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FEP Medical Policy Manual

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

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Original Policy Date: December 2011

Related Policies:

5.21.018 Jakafi (ruxolitinib)

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 MPN.

OBJECTIVE

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

POLICY STATEMENT

JAK2 testing may be considered **medically necessary** in the diagnosis of individuals presenting with clinical, laboratory, or pathologic findings suggesting polycythemia vera, essential thrombocythemia (ET), or primary myelofibrosis (PMF). Based on criteria from the World Health Organization and the International Consensus Classification for diagnosis of PV, 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 individuals presenting with clinical, laboratory, or pathologic findings suggesting ET or PMF.

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 (MPNs)
- Molecular phenotyping of individuals with MPNs
- Monitoring, management, or selecting treatment in individuals with MPNs.

POLICY GUIDELINES

Testing Strategy

Individuals suspected to have polycythemia vera (PV) 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.

Individuals 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 Vera Testing

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

Table PG1. World Health Organization 5th Edition and the International Consensus Classification Diagnostic Criteria for Polycythemia Vera

Major Criteria[a]
• Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women); or • Increased hematocrit (>49% in men or >48% in women); or
• 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 (2022) and Khoury et al (2022).

The diagnosis of PV requires the presence of all 3 major criteria or the presence of the first 2 major criteria together with the minor criterion.

[a] The World Health Organization 2022 5th edition removed red cell mass as a major criterion since this is not commonly evaluated in clinical practice. The International Consensus Classification still includes increased red blood cell mass as a major criterion.

BENEFIT APPLICATION

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

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.

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. Relevant outcomes are overall survival (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 thrombocythemia (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 International Consensus Classification (2022) and World Health Organization (WHO) 2022 (5th edition) 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 an 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. Relevant outcomes are 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 International Consensus Classification (2022) and WHO (2022, 5th edition) 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 an 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 are 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 International Consensus Classification (2022) and WHO (2022, 5th edition) 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 an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

World Health Organization

The 2022 (5th edition) World Health Organization (WHO) major criteria for myeloproliferative neoplasms (MPNs) are unchanged from the 2016 (4th edition) criteria and are as follows[6,7,]:

- Polycythemia vera (PV): " Presence of *JAK2,* V617F, or *JAK2* exon 12 mutation"
- Essential thrombocythemia (ET): " Presence of *JAK2*, *CALR*, or *MPL* mutation"
- Primary myelofibrosis (PMF): " Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis."

International Consensus Classification

In 2022, an international clinical advisory committee endorsed by the Society for Hematopathology (SH) and the European Association for Haematopathology (EAHP) published a new classification schema for myeloid neoplasms and acute leukemias.[8,] Many of the clinical advisory committee authors were authors on the 2016 (4th edition) of the WHO criteria, but the International Consensus Classification was developed independently of the WHO. The gene-related major criteria for MPNs are as follows:

- PV: "Presence of *JAK2* V617F or *JAK2* exon 12 mutation"
- ET: "JAK2, CALR, or MPL mutation"
- PMF: "JAK2, CALR, or MPL mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis"

For PV, it is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level , <1%); in negative cases, searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15 can be considered. For ET and MPF, it is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level , <1%) and *CALR* and *MPL* (sensitivity level, 1% to 3%); in negative cases, a search for noncanonical *JAK2* and *MPL* mutations can be considered. Other clonal markers that can be assessed in MPF include mutations associated with myeloid neoplasms (eg, *ASXL1*, *EZH2*, *IDH1*, *IDH2*, *SF3B1*, *SRSF2*, and *TET2* mutations).

National Comprehensive Cancer Network

The National Comprehensive Cancer Network published guidelines (v.1.2023) on the workup, diagnosis, and treatment of suspected MPNs.[38,] For patients with suspicion of MPNs, the guidelines recommend "molecular testing (blood or bone marrow) 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) or molecular testing using multigene NGS [next-generation sequencing] panel that includes *JAK2*, *CALR*, and *MPL*. Once an MPN diagnosis is confirmed, NGS is recommended for mutational prognostication."

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.

REFERENCES

1. Jones AV, Kreil S, Zoi K, et al. Widespread occurrence of the JAK2 V617F mutation in chronic myeloproliferative disorders. Blood. Sep 15 2005; 106(6): 2162-8. PMID 15920007
2. Murphy S, Peterson P, Iland H, et al. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. Semin Hematol. Jan 1997; 34(1): 29-39. PMID 9025160
3. Pearson TC, Messinezy M. The diagnostic criteria of polycythaemia rubra vera. Leuk Lymphoma. Sep 1996; 22 Suppl 1: 87-93. PMID 8951778
4. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. Oct 01 2002; 100(7): 2292-302. PMID 12239137
5. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. Jul 30 2009; 114(5): 937-51. PMID 19357394
6. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. May 19 2016; 127(20): 2391-405. PMID 27069254
7. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. Jul 2022; 36(7): 1703-1719. PMID 35732831
8. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. Sep 15 2022; 140(11): 1200-1228. PMID 35767897
9. Tefferi A, Strand JJ, Lasho TL, et al. Bone marrow JAK2V617F allele burden and clinical correlates in polycythemia vera. Leukemia. Sep 2007; 21(9): 2074-5. PMID 17476276
10. Wilkins BS, Erber WN, Bareford D, et al. Bone marrow pathology in essential thrombocythemia: interobserver reliability and utility for identifying disease subtypes. Blood. Jan 01 2008; 111(1): 60-70. PMID 17885079
11. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. Mar 2005; 365(9464): 1054-61. PMID 15781101
12. NIH Genetics Home Reference. JAK2 gene: Janus kinase 2. 2014. https://ghr.nlm.nih.gov/gene/JAK2. Accessed June 17, 2023.
13. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell. Apr 2005; 7(4): 387-97. PMID 15837627
14. James C, Ugo V, Le Coudic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature. Apr 28 2005; 434(7037): 1144-8. PMID 15793561
15. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med. Apr 28 2005; 352(17): 1779-90. PMID 15858187
16. Tefferi A, Sirhan S, Lasho TL, et al. Concomitant neutrophil JAK2 mutation screening and PRV-1 expression analysis in myeloproliferative disorders and secondary polycythaemia. Br J Haematol. Oct 2005; 131(2): 166-71. PMID 16197445
17. Zhao R, Xing S, Li Z, et al. Identification of an acquired JAK2 mutation in polycythemia vera. J Biol Chem. Jun 17 2005; 280(24): 22788-92. PMID 15863514
18. Campbell PJ, Scott LM, Buck G, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet. Dec 03 2005; 366(9501): 1945-53. PMID 16325696
19. Wolanskyj AP, Lasho TL, Schwager SM, et al. JAK2 mutation in essential thrombocythaemia: clinical associations and long-term prognostic relevance. Br J Haematol. Oct 2005; 131(2): 208-13. PMID 16197451
20. Campbell PJ, Griesshammer M, Dhner K, et al. V617F mutation in JAK2 is associated with poorer survival in idiopathic myelofibrosis. Blood. Mar 01 2006; 107(5): 2098-100. PMID 16293597
21. Tefferi A, Lasho TL, Schwager SM, et al. The JAK2(V617F) tyrosine kinase mutation in myelofibrosis with myeloid metaplasia: lineage specificity and clinical correlates. Br J Haematol. Nov 2005; 131(3): 320-8. PMID 16225651
22. Xu X, Zhang Q, Luo J, et al. JAK2(V617F): Prevalence in a large Chinese hospital population. Blood. Jan 01 2007; 109(1): 339-42. PMID 16946305
23. Sidon P, El Housni H, Dessars B, et al. The JAK2V617F mutation is detectable at very low level in peripheral blood of healthy donors. Leukemia. Sep 2006; 20(9): 1622. PMID 16775613
24. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med. Feb 01 2007; 356(5): 459-68. PMID 17267906
25. Pardanani A, Lasho TL, Finke C, et al. Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. Leukemia. Sep 2007; 21(9): 1960-3. PMID 17597810
26. Siemiatkowska A, Bieniaszewska M, Hellmann A, et al. JAK2 and MPL gene mutations in V617F-negative myeloproliferative neoplasms. Leuk Res. Mar 2010; 34(3): 387-9. PMID 19643476
27. Cazzola M, Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood. Jun 12 2014; 123(24): 3714-9. PMID 24786775

28. Makarik TV, Abdullaev AO, Nikulina EE, et al. Low JAK2 V617F Allele Burden in Ph-Negative Chronic Myeloproliferative Neoplasms Is Associated with Additional CALR or MPL Gene Mutations. Genes (Basel). Apr 12 2021; 12(4). PMID 33921387
29. Meja-Ochoa M, Acevedo Toro PA, Cardona-Arias JA. Systematization of analytical studies of polycythemia vera, essential thrombocythemia and primary myelofibrosis, and a meta-analysis of the frequency of JAK2, CALR and MPL mutations: 2000-2018. BMC Cancer. Jun 17 2019; 19(1): 590. PMID 31208359
30. Kumar C, Purandare AV, Lee FY, et al. Kinase drug discovery approaches in chronic myeloproliferative disorders. Oncogene. Jun 18 2009; 28(24): 2305-13. PMID 19421140
31. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med. Sep 16 2010; 363(12): 1117-27. PMID 20843246
32. Rambaldi A, Dellacasa CM, Finazzi G, et al. A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. Br J Haematol. Aug 2010; 150(4): 446-55. PMID 20560970
33. Santos FP, Kantarjian HM, Jain N, et al. Phase 2 study of CEP-701, an orally available JAK2 inhibitor, in patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis. Blood. Feb 11 2010; 115(6): 1131-6. PMID 20008298
34. Quints-Cardama A, Verstovsek S. Spleen deflation and beyond: the pros and cons of Janus kinase 2 inhibitor therapy for patients with myeloproliferative neoplasms. Cancer. Feb 15 2012; 118(4): 870-7. PMID 21766300
35. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. Mar 01 2012; 366(9): 799-807. PMID 22375971
36. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. Mar 01 2012; 366(9): 787-98. PMID 22375970
37. Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica. Apr 2015; 100(4): 479-88. PMID 25616577
38. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative neoplasms. Version.1.2023. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf Accessed June 16, 2023.

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.
December 2020	Replace policy	Policy updated with literature review through June 29, 2020; no references added. Policy statements unchanged.
December 2021	Replace policy	Policy updated with literature review through June 21, 2020; reference added. Policy statements unchanged.
December 2022	Replace policy	Policy updated with literature review through June 13, 2022; no references added. Minor editorial refinements to policy statements; intent unchanged.
December 2023	Replace policy	Policy updated with literature review through June 16, 2023; references added. Minor editorial refinements to policy statements; intent unchanged.