MEDICAL POLICY

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Medical Policy Title	**JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms**
Policy Number	**2.02.53**
Current Effective Date	**March 19, 2026**
Next Review Date	**March 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service. (Link to Product Disclaimer)

POLICY STATEMENT(S)

Myelofibrosis (MF) and Essential Thrombocythemia (ET)

I. Molecular testing for suspicion of myelofibrosis (MF) or Essential Thrombocythemia (ET) is considered **medically necessary** when **ALL** of the following criteria are met:
   A. Test is completed on blood or bone marrow;
   B. Patient presents with clinical, laboratory, or pathologic findings suggesting MF or ET;
   C. After evaluation for secondary causes; **and**
   D. For **ANY** of the following molecular mutations:
      1. Janus kinase 2 (JAK2);
      2. Myeloproliferative Leukemia (MPL); **or**
      3. Calreticulin (CALR).

Polycythemia Vera (PV)

II. Molecular testing for suspicion of PV is considered **medically necessary** when **ALL** of the following criteria are met:
   A. Test is completed on blood or bone marrow;
   B. Patient is presenting with clinical, laboratory, or pathologic findings suggesting PV;
   C. Evaluation for secondary causes have been completed;
   D. Test is for molecular mutations JAK2.

III. JAK2, MPL, and CALR testing is considered **investigational** in all other circumstances including, but not limited to, the following indications:
   A. Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs);
   B. Molecular phenotyping of patients with MPNs.

Panel Testing

IV. Broad molecular panel testing has not been medically proven to be effective and, therefore, is considered **investigational**.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization, not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Patients suspected to have polycythemia vera (PV) should first be tested for JAK2 V617F. If the testing is negative, further testing to detect other JAK2 tyrosine kinase variants (e.g., in exon 12) is warranted.

V. Patients suspected of having essential thrombocythemia (ET) or primary myelofibrosis (PMF) should first be tested for JAK2 V617F mutation. If testing is negative, further testing to detect MPL and CALR variants is warranted.

VI. 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.

VII. It is recommended by NCCN to use highly sensitive assays for JAK2 V617F (sensitivity level <1%) and CALR and MPL (sensitivity level 1%–3%) in negative cases, consider searching for non-standard or atypical JAK2 mutations.

VIII. Multigene NGS may be useful to establish clonality in selected circumstances (e.g., triple-negative non-mutated JAK2, MPL, and CALR) and to detect high-molecular-risk mutations associated with myeloid neoplasms (e.g., ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2, and TET2 mutations).

DESCRIPTION

Myeloproliferative Neoplasms (MPNs)

MPNs are hematologic malignancies classified as myeloid vs lymphoid and then further subdivided into acute and chronic. Myeloproliferative neoplasms are a subsect of chronic myeloid disorders that usually exhibit terminal expansion in the peripheral blood as opposed to the bone marrow. MPNs cause thrombocytosis and erythrocytosis in the peripheral blood. The four main types of MPNs are PV (Polycythemia Vera), ET (Essential Thrombocythemia), PMF (primary myelofibrosis), and CML (chronic myeloid leukemia).

MPN, unclassifiable is an appropriate diagnosis for cases presenting with clinical, morphologic, and molecular features that prevent a clear diagnosis of a specific MPN subtype. In addition, this category is appropriate for patients presenting in very early phase disease in which the required diagnostic features are not yet fully developed and relevant diagnostic thresholds not met (Arber 2022).

Janus Kinase 2 (JAK2)

JAK2 tyrosine kinase 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. A JAK2 mutation keeps the JAK2 protein switched on all the time. This leads to a subsequent uncontrolled cell proliferation in hematocrit, red blood cells, and platelets, and subsequent decrease in erythropoietin level. Somatic (acquired) variants in the JAK2 gene are found in patients with MPNs such as PV, ET, and PMF. There are two JAK2 variants associated with MPN disorders, the JAK2 V617F variant and JAK2 Exon 12 Variants (4 different variants). The JAK2 V617F gene is found in 95% of patients with PV, 60% to 65% of patients with ET, and 60 to 65% of patients with PMF. JAK2 exon 12 variants are also found in 5% of PV cases.

Myeloproliferative Leukemia (MPL)

The MPL gene, located on chromosome 1, contains the genetic code for making the thrombopoietin receptor, a cell surface protein, which 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.

Calreticulin (CALR)

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.

The International Consensus Classification (ICC) and World Health Organization (WHO) Diagnostic Criteria

Polycythemia Vera

Major criteria

1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass.
2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia.
3. Presence of JAK2 V617F or JAK2 exon 12 mutation.

Minor criteria

1. Subnormal serum erythropoietin level.

The diagnosis of PV requires either all three (3) major criteria or the first two (2) major criteria plus the minor criterion.

Primary Myelofibrosis

Major criteria

1. Bone marrow biopsy showing megakaryocytic proliferation and atypia, bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased. erythropoiesis
2. JAK2, CALR, or MPL mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis.
3. Diagnostic criteria for BCR: ABL1-positive CML, PV, ET, Myelodysplastic syndromes, or other myeloid neoplasms are not met.

Minor criteria

1. Anemia not attributed to a comorbid condition.
2. Leukocytosis ≥11 x 10^9/L.
3. Palpable splenomegaly.
4. Lactate Dehydrogenase (LDH) level above the above reference range.

The diagnosis of pre-PMF or overt PMF requires all three (3) major criteria and at least one (1) minor criterion confirmed in two (2) consecutive determinations.

Essential Thrombocythemia

Major criteria

1. Platelet count ≥450 × 10^9/L.

2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant bone marrow fibrosis.
3. Diagnostic criteria for BCR: ABL1-positive CML, PV, PMF, or other myeloid neoplasms are not met.
4. JAK2, CALR, or MPL mutation.

Minor criteria

1. Presence of a clonal marker or absence of evidence of reactive thrombocytosis

The diagnosis of ET requires either all major criteria or the first three (3) major criteria plus the minor criteria.

SUPPORTIVE LITERATURE

Soderquist et al (2024) evaluated ordering practices, prior authorization requirements, clinical impact, and reimbursement outcomes from 477 individuals with known or suspected myeloid malignancies that underwent testing with either a 50-gene myeloid next generation sequencing (NGS) panel or a 15-gene myeloproliferative neoplasm subpanel. The results determined that 98% (496/505) of all test outcomes afforded helpful clinical data; 89% of results either led to a diagnosis or clarified a potential diagnosis, 94% provided information regarding possible prognoses, and 19% detected a potential therapeutic target. The study results show that use of a broad NGS panel significantly improves diagnostic and prognostic yield when compared to limited testing of Individual genes such as JAK2, CALR, and MPL and add to the existing evidence supporting the broad clinical usefulness of NGS tests in individuals with myeloid neoplasia.

Grinfeld et al (2018) conducted a multicenter study. They sequenced coding exons from 69 myeloid cancer genes in 2035 individuals with MPN. From those individuals they developed a genomic classifier for MPNs and multistage prognostic models to predict individual outcomes. Results showed that 33 genes carried a driver mutation in less than 4 individuals, with JAK2, CALR, or MPL as the only abnormality detected in 45% individuals. Volumes of driver mutations increased in parallel with age and advancement of disease. Demographic variables, germline polymorphisms, and driver mutations independently predicted disease and eight genomic subgroups with distinct clinical phenotypes were defined. Ultimately, prognostic models which could generate tailored prediction of clinical outcomes in individuals with chronic-phase myeloproliferative neoplasms and myelofibrosis were created. They predicted/observed outcomes correlated in internal cross-validation of a training group and an independent external group. The conclusion was that characterization may enable personalized prediction of outcomes and better support individuals diagnosed with myeloproliferative neoplasms.

PROFESSIONAL GUIDELINE(S)

National Comprehensive Cancer Network (NCCN) Version 1.2026 for Myeloproliferative Neoplasms

"Molecular testing (blood or bone) with multigene panel testing to detect driver mutations (JAK2, CALR, MPL) and other pathogenic variants for diagnosis and prognostic risk stratification."

The ICC of Myeloid Neoplasm and Acute Leukemias 2022

Accurate identification of MPN-associated driver mutations, JAK2 V617F, JAK2 exon 12, MPL W515L/K, and calreticulin (CALR) by highly sensitive single target (quantitative reverse transcriptase-polymerase chain reaction [RT-qPCR], digital droplet PCR [ddPCR]) or multitarget panel/NGS assays with a minimal sensitivity of variant allele frequency (VAF) 1%, is important to support a diagnosis of PV, ET, or PMF and to separate wild-type or triple-negative cases. In triple-negative cases, the search for noncanonical JAK2 and MPL mutations (the latter for suspected ET and PMF) is encouraged, whereas a JAK2 V617F VAF of <1% should prompt the search for coexisting standard CALR (and MPL) mutations. In PV, high VAF for JAK2 V617F is associated with older age, higher hemoglobin level, leukocytosis, and lower platelet count. JAK2 exon 12 mutated cases are prognostically similar to JAK2 V617F mutated cases, although they may occur at a younger age. Because a proportion of these cases may be characterized by isolated erythrocytosis associated with erythroid preponderance in the BM, the diagnostic criterion of panmyelosis may not be applicable to this patient subset (Arber, 2022).

REGULATORY STATUS

Not Applicable

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
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)

Code	Description
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81450 (E/I)	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81451 (E/I)	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
81455 (E/I)	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81456 (E/I)	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
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 (JAK2 Mutation, University of Iowa, Department of Pathology)
0027U	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15 (JAK2 Exons 12 to 15 Sequencing, Mayo Clinic, Mayo Clinic)
0592U (E/I)	Oncology (hematolymphoid neoplasms), DNA, targeted genomic sequence of 417 genes, interrogation for gene fusions, translocations, rearrangements, utilizing formalin-fixed paraffin- embedded (FFPE) tumor tissue, results report clinically significant variant(s) (Effective 10/01/25) (Aventa Lymphoma, Aventa Genomics, LLC)

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
C96.2	Malignant mast cell tumors
C92.10-C92.12	Chronic myeloid leukemia code range
D45	Polycythemia vera
D47.3	Essential (hemorrhagic) thrombocythemia
D47.4	Osteomyelofibrosis

REFERENCES

American Society of Hematology, from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127:2391.

Arber DA, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022 Sep 15;140(11):1200-1228.

Baxter EJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005 Mar; 365(9464): 1054-61.

Campbell PJ, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet. 2005 Dec; 366(9501):1945-53.

Cazzola M and Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood. 2014 Jun;123(24):3714-9.

James C, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature. 2005 Apr 28;434(7037):1144-8.

Campbell PJ, et al. V617F mutation in JAK2 is associated with poorer survival in idiopathic myelofibrosis. Blood. 2006 Mar 01;107(5):2098-100.

Chen K, Shih AH. Murine modeling of myeloproliferative neoplasms. Hematol Oncol Clin North Am. 2021 Apr;35(2):253-265.

Dickstein JI and Vardiman JW. Hematopathologic findings in the myeloproliferative disorders. Semin Oncol. 1995 Aug;22(4):355-73.

Easwar A, Siddon AJ. Genetic landscape of myeloproliferative neoplasms with an emphasis on molecular diagnostic laboratory testing. Life (Basel). 2021 Oct 30;11(11):1158.

Grinfeld J, et al. Classification and personalized prognosis in myeloproliferative neoplasms. N Engl J Med. 2018 Oct 11;379(15):1416-1430.

Harrison C, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl JMed. 2012 Mar 01;366(9):787-98.

Hussein K, et al. Chronic myeloproliferative diseases with concurrent BCR-ABL junction and JAK2V617F mutation. Leukemia. 2008 May;22(5):1059-62.

Jang MA, Choi CW. Recent insights regarding the molecular basis of myeloproliferative neoplasms. Korean J Intern Med. 2020 Jan;35(1):1-11.

Kanagal-Shamanna R, et al. Myelodysplastic/myeloproliferative neoplasms-unclassifiable with isolated isochromosome 17q represents a distinct clinico-biologic subset: a multi-institutional collaborative study from the Bone Marrow Pathology Group. Mod Pathol. 2022 Apr;35(4):470-479.

Khoury JD, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022 Jul;36(7):1703-1719.

Kralovics R, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. 2005 Apr 28;352(17):1779-90.

Kvasnicka HM. The differential diagnosis of classical myeloproliferative neoplasms (MPN): the updated WHO criteria. Rinsho Ketsueki. 2019;60(9):1166-1175.

Lee J, et al. Genomic heterogeneity in myeloproliferative neoplasms and applications to clinical practice. Blood Rev. 2020 Jul;42:100708.

Levine RL, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell. 2005 Apr;7(4):387-97.

Li W. The 5th edition of the World Health Organization classification of hematolymphoid tumors. Brisbane (AU): Exon Publications. 2022 Oct 16. Chapter 1.

Makarik TV, et al. Low JAK2 V617F allele burden in Ph-negative chronic myeloproliferative neoplasms is associated with additional CALR or MPL gene mutations. Genes (Basel). 2021 Apr 12;12(4):559.

Mejía-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. 2019 Jun 17;19(1):590.

Mesa RA, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer. 2007 Jan 1;109(1):68-76.

National Comprehensive Cancer Network (NCCN) [Internet]. NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative neoplasms. Version.1.2026. 2026 Jan 22 [accessed 2026 Feb 10] available from: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf

NIH Genetics Home Reference [Internet]. JAK2 gene: Janus kinase 2. 2014 Sep 1 [accessed 2026 Feb 10] available from: https://ghr.nlm.nih.gov/gene/JAK2

Siemiatkowska A, et al. JAK2 and MPL gene mutations in V617F-negative myeloproliferative

neoplasms. Leuk Res. 2010 Mar;34(3):387-9.

Soderquist CR, et al. Clinical utility and reimbursement of next-generation sequencing-based testing for myeloid malignancies. J Mol Diagn. 2024 Jan;26(1):5-16.

Stivala S, Meyer SC. Recent advances in molecular diagnostics and targeted therapy of myeloproliferative neoplasms. Cancers (Basel). 2021 Oct 9;13(20):5035.

Tefferi A, et al. Concomitant neutrophil JAK2 mutation screening and PRV-1 expression analysis in myeloproliferative disorders and secondary polycythaemia. Br J Haematol. 2005 Oct;131(2):166-71.

Tefferi A, et al. The JAK2(V617F) tyrosine kinase mutation in myelofibrosis with myeloid metaplasia: lineage specificity and clinical correlates. Br J Haematol. 2005 Nov;131(3):320-8.

Verstovsek S, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J. Med. 2012 Mar 01;366(9):799-807.

Verstovsek S, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica. 2015 Apr;100(4):479-88.

Wolanskyj AP, et al. JAK2 mutation in essential thrombocythaemia: clinical associations and longterm prognostic relevance. Br J Haematol. 2005 Oct;131(2) 208-13.

Xia D, Hasserjian RP. Molecular testing for JAK2, MPL, and CALR in myeloproliferative neoplasms. Am J Hematol. 2016 Dec;91(12):1277-1280.

Zhao R, et al. Identification of an acquired JAK2 mutation in polycythemia vera. J Biol Chem. 2005 Jun 17;280(24):22788-92.

SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Molecular Pathology Procedures (LCD L35000) [accessed 2026 Feb 10]

Article - Billing and Coding: Molecular Pathology Procedures (A56199) [accessed 2026 Feb 10]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.

- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
06/17/21, 04/21/22, 03/23/23, 03/21/24, 05/22/25, 03/19/26	
Date	**Summary of Changes**
03/19/26	• Annual review. Policy intent unchanged.
05/22/25	• Annual review. Policy statement added for broad molecular panels considered investigational.
01/01/25	• Summary of changes tracking implemented.
06/17/21	• Original effective date