MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**JAK2, MPL, and CALR Molecular Testing for Myeloproliferative Neoplasms**
Policy Number	**2.02.53**
Category	**Technology Assessment**
Original Effective Date	**06/17/21**
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Archive Review Date	**N/A**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program(DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, Janus kinase 2 (JAK2) testing may be considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera (PV), essential thrombocythemia (ET), or primary myelofibrosis (PMF) after evaluation for secondary causes.

II. Based upon our criteria and assessment of the peer-reviewed literature, Myeloproliferative Leukaemia (MPL) and calreticulin (CALR) testing may be considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting ET or PMF.

III. Based upon our criteria and assessment of the peer-reviewed literature, JAK2, MPL, and CALR testing is considered **investigational** in all other circumstances including, but not limited to, the following situations:
A. Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs);
B. Molecular phenotyping of patients with MPNs; and
C. Monitoring, management, or selecting treatment in patients with MPNs.

POLICY GUIDELINES

I. Patients suspected to have polycythemia vera (PV) should first be tested for JAK2 V617F. If the testing is negative, further testing to detect other JAK2 tyrosine kinase variants (e.g., in exon 12) is warranted.

II. Patients suspected to have essential thrombocythemia (ET) or primary myelofibrosis (PMF) should first be tested for JAK2 V617F mutation. If testing is negative, further testing to detect MPL and CALR variants is warranted.

DESCRIPTION

Myeloproliferative neoplasms (MPNs) are hematologic malignancies classified as myeloid vs lymphoid and then further subdivided into acute and chronic. Myeloproliferative neoplasms are a subsect of chronic myeloid disorders that usually

exhibit terminal expansion in the peripheral blood as opposed to the bone marrow. MPNs cause thrombocytosis and erythrocytosis in the peripheral blood. The four main types of MPNs are PV (Polycythemia Vera), ET (Essential Thrombocythemia), PMF (primary myelofibrosis), and CML (chronic myeloid leukemia).

The Janus kinase 2 (JAK2) tyrosine kinase protein is part of the JAK/signal transduction pathway and activators of transcript (STAT) proteins that are important for the controlled production of blood cells from hematopoietic cells. Mutation of JAK2 causes an always on mutation that leads to cell proliferation myeloid cells. This leads to a subsequent uncontrolled cell proliferation in hematocrit, red blood cells, and platelets, and subsequent decrease in epo level. Somatic (acquired) variants in the JAK2 gene are found in patients with MPNs such as PV, ET, and PMF. There are two JAK2 variants associated with MPN disorders, the JAK2 V617F variant and JAK2 Exon 12 Variants (4 different variants). The JAK2 V617F gene is found in 95% of patients with PV, 60% to 65% of patients with ET, and 60 to 65% of patients with PMF. JAK2 exon 12 variants are also found in 5% of PVcases.

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.

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.

RATIONALE

JAK2

Evidence for the clinical utility of JAK2 testing includes meta-analyses, retrospective studies, and RCTs. Evidence for JAK2 testing for phenotyping and monitoring provide conflicting results. However, the presence of JAK2 V617F or JAK2 exon 12 variants is considered a major criterion for the diagnosis of PV, ET, and PMF. JAK2 V617F and JAK2 exon 12 testing allow secondary or reactive erythrocytosis or thrombocytosis to be differentiated from PV, ET, and PMF.

For individuals with a suspected MPN who receive genetic testing for JAK2, the evidence includes case series, retrospective studies, meta-analyses, and randomized controlled trials. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, and resource utilization. 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.

MPL

Direct evidence for the clinical utility of MPL testing is lacking. While MPL exon 10 testing has potential utility in diagnosing ET and PMF using the WHO (2016) major criteria for MPNs and excluding reactive or secondary causes of thrombocytosis, there is no change in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established. Given that genetic testing for MPL is included in the WHO (2016) major criteria and the National Comprehensive Cancer Network (NCCN) guidelines (2019-2020) for MPNs, MPL testing may be consistent with clinical practice in the diagnosis of patients with clinical, laboratory, or pathological findings suggesting ET and PMF.

For individuals with a suspected MPN who receive genetic testing for MPL, the evidence includes case series and retrospective studies. Relevant outcomes include overall survival, 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.

CALR

Direct evidence for the clinical utility of CALR testing is lacking. While CALR exon 9 testing has potential clinical utility in diagnosing ET and PMF using the WHO (2016) major criteria for MPNs and excluding reactive or secondary causes of thrombocytosis, there is no change in management that would be expected to improve net health outcome. Thus, the clinical utility has not been established. Given that genetic testing for CALR is included in the WHO (2016) major criteria and the NCCN guidelines (2020) for myeloproliferative neoplasms, CALR testing may be consistent with clinical practice in the diagnosis of patients with clinical, laboratory, or pathological findings suggesting ET and PMF.

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. Relevant outcomes include overall survival, disease-specific survival, test accuracy and validity, and resource utilization. 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.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

Code	Description
81451	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NOTCH1, NPM1, NRAS), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis *(Effective 01/01/2023)*
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81456	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis *(Effective 01/01/2023)*
0017U	Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected (*JAK2* Mutation, University of Iowa, Department of Pathology)
0027U	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15 (JAK2 Exons 12 to 15 Sequencing, Mayo Clinic, Mayo Clinic)

HCPCS Codes

Code	Description
No Codes	

ICD10 Codes

Code	Description
C96.2	Malignant mast cell tumors
C92.10-C92.12	Chronic myeloid leukemia code range
D45	Polycythemia vera
D47.3	Essential (hemorrhagic) thrombocythemia
D47.4	Osteomyelofibrosis

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KEY WORDS

Janus kinase 2, JAK2, Myeloproliferative Leukaemia, MPL, calreticulin, CALR, polycythemia vera, PV, essential thrombocythemia, ET, primary myelofibrosis, PMF, myeloproliferative neoplasms, MPNs.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare members https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ContrId=298&ver=133&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAAAAA&

There is currently a Local Coverage Article (LCA) for Molecular Pathology Procedures. Please refer to the following LCA website for Medicare Members:https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=82&LCDId=35000&ContrId=298&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAIAAA&=