BCR-ABL Negative Myeloproliferative Neoplasm Genetic Testing

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Introduction

BCR-ABL negative myeloproliferative neoplasm (MPN) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
ASXL1 Mutation Analysis	81175
CALR Exon 9 Mutation Analysis	81219
DNMT3A Targeted Mutation Analysis	81403
EZH2 Common Variant(s) (e.g. codon 646)	81237
EZH2 Full Gene Sequencing	81236
IDH1 Common Variants	81120
IDH2 Common Variants	81121
JAK2 Exons 12 to 15 Sequencing	0027U
JAK2 Mutation	0017U
JAK2 Targeted Mutation Analysis (e.g exons 12 and 13)	81279
JAK2 V617F Mutation Analysis	81270
MPL Common Variants (e.g. W515A, W515K, W515L, W515R)	81338
MPL Mutation Analysis, Exon 10	81339
SF3B1 Common Variants (e.g. A672T, E622D, L833F, R625C, R625L)	81347
SRSF2 Common Variants (e.g. P95H, P95L)	81348
TET2 Mutation Analysis	81479

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Procedures addressed by this guideline	Procedure codes
U2AF1 Common Variants (e.g. S34F, S34Y, Q157R, Q157P)	81357
Targeted Genomic Sequence Analysis Panel, Hematolymphoid Neoplasm or Disorder	81450

Criteria

Introduction

Requests for genetic testing for BCR-ABL negative myeloproliferative neoplasm (MPN) are reviewed using these criteria.

JAK2 V617F Mutation Analysis

- Member does not meet WHO criteria for BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms, AND
- Member meets at least ONE of the following diagnostic criteria for MPN:
    - Bone marrow biopsy results that are consistent with WHO diagnostic criteria for prePMF, overt primary myelofibrosis (PMF), essential thrombocythemia (ET), or polycythemia vera (PV), or
    - Platelet count ≥ 450 x 10^9/L, or
    - Hemoglobin > 16.5 g/dL in men, > 16.0 g/dL in women, or
    - Hematocrit >49% in men, >48% in women, or
    - Increased red cell mass (RCM), defined as >25% above the mean normal predicted value, or
    - A combination of two of the following symptoms:
        - Anemia not attributed to a comorbid condition, or
        - Leukocytosis ≥ 11 x 10^9/L, or
        - Palpable splenomegaly, or
        - LDH increased to above upper normal limit of institutional reference range, or
        - Leukoerythroblastosis, OR
- MPN is being considered in the differential diagnosis with the member meeting both of the following:

  - Variable lab abnormalities, including erythrocytosis, thrombocytosis and leukocytosis, which are not otherwise assigned an etiology, and
  - Constitutional symptoms, including fatigue, pruritus, weight loss and symptoms of splenomegaly, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

JAK2 Exon 12 Analysis

- Member does not meet WHO criteria for BCR-ABL1+ CML, myelodysplastic syndromes, or other myeloid neoplasms, AND
- JAK2 V617F mutation analysis is negative, AND
- Member meets at least ONE of the following diagnostic criteria for PV:
  - Bone marrow biopsy results that are consistent with WHO diagnostic criteria for PV, or
  - Hemoglobin > 16.5 g/dL in men, > 16.0 g/dL in women, or
  - Hematocrit >49% in men, >48% in women, or
  - Increased red cell mass (RCM), defined as >25% above the mean normal predicted value, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CALR Exon 9 and MPL Mutation Analysis

- Member does not meet WHO criteria for BCR-ABL1+ CML, PV, myelodysplastic syndromes, or other myeloid neoplasms, AND
- JAK2 V617F mutation analysis is negative, AND
- Member meets at least ONE of the following diagnostic criteria for ET or PMF:
  - Bone marrow biopsy results that are consistent with WHO diagnostic criteria for prePMF, overt PMF, or ET, or
  - Platelet count ≥ 450 x 10^9/L, or
  - A combination of two of the following symptoms:
    - Anemia not attributed to a comorbid condition, or
    - Leukocytosis ≥ 11 x 10^9/L, or
    - Palpable splenomegaly, or
    - LDH increased to above upper normal limit of institutional reference range, or
    - Leukoerythroblastosis, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Analysis of ASXL1, DNMT3A, EZH2, TET2, IDH1, IDH2, SRSF2, And/Or SF3B1

- Member does not meet WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms, AND
- JAK2, CALR, and MPL mutation analyses are all negative, AND
- Member meets at least ONE of the following diagnostic criteria for PMF:
    - Bone marrow biopsy results that are consistent with WHO diagnostic criteria for prePMF or overt PMF, or
    - A combination of two of the following symptoms:
        - Anemia not attributed to a comorbid condition, or
        - Leukocytosis ≥ 11 x 10^9/L, or
        - Palpable splenomegaly, or
        - LDH increased to above upper normal limit of institutional reference range, or
        - Leukoerythroblastosis, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

If requested, gene panels that include the following genes will be eligible for reimbursement according to the criteria outlined in this guideline: ASXL1, DNMT3A, EZH2, TET2, IDH1, IDH2, SRSF2, and SF3B1. This sequencing panel will only be considered for reimbursement when billed with the appropriate panel CPT code: 81450.

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What are BCR-ABL Negative Myeloproliferative Neoplasms?

Definition

Myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET) are a group of heterogeneous disorders of the hematopoietic system collectively known as Philadelphia chromosome-negative myeloproliferative neoplasms (MPN).

Prevalence

The following table describes the prevalence of Philadelphia chromosome-negative MPNs in the U.S.[1]

Disorder	Prevalence in the U.S.
MF	13,000
ET	134,000
PV	148,000

Symptoms

Symptoms vary among the subtypes, but generally include

- constitutional symptoms
- fatigue
- pruritus
- weight loss
- symptoms of splenomegaly, and
- variable lab abnormalities, including
    - erythrocytosis
    - thrombocytosis, and
    - leukocytosis.[1]

Risks

Individuals with MPNs are at risk of the condition transforming into acute myeloid leukemia (AML), which is associated with a poor response to therapy and short survival. These disorders are also associated with an increased risk of major bleeding and thrombosis or thromboembolism compared to the general population.[1]

Diagnosis

The diagnosis and management of individuals with MPN has evolved since the identification of mutations that activate the JAK pathway, including JAK2, CALR, and MPL. The development of targeted therapies has resulted in significant improvements in disease-related symptoms and quality of life.[1] In a minority of individuals, recurrent mutations in other genes contribute to initiation or progression of disease. These mutations may serve as markers of clonality in cases where mutations in JAK2, MPL or CALR are not detected.[2]

- **JAK2 V617F mutations** — JAK2 V617F mutations account for the majority of individuals with PV (greater than 90%), ET or MF (60%). Most of the mutations occur in exon 14 with rare insertions/deletions in exon 12.[1]
- **JAK2 exon 12 mutations** — JAK2 exon 12 mutations have been seen in approximately 2-3% of individuals with PV.[1] Individuals "with JAK2 exon 12-mutated PV exhibit younger age, increased mean hemoglobin/hematocrit, and lower mean WBC [white blood cell] and platelet counts at diagnosis compared to those with JAK2 V617F-mutated PV. However, both JAK2 mutations are associated with similar rates of thrombosis, evolution to MF or leukemia, and death."[1]
- **MPL mutations** — MPL mutations have been reported in 5-8% of individuals with MF and 1-4% of individuals with ET. "MPL mutations are associated with lower hemoglobin levels at diagnosis and increased risk of transfusion dependence in patients with MF."[1]
- **CALR mutations** — CALR frameshift mutations in exon 9 are reported in approximately 20-35% of individuals with ET and MF, accounting for approximately 60-80% of individuals with JAK2/MPL-negative ET and MF. CALR deletion mutations are more commonly seen in individuals with MF, and CALR insertion mutations are associated with ET. CALR-mutated ET is associated with a lower hemoglobin level, lower WBC count, higher platelet count and lower incidence of thrombosis than JAK2-mutated ET.[1]

Test information

Introduction

Testing for BCR-ABL negative MPN may include cytogenetic testing, single gene mutation analysis, or multi-gene panel testing.

Types of tests

There are various methods used to test for the cytogenetic and molecular abnormalities associated with MPN.[1,3] Tests for the cytogenetic and molecular abnormalities include:

- bone marrow (BM) cytogenetics: karyotype, with or without FISH

- single gene mutation analysis for JAK2, MPL, and CALR, and
- panel testing using next generation sequencing for somatic mutations in genes associated with MPN.

This guideline only addresses single gene mutation analysis and multi-gene panel testing.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to BCR-ABL negative MPN genetic testing.

International Consensus Classification

The International Consensus Classification of myeloid neoplasms and acute leukemias (ICC, 2022) revised and updated established diagnostic criteria for these conditions.[4]

- The major MPN categories remain unchanged compared to other society guidelines, but "new molecular data and improved understanding of morphology have sharpened the proposed diagnostic criteria." The differences in classifications between ICC and other societies are minor and unlikely to markedly impact MPN categorizations.
- "The classical BCR::ABL1-negative MPN subtypes include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The principal objective in the classification of these cases it to reduce diagnostic uncertainty especially in initial/early disease stages presenting with elevated platelet counts and to optimize clinical management of patients. The integration of molecular findings with BM morphology and blood counts remains the cornerstone of diagnosis. Importantly, morphologic diagnosis should not only focus on megakaryocytic atypia but has to consider characteristic patterns of other features like age-related cellularity, changes in erythropoiesis, and neutrophil granulopoiesis in context with the grade of BM fibrosis."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN, 2023) evidence and consensus-based guidelines recommended the following initial laboratory evaluations for individuals suspected to have MPN:[1]

- “Laboratory evaluations should include complete blood count (CBC) with differential, microscopic examination of the peripheral smear, comprehensive metabolic panel with serum uric acid, serum LDH, liver function tests, serum EPO level, and serum iron studies.”

- “Fluorescence in situ hybridization (FISH) or a multiplex reverse transcriptase polymerase chain reaction (RT-PCR), if available, on peripheral blood to detect BCR-ABL1 transcripts and exclude the diagnosis of CML [chronic myelogenous leukemia] is especially recommended for patients with left-shifted leukocytosis and/or thrombocytosis with basophilia.”
- "Molecular testing on blood or bone marrow for JAK2 V617F mutations is recommended as part of initial workup for all patients. If JAK2 V617F mutation testing is negative, molecular testing for CALR and MPL mutations should be performed for patients with suspected ET and MF; molecular testing for the 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 [next generation sequencing] panel that includes JAK2, CALR, and MPL can be used as part of initial workup for all patients.”
- "Once an MPN diagnosis is confirmed, NGS is recommended for mutational prognostication. The application of an NGS-based 28-gene panel in patients with MPN identified significantly more mutated splicing genes (SF3B1, SRSF2, and U2AF1) in patients with PMF compared to those with ET, and no mutations in splicing genes were found in patients with PV. NGS may also be useful to establish the clonality in selected circumstances (eg, triple-negative MPN with non-mutated JAK2, MPL, and CALR). It can also identify second, third, and fourth mutations that may hold prognostic relevance."
- “Bone marrow aspirate with iron stain and biopsy with trichrome and reticulin stains and bone marrow cytogenetics (karyotype, with or without FISH; peripheral blood for FISH, if bone marrow is inaspirable) are necessary to accurately distinguish the bone marrow morphological features between the disease subtypes (early or prefibrotic PMF, ET and masked PV).”

World Health Organization: PMF

The World Health Organization (WHO, 2016; reaffirmed 2022) established diagnostic criteria for PMF.[3,5]

PMF, early/prefibrotic stage (pre-PMF)	PMF, overt fibrotic stage
[Diagnosis requires meeting all 3 major criteria, and at least 1 minor criterion]	**[Diagnosis requires meeting all 3 major criteria, and at least 1 minor criterion]**
Major criteria: • Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis • Not meeting WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms • Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive BM reticulin fibrosis	Major criteria: • Megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3 • Not meeting WHO criteria for BCR-ABL1+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms • Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive BM myelofibrosis
Minor criteria: Presence of at least one of the following, confirmed in 2 consecutive determinations: • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 x 10^9/L • Palpable splenomegaly • LDH increased to above upper normal limit of institutional reference range	Minor criteria: Presence of at least one of the following, confirmed in 2 consecutive determinations: • Anemia not attributed to a comorbid condition • Leukocytosis ≥ 11 x 10^9/L • Palpable splenomegaly • LDH increased to above upper normal limit of institutional reference range • Leukoerythroblastosis

Absence of 3 major clonal mutations

In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations help determine the clonal nature of the disease.[2] Examples of frequent accompanying mutations include:

- ASXL1
- DNMT3A

- EZH2
- TET2
- IDH1
- IDH2
- SRSF2
- SF3B1

World Health Organization: PV

The World Health Organization (WHO, 2022) updated diagnostic criteria for PV.[5]

Polycythemia Vera (PV)
[Diagnosis requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion]
Major criteria: • Hemoglobin > 16.5 g/dL in men, > 16.0 g/dL in women OR Hematocrit >49% in men, >48% in women • Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) • Presence of JAK2 V617F or JAK2 exon 12 mutation Minor criteria: • Subnormal serum EPO level

Bone marrow biopsy not required in some cases

A bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis; hemoglobin levels >18.5 g/dL in men (hematocrit, >55.5%) or >16.5 g/dL in women (hematocrit, >49.5%) if 3 major criterion and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV PMF).

World Health Organization: ET

The World Health Organization (WHO, 2016; reaffirmed 2022) established diagnostic criteria for ET.[3,5]

Essential Thrombocythemia (ET)
[Diagnosis requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion]
Major criteria: • Platelet count ≥ 450 x 10^9/L • Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers • Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms • Presence of JAK2, CALR, or MPL mutation Minor criteria: • Presence of a clonal marker or absence of evidence for reactive thrombocytosis

References

Introduction

These references are cited in this guideline.

1. National Comprehensive Cancer Network (NCCN) Guidelines – 3.2023 Myeloproliferative Neoplasms available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) for Myeloproliferative Neoplasms – 3.2023. © 2023 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines™ and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN.

2. Vainchenker W, Kralovics R. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. *Blood.* 2017;Feb 9;129(6):667-679.

3. Arber D, Orazi A, Hasserjian R et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood.* 2016;127(20):2391-2405.

4. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228.

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5. 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*. 2022;36(7):1703-1719.

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