Medicare Local Coverage Determination Policy

MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease

CPT: 81206,81207,81219,81270,81279,81339,81450

CMS Policy for Iowa, Kansas, Missouri, and Nebraska

Local policies are determined by the performing test location. This is determined by the state in which your performing laboratory resides and where your testing is commonly performed.

Medically Supportive ICD Codes are listed on subsequent page(s) of this document.

Coverage Indications, Limitations, and/or Medical Necessity

This policy provides coverage for multi-gene non-next generation sequencing (NGS) panel testing and NGS testing for the diagnostic workup for myeloproliferative disease (MPD), also known as myeloproliferative neoplasms (MPNs), and limited coverage for single-gene testing of patients with BCR-ABL negative MPD. BCR-ABL negative MPD includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).

For laboratories performing single gene technologies, a sequential genetic testing approach is expected. Once a positive result is obtained and the appropriate diagnosis is established, further testing should stop. Reflex testing to the next gene will be considered reasonable and necessary if the following sequence of genetic tests produce a negative result:

1. BCR-ABL negative test results, progress to #2

2. JAK 2, cv negative test results, progress to #3 or #4

3. JAK, exon 12 (JAK2 exon 12 is only done when PV is suspected)

4. Calreticulin (CALR)/MPL (CALR/MPL is only done when either ET or PMF is suspected; testing for CALR/MPL does NOT require a negative JAK2 exon 12, just a negative JAK2 V617F result)

Genetic testing of the JAK2 V617F mutation is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet World Health Organization's (WHO) diagnostic criteria for myeloproliferative disease (i.e., PV, ET, PMF) **if** JAK2 V617F were identified.

Genetic testing of JAK2 exon 12, performed to identify PV, is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet WHO's diagnostic criteria for PV, if JAK2 exon 12 testing were positive; **and**
- JAK2 V617F mutation analysis was previously completed and was negative.

Genetic testing of the CALR gene (only found in ET and PMF) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet WHO's diagnostic criteria for MPD (i.e. ET, PMF) if a clonal marker were identified.

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Note: In a single-gene sequential approach (not mandated by this policy), CALR would be a higher priority single gene test than MPL because:

- CALR mutations is more prevalent than MPL mutations in ET/PMF patients; and
- CALR mutations are reported to predict a more indolent disease course than that of patients with JAK2 mutations.

For laboratories performing NGS or "hotspot" testing platforms: Molecular testing for BCR-ABL, JAK 2, JAK, exon 12, and CALR/MPL genes by NGS is covered as medically necessary for the identification of myeloproliferative disorders.

Summary of Evidence

Myeloproliferative Disorders

Myeloproliferative disorders are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include PV, ET, PMF, and chronic myelogenous leukemia (CML). The WHO further classifies PV, ET, and PMF as Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). The diagnosis of an MPN is suspected based upon clinical, laboratory, and pathological findings (i.e., bone marrow morphology). MPNs are related, but distinct from, myelodysplastic syndromes (MDS). In general, MDS are characterized by ineffective or dysfunctional blood cells, while MPN are characterized by an increase in the number of blood cells.

Polycythemia Vera (PV)

PV is a chronic MPD characterized by increased hemoglobin, hematocrit, and red blood cell mass. There is an associated increased risk for thrombosis and transformation to acute myelogenous leukemia (AML) or PMF; however, patients are often asymptomatic. Criteria for a diagnosis of PV are based upon complete blood count (CBC) and clinical features. The JAK2 V617F mutation is present in the vast majority of PV, accounting for approximately 90% of cases. Functionally similar mutations in JAK2 exon 12 account for most remaining cases of JAK2 V617F mutation-negative PV. Together, they are identified in 98% of PV cases and lead to high diagnostic certainty.

Among the proposed revised WHO criteria for diagnosis is presence of the somatic JAK2 V617F mutation or functionally similar exon 12 mutation. Absence of a JAK2 mutation, combined with normal or increased serum erythropoietin level, greatly decreases the likelihood of a PV diagnosis. WHO proposed revision criteria for PV do not address additional molecular markers, including CALR mutation status.

Essential Thrombocythemia (ET)

ET is a disorder of sustained increased platelet count. The majority of ET patients (60%) carry a somatic JAK2 V617F mutation, while a smaller percentage (5-10%) have activating MPL mutations. Revision to the WHO criteria for diagnosis of ET has been proposed and includes exclusion of PV, PMF, CML, MDS, or other myeloid neoplasm. Also included in the proposed major criteria for diagnosis is demonstration of somatic JAK2 V617F mutation or MPL exon 10 mutation.[12] Proposed criteria additionally state that 70% of patients without a JAK2 or MPL mutation carry a somatic mutation of the calreticulin gene. Among confirmed ET cases, mutations in CALR are more common than MPL. Positive CALR mutation status is suggested as indicating a more indolent course.[5]

Primary Myelofibrosis (PMF)

PMF is a rare disorder in which the bone marrow is replaced with fibrous tissue, leading to bone marrow failure. Clinical features are similar to ET. The approximate incidence is 1 in 100,000 individuals. Persons can be asymptomatic in the early stages of the disease. For such patients, treatment may not initially be necessary. Progression of the disease can include transformation to AML. Treatment is generally symptomatic and aimed at preventing complications.

Demonstration of a clonal marker is important for diagnosis. Somatic molecular markers in PMF patients are similar to those in patients with ET, and include JAK2 V617F, MPL, and CALR. Somatic mutations in JAK2 are identified in 50-60% of PMF cases, and MPL mutations in 10%. Mutations in CALR are less common than JAK2, but more common than MPL.

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Molecular Genetic Testing
One JAK2 gene mutation, V617F, is most commonly reported, occurring in over 90% of all PV cases and about 50% of ET cases. Testing for JAK2 V617F gene mutations can be useful in diagnosis and is incorporated into the WHO's diagnostic criteria for these conditions.

The thrombopoietin receptor MPL is one of several JAK2 cognate receptors and is considered essential for myelopoiesis. The mutation frequency of MPL mutations associated with myeloproliferative disorders is substantially less (<10%) than JAK2 mutations. The guideline group for the British Committee for Standards in Haematology recommended a modification to the 2008 WHO criteria for ET to include the presence of an acquired pathogenetic mutation (e.g., in the JAK2 or MPL genes).3 Therefore, MPL gene testing may be indicated for individuals who would meet WHO's diagnostic criteria for MPD if a clonal marker were identified.

CALR mutations have been identified in patients with MPNs and recent studies have investigated the utility of CALR mutation testing for the diagnosis and classification of MPNs. The mutations themselves are variable; however, generally focused in the exon 9 region.

Studies have shown that a significant proportion of patients with MPNs and normal JAK2 V617F mutation testing have a CALR gene mutation. CALR mutations account for a large proportion of JAK2/MPL-negative ET and PMF cases. Approximately 60% of JAK2/MPL-negative ET patients are CALR-positive and 30% of JAK2/MPL-negative PMF patients are CALR-positive. Overall, CALR mutations are identified in approximately 21% of ET cases and 16% of PMF cases. CALR mutations have not been reported in PV case series.2

For this reason, CALR gene testing may be indicated for individuals who would meet WHO's diagnostic criteria for MPD if a clonal marker were identified. Proponents have argued for revised WHO criteria that includes CALR mutation status in the classification system for ET and PMF.12 Current National Comprehensive Cancer Network® (NCCN) guidelines do not make recommendations for CALR genetic testing; however, these guidelines are specific to MDS and do not broadly address MPNs, such as ET or PMF. Somatic mutations in non-MDS genes, such as CALR, are listed as being associated with conditions that can mimic other myelodysplastic syndromes.

Aside from diagnostic utility, some research suggests distinct clinical outcomes associated with CALR mutation status; however, the findings have not been confirmed in other studies. It is suggested that ET patients with CALR mutations have lower polycythemic transformation rates, but not lower myelofibrotic transformation rate, compared with ET patients harboring a JAK2 mutation. Others reported a higher platelet count, younger age of diagnosis, lower leukocyte count, and decreased risk for thrombosis, compared with a JAK2 positive ET population.1 CALR-mutated ET has also been associated with better thrombosis-free survival and lower leukocyte counts; overall survival has been reported as not different among CALR mutated and non-mutated ET.2,15

Although they are useful for establishing a diagnosis, the presence of specific clonal markers does not dictate treatment. Controversy exists generally regarding the treatment of asymptomatic individuals with ET. Some argue against treatment if there are no associated complications. In general, the main goal of treatment with PV and ET is to identify persons at high risk for thrombosis and prevent complications. Persons with PV and ET are determined to be at high-risk due to age >60 years and past history of thrombotic event(s). CALR mutational status is not currently used for risk stratification.11

Analysis of Evidence (Rationale for Determination)Level of evidence
Quality – Strong
Strength – Strong
Weight – Moderate

In summary, multiple studies have demonstrated the diagnostic value of CALR mutation status in a population of JAK2 and MPL negative patients with suspected ET and PMF. The presence of a somatic CALR mutation can prove useful in obtaining an accurate diagnosis. Emerging evidence suggests possible differences in clinical phenotype among the associated clonal markers, including CALR-positive ET cases. However, CALR mutation status is currently not incorporated into clinical risk stratification and more research is needed in this area.

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Please refer to the Limitations or Utilization Guidelines section on previous page(s) for frequency information.

The ICD10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the limited coverage test highlighted above that are also listed as medically supportive under Medicare's limited coverage policy. **If you are ordering this test for diagnostic reasons that are not covered under Medicare policy, an Advance Beneficiary Notice form is required.**
Note—Bolded diagnoses below have the highest utilization

Code	Description
DX Codes	Description
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C92.11	Chronic myeloid leukemia, BCR/ABL-positive, in remission
D72.829	Elevated white blood cell count, unspecified
D47.3	Essential (hemorrhagic) thrombocythemia
D75.1	Secondary polycythemia
D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease
D75.89	Other specified diseases of blood and blood-forming organs

Visit **QuestDiagnostics.com/MLCP** to view current limited coverage tests, reference guides, and policy information.
To view the complete policy and the full list of medically supportive codes, please refer to the CMS website reference www.cms.gov ►

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