LCD - MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease (L36186)

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CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATES
Noridian Healthcare Solutions, LLC	A and B MAC	02101 - MAC A	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02102 - MAC B	J - F	Alaska
Noridian Healthcare Solutions, LLC	A and B MAC	02201 - MAC A	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02202 - MAC B	J - F	Idaho
Noridian Healthcare Solutions, LLC	A and B MAC	02301 - MAC A	J - F	Oregon
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Noridian Healthcare Solutions, LLC	A and B MAC	03101 - MAC A	J - F	Arizona
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Noridian Healthcare Solutions, LLC	A and B MAC	03402 - MAC B	J - F	South Dakota
Noridian Healthcare Solutions, LLC	A and B MAC	03501 - MAC A	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03502 - MAC B	J - F	Utah
Noridian Healthcare Solutions, LLC	A and B MAC	03601 - MAC A	J - F	Wyoming
Noridian Healthcare Solutions, LLC	A and B MAC	03602 - MAC B	J - F	Wyoming

LCD Information

Document Information

LCD ID

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LCD Title

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MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease

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N/A

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Issue

Issue Description

This LCD outlines limited coverage for this service with specific details under **Coverage Indications, Limitations and/or Medical Necessity.**

CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A) allows coverage and payment for only those services that are considered to be reasonable and necessary.

42 CFR §410.32(a) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions

CMS Internet-Only Manual, Pub. 100-02, Medicare Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests, §80.1.1 Certification Changes

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Indications and Limitations of Coverage

This policy provides coverage for multi-gene non-next generation sequencing (NGS) panel testing and NGS testing for the diagnostic workup for myeloproliferative disease (MPD), also known as myeloproliferative neoplasms (MPNs), and limited coverage for single-gene testing of patients with BCR-ABL negative MPD. BCR-ABL negative MPD includes polycythemia vera (PV), essential thrombocythemia (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. Calreticulin (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 is medically necessary when the following criteria are met:

- Genetic testing impacts medical management; and
- Patient would meet World Health Organization’s (WHO) diagnostic criteria for myeloproliferative disease (i.e., PV, ET, PMF) if JAK2 V617F were identified.

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

- Genetic testing impacts medical management; and
- Patient would meet WHO'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 (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 WHO's diagnostic criteria for MPD (i.e., ET, PMF) if a clonal marker were identified.

Genetic testing of the MPL gene 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 WHO's diagnostic criteria for MPD (i.e., ET, MPF) 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
- CALR mutations are reported to predict a more indolent disease course than that of patients with JAK2 mutations.

For laboratories performing NGS or "hotspot" testing platforms: Molecular testing for BCR-ABL, JAK 2, JAK2exon 12, and CALR/MPL genes by NGS is covered as medically necessary for the identification of myeloproliferative disorders.

Summary of Evidence

Myeloproliferative Disorders

Myeloproliferative disorders are a group of conditions that cause abnormal growth of blood cells in the bone marrow. They include PV, ET, PMF, and chronic myelogenous leukemia (CML). The WHO further classifies PV, ET, and PMF as Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). The diagnosis of a 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 (PV)

PV is a chronic MPD characterized by increased hemoglobin, hematocrit, and red blood cell mass. There is an associated increased risk for thrombosis and transformation to acute myelogenous leukemia (AML) or PMF; however, patients are often asymptomatic. Criteria for a diagnosis of PV are based upon complete blood count (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 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 (ET)

ET 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, MDS, or other myeloid neoplasm. Also included in the proposed major criteria for diagnosis is demonstration of somatic JAK2 V617F mutation or MPL exon 10 mutation.[12] Proposed criteria additionally state that 70% of patients without a JAK2 or MPL mutation carry a somatic mutation of the 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 course.[5]

Primary Myelofibrosis (PMF)

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 AML. 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, V617F, is most commonly reported, occurring in over 90% of all PV cases and about 50% of ET cases. Testing for JAK2 V617F 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 Hematology 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 WHO's diagnostic criteria for MPD if a clonal marker were identified.

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

Studies have shown that a significant proportion of patients with MPNs 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 series.[2]

For this reason, CALR gene testing may be indicated for individuals who would meet WHO's diagnostic criteria for MPD 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 National Comprehensive Cancer Network® (NCCN) guidelines do not make recommendations for CALR genetic testing; however, these guidelines are specific to MDS and do not broadly address MPNs, 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]

Analysis of Evidence (Rationale for Determination)

Level of evidence

Quality – Strong

Strength – Strong

Weight – Moderate

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.

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 Local Coverage Determination (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 Medicare Administrative Contractor (MAC) upon request.

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
07/16/2023	R12	Under **CMS National Coverage Policy** updated section headings for regulations and revised the following regulation: CMS Internet-Only Manual, Pub. 100-02, Medicare Policy Manual, Chapter 15, §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests, to include section 80.1.1. Under **Bibliography** changes were made to citations to reflect AMA citation guidelines. Formatting, punctuation and	• Provider Education/Guidance

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
		typographical errors were corrected throughout the LCD.	
06/30/2022	R11	Under **Coverage Indications, Limitations and/or Medical Necessity** revised the first sentence to read, "This policy provides coverage for multi-gene non-next generation sequencing (NGS) panel testing and NGS testing for the diagnostic workup for myeloproliferative disease (MPD), also known as myeloproliferative neoplasms (MPNs), and limited coverage for single-gene testing of patients with BCR-ABL negative MPD. BCR-ABL negative MPD includes polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF)." This revision is effective on 6/30/2022.	• Provider Education/Guidance
07/01/2021	R10	Under **CMS National Coverage Policy** added regulation CMS Internet-Only Manual, Pub. 100-02, Medicare Benefit Policy Manual, Chapter 15 §80 Requirements for Diagnostic X-Ray, Diagnostic Laboratory, and Other Diagnostic Tests. Under **Bibliography** changes were made to citations to reflect AMA citation guidelines. Formatting, punctuation and typographical errors were corrected throughout the LCD. Acronyms were defined and inserted where appropriate throughout the LCD.	• Provider Education/Guidance
11/01/2019	R9	The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)
11/01/2019	R8	LCD is revised to move several CMS references to the companion billing and coding article. CPT codes in Indications and Limitations were removed. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage.	• Creation of Uniform LCDs With Other MAC Jurisdiction

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
11/01/2019	R7	As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD.	• Revisions Due To Code Removal
10/01/2017	R6	Added ICD-10 codes C91.00, C91.01, and C91.02 to Group 1: Codes that Support Medical Necessity. These codes are retro-effective 7/1/2017. Expansion of ICD-10 codes is required to not restrict the use of testing for BCR-ABL in patients with acute lymphoblastic leukemia.	• Creation of Uniform LCDs With Other MAC Jurisdiction • Revisions Due To ICD-10-CM Code Changes
10/01/2017	R5	Added ICD-10 code D47.02, effective 10/1/2017. Added 21st Century Act required fields. Added ICD-10 codes C92.11 and C92.12 effective 10/13/2016.	• Creation of Uniform LCDs With Other MAC Jurisdiction
01/01/2017	R4	Changed MPD to MPL in reference to the MPL gene mutation. MPD refers to myeloproliferative disease.	• Creation of Uniform LCDs Within a MAC Jurisdiction • Creation of Uniform LCDs With Other MAC Jurisdiction
01/01/2017	R3	CPT code 81402 descriptor was changed in Group 1, under CPT/HCPCS Codes. There may not be any change in how the code displays in the document. Minor typographical errors were corrected: Indications and Limitations of Coverage- (bullet 13) • CALR mutations are reported to predict a more indolent disease course than (added "that of") patients with JAK2 mutations and changed CALF to CALR. Molecular Genetic Testing- (3rd paragraph) Studies have shown that a significant proportion of patients with myeloproliferative neoplasms and normal JAK2 (added "v")617F mutation testing have a CALR gene mutation.	• Revisions Due To CPT/HCPCS Code Changes
04/19/2016	R2	The acronym for myeloproliferative disease was previously noted primarily as MPL with a few notations as MPD. LCD was revised to consistently use MPD to describe myeloproliferative disease.	• Creation of Uniform LCDs With Other MAC Jurisdiction

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASONS FOR CHANGE
04/19/2016	R1	LCD is revised to include the following diagnoses per the MolDX contractor effective 04/19/2016: C88.8, C92.10, C93.10, C94.40, C94.41, C94.42, C94.6, D46.0-D46.9, D46.Z, D47.4, D47.9, D47.Z9, D72.821, D72.829 and D75.9	• Creation of Uniform LCDs With Other MAC Jurisdiction

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Articles

A55600 - Billing and Coding: MolDX: BCR-ABL

A57422 - Billing and Coding: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease

A54916 - Response to Comments: MolDX: Genetic Testing for BCR-ABL Negative Myeloproliferative Disease

LCDs

DL36182 - (MCD Archive Site)

DL36186 - (MCD Archive Site)

Related National Coverage Documents

N/A

Public Versions

UPDATED ON	EFFECTIVE DATES	STATUS
06/29/2023	07/16/2023 - N/A	Currently in Effect (This Version)
06/23/2022	06/30/2022 - 07/15/2023	Superseded
Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.		

Keywords

N/A