Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia

Policy # 00459
Original Effective Date: 01/21/2015
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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 *FLT3* internal tandem duplication (*FLT3-ITD*), *NPM1*, and *CEBPA (CCAAT*/enhancer binding protein) variants in cytogenetically normal acute myeloid leukemia (CN-AML) to be **eligible for coverage.**** (see Policy Guidelines section).

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 *FLT3* internal tandem duplication *(FLT3-ITD)*, *NPM1*, and *CEBPA (CCAAT/*enhancer binding protein) variants in all other situations to be **investigational.***

Based on review of available data, the Company considers genetic testing for *FLT3* tyrosine kinase domain (*FLT3-TKD*) variants to be **investigational.***

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Based on review of available data, the Company considers genetic testing for *FLT3, NPM1* and *CEBPA (CCAAT/*enhancer binding protein) variants to detect minimal residual disease 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.

Background/Overview

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 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017.

Diagnosis and Prognosis of AML

The most recent World Health Organization classification (2016) 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). 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 mutated *NPM1 or CEBPA*" were included as categories in the 2016 World Health Organization classification of acute leukemias. AML with *FLT3* variants is not considered a distinct entity in the 2016 classification. The 2008 World Health Organization classification recommended determining the presence of *FLT3* variants because of the prognostic significance.

Recent reviews (2012-2014) have highlighted the evolving classification of AML into distinct molecular subtypes.

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.

***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, and approximately 30% of AML patients harbor some form of *FLT3* variant. *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 25% of newly diagnosed adult cases of AML, versus *FLT3*-TKD variants, occurring in about 7% of patients. *FLT3*-ITD variants are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age and 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. Once *FLT3*-ITD AML relapses, the disease is rapidly fatal.

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.

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 reduced remission rates and/or worse survival in some studies.

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. For this reason, and the overall lack of sensitivity of the assay (see the Clinically Valid section), the assay is 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 has only been studied in small numbers of patients. FLT3 tyrosine kinase inhibitors{Arcovito, 2014 #208} are under active clinical investigation.

NPM1 Variants

The most common molecular aberration in AML is a variant of *NPM1*, which is found in 46% to 64% of patients with cytogenetically normal AML and in 9% to 18% of patients with cytogenetically abnormal 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 to *CEBPA* are found in approximately 15% of AML patients with a normal karyotype. *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 prognosis in cytogenetically normal AML; double variants of *CEBPA* 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, 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 FDA has chosen not to require any regulatory review of this test.

In May 2017, the FDA granted approval for midostaurin (Rydapt®‡, Novartis Pharmaceuticals). Rydapt is a targeted therapy to be used in combination with chemotherapy when an *FLT3* variant is detected by the LeukoStrat®‡ CDx *FLT3* Mutation Assay (Invivoscribe).

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Rationale/Source

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 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.

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. The 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 biallelic *CEBPA* variants 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. 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (v.2.2020) provide the following recommendations:

> For the evaluation for acute leukemia, "bone marrow core biopsy and aspirate analysis, including immunophenotyping and cytochemistry."

> "A variety of gene mutations are associated with specific prognoses (category 2A) and may guide medical decision making (category 2B). Other mutations, such as ASXL1, BCR-ABL, and PML-RAR alpha may have therapeutic implications. The field of genomics in myeloid malignancies, and related implications in AML, are evolving rapidly. While the above mutations should be tested in all patients, multiplex gene panels and next-generation sequencing analysis are recommended for a comprehensive prognostic assessment... Peripheral blood may alternatively be used to detect molecular abnormalities in patients with morphologically detectable, circulating leukemic blasts."

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

Table 1. Risk Factors Based on Genetic Abnormalities

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); RUNX!-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Bialletic mutated CEBPA Mutated NPM1 without FLT3-ITD or with FLT3-ITD
Intermediate	Mutated NPM1 and FLT3-ITD Wild-type NPM1 without FLT3-ITD or with FLT3-ITD (without adverse-risk genetic lesions) T(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal dryotype Wild-type NPM1 and FLT3-ITD Mutated RUNX1 Mutated ASXL1

	Mutated TP53

Adapted from NCCN guidelines for AML (v.2.2020).

European Leukemia Net

The European Leukemia Net (2010) international expert panel recommendations for the diagnosis and management of adults with AML were updated in 2017. The panel of 22 international experts on AML 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 1 outlines the risk stratification by genetic variants, and Table 2 summarizes recommended conventional care regimens based on risk category and age.

Table 2. Risk Stratification by Genetic Variant

Genetic Variant	Risk Category
Biallelic *CEBPA*	Favorable
Mutated *NPM1* without *FLT3*-ITD	Favorable
Mutated *NPM1* with *FLT3*-ITD (low allelic ratio)	Favorable
Mutated *NPM1* with *FLT3*-ITD (high allelic ratio)	Intermediate
Wild-type *NPM1*without *FLT3*-ITD	Intermediate
Wild-type *NPM1* with *FLT3*-ITD (low allelic ratio)	Intermediate
Wild-type *NPM1* with *FLT3*-ITD (high allelic ratio)	Adverse

Adapted from Dohner et al (2017).
ITD: internal tandem duplication.

Table 3. Conventional Care Regimens by Risk and Age Categories

Risk and Age Categories	Conventional Care
Patients 18 to 60/65 years	

Favorable	• 2 to 4 cycles intermediate-dose cytarabine
Intermediate	• Allogeneic HCT from matched related or unrelated donor • 2 to 4 cycles intermediate-dose cytarabine • High-dose therapy and autologous HCT
Adverse	• Allogeneic HCT from matched related or unrelated donor
Patients >60/65 years	
Favorable	• 2 to 3 cycles intermediate-dose cytarabine
Intermediate/adverse	• Consider allogeneic HCT from matched related or unrelated donor • Investigational therapy

Adapted from Dohner et al (2017).
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.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02474290	Sorafenib for Prophylaxis of Leukemia Relapse in Allogeneic Hematopoietic Stem Cell Transplant Recipients With FLT3-ITD Positive Acute Myeloid Leukemia	196	Aug 2019(completed)
NCT02039726[a]	Phase 3 Open-label Randomized Study of Quizartinib Monotherapy Versus Salvage Chemotherapy in Subjects With FLT3-ITD Positive AML Refractory to or Relapsed After First-line Treatment With or Without HSCT Consolidation	367	Jul 2019
NCT01296178	PROTOCOL FOR First Line TREATMENT ADAPTED TO RISK of Acute Myeloblastic Leukemia in Patients LESS THAN OR EQUAL TO 65 YEARS	200	Dec 2019
NCT02156297	Sorafenib to Treat AML Patients with FLT3-ITD Mutation, a Non-interventional Cohort Study	100	Aug 2019 (Last update posted 10/08/2015)
NCT01477606[a]	Phase II Study Evaluating Midostaurin in Induction, Consolidation, and Maintenance Therapy also after Allogeneic Blood Stem Cell Transplantation in Patients with Newly Diagnosed Acute Myeloid Leukemia Exhibiting an FLT3 internal Tandem Duplication	440	Jun 2020

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT00893399	Phase III Study of Chemotherapy in Combination With ATRA With or Without Gemtuzumab Ozogamicin in Patients With Acute Myeloid Leukemia and NPM1 Gene Mutation	588	Jul 2020
NCT02668653[a]	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)	536	Nov 2020
NCT03031249	Efficacy and Safety of ATO Plus ATRA in Nucleophosmin-1 Mutated Acute Myeloid Leukemia	250	Dec 2022
NCT02927262[a]	A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-controlled Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission	354	Mar 2021
Unpublished			
NCT01237808	Study of Low-Dose Cytarabine and Etoposide With or Without All-Trans Retinoic Acid in Older Patients Not Eligible for Intensive	144	Jul 2018

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Chemotherapy With Acute Myeloid Leukemia and NPM1 Mutation		
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.
[a] 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 *CEBPA* 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, *NPM1*, and *CEBPA* Mutations in Acute Myeloid Leukemia" to "Genetic Testing for FLT3, *NPM1*, and *CEBPA* 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

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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.

Next Scheduled Review Date: 01/2022

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia

Policy # 00459
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Current Effective Date: 02/08/2021

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0023U, 0046U, 0049U, 0050U, 0056U, 81218, 81245, 81246, 81310, 81403, 81450
HCPCS	No codes
ICD-10 Diagnosis	C92.00-C92.02, C92.20-C92.22, C92.40-C92.42, C92.50-C92.52, C92.60-C92.62, C92.A0-C92.A2

*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 the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated 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, 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: 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.