Regence

Medical Policy Manual Genetic Testing, Policy No. 59

Genetic Testing for Myeloid Neoplasms and Leukemia

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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 testing, including testing for BCR/ABL1 (t(9;22)) translocations and for *ABL1, ASXL1, CALR, CEBPA, FLT3, IDH1, IDH2, JAK2*, *KIT, MPL, NPM1*, *RUNX1*, and/or *TP53* variants may inform the diagnostic, prognostic, and treatment selection processes for myelodysplastic-myeloproliferative neoplasms and select myeloid neoplasms.

MEDICAL POLICY CRITERIA

Note: 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. Genetic testing, including panel testing, for *BCR/ABL1* translocation (Philadelphia chromosome) and/or variants in any of the following genes may be considered **medically necessary** for evaluation, diagnosis, and/or treatment monitoring in myeloid neoplasms and leukemia: *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA*, *FLT3*, *KIT*, *NPM1* and/or *RUNX1*.

II. Targeted genetic panel testing for myeloproliferative neoplasms (MPN), myelodysplastic syndromes (MDS), and myelodysplastic myeloproliferative neoplasms (MPN/MDS), including acute myeloid leukemia (AML), may be considered **medically**

necessary for patients being evaluated for these disorders (see Policy Guidelines and Table 1).

III. Genetic testing for *ABL1* may be considered **medically necessary** to evaluate patients when either of the following are met:

A. In patients with chronic myelogenous (myeloid) leukemia (CML), to monitor response to tyrosine kinase inhibitor therapy; or

B. In patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), to evaluate for tyrosine kinase inhibitor resistance.

IV. Genetic testing for *ABL1* is considered **investigational** when Criterion III. is not met.

V. Non-targeted profiling panels for hematologic disorders are considered **investigational** (see Policy Guidelines).

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

POLICY GUIDELINES

PANEL TESTING

Targeted Panels for Myeloid Neoplasms

Targeted panel testing for myeloid neoplasms, (i.e., MPN, MDS, MPN/MDS, and AML, see Table 1 below) includes panels that are specifically designed to assess variants in patients suspected of having a myeloproliferative neoplasm, a myelodysplastic syndrome, or a disorder with overlapping features. They are generally less than 50 genes and may include the following genes: *ASXL1*, *CALR, CBL, EZH2*, *KIT*, *FLT3, JAK2, MPL*, *NMP1*, *CEBPA*, *IDH1*, *IDH2*, and *TP53*.

Examples of targeted panels for MPN/MDS/AML include, but are not limited to:

- NeoTYPE™ Myeloid Disorders Profile (Neogenomics)
- NGS Myeloid 37 Gene panel (Cellnetix)
- MyeloSeq™ (Washington University School of Medicine)
- NGS_AML Panel (Cellnetix)
- AML Mutation Analysis Panel (Molecular Pathology Laboratory Network)
- Onkosight™ Myeloid Malignancies Panel, MPN Panel, MDS Panel, or AML Panel
- Myeloid MPN/MDS/CMML Comprehensive Panel (Providence)
- Myeloid Gene Panel by NGS (University of Washington)
- TruSight® Myeloid Sequencing Panel

Non-targeted Panels

Some commercially available panels are not targeted toward genes that have clinical significance for a specific type of hematolymphoid disorder. They often include testing for a large number of genes that do not have demonstrated clinical utility, as well as testing for many disorders that could be distinguished based on clinical presentation.

Non-targeted panels for hematologic disorders include, but are not limited to:

- FoundationOne Heme (Foundation Medicine)
- FusionPlex Pan-Heme Panel (Laboratory for Precision Diagnostics, University of Washington)
- GeneTrails® Hematologic Malignancies 220 Gene Panel (Knight Diagnostic Laboratories)
- GeneTrails® Heme Fusion Gene Panel
- MyAML® 194 Targeted NGS Gene Panel (Invivoscribe)
- HopeSeq HemeComplete (City of Hope)
- NGS Hematology Molecular Profile (Sonora Quest Laboratories)
- Rapid Heme Panel (Dana-Farber Cancer Institute)
- Hematologic Malignancy Sequencing Panel (Penn Medicine)
- Neo Comprehensive™ - Myeloid Disorders (Neogenomics)

Table 1. Selected Diagnoses from the World Health Organization Classification of Hematolymphoid Disorders[1 2]

Myeloproliferative neoplasms (MPN)
Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia
Chronic eosinophilic leukemia
Polycythemia vera
Essential thrombocythemia
Primary myelofibrosis
Juvenile myelomonocytic leukemia (JMML)
Mastocytosis
Cutaneous mastocytosis
Systemic mastocytosis
Mast cell sarcoma
Myelodysplastic neoplasms (MDS)
MDS with low blasts and 5q deletion
MDS with low blasts and *SF3B1* mutation
Myelodysplastic neoplasm with increased blasts
Refractory cytopenia of childhood
Chronic myelomonocytic leukemia (CMML)
Acute myeloid leukemia (AML) and related neoplasms
AML with defining genetic abnormalities
AML, defined by differentiation
Acute basophilic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Myeloid sarcoma

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. 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 variant(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:
    - History and physical exam including any relevant diagnoses related to the genetic testing
    - Sample collection (e.g., blood draw) date
    - Conventional testing and results

CROSS REFERENCES

1. Genetic Testing for Hereditary Breast and Ovarian Cancer and Li-Fraumeni Syndrome, Genetic Testing, Policy No. 02
2. Genetic Testing for α-Thalassemia, Genetic Testing, Policy No. 19
3. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
4. ClonoSEQ® Testing for the Assessment of Measurable Residual Disease (MRD), Genetic Testing, Policy No. 88
5. Hematopoietic Cell Transplantation for Acute Myeloid Leukemia, Transplant, Policy No. 45.28
6. Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia, Transplant, Policy No. 45.31
7. Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia, Transplant, Policy No. 45.36
8. Medication Policy Manual, Note: Click the link for the appropriate Medication Policy. Once the medication policy site is open, 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 of hematopoietic and lymphoid tissues is a result of collaboration between the Society for Hematopathology and the European Association for Haematopathology and is published by the WHO, most recently in 2022.[2] This edition varies from the previous versions with a refinement of diagnostic criteria and emphasis on actionable biomarkers. The current classification of myeloid neoplasm and acute leukemia subgroups are delineated in Table 2.

Table 2. WHO Myeloid Proliferations and Neoplasms Classification, adapted[2]

MYELOID NEOPLASMS, CHRONIC

Myeloproliferative Neoplasms (MPN)

- Chronic myeloid leukemia (CML), *BCR-ABL1*$^{+}$
- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia
- Juvenile myelomonocytic leukemia (JMML)
- MPN, not otherwise specified (NOS)

Mastocytosis

- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell sarcoma

Myelodysplastic Neoplasms (MDS)

- MDS with low blasts and isolated 5q deletion
- MDS with low blasts and SF3B1 mutation
- MDS with low blasts, NOS
- MDS with increased blasts
- MDS with fibrosis
- MDS, NOS
- MDS with biallelic TP53 alteration (provisional)
- MDS with other defined driver gene alterations

MDS / acute myeloid leukemia (MDS/AML)

- MDS/AML with *NMP1* mutation
- MDS/AML with *MECOM* rearragement
- MDS/AML, NOS

MDS of childhood

- Refractory cytopenia of childhood
- Childhood MDS

MDS with proliferative evolution

- Chronic myelomonocytic leukemia
- MDS with proliferative evolution and neutrophilia
- MDS with proliferative evolution, SF3B1 mutation and thrombocytosis
- MDX with proliferative evolution, NOS

MYELOID NEOPLASMS, ACUTE

AML with defining genetic abnormalities

- Acute promyelocytic leukemia
- AML with *RUNX1::RUNX1T1* fusion
- AML with *CBFB::MYH11* fusion
- AML with *DEK::NUP214* fusion
- AML with *RBM15::MRTFA* fusion
- AML with *BCR::ABL1* fusion
- AML with *NUP98* rearrangement
- AML with *NPM1* mutation
- AML with *NUP98* rearrangement
- AML with other defined driver gene alterations
- AML with myelodysplasia-related cytogenetics

AML, defined by differentiation

- AML with minimal differentiation
- AML with without maturation
- AML with maturation
- Acute basophilic leukemia
- AML with myelomonocytic differentiation
- AML with monocytic differentiation
- AML with plasmacytoid dendritic cell differentiation (provisional)
- Pure erythroid leukemia
- Acute megakaryoblastic leukemia

Myeloid sarcoma

MYELOID NEOPLASMS, SECONDARY

Myeloid neoplasms and proliferations associated with antecedent or predisposing conditions

- Myeloid neoplasm post cytotoxic therapy
- Myeloid neoplasm associated with germline predisposition
- AML following other hematolymphoid malignancy
- Myeloid proliferations associated with Down syndrome
- Myeloid neoplasm associated with malignant germ cell tumor

MYELOID/LYMPHOID NEOPLASMS AND OTHER LEUKAEMIAS OF AMBIGUOUS LINEAGE

Myeloid/Lymphoid neoplasms with eosinophilia and defining gene rearrangement

- Myeloid/lymphoid neoplasm with *PDGFRA* rearrangement
- Myeloid/lymphoid neoplasm with *PDGFRB* rearrangement
- Myeloid/lymphoid neoplasm with *FGFR1* rearrangement
- Myeloid/lymphoid neoplasms with *PMC1-JAK2* fustion

Acute leukemias of ambiguous lineage

Mixed-phenotype acute leukaemia with *BCR-ABL1* fusion

Mixed-phenotype acute leukaemia with *KMT2A* rearrangement

Mixed-phenotype acute leukaemia, B/myeloid

Acute leukaemia of ambiguous lineage, NOS

It is important to note that the presence of any one or more of the gene variants included in this policy may not be sufficient to confirm a diagnosis, rather, testing may help support other clinical, laboratory, or pathological findings.

TREATMENT MONITORING

CML represents one of the earliest examples of the use of molecular information to revolutionize patient management. 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 variant 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,[9] 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), Xospata® (gilteritinib), and Vanflyta® (quizartinib), and may also be used for risk stratification.[10] The assay includes internal tandem duplication variant testing for *FLT3* as well as variants in the tyrosine kinase domain. The assay is an FDA-approved companion diagnostic test for use with these medications and therefore may be standard of care in screening patients for use with this specific kinase inhibitor.

Abbott Real*Time* 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 Real*Time* 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.[11] 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

Screening for *BCR-ABL1* kinase domain variants 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 variants and treatment outcomes in 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.[12] Thirty-one publications of *BCR-ABL1* testing met the eligibility criteria and were included in the review (20 of dasatinib, seven of imatinib, three of nilotinib, and one with various TKIs). The report concluded that the presence of any *BCR-ABL1* variant does not predict differential response to TKI therapy, although the presence of the T315I variant 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 variant screening methods with those that used targeted methods and combined studies that used variant 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 (2009) summarized much of the available evidence regarding kinase domain variants detected at imatinib failure, and subsequent treatment success or failure with dasatinib or

nilotinib.[13] The T315I variant was most common; although about 100 variants have been reported, the seven most common (at residues T315, Y253, E255, M351, G250, F359, and H396) accounted for 60-66% of all variants. However, preexisting or emerging variants T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Detection of the T315I variant 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.[14] However these variants do not correspond to clinical significance, and based on clinical studies, the majority of imatinib-resistant variants remain sensitive to dasatinib and nilotinib.

Preexisting or emerging variants T315A, F317L/I/V/C, and V299L are associated with decreased clinical efficacy with dasatinib treatment following imatinib failure. Similarly, preexisting or emerging variantsY253H, 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 variants. In the absence of any of these actionable variants, 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 variants developing during first-line therapy with dasatinib or nilotinib.[15]

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.[16] 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 variant analysis.

***ASXL1*, *CALR*, *IDH1, IDH2* AND *TP53* 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.. The most recent revisions to the WHO criteria (2022) 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 National Comprehensive Cancer Network (NCCN) guidelines.

ASXL1

For chronic myelomonocytic leukemia (CMML), *ASXL1* is amongst the most frequently mutated genes, observed in 40-50% of CMML patients.[17 18] *ASXL1* is also reported to be associated with chromatin modification in MPNs, including polycythemia vera, as well as pre- and overt primary myelofibrosis.[19 20]

CALR

Evidence for *CALR* demonstrates that a significant proportion of patients with myeloproliferative neoplasms and normal *JAK2* V617F status have a *CALR* variant.[21-23] Variants in exon 9 of *CALR* are found in 20-35% of all patients with ET and myelofibrosis. 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* variants 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.[24] Tefferi (2014) reported survival and blast transformation in primary myelofibrosis (PMF) were significantly affected by variant status, though not in ET.[25] The outcome was best in *CALR*-variant patients and worst in *JAK2/CALR/MPL*-negative PMF patients. *CALR*-variant 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*-variant and non-variant ET.[26 27]

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* variants. In myeloproliferative neoplasms, *IDH1* and *IDH2* variants are among 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.[20 28] In a study of the prognostic significance of *ASXL1, EZH2, SRSF2, IDH1* and *IDH2,* Vannucchi (2013) analyzed samples from 897 PMF patients (483 European patients and 396 from the Mayo clinical validation cohort). Median survival was significantly shorter (81 vs. 148 months, $p<0.0001$) in PMF patients with at least one of the genes.

TP53

Like *IDH1/2* described above, for PMF, *TP53* is associated with leukemic transformation, which is a common risk amongst patients with myeloproliferative neoplasms.[29] Furthermore, *TP53* is associated with inferior leukemia-free survival in those with ET. This progression is associated with poor clinical outcomes and resistance to standard AML therapies. Thus, *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.[30-32]

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 one in three patients diagnosed at 75 years of age or older.[33]

Conventional cytogenetic analysis (karyotyping) is a key component of the diagnostic evaluation of patients with suspected acute leukemia. The cytogenetic profile of the tumor is currently the most powerful predictor of prognosis in AML and is used to guide risk-adapted treatment strategies. Molecular variants, including those in *CEBPA*, *FLT3*, *KIT*, *NPM1*, *RUNX1*, and *TP53* genes, can be used to subdivide AML into prognostic subsets. (See Table 3.) Patients with better-prognosis disease based on cytogenetics (e.g., core-binding factor AML) who have a *c-KIT* variant in leukemic blast cells do just as poorly with post-remission standard chemotherapy as patients with cytogenetically poor-risk AML.[34] Similarly, individuals with cytogenetically normal AML (intermediate-prognosis disease) can be subcategorized into groups with better or worse prognosis based on the variant status of the *NPM1* and *FLT3* genes. Patients with variants in *NPM1* but without a *FLT3-ITD* fusion have post-remission

outcomes with standard chemotherapy that are similar to those with better-prognosis cytogenetics; in contrast, patients with any other combination of variants in those genes have outcomes similar to those with poor-prognosis cytogenetics.[35] A provisional category of AML with a *RUNX1* variant 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.[36-39]

The World Health Organization (WHO) classification of AML was adapted by the NCCN to estimate individual patient prognosis to guide management, as shown in Table 3:[40]

Table 3. Risk Status of AML Based on Cytogenetic and Molecular Factors

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1)/ *RUNX1*::*RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB::MYH11* Mutated *NPM1* without *FLT3*-ITD bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD Wild-type *NPM1* with FLT3-ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/ *MLLT3::KMT2A* Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1)/ *DEK*::*NUP214* t(v;11q23.3)/ *KMT2A*-rearranged t(9;22)(q34.1;q11.2)/ *BCR::ABL1* t(8;16)(p11.2;p13.3)/ *KAT6A::CREBBP* inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2)/ *GATA2*, *MECOM*(*EVI1*) -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* Mutated *TP53*

Genetic Testing for Molecular Subtypes of AML

A number of systematic reviews with meta-analyses have highlighted the evolving classification of AML into distinct molecular subtypes based on *CEBPA*, *FLT3-ITD*, *KIT*, *NPM1*, and *TP53*, particularly in patients with normal karyotype.[41-46] 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.

PANEL TESTING FOR MYELOID NEOPLASMS

As indicated in NCCN guidelines and the WHO classification system, testing for variants in multiple genes may be indicated for diagnosis or treatment decisions in patients diagnosed with, or suspected of having, a myeloid neoplasm (see Practice Guideline Summary below). A number of studies have been published that describe the use of genetic panel tests that include these genes for diagnosis and prognosis of AML[47-51] and MDS[52-54].

PRACTICE GUIDELINE SUMMARY

WORLD HEALTH ORGANIZATION

In 2016 the WHO published diagnostic criteria for myeloid neoplasms and acute leukemia, which include testing for a number of genetic variants, as shown in Table 2.[1] The 2022 major criteria for myeloproliferative neoplasms are unchanged.[2]

NATIONAL COMPREHENSIVE CANCER NETWORK

The NCCN has published guidelines for Chronic Myeloid Leukemia (v.3.2025)[55], Acute Lymphoblastic Leukemia (v.2.2025)[56], which include recommendations regarding *BCR-ABL1* testing.

NCCN guidelines for Acute Myeloid Leukemia (v.2.2025)[40], Myelodysplastic Syndromes (v.2.2025)[57], and Myeloproliferative Neoplasms (v.1.2025)[58] include recommendations for testing a number of genes that have clinical significance for these disorders, including *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA*, *FLT3*, *KIT*, *NPM1,* and *RUNX1*.

SUMMARY

BCR/ABL1 (t(9;22)) TRANSLOCATION ANALYSIS, *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA*, *FLT3*, *KIT*, *NPM1* AND/OR *RUNX1*

There is enough research to show that *BCR/ABL1* (t(9;22)) translocation analysis (Philadelphia chromosome) and genetic testing for *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA, FLT3, KIT, NPM1 and/or RUNX1* variants is important to guide diagnosis and treatment of myeloid neoplasms and leukemia. Additionally, these tests are recommended by clinical practice guidelines for various myeloid disorders. Therefore, testing for *BCR/ABL1* (t(9;22)) translocation analysis (Philadelphia chromosome) and genetic testing for *JAK2, CALR, MPL, ASXL1, IDH1, IDH2, TP53, CEBPA, FLT3, KIT, NPM1 and/or RUNX1* variants is considered medically necessary for evaluation, diagnosis, and/or treatment monitoring for myeloid neoplasms and leukemia.

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.

TARGETED PANEL TESTING

There is enough research to show that targeted panel testing may be important for diagnosis and guide treatment decisions for patients suspected of having or diagnosed with myeloproliferative neoplasms (MPN), myelodysplastic neoplasms (MDS), and myelodysplastic myeloproliferative neoplasms (MPN/MDS), including acute myeloid leukemia (AML). Clinical practice guidelines recommend panel testing for these disorders.

Therefore, targeted panel testing for MPN, MDS, MPN/MDS or AML may be considered medically necessary.

NON-TARGETED PANEL TESTING

Non-targeted panels include testing for a large number of genes and are not targeted toward genes that have clinical significance for a specific type of hematolymphoid disorder. They often include testing for many genes that are not necessary to guide treatment, as well as testing for disorders that could be distinguished based on clinical presentation. There are no clinical practice guidelines based on research that recommend testing for all of the genes in these panels. Therefore, the use of non-targeted hematologic panel testing is considered investigational.

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CODES

NOTE: BCR/ABL1 (t(9;22)) translocation analysis has specific CPT codes: 81206-8, 0016U, and 0040U. This differs from than BCR-ABL kinase domain (*ABL1*) variant analysis.

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
	0017U	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
	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
	0027U	*JAK2* (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15
	0040U	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative
	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
	0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements
	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	*ASXL1* (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
	81176	*ASXL1* (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, EXON 12)
	81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
	81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
	81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative

Codes	Number	Description
	81218	*CEBPA* (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
	81219	*CALR* (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
	81245	*FLT3* (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
	81246	*FLT3* (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
	81270	*JAK2* (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81272	*KIT* (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	*KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
	81279	*JAK2* (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
	81310	*NPM1* (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
	81334	*RUNX1* (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)
	81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
	81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
	81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
	81353	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; known familial variant
	81401	Molecular pathology procedure, Level 2 - which includes *ABL1 (ABL proto oncogene 1, non-receptor tyrosine kinase)* (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)
	81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
	81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis

Codes	Number	Description
	81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed DNA analysis or combined DNA and RNA analysis
	81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
HCPCS	None	

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