Genetic Testing for Myeloid Neoplasms and Leukemia

Effective: August 1, 2017

Next Review: February 2018
Last Review: June 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic mutation testing for ABL1, CALR, JAK2, and/or MPL genes may inform the diagnostic, prognostic, and treatment selection processes for select myeloid neoplasms and leukemias (acute or chronic).

MEDICAL POLICY CRITERIA

Notes:

- This policy does not address testing for BCR/ABL1 (t(9;22)) translocation analysis (i.e., CPT codes 81206-8 and 0016U) which may be considered medically necessary.
- Please refer to the Cross References section below for genetic testing not addressed in this policy, including but not limited to single-gene testing.

I. BCR-ABL kinase domain (ABL1)
   
   A. Genetic mutation testing for ABL1 may be considered medically necessary to evaluate patients when either of the following (1. or 2.) are met:
      
      1. In patients with chronic myelogenous (myeloid) leukemia (CML), to monitor response to tryosine kinase inhibitor therapy, when either of the following (a.
or b.) are met: (See Policy Guidelines)

a. In chronic phase, when there is failure to reach response milestones; or when there is any sign of loss of response (defined as hematologic or cytogenetic relapse); or when there is 1-log increase in BCR-ABL1 transcript levels and loss of major molecular response (MMR); OR

b. When there is progression of the disease to the accelerated or blast phase.

2. In patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), to evaluate for tyrosine kinase inhibitor resistance when there is an inadequate initial response to treatment or any sign of loss of response. (See Policy Guidelines)

B. Genetic mutation testing for ABL1 is considered investigative for all other circumstances, including but not limited to monitoring, management, or selecting treatment for patients with any condition.

II. CALR, JAK2, and/or MPL

A. Genetic mutation testing may be considered medically necessary to confirm a diagnosis for myeloid neoplasms when any of the following are met:

1. CALR, JAK2, and/or MPL when clinical, laboratory, or pathological findings suggest the following:
   a. Essential thrombocythemia (ET)
   b. Prefibrotic/early stage primary myelofibrosis (pre-PMF)
   c. Primary myelofibrosis (PMF) (overt PMF)

2. CALR, JAK2 (V617F), and/or MPL when clinical, laboratory, or pathological findings suggest myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

3. JAK2 (V617F) and/or JAK2 exon 12 when clinical, laboratory, or pathological findings suggest polycythemia vera (PV).

B. CALR, JAK2, and/or MPL genetic mutation testing is considered investigative for all other circumstances, including but not limited to monitoring, management, or selecting treatment for patients with any condition.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
   o History and physical exam including any relevant diagnoses related to the genetic testing
   o Conventional testing and outcomes
   o Conservative treatments, if any

Strategies for testing may include testing for individual genes or in combination, such as in a panel.

**BCR-ABL KINASE DOMAIN MUTATION ANALYSIS**

**Chronic Myelogenous (Myeloid) Leukemia**

In chronic phase CML, following primary treatment, National Comprehensive Cancer Network Guidelines for Chronic Myeloid Leukemia (v2.2017) response milestones are defined at 3-, 6-, 12-, and >12-months for BCR-ABL1 measurements according to the International Scale (IS).[1] Measurements are expressed as ratios, which correspond to the percent ratio between BCR-ABL1 and the endogenous control transcript.

Accelerated or blast phase CML are defined by hematologic, cytogenetic, and/or response-to-tyrosine kinase inhibitor (TKI) criteria.[1,2]

**Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia**

Unlike in CML, resistance in ALL to TKIs is less well studied. In patients with ALL that are receiving a TKI, a rise in the BCR-ABL level while in hematologic complete response or clinical relapse warrants mutational analysis.

**CROSS REFERENCES**

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Genetic Panel Testing (5-50 genes) for Hematolymphoid Neoplasms or Disorders, Genetic Testing, Policy No. 09
3. Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia, Transplant, Policy No. 45.36
4. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31
5. RegenceRx Medication Policy Manual NOTE: enter drug name in the search bar to find appropriate policy.

**BACKGROUND**

**DIAGNOSING MYELOID NEOPLASMS AND ACUTE LEUKEMIA**

Myeloid neoplasms may be acute or chronic, are a type of hematologic malignancy, and usually derive from bone marrow progenitor cells that normally develop into erythrocytes, granulocytes (neutrophils, basophils, and eosinophils), monocytes, or megakaryocytes. Classification of myeloid neoplasms and acute leukemias has evolved over the past decade, based in part on the advancement of available technologies and results from repeat validation studies.
In recent history, diagnosis of the various forms of myeloid neoplasms has been based on a complex set of clinical, pathological, and biological criteria first introduced by the Polycythemia Vera Study Group (PVSG) in 1996\(^3,4\) and the World Health Organization (WHO) in 2001.\(^5\) Both of these classifications use a combination of clinical, pathological, and/or biological criteria to arrive at a definitive diagnosis, predominantly reliant on status of Philadelphia chromosome presence. An important component of the diagnostic process is a clinical and laboratory assessment to rule out reactive or secondary causes of disease. Some diagnostic methods (e.g., bone marrow microscopy) are not well standardized and others (e.g., endogenous erythroid colony formation) are neither standardized nor widely available.\(^6-8\) Diagnosis and monitoring of patients with Philadelphia chromosome negative myeloid neoplasms poses a challenge because many of the laboratory and clinical features of these diseases can be mimicked by other conditions such as reactive or secondary erythrocytosis, thrombocytosis or myeloid fibrosis. In addition, these entities can be difficult to distinguish on morphological bone marrow exam and diagnosis can be complicated by changing disease patterns.

The most up-to-date classification and benchmark for diagnosis is a result of collaboration between the Society for Hematopathology and the European Association for Haematopathology, and is published by the World Health Organization (WHO).\(^2,9\) The 2016 version is the fourth edition published by the WHO for classification of tumors of the hematopoietic and lymphoid tissues. This edition varies from the previous WHO versions predominantly due to advances in available technologies to identify unique biomarkers associated with myeloid neoplasms and acute leukemias. The current classification of myeloid neoplasm and acute leukemia subgroups are delineated in Table 1.

**Table 1. WHO myeloid neoplasm and acute leukemia classification**\(^2\)

<table>
<thead>
<tr>
<th>WHO myeloid neoplasm and acute leukemia classification</th>
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<tr>
<td><strong>Myeloproliferative neoplasms (MPN)</strong></td>
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<tr>
<td>Chronic myeloid leukemia (CML), \textit{BCR-ABL1} (^+)</td>
<td>Juvenile myelomonocytic leukemia (JMML)</td>
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<td>Chronic neutrophilic leukemia (CNL)</td>
<td>MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)</td>
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<td>Primary myelofibrosis (PMF)</td>
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<td>PMF, prefibrotic/early stage</td>
<td>MDS with single lineage dysplasia</td>
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<td>PMF, overt fibrotic stage</td>
<td>MDS with ring sideroblasts (MDS-RS)</td>
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<td>Essential thrombocythemia (ET)</td>
<td>MDS-RS and single lineage dysplasia</td>
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<tr>
<td>Chronic eosinophilic leukemia, not otherwise specified (NOS)</td>
<td>MDS-RS and multilineage dysplasia</td>
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<tr>
<td>MPN, unclassifiable</td>
<td>MDS with multilineage dysplasia</td>
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<td>Mastocytosis</td>
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<td><strong>Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFA, PDGFRB, or FGFR1, or with PCM1-JAK2</strong></td>
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<td>Myeloid/lymphoid neoplasms with \textit{PDGFA} rearrangement</td>
<td>MDS with excess blasts</td>
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<td>Myeloid/lymphoid neoplasms with \textit{PDGFRB} rearrangement</td>
<td>MDS with isolated del(5q)</td>
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<td>Myeloid/lymphoid neoplasms with \textit{FGFR1} rearrangement</td>
<td>MDS, unclassifiable</td>
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<td><strong>Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2</strong></td>
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<td><strong>Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)</strong></td>
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<td>Chronic myelomonocytic leukemia (CMML)</td>
<td><strong>Provisional entity: Refractory cytopenia of childhood</strong></td>
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<td>Atypical chronic myeloid leukemia (aCML), \textit{BCR-ABL1} (^-)</td>
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<td>Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)</td>
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**Acute myeloid leukemia (AML) and related neoplasms**

AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22.1);\textit{RUNX1-RUNX1T1}
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);\textit{CBFB-MYH11}
- APL with \textit{PML-RARA}
- AML with t(9;11)(p21.3;q23.3);\textit{MLLT3-KMT2A}
- AML with t(6;9)(p23;q34.1);\textit{DEK-NUP214}
It is important to note that the presence of any one or more of the mutations included in this policy in itself may not be sufficient to confirm a diagnosis, rather, testing may help support other clinical, laboratory, or pathological findings.

**TREATMENT MONITORING**

The paradigm for use of molecular information to revolutionize patient management is CML. A unique chromosomal change (the Philadelphia chromosome) and an accompanying unique gene rearrangement (BCR-ABL) resulting in a continuously activated tyrosine kinase enzyme were identified. These led to the development of a targeted tyrosine kinase inhibitor drug therapy (imatinib) that produces long-lasting remissions.

**REGULATORY STATUS**

More than a dozen commercial laboratories currently offer a wide variety of diagnostic procedures for gene mutation testing related to myeloid neoplasms and acute lymphoblastic leukemia. These tests are available as laboratory developed procedures under the U.S. Food and Drug Administration (FDA) enforcement discretion policy for laboratory developed tests (LDTs). Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; LDTs must meet the general regulatory standards of Clinical Laboratory
Improvement Act (CLIA) and laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, FDA does not require regulatory review of LDTs.

**EVIDENCE SUMMARY**

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The focus of this review is on evidence related to the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention, and
- Improve health outcomes as a result of those decisions.

**BCR-ABL1 (ABL1) KINASE DOMAIN MUTATION ANALYSIS IN CML AND ALL**

**ABL1 Mutations for CML**

Screening for BCR-ABL1 kinase domain point mutations (i.e. single nucleotide polymorphisms) in chronic phase CML is recommended for patients with inadequate initial response to TKI treatment, those with evidence of loss of response, and for patients who have progressed to accelerated or blast phase CML.[3] The focus of the following discussion is on kinase domain point mutations and treatment outcomes in systematic reviews.

**Systematic Reviews**

In 2010, the Agency for Healthcare Research and Quality published a systematic review on BCR-ABL1 pharmacogenetic testing for tyrosine kinase inhibitors in CML.[10] Thirty-one publications of BCR-ABL1 testing met the eligibility criteria and were included in the review (20 of dasatinib, 7 of imatinib, 3 of nilotinib, and 1 with various TKIs). The report concluded that the presence of any BCR-ABL1 mutation does not predict differential response to TKI therapy, although the presence of the T315I mutation uniformly predicts TKI failure. However, during the public comment period the review was strongly criticized by respected pathology organizations for lack of attention to several issues that were subsequently insufficiently addressed in the final report. Importantly, the review grouped together studies that used kinase domain mutation screening methods with those that used targeted methods, and grouped together studies that used mutation detection technologies with very different sensitivities. The authors dismissed the issues as related to analytic validity and beyond the scope of the report. However, in this clinical scenario assays with different intent (screening vs. targeted) and assays of very different sensitivities may lead to different clinical conclusions, so an understanding of these points is critical.

Branford et al. summarized much of the available evidence regarding kinase domain mutations detected at imatinib failure, and subsequent treatment success or failure with dasatinib or
The T315I mutation was most common; although about 100 mutations have been reported, the 7 most common (at residues T315, Y253, E255, M351, G250, F359, and H396) accounted for 60-66% of all mutations. However, preexisting or emerging mutations T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Detection of the T315I mutation at imatinib failure is associated with lack of subsequent response to high-dose imatinib, or to dasatinib or nilotinib. For these patients, allogeneic stem-cell transplantation remained the only available treatment until the advent of new agents such as ponatinib. However these mutations do not correspond to clinical significance, and based on clinical studies, the majority of imatinib-resistant mutations remain sensitive to dasatinib and nilotinib.

Preexisting or emerging mutations T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging mutations Y253H, E255K/V, and F359V/C have been reported for decreased clinical efficacy with nilotinib treatment following imatinib failure. In the survey reported by Branford et al., a total of 42% of patients tested had T315I or one of these dasatinib- or nilotinib-resistant mutations. In the absence of any of these actionable mutations, various treatment options are available. Note that these data have been obtained from studies in which patients were all initially treated with imatinib; no data are available regarding mutations developing during first-line therapy with dasatinib or nilotinib.

**ABL1 Mutations for ALL**

Unlike in CML, resistance in ALL to TKIs is less well studied. Resistance does not necessarily arise from dominant tumor clone(s), but possibly in response to TKI-driven selective pressure and/or by competition of other coexisting subclones. In patients with ALL that are receiving a TKI, a rise in the BCR-ABL level while in hematologic CR or clinical relapse warrants mutational analysis.

**CALRETICULIN (CALR), JANUS KINASE 2 (JAK2), AND MPL PROTO-ONCOGENE, THROMBOPOIETIN RECEPTOR (MPL) MUTATION ANALYSIS**

**Diagnosing Myeloid Neoplasms**

Testing for the following markers is required to meet WHO diagnostic criteria for patients with all of the most common Philadelphia chromosome-negative MPNs. It is important to note that the 2008 WHO revision represents expert consensus and is not based on independent validation of the 2008 criteria compared to earlier diagnostic criteria or on clinical outcomes. However, the most recent revisions to the WHO criteria are heavily based on repeat validation studies.

**JAK2**

In 2005, a novel somatic gain-of-function point mutation was discovered in the conserved autoinhibitory pseudokinase domain of the Janus kinase 2 (JAK2) protein in patients with MPNs. The mutation was present in blood and bone marrow from a variable portion of patients with BCR-ABL negative (i.e., Philadelphia chromosome-negative) MPNs including 65% to 97% of patients with PV, 23% to 57% with ET, and 35% to 56% with IMF. It was initially reported to be absent in all normal subjects and in patients studied with secondary erythrocytosis, although recently very low levels of mutated cells have been
reported to be found in a small subset of the healthy population.\textsuperscript{[25,26]} Reports have appeared identifying JAK2$^{V617F}$ mutations in some of these cases.\textsuperscript{[17,27]}

In 2007 Scott et al.\textsuperscript{[28]} identified four somatic gain-of-function mutations in the JAK2 exon 12 section of 10 of 11 PV patients without the JAK2$^{V617F}$ mutation. Patients with a JAK2 exon 12 mutation differed from those with the JAK2$^{V617F}$ mutations, presenting at a younger age with higher hemoglobin levels and lower platelet and white cell counts. Erythroid colonies could be grown from their blood samples in the absence of exogenous erythropoietin, and mice treated with transfected bone marrow transplants developed a myeloproliferative syndrome.

Findings were subsequently confirmed by a number of investigators who identified additional mutations with similar functional consequences in patients with PV and in patients with idiopathic erythrocytosis.\textsuperscript{[29,30]} Based on these findings it was concluded that the identification of JAK2 exon 12 mutations provides a diagnostic test for JAK2$^{V617F}$ -negative patients who present with erythrocytosis. Of note, different mutations in the same gene appear to have different effects on signaling, resulting in distinct clinical phenotypes.\textsuperscript{[28]}

**MPL**

In 2006 Pikman et al.\textsuperscript{[31]} surveyed JAK2 mutation-negative patients with suspected ET and PMF to determine if mutations in pathways complementary to Janus kinase two signaling could be identified. A mutation of the thrombopoietin receptor gene (MPL) at codon 515 (exon 10) causing a change from tryptophan to leucine (MPL$^{W515L}$) was discovered.

Subsequent studies identified additional mutations including MPL$^{S505N}$, MPL$^{W515K_i}$, and MPL$^{W515K_{ii}}$ in a small but growing number of patients with ET and PMF.\textsuperscript{[32-36]} While this mutation can be found in both JAK2$^{V617}$-positive and negative patients, it is obviously of value in the latter in helping to establish a clonal basis of the observed disease process.

**CALR**

Evidence for CALR demonstrates that a significant proportion of patients with myeloproliferative neoplasms and normal JAK2V617F status.\textsuperscript{[37-39]} Mutations in exon 9 of CALR are found in 20-35\% of all patients with ET and myelofibrosis (MF). Fifty-two base pair deletions (Type 1) and five base pair insertions (Type 2) are the most common.

**Phenotype/Genotype Associations and Impact on Prognosis**

While there has been great interest in the use of the JAK2$^{V617F}$ test as a front-line diagnostic test in the evaluation of myeloproliferative patients, there has also been a growing effort to link the presence of this mutation and the quantitative measurement of its allele burden with clinical features and biological behavior. Unfortunately, due to differences in disease definitions testing methods, sample type (bone marrow versus circulating blood cells) and study design, the literature in this area is conflicting and inconclusive.

Since most patients with PV do exhibit the mutation, attention has been focused in this disease on differences in its presence in the homozygous versus heterozygous state and on whether allele burden correlates with clinical or laboratory features. Studies have suggested a range of findings including association of homozygous states with older age, higher hemoglobin level at diagnosis, leukocytosis, more frequent pruritus, increased incidence of fibrotic transformation, and larger spleen volumes.\textsuperscript{[21,40]} Studies comparing quantitative measurements of allele
burden with disease manifestations have demonstrated both a positive and a lack of
association with thrombosis, fibrotic transformation, and need for chemotherapy.[41,42]

The impact of the presence of $JAK2^{V617F}$ in patients with ET is also controversial. In several
studies, the presence of this mutation has been associated with advanced age, higher
hemoglobin levels, increased leukocyte count, lower platelet count, and a higher rate of
transformation to PV.[15,22] Discrepant results have been reported for thrombotic events and for
fibrotic transformation.[43] A recent meta-analysis by Dahabreh et al.[44] surveyed some 394
studies on the subject of outcomes in ET. Dahabreh concluded thrombosis but not
myelofibrosis or leukemia appeared to be influenced by the presence of $JAK2$ mutations.
Dahabreh cautioned that there was a need for prospective studies to determine how this
information might be used in treatment choices.

Thrombotic effects have been reported to be most pronounced for splanchic vascular
events[45] and there has been little support for use of testing in patients with more general
thrombosis or primary thrombocytosis.[46] Results for splanchic events have been
contradictory. In one retrospective study performed looking at $JAK2^{V617F}$ in patients treated for
thrombosis in ET and in unselected patients with splanchnic vein thrombosis,[47] $JAK2^{V617F}$
mutations did occur with increased frequency in patients with splanchnic vein thrombosis and
appeared to identify a subset of patients who might benefit from antiplatelet therapy.[47]
However, the outcome of routine testing in both settings remained unclear. In a recent
international collaborative study of patients with ET, patients with $JAK2^{V617F}$ mutations
appeared at risk for arterial thrombosis but not for venous thrombosis.[48]

A 2009 report by Hussein et al.[49] demonstrated that although there was significant overlap in
$JAK2^{V617F}$ F allele burden among various MPN entities, quantitative measurements suggested
discriminatory differences between patients with ET and the prefibrotic-stage of PMF.

$JAK2^{V617F}$ mutational status and allele burden appear particularly poorly defined in patients
with PMF. A series of confusing and non-congruent articles has resulted in the following
conclusions:

- Patients with $JAK2^{V617F}$ mutations required fewer blood transfusions but exhibited
  poorer overall survival than those without the mutation.[12]
- Patients with $JAK2^{V617F}$ mutations did not show differences in the incidence of
  thrombosis, overall survival, or leukemia-free survival.[50]
- Patients with homozygous $JAK2^{V617F}$ mutations show an increased evolution toward
  large splenomegaly, need of splenectomy and leukemic transformation.[51]
- Patients with low allele burdens appeared to exhibit shortened survival, perhaps
  because they represented a myelodepleted subset of affected patients.[50,52]

In 2013, a joint systematic evaluation of $JAK2^{V617F}$ quantitative polymerase chain reaction
(qPCR) assays was conducted to identify “an assay that, beyond being robust enough for
routine diagnostic purposes, also showed the best performance profile when used for
predicting outcome following an allogeneic transplant.” Effective assays can detect an allele
burden as low as 1%.[53] Investigators assessed three unpublished laboratory-developed tests
and six published assays in 12 laboratories. The detection limit of each assay was determined
in seven quality control rounds comprising serial dilutions of centrally-distributed wild-type
and mutated cell line DNA and plasmid standards. DNA detection was verified by pyrosequencing.
Sensitivity and specificity of the two best-performing assays were further assessed in serial
samples from 28 patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) for JAK2<sup>V617F</sup>-positive disease and in 100 peripheral blood samples from healthy controls, respectively. The most sensitive assay performed consistently across various qPCR platforms and detected mutant allele (ie, minimal residual disease) in transplant recipients a median of 22 weeks (range, 6-85 weeks) before relapse. The authors suggested that the assay could be used to guide management of patients undergoing allogeneic HSCT. Although the study supports the analytic validity of the assay, given the inconsistency of outcomes when JAK2<sup>V617F</sup> testing is used for treatment monitoring (described above), utility of this assay or any JAK2<sup>V617F</sup> test for treatment monitoring is uncertain. Other investigators have studied methods to improve JAK2 and MPL mutation testing using qPCR<sup>[55,56]</sup> and novel approaches (eg, an electrochemical DNA biosensor).<sup>[57]</sup>

Limited studies suggest distinct clinical outcomes associated with MPL and CALR mutation status; however, the findings should be confirmed by additional research.

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. Chen et al. (2014) reported a higher platelet count, younger age of diagnosis, lower leukocyte count, and decreased risk for thrombosis, compared with a JAK2 positive ET population.<sup>[58]</sup> In 2014, Tefferi et al. reported survival and blast transformation in PMF were significantly affected by mutational status, though not in ET.<sup>[59]</sup> The outcome was best in CALR-mutated patients and worst in JAK2/CALR/MPL negative PMF patients. CALR-mutated ET has also been associated with better thrombosis-free survival and lower leukocyte counts. However, overall survival has been reported as not different among CALR mutated and non-mutated ET.<sup>[60,61]</sup>

**Treatment**

Due to the strong epidemiologic and biologic literature linking JAK2 pathway mutations to occurrence of MPNs, there has been considerable recent attention on using JAK2 as a molecular target for drug discovery. In preclinical and early clinical studies, a number of promising JAK2 inhibitors have been identified and reports have suggested some of these are useful in symptom relief.<sup>[62]</sup> Many patients with these diseases have a good response to other therapies with cytotoxic drugs, and the natural course of disease, particularly for PV and ET, can be quite indolent. A considerable amount of study will be required to sort through issues of safety and efficacy of these new treatments before they enter routine clinical use. Several early phase and preliminary treatment trials evaluating the safety and efficacy of tyrosine kinase inhibitors in patients with JAK2<sup>V617F</sup>-positive myeloproliferative neoplasms have been reported.<sup>[63-65]</sup> It has recently been noted that benefits from tyrosine kinase therapy may not be specific for JAK2<sup>V617F</sup>-positive myeloproliferative neoplasms but may be observed in wild type disease as well.<sup>[66]</sup>

**PRACTICE GUIDELINE SUMMARY**

**WORLD HEALTH ORGANIZATION (WHO)**

Policy criteria are consistent with WHO (2016) diagnostic criteria for myeloid neoplasms and acute leukemia for JAK2, MPL, and CALR.

**NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN)**
Policy criteria are mostly consistent with NCCN guidelines for Chronic Myeloid Leukemia (v2.2017)[1], Acute Lymphoblastic Leukemia (v2.2016)[67], and Myeloproliferative Neoplasms (v2.2017)[68].

**SUMMARY**

**BCR-ABL kinase domain (ABL1)**

In chronic myeloid leukemia, there is enough research to show clinical utility for evaluation of ABL1 mutations for tyrosine kinase inhibitor (TKI) resistance. TKI resistance in acute lymphoblastic leukemia (ALL) has not been studied as well as in CML. However, there is enough research to show ABL1 mutation testing for evaluation of TKI resistance may lead to an improvement in health outcomes for patients with ALL who are receiving a TKI. Practice guidelines based on research recommend ABL1 testing for ALL and CML in specific clinical scenarios. Therefore, ABL1 mutation testing for evaluation of TKI resistance may be considered medically necessary when policy criteria are met. Due to insufficient evidence, evaluation of ABL1 mutations is considered investigational when policy criteria are not met.

**CALR, JAK2, and/or MPL**

There is enough research on the clinical validation of JAK2 (in some scenarios for select mutations only), MPL, and CALR as a distinctive marker of patients with select myeloid neoplasms. Testing for these markers is recommended in practice guidelines based on research for patients with the most common Philadelphia chromosome-negative neoplasms. Therefore, JAK2, MPL, and/or CALR genetic testing may be considered medically necessary as a diagnostic test when policy criteria are met. There is not enough research to know if JAK2, MPL, and CALR mutation testing to establish disease prognosis or to select or monitor therapy leads to changes that improve overall health outcomes. This remains an active area of investigation. Therefore, JAK2, MPL, and/or CALR mutation testing is considered investigational for prognostic testing or to direct therapeutic treatments for any condition due to insufficient evidence.

**REFERENCES**


35. Ruan, GR, Jiang, B, Li, LD, et al. MPL W515L/K mutations in 343 Chinese adults with JAK2V617F mutation-negative chronic myeloproliferative disorders detected by a newly


50. Tefferi, A, Lasho, TL, Huang, J, et al. Low JAK2V617F allele burden in primary myelofibrosis, compared to either a higher allele burden or unmutated status, is associated with inferior overall and leukemia-free survival. *Leukemia.* 2008 Apr;22(4):756-61. PMID: 18216871


70. BlueCross BlueShield Association Medical Policy Reference Manual "JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms." Policy No. 2.04.60

### CODES

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<td>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</td>
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<tr>
<td></td>
<td>81270</td>
<td>JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant</td>
</tr>
<tr>
<td></td>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 - which includes ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib resistance), T315I variant</td>
</tr>
<tr>
<td></td>
<td>81402</td>
<td>Molecular pathology procedure, Level 3 (eg, &gt;10 SNPs, 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 1 exon) – which includes MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor TPOR) (eg, myeloproliferative disorder), common variants (eg, W515A, W515K, W515L, W515R)</td>
</tr>
<tr>
<td></td>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons – which includes JAK2 (Janus kinase 2) (eg, myeloproliferative disorder), exon 12 sequence and exon 13 sequence, if performed</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

*Date of Origin: August 2010*