Medical Policy

**Tyrosine Kinase Mutations in Myeloproliferative Neoplasms**

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- Policy: Medicare
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**Policy Number:** 079
BCBSA Reference Number: 2.04.60

**Related Policies**
None

**Policy**

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**
**Medicare HMO BlueSM and Medicare PPO BlueSM Members**

Janus kinase 2 (JAK2) and MPL mutation testing in the diagnosis of patients presenting with clinical, laboratory, or pathological findings suggesting classic forms of myeloproliferative neoplasms (MPN), that is, polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) may be considered **MEDICALLY NECESSARY**.

**Note:**
- Patients suspected to have polycythemia vera (PV) should first be tested for the most common finding JAK2V617F. If testing is negative, further testing to detect other JAK2 tyrosine kinase mutations, e.g., in exon 12, is warranted.
- Patients suspected to have essential thrombocythemia (ET) or primary myelofibrosis (PMF) should first be tested for JAK2 mutations, as noted. If testing is negative, further testing to detect MPL mutations is warranted.

JAK2 tyrosine kinase and MPL mutation testing in all other circumstances including, but not limited to, the following situations is **INVESTIGATIONAL**:
- Diagnosis of nonclassic forms of MPNs,
- Molecular phenotyping of patients with MPNs,
- Monitoring, management, or selecting treatment in patients with MPNs, and
- Diagnosis or selection of treatment in patients with Down syndrome and acute lymphoblastic leukemia.

**Prior Authorization Information**

**Commercial Members: Managed Care (HMO and POS)**
Prior authorization is **NOT** required.

**Commercial Members: PPO, and Indemnity**
Prior authorization is **NOT** required.

**Medicare Members: HMO Blue**
Prior authorization is **NOT** required.

**Medicare Members: PPO Blue**
Prior authorization is **NOT** required.

**CPT Codes / HCPCS Codes / ICD-9 Codes**
The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member. A draft of future ICD-10 Coding related to this document, as it might look today, is included below for your reference.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81270</td>
<td>JAK2 (Janus kinase 2) <em>(e.g., myeloproliferative disorder)</em> gene analysis, p.Val617Phe (V617F) variant</td>
</tr>
<tr>
<td>81402</td>
<td>Molecular pathology procedure, Level 3 *(e.g., &gt;10 SNPs [single-nucleotide polymorphism], 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T cell receptor gene rearrangements, duplication/deletion variants 1 exon) – which includes MPL <em>(myeloproliferative leukemia virus oncogene, thrombopoietin receptor TPOR)</em> <em>(e.g., myeloproliferative disorder), common variants (e.g., W515A, W515K, W515L, W515R)</em></td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 *(e.g., analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR [polymerase chain reaction] in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) – which includes JAK2 <em>(Janus kinase 2)</em> <em>(e.g., myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed</em></td>
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### ICD-9 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-9-CM diagnosis codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>202.60</td>
<td>Malignant mast cell tumors, unspecified site, extranodal and solid organ sites</td>
</tr>
<tr>
<td>202.61</td>
<td>Malignant mast cell tumors, lymph nodes of head, face, and neck</td>
</tr>
<tr>
<td>202.62</td>
<td>Malignant mast cell tumors, intrathoracic lymph nodes</td>
</tr>
<tr>
<td>202.63</td>
<td>Malignant mast cell tumors, intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>202.64</td>
<td>Malignant mast cell tumors, lymph nodes of axilla and upper limb</td>
</tr>
<tr>
<td>202.65</td>
<td>Malignant mast cell tumors, lymph nodes of inguinal region and lower limb</td>
</tr>
<tr>
<td>202.66</td>
<td>Malignant mast cell tumors, intrapelvic lymph nodes</td>
</tr>
<tr>
<td>202.67</td>
<td>Malignant mast cell tumors, spleen</td>
</tr>
<tr>
<td>202.68</td>
<td>Malignant mast cell tumors, lymph nodes of multiple sites</td>
</tr>
<tr>
<td>205.10</td>
<td>Chronic myeloid leukemia, without mention of having achieved remission</td>
</tr>
<tr>
<td>205.11</td>
<td>Chronic myeloid leukemia, in remission</td>
</tr>
<tr>
<td>205.12</td>
<td>Chronic myeloid leukemia, in relapse</td>
</tr>
<tr>
<td>238.4</td>
<td>Polycythemia vera</td>
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### ICD-10 Diagnosis Codes

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>C96.2</td>
<td>Malignant mast cell tumor</td>
</tr>
<tr>
<td>C92.10</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission</td>
</tr>
<tr>
<td>C92.11</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, in remission</td>
</tr>
<tr>
<td>C92.12</td>
<td>Chronic myeloid leukemia, BCR/ABL-positive, in relapse</td>
</tr>
<tr>
<td>C94.40</td>
<td>Acute panmyelosis with myelofibrosis not having achieved remission</td>
</tr>
<tr>
<td>C94.41</td>
<td>Acute panmyelosis with myelofibrosis, in remission</td>
</tr>
<tr>
<td>C94.42</td>
<td>Acute panmyelosis with myelofibrosis, in relapse</td>
</tr>
<tr>
<td>C94.6</td>
<td>Myelodysplastic disease, not classified</td>
</tr>
<tr>
<td>D45</td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td>D47.1</td>
<td>Chronic myeloproliferative disease</td>
</tr>
<tr>
<td>D47.3</td>
<td>Essential (hemorrhagic) thrombocythemia</td>
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### Description

Myeloproliferative neoplasms (MPNs) are a category of uncommon overlapping blood diseases characterized by the production of one or more blood cells -- chronic myeloid leukemia, polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis, chronic eosinophilic leukemia, and others. Mutations in the gene coding for the JAK2 protein and in the gene MPL coding for the thrombopoietin receptor that result in constitutive activation of the kinase have been associated with myeloproliferative neoplasms and with acute lymphoblastic leukemia in Down syndrome patients.

A common finding in many of the MPNs is clonality, and a central pathogenic feature is the presence of a mutated version of the tyrosine kinase enzyme, such that it is abnormally constitutively activated.

These mutations are used as laboratory tools to aid in diagnosis and management of disease. To that end, at least four potential intended uses for mutation testing have been considered, including:

- Diagnosis of patients with clinical, laboratory or pathological findings suggesting classic MPNs (PV, ET, or PMF),
- Diagnosis or selection of treatment for patients with Down syndrome acute lymphoblastic leukemia,
- Phenotyping of disease subtypes in patients with MPNs to establish disease prognosis, and
- Identification, selection and monitoring of treatment.

### Summary

There is an extensive and growing body of literature providing information on the clinical validation of the JAK2V617F as a distinctive marker of patients with Philadelphia chromosome-negative classic MLNs. In almost a dozen reports (all case series), JAK2V617F has been found as a unique clonal finding in patients with PV, ET, or PMF.

While multiple reports have replicated the finding of high specificity in patients with ET and PMF, unfortunately, these diseases appear more heterogeneous than PV, and the mutation can be identified in only 30% to 50% of cases. However, high specificity assures that even in the absence of high sensitivity, the predictive value of a positive test approaches 100%. Testing for these mutations appears medically necessary in the diagnosis of patients with signs and symptoms of suspected PV, ET, or PMF.
The value of treatment itself remains uncertain and is likely to be complicated by the finding that the JAK2 mutation alone may not be necessary or sufficient to cause clinically relevant disease. For this reason, these uses of JAK2 mutation testing is investigational in these situations.

Interesting reports have appeared in the literature linking JAK2 mutations to patients with Down syndrome developing ALL. This information is of uncertain diagnostic value and to date has no prognostic or therapeutic use. Therefore, the test is investigation for this use.

### Policy History

<table>
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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>3/2014</td>
<td>Coding information clarified</td>
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<tr>
<td>1/2014</td>
<td>Removed CPT codes: 83890-83898; 83900-83909; 82908; 83912-83914; 88384-88386 as the codes have been deleted since 1/1/2013</td>
</tr>
<tr>
<td>4/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
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### Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

### References

11. Jones AV, Kreil S, Zoi K et al. Widespread occurrence of the JAK2 V617F mutation in chronic
expression analysis in myeloproliferative disorders and secondary polycythaemia. Br J Haematol
14. Campbell PJ, Scott LM, Buck G et al. Definition of subtypes of essential thrombocythaemia and
relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet
15. Wolanskyj AP, Lasho TL, Schwager SM et al. JAK2 mutation in essential thrombocythaemia: clinical
16. Campbell PJ, Griesshammer M, Dohner K et al. V617F mutation in JAK2 is associated with poorer
17. Tefferi A, Lasho TL, Schwager SM et al. The JAK2(V617F) tyrosine kinase mutation in myelofibrosis
19. Sidon P, El Housni H, Dessars B et al. The JAK2V617F mutation is detectable at very low level in
peripheral blood of healthy donors. Leukemia 2006; 20(9):1622.
20. Steensma DP. JAK2 V617F in myeloid disorders: molecular diagnostic techniques and their clinical
22. McMullin MF, Reilly JT, Campbell P et al. Amendment to the guideline for diagnosis and investigation
diagnostic criteria for polycythemia vera, essential thrombocythaemia, and primary myelofibrosis:
24. Kondo T, Okuno N, Naruse H et al. Validation of the revised 2008 WHO diagnostic criteria in 75
suspected cases of myeloproliferative neoplasm. Leuk Lymphoma 2008; 49(9):1784-91.
25. Steensma DP, Dewald GW, Lasho TL et al. The JAK2 V617F activating tyrosine kinase mutation is
an infrequent event in both "atypical" myeloproliferative disorders and myelodysplastic syndromes.
26. Scott LM, Tong W, Levine RL et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic
mutations in JAK2V617F-negative polycythemia vera. Leukemia 2007; 21(9):1960-3.
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30. Pardanani AD, Levine RL, Lasho T et al. MPL515 mutations in myeloproliferative and other myeloid
31. Beer PA, Campbell PJ, Scott LM et al. MPL mutations in myeloproliferative disorders: analysis of the
MPLW515K mutation in chronic myeloproliferative disorders with locked nucleic acid-modified probes


49. Tefferi A, Lasho TL, Huang J et al. Low JAK2V617F allele burden in primary myelofibrosis, compared to either a higher allele burden or unmutated status, is associated with inferior overall and leukemia-free survival. Leukemia 2008; 22(4):756-61.


