FEP Medical Policy Manual

FEP 2.04.60 JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

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Related Policies:

None

JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms

Description

Somatic (acquired) genetic variants in *JAK2*, *MPL*, and *CALR* genes have been implicated as the underlying molecular genetic drivers for the pathogenesis of myeloproliferative neoplasms (MPN). This evidence review addresses the use of genetic testing for *JAK2*, *MPL*, and *CALR* genes for diagnosis, prognosis, and treatment selection of patients with myeloproliferative neoplasms (MPN).

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for *JAK2*, *MPL*, and *CALR* genes improve the net health outcome in individuals with a suspected myeloproliferative neoplasm.

POLICY STATEMENT

JAK2 testing may be considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera, essential thrombocythemia, or primary myelofibrosis. Based on criteria from the World Health Organization, documentation of a serum erythropoietin level below the reference range for normal is recommended before *JAK2* testing (See Policy Guidelines).

MPL and *CALR* testing may be considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting essential thrombocythemia or primary myelofibrosis.

JAK2, *MPL*, and *CALR* testing is considered **investigational** in all other circumstances including, but not limited to, the following situations:

- Diagnosis of nonclassic forms of myeloproliferative neoplasms
- Molecular phenotyping of patients with myeloproliferative neoplasms
- Monitoring, management, or selecting treatment in patients with myeloproliferative neoplasms.

POLICY GUIDELINES

Testing strategy

Patients suspected to have polycythemia vera should first be tested for the most common finding, *JAK2* V617F. If the testing is negative, further testing to detect other *JAK2* tyrosine kinase variants (eg, in exon 12) is warranted.

Patients suspected to have essential thrombocythemia or primary myelofibrosis should first be tested for *JAK2* variants, as noted. If testing is negative, further testing to detect *MPL* and *CALR* variants is warranted.

Criteria for Polycythemia Testing

Based on the World Health Organization (WHO) major and minor criteria (see Table PG1), documentation of serum erythropoietin level below the reference range for normal meets a minor criterion for polycythemia vera. Therefore, serum erythropoietin testing is recommended before *JAK2* testing.

Table PG1. WHO Diagnostic Criteria for Polycythemia Vera

Major Criteria
• Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women)
• Increased hematocrit (>49% in men or >48% in women)
• Other evidence of increased red cell volume
• Bone marrow biopsy showing hypercellularity for age with trilineage maturation, including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
• *JAK2* V617F or *JAK2* exon 12 variant detected
Minor Criterion

- Serum erythropoietin level below the reference range for normal

Adapted from Arber et al (2016).

WHO: World Health Organization.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG2). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology-"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"-to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence

Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for *JAK2*, *CALR*, and *MPL* testing under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals with a suspected myeloproliferative neoplasm (MPN) who receive genetic testing for *JAK2*, the evidence includes case series, retrospective studies, meta-analyses, and randomized controlled trials (RCTs). The relevant outcomes include OS, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *JAK2* variants are found in nearly 100% of those with polycythemia vera (PV), 60% to 65% of those with essential thrombocytopenia (ET), and 60% to 65% of those with primary myelofibrosis (PMF). In individuals with suspected MPN, a positive genetic test for *JAK2* satisfies a major criterion for the World Health Organization (2016) classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocythemia from the differential diagnosis. The presence of a documented *JAK2* variant may aid in the selection of ruxolitinib, a *JAK2* inhibitor; ruxolitinib, however, is classified as second-line therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *MPL*, the evidence includes case series and retrospective studies. The relevant outcomes include overall survival (OS), disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *MPL* variants are found in approximately 5% of those with ET and PMF. In individuals with suspected MPN, a positive genetic test for *MPL* satisfies a major criterion for the World Health Organization (2016)classification for ET

and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *MPL* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *MPL* genetic testing does not in and of itself result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals with a suspected MPN who receive genetic testing for *CALR*, the evidence includes case series and retrospective studies. The relevant outcomes include OS, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Ph-negative MPN, *CALR* variants are found in approximately 20% to 25% of those with ET and PMF. For individuals with suspected MPN, a positive genetic test for *CALR* satisfies a major criterion for the World Health Organization classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of *CALR* variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through *CALR* genetic testing does not result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

World Health Organization (2016) major criteria for myeloproliferative neoplasms are as follows[6]:

Polycythemia vera: "Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation"

Essential thrombocythemia: "Demonstration of *JAK2* V617F or other clonal markers, or in the absence of a clonal marker, no evidence for reactive thrombocytosis"

Primary myelofibrosis: "Demonstration of *JAK2* V617F or other clonal markers (eg, *MPL* W515K/L), or, in the absence of a clonal marker, no evidence of bone marrow fibrosis [due to underlying inflammatory or other neoplastic disease]."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network published guidelines (v.2.2018) on the workup, diagnosis, and treatment of suspected myeloproliferative neoplasms. For patients with suspicion of myeloproliferative neoplasms, the guidelines recommend "molecular testing (blood) for JAK2 V617F mutation; if negative, test for CALR and MPL mutations (for patients with ET and MF) and JAK2 Exon 12 mutations (for patients with PV)."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
June 2013	Replace policy	References 46, 47, 55, 57 and 58 added. Policy title changed to reflect that MPL is not a tyrosine kinase. No change to policy statements
June 2014	Replace policy	Policy updated with literature review; references 52-56 added. No change in policy statements. Policy title change
June 2015	Replace policy	Policy updated with literature review through January 17, 2015, no references added. Policy statements unchanged.
September 2017	Replace policy	Policy updated with literature review through April 25, 2017; references 3-7, 15-16, 52, 66, and 73-78 added. CALR testing added to the policy. Policy revised with updated genetics nomenclature. Policy statements updated to clarify that JAK2 testing is medically necessary for PV, ET and PMF and added recommendation for documentation of serum erythropoietin levels prior to JAK2 testing, MPL testing is medically necessary for ET and PMF; new medical necessity statement added for CALR testing in ET and PMF. Title changed to “JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms”.
September 2018	Replace policy	Policy updated with literature review through May 10, 2018; reference 64 added. Policy statements unchanged.
December 2019	Replace policy	Policy updated with literature review through June 10, 2019; references added. Policy statements unchanged.