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| <b>MEDICAL POLICY</b>   | <b>Genetic Testing: <i>JAK2, CALR, and MPL</i></b><br><b>(All Lines of Business Except Medicare)</b> |
| <b>Effective Date: 04/01/2021</b>   | Medical Policy Number: 72  |
| <br>4/1/2021 | Medical Policy Committee Approved Date: 12/17;<br>7/18; 7/19; 2/2020; 4/2020; 12/2020; 3/2021        |
| Medical Officer   | Date   |

See Policy CPT CODE section below for any prior authorization requirements

**SCOPE:**

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

**APPLIES TO:**

All lines of business except Medicare

**BENEFIT APPLICATION**

Medicaid 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.

**POLICY CRITERIA**

**Note:**

- This policy does not address genetic testing for the BCR-ABL1 (t(9;22)) fusion gene, which may be considered medically necessary.

**Qualitative Testing**

JAK2 Gene, V617F Mutation Testing

- I. Genetic testing for the JAK2 V617F mutation may be considered **medically necessary and covered** when **both** of the following criteria are met (A.- B.):
  - A. Suspicion of essential thrombocythemia (ET), primary myelofibrosis (PMF) or polycythemia vera (PV) based on the presence of characteristic clinical, pathological

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and/or histological findings outlined in the 2016 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.

### JAK2 Gene, Exon 12 Testing

- II. Genetic testing for mutations in exon 12 of JAK2 may be considered **medically necessary and covered** when **all** of the following criteria are met (A.- C.):
  - A. Suspicion of polycythemia vera (PV) based on the presence of characteristic clinical, pathological and/or histological findings (see [Policy Guidelines](#) below for WHO criteria for PV); **and**
  - B. JAK2 V617F testing is negative; **and**
  - C. Genetic test results will directly impact medical management of the individual being tested.

### CALR and/or MPL Gene Testing

- III. Genetic testing for mutations in CALR **and/or** MPL may be considered **medically necessary and covered** when **all** of the following criteria are met (A.- C.):
  - A. Suspicion of essential thrombocythemia (ET) or primary myelofibrosis (PMF) based on the presence of characteristic clinical, pathological and/or histological findings (see [Policy Guidelines](#) below for WHO criteria for ET and PMF); **and**
  - B. JAK2 V617F testing is negative; **and**
  - C. Genetic test results will directly impact medical management of the individual being tested.

### Non-Covered Qualitative Testing

- IV. Genetic testing of JAK2, CALR **and/or** MPL gene mutations is considered **investigational and is not covered** 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. Patients wanting to undergo JAK2 exon 12, CALR and/or MPL testing without having first received a negative test result for JAK2 V617F.
- V. Multi-gene panel testing is considered **investigational and is not covered** for the evaluation of BCR-ABL1 negative MPNs.

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### Quantitative Testing

- VI. Quantitative genetic testing (e.g., to determine allele burden) for **any** mutation in the *JAK2*, *CALR* or *MPL* genes is considered **investigational and is not covered** for any indication.

Link to [Policy Summary](#)

## 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.<sup>1-3</sup>

### 2016 World Health Organization [WHO] Classification Criteria for Myeloproliferative Neoplasms<sup>1</sup>

#### *Essential Thrombocythemia (ET)*

- Platelet count  $\geq 450 \times 10^9/L$
- 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
- Presence of a clonal marker or absence of evidence for reactive thrombocytosis

#### *Polycythemia Vera (PV)*

- Hemoglobin  $>16.5$  g/dL in men, or  $>16.0$  g/dL in women
- Hematocrit  $>49\%$  in men, or  $>48\%$  in women
- Increased red cell mass (RCM)
- BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- Subnormal serum erythropoietin level

#### *Primary Myelofibrosis (PMF)*

- Megakaryocytic proliferation and atypia, without reticulin fibrosis  $>$ grade 1\*, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis (Pre-PMF only)
- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 (overt PMF only)
- absence of minor reactive BM reticulin fibrosis

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

Definitions

*Qualitative Testing:* Testing for the presence or 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).

**CPT CODES**

| All Lines of Business Except Medicare |  |
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| Prior Authorization Required          |  |
| 0017U                                 | Oncology (hematolymphoid neoplasia), <i>JAK2</i> mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of <i>JAK2</i> mutation not detected or detected  |
| 0027U                                 | <i>JAK2</i> (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15   |
| 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 |
| 81219                                 | <i>CALR</i> (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9  |
| 81270                                 | <i>JAK2</i> (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant  |
| 81279                                 | <i>JAK2</i> (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)  |
| 81338                                 | <i>MPL</i> ( <i>MPL</i> proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)   |
| 81339                                 | <i>MPL</i> ( <i>MPL</i> proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10   |
| 81402                                 | Molecular pathology procedure level 3 – which includes <i>MPL</i> (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) (eg, myeloproliferative disorder), common variants (eg, W515A, W515K, W515L, W515R)                                    |

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| 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   | Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed                                  |
| 81455   | Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (EG, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed |
| <b>No Prior Authorization Required</b>  |   |
| 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   |
| 0040U   | BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative  |
| 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   |
| <b>Unlisted Codes</b><br>All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b> |   |
| 81479   | Unlisted molecular pathology procedure  |

**DESCRIPTION**

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.

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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<sup>-</sup> 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.<sup>2</sup>

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.<sup>4</sup> However, transformation to AML is the most frequent cause of death among PMF patients.<sup>5</sup>

#### Genetic Abnormalities in BCR-ABL1<sup>-</sup> MPNs

The clinical presentation of patients with BCR-ABL1<sup>-</sup> 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.<sup>2</sup> 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.<sup>2</sup>

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.<sup>2</sup>

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, DNMT3A, SF3B1, SRSF2, U2AF1 and TP53, but their prevalence is unknown.<sup>2</sup>

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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)

**REVIEW OF EVIDENCE**

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 January of 2021.

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 JAK2, 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.<sup>6,7</sup>

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.<sup>8</sup> 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.<sup>9,10</sup> 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, Dahebre 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).<sup>11</sup> 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-

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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.<sup>12</sup> Subsequent studies identified additional mutations in the MPL gene in a small but growing number of patients with ET and PMF.<sup>10,12-14</sup>

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.<sup>13,15-17</sup> However, association with platelet counts showed conflicting results, being associated with high platelet levels in two studies ( $p \leq 0.004$ )<sup>13,17</sup> and low platelet levels ( $p = 0.0001$ ) in one study.<sup>15</sup>

*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.<sup>18-20</sup> 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 ( $p = 0.02$ ).<sup>18</sup> 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.<sup>19</sup> 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.<sup>21</sup> 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%;  $p < 0.05$ ).



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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.<sup>22</sup> 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*.<sup>23,24</sup> 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.<sup>25,26</sup> Other case series reported that low allele burden was associated with increased platelet count.<sup>27</sup>

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.<sup>28</sup> 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).<sup>29</sup> 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

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myelofibrosis (p=0.03).<sup>27</sup> 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.<sup>30,31</sup>

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).<sup>32</sup> 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..<sup>28</sup> 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.<sup>33</sup> 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.<sup>28</sup>

*MPL*

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.<sup>15</sup> 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 May 2020, NCCN updated their clinical practice guidelines for myeloproliferative neoplasms (MPNs) in **adults**. The guidelines state that their diagnostic criteria for MPNs are based on the 2017 WHO criteria (described below), requiring a combination of clinical, laboratory, cytogenetics and molecular tests.

The current NCCN guidelines recommended that workup based on the suspicion of myeloproliferative neoplasms (MPN) included molecular testing, with two options for the initial work-up of all patients (1. or 2.):<sup>2</sup>

1. Patients with suspicion of:
  - a. Essential thrombocythemia (ET) and primary myelofibrosis (PMF):
    - Test for JAK2 V617F
    - If negative for JAK2 V617F, then test for CALR and MPN
  - b. Polycythemia vera (PV):
    - Test for JAK2 V617F
    - If negative for JAK2 V617F, then test for mutations in JAK2 exon 12; **OR**
2. Patients with suspicion of any MPN: use multigene NGS panel that includes JAK2, CALR, and MPL.

However, NCCN states that “next generation sequencing (NGS) remains a research tool in many situations” and that multi-gene NGS panels “may be useful to establish clonality in select circumstances.”

### 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:<sup>34</sup>

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

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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.<sup>1</sup> 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.

**POLICY 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 investigational for any indication, including prognosis or management.

**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 Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days’ notice of policy changes that are restrictive in nature.

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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.

## REGULATORY STATUS

### Mental Health Parity Statement

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.

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