

Genetic Testing for Myeloid Neoplasms and Leukemia

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Next Review: February 2019

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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*, *ASXL1*, *CALR*, *CEBPA*, *FLT3*, *IDH1*, *IDH2*, *KIT*, *NPM1*, *RUNX1*, and/or *TP53* 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, 0016U, and 0040U), *JAK2* (i.e., CPT codes 0017U, 0027U, and 81270), or *MPL* 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 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 tryosine kinase inhibitor resistance when there is an inadequate initial response to treatment or any sign of loss of response. (See *Policy Guidelines*)

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

II. ***ASXL1, CALR, IDH1, IDH2* and/or *TP53***

- A. Genetic testing for *ASXL1, CALR, IDH1, IDH2* and/or *TP53* variants may be considered **medically necessary** when clinical, laboratory, or pathological findings suggest a myeloid neoplasm or leukemia, but a diagnosis is uncertain.
- B. Genetic testing for *ASXL1, CALR, IDH1, IDH2* and/or *TP53* variants may be considered **medically necessary** for evaluation in patients with a myeloid neoplasm or leukemia.
- C. Genetic testing for *ASXL1, CALR, IDH1, IDH2* and *TP53* variants is considered **investigational** for all other circumstances.

III. ***CEBPA, FLT3, KIT, NPM1,* and/or *RUNX1* for Acute Myeloid Leukemia**

- A. Genetic testing for *CEBPA, FLT3* internal tandem duplication (*FLT3-ITD*), *KIT, NPM1* and/or *RUNX1* variants may be considered **medically necessary** when either of the following (1. or 2.) are met:
 1. Evaluation for acute leukemia, or
 2. Risk stratification for patients with acute myeloid leukemia.
- B. Genetic testing of *FLT3-ITD* and *FLT3* tryosine kinase domain (*FLT3-TKD*) variants may be considered **medically necessary** for patients with newly diagnosed acute myeloid leukemia for treatment selection with FDA-approved kinase inhibitors (See *Policy Guidelines*).
- C. Genetic testing for a *CEBPA, FLT3, KIT, NPM1,* and/or *RUNX1* variant associated with acute myeloid leukemia is considered **investigational** for all other circumstances.

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

POLICY GUIDELINES

SUBMISSION OF DOCUMENTATION

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](#) (v3.2018) 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 genetic analysis.

FLT3 TESTING FOR TREATMENT WITH RYDAPT® (MIDOSTAURIN)

For patients who have newly diagnosed acute myeloid leukemia, eligibility for Rydapt® (midostaurin) may be guided by testing with the LeukoStrat® CDx FLT3 Mutation Assay offered by Invivoscribe.

IDH2 TESTING FOR TREATMENT WITH IDHIFA® (ENASIDENIB)

For patients who have relapsed or refractory acute myeloid leukemia, eligibility for Idhifa® (enasidenib) may be guided by testing with Abbott RealTime IDH2 (Abbott Molecular, Inc.).

CROSS REFERENCES

1. [Genetic Testing for Hereditary Breast and/or Ovarian Cancer and Li-Fraumeni Syndrome](#), Genetic Testing,

Policy No. 02

2. [Genetic Testing for \$\alpha\$ -Thalassemia](#), Genetic Testing, Policy No. 19
3. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
4. [Hematopoietic Cell Transplantation for Acute Myeloid Leukemia](#), Transplant, Policy No. 45.28
5. [Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia](#), Transplant, Policy No. 45.31
6. [Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia](#), Transplant, Policy No. 45.36
7. [Medication Policy Manual](#), Do a find (Ctrl+F) and enter drug name in the find bar to locate the 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]

WHO myeloid neoplasm and acute leukemia classification	WHO myeloid neoplasm and acute leukemia classification
Myeloproliferative neoplasms (MPN)	Primary myelofibrosis (PMF)
Chronic myeloid leukemia (CML), <i>BCR-ABL</i> 1+	PMF, prefibrotic/early stage
Chronic neutrophilic leukemia (CNL)	PMF, overt fibrotic stage
Polycythemia vera (PV)	Essential thrombocythemia (ET)

WHO myeloid neoplasm and acute leukemia classification

Chronic eosinophilic leukemia, not otherwise specified (NOS)
MPN, unclassifiable
Mastocytosis
Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
Myeloid/lymphoid neoplasms with *PDGFRA* rearrangement
Myeloid/lymphoid neoplasms with *PDGFRB* rearrangement
Myeloid/lymphoid neoplasms with *FGFR1* rearrangement
Provisional entity: Myeloid/lymphoid neoplasms with PCM1-JAK2
Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
Chronic myelomonocytic leukemia (CMML)
Atypical chronic myeloid leukemia (aCML), *BCR-ABL1*⁻
Juvenile myelomonocytic leukemia (JMML)
MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
MDS/MPN, unclassifiable
Myelodysplastic syndromes (MDS)
MDS with single lineage dysplasia
MDS with ring sideroblasts (MDS-RS)
 MDS-RS and single lineage dysplasia
 MDS-RS and multilineage dysplasia
MDS with multilineage dysplasia
MDS with excess blasts
MDS with isolated del(5q)
MDS, unclassifiable
Provisional entity: Refractory cytopenia of childhood
Myeloid neoplasms with germ line predisposition
Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
 AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
 AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
 APL with *PML-RARA*
 AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
 AML with t(6;9)(p23;q34.1);*DEK-NUP214*
 AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
 AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
 Provisional entity: AML with BCR-ABL1
 AML with mutated *NPM1*
 AML with biallelic mutations of *CEBPA*
 Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes

WHO myeloid neoplasm and acute leukemia classification

Therapy-related myeloid neoplasms
AML, NOS
 AML with minimal differentiation
 AML without maturation
 AML with maturation
 Acute myelomonocytic leukemia
 Acute monoblastic/monocytic leukemia
 Pure erythroid leukemia
 Acute megakaryoblastic leukemia
 Acute basophilic leukemia
 Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
 Transient abnormal myelopoiesis (TAM)
 Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
 Acute undifferentiated leukemia
 Mixed phenotype acute leukemia (MPAL) with t(9;22)(q34.1;q11.2); *BCR-ABL1*
 MPAL with t(v;11q23.3); *KMT2A* rearranged
 MPAL, B/myeloid, NOS
 MPAL, T/myeloid, NOS
B-lymphoblastic leukemia/lymphoma
 B-lymphoblastic leukemia/lymphoma, NOS
 B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
 B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
 B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
 B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
 B-lymphoblastic leukemia/lymphoma with hyperdiploidy
 B-lymphoblastic leukemia/lymphoma with hypodiploidy
 B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
 B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
 Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
 Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
 Provisional entity: Early T-cell precursor lymphoblastic leukemia
 Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

It is important to note that the presence of any one or more of the gene variants 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.

The FDA Centers for Devices and Radiological Health (CDRH), for Biologics Evaluation and Research (CBER), and for Drug Evaluation and Research (CDER) developed a draft guidance on *in vitro* companion diagnostic devices, which was released on July 14, 2011,^[10] to address the “emergence of new technologies that can distinguish subsets of populations that respond differently to treatment.” As stated, the FDA encourages the development of treatments that depend on the use of companion diagnostic devices “when an appropriate scientific rationale supports such an approach.” In such cases, the FDA intends to review the safety and effectiveness of the companion diagnostic test as used with the therapeutic treatment that depends on its use. The rationale for co-review and approval is the desire to avoid exposing patients to preventable treatment risk.

The LeukoStrat[®] CDx *FLT3* Mutation Assay offered by Invivoscribe. According to Invivoscribe, the test is indicated at initial diagnosis of AML to determine eligibility for Rydapt[®] (midostaurin), and may also be used for risk stratification.^[11] The assay includes internal tandem duplication mutation testing for *FLT3* as well as mutations in the tyrosine kinase domain. Rydapt[®] (midostaurin) is an FDA-approved kinase inhibitor, indicated for adult patients, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.^[12] The assay is an FDA-approved companion diagnostic test for use with Rydapt[®] (midostaurin) and therefore may be standard of care in screening patients for use with this specific kinase inhibitor.

Abbott RealTime IDH2 is an *in vitro* polymerase chain reaction (PCR) assay for the qualitative detection of single nucleotide variants (SNVs) in the human isocitrate dehydrogenase-2 (IDH2) gene. The test aids in identifying acute myeloid leukemia patients for treatment with Idhifa[®] (enasidenib). Enasidenib is an oral medication used to treat patients with AML when the disease recurs after, or does not respond to front-line therapies. The Abbott RealTime IDH2 assay received FDA premarket approval in August 2017.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature is used to describe variants found in DNA and serves as an international standard.^[13] It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

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 variant that is present or in excluding a variant 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 ANALYSIS IN CML AND ALL

***ABL1* Variants 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.^[14] 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 summarized much of the available evidence regarding kinase domain mutations detected at imatinib failure, and subsequent treatment success or failure with dasatinib or nilotinib.^[15] 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.^[16] 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, 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.^[17]

ABL1 Variants 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.^[18] 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.

DIAGNOSES AND PROGNOSIS IN MYELOID NEOPLASMS AND LEUKEMIA

Testing for the *ASXL1*, *CALR*, *IDH1*, *IDH2* and *TP53* 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 (2016) are heavily based on repeat validation studies.^[2] The following evidence highlights the diagnostic and prognostic significance of *ASXL1*, *CALR*, *IDH1*, *IDH2* and *TP53* as specified by WHO diagnostic criteria and NCCN guidelines.

ASXL1

For chronic myelomonocytic leukemia (CMML), *ASXL1* is amongst the most frequently mutated genes, observed in 40-50% of CMML patients.^[19,20] *ASXL1* is also reported to be associated with chromatin modification in MPNs, including polycythemia vera, as well as pre- and overt primary myelofibrosis.^[21,22]

CALR

Evidence for *CALR* demonstrates that a significant proportion of patients with myeloproliferative neoplasms and normal *JAK2V617F* status have a *CALR* variant.^[23-25] 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.

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* variant. Chen (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.^[26] In 2014, Tefferi reported survival and blast transformation in PMF were significantly affected by mutational status, though not in ET.^[27] 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.^[28,29]

IDH1/2

For PMF and ET, WHO criteria specify *IDH1/2* (as well as others, including *ASXL1*) as having diagnostic significance for those without *JAK2*, *CALR*, and *MPL* mutations. In myeloproliferative neoplasms, *IDH1* and *IDH2* mutations are amongst a growing number of higher-risk molecular markers. Both are associated with shorter overall survival and leukemia-free survival in patients with PMF and polycythemia vera.^[22,30] In a study of the prognostic significance of *ASXL1*, *EZH2*, *SRSF2*, *IDH1* and *IDH2*, Vannucchi analyzed samples from 897 PMF patients (European patients = 483; Mayo clinical validation cohort = 396). Median survival was significantly shorter (81 vs 148 months; $p < .0001$) in PMF patients with at least one of the genes.

TP53

Similar to *IDH1/2* described above, for PMF, *TP53* is associated with leukemic transformation, which is a common risk amongst patients with myeloproliferative neoplasms.^[31] Furthermore, *TP53* is associated with inferior leukemia-free survival in those with essential thrombocythemia. This progression is associated with poor clinical outcomes and resistance to standard AML therapies. Thus, tumor protein p53 (*TP53*) variants have also been analyzed to subdivide AML into prognostic subsets (see below). Additionally, *TP53* variants have been identified as one of the most common molecular abnormalities associated with myelodysplastic syndromes, and may aid in diagnosis.^[32-34]

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a group of diverse hematologic malignancies characterized by the clonal expansion of myeloid blasts in the bone marrow, blood, and/or other tissues. It is the most common type of leukemia in adults, and is generally associated with a poor prognosis. It was estimated that, in 2014, 18,860 people would be diagnosed with AML and 10,460 would die of the disease. Median age at diagnosis is 66 years, with approximately 1 in 3 patients diagnosed at 75 years of age or older.^[35]

Diagnosis and Prognosis of AML

Conventional cytogenetic analysis (karyotyping) is considered to be a mandatory component in the diagnostic evaluation of a patient with suspected acute leukemia, because the cytogenetic profile of the tumor is considered to be the most powerful predictor of prognosis in AML and is used to guide the current risk-adapted treatment strategies. Molecular variants including those in CCAAT/enhancer-binding protein alpha (CEBPA); FMS-like tyrosine kinase 3 (FLT3); the tyrosine kinase receptor, KIT; nucleophosmin (NPM1); Runt-related transcription factor 1 (RUNX1), and tumor protein p53 (TP53) genes have been analyzed to subdivide AML into prognostic subsets. (See Table 2.) Patients with better-prognosis disease (for example, core-binding factor AML) based on cytogenetics, and a mutation in the c-KIT gene of leukemic blast cells, do just as poorly with postremission standard chemotherapy as patients with cytogenetically poor-risk AML.^[36] Similarly, individuals with cytogenetically normal AML (intermediate-prognosis disease) can be subcategorized into groups with better or worse prognosis based on the mutational status of the NPM1 and the FLT3 gene. Thus, patients with mutations in NPM1 but without FLT3-ITD have postremission outcomes with standard chemotherapy that are similar to those with better-prognosis cytogenetics; in contrast, patients with any other combination of mutations in those genes have outcomes similar to those with poor-prognosis cytogenetics.^[37] A provisional category of AML with mutated RUNX1 classifies de novo cases which are not associated with MDS-related cytogenetic abnormalities. This distinct group of AML patients also appears to have a worse prognosis than other AML types.^[38-41]

The World Health Organization (WHO) classification of AML was adapted by the National Comprehensive Cancer Network (NCCN) to estimate individual patient prognosis to guide management, as shown in Table 2:^[42]

Table 2. Risk Status of AML Based on Cytogenetic and Molecular Factors

Risk Status	Cytogenetic Factors	Molecular Abnormalities
Favorable-risk	Core binding factor: inv(16) or t(16;16) or t(8;21) or t(15;17)	Normal cytogenetics: <i>NPM1</i> mutation in the absence of <i>FLT3</i> -ITD or isolated biallelic (double) <i>CEBPA</i> mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	Core binding factor with <i>KIT</i> mutation
Poor-risk	Complex (≥ 3 clonal chromosomal abnormalities) -5, 5q-, -7, 7q-, 11q23 - non t(9;11) Inv3, t(3;3) t(6;9) t(9;22)	Normal cytogenetics: with <i>FLT3</i> -ITD mutation <i>TP53</i> mutation

Systematic Reviews for Molecular Subtypes of AML

Recent systematic reviews with meta-analyses have highlighted the evolving classification of AML into distinct molecular subtypes based on for CEBPA, FLT3-ITD, KIT, NPM1, and TP53, particularly in patients with normal karyotype.^[43-48] These studies support the WHO and NCCN risk status classifications, and additionally highlight the importance of KIT testing in the initial evaluation and for prognosis.

FLT3-ITD and FLT3-TKD for AML

The *FLT3* gene encodes a receptor tyrosine kinase involved in hematopoiesis, of which two major activating mutations have been identified in patients with AML: the internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. While a significant body of literature demonstrates the diagnostic and prognostic value of *FLT3*-ITD testing, *FLT3*-TKD research is controversial. Studies have found presence of *FLT3*-TKD mutations to be associated with shorter disease free survival time and decreased overall survival,^[49-52] though other studies have reported no impact on prognosis,^[37,53-55] and even favorable outcomes with overall survival when compared to those with *FLT3*-wild type^[56,57]. Therefore, risk stratification with *FLT3*-TKD warrants additional research in well-designed studies.

PRACTICE GUIDELINE SUMMARY

WORLD HEALTH ORGANIZATION

Policy criteria are consistent with WHO (2016) diagnostic criteria for myeloid neoplasms and acute leukemia.^[2]

NATIONAL COMPREHENSIVE CANCER NETWORK

Policy criteria are mostly consistent with NCCN guidelines for Chronic Myeloid Leukemia (v2.2017)^[1], Acute Lymphoblastic Leukemia (v2.2016)^[58], Acute Myeloid Leukemia (v1.2017)^[42], Myelodysplastic Syndromes (v1.2018)^[59], and Myeloproliferative Neoplasms (v2.2017)^[60].

SUMMARY

BCR-ABL KINASE DOMAIN (*ABL1*)

In chronic myeloid leukemia, there is enough research to show clinical utility for evaluation of *ABL1* variants 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* genetic 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* genetic testing for evaluation of TKI resistance may be considered medically necessary when policy criteria are met. Due to insufficient evidence, evaluation of *ABL1* variants is considered investigational when policy criteria are not met.

ASXL1, CALR, IDH1, IDH2 AND/OR TP53

There is enough research on the clinical validation of *ASXL1*, *CALR*, *IDH1*, *IDH2*, and *TP53* as distinctive markers of patients with several myeloid neoplasms and leukemia. Testing for these genes is recommended in practice guidelines based on research for patients with numerous myeloid neoplasms and leukemia, including but not limited to primary myelofibrosis, polycythemia vera, essential thrombocythemia, chronic myelomonocytic leukemia, and acute myeloid leukemia. Therefore, *ASXL1*, *CALR*, *IDH1*, *IDH2*, and/or *TP53* genetic testing may be considered medically necessary for diagnosis and evaluation of myeloid neoplasms or leukemia when policy criteria are met. Due to insufficient evidence

and no recommendations from practice guidelines, testing for these genes is considered investigational when policy criteria are not met.

CEBPA, FLT3, KIT, NPM1, AND/OR RUNX1 FOR ACUTE MYELOID LEUKEMIA

There is enough research to know that evaluation of *CEBPA*, *FLT3* internal tandem duplication (*FLT3*-ITD), *KIT*, *NPM1*, and/or *RUNX1* genetic variants inform the diagnostic process for acute leukemia. These genes are also important molecular markers for risk stratification for patients with acute myeloid leukemia (AML). Policy criteria are in alignment with practice guidelines based on research which recommend testing for these markers. There is less research to support genetic testing for *FLT3* tyrosine kinase domain (*FLT3*-TKD). It is unclear if *FLT3*-TKD testing impacts overall health outcomes. However, both *FLT3*-ITD and *FLT3*-TKD are included in at least one FDA-approved companion diagnostic test. Therefore, genetic testing for *CEBPA*, *FLT3*, *KIT*, *NPM1*, and/or *RUNX1* may be considered medically necessary for select patients when policy criteria are met. Due to insufficient evidence and no recommendations from practice guidelines, testing for these genes is considered investigational when policy criteria are not met.

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 62. BlueCross BlueShield Association Medical Policy Reference Manual "JAK2 and MPL Mutation Analysis in Myeloproliferative Neoplasms." Policy No. 2.04.60
 63. BlueCross BlueShield Association Medical Policy Reference Manual "BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia." Policy No. 2.04.85

CODES

Codes	Number	Description
CPT	0016U	Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
	0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
	0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
	0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
	81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
	81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
	81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain

81175	<i>ASXL1</i> (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	<i>ASXL1</i> (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, EXON 12)
81218	<i>CEBPA</i> (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81219	<i>CALR</i> (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81245	<i>FLT3</i> (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	<i>FLT3</i> (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81272	<i>KIT</i> (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81273	<i>KIT</i> (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81310	<i>NPM1</i> (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81334	<i>RUNX1</i> (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, EXONS 3-8)
81401	Molecular pathology procedure, Level 2 - which includes <i>ABL1</i> (<i>ABL proto oncogene 1, non-receptor tyrosine kinase</i>) (eg, acquired imatinib resistance), T315I variant
81402	Molecular pathology procedure, Level 3 (eg, >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)
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
HCPCS	None

Date of Origin: August 2010