



## Genetic Testing in Acute Myeloid Leukemia

**Policy #** 00459

**Original Effective Date:** 01/21/2015

**Current Effective Date:** 12/11/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

*Note: Hematopoietic Cell Transplantation for Acute Myeloid Leukemia is addressed separately in medical policy 00049.*

### When Services Are Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for *c-KIT*, *FLT3* internal tandem duplication and tyrosine kinase domain mutations (*ITD* and *TKD*), *NPM1*, *CEBPA* (biallelic), *IDH1*, *IDH2*, *RUNX1*, *ASXL1*, *TP53*, *BCR-ABL*, and *PML-RAR* alpha variants in adult and pediatric patients with suspected or confirmed acute myeloid leukemia (AML) for prognostic and/or therapeutic purposes to be **eligible for coverage.\*\*** (see Policy Guidelines section).

*Note:*

*When a multi-gene panel is being requested, it will be approved when billed with a single small panel CPT code (i.e., 81450). Based on NCCN guidelines, comprehensive next-generation sequencing (NGS) analysis is recommended for the ongoing management of AML and various phases of treatment.*

### When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for *c-KIT*, *FLT3-ITD*, *FLT3-TKD*, *NPM1*, *CEBPA* (biallelic), *IDH1/IDH2*, *RUNX1*, *ASXL1*, *TP53*, *BCR-ABL*, and *PML-RAR* variants in all other situations to be **investigational.\***

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Based on review of available data, the Company considers genetic testing for micro RNA (miRNA) expression or gene expression analysis for diagnosis or prognosis in patients with confirmed acute myeloid leukemia (AML) to be **investigational**.\*

### **Policy Guidelines**

Genetic testing for cytogenetically normal acute myeloid leukemia is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.

Analysis of gene sequencing of AML cases generally reveal more than 10 significant gene mutations; many of which are thought to participate in leukemogenesis. The most common gene mutations are as follows: FLT3 (28%), NPM1 (27%), DNMT3A (26%), IDH1 or IDH2 (20%), NRAS or KRAS (12%), RUNX1 (10%), TET2 (8%), TP53 (8%), CEBPA (6%), and WT1 (6%).

Gene expression profiling and microRNA expression profiling may also contribute to assessment and management of AML. Gene expression profiling has been used to differentiate between risk groups based on cytogenetic evaluation whereas microRNA profiling evaluates the regulation of gene expression. However, neither technique is used regularly in clinical practice as these techniques have yet to be widely validated.

### **Background/Overview**

#### **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. The American Cancer Society has estimated there will be 20,050 new cases of AML and 11,540 deaths from AML in the United States in 2022.

#### **Diagnosis and Prognosis of Acute Myeloid Leukemia**

The most recent World Health Organization classification (2022) reflects the increasing number of acute leukemias that can be categorized based on underlying cytogenetic abnormalities (ie, at the level of the chromosome including chromosomal translocations or deletions) or molecular genetic abnormalities (ie, at the level of the function of individual genes, including gene variants) and those

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distinguished by differentiation without defining genetic abnormalities. These cytogenetic and molecular changes form distinct clinicopathologic-genetic entities with diagnostic, prognostic, and therapeutic implications. 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 have been analyzed to subdivide AML with normal cytogenetics into prognostic subsets. In AML, 3 of the most frequent molecular changes with prognostic impact are variants of *CEBPA*, encoding a transcription factor, variants of the *FLT3* gene, encoding a receptor of tyrosine kinase involved in hematopoiesis, and a variant of the *NPM1* gene, encoding a shuttle protein within the nucleolus. "AML with *NPM1* mutation" and "AML with *CEBPA* mutation" were included as categories in the 2022 World Health Organization classification of acute leukemias. AML with *FLT3* variants is not considered a distinct entity in the 2022 or prior 2016 classifications. The 2008 World Health Organization classification recommended determining the presence of *FLT3* variants because of the prognostic significance.

### **Treatment**

AML has a highly heterogeneous clinical course, and treatment generally depends on the different risk stratification categories. Depending on the risk stratification category, treatment modalities may include intensive remission induction chemotherapy, hypomethylating agents, enrollment in clinical trials with innovative compounds, palliative cytotoxic treatment, or supportive care only. For patients who achieve complete remission after induction treatment, possible postremission treatment options include intensive consolidation therapy, maintenance therapy, or autologous or allogeneic hematopoietic cell transplant.

### **Measurable (Minimal) Residual Disease Monitoring**

Relapse in AML is believed to be due to residual clonal cells that remain following "complete response" after induction therapy but are below the limits of detection using conventional morphologic assessment. Residual clonal cells that can be detected in the bone marrow or blood are referred to as measurable residual disease (MRD), also known as minimal residual disease. Measurable residual disease assessment is typically performed by multiparameter flow cytometry or polymerase chain reaction with primers for common variants. It is proposed that finding MRD at different time points in the course of the disease (eg, after initial induction, prior to allogeneic

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transplantation) may be able to identify patients at a higher risk for relapse. In those with a high risk of relapse during the first remission, stem cell transplantation may be a more appropriate treatment approach. Studies in both children and adults with AML have demonstrated the correlation between MRD and risk for relapse. The role of MRD monitoring in AML is evolving, and important limitations remain. Some patients may have relapse despite having no MRD, while others do not relapse despite being MRD positive. Standards have recently been introduced for identifying certain individual markers for MRD assessment, and threshold values delineating MRD positivity and negativity have recently been defined for multiparameter flow cytometry and some variants detected by polymerase chain reaction or other methods.

### ***FLT3* Variants**

FMS-like tyrosine kinase (*FLT3*) plays a critical role in normal hematopoiesis and cellular growth in hematopoietic stem and progenitor cells. Variants in *FLT3* are among the most frequently encountered in AML. *FLT3* variants are divided into 2 categories: (1) internal tandem duplications (*FLT3*-ITD) variants, which occur in or near the juxtamembrane domain of the receptor, and (2) point mutations resulting in single amino acid substitutions within the activation loop of the tyrosine kinase domain (*FLT3*-TKD).

*FLT3*-ITD variants are much more common than *FLT3*-TKD variants, occurring in 30% of newly diagnosed adult cases of AML, versus *FLT3*-TKD variants, occurring in about 10% of patients. *FLT3*-ITD variants are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age with normal- or intermediate-risk cytogenetics, and are associated with an increased risk of relapse and inferior overall survival. Patients with *FLT3*-ITD variants have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild-type (WT; ie, nonmutated) *FLT3*. Although remission can be achieved in patients with *FLT3*-ITD variants using conventional induction chemotherapy at a frequency similar to other AML patients, the remission durations are shorter, and relapse rates are higher. The median time to relapse in patients with an *FLT3*-ITD variant is 6 to 7 months compared with 9 to 11 months in patients with other AML subtypes.

Because of the high-risk of relapse, hematopoietic cell transplantations as consolidation therapy of the first remission for an *FLT3*-ITD AML patient is often considered. However, this treatment must be weighed against the treatment-related mortality associated with a transplant.

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The clinical significance of an *FLT3* variant varies by the nature of the variant and the context in which it occurs. Longer *FLT3*-ITD variants have been associated with worse overall survival.

For *FLT3*-ITD variants, the *allelic ratio* refers to the number of ITD-mutated alleles compared with the number of WT (nonmutated) alleles. This ratio is influenced by the number of malignant versus benign cells in the sample tested and by the percentage of cells with 0, 1, or 2 mutated alleles. In most cases, the variant detected at diagnosis is also present at relapse. However, in some cases, as *FLT3*-ITD positive AML evolves from diagnosis to relapse, the variant present at diagnosis may be absent (or undetectable) at relapse. This is most commonly seen where the mutant allele burden is low (5%-15%) at diagnosis. The assays for detecting *FLT3*-ITD, was previously considered to be unsuitable for use as a marker of minimal residual disease. Higher mutant-to-WT allelic ratios have been associated with worse outcomes.

The prognostic impact of *FLT3*-TKD variants is less certain and conflicting. Some studies have suggested a negative impact of tyrosine kinase domain variants on event-free survival and overall survival, while other studies have found no prognostic value, or potentially a benefit if a *NPM1* mutation is also present. Next generation *FLT3* tyrosine kinase inhibitors with greater specificity for *FLT3* have been under clinical investigation, including gilteritinib, which was approved by the U.S. Food and Drug Administration (FDA) in 2018.

### ***NPM1* Variants**

A common molecular aberration in AML is a variant of *NPM1*, which is found in 28% to 35% of AML cases and is more common in cytogenetically normal AML. Up to 50% of AML with mutated *NPM1* also carry an *FLT3*-ITD. Mutated *NPM1* confers an independent favorable prognosis for patients with cytogenetically normal AML and either the presence or absence of an *FLT3*-ITD variant. Retrospective studies of banked clinical samples have suggested that an *NPM1* variant may mitigate the negative prognostic effect of an *FLT3*-ITD variant, but possibly only if the *FLT3*-ITD-to-WT allelic ratio is low. The prognostic impact in patients with an abnormal karyotype is unclear.

### ***CEBPA* Variants**

*CEBPA* (CCAAT/enhancer-binding protein) is a transcription factor gene that plays a role in cell cycle regulation and cell differentiation. Variants of *CEBPA* are found in approximately 7% to 11% of AML patients. *CEBPA* variants can be either biallelic (double variants) or monoallelic. Monoallelic variants are prognostically similar to *CEBPA* WT variant and do not confer a favorable

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prognosis in cytogenetically normal AML, with the exception of mutations in the basic leucine zipper region; double variants of *CEBPA* and variants with single mutations in the basic leucine zipper region have shown a better prognosis with higher rates of complete remission and overall survival after standard induction chemotherapy.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Several laboratories offer these tests, including Quest Diagnostics, Medical Genetic Laboratories of Baylor College, Geneva Labs of Wisconsin, LabPMM, and ARUP Laboratories, and they are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In May 2017, the FDA granted approval for midostaurin (Rydapt<sup>®†</sup>, Novartis Pharmaceuticals). Rydapt is a targeted therapy to be used in combination with chemotherapy when an *FLT3* variant is detected by the LeukoStrat<sup>®†</sup> CDx *FLT3* Mutation Assay (Invivoscribe). In 2018, gilteritinib (Xospata<sup>®†</sup>, Astellas Pharma US) was approved by the FDA for the treatment of relapsed or refractory acute myeloid leukemia with a *FLT3* mutation as detected by an FDA-approved test.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Treatment of acute myeloid leukemia (AML) is based on risk stratification, primarily related to patient age and tumor cytogenetics. In patients with cytogenetically normal AML, the identification

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of variants in several genes, including *FLT3*, *NPM1*, and *CEBPA*, has been proposed to allow for further segregation in the management of this heterogeneous disease.

### Summary of Evidence

For individuals who have cytogenetically normal AML who receive genetic testing for variants in *FLT3*, *NPM1*, and *CEBPA* to risk-stratify AML, the evidence includes RCTs, retrospective observational studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related mortality and morbidity. *FLT3* internal tandem duplication variants confer a poor prognosis, whereas *NPM1* (without the *FLT3* internal tandem duplication variant) and *CEBPA* variants (including biallelic mutations and single mutations in the basic leucine zipper region) confer a favorable prognosis. The prognostic effect of *FLT3* tyrosine kinase domain variants is uncertain. Data have suggested an overall survival benefit with transplantation for patients with *FLT3* internal tandem duplication, but do not clearly demonstrate an overall survival benefit of transplantation for patients with *NPM1* and *CEBPA* variants. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have AML with a genetic variant in *FLT3*, *NPM1*, or *CEBPA*, the evidence for measurable residual disease (MRD) monitoring of these genetic variants is limited to retrospective observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related mortality and morbidity. Detection of MRD based on *NPM1* variant presence is associated with higher risks for relapse and lower overall survival; prospective evaluations using MRD results to direct prognostic evaluation and treatment decisions are needed. For the use of genetic variants to detect MRD, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### Additional Information

Major professional societies and practice guidelines have recommended testing for these variants to risk-stratify and to inform treatment management decisions, including possible hematopoietic cell transplant. Specifically, guidelines from the National Comprehensive Cancer Network (AML, version 2.2022) recommend workup of certain karyotypic and molecular abnormalities as they provide prognostic information for both treatment decisions and risk of relapse. Several gene mutations are associated with specific prognoses and may guide treatment decisions; these include *FLT3* internal tandem duplication, *FLT3* tyrosine kinase domain, *NPM1*, and *CEBPA* (biallelic). The

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guidance recommends that all patients should be tested for mutations in these genes. The role of MRD assessment for prognosis and treatment is evolving and the use of MRD is still under investigation.

### **Supplemental Information**

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### **National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (v 5.2023) provide the following recommendations:

For the evaluation for acute leukemia, bone marrow core biopsy and aspirate analysis, including immunophenotyping, cytogenetic analyses, and molecular analyses for *FLT3*, *NPM1*, *CEBPA*, and other mutations, are needed to risk stratify patients.

"Several gene mutations are associated with specific prognoses in a subset of patients (category 2A) and may guide treatment decisions (category 2B). Presently, *c-KIT*, *FLT3-ITD*, *FLT3-TKD*, *NPM1*, *CEBPA* (biallelic), *IDH1/IDH2*, *RUNX1*, *ASXL1*, *TP53*, *BCR-ABL*, and *PML-RAR* alpha are included in this group. All patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment. To appropriately stratify therapy options, test results of molecular and cytogenetic analyses of immediately actionable genes or chromosomal abnormalities (eg, *CBF*, *FLT3* [ITD or TKD], *NPM1*, *IDH1*, or *IDH2*) should be expedited."

The guideline defined the following risk status based on molecular abnormalities:

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**Table 1. Risk Factors Based on Genetic Abnormalities**

Risk Category	Genetic Abnormality
Favorable	<ul style="list-style-type: none"><li>• t(8;21)(q22;q22.1); <i>RUNX 1-RUNX1T1</i></li><li>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22); <i>CBFB-MYH11</i></li><li>• Biallelic mutated <i>CEBPA</i></li><li>• Mutated <i>NPM1</i> without <i>FLT3</i>-ITD or with <i>FLT3</i>-ITD<sup>low</sup></li></ul>
Intermediate	<ul style="list-style-type: none"><li>• Mutated <i>NPM1</i> and <i>FLT3</i>-ITD<sup>high</sup></li><li>• Wild-type <i>NPM1</i> without <i>FLT3</i>-ITD or with <i>FLT3</i>-ITD<sup>low</sup> (without adverse-risk genetic lesions)</li><li>• t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i></li><li>• Cytogenetic abnormalities not classified as favorable or adverse</li></ul>
Poor/Adverse	<ul style="list-style-type: none"><li>• t(6;9)(p23;q34.1); <i>DEK-NUP214</i></li><li>• t(v;11q23.3); <i>KMT2A</i> rearranged</li><li>• t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i></li><li>• inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); <i>GATA2,MECOM(EV11)</i></li><li>• -5 or del(5q); -7; -17/abn(17p)</li><li>• Complex karyotype, monosomal karyotype</li><li>• Wild-type <i>NPM1</i> and <i>FLT3</i>-ITD<sup>high</sup></li><li>• Mutated <i>RUNX1</i></li><li>• Mutated <i>ASXL1</i></li><li>• Mutated <i>TP53</i></li></ul>

Adapted from NCCN guidelines for AML (v 5.2023).

ITD: internal tandem duplication

The role of measurable (minimal) residual disease (MRD) assessment for prognosis and treatment is evolving and the use of MRD is still under investigation. Currently available evidence has "demonstrated the correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements after initial induction therapy." Limitations of incorporating MRD into routine practice include "a lack of standardization and established cutoff values." The guideline notes that "the most frequently employed methods for MRD assessment include real-time quantitative polymerase chain reactions (RQ-PCR) assays (ie, *NPM1*, *CBFB-MYH11*, *RUNX1*-

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*RUNX1T1*) and multicolor flow cytometry (MFC) assays specifically designed to detect abnormal MRD immunophenotypes. The threshold to define MRD+ and MRD- samples depends on the technique and subgroup of AML. Next-generation sequencing (NGS)-based assays to detect mutated genes (targeted sequencing, 20 to 50 genes per panel) is not routinely used, as the sensitivity of PCR-based assays and flow cytometry is superior to what is achieved by conventional NGS."

### European LeukemiaNet

The European LeukemiaNet international expert panel recommendations for the diagnosis and management of adults with AML were updated in 2017 and again in 2022. The most recent update reflects the 2022 changes to the World Health Organization classification of AML. The panel recommended that screening for *NPM1*, *CEBPA*, and *FLT3* variants should be part of the diagnostic workup in patients with cytogenetically normal AML because they define disease categories that can inform treatment decisions. Table 2 outlines the risk stratification by genetic variants, and Table 3 summarizes recommended conventional care regimens based on patient fitness and risk characteristics, including mutations and other considerations.

The European LeukemiaNet MRD Working Party is an international expert panel convened with the objective of providing guidelines for technical assessment and clinical use of immunophenotypic and molecular MRD testing in AML; the panel's first consensus recommendations were published in 2018, and updated recommendations were published in 2021. In the 2021 update, the panel recommended that molecular MRD be assessed by real-time quantitative or digital polymerase chain reaction in patients with *NPM1*, *CBFB-MYH11*, or *RUNX1-RUNX1T1* mutations, and by MFC in all other patients. NGS-based MRD monitoring is considered by the panel to be "useful to refine prognosis in addition to MFC but, to date, there are insufficient data to recommend NGS-MRD as a stand-alone technique." The panel also defined MRD positivity thresholds according to whether <FC or polymerase chain reaction techniques were used, and provisional MRD positivity thresholds for NGS techniques.

**Table 2. Risk Stratification by Genetic Variant**

Risk Category	Genetic Abnormality
Favorable	<ul style="list-style-type: none"><li>• t(8;21)(q22;q22.1)/<i>RUNX1::RUNX1T1</i></li><li>• inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ <i>CBFB::MYH11</i></li><li>• Mutated <i>NPM1</i> without <i>FLT3</i>-ITD</li></ul>

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	<ul style="list-style-type: none"> <li>Basic leucine zipper in-frame mutated <i>CEBPA</i></li> </ul>
Intermediate	<ul style="list-style-type: none"> <li>Mutated <i>NPM1</i> with <i>FLT3</i>-ITD</li> <li>Wild-type <i>NPM1</i> with <i>FLT3</i>-ITD (without adverse-risk genetic lesions)</li> <li>t(9;11)(p21.3;q23.3)/<i>MLLT3::KMT2A</i></li> <li>Cytogenetic and/or molecular abnormalities not classified as favorable or adverse</li> </ul>
Adverse	<ul style="list-style-type: none"> <li>t(6;9)(p23.3;q34.1)/<i>DEK::NUP214</i></li> <li>t(v;11q23.3)/<i>KMT2A</i>-rearranged</li> <li>t(9;22)(q34.1;q11.2)/<i>BCR::ABL1</i></li> <li>t(8;16)(p11.2;p13.3)/<i>KAT6A::CREBBP</i></li> <li>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ <i>GATA2</i>, <i>MECOM(EV11)</i></li> <li>t(3q26.2;v)/<i>MECOM(EV11)</i>-rearranged</li> <li>-5 or del(5q); -7; -17/abn(17p)</li> <li>Complex karyotype, monosomal karyotype</li> <li>Mutated <i>ASXL1</i>, <i>BCOR</i>, <i>EZH2</i>, <i>RUNX1</i>, <i>SF3B1</i>, <i>SRSF2</i>, <i>STAG2</i>, <i>U2AF1</i>, and/or <i>ZRSR2</i></li> <li>Mutated <i>TP53</i></li> </ul>

Adapted from Döhner et al (2022).

ITD: internal tandem duplication.

**Table 3. Selected Conventional Care Regimens by Fitness and Risk Characteristics**

Patient Characteristics	Induction Therapy	Consolidation Therapy	Maintenance Therapy	Salvage therapy
Considered fit for intensive therapy				
With <i>FLT3</i> mutation	Anthra-cycline plus cytarabine ("7 + 3") plus mido-staurin	<ul style="list-style-type: none"> <li>Intermediate-dose cytarabine plus midostaurin and/or</li> <li>If relapse probability with chemotherapy alone</li> </ul>	Mido-staurin	Gilteritinib or options for other fit patients listed below

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		>35% to 40%*: allo-HCT		
Without <i>FLT3</i> mutation	"7 + 3"	<ul style="list-style-type: none"> <li>Intermediate-dose cytarabine <u>and/or</u></li> <li>If relapse probability with chemotherapy alone &gt;35% to 40%*: allo-HCT</li> </ul>	Oral azacitidine	
CD33-positive AML with favorable- or intermediate-risk disease	"7 + 3" with ("other" option) or without gemtuzumab ozogamicin	<ul style="list-style-type: none"> <li>Intermediate-dose cytarabine with ("other" option) or without gemtuzumab ozogamicin, and/or</li> <li>If relapse probability with chemotherapy alone &gt;35% to 40%*: allo-HCT</li> </ul>	--	<ul style="list-style-type: none"> <li>Intermediate-dose cytarabine with or without anthracycline</li> <li>FLAG-IDA chemotherapy</li> <li>MEC chemotherapy</li> <li>CLAG-M chemotherapy</li> <li>allo-HCT</li> </ul>
AML with myelodysplasia-related changes or therapy-related AML	"7 + 3" or liposomal-coformulated daunorubicin and cytarabine ("other" option)	<ul style="list-style-type: none"> <li>Intermediate-dose cytarabine <u>or</u> liposomal-coformulated daunorubicin and cytarabine ("other" option), and/or</li> <li>If relapse probability with chemotherapy alone</li> </ul>	--	

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		>35% to 40%*: allo-HCT		
Not considered fit for intensive therapy				
With <i>FLT3</i> mutation	<ul style="list-style-type: none"> <li>Venetoclax plus either azacitidine or decitabine</li> <li>Venetoclax plus low-dose cytarabine</li> <li><i>IDH1</i> mutation: ivosidenib with or without azacitidine</li> <li>Best supportive care</li> </ul>			Gilteritinib
Without <i>FLT3</i> mutation				<ul style="list-style-type: none"> <li><i>IDH1</i> mutation: ivosidenib</li> <li><i>IDH2</i> mutation: enasidenib</li> </ul>

Adapted from Döhner et al (2022).

\*Examples include intermediate- or adverse-risk disease and/or inadequate clearance of measurable residual disease.

allo: allogeneic, AML: acute myeloid leukemia, HCT: hematopoietic cell transplant.

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

## Ongoing and Unpublished Clinical Trials

Select currently ongoing and unpublished trials that might influence this review are listed in Table 4.





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**Table 4. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01296178	PROTOCOL FOR First Line TREATMENT ADAPTED TO RISK of Acute Myeloblastic Leukemia in Patients LESS THAN OR EQUAL TO 65 YEARS	200	Dec 2021 (last update posted Mar 2021)
NCT02156297	Sorafenib to Treat AML Patients with FLT3-ITD Mutation, a Non-interventional Cohort Study	100	Aug 2022 (last update posted Feb 2020)
NCT02668653 <sup>a</sup>	Phase 3, Double-Blind, Placebo-controlled Study of Quizartinib Administered in Combination With Induction and Consolidation Chemotherapy, and Administered as Maintenance Therapy in Subjects 18 to 75 Years Old With Newly Diagnosed FLT3-ITD (+) Acute Myeloid Leukemia (QuANTUM-First)	539	Aug 2023
NCT03031249	Efficacy and Safety of ATO Plus ATRA in Nucleophosmin-1 Mutated Acute Myeloid Leukemia	80	Dec 2022
NCT02927262 <sup>a</sup>	A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission	98	Feb 2024
NCT02997202 <sup>a</sup>	A Trial of the FMS-like Tyrosine Kinase 3 (FLT3) Inhibitor Gilteritinib Administered as Maintenance	356	Jul 2025

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NCT No.	Trial Name	Planned Enrollment	Completion Date
	Therapy Following Allogeneic Transplant for Patients With FLT3/Internal Tandem Duplication (ITD) Acute Myeloid Leukemia (AML)		
<i>Unpublished</i>			
NCT01237808	Study of Low-Dose Cytarabine and Etoposide With or Without All-Trans Retinoic Acid in Older Patients Not Eligible for Intensive Chemotherapy With Acute Myeloid Leukemia and NPM1 Mutation	144	Jul 2018 (completed; last update posted 8/01/2018)
NCT00860639	Randomized Open Phase III Trial Testing Efficacy of Gemtuzumab Ozogamycin Associated to Intensive Chemotherapy for Patients Aged Between 18-60 Years and Presenting an AML With Intermediate Risk	327	Sep 2016 (completed; last update posted 01/27/2017)

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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### **Policy History**

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01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. New policy.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. Added <i>CEBPA</i> mutations to title and policy statements. Updated rationale/references.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/04/2018	Medical Policy Committee review
01/17/2018	Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for FLT3, <i>NPM1</i> , and <i>CEBPA</i> Mutations in Acute Myeloid Leukemia” to “Genetic Testing for FLT3, <i>NPM1</i> , and <i>CEBPA</i> Mutations in Cytogenetically Normal Acute Myeloid Leukemia”. Changed genetic nomenclature from “mutations” to “variants” throughout the policy. Coverage eligibility unchanged.
04/01/2018	Coding update
07/01/2018	Coding update
09/20/2018	Coding update
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/03/2020	Medical Policy Committee review
01/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/07/2021	Medical Policy Committee review
01/13/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/06/2022	Medical Policy Committee review

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- 01/12/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 03/02/2022 Coding update
- 11/03/2022 Medical Policy Committee review
- 11/09/2022 Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia” to “Genetic Testing in Acute Myeloid Leukemia”. Revised the coverage section. Added information to the Policy Guidelines.
- 01/25/2023 Coding update
- 11/02/2023 Medical Policy Committee review
- 11/08/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 11/2024

## **Coding**

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HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

**\*Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

**\*\*Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

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## Genetic Testing in Acute Myeloid Leukemia

Policy # 00459

Original Effective Date: 01/21/2015

Current Effective Date: 12/11/2023

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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