Corporate Medical Policy

Genetic Testing for Myeloproliferative Neoplasms

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 (MPNs). This policy addresses the use of genetic testing of JAK2 and CALR genes for the diagnosis, prognosis, and treatment selection in patients with MPNs.

Myeloproliferative Neoplasms
Myeloproliferative neoplasms (MPNs) are rare overlapping blood diseases characterized by the production of one or more blood cell lines. The most common forms of MPNs include chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), systemic mastocytosis, chronic eosinophilic leukemia, and others. A common finding in many of the MPNs is clonality, and a central pathogenic feature the detection of a somatic (acquired) pathogenic variant in disease-associated genes. Pathogenic variants in disease-associated genes result in constitutively activated tyrosine kinase enzyme or cell surface receptor.

CML and Philadelphia Chromosome
The paradigm for use molecular genetics to revolutionize patient management is CML. A unique chromosomal translocation, (the Philadelphia chromosome Ph) leads to a unique gene rearrangement (BCR-ABL) creating a fusion gene that encodes for a constitutively active Bcr-abl fusion protein. These findings led to the development of targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions.

Ph Negative MPNs
Diagnosis and monitoring of patients with Philadelphia chromosome, Ph negative MPNs have been challenging because many of the laboratory and clinical features of the classic forms of these diseases PV, ET, and PMF can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis or myeloid fibrosis. In addition, these entities can be difficult to distinguish on morphologic bone marrow exam, and diagnosis can be complicated by changing disease patterns: PV and ET can evolve into PMF or undergo leukemic transformation. World Health Organization (WHO) criteria were published as a benchmark for diagnosis in 2001 and updated in 2008. These have been challenging to use because they involve complex diagnostic algorithms, rely on morphologic assessment of uncertain consistency, and require tests that are not well standardized or widely available, such as endogenous erythroid colony formation.

Molecular Genetics of Ph-Negative MPNs

JAK2 Gene
The JAK2 gene, located on chromosome 9, contains the genetic code for making the Janus kinase 2...
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protein, a nonreceptor tyrosine kinase. The Janus kinase 2 (JAK2) protein is part of the JAK/STAT signal transduction pathway that is important for the controlled production of blood cells from hematopoietic stem cells. Somatic (acquired) variants in the JAK2 gene are found in patients with PV (96%), ET (50%), and PMF (50%).

**JAK2 V617F Variant**

In March and April 2005, 4 separate groups using different modes of discovery and different measurement techniques reported on the presence of a novel somatic (acquired) single nucleotide variant in the conserved autoinhibitory pseudokinase domain of the gene encoding JAK2 protein in patients with classic MPNs. The single nucleotide variant caused a valine-to-phenylalanine substitution at amino acid position 617 (JAK2 V617F) leading to a novel somatic gain-of-function single nucleotide variant that resulted in the loss of autoinhibition of the JAK2 tyrosine kinase. JAK2 V617F is a constitutively activated kinase that recruits and phosphorylates substrate molecules including signal transducers and activators of transcript (STAT) proteins (so-called JAK-STAT signaling). The result is cell proliferation independent of normal growth factor control.

The JAK2 V617F variant was present in blood and bone marrow from a variable portion of patients with classic BCR-ABL−negative (ie, Ph-negative) MPNs including 65% to 97% of patients with PV, 23% to 57% with ET, and 35% to 56% with PMF (see Table 1). The variant was initially reported to be absent in all normal subjects and patients with secondary erythrocytosis, although very low levels of cells carrying the variant have been reported in a small subset of healthy individuals.

In vivo, mice irradiated and then given transplanted bone marrow cells infected with a retrovirus containing the variant developed a myeloproliferative syndrome.

Although almost all studies were retrospective case series and/or cross-sectional studies, and although both the analytic and clinical performances appeared dependent on the laboratory method used to detect the variant, there has been consistency across studies in demonstrating that the JAK2 V617F variant is a highly specific marker for clonal evidence of an MPN.

**JAK2 Exon 12 Variants**

Scott et al (2007) identified 4 somatic gain-of-function variants in JAK2 exon 12 in 10 of 11 PV patients without the JAK2 V617F variant. Patients with a JAK2 exon 12 variant differed from those with the JAK2 V617F variant, presenting at a younger age with higher hemoglobin levels and lower platelet and white cell counts. Erythroid colonies could be grown from their blood samples in the absence of exogenous erythropoietin, and mice treated with transfected bone marrow transplants developed a myeloproliferative syndrome. Findings have been confirmed by a number of investigators who identified additional variants with similar functional consequences in patients with PV and patients with idiopathic erythrocytosis. Based on these findings, it has been concluded that the identification of JAK2 exon 12 variants provides a diagnostic test for JAK2 V617F−negative patients who present with erythrocytosis. Of note, different variants in the same gene appear to have different effects on signaling, resulting in distinct clinical phenotypes.

**CALR Gene**

The CALR gene, located on chromosome 19, contains the genetic code for making the calreticulin protein, a multifunctional protein located in the endoplasmic reticulum, cytoplasm, and cell surface. The calreticulin protein is thought to play a role in cell growth and division and regulation of gene activity. Somatic variants in the CALR gene are associated with ET and PMF.

**MPL Gene**

The MPL gene, located on chromosome 1, contains the genetic code for making the thrombopoietin receptor, a cell surface protein that stimulates the JAK/STAT signal transduction pathway. The thrombopoietin receptor is critical for the cell growth and division of megakaryocytes, which produce platelets involved in blood clotting. Somatic variants in the MPL gene are associated with ET and PMF.
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More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for JAK2, CALR, and MPL testing. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory–developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA), and laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA does not require regulatory review of LDTs.

Related Policies:
Molecular Panel Testing of Cancers to Identify Targeted Therapies

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for myeloproliferative neoplasms when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Myeloproliferative Neoplasms is covered

Genetic testing (JAK2) for myeloproliferative neoplasms may be considered medically necessary in the diagnosis of patients presenting with clinical, laboratory, or pathological findings suggesting polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF). 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.

When Genetic Testing for Myeloproliferative Neoplasms is not covered

Genetic testing (JAK2, MPL and CALR) for myeloproliferative neoplasms may be considered investigational in all other circumstances including, but not limited to, the following situations.

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

Panel testing for myeloproliferative disorders is considered not medically necessary.

Policy Guidelines

For individuals with a suspected MPN who receive genetic testing for JAK2, the evidence includes case series, retrospective studies, meta-analyses, and randomized control trials. Relevant outcomes include
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overall survival, disease-specific survival, test accuracy and validity, and resource utilization. For patients with suspected Philadelphia chromosome-negative (Ph-negative) MPN, JAK2 variants are found in nearly 100% of those with polycythemia vera, 60% to 65% of those with essential thrombocytopenia, and 60% to 65% of those with primary myelofibrosis. In individuals with suspected MPN, a positive genetic test for JAK2 satisfies a major criterion for the 2016 World Health Organization classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocytopenia 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 a second-line therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For patients with suspected Ph-negative MPN, MPL variants are found in approximately 5% of those with essential thrombocytopenia (ET) and primary myelofibrosis cases (PMF). In individuals with suspected MPN, a positive genetic test for MPL satisfies a major criterion for the 2016 World Health Organization classification for ET and PMF and eliminates secondary or reactive causes of thrombocytopenia 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 alleviation of symptoms. However, in both ET and PMF, establishing the diagnosis through MPL genetic testing does not result in changes in management that would be expected to improve net health outcome. Thus 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 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 WHO classification for ET and PMF and eliminates secondary or reactive causes of thrombocytopenia 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 alleviation of symptoms. 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 net health outcome. Thus 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0016U, 0017U, 0027U, 0040U, 81219, 81270, 81402, 81403, G0452

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
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**Scientific Background and Reference Sources**

**Tyrosine Kinase Mutation Analysis in Myeloproliferative Neoplasms**


Medical Director 6/2011


**JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms**


Medical Director – 3/2012


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Senior Medical Director review 8/2017


**Policy Implementation/Update Information**

**Tyrosine Kinase Mutation Analysis in Myeloproliferative Neoplasms**

7/19/11 New policy. “JAK2 tyrosine kinase and MPL mutation testing may be considered medically necessary 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). JAK2 tyrosine kinase and MPL mutation testing may be
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considered investigational in all other circumstances” Notification given July 19, 2011. Policy effective October 25, 2011. (btw)

1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/11. No change to policy. Added new 2012 CPT code, 81275, to the “Billing/Coding” section. (btw)

1/24/12 Removed 81275 from Billing/Coding section as it does not pertain to this policy. Added new 2012 CPT code, 81270 to Billing/Coding section. (btw)

JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms

4/17/12 Policy name changed from “Tyrosine Kinase Mutation Analysis in Myeloproliferative Neoplasms” to “JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms”. MPL is not a tyrosine kinase. No change to policy intent. Policy Guidelines updated. Medical Director review 3/29/12. Reference added. (btw)

12/28/12 Specialty Matched Consultant Advisory Panel review 12/4/2012. No change to policy intent. Added CPT codes 81402, 81403, and G0452 to Billing/Coding section. (btw)

4/1/2013 Reference added. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. Policy Guidelines revised. No change to policy intent. (btw)

4/15/14 Reference added. (btw)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)

3/31/15 Updated the “Description, Regulatory Status, and Policy Guidelines” sections. No change to policy intent. Reference added. (lpr)

Policy Retitled: Genetic Testing for Myeloproliferative Neoplasms

12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. Policy title changed from “JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms” to “Genetic Testing for Myeloproliferative Neoplasms.” No change to policy statement or intent. Added CPT code 81219 to Billing/Coding section effective 1/1/2016. (lpr)

12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

7/28/17 Added CPT codes 0016U, 0017U to Billing/Coding section. (lpr)

8/25/17 Updated Description and Policy Guidelines sections. Under “When Covered” section: added CALR testing; clarified JAK2 testing is medically necessary for PV, ET, and PMF; MPL testing is medically necessary for ET and PMF. Under “When Not Covered” section: added statement “Panel testing for myeloproliferative disorders is considered not medically necessary.” Referenced related policy “Molecular Panel Testing of Cancers to Identify Targeted Therapies.” Senior Medical Director review 8/2017. Reference added. (lpr)

12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)
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12/29/17 Added PLA code 0027U to Billing/Coding section. (lpr)

3/29/18 Added PLA code 0040U to Billing/Coding section for 4/1/18 code update. (lpr)

9/7/18 Updated Policy Guidelines section. Reference added. No change to policy statement. (lpr)

12/14/18 Specialty Matched Consultant Advisory Panel review 11/28/2018. No change to policy statement. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.