the *MPL* gene are associated with ET and PMF.

CALR Gene

The *CALR* gene, located on chromosome 19, contains the genetic code for making the calreticulin protein, a multifunctional protein located in the endoplasmic reticulum, cytoplasm, and cell surface. The calreticulin protein is thought to play a role in cell growth and division and regulation of gene activity. Somatic variants in the *CALR* gene are associated with ET and PMF.

Frequency of *JAK2*, *CALR*, and *MPL* Somatic Variants in Philadelphia Chromosome-Negative Myeloproliferative Neoplasms

Philadelphia chromosome-negative MPNs are characterized by their molecular genetic alterations. Table 2 summarizes the driver genes and somatic variants associated with specific Ph-negative MPNs.

Table 2. Frequency of *JAK2*, *CAL4*, and *MPL* Somatic Variants in Ph-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 exon 12 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).

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. 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%

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.

IV. RATIONALE

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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.

Additional Information

Given that genetic testing for *MPL and CALR* variants is included in the WHO (2022, 5th edition) and International Consensus Classification (2022) major criteria and the National Comprehensive Cancer Network 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.

V. DEFINITIONS

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NA

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
0017U	0027U	81219	81270	81279	81338	81339		

ICD-10-CM Diagnosis Codes	Description
D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease
D47.3	Essential (hemorrhagic) thrombocythemia

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.281	**03/19/2020 Consensus Review.** No change to policy statements. References updated; coding reviewed.
	09/22/2020 Administrative Update. New CPT codes 81279, 81338, 81339 effective 01/01/2021 were added.
	10/13/2021 Consensus Review. No change to policy statements, NCCN statement added. Description/background section and references updated, FEP statement revised.
	12/02/2022 Consensus Review. No change to policy statement. Updated background and references. No coding changes.
	04/27/2023 Minor Review. Deleted criteria regarding serum erythropoietin level in the statement and the policy guidelines. Updated policy guidelines, background, rationale, coding table and references.
	05/30/2024 Consensus Review. Updated policy guidelines, background, and references. No changes to coding.
	11/19/2024 Administrative Update. Removed NCCN statement.
	05/06/2025 Minor Review. Added statement regarding serum erythropoietin level for PV. Updated policy guidelines, background, summary of evidence, and references. No changes to coding.
	09/09/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	02/10/2026 Retirement Review. Evicore delegation

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MEDICAL POLICY

POLICY TITLE	JAK2, MPL, AND CALR TESTING FOR MYELOPROLIFERATIVE NEOPLASMS
POLICY NUMBER	MP 2.281

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