Medical Policy
Tyrosine Kinase Mutations in Myeloproliferative Neoplasms

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Policy Number: 079
BCBSA Reference Number: 2.04.60
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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.
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.

See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this procedure is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Service Type</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Commercial PPO and Indemnity</th>
<th>Medicare HMO Blue℠</th>
<th>Medicare PPO Blue℠</th>
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<tbody>
<tr>
<td></td>
<td>No</td>
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CPT Codes / HCPCS Codes / ICD Codes

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.

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

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
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<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>81270</td>
<td>JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant</td>
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<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 (myeloproliferative leukemia virus oncogene, thrombopoietin receptor TPOR) (e.g., myeloproliferative disorder), common variants (e.g., W515A, W515K, W515L, W515R)</td>
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<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 (Janus kinase 2)</td>
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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.

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.

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<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>8/2015</td>
<td>Clarified coding information.</td>
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<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>
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<tr>
<td>4/2013</td>
<td>New references from BCBSA National medical policy.</td>
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</table>
No changes to policy statements.

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