

Local Coverage Determination (LCD): MoIDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease (L36044)

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Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
Palmetto GBA	A and B and HHH	MAC 11201 - MAC A	J - M	South Carolina
Palmetto GBA	A and B and HHH	MAC 11202 - MAC B	J - M	South Carolina
Palmetto GBA	A and B and HHH	MAC 11301 - MAC A	J - M	Virginia
Palmetto GBA	A and B and HHH	MAC 11302 - MAC B	J - M	Virginia
Palmetto GBA	A and B and HHH	MAC 11401 - MAC A	J - M	West Virginia
Palmetto GBA	A and B and HHH	MAC 11402 - MAC B	J - M	West Virginia
Palmetto GBA	A and B and HHH	MAC 11501 - MAC A	J - M	North Carolina
Palmetto GBA	A and B and HHH	MAC 11502 - MAC B	J - M	North Carolina

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LCD Information

Document Information

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L36044

Original Effective Date
For services performed on or after 10/05/2015

Original ICD-9 LCD ID
N/A

Revision Effective Date
For services performed on or after 01/22/2016

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MoIDX: Genetic Testing for BCR-ABL Negative
Myeloproliferative Disease

Revision Ending Date
N/A

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CMS National Coverage Policy Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."

Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim lacking the necessary documentation to process the claim.

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS Internet Online Manual Pub. 100-02 (Medicare Benefit Policy Manual), Chapter 15, Section 80, "Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests"

CMS Internet-Only Manuals, Publication 100-04, Medicare Claims Processing Manual, Chapter 16, §50.5 Jurisdiction of Laboratory Claims, 60.12 Independent Laboratory Specimen Drawing, 60.2. Travel Allowance.

CMS Internet Online Manual Pub. 100-04 (Medicare Claims Processing Manual), Chapter 23 (Section 10) "Reporting ICD Diagnosis and Procedure Codes"

CMS Internet-Only Manual, Pub 100-04, Medicare Claims Processing Manual, Chapter 12, §30-Correct Coding Policy

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Indications and Limitations of Coverage

This policy provides coverage for multi-gene non-NGS panel testing and NGS testing for the diagnostic workup for myeloproliferative disease (MPL), and limited coverage for single-gene testing of patients with BCR-ABL negative myeloproliferative disease (MPD). MPD includes polycythemia vera (PV), essential thrombocytopenia (ET), and primary myelofibrosis (PMF).

For laboratories performing single gene technologies, a sequential genetic testing approach is expected. Once a positive result is obtained and the appropriate diagnosis is established, further testing should stop. Reflex testing to the next gene will be considered reasonable and necessary if the following sequence of genetic tests produce a negative result:

1. BCR-ABL negative test results, progress to #2
2. JAK 2, cv negative test results, progress to #3 or #4
3. JAK, exon 12 (JAK2 exon 12 is only done when PV is suspected)
4. CALR/MPL (CALR/MPL is only done when either ET or PMF is suspected; testing for CALR/MPL does NOT require a negative JAK2 exon 12, just a negative JAK2 V617F result)

Genetic testing of the JAK2 V617F mutation (81270) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet World Health Organization’s diagnostic criteria for myeloproliferative disease (i.e. polycythemia vera, essential thrombocytopenia, primary myelofibrosis) **if** JAK2 V617F were identified.

Genetic testing of JAK2 exon 12 (81403), performed to identify PV, is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- Patient would meet World Health Organization’s diagnostic criteria for PV, if JAK2 exon 12 testing were positive; **and**
- JAK2 V617F mutation analysis was previously completed and was negative.

Genetic testing of the CALR gene (81479) (only found in ET and PMF) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet World Health Organization’s diagnostic criteria for MPD (i.e. ET, PMF) if a clonal marker were identified.

Genetic testing of the MPL gene (81402) is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; **and**
- JAK2 V617F mutation analysis was previously completed and negative; **and**
- Patient would meet World Health Organization’s diagnostic criteria for MPD (i.e. ET, PMF) if a clonal marker were identified.

Note: In a single-gene sequential approach (not mandated by this policy), CALR would be a higher priority single gene test than MPL because:

- CALR mutations is more prevalent than MPL mutations in ET/PMF patients; and
- CALF mutations are reported to predict a more indolent disease course than patients with JAK2 mutations.

Background

Myeloproliferative Disorders

Myeloproliferative disorders are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include polycythemia vera (PV), essential thrombocytosis (ET), primary myelofibrosis (PMF), and chronic myelogenous leukemia (CML). The World Health Organization (WHO) further classifies PV, ET, and PMF as

Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). The diagnosis of an MPN is suspected based upon clinical, laboratory, and pathological findings (i.e. bone marrow morphology). MPNs are related, but distinct from, myelodysplastic syndromes (MDS). In general, MDS are characterized by ineffective or dysfunctional blood cells, while MPN are characterized by an increase in the number of blood cells.

Polycythemia Vera

Polycythemia vera is a chronic myeloproliferative disease characterized by increased hemoglobin, hematocrit, and red blood cell mass. There is an associated increased risk for thrombosis and transformation to acute myelogenous leukemia or primary myelofibrosis; however, patients are often asymptomatic. Criteria for a diagnosis of PV are based upon CBC and clinical features. The JAK2 V617F mutation is present in the vast majority of PV, accounting for approximately 90% of cases. Functionally similar mutations in JAK2 exon 12 account for most remaining cases of JAK2 V617F mutation-negative PV. Together, they are identified in 98% of PV cases and lead to high diagnostic certainty.

Among the proposed revised World Health Organization (WHO) criteria for diagnosis is presence of the somatic JAK2 V617F mutation or functionally similar exon 12 mutation. Absence of a JAK2 mutation, combined with normal or increased serum erythropoietin level, greatly decreases the likelihood of a PV diagnosis. WHO proposed revision criteria for PV do not address additional molecular markers, including CALR mutation status.

Essential Thrombocythemia

Essential thrombocythemia is a disorder of sustained increased platelet count. The majority of ET patients (60%) carry a somatic JAK2 V617F mutation, while a smaller percentage (5-10%) have activating MPL mutations. Revision to the WHO criteria for diagnosis of ET has been proposed and includes exclusion of PV, PMF, CML, myelodysplastic syndrome, or other myeloid neoplasm. Also included in the proposed major criteria for diagnosis is demonstration of somatic JAK2 V617F mutation or MPL exon 10 mutation¹². Proposed criteria additionally state that 70% of patients without a JAK2 or MPL mutation carry a somatic mutation of the calreticulin (CALR) gene. Among confirmed ET cases, mutations in CALR are more common than MPL. Positive CALR mutation status is suggested as indicating a more indolent course⁵.

Primary Myelofibrosis

Primary myelofibrosis (PMF) is a rare disorder in which the bone marrow is replaced with fibrous tissue, leading to bone marrow failure. Clinical features are similar to ET. The approximate incidence is 1 in 100,000 individuals. Persons can be asymptomatic in the early stages of the disease. For such patients, treatment may not initially be necessary. Progression of the disease can include transformation to acute myeloid leukemia. Treatment is generally symptomatic and aimed at preventing complications.

Demonstration of a clonal marker is important for diagnosis. Somatic molecular markers in PMF patients are similar to those in patients with ET, and include JAK2 V617F, MPL, and CALR. Somatic mutations in JAK2 are identified in 50-60% of PMF cases, and MPL mutations in 10%. Mutations in CALR are less common than JAK2, but more common than MPL.

Molecular Genetic Testing

One JAK2 gene mutation, V617K, is most commonly reported, occurring in over 90% of all polycythemia vera (PV) cases and about 50% of ET cases. Testing for JAK2 V617K gene mutations can be useful in diagnosis and is incorporated into the WHO's diagnostic criteria for these conditions.

The thrombopoietin receptor MPL is one of several JAK2 cognate receptors and is considered essential for myelopoiesis. The mutation frequency of MPL mutations associated with myeloproliferative disorders is substantially less (<10%) than JAK2 mutations. The guideline group for the British Committee for Standards in Haematology recommended a modification to the 2008 WHO criteria for ET to include the presence of an acquired pathogenetic mutation (e.g. in the JAK2 or MPL genes)³. Therefore, MPL gene testing may be indicated for individuals who would meet World Health Organization's diagnostic criteria for myeloproliferative disease if a clonal marker were identified.

Calreticulin (CALR) mutations have been identified in patients with myeloproliferative neoplasms and recent studies have investigated the utility of CALR mutation testing for the diagnosis and classification of myeloproliferative neoplasms. The mutations themselves are variable; however, generally focused in the exon 9 region.

Studies have shown that a significant proportion of patients with myeloproliferative neoplasms and normal JAK2 V617F mutation testing have a CALR gene mutation. CALR mutations account for a large proportion of JAK2/MPL-negative ET and PMF cases. Approximately 60% of JAK2/MPL-negative ET patients are CALR-positive and 30% of JAK2/MPL-negative PMF patients are CALR-positive. Overall, CALR mutations are identified in approximately 21% of ET cases and 16% of PMF cases. CALR mutations have not been reported in PV case series².

For this reason, CALR gene testing may be indicated for individuals who would meet World Health Organization's diagnostic criteria for myeloproliferative disease if a clonal marker were identified. Proponents have argued for revised WHO criteria that includes CALR mutation status in the classification system for ET and PMF ¹². Current NCCN guidelines do not make recommendations for CALR genetic testing; however, these guidelines are specific to MDS and do not broadly address myeloproliferative neoplasms, such as ET or PMF. Somatic mutations in non-MDS genes, such as CALR, are listed as being associated with conditions that can mimic other myelodysplastic syndromes.

Aside from diagnostic utility, some research suggests distinct clinical outcomes associated with CALR mutation status; however, the findings have not been confirmed in other studies. It is suggested that ET patients with CALR mutations have lower polycythemic transformation rates, but not lower myelofibrotic transformation rate, compared with ET patients harboring a JAK2 mutation. Others reported a higher platelet count, younger age of diagnosis, lower leukocyte count, and decreased risk for thrombosis, compared with a JAK2 positive ET population ¹. CALR-mutated ET has also been associated with better thrombosis-free survival and lower leukocyte counts; overall survival has been reported as not different among CALR mutated and non-mutated ET ^{2,15}.

Although they are useful for establishing a diagnosis, the presence of specific clonal markers does not dictate treatment. Controversy exists generally regarding the treatment of asymptomatic individuals with ET. Some argue against treatment if there are no associated complications. In general, the main goal of treatment with PV and ET is to identify persons at high risk for thrombosis and prevent complications. Persons with PV and ET are determined to be at high-risk due to age >60 years and past history of thrombotic event(s). CALR mutational status is not currently used for risk stratification ¹¹.

In summary, multiple studies have demonstrated the diagnostic value of CALR mutation status in a population of JAK2 and MPL negative patients with suspected ET and PMF. The presence of a somatic CALR mutation can prove useful in obtaining an accurate diagnosis. Emerging evidence suggests possible differences in clinical phenotype among the associated clonal markers, including CALR-positive ET cases. However, CALR mutation status is currently not incorporated into clinical risk stratification and more research is needed in this area.

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

N/A

CPT/HCPCS Codes

Group 1 Paragraph: N/A

Group 1 Codes:

81206 BCR/ABL1 (T(9;22)) (EG, CHRONIC MYELOGENOUS LEUKEMIA) TRANSLOCATION ANALYSIS; MAJOR BREAKPOINT, QUALITATIVE OR QUANTITATIVE

- 81207 BCR/ABL1 (T(9;22)) (EG, CHRONIC MYELOGENOUS LEUKEMIA) TRANSLOCATION ANALYSIS; MINOR BREAKPOINT, QUALITATIVE OR QUANTITATIVE
- 81208 BCR/ABL1 (T(9;22)) (EG, CHRONIC MYELOGENOUS LEUKEMIA) TRANSLOCATION ANALYSIS; OTHER BREAKPOINT, QUALITATIVE OR QUANTITATIVE
- 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
MOLECULAR PATHOLOGY PROCEDURE, LEVEL 3 (EG, >10 SNPS, 2-10 METHYLATED VARIANTS, OR 2-10 SOMATIC VARIANTS [TYPICALLY USING NON-SEQUENCING TARGET VARIANT ANALYSIS],
- 81402 IMMUNOGLOBULIN AND T-CELL RECEPTOR GENE REARRANGMENTS, DUPLICATION/DELETION VARIANTS OF 1 EXON, LOSS OF HETEROZYGOSITY [LOH], UNIPARENTAL DISOMY [UPD])
MOLECULAR PATHOLOGY PROCEDURE, LEVEL 4 (EG, ANALYSIS OF SINGLE EXON BY DNA SEQUENCE
- 81403 ANALYSIS, ANALYSIS OF >10 AMPLICONS USING MULTIPLEX PCR IN 2 OR MORE INDEPENDENT REACTIONS, MUTATION SCANNING OR DUPLICATION/DELETION VARIANTS OF 2-5 EXONS)
TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN NEOPLASM, DNA ANALYSIS, AND RNA
- 81445 ANALYSIS WHEN PERFORMED, 5-50 GENES (EG, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), INTERROGATION FOR SEQUENCE VARIANTS AND COPY NUMBER VARIANTS OR REARRANGEMENTS, IF PERFORMED
TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, HEMATOLYMPHOID NEOPLASM OR DISORDER, DNA
- 81450 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
TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, SOLID ORGAN OR HEMATOLYMPHOID NEOPLASM, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 51 OR GREATER GENES (EG, ALK, BRAF,
- 81455 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, IF PERFORMED
- 81479 UNLISTED MOLECULAR PATHOLOGY PROCEDURE

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph: N/A

Group 1 Codes:

ICD-10 Codes

Description

C92.20	Atypical chronic myeloid leukemia, BCR/ABL-negative, not having achieved remission
C92.21	Atypical chronic myeloid leukemia, BCR/ABL-negative, in remission
C92.22	Atypical chronic myeloid leukemia, BCR/ABL-negative, in relapse
D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease
D47.3	Essential (hemorrhagic) thrombocythemia
D75.1	Secondary polycythemia
D75.81	Myelofibrosis
D75.89	Other specified diseases of blood and blood-forming organs

ICD-10 Codes that DO NOT Support Medical Necessity N/A

ICD-10 Additional Information

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[General Information](#)

Associated Information

Documentation Requirements

The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See "Coverage Indications, Limitations, and/or Medical Necessity") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

Documentation supporting the medical necessity should be legible, maintained in the patient's medical record, and must be made available to the MAC upon request.

Sources of Information and Basis for Decision

References

1. Chen CC, Gau JP, Chou HJ, et al. Frequencies, clinical characteristics, and outcome of somatic CALR mutations in JAK2-unmutated essential thrombocythemia. *Ann Hematol.* 2014;93(12):2029-36.
2. Ha JS, Kim YK. Calreticulin exon 9 mutations in myeloproliferative neoplasms. *Ann Lab Med.* 2015;35(1):22-7.
3. Harrison CN, Bareford D, Butt N, et al. British Committee for Standards in Haematology. Guideline for investigation and management of adults and children presenting with a thrombocytosis. *Br J Haematol.* 2010;149(3):352-75.
4. Haslam K, Langabeer SE. Considerations and recommendations for a new molecular diagnostic algorithm for the myeloproliferative neoplasms. *Genet Test Mol Biomarkers.* 2014; 18(11):749-53.
5. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of Calreticulin in Myeloproliferative neoplasms. *N Engl J Med* 2013;369(25):2379-90.
6. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med* 2013;369(25):2391-405.
7. NCCN Clinical Practice Guideline. Myelodysplastic Syndromes. V2.2015; Accessed 2/5/15.
8. Pardanani AD, Levine RL, Lasho T, et al. MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. *Blood.* 2006;108:3472-6.
9. Rotunno G, Mannarelli C, Guglielmelli P, et al. Impact of calreticulin mutations on clinical and hematological phenotype and outcome in essential thrombocythemia. *Blood.* 2014;123(10):1552-5.
10. Rumi E, Pietra D, Ferretti V, et al. JAK2 or CALR mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. *Blood.* 2014;123(10):1544-51.
11. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2015 update on diagnosis, risk-stratification and management. *Am J Hematol.* 2015 Feb;90(2):162-73.
12. Tefferi A, Thiele J, Vannucchi AM, et al. An overview on CALR and CSF3R mutations and a proposal for revision of WHO diagnostic criteria for myeloproliferative neoplasms. *Leukemia.* 2014;28(7):1407-13.
13. Tefferi A, Thiele J, Vardiman JW: The 2008 World Health Organization classification system for myeloproliferative neoplasms: order out of chaos. *Cancer.* 2009;115(17):3842-7.
14. Wojtaszewska M, Iwola M, Lewandowski K. Frequency and molecular characteristics of calreticulin gene (CALR) mutations in patients with JAK2-Negative myeloproliferative neoplasms. *Acta Haematol.* 2014;133(2):193-8.
15. Yang Y, Wang X, Wang C, Qin Y. A meta-analysis comparing clinical characteristics and outcomes in CALR-mutated and JAK2V617F essential thrombocythaemia. *Int J Hematol.* 2015;101(2):165-72.

Revision History Information

Please note: Most Revision History entries effective on or before 01/24/2013 display with a Revision History Number of "R1" at the bottom of this table. However, there may be LCDs where these entries will display as a separate and distinct row.

Revision History Date	Revision History Number	Revision History Explanation	Reason(s) for Change
01/22/2016	R2	Added C92.20, C92.21 and C92.22 to Group 1: Codes for ICD-10 Codes that Support Medical Necessity Updated the Annual Review Date field with 10/05/2015	<ul style="list-style-type: none">Request for Coverage by a Provider (Part A)
01/01/2016	R1	Added 2016 CPT code 81219	<ul style="list-style-type: none">Revisions Due To CPT/HCPCS Code Changes

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Associated Documents

Attachments N/A

Related Local Coverage Documents N/A

Related National Coverage Documents N/A

Public Version(s) Updated on 01/12/2016 with effective dates 01/22/2016 - N/A [Updated on 12/22/2015 with effective dates 01/01/2016 - 01/21/2016](#) [Updated on 08/13/2015 with effective dates 10/05/2015 - N/A](#) [Back to Top](#)

Keywords

N/A Read the [LCD Disclaimer](#) [Back to Top](#)