

## Mutation Analysis in Myeloproliferative Neoplasms

Policy Number: AHS – M2101 – Mutation Analysis in Myeloproliferative Neoplasms	Policy Revision Date: 07/01/2025 Initial Policy Effective Date: 12/01/2024
--	---

[POLICY DESCRIPTION](#) | [RELATED POLICIES](#) | [INDICATIONS AND/OR LIMITATIONS OF COVERAGE](#) | [TABLE OF TERMINOLOGY](#) | [SCIENTIFIC BACKGROUND](#) | [GUIDELINES AND RECOMMENDATIONS](#) | [APPLICABLE STATE AND FEDERAL REGULATIONS](#) | [APPLICABLE CPT/HCPCS PROCEDURE CODES](#) | [EVIDENCE-BASED SCIENTIFIC REFERENCES](#) | [REVISION HISTORY](#)

### I. Policy Description

Myeloproliferative neoplasms (MPN) are a heterogeneous group of clonal disorders characterized by overproduction of one or more differentiated myeloid lineages.<sup>1</sup> These include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The majority of MPN result from somatic mutations in the three driver genes, *JAK2*, *CALR*, and *MPL*, which represent major diagnostic criteria in combination with hematologic and morphological abnormalities.<sup>2</sup>

Terms such as male and female are used when necessary to refer to sex assigned at birth.

### II. Related Policies

Policy Number	Policy Title
AHS-M2182	Genomic Testing for Hematopoietic Neoplasms

### III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) For the diagnosis of individuals presenting with clinical, laboratory, or pathological findings suggesting classic forms of myeloproliferative neoplasms (MPN) (e.g., polycythemia vera [PV], essential thrombocythemia [ET], or primary myelofibrosis [PMF]), *JAK2*, *CALR*, or *MPL* mutation testing **MEETS COVERAGE CRITERIA** in any of the following situations:
  - a) For individuals suspected to have PV who meet at least **one** of the following testing criteria:
    - i) Hemoglobin greater than 16.5 g/dL in men or greater than 16.0 g/dL in women; **or** hematocrit greater than 49% in men or greater than 48% in women; **or** increased red cell mass (more than 25% above mean normal predicted value), **and** no other known cause of erythrocytosis, when measured on two separate occasions.
    - ii) A bone marrow (BM) biopsy showing hypercellularity for age with trilineage hyperplasia including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size).

- b) For individuals suspected to have ET who meet at least **one** of the following testing criteria:
  - i) Platelet count greater than or equal to  $450 \times 10^9/L$  that has persisted for more than three months.
  - ii) A BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers.
- c) For individuals suspected to have PMF who meet at least **one** of the following testing criteria:
  - i) The individual has demonstrated leukocytosis of greater than or equal to  $11 \times 10^9/L$  on two separate occasions in the absence of other conditions that can cause leukocytosis.
  - ii) The individual has an enlarged spleen.
  - iii) A BM biopsy shows megakaryocytic proliferation and atypia, BM fibrosis Grade <2, increased age-adjusted BM cellularity, and granulocytic proliferation; may show erythropoiesis.
  - iv) A BM biopsy shows presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3.
- 2) To exclude a diagnosis of chronic myeloid leukemia (CML) for individuals with a suspected MPN, fluorescence in situ hybridization (FISH) or reverse transcriptase polymerase chain reaction (RT-PCR) testing on a peripheral blood sample to detect *BCR::ABL1* transcripts **MEETS COVERAGE CRITERIA.**
- 3) For individuals with a clinical suspicion of prePMF or overt PMF who have already tested negative for mutations in *JAK2*, *CALR*, or *MPL* and who do not meet the WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms, screening for mutations in *ASXL1*, *CBL*, *DNMT3A*, *EZH2*, *IDH1/IDH2*, *RAS*, *SRSF2*, *SFS3B1*, *TET2*, *TP53*, and *U2AF1* (see Note 1) **MEETS COVERAGE CRITERIA.**
- 4) For individuals diagnosed with Budd-Chiari Syndrome, *JAK2*, *CALR*, or *MPL* mutation testing **MEETS COVERAGE CRITERIA.**
- 5) For individuals with normal blood counts and unexplained splanchnic vein thrombosis, screening for *JAK2* V617F **MEETS COVERAGE CRITERIA.**
- 6) For individuals suspected to have chronic neutrophilic leukemia, testing for *CSF3R* mutations **MEETS COVERAGE CRITERIA.**
- 7) For individuals with a clinical suspicion of mastocytosis, screening for *KIT* D816V **MEETS COVERAGE CRITERIA.**
- 8) The above gene studies may be tested sequentially at the same time if above criteria is met for myeloproliferative disorder overlap syndromes (MPDs and MDDs), use the myelodysplastic protocol and **MEETS COVERAGE CRITERIA.**

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.*

- 9) For all other situations not described above, *JAK2* tyrosine kinase, *CALR*, and *MPL* mutation testing **DOES NOT MEET COVERAGE CRITERIA.**

**NOTES:**

**Note 1:** For two or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

**IV. Table of Terminology**

Term	Definition
<i>ABL</i>	<i>Abelson murine leukemia viral oncogene</i>
aCML	Atypical chronic myeloid leukemia
AHN	Associated Hematologic Neoplasm
ARMS	Amplification refractory mutation system
<i>ASXL1</i>	<i>additional sex combs like 1, transcriptional regulator</i>
BCR	Breakpoint cluster region
<i>BPGM</i>	<i>Bisphosphoglycerate mutase</i>
BSH	British Society for Haematology
<i>CALR</i>	<i>Calreticulin</i>
<i>CBL</i>	<i>Casitas B-lineage lymphoma proto-oncogene</i>
CELNOS	Chronic eosinophilic leukemia, not otherwise specified
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
CNL	Chronic neutrophilic leukemia
<i>CSF3R</i>	<i>Colony stimulating factor 3 receptor</i>
ddPCR	Digital droplet polymerase chain reaction
<i>DNM3TA</i>	<i>DNA methyltransferase 3 alpha</i>
EASL	European Association for the Study of the Liver
ELN	European Leukemia Net
ESMO	European Society of Medical Oncology
ET	Essential thrombocythemia
<i>EZH2</i>	<i>Enhancer of zeste 2 polycomb repressive complex 2 subunit</i>
<i>FLT3</i>	<i>Fms related receptor tyrosine kinase 3</i>
<i>FLT3-ITD</i>	<i>FLT3- internal duplications</i>
<i>HBA1</i>	<i>Hemoglobin subunit alpha 1</i>
<i>HBA2</i>	<i>Hemoglobin subunit alpha 2</i>
<i>HBB</i>	<i>Hemoglobin subunit beta</i>
HSC	Hematopoietic stem cell
HTLV	Human T-lymphotropic virus type 1
<i>IDH1</i>	<i>Isocitrate dehydrogenase (NADP(+)) 1</i>

<i>IDH2</i>	<i>Isocitrate dehydrogenase (NADP(+)) 2</i>
IR	Ionizing radiation
<i>JAK2</i>	<i>Janus Kinase 2</i>
JMML	Juvenile myelomonocytic leukemia
<i>LNK</i>	<i>Lymphocyte adapter protein</i>
MF	Myelofibrosis
MONU	MPN unclassifiable
<i>MPL</i>	<i>MPL proto-oncogene, thrombopoietin receptor</i>
MPN	Myeloproliferative neoplasms
NCCN	National Comprehensive Cancer Network
PCR	Polymerase chain reaction
PMF	Primary myelofibrosis
PV	Polycythemia vera
<i>RAS</i>	<i>Rat sarcoma virus gene</i>
<i>SETBP</i>	<i>SET binding protein</i>
<i>SF3B1</i>	<i>Splicing factor 3b subunit 1</i>
<i>SH2B3</i>	<i>SH2B adaptor protein 3</i>
<i>SM-AHN</i>	Systemic Mastocytosis with Associated Hematologic Neoplasm
<i>SRSF2</i>	<i>Serine and arginine-rich splicing factor 2</i>
STAT	Signal transducer and activator of transcription
<i>TET2</i>	<i>Tet methylcytosine dioxygenase 2</i>
<i>TP53</i>	<i>Tumor protein p53</i>
<i>U2AF1</i>	<i>U2 small nuclear RNA auxiliary factor 1</i>
WHO	World Health Organization

## V. Scientific Background

Myeloproliferative neoplasms, including PV, essential thrombocythemia (ET), and primary myelofibrosis (PMF), arise from somatic mutation in hematopoietic stem cell (HSC) that clonally expand resulting in single or multilineage hyperplasia.<sup>3</sup> They are relatively rare, affecting 0.84 (PV), 1.03 (ET), and 0.47 (PMF) per 100,000 people worldwide; however, these may not be reflective of its true incidence due to the high heterogeneity of MPN.<sup>4</sup>

Myeloproliferative neoplasms share features of bone marrow hypercellularity, increased incidence of thrombosis or hemorrhage, and an increased rate of progression to acute myeloid leukemia. Abnormalities in cytokine signaling pathways are common and usually lead to increased JAK-STAT signaling.<sup>1</sup> PV is characterized by erythrocytosis with suppressed endogenous erythropoietin production, bone marrow panmyelosis, and *JAK2* mutation leading to constitutive activation. ET is defined by thrombocytosis; bone marrow megakaryocytic proliferation; and presence of *JAK2*, *CALR*, or *MPL* mutation. PMF is characterized by bone marrow megakaryocytic proliferation; reticulin and/or collagen fibrosis; and presence of *JAK2*, *CALR*, or *MPL* mutation.<sup>2</sup> Mutations in other genes involved in signal transduction (*CBL*, *LNK/SH2B3*), chromatin modification (*TET2*, *EZH2*, *IDH1/2*, *ASXL1*, *DNM3TA*), RNA splicing (*SF3B1*, *SRSF2*, *U2AF1*), and tumor suppressor function (*TP53*) have also been reported and are considered “high-risk.”<sup>5</sup>

The gene *JAK2*, which stands for “Janus Kinase 2,” is a gene whose mutation is responsible for a significant amount of MPNs. It is a mutation that causes hypersensitivity of hematopoietic progenitor cells to other cytokines, and this mutation typically appears on red blood cells or bone marrow cells. This mutation is often found on exon 12 or 14, and the exon 14 mutation results in a cytokine-independent activation of several regulatory pathways. *JAK2* mutations contribute to at least 95% of PV cases, about 50-65% of ET cases, and 60-65% of PMF cases.<sup>6-8</sup>

The gene *MPL*, which encodes a thrombopoietin receptor, also contributes to MPNs. *MPL* mutations result in a similar phenotype to *JAK2* mutations; both result in cytokine-independent growth of their targets. However, *MPL* mutations are not nearly as common as *JAK2* and *CALR* mutations, casting doubt on the clinical utility for testing. *MPL* mutations comprise up to 4% of ET cases and 5% of PMF cases.<sup>6-8</sup>

The gene *CALR* encodes calreticulin (or calregulin), which is a Ca<sup>2+</sup> binding protein. The mutation typically involves the creation of the incorrect Ca<sup>2+</sup> binding region, thereby not allowing the protein to perform its regular duties such as maintaining calcium homeostasis. This results in a similar phenotype to the *JAK2* mutation, which is the cytokine-independent activation of regulatory pathways. *CALR* mutations contribute to approximately 15-25% of ET cases and 20-25% of PMF cases, and about 70% of ET or PMF patients without a *JAK2* or *MPL* mutation have this mutation.<sup>6-8</sup>

The significance of *JAK2*, *MPL*, *CALR* and other mutations in the genesis of the MPNs as well as their roles in determining phenotype are unclear.<sup>9</sup> However, integrated genomic analyses suggest that regardless of diagnosis or *JAK2* mutational status, MPNs are characterized by upregulation of JAK-STAT target genes, demonstrating the central importance of this pathway in the pathogenesis.<sup>10</sup> This may lead to development of novel *JAK2* therapeutics.<sup>11</sup> Thus, mutation analysis at the time of diagnosis has value for determining prognosis as well as individual risk assessment and guide treatment-making decisions.<sup>9,12</sup>

Neutrophilia, an increase in peripheral blood neutrophils at least two standard deviations above the mean, can be associated with any of the MPNs. In chronic neutrophilic leukemia (CNL), *CSF3R* mutations have been discovered in most patients with CNL.<sup>13,14</sup> A study released in 2013 reported 16 of 27 patients with CNL or atypical chronic myeloid leukemia (aCML) had activating mutations in *CSF3R*.<sup>15</sup> *SETBP1* has also been used as a part of comprehensive mutation profiling in distinguishing aCML and chronic myelomonocytic leukemia (CMML). A 2019 NGS study reports significant differences in the profiles of patients with aCML or CMML when comparing *TET2*, *SETBP1*, and *CSF3R*. The researchers conclude, “differential mRNA expression could be detected between both cohorts in a subset of genes (*FLT3*, *CSF3R*, and *SETBP1* showed the strongest correlation). However, due to high variances in the mRNA expression, the potential utility for the clinic is limited.”<sup>16</sup>

Dharmawickreme and Witharana (2023) published a 2023 review of allele burden as a valuable biomarker to incorporate in the diagnostic workflow for diagnosis of MPNs. Allele burden refers to the proportion of cells that have a mutation and reflects the ratio of mutant to wild-type *JAK2* alleles, providing key insights into disease phenotype and progression. Additionally, the level of *JAK2* allele burden differs significantly across the MPN subtypes. For example, a low allele burden is common in ET, and correlates with milder disease phenotypes. A high allele burden is frequently observed in PV and PMF and is associated with more aggressive disease and higher myeloproliferative activity.<sup>17</sup> The presence of a *JAK2* mutation and the measurement of allele burden may also help differentiate PV from secondary polycythemia (SE), and ET from reactive thrombocytosis (RT).<sup>9</sup>

Allele burden serves as a promising indicator for prognosis and outcomes for patients. Measuring allele burden can help differentiate between MPN subtypes early, often before clinical manifestation. For example, higher allele burdens are linked to phenotypic expression such as elevated hemoglobin and white blood cells counts, increased spleen size, and more pronounced symptoms in PV and a risk of evolution to post-PV myelofibrosis, PMF or acute myeloid leukemia (AML). Additionally, high allele burden can stratify the risk of thrombosis, as it is associated with a greater risk of thrombotic complications, which are a major cause of mortality in MPNs. Allele burden can also serve as a predictive factor for disease progression and the likelihood of relapse after stem cell transplantation. Thus, measuring allele burden can help serve as a marker to assess measurable residual disease (MRD) following treatment with interferon or hematopoietic cell transplantation.<sup>9</sup>

Mutation analysis can be completed with equivalent sensitivity and specificity through use of either peripheral blood granulocytes or bone marrow.<sup>9</sup> Currently, qPCR is the most widely used method for allele burden measurement as it offers high-sensitivity. Droplet digital PCR (ddPCR) is emerging as a potentially more precise quantification method. NGS also detects *JAK2* and other potential pathogenic mutations.<sup>17</sup>

### **Proprietary Testing**

In 2017 the FDA approved ipsogen® *JAK2* RGQ PCR Kit (FDA, 2017b) to detect Janus Tyrosine Kinase 2 (*JAK2*) gene mutation G1849T (V617F) with an allele-specific, quantitative, PCR using an amplification refractory mutation system (ARMS). The device marketing authorization was based on data from a clinical study of 473 suspected patients with MPNs, 276 with suspected PV, 98 with suspected ET, and 99 with suspected PMF. The study compared results from the ipsogen *JAK2* RGQ PCR Kit to results obtained with independently validated bi-directional sequencing. The study found that the ipsogen *JAK2* RGQ PCR Kit test was in 96.8% agreement with the reference method, 100% in positive agreement, and 95.1% in negative agreement, with 458 samples in agreement out of 473. The concordance with each condition was also high; agreement of 90.8% within the ET samples (89/98), 94.9% agreement within the PMF samples (94/99), and 99.6% within the PV samples (275/276). All three conditions had positive agreements of 100%. The authors went on to note that the 15 samples with disagreeing results had mutation levels under the detection capability of bi-directional sequencing. To validate these 15 samples, an independently validated NGS panel was used to compare results with the kit, and all 15 samples were found to test positive, thereby agreeing with the kit. The authors concluded that the kit was accurate for any mutation levels at or above 1%.<sup>18</sup>

Other proprietary tests are available for mutational analysis in MPN. IntelliGEN® Myeloid is a NGS assay that analyzes fifty genes for somatic mutations that could be useful in providing diagnostic or prognostic information for patients with MDS, AML, or MPN.<sup>19</sup> The LeukoVantage® Myeloid Neoplasm Mutation Panel detects myeloid neoplasm-associated mutations in 48 genes associated with AML, MDS, and MPN. The LeukoVantage AML panel can be used to assess AML subclass and prognosis based on genetic abnormalities in *NPM1*, *CEBPA*, and *RUNX1*.<sup>20</sup> NeoGenomics offers tests such as the MPN Reflex Test, a sequential testing panel for qualitative detection of *JAK2* V617F, *JAK2* Exon 12-14, *CALR* exon 9, and *MPL* exon 10.<sup>21</sup> Centogene has released a Myeloid Tumor Panel which targets 35 genes that are associated with myeloid malignancies which also include AML, MPN, MDS, CML, CMML, and JMML.<sup>22</sup>

### **Analytical Validity**

Poluben, et al. (2019) analyzed the characteristics of myeloproliferative neoplasms (MPN) in patients exposed to ionizing radiation (IR) from the 1986 Chernobyl accident. 281 patients (90 exposed to radiation, 181 unexposed) were included. *JAK2*, *MPL*, and *CALR* mutations were identified. IR-exposed patients had several different genetic features compared to the unexposed cohort: lower rate of *JAK2* V617F mutations (58.4% vs 75.4%), higher rate of type 1-like *CALR* mutations (12.2% vs 3.1%), higher rate of triple-negative cases (27.8% vs 16.2%), and higher rate of “potentially pathogenic” sequence variants (4.8 vs 3.1). The authors suggested IR-exposed patients as a cohort with “distinct” genomic characteristics.<sup>23</sup>

Rosenthal, et al. (2021) studied the analytical validity of a 48-gene NGS panel for detecting mutations in myeloid neoplasms. The panel detects single nucleotide variations (SNVs), insertions/deletions, and *FLT3* internal tandem duplications (*FLT3*-ITD). 184 samples were analyzed using the 48-gene panel and compared to those identified by a 35-gene hematologic neoplasms panel using an additional 137 samples. Analytical validation yielded 99.6% sensitivity and 100% specificity. Concordance of variants detected by the two tested panels was 100%. “Among patients with suspected myeloid neoplasms, 54.5% patients had at least one clinically significant mutation: 77% in AML patients, 48% in MDS, and 45% in MPN.” The authors conclude that “the assay can identify mutations associated with diagnosis, prognosis, and treatment options of myeloid neoplasms even in technically challenging genes.”<sup>24</sup>

### ***Clinical Utility and Validity***

An Argentinean study focusing on establishing the frequency of *JAK2*, *MPL*, and *CALR* mutations and comparing their clinical and hematological features corroborates this importance. Mutations of *JAK2*V617F, *JAK2* exon 12, *MPL* W515L/K and *CALR* were analyzed in 439 patients with *BCR-ABL1*-negative MPN, and it was demonstrated that these mutations were present in 94.9% of the cases of PV, 85.5% in patients with essential thrombocythemia (ET), and 85.2% with primary myelofibrosis, leading the researchers to conclude that “the combined genetic tests of these driver mutations are essential for accurate diagnoses of *BCR-ABL1*-negative MPN.”<sup>25</sup>

## **VI. Guidelines and Recommendations**

### **International Consensus Classification for Myeloproliferative Neoplasms**

In 2022, a new International Consensus Classification (ICC) was introduced for myeloid neoplasms and acute leukemias by experts involved in prior editions of the WHO classification. The group attempted to refine the diagnostic criteria to show a distinction between the subtypes. They proposed the following criteria for the diagnosis of PV, ET and PMF with subtypes of each.<sup>26</sup>

#### Criteria for PV

Diagnosis of PV requires meeting either all three major criteria, or the first two major criteria and the minor criterion:

##### Major Criteria

1. Hemoglobin >16.5 g/dL in men; Hemoglobin >16.0 g/dL in women, or Hematocrit >49% in men; Hematocrit >48% in women, or Increased red cell mass (More than 25% above mean normal predicted value)
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of *JAK2 V617F* or *JAK2* exon 12 mutation

Minor Criteria

Subnormal serum erythropoietin level

Criteria for Post-PV myelofibrosis (MF)

Diagnosis of Post-PV MF requires meeting all required criteria and at least two additional criteria:

Major Criteria

1. A prior diagnosis of PV
2. Bone marrow fibrosis Grade 2/3

Additional Criteria

1. Anemia or a reduced need for either phlebotomy or cytoreductive treatment to manage erythrocytosis.
2. Presence of leukoerythroblastosis (immature white and red blood cells in the bloodstream)
3. An increase in palpable splenomegaly of more than 5 cm from baseline or development of a newly palpable spleen.
4. Development of at least 2 (or all 3) of the following constitutional symptoms: weight loss greater than 10% in 6 months, night sweats, unexplainable fever greater than 37.5 degrees Celsius (99.5 degrees Fahrenheit)

Criteria for ET

Diagnosis of ET requires meeting all four major criteria or the first three major criteria and the minor criterion:

Major Criteria

1. Platelet count  $\geq 450 \times 10^9/L$
2. Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis.
3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms.
4. Presence of *JAK2*, *CALR*, or *MPL* mutation

Minor Criteria

Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Criteria for Post-ET MF

Diagnosis of Post-ET MF requires meeting all required criteria and at least 2 additional criteria

Required Criteria

1. Previous diagnosis of ET
2. Bone marrow fibrosis grade 2/3

Additional criteria

1. Anemia, with a decrease in hemoglobin (b) concentration of more than 2 g/dL from baseline
2. Presence of leukoerythroblastosis (immature white and red blood cells in the bloodstream)
3. An increase in palpable splenomegaly of more than 5 cm from baseline or the development of a newly palpable spleen
4. Elevated LDH levels
5. Development of at least 2 (or all 3) of the following constitutional symptoms: weight loss greater than 10% in 6 months, night sweats, unexplainable fever greater than 37.5 degrees Celsius (99.5 degrees Fahrenheit)

#### Criteria for PMF, early/prefibrotic stage

Diagnosis of prePMF requires meeting all three major criteria, and at least one minor criterion:

##### Major Criteria

1. Megakaryocytic proliferation and atypia, BM fibrosis Grade <2, increased age-adjusted BM cellularity, granulocytic proliferation, and may show decreased erythropoiesis
2. Not meeting the WHO criteria for BCR-ABL1<sup>+</sup> CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker (e.g., *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*), or absence of minor reactive BM reticulin fibrosis

##### Minor Criteria (presence of one of the following):

1. Anemia not attributed to a comorbid condition
2. Leukocytosis  $\geq 11 \times 10^9/L$
3. Palpable splenomegaly
4. LDH increased to above upper normal limit of institutional reference range

#### Criteria for overt fibrotic stage PMF

Diagnosis of overt PMF requires meeting all three major criteria, and at least 1 minor criterion (confirmed in 2 consecutive determinations).

##### Major Criteria

1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
2. Not meeting WHO criteria for ET, PV, BCR-ABL1<sup>+</sup> CML, myelodysplastic syndromes, or other myeloid neoplasms
3. Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker (e.g., *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*), or absence of reactive myelofibrosis

##### Minor Criteria

1. Anemia not attributed to a comorbid condition
2. Leukocytosis  $\geq 11 \times 10^9/L$
3. Palpable splenomegaly
4. LDH increased to above upper normal limit of institutional reference range
5. Leukoerythroblastosis

These guidelines also list additional “clinicopathologic entities” for MPNs: “chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, and MPN, unclassifiable (MPN-U).”<sup>26</sup>

#### **European LeukemiaNet (ELN)**

ELN guidelines also recommend “strict adherence” to these guidelines for the three categories of Philadelphia-negative MPNs, (i.e. ET, PV, and MF).<sup>27</sup>

However, they also recommend “searching” for complementary clonal markers such as *ASXL1*, *EZH2*, *IDH1/2*, and *SRSF2* for patients that tested negative for the three driver mutations and have bone marrow features as well as a clinical phenotype consistent with myelofibrosis.<sup>27</sup>

#### **National Comprehensive Cancer Network (NCCN)**

The NCCN Guidelines Version 2.2024 Myeloproliferative Neoplasms recommends molecular testing for *JAK2* V617F mutations as part of an initial workup for all patients. If *JAK2* mutation testing is negative, molecular testing for *CALR* and *MPL* mutations should be performed for patients with suspected ET and MFA, and molecular testing for *JAK2* exon 12 should be done for patients who test negative for *JAK2* but are suspected of PV. An NGS panel including *JAK2*, *CALR*, and *MPL* may also be used for the workup of all patients.

The NCCN lists the 2022 edition of the ICC diagnostic criteria. The NCCN does state that NGS “may be useful to establish clonality in selected circumstances (e.g., triple negative non-mutated *JAK2*, *MPL*, and *CALR*.)” The NCCN includes a list of somatic mutations with prognostic significance in individuals with MPN that includes the *ASXL1*, *EZH2*, *RAS*, *IDH1/2*, *SRSF2*, *TP53*, *U2AF1*, *DNMT3A*, and *CBL*.

For individuals suspected of MPN, the NCCN recommends excluding a diagnosis of chronic myeloid leukemia: “Fluorescence in situ hybridization (FISH) or a multiplex reverse transcriptase polymerase chain reaction (RT-PCR), if available, on peripheral blood to detect *BCR::ABL1* transcripts and exclude the diagnosis of CML is especially recommended for patients with left-shifted leukocytosis and/or thrombocytosis with basophilia.”<sup>5</sup>

Currently, the NCCN reports that “at the present time, the utility of *JAK2* V617F allele burden reduction as a predictor of treatment efficacy remains unclear. . . Therefore, measurement of the *JAK2* V617F allele burden is not currently recommended for use in routine clinical practice to guide treatment decisions.”<sup>5</sup>

### **British Society for Haematology (BSH)**

The BSH recommends testing for *CALR* for patients suspected of ET and PMR, as *CALR* mutations account for most patients without either a *JAK2* or *MPL* mutation. The authors found that as many as one third of ET and PMF patients had a mutation in exon 9 of the *CALR* gene.<sup>28</sup>

The BSH also published guidelines on the diagnosis of polycythaemia vera. In it, they divide PV into *JAK2*-positive and *JAK2*-negative PV. For *JAK2*-positive PV, the only two diagnostic criteria are as follows:

- “High haematocrit (>0.52 in men, >0.48 in women) OR raised red cell mass (>25% above predicted)”
- “Mutation in *JAK2*”

For *JAK2*-negative PV, the diagnostic criteria are as follows (requiring A1-A4, as well as another “A” criteria or two “B” criteria).

- “A1 Raised red cell mass (>25% above predicted) OR haematocrit  $\geq 0.60$  in men,  $\geq 0.56$  in women”
- “A2 Absence of mutation in *JAK2*”
- “A3 No cause of secondary erythrocytosis”
- “A4 Bone marrow histology consistent with polycythaemia vera”
- “A5 Palpable splenomegaly”
- “A6 Presence of an acquired genetic abnormality (excluding *BCR-ABL1*) in the haematopoietic cells”
- “B1 Thrombocytosis (platelet count  $>450 \times 10^9 /l$ )”
- “B2 Neutrophil leucocytosis (neutrophil count  $>10 \times 10^9 /l$  in non-smokers,  $\geq 12.5 \times 10^9 /l$  in smokers)”

- “B3 Radiological evidence of splenomegaly”
- “B4 Low serum erythropoietin”

The guidelines also note that investigation of erythrocytosis should be undertaken to properly identify the diagnosis. The BSH remarks that EPO receptor mutations may be a primary cause for erythrocytosis and that *EGN1*, *VHL*, and *EPAS1* mutations may be a secondary cause. Other hemoglobinopathies caused by mutations in genes such as *HBA1*, *HBA2*, *HBB*, or *BPGM* may also be a factor.<sup>29</sup>

In 2021, the BSH published guidelines on the use of genetic tests to diagnose and manage patients with myeloproliferative neoplasms. The following recommendations were made:

1. “Molecular screening for *JAK2*, *CALR* and *MPL* variants as appropriate is recommended in patients with persistent erythrocytosis or thrombocytosis (GRADE 1B).
2. Screening for *JAK2* V617F is recommended in cases with normal blood counts and unexplained splanchnic vein thrombosis (GRADE 1B) and may be considered in selected patients with unexplained cerebral vein thrombosis (GRADE 2C).
3. Screening for *CALR* variants may be considered in patients with splanchnic vein thrombosis or cerebral vein thrombosis (GRADE 2C).
4. Screening for *JAK2*, *CALR* and *MPL* variants should be considered for patients with arterial or unprovoked venous thrombosis who have a mildly or variably elevated haematocrit or platelet count that persists for 2–3 months (GRADE 2C).
5. *BCR-ABL1* should be excluded in cases with persistent thrombocytosis negative for *JAK2*, *CALR* and *MPL* variants or with atypical features (GRADE 1B).
6. Younger patients (e.g., under 60 years) with bone marrow histology typical of ET [or myeloproliferative neoplasm, unclassifiable (MPN-U) or suspected prefibrotic MF] where confirmation of a clonal disorder would be useful in view of the patient’s likely long-term disease course and ideally where a broad panel that covers non-canonical variants in *JAK2* and *MPL* and a range of other driver genes is available.
7. Patients with significant thrombocytosis (e.g., platelet count > 600 × 10<sup>9</sup>/l), no reactive cause and borderline bone marrow histology, where cytoreduction would be indicated if there was convincing evidence of a clonal disorder. Examples would include those with an unexplained thrombotic event, particularly younger patients. For older patients without thrombosis, testing may be considered but results must be interpreted with caution in view of the possibility of incidental CH.
8. A myeloid gene panel and cytogenetic analysis (or equivalent) is recommended for patients with bone marrow histology and clinical features consistent with PMF (+/- suggestive features of MDS or MDS/MPN) who test negative for *JAK2/CALR/MPL* (GRADE 1B).
9. A myeloid gene panel and cytogenetic analysis (or equivalent) is not recommended for most patients with *JAK2/CALR/MPL*-negative erythrocytosis or thrombocytosis but may be considered in individual cases (GRADE 2C).
10. Myeloid gene panel testing is recommended for MPN cases who test positive for *JAK2/CALR/MPL* mutations and have additional cytopenias(s) at diagnosis, unexplained ring sideroblasts or other dysplasia, increased blasts (including blastic transformation), peripheral-blood monocytosis or atypical clinical features (GRADE 1B).
11. Myeloid gene panel testing and conventional karyotyping are recommended for all patients with PMF, post-PV or post-ET MF who are candidates for allogeneic stem cell transplant (GRADE 1B).
12. Myeloid gene panel testing should be considered for other patients if the additional genomic data will guide clinical management (GRADE 2C).

13. High-sensitivity assays of mutant allele burden are recommended following post-allogeneic stem cell transplant to monitor for residual disease (GRADE 1C).
14. Quantitative assays of mutant allele burden are not recommended for most MPN patients but may be considered where demonstration of molecular response would influence clinical management (GRADE 2C).
15. Patients with persistent eosinophilia should be investigated initially for *FIP1L1–PDGFRA* by FISH and/or nested RT-PCR (GRADE 1B).
16. BM cytogenetics or FISH is recommended to screen for other fusion genes, which must then be confirmed by molecular methods (GRADE 1B).
17. Myeloid gene panel and *KIT* D816V testing should be considered for patients with persistent unexplained eosinophilia who test negative for fusion genes (GRADE 2B).
18. Testing for *CSF3R* variants, preferably as part of wider myeloid panel, is recommended for all patients with suspected CNL (Grade 2B).
19. Sensitive testing for *KIT* D816V is recommended for all patients with a clinical suspicion of mastocytosis (GRADE 1B).
20. If negative for *KIT* D816V, screening for other *KIT* mutations should be considered for adults (but is recommended for children) (GRADE 1B).
21. Myeloid panel analysis is recommended for patients with advanced SM who are candidates for allogeneic stem cell transplantation (GRADE 1B).
22. Myeloid panel analysis may be considered for other SM patients if the apparent aggressiveness of the disease might influence options for therapy (GRADE 2B).
23. Myeloid panel and/or BM cytogenetics should be considered to characterise the AHN component of SM-AHN (GRADE 2B).
24. *BCR–ABL1* should be excluded in all cases of suspected MDS/MPN, and rearrangements associated with MLN-eo should be excluded in cases with eosinophilia (GRADE 1B).
25. Myeloid gene panel analysis and BM cytogenetics or SNP array is recommended for patients diagnosed with MDS/MPN and for cases with suspected MDS/MPN but with indeterminate morphology (GRADE 1B).<sup>30</sup>

### European Association for the Study of the Liver (EASL)

For myeloproliferative neoplasms, the EASL recommends testing for *JAK2* V617F mutations in splanchnic vein thrombosis patients, as well as patients with normal peripheral blood cell counts. If the *JAK2* mutation test is negative, a calreticulin mutation test should be performed, and if both are negative, a bone marrow histology analysis should be performed.<sup>31</sup>

### European Society of Medical Oncology (ESMO)

The ESMO recommends that anyone with a suspected MPN be tested for the three driver mutations (*JAK2*, *CALR*, *MPL*) and that genotyping should be obtained at diagnosis. However, the ESMO states that it is not recommended to repeat testing in follow-up or assessing response to treatment, except for “allogeneic stem-cell transplantation and possibly interferon treatment.” For these two assessments a detection limit of  $\leq 1\%$  is recommended. The ESMO also notes that conventional sequencing methods (PCR, melting analysis) may be used for detecting mutations.<sup>32</sup>

## VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website <http://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the applicable state Medicaid website.

### Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

On July 28, 2017 the FDA approved ipsogen® JAK2 RGQ PCR Kit<sup>33</sup> to detect Janus Tyrosine Kinase 2 (JAK2) gene mutation G1849T (V617F) with an allele-specific, quantitative, PCR using an amplification refractory mutation system. This is the first FDA-authorized test intended to help physicians in evaluating patients for suspected PV. However, the FDA specifically states that this test is not intended for a stand-alone diagnosis of an MPN, nor can it detect less common mutations for MPN such as an exon 12 mutation.<sup>18</sup>

## VIII. Applicable CPT/HCPCS Procedure Codes

CPT	CPT Description
81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence

CPT	CPT Description
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer, hereditary pancreatic cancer, hereditary prostate cancer), genomic sequence analysis panel, 5 or more genes, interrogation for sequence variants and copy number variants
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or

CPT	CPT Description
	isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81455	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
81479	Unlisted molecular pathology procedure
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. Proprietary test: JAK2 Mutation Lab/Manufacturer: University of Iowa, Department of Pathology
0027U	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15 Proprietary test: JAK2 Exons 12 to 15 Sequencing Lab/Manufacturer: Mayo Clinic

Current Procedural Terminology © American Medical Association. All Rights reserved.

*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

#### IX. Evidence-based Scientific References

- Grinfeld J, Nangalia J, Green AR. Molecular determinants of pathogenesis and clinical phenotype in myeloproliferative neoplasms. *Haematologica*. 2017;102(1):7-17. doi:10.3324/haematol.2014.113845
- Rumi E, Cazzola M. Diagnosis, risk stratification, and response evaluation in classical myeloproliferative neoplasms. *Blood*. Feb 9 2017;129(6):680-692. doi:10.1182/blood-2016-10-695957
- Vainchenker W, Kralovics R. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. *Blood*. Feb 9 2017;129(6):667-679. doi:10.1182/blood-2016-10-695940
- Titmarsh GJ, Duncombe AS, McMullin MF, et al. How common are myeloproliferative neoplasms? A systematic review and meta-analysis. *American journal of hematology*. Jun 2014;89(6):581-7.
- NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines: Myeloproliferative Neoplasms v2.2024. NCCN. [https://www.nccn.org/professionals/physician\\_gls/pdf/mpn.pdf](https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf)
- Tefferi A. Clinical manifestations and diagnosis of primary myelofibrosis. Updated September 13, 2022. <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-primary-myelofibrosis>
- Tefferi A. Clinical manifestations and diagnosis of polycythemia vera. Updated November 27, 2024. <https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-polycythemia-vera>
- Tefferi A. Clinical manifestations, pathogenesis, and diagnosis of essential thrombocythemia. Updated January 9, 2023. <https://www.uptodate.com/contents/diagnosis-and-clinical-manifestations-of-essential-thrombocythemia>
- Tefferi A. Overview of the myeloproliferative neoplasms. Updated September 13, 2022. <https://www.uptodate.com/contents/overview-of-the-myeloproliferative-neoplasms>

10. Rampal R, Al-Shahrour F, Abdel-Wahab O, et al. Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis. *Blood*. May 29 2014;123(22):e123-33. doi:10.1182/blood-2014-02-554634
11. Silvennoinen O, Hubbard SR. Molecular insights into regulation of JAK2 in myeloproliferative neoplasms. *Blood*. May 28 2015;125(22):3388-92. doi:10.1182/blood-2015-01-621110
12. Hussein K, Granot G, Shpilberg O, Kreipe H. Clinical utility gene card for: familial polycythaemia vera. *Eur J Hum Genet*. 2013;21(6)doi:10.1038/ejhg.2012.216
13. Coates TD. Approach to the patient with neutrophilia. Updated June 28, 2024. <https://www.uptodate.com/contents/approach-to-the-patient-with-neutrophilia>
14. Tefferi A, Thiele J, Vannucchi AM, Barbui T. An overview on CALR and CSF3R mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms. *Leukemia*. Jul 2014;28(7):1407-13. doi:10.1038/leu.2014.35
15. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. *The New England journal of medicine*. May 9 2013;368(19):1781-90. doi:10.1056/NEJMoa1214514
16. Faisal M, Stark H, Busche G, et al. Comprehensive mutation profiling and mRNA expression analysis in atypical chronic myeloid leukemia in comparison with chronic myelomonocytic leukemia. *Cancer medicine*. Jan 11 2019;doi:10.1002/cam4.1946
17. Dharmawickreme B, Witharana C. Review: JAK2V617F Allele Burden in Diagnosis and Therapeutic Monitoring of Myeloproliferative Neoplasms. *European Journal of Medical and Health Sciences*. 02/18 2023;5(1):35-40. doi:10.24018/ejmed.2023.5.1.1587
18. FDA. ipsogen® JAK2 RGQ PCR Kit. [https://www.accessdata.fda.gov/cdrh\\_docs/pdf17/K172287.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf17/K172287.pdf)
19. Labcorp. IntelliGEN® Myeloid. <https://oncology.labcorp.com/cancer-care-team/test-menu/intelligen-myeloid>
20. Quest Diagnostics. LeukoVantage® Myeloid Neoplasm Mutation Panels. <https://www.questdiagnostics.com/healthcare-professionals/clinical-education-center/faq/faq208>
21. NeoGenomics. MPN JAK2 V617F with Sequential Reflex to JAK2 Exon 12-13, CALR, and MPL. <https://neogenomics.com/test-menu/mpn-jak2-v617f-sequential-reflex-jak2-exon-12-13-calr-and-mpl>
22. Centogene. Myeloid Tumor Panel. <https://www.centogene.com/diagnostics/our-tests/somatic-mutation-testing/somatic-mutation-testing-for-myeloid-tumors>
23. Poluben L, Puligandla M, Neuberg D, et al. Characteristics of myeloproliferative neoplasms in patients exposed to ionizing radiation following the Chernobyl nuclear accident. *American journal of hematology*. Jan 2019;94(1):62-73. doi:10.1002/ajh.25307
24. Rosenthal SH, Gerasimova A, Ma C, et al. Analytical validation and performance characteristics of a 48-gene next-generation sequencing panel for detecting potentially actionable genomic alterations in myeloid neoplasms. *PLoS One*. 2021;16(4):e0243683. doi:10.1371/journal.pone.0243683
25. Ojeda MJ, Bragós IM, Calvo KL, Williams GM, Carbonell MM, Pratti AF. CALR, JAK2 and MPL mutation status in Argentinean patients with BCR-ABL1- negative myeloproliferative neoplasms. *Hematology*. 2018/04/21 2018;23(4):208-211. doi:10.1080/10245332.2017.1385891
26. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850
27. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia*. 2018/05/01 2018;32(5):1057-1069. doi:10.1038/s41375-018-0077-1

28. Harrison CN, Butt N, Campbell P, et al. Modification of British Committee for Standards in Haematology diagnostic criteria for essential thrombocythaemia. *British Journal of Haematology*. 2014/11/01 2014;167(3):421-423. doi:10.1111/bjh.12986
29. McMullin MF, Harrison CN, Ali S, et al. A guideline for the diagnosis and management of polycythaemia vera. A British Society for Haematology Guideline. *British Journal of Haematology*. 2019/01/01 2019;184(2):176-191. doi:10.1111/bjh.15648
30. Cross NCP, Godfrey AL, Cargo C, Garg M, Mead AJ. The use of genetic tests to diagnose and manage patients with myeloproliferative and myeloproliferative/myelodysplastic neoplasms, and related disorders. *British Journal of Haematology*. 2021;195(3):338-351. doi:10.1111/bjh.17766
31. EASL. EASL Clinical Practice Guidelines: Vascular diseases of the liver. *Journal of hepatology*. Jan 2016;64(1):179-202. doi:10.1016/j.jhep.2015.07.040
32. Vannucchi AM, Barbui T, Cervantes F, et al. Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. Sep 2015;26 Suppl 5:v85-99. doi:10.1093/annonc/mdv203
33. FDA. Approved Drugs - Ipsogen JAK2 RGQ PCR Kit. WebContent. <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm551474.htm>

## X. Revision History

Effective Date	Summary
07/01/2025	<p>Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria:</p> <p>CC1.c.iii. changed from “without reticulin fibrosis &gt;grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis.” to “BM fibrosis Grade &lt;2, increased age-adjusted BM cellularity, and granulocytic proliferation; may show erythropoiesis.”, now reads: “(iii) A BM biopsy shows megakaryocytic proliferation and atypia, BM fibrosis Grade &lt;2, increased age-adjusted BM cellularity, and granulocytic proliferation; may show erythropoiesis.”</p> <p>CC3, corrected spelling of BCR-ABL1+ CML</p> <p>Note 1 edited to change “5” to “two” to align with guidance in R2162: “Note 1: For two or more gene tests being run on the same platform, please refer to AHS-R2162-Reimbursement policy.”</p> <p>Client requested variance: Added new CC8 – “8) The above gene studies may be tested sequentially at the same time if above criteria is met for myeloproliferative disorder overlap syndromes (MPDs and MDDs), use the myelodysplastic protocol and MEETS COVERAGE CRITERIA.”</p>
12/04/2024	Off-cycle coding modification: Revised CPT code description for CPT code 81432 (effective date 1/1/2025)
12/01/2024	Initial Policy Implementation