Genetic Testing for Myeloproliferative Diseases

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as “Company” and collectively as “Companies”).

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

For comprehensive rules and guidelines pertaining to this policy, readers are advised to consult the Oregon Health Authority. It is essential to ensure full understanding and compliance with the state's regulations and directives. Please refer to OHA's prioritized list for the following coverage guidelines:

Medicaid members must also meet the genetic testing criteria governed by the Oregon Health Plan (OHP) Prioritized List Guideline Notes D1 and D17.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Qualitative Testing

I. Genetic testing for the BCR-ABL1 fusion gene may be considered **medically necessary** for suspected myeloproliferative neoplasms and leukemia.

II. Genetic testing for polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) may be considered medically necessary when the following criteria are met:

A. Suspicion of essential thrombocythemia (ET), primary myelofibrosis (PMF) or polycythemia vera (PV) based on the World Health Organization (WHO) classification criteria for MPNs (See Policy Guidelines); **and**
B. Genetic test results will directly impact medical management of the individual being tested; **and**
C. Testing meets the following strategies:
    a. Testing JAK2 V617F initially, with further testing if results are negative; or

b. Sequential testing of JAK2 V617F, reflexing to JAK2 exon 12, CALR, and/or MPL gene testing when JAK2 V617F results are negative; or
c. Targeted multigene panel for myeloid neoplasms, including JAK2, CALR, and MPL genes.

Non-Covered Qualitative Testing

III. Genetic testing of JAK2, CALR **and/or** MPL gene mutations is considered **not medically necessary** when the above criteria (I., II., or III.) are not met, including but not limited to (A.-C.):

A. Patients who do not have the characteristic clinical, pathological and/or histological findings indicative of ET, PV or PMF.
B. Patients confirmed BCR-ABL1 positive.
C. Member has previously been tested for the same mutation/s for the same indication.

Quantitative Testing

IV. Quantitative genetic testing (e.g., to determine allele burden) for **any** mutation in the JAK2, CALR or MPL genes is considered **not medically necessary** for any indication.

Link to Evidence Summary

POLICY CROSS REFERENCES

None

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

Genetic Testing for the BCR-ABL1 (t(9;22)) Fusion Gene (also known as the Philadelphia chromosome)

According to the National Comprehensive Cancer Network (NCCN) and the World Health Organization (WHO), BCR-ABL1 fusion gene testing is considered **standard of care** for the initial evaluation of patients suspected of having chronic myeloid leukemia and the other classic myeloproliferative neoplasms.[1-3]

2016 World Health Organization [WHO] Classification Criteria for Myeloproliferative Neoplasms[1]

Essential Thrombocythemia (ET)

The diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion:

Major Criteria

1. Platelet count ≥450 × 109/L
2. Bone marrow (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
3. Not meeting WHO criteria for BCR-ABL1 + CML, PV, PMF, MDS, or other myeloid neoplasms
4. Presence of a JAK2, CALR, or MPL mutation

Minor Criteria

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

<u>Polycythemia Vera (PV)</u>

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion:

Major Criteria

1. Hemoglobin >16.5 g/dL in men/ >16.0 g/dL in women, *OR*
   Hematocrit >49% in men/ >48% in women, *OR*
   Increased red cell mass (RCM)
2. BM 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 JAK2V617F or JAK2 exon 12 mutation

Minor Criteria

1. Subnormal serum erythropoietin level

<u>Primary Myelofibrosis (PMF): prePMF</u>

Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion:

Major Criteria

1. Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting WHO criteria for BCR-ABL1 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, or the absence of minor reactive BM reticulin fibrosis

Minor Criteria

Presence of at least one of the following, confirmed in 2 consecutive determinations:

a) Anemia not attributed to a comorbid condition
b) Leukocytosis ≥11 × 10^9/L
c) Palpable splenomegaly
d) LDH increased to above upper normal limit of institutional reference range

<u>Primary Myelofibrosis (PMF): overt PMF</u>

Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion:

Major Criteria

1. Megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
2. Not meeting WHO criteria for BCR-ABL1 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, or the absence of minor reactive BM reticulin fibrosis

Minor Criteria

Presence of at least one of the following, confirmed in 2 consecutive determinations:

a) Anemia not attributed to a comorbid condition
b) Leukocytosis ≥11 × 10^9/L
c) Palpable splenomegaly
d) LDH increased to above upper normal limit of institutional reference range
e) Leukoerythroblastosis

DEFINITIONS

Qualitative Testing: Testing for the presence of absence of a mutation. The results of a qualitative test will simply indicate if a patient is mutation positive or negative.

Quantitative Testing: Testing that indicates the number of mutated alleles a patient carries. The results of these tests would either be reported as heterozygous versus homozygous or as a percentage of "allele burden" (e.g. the number of copies of the JAK2 V617F mutation a patient carries).

BACKGROUND

Classic Myeloproliferative Neoplasms (MPNs) and Genetic Testing for the BCR-ABL1 (t(9;22)) Fusion Gene

There are four classic MPNS: chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). CML can be distinguished from the other three MPNs on a molecular level by the presence of an abnormal fusion of the BCR and ABL1 genes.

The BCR-ABL1 fusion gene is a hallmark genetic abnormality that occurs in the vast majority of chronic myeloid leukemia patients. This fusion gene results from a reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11), that gives rise to an abnormal chromosome 22 called the Philadelphia (Ph) chromosome. Testing for the BCR-ABL fusion gene can be done via peripheral blood sample and testing using either qualitative or quantitative genetic analysis. BCR-ABL1 fusion gene testing is considered standard of care for the initial evaluation of patients suspected of having a classic MPN.

BCR-ABL1 Negative Myeloproliferative Neoplasms (BCR-ABL1$^-$ MPNs)

Essential thrombocythemia (ET), primary myelofibrosis (PMF) and polycythemia vera (PV) are a group of heterogeneous myeloid hematologic malignancies collectively known as BCR-ABL1 negative (or Philadelphia chromosome-negative) classic myeloproliferative neoplasms (MPNs). The prevalence of PMF is 1/3,000, while the prevalence of ET and PV are 1/134,000 and 1/148,000 respectively.[2]

Individuals diagnosed with MPNs have a high risk of the disease transforming into acute myeloid leukemia (AML). The risk of transformation into AML differs among the subgroups, as patients with PV have an approximately 10- 25% chance of transforming into AML, while those with ET or PMF have less than a 5% risk of transformation.[4] However, transformation to AML is the most frequent cause of death among PMF patients.[5]

Genetic Abnormalities in BCR-ABL1$^-$ MPNs

The clinical presentation of patients with BCR-ABL1- MPNs is thought to differ somewhat depending upon the mutation present. Janus Kinase 2 (JAK2 gene) V617F mutations account for more than 90% of patients with PV, and 60% of patients with ET and PMF. A small number of mutations have been reported in exon 14 of JAK2, and rare insertions and deletions in exon 12 have also been confirmed in 2-3% of PV patients.[2] Activating mutations in the MPL proto-oncogene, thrombopoietin receptor (MPL) have been reported in 5-8% of patients with PMF, and 1-4% of patients with ET.[2]

Mutations in exon 9 of the calreticulin (CALR) gene have been reported in 20-35% of all patients with ET and PMF, accounting for 60-80% of patients with JAK2/MPL-negative ET and PMF. The CALR-type 1 mutation is a 52-base pair deletion that is more frequent in patients with PMF and is associated with a higher myelofibrotic transformation in ET. The CALR-type 2 mutation is a 52-base pair insertion seen more often in ET and carries a lower risk of thrombosis and an indolent clinical course. CALR mutations are often associated with lower hemoglobin levels, higher platelet counts and lower incidence of thrombosis than the JAK2 V617F mutation.[2]

Approximately 10% of patients with PMF and ET lack mutations in JAK2, CALR, or MPL (referred to as triple-negative MPN). Triple-negative MPN is associated with a worse prognosis. Mutations in several other genes have been reported in patients with MPN, including CBL, LNK, TET2, EZH2, IDH1/2, ASXL1, DNM3TA, SF3B1, SRSF2, U2AF1 and TP53, but their prevalence is unknown.[2]

Qualitative Testing

Quantitative testing has been proposed to correlate with disease severity as well as for use in monitoring changes in the number of cells with specific mutations over time, the latter of which may be useful in monitoring treatment effectiveness. The results of these tests would either be reported as heterozygous versus homozygous or as a percentage of “allele burden” (e.g. the number of copies of the JAK2 V617F mutation a patient carries).

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of genetic testing of the JAK2, CALR and MPL genes for the diagnosis of BCR-ABL1 negative myeloproliferative neoplasms. Below is a summary of the available evidence identified through April 2025.

Qualitative Testing of JAK2, CALR and MPL

Genetic testing for the presence of mutations in JAK2, CALR and MPL are required to meet both WHO diagnostic criteria and NCCN criteria for workup of suspected for PMF, ET and PV. Despite the lack of evidence published on the clinical utility of testing of these genes, both NCCN and the WHO recommend testing of the JAKL2, CALR and/or MPL genes as a standard step in the evaluation of these related conditions, as mutation status of these genes is known to have diagnostic utility as well as prognostic significance. The true benefit of testing is that it ends the diagnostic odyssey for patients suspected of a BCR-ABL1 negative MPN. The evidence review below will focus on key studies for each of the three main MPN-associated genes.

JAK2

In 2005, two case series (n=116 and 679) reported the presence of acquired JAK2 mutations in patients with MPNs. The mutation was present in 65% to 97% of patients with PV, 23% to 57% with ET, and 35% to 56% with IMF.[6,7]

In 2007 Scott et al. published a small case series of JAK2 V617F-negative MPN patients and identified four gain-of-function mutations in JAK2 exon 12.[8] Patients with a JAK2 exon 12 mutation differed from those with the JAK2 V617F mutations, presenting at a younger age with higher hemoglobin levels and lower platelet and white cell counts. These findings were subsequently in additional case series that identified additional mutations JAK2 exon 12 mutations with similar functional consequences in patients with PV.[9,10] Based on these seminal studies, it was concluded that the identification of JAK2 exon 12 mutations provides a diagnostic test for JAK2V617F -negative patients who present with MPNs.

In 2009, Dahebreh et al. published the results of a systematic review that compared the frequency of clinically significant outcomes between JAK2 V617F positive and wild type patients with essential thrombocythemia (ET).[11] The review reported that JAK2 V617F positive mutation status in patients with ET was associated with a highly significant increase in the odds of thrombosis (OR=1.83; 95% CI, 1.32-2.53, p<0.0001), and much higher odds of transformation to polycythemia vera (OR=7.67; 95% CI, 2.04-28.87, p=0.0009) compared to ET patients without the JAK2 V617F mutation. In addition, patients with JAK2 V617F mutations had a higher white blood cell count compared to patients without the mutation, and this was associated with an increased odds ratio for thrombosis (p=0.02).

MPL

In 2006, Pikman et al. reported on a small case series of JAK2 mutation-negative patients with suspected ET and PMF, identifying the W515L mutation in the MPL gene in exon 10.[12] Subsequent studies identified additional mutations in the MPL gene in a small but growing number of patients with ET and PMF.[10,12-14]

There have been several case series (n= 18 - 60 MPL mutation positive patients) that have evaluated associations between MPL variants and clinical variables/risk factors. MPL-positive mutation status was significantly associated with lower hemoglobin levels ($p \leq 0.004$) in four case series.[13,15-17] However, association with platelet counts showed conflicting results, being associated with high platelet levels in two studies ($p \leq 0.004$)[13,17] and low platelet levels (p=0.0001) in one study.[15]

CALR

Large case series published in 2013 and 2014 have now determined the mutations in the CALR gene are common in JAK2-negative patients with PMF and ET.[18-20] One series reported that CALR mutations, found in 25% of patients with PMF, were associated with younger age ($p<0.0001$), higher platelet count ($p<0.0001$) and lower DIPSS-plus score ($p=0.02$).[18] In addition, CALR-mutated patients were also less likely to be anemic, require transfusions or display leukocytosis than patients with JAK2 or MPL mutations.

In 2013, Klampfl et al. published the results of a large retrospective series that resequencing 1107 samples from patients with MPNs, reporting that CALR mutations were absent in patients with PV.[19] In ET and PMF, CALR mutations and JAK2 and MPL mutations were mutually exclusive. Among patients with ET or PMF with nonmutated JAK2 or MPL, CALR mutations were detected in 67% of those with ET and 88% of those with PMF. Patients with mutated CALR were reported to have had a lower risk of thrombosis and longer overall survival than patients with mutated JAK2.

In 2017, Kobuki et al. published the results of a large case series that evaluated hematological and clinical features of essential thrombocythemia cases CALR-mutations, including 149 ET patients.[21] The JAK2 V617F mutation was detected in 78 (52%) patients, CALR mutations in 39 (26%), and MPL mutations in five (3%). The authors reported that patients with CALR-mutated ET exhibited lower hemoglobin levels and higher platelet counts, indicating that patients with CALR-mutated ET display a phenotype favoring megakaryopoiesis as opposed to the skewed erythropoiesis found in patients with JAK2-mutated ET. Lastly, patients with CALR-mutated ET had a significantly lower risk of thrombosis than patients with JAK2-mutated ET thrombotic events (7.7% versus 26%; $p < 0.05$).

Quantitative Measurement of Allelic Burden

Recent efforts are underway to link the presence of JAK2, MPL and CALR mutations and the quantitative measurement of mutation allele burden with clinical features and biological behavior.

CALR

In 2018, Oh et al. published the results of a small case series (n=24) to evaluate the clinical implications of CALR allele burden in patients with MPNs.[22] The study reported that an increased CALR mutation allele burden was associated with overt primary myelofibrosis. Patients with >70% mutation allele burdens in myeloid cells had a significantly longer time from diagnosis ($P = 0.007$), more bone marrow fibrosis ($P = 0.010$), and lower hemoglobin ($P = 0.007$).

JAK2

In 2007, two large case series were published that assessed the clinical differences between PV patients that were homozygous versus heterozygous for the V617F allele in JAK2.[23,24] These studies reported associations of homozygous states with older age, higher hemoglobin level at diagnosis, leukocytosis, more frequent pruritus, increased incidence of fibrotic transformation, and larger spleen volumes.

Two case series published in 2008 and 2009 reported that patients with low JAK2 V617F allele burdens (1-25%) appeared to exhibit shortened survival, postulating that these patients represented a myelodepleted subset of affected patients.[25,26] Other case series reported that low allele burden was associated with increased platelet count.[27]

In 2009 Hussein et al. reported on a large case series which demonstrated that although there was significant overlap in JAK2 V617F allele burden among various MPNs, quantitative measurements suggested discriminatory differences between patients with ET and pre-PMF.[28] PMF with different stages of myelofibrosis all yielded similar V617F allele burden. At initial presentation 25% of pre-PMF cases exhibited an allele burden exceeding 50% (n=102). In ET, all patients had <40% V617F alleles burden (n=90; p<0.001). However, an increase in V617F alleles during follow-up could not be linked to fibrosis or blastic progression but was related to polycythemic transformation in ET.

Two of the largest case series published to date on quantitative testing of JAK2 V617F have reported conflicting results with regard to increased allele burden being associated with increased thrombosis. In 2009, Carobbio et al. reported on 390 ET and 329 PV patients that were positive for JAK2 V617F. This case series reported that the presence of JAK2 V617F was associated with increases in disease duration (p=0.02 and p<0.001 for ET and PV, respectively).[29] In addition, for the entire sample, allele burden >50% was associated with increased thrombosis (p=0.002), with thrombosis being higher in PV patients compared with ET patients.

However, in 2010, Passamonti et al. reported on 320 patients with PV who were positive for JAK2 V617F, reporting that high allele burden (≥50%) was associated with increases in disease duration (p<0.001), hemoglobin levels (p=0.001), WBC count (p=0.001), spleen size (p=0.001), and occurrence of myelofibrosis (p=0.03).[27] By contrast, the risk of developing AML as well as that of thrombosis was not significantly related to mutant allele burden.

Studies published in 2010 and 2013 that evaluated allele burden with respect to the spleen reported that decreased allele burden of JAK2 V617F correlated with reductions in spleen volume, but was not associated with a decrease risk of relapse after an allogeneic hematopoietic cell transplant.[30,31]

More recently, in 2018, Kuo et al. published the results of a large case series (n=203) that evaluated the clinical and prognostic significance of JAK2 V617F and CALR allele burden in Taiwanese patients with primary myelofibrosis (PMF).[32] The authors reported that pre-PMF patients had a lower JAK2 V617F allele burden than patients with PMF, which is in directly conflict to the results published earlier by Hussein et al..[28] In addition, a lower JAK2 V617F allele burden was associated with shorter OS and decreased leukemia-free survival (LFS). Lastly, the allele burden of CALR mutations remained unchanged, while some JAK2 V617F mutations showed clonal expansion in patients during secondary acute myeloid leukemia transformation. The authors concluded that a higher JAK2 V617F allele burden was an independent predictor of better outcomes in PMF.

Also in 2018, Misawa et al. reported on allele burden of JAK2 V617F in a Japanese case series including 166 patients with PV, 212 patients with ET, 23 patients with pre-PMF, 65 patients with overt PMF, and 27 patients as secondary myelofibrosis.[33] Median JAK2V617F allele burdens calculated within JAK2V617F mutation-positive patients were 77.6% in PV, 30.7% in ET, 38.0% in pre-PMF, and 48.2% in overt PMF. Therefore, compared with ET patients, pre-PMF patients showed higher JAK2V617F allele burden. In addition, overt PMF patients tended to show similar JAK2V617F allele burdens compared to pre-PMF patients (p = 0.372). Both of these findings are similar to those reported by Hussein et al. in an earlier study.[28]

<u>MPL</u>

In 2013, Rumi et al. published the results of a case series of 62 MPL positive patients (n= 40 ET, 14 PMF, and 8 post-ET myelofibrosis) that assessed MPL allele burden.[15] Allele burden ranged from 0.8%-94.7%. Allele burden in patients with ET was statistically significantly lower compared with PMF or post-ET myelofibrosis patients (p≤0.02). Higher median allele burden was observed in patients with the MPL p.Trp515Lys mutation (56.2%) compared to those with the MPL p.Trp515Leu mutation (32.9%). Overall, MPL allele burden was significantly associated with increased disease duration (p<0.013) and a significant association was found between MPL-mutant allele burden > 50% and marrow fibrosis.

Overall, studies reporting on qualitative allele burden have mainly evaluated the JAK2 V617F mutation, and have been heterogeneous in terms the disease definitions used, testing methods, sample type (bone marrow versus circulating blood cells), study design and patient ethnicity. As a result, the reports have been conflicting and inconclusive. Therefore the analytic and clinical validity, as well as the clinical utility of these quantitative assays has not been proven for any JAK2/MPL or CALR variant.

CLINICAL PRACTICE GUIDELINES

National Comprehensive Cancer Network (NCCN)

In 2024, NCCN updated their clinical practice guidelines for Myeloproliferative Neoplasms (Version 1.2025) in **adults.**[2] The guidelines state the following:

"Molecular testing on blood or bone marrow for JAK2 V617F mutations is recommended as part of initial workup for all patients. If JAK2 V617F mutation testing is negative, molecular testing for CALR and MPL mutations should be performed for patients with suspected ET and MF; molecular testing for the JAK2 exon 12 mutation should be done for those with suspected PV and negative for the JAK2 V617F mutation. Alternatively, molecular testing using the multigene NGS panel that includes JAK2, CALR, and MPL can be used as part of initial workup for all patients."

World Health Organization (WHO)

In 2017, the WHO updated their diagnostic criteria for MPNs. This update was not based on a systematic review of the evidence, but on repeat validation studies. Currently, the WHO diagnostic criteria requires the following genetic tests as one of several major criteria that must be fulfilled:[34]

1. Patients with suspicion of primary myelofibrosis (PMF):
    - Presence of JAK2, CALR, or MPL mutation
    - If negative for JAK2, CALR or MPN mutations, "searching for the most frequent accompanying mutations (eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*) *are of help*"
2. Patients with suspicion of essential thrombocythemia (ET):
    - Presence of JAK2, CALR, or MPL mutation
3. Patients with suspicion of polycythemia vera (PV)
    - Presence of JAK2V617F or JAK2 exon 12 mutation

The additional genes mentioned in the WHO criteria as being "of help" in evaluating MPN in triple-negative patients, are not backed by any references or additional information in the 2017 update. However, in the 2016 update, this optional criteria is backed by two references in the WHO publication.[1]

The additional genes to assess in triple-negative cases are frequently found in heterogeneous patients that have features that overlap between MPN and myelodysplastic syndrome. The genes most commonly mutated in chronic myelomonocytic leukemia (CMML) (SRSF2, TET2, and/or ASXL1) are those suggested for additional work-up in triple-negative MPN patients.

The references that back this suggestion report the results of studies done in research settings and used non-standard, cost-prohibitive deep-sequencing as the method of mutation detection.

EVIDENCE SUMMARY

Despite insufficient evidence of clinical utility, genetic testing for the presence of mutations in JAK2, CALR and/or MPL are required to meet both the National Comprehensive Cancer Network (NCCN) and the World Health Organization (WHO) criteria as part of the diagnostic workup of patients for classic BCR-ABL1 negative MPNs, including essential thrombocythemia, primary myelofibrosis and polycythemia vera. One of the benefits of testing lies in the prognostic significance of mutation status in one or more of the three genes associated with BCR-ABL1 MPNs, as it has been established that that mutations in JAK2 and MPL confer decreased overall survival and higher risk of thrombosis than patients carrying a CALR mutation. In addition, the presence of a CALR mutation correlates with decreased leukemic transformation compared to the presence of mutations in MPL or JAK2. However, the true benefit of testing is that it ends the diagnostic odyssey for patients suspected of a BCR-ABL1 negative MPN. Therefore, JAK2, MPL, and/or CALR genetic testing may be considered medically necessary as part of the diagnostic workup when criteria are met.

There is insufficient evidence to show that JAK2, MPL, and/or CALR quantitative testing can predict disease prognosis or leads to changes that improve overall health outcomes in patients with classic MPNs. In addition, NCCN currently recommends against the use of quantitative testing of the JAK2V617F allele because its ability to determine treatment efficacy is not well-established at this time. NCCN does not address quantitative testing of any other JAK2 variants or any variants in CALR or MPL at this time. Therefore, quantitative testing of JAK2, MPL, and/or CALR genes and allele is considered not medically necessary for any indication, including prognosis or management.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.
The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the

research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

CODES*		
CPT	0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
	0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected
	0027U	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
	0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
	0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
	0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
	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
	81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
	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
	81402	Molecular pathology procedure level 3 – which includes MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), common variants (eg, W515A, W515K, W515L, W515R)
	81403	Molecular pathology procedure, Level 4 – which includes JAK2 (Janus kinase 2) (eg, myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed, and MPL (myeloproliferative leukemia virus oncogene,

		thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), exon 10 sequence.
	81450	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
	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
HCPCS	None	

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

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POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
7/2023	Annual Review. Non-covered indications changed from investigational to not medically necessary. Added not medically necessary criteria for repeat testing.
1/2024	Q1 2024 code set update. Revised code descriptions
6/2024	Annual review. Criteria expanded to allow for tests that reflex to additional gene testing.
12/2024	Interim update. Add medical necessity criteria for targeted multi-gene testing for MPNs.
5/2025	Annual review. No changes to codes or criteria.