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Clinical UM Guideline

Subject:	Janus Kinase 2, ~~(JAK2)^{V617F} and JAK2 exon 12~~CALR and MPL Gene Mutation Assays		
Guideline #:	CG-GENE-01	**Publish Date:**	04/24/2019~~12/12/2018~~
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Description

This document addresses testing for the Janus Kinase 2 (JAK2) ^{V617F}~~,and~~ JAK2 exon 12, calreticulin (CALR) and thrombopoietin receptor (MPL) gene mutation~~s~~ testing for myeloproliferative neoplasms (MPNs), historically referred to as myeloproliferative disorders (MPDs) and referred to in this document as MPD/MPN. This document does not address JAK2 ^{V617F}, JAK2 exon 12, CALR or MPL gene mutation testing for myelodysplastic syndromes.

Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are a group of heterogeneous disorders of the hematopoietic system collectively known as Philadelphia chromosome (BCR-ABL)-negative MPNs. Genetic testing for JAK2, CALR, and MPL gene mutations is being explored as a means to aid in the diagnosis, clinical management and prognostication of individuals with MPD/MPN.

~~The myeloproliferative disorders (MPD) also referred to as myeloproliferative neoplasms (MPN) are a large group of relatively rare pathogenetically related diseases arising in the bone marrow and characterized by the proliferation of one or more myeloid cell lines in the bone marrow resulting in increased numbers of relatively mature neoplastic cells in the peripheral blood. A point mutation (V617F) in the Janus Kinase 2 gene has been identified and found to be expressed in some individuals with one of three myeloproliferative diseases: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).~~

~~The Janus Kinase 2 (JAK2) mutation assay has been developed to aid in the diagnosis of myeloproliferative disorders. A commercially available JAK2^{V617F} mutation genetic test uses genomic DNA isolated from an individual's blood. Polymerase chain reaction (PCR) assay technologies are used to analyze the specimen for the presence of the JAK2^{V617F} gene mutation.~~

This Clinical UM Guideline is intended to provide assistance in interpreting Healthy Blue's standard Medicaid benefit plan. When evaluating insurance coverage for the provision of medical care, federal, state and/or contractual requirements must be referenced, since these may limit or differ from the standard benefit plan. In the event of a conflict, the federal, state and/or contractual requirements for the applicable benefit plan coverage will govern. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Clinical UM Guideline is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.~~Federal and State law, as well as contract language, and Medical Policy take precedence over Clinical UM Guidelines. We reserve the right to review and update Clinical UM Guidelines periodically. Clinical guidelines approved by the Medical Policy & Technology Assessment Committee are available for general adoption by plans or lines of business for consistent review of the medical necessity of services related to the clinical guideline when the plan performs utilization review for the subject. Due to variances in utilization patterns, each plan may choose whether to implement a particular Clinical UM Guideline. To determine if review is required for this Clinical UM Guideline, please contact the customer service number on the member's card.~~

~~Alternatively, commercial or FEP plans or lines of business which determine there is not a need to adopt the guideline to review services generally across all providers delivering services to Plan's or line of business's members may instead use the clinical guideline for provider education and/or to review the medical necessity of services for any provider who has been notified that his/her/its claims will be reviewed for medical necessity due to billing practices or claims that are not consistent with other providers, in terms of frequency or in some other manner.~~

Clinical Indications

Medically Necessary:

In individuals presenting with clinical, laboratory, or pathological findings suggesting classic forms of MPD/MPN, testing for the Janus Kinase 2 (JAK2; JAK2^{V617F}) gene mutation is considered **medically necessary**.

In individuals presenting with clinical, laboratory, or pathological findings suggesting classic forms of MPD/MPN who were negative for Janus Kinase 2 (JAK2; JAK2^{V617F}) gene mutation, testing for the JAK2 exon 12 gene mutation, CALR and MPL is considered **medically necessary**.~~Testing for the Janus Kinase 2 (JAK2; JAK2^{V617F}) gene mutation is considered **medically necessary** for the initial diagnostic assessment of adults presenting with clinical, laboratory, or pathological findings suggesting classic forms of polycythemia vera.~~

~~Testing for the Janus Kinase 2 exon 12 gene mutation is considered **medically necessary** for the diagnosis of polycythemia vera when testing for the JAK2^{V617F} gene mutation was previously completed and was negative.~~

~~Testing for the Janus Kinase 2 (JAK2; JAK2^{V617F}) gene mutation is considered **medically necessary** for the initial diagnostic assessment of BCR-ABL negative adults presenting with clinical, laboratory, or pathological findings suggesting classic forms of essential thrombocythemia or primary myelofibrosis.~~

Not Medically Necessary:

Testing for the Janus Kinase 2 (JAK2; JAK2^{V617F}, JAK2 exon 12) gene mutation is considered **not medically necessary** for any other indication including but not limited to:

- Diagnostic assessment of ~~myeloproliferative disorders~~MPD ~~-~~/~~myeloproliferative neoplasms~~MPN in children;
- Quantitative assessment of JAK2^{V617F} allele burden subsequent to qualitative detection of JAK2^{V617F}.

Testing for the CALR or MPL gene mutation is considered **not medically necessary** when the criteria above have not been met.

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Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT	
81219	*CALR (calreticulin)* (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
~~81270~~ 81270	*JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81402	Molecular pathology procedure, Level 3 (eg, > 10 SNP's 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 of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) [when specified as the following]: • *MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR)* (eg myeloproliferative disorder), common variants (eg, W515A, W515K, W515L, W515R)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons) [when specified as the following]: • *JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed • *MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR)* (eg, myeloproliferative disorder), exon 10 sequence
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~~ Por, Procedure codes	*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

ICD-10 Diagnosis

D45	Polycythemia vera
~~D46.0-D46.9~~	~~Myelodysplastic syndromes~~
D47.1	Chronic myeloproliferative disease [primary myelofibrosis]
D47.3	Essential (hemorrhagic) thrombocythemia
D47.4	Osteomyelofibrosis

Discussion/General Information

~~MPD/MPN are a group of clonal malignancies characterized by dysregulation of a single hematopoietic stem cell, abnormal proliferation of one or more mature blood cell types in the bone marrow with associated increases in peripheral blood parameters, and varying propensity to progress to bone marrow failure or acute myeloid leukemia (AML) (Spivak, 2003). Classification of the chronic myeloid processes is based primarily on the presence or absence of the Philadelphia (Ph) chromosome, (BCR-ABL translocation) and secondarily on the morphologic picture of the bone marrow in conjunction with the clinical manifestation. ET, PV and PMF constitute the classical group of BCR-ABL- negative chronic myeloproliferative disorders. These disorders share a common stem cell derived clonal heritage and their diversity is attributed to different mutations affecting tyrosine kinases or related molecules resulting in different configurations of abnormal signal transduction (Tefferi, 2007).~~ The ~~myeloproliferative disorders (~~MPDs~~/)~~ ~~also referred to as myeloproliferative neoplasms (~~MPNs~~)~~ are a large group of relatively rare pathogenetically related diseases arising in the bone marrow and characterized by the proliferation of one or more myeloid cell lines in the bone marrow resulting in increased numbers of relatively mature neoplastic cells in the peripheral blood. ET, PV and PMF constitute the classical group of BCR-ABL–negative chronic MPNs.

According to the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissue, MPNs include chronic myelogenous leukemia (BCR-ABL1 positive [CML]), PV, PMF and ET. However, CML is unique in that it is the only one of these conditions that is positive for the BCR-ABL1 translocation. The others, PV, MF and ET are considered part of the operational sub-category of BCR-ABL1 negative conditions (Swerdlow, 2017).

MPNs are characterized by a complex collection of symptoms. The symptoms vary within and between each MPN subtype, but typically include~~s~~ constitutional symptoms such as fatigue, weight loss, pruritus, symptoms associated with splenomegaly, and a variety of laboratory abnormalities, including leukocytosis, thrombocytosis and erythrocytosis. And while there are a number of shared clinical features across the conditions, each of the three BCR-ABL–negative MPN~~s~~ is considered a distinct clinical entity. ET is characterized by elevation in platelet count and megakaryocyte proliferation in the bone marrow. PV is distinguished by an increase in red blood cell production, with resulting increases in RBC mass and hemoglobin and hematocrit levels. Frequently, platelet and white blood cell count are also elevated. PMF is characterized by anemia, progressive splenomegaly and bone marrow fibrosis, and multi-organ extramedullary hematopoiesis. Most of these features, however, are not diagnostically specific, and secondary causes of erythrocytosis, thrombocytosis and bone marrow fibrosis must be excluded.

The BCR-ABL1–negative MPNs are genetically characterized by the overlapping presence of mutations in three driver genes—JAK2, CALR, and MPL. Mutations in either of these driver genes results in increased activity in the JAK/STAT signal transduction pathway.

The diagnosis and management of individuals with MPN has evolved since the identification of the "driver" mutations (JAK2, CALR, and MPL). ~~-~~However, the diagnosis and monitoring of individuals with BCR-ABL–negative MPN can be challenging because several of the clinical and laboratory features of the classic forms of these diseases-PV, ET, or PMF-can be mimicked by other conditions such as myeloid fibrosis. Additionally, these diseases cannot always be identified with certainty on morphologic bone marrow exam, and diagnosis can be complicated by altering disease patterns. As an example, PV and ET can undergo a leukemic transformation or evolve into PMF.

~~A point mutation (V617F) in the Janus Kinase 2 gene has been identified and found to be expressed in some individuals with one of three myeloproliferative diseases: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF).~~

~~Although there are a number of shared clinical features across the conditions, each of the three BCR-ABL- negative MPD/MPN is considered a distinct clinical entity. ET is characterized by elevation in platelet count and megakaryocyte proliferation in the bone marrow. PV is distinguished by an increase in red blood cell (RBC) production, with resulting increases in RBC mass and hemoglobin and hematocrit levels. Frequently, platelet and white blood cell (WBC) count are also elevated. PMF is characterized by anemia, progressive splenomegaly and bone marrow fibrosis, and multi-organ extramedullary hematopoiesis. Most of these features, however, are not diagnostically specific, and secondary causes of erythrocytosis, thrombocytosis and bone marrow fibrosis must be excluded.~~

~~According to the World Health Organization (WHO) classification system for hematopoietic tumors, MPNs include chronic myelogenous leukemia (BCR-ABL1 positive [CML]), PV, PMF and ET. However, CML is unique in that it is the only one of these conditions that is positive for the BCR-ABL1 translocation. The others, PV, MF and ET are considered part of the operational sub-category of BCR-ABL1 negative conditions (Tefferi, 2012).~~

Janus Kinase 2 ^{V617F} (JAK2 ^{V617F}) Gene Mutation

The Janus Kinase 2 V617F (JAK2^{V617F}) point mutation a somatic (acquired) hematopoietic stem cell mutation where phenylalanine is substituted for valine at amino acid position 617 that results in unregulated JAK2 tyrosine kinase activity and JAK2 STAT signaling. Prior to the discovery of the JAK2^{V617F} sequence variant, diagnosis for ~~MPD/~~MPN was based on consensus criteria that relied primarily on measured variables, such as red cell mass, hematocrit, platelet count, and serum erythropoietin level, or on subjective techniques, such as bone marrow histology assessment. Use of arbitrary threshold levels increased concern that early-phase disease could be missed.

Tefferi (2005) and James (2006) found that it is possible that the JAK2^{V617F} mutation is responsible for some portions of but not the complete phenotype in ~~MPD/~~MPN. In 2007, Tefferi concluded that JAK2^{V617F} is myeloid neoplasm-specific and its presence excludes secondary polycythemia, thrombocytosis, or bone marrow fibrosis from other causes. Furthermore, a JAK2^{V617F} is present in approximately 96% of individuals with PV, whereas JAK2^{V617F} also occurs in approximately half of those with ET or PMF. Therefore, JAK2^{V617F} mutation is diagnostic

for PV and complementary to histology for the diagnosis of ET and PMF and the combination of molecular testing. Histologic review should also facilitate diagnosis of ET associated with borderline thrombocytosis (Genetics Home Reference, 2018).

Further studies demonstrated that combination of $JAK2^{V617F}$ PCR testing and increased hematocrit is diagnostic for PV (sensitivity 95%, specificity 100%) (Michiels, 2007). Since the exclusion of PV is mandatory for the diagnosis of ET within the context of ~~MPD/~~MPN, use of the test may facilitate the diagnosis of $JAK2^{V617F}$ –negative ET as well (Spivak, 2008). Additional information can be obtained from the degree of positivity of granulocytes. Homozygosity for $JAK2^{V617}$, reflecting loss of heterozygosity as a result of mitotic recombination, is relatively specific to PV; the variant occurs in a homozygous state in 25% to 30% of those with PV but only in 2% to 4% of those with ET (Levinel, 2005; Vannucchi, 2007).

Research has also investigated whether the presence of the $JAK2^{V617F}$ sequence variant and mutational load in ET and PMF is associated with disease severity and with prognostic or therapeutic implications. There is insufficient knowledge to allow risk-stratification of individuals with ET and PMF based on qualitative or quantitative results of JAK2 variant testing. Furthermore, variant status designation is dependent on assay sensitivity and the issue is further confounded by the occurrence of marked variation in variant allele burden within this group.

The $JAK2^{V617F}$ sequence variant has lower penetrance among children with myeloproliferative disorders and cannot be used for diagnostic purposes in this age group. Currently available information does not warrant testing unaffected family members of individuals found to carry the $JAK2^{V617F}$ sequence variant.

The 2017 WHO guidelines on the Classification of Tumours of Haematopoietic and Lymphoid Tissue ~~classification of myeloid neoplasm and acute leukemia~~ were revised in ~~2016~~ 2017 ~~to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the publication of the 2008 WHO classification document.~~to reflect the recent discovery of genetic abnormalities involved in the pathogenesis of BCR-ABL1 negative MPN. The WHO diagnostic criteria includes a combination of clinical, laboratory cytogenetic, and molecular testing ~~which are listed in either the major or minor category~~. The diagnosis of PMF requires the individual to meet 3 major and 2 minor criteria~~all 3 major criteria and at least one minor criterion~~. The diagnosis of PV requires meeting both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria~~either all 3 major criteria or the first 2 major criteria and the minor~~

~~criterion~~, whereas the diagnosis of ET requires meeting all 4 ~~major~~ criteria ~~or the first 3 major criteria and the minor criterion.~~ The ~~2016~~ 2017 WHO criteria recommends that JAK2^{V617F} and other clonal markers be tested in individuals suspected of having ET and PMF. WHO also recommends that testing for JAK2^{V617F} and JAK2 exon 12 variants be conducted in individuals suspected of having PV (~~Arber, 2016).~~ These guidelines also provide the following information regarding JAK2 mutation testing:

> JAK2 mutations are not specific for any single clinical or morphologic MPN phenotype, and are also reported in some cases of myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN) and acute myeloid leukaemia (AML). Thus, an integrated, multidisciplinary approach is necessary for the classification of myeloid neoplasms (Swerdlow, 2017).

The National Comprehensive Cancer Network (NCCN) guidelines on Myeloproliferative Neoplasms recommends that molecular testing for JAK2^{V617F} mutations be performed in all individuals suspected of having ET, MF or PV. For individuals suspected of having PV, when JAK2^{V617F} mutation testing is negative, molecular testing for the JAK2 exon 12 mutation should also be conducted (NCCN, ~~2018~~2019).

JAK 2 Exon 12 Gene Mutation
JAK2^{V617F} mutation, which is found in exon 14, can be detected in approximately 96% of individuals with PV. Of the remaining 4% of individuals with PV, 3% have the mutation in the exon 12 region of the JAK2 gene. Therefore, the JAK2 mutation (V617F and the exon 12 region) has been estimated to occur in as much as 99% of the individuals with PV. A small number of individuals with essential thrombocytopenia and primary myelofibrosis have a somatic mutation in exon 12 of the JAK2 gene (Genetics Home Reference, ~~2018~~2019).

JAK2 exon 12-mutated PV is characterized by significantly higher hemoglobin level and lower platelet and leukocyte counts at diagnosis compared to JAK2 ^{V617F}-mutated PV. Individuals with JAK2 exon 12-mutated PV also exhibit younger age at diagnosis. However, both JAK2^{V617F} and JAK2 exon 12 mutations are reflect similar rate of thrombosis, transformation to MF or leukemia, and death (NCCN, ~~2018~~2019).

As mentioned above, the NCCN guidelines recommend that when there is a suspicion of polycythemia vera, that molecular testing (blood) for JAK2^{V617F} mutation testing be conducted and, if negative, that testing for JAK2 exon

12 mutations be conducted (NCCN. 2018). WHO also recommends that testing for JAK2^{V617F} and JAK2 exon 12 variants be conducted in individuals suspected of having PV (~~Arber, 2016~~Swerdlow, 2019)~~.~~.

CALR Gene Mutation

The CALR gene located on chromosome 19 contains the genetic code for the production of the calreticulin protein which is believed to play a role in the regulation of gene activity as well as the growth and division of cells. Acquired variants in the CALR gene are associated with ET and PMF.

Alterations in exon 9 of CALR have been estimated to be present in approximately 20-35% of all individuals with ET and PMF (which accounts for approximately 60%-80% of individuals with JAK2/MPL-negative ET and MF). CALR-Type 1 mutations (52 base pair deletions) occur more frequently in individuals with MF while CALR-Type 2 mutations (5 base pair insertions) are preferentially associated with ET.

Guglielmelli and colleagues (2015) evaluated the prognostic impact of the two different types of CALR mutation in a group of 396 subjects with PMF. The median survival was significantly better for subjects with 1/type 1-like mutation (26 years; p<.0001) compared to 7 years for subjects with type2/type 2-like mutation of JAK2 ^{V617F} mutation. The rate of leukemic transformation was also higher among the participants with type 2/type 2-like mutation than for those with 1/type 1-like mutation and JAK2 ^{V617f} mutation.

Better overall survival has been associated with CALR mutation than JAK2 ^{V617F} or MPL W515 mutation. The survival advantage is significant in individuals with the 1 type/type 1-like mutation. Rumi and colleagues (2014) assessed the impact of driver mutations of JAK2, CALR, or MPL on clinical course, leukemic transformation, and survival of subjects with PMF. Of the 617 subjects evaluated, 399 (64.7%) carried JAK2 ^{V617F}, 140 (22.7%) had a CALR exon 9 indel, 25 (4.0%) carried an MPL (W515) mutation, and 53 (8.6%) had nonmutated JAK2, CALR, and MPL (so-called triple-negative PMF). The participants with CALR mutation had a smaller risk of developing thrombocytopenia, anemia, and marked leukocytosis compared with other subtypes. They also had a decreased risk of thrombosis compared with subjects carrying JAK2 ^{V617F}. Conversely, triple-negative subjects had higher incidence of leukemic transformation compared with either CALR-mutant or JAK2-mutant participants. Median overall survival was 17.7 years in CALR-mutant cohort, 9.2 years in JAK2-mutant cohort, 9.1 years in MPL-mutant cohort, and 3.2 years in triple-negative participants. In multivariate analysis corrected for age, CALR-mutant subjects demonstrated better overall survival than either JAK2-mutant or triple-negative subjects.

The "triple-negative" mutation status (the absence of all 3 driver mutations [JAK2, CALR, or MPL) occurs in approximately 10% of individuals and is associated with a worse prognosis in individuals with MF (Milosevic, 2016; Tefferi, 2014).

According to the NCCN:

> CALR-mutated ET is characterized by younger age, male sex, higher platelet count, lower hemoglobin, lower leukocyte count, and lower risk of thrombosis than JAK2- or MPL-mutated ET, whereas the presence of MPL mutations might be associated with a higher risk of fibrotic transformation. CALR mutation status also did not have a significant impact on the International Prognostic Score for ET (IPDET)-thrombosis prognostic score for predicting the risk of thrombosis.

NCCN guidelines on Myeloproliferative Neoplasms V2.2019 include the following recommendations for CALR mutation testing:

> Molecular testing for JAK2 ^{V617F} mutations is recommended as part of initial workup for all patients. If JAK2 ^{V617F} mutation testing is negative, molecular testing for MPL and CALR mutations should be performed for patients with MF and ET; molecular testing for JAK2 exon 12 mutation should be done for those with suspected PV and negative for the JAK2 ^{V617F} mutation. Alternatively, molecular testing using the multi-gene NGS panel that includes JAK2, CALR, and MPL can be used as part of initial workup for all patients.

The 2017 WHO guidelines do not specifically address the CALR mutation, but do indicate that "other clonal maker" may be used to satisfy one of the major criteria for establishing a diagnosis of MF, PV or ET (Swerdlow, 2017).

CALR mutation testing to establish a diagnosis in individuals suspected of having an MPN is considered standard of care in the medical community (as evidenced by the NCCN and WHO guideline recommendations). In individuals who have already received a diagnosis of ET, treatment is generally focused on the alleviation of

symptoms while minimizing the frequency and severity of bleeding and thrombotic events. Clinical decisions regarding treatment are not dependent upon and generally not influenced by the results of CALR gene mutation status. Although researchers are exploring the use of genetic testing for prognostication, it is not yet clear how this information impacts treatment decisions or results in improved net health outcomes. Similarly, in individuals with PMF, hematopoietic cell transplantation is currently the only potentially curative treatment; all other treatment measures are focused on the alleviation of symptoms. However, in individuals that have been diagnosed with MPN, the CALR mutation status does not result in alterations in clinical management that would be expected to improve the net health outcome.

MPL Gene Mutation

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 that are involved in blood clotting. Somatic variants in the MPL gene are associated with ET and PMF. Activating mutations in MPL $^{W515l/K}$ have been reported in approximately 5-8% of individuals with PMF and 1-4% of individuals with ET.

MPL mutations are associated with lower hemoglobin levels at the time of diagnosis and an increased risk of transfusion dependence in individuals with MF. Guglielmelli and colleagues (2007) investigated clinical and hematological phenotype of individuals with myelofibrosis harboring MPL $^{W515L/K}$ mutation. Of the 217 myelofibrosis subjects, 18 (8.2%) had an MPL mutation, including four of which (22%) co-existed with JAK2 ^{V617F} mutation. When compared with MPL wild-type subjects, irrespective of JAK2 ^{V617F} status, those with MPL $^{W515L/K}$, were more often female, were older (61 years vs. 57 years; p=0.02), presented with more severe anemia (hemoglobin, 101 g/l vs. 121 g/l; p=0.002) and were more likely to need regular blood transfusions (p=0.012). These data indicate that MPL mutation in MF exemplifies individuals with more severe anemic phenotype.

As mentioned above, the NCCN guidelines on Myeloproliferative Neoplasms V2.2019 include MPL mutation testing in the initial workup of all individuals suspected of having an MPN. The NCCN recommends that when JAK2 V^{617F} mutation testing is negative, molecular testing for MPL and CALR mutations should be performed for individuals with MF and ET (NCCN, 2019).

Definitions

Allele: Any of the possible forms in which a gene for a specific trait can occur. In almost all animal cells, two alleles for each gene are inherited, one from each parent. Paired alleles (one on each of two paired chromosomes) that are the same are called homozygous, and those that are different are called heterozygous. In heterozygous pairings, one allele is usually dominant, and the other recessive. Complex traits such as height and longevity are usually caused by the interactions of numerous pairs of alleles, while simple traits such as eye color may be caused by just one pair.

BCR-ABL: A tyrosine-kinase oncogene. The Abelson leukemia-virus protein (ABL) is fused with the breakpoint-cluster region (BCR) in the Philadelphia-chromosome translocation found in chronic myeloid leukemia.

Driver mutation: An alteration within a gene that confers a selective growth advantage (thus promoting the development of cancer).

Mutation: A permanent transmissible change in DNA sequence. It can be an insertion or deletion of genetic information, or an alteration in the original genetic information.

Myeloid: Pertaining to, derived from, or manifesting certain features of the bone marrow.

Neoplasm: An abnormal growth of tissue caused by the division of cells that have experienced some type of genetic transformation or mutation.

Polycythemia: A condition marked by an abnormally large number of red blood cells in the circulatory system.

Polymerase chain reaction (PCR): A laboratory technique that employs artificial synthesis in a cyclic manner to amplify a specific target DNA fragment from a pool of DNA.

Proliferation: Rapid and repeated production of new parts (as in a mass of cells by a rapid succession of cell divisions).

Thrombocythemia: An increase above normal in the concentration of the blood platelets.

Triple-negative mutation status: The absence of all 3 driver mutations (JAK2, CALR, or MPL).

Tyrosine kinase: An enzyme involved in communication within cells, or signaling pathways. A mutation that causes certain tyrosine kinases to be constitutively active has been associated with several cancers.

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Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Revised	03/21/2019	Medical Policy & Technology Assessment Committee (MPTAC) review.
Revised	03/20/2019	Hematology/Oncology Subcommittee review. Title changed to "Janus Kinase 2, CALR and MPL Gene Mutation Assays"". Revised medically necessary and not medically necessary criteria to address CALR and MPL gene mutation testing. Updated the Description, Discussion/General Information, Definitions, References and Index sections. Updated Coding section; added CPT codes 81219, 81402; removed ICD-10-CM D46.0-D46.9 (not addressed).
Revised	11/08/2018	Medical Policy & Technology Assessment Committee (MPTAC) review.
Revised	10/31/2018	Hematology/Oncology Subcommittee review. Title changed to "Janus Kinase 2 (JAK2)^{V617F} and JAK2 exon 12 Gene Mutation Assays ". Added medically necessary and not medically necessary criteria for Janus Kinase 2 exon 12 gene mutation testing. Removed select abbreviations from the Clinical Indications section. Updated Coding, Discussion/General Information, References and Index sections.
New	11/02/2017	MPTAC review.
New	11/01/2017	Hematology/Oncology Subcommittee review. Initial document development. Moved content of GENE.00004 to new clinical utilization management guideline document with the same title.