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

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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.**

Note: Genetic testing for CN-AML is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.

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.***

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.***

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. It was estimated that, in 2014, 18,860

people would be diagnosed with AML and 10,460 would die of the disease. Median age at diagnosis is 66 years, with approximately 1 in 3 patients diagnosed at 75 years of age or older.

Diagnosis and Prognosis of AML
The most recent World Health Organization (WHO) classification (2016) reflects the increasing number of acute leukemias that can be categorized based on underlying cytogenetic abnormalities (i.e., at the level of the chromosome including chromosomal translocations or deletions) or molecular genetic abnormalities (i.e., at the level of the function of individual genes, including gene variants). These cytogenetic and molecular changes form distinct clinico-pathologic-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 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 WHO classification of acute leukemias. AML with *FLT3* variants is not considered a distinct entity in the 2016 classification. The 2008 WHO classification recommends determining the presence of *FLT3* variants because of the prognostic significance.

Recent reviews (2012-2013) 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, clinical trials with innovative compounds, palliative cytotoxic treatment, or supportive care only. For patients who achieve complete remission (CR) 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 one of the most frequently encountered variants 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 variants 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 (OS). Patients with *FLT3*-ITD variants have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild-type (WT; i.e., 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, HCT as consolidation therapy of a 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 Clinical Validity 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 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 CN-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 CN-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 CN-AML; double variants of *CEBPA* have shown a better prognosis with higher rates of CR and OS 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Several laboratories offer these tests, including Quest Diagnostics, Medical Genetic Laboratories of Baylor College, Geneva Labs of Wisconsin, LabPMM, and ARUP Laboratories, available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

In November 2016, Invivoscribe Technologies submitted a premarket approval application for a *FLT3* companion diagnostic for Novartis's PKC412 (midostaurin).

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

The evaluation of a prognostic genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (prognostic performance of a test [sensitivity, specificity, positive and negative predictive values] in predicting course of clinical disease); and (3) clinical utility (i.e., a demonstration that the prognostic information can be used to improve patient health outcomes).

CLINICAL CONTEXT AND TEST PURPOSE

Optimal decisions regarding treatment intensity and chemotherapy-based consolidation therapy versus allogeneic transplantation remains unclear in CN-AML). The purpose of genetic testing is to provide prognostic risk-stratification information, in patients who have CN-AML, that may inform decisions regarding:

- whether to use standard or increased treatment intensity in induction therapy, consolidation therapy, or in relapsed/refractory AML;

- whether to do allogeneic or autologous transplantation versus chemotherapy as consolidation therapy for an AML patient in first remission;
- whether to use investigational therapies such as FLT3 inhibitors.

Induction therapy usually consists of 7 days of continuous-infusion cytarabine at 100 to 200 mg/m^2 with 3 days of anthracycline. Studies have shown greater efficacy at higher doses but also increased toxicity.

Transplantation reduces risk of recurrence but is typically associated with at least a 20% treatment-related mortality risk.

Side effects of FLT3 inhibitors (e.g., sorafenib, sunitinib, midostaurin, lestaurtinib, quizartinib) include QT prolongation, nausea, vomiting, diarrhea, anemia, abnormal liver function tests, increased bilirubin, fever, and fatigue. Currently no FLT3 inhibitor is approved for this indication, although midostaurin is under priority review at the FDA. Sorafenib and sunitinib are approved for treatment of other malignancies.

The question addressed in this evidence review is: Does *FLT3, NMP1,* or *CEBPA* genetic testing in patients with AML improve outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The populations of interest are patients with newly diagnosed CN-AML, those in first remission, and those who have relapsed.

Intervention
The intervention of interest is *FLT3*, *NMP1*, or *CEBPA* genetic testing.

Comparator
The comparator of interest is risk stratification without *FLT3*, *NMP1*, or *CEBPA* genetic testing.

Outcomes
Outcomes are focused on overall- and cancer-specific mortality, although treatment-related morbidity in the short- and long term is also a focus.

Timing
Mortality and morbidity over the short (i.e., 1 year) and long term (5-10 years) are of interest.

Setting
Decisions about management of AML are generally made by patients and hematologists or oncologists in the secondary or tertiary care setting.

ANALYTIC VALIDITY
Analytic validity is the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent.

No published data on the analytic validity of *NPM1* or *CEBPA* variant testing were identified.

Clinically validated *FLT3* variant testing is performed with a polymerase chain reaction (PCR)–based assay of genomic deoxyribonucleic acid (DNA) isolated from the leukemic cells, either from blood or bone marrow. Testing for *FLT3* may involve a duplex assay, which tests for both types of *FLT3* variants (internal tandem duplication [ITD], tyrosine kinase domain [TKD]), however, some laboratories only test for ITD variants, because the prognostic effect of TKD variants in uncertain. Published data on the analytic validity of *FLT3* testing is lacking, however, a review article has highlighted that a major limitation of most PCR assays for *FLT3* internal tandem duplication (*FLT3*-ITD) variants is lack of sensitivity compared with PCR assays for other AML-associated genetic alterations. The sensitivity of the PCR assays is a function of the amount of sample DNA and the number of PCR cycles. However, for the *FLT3*-ITD assay, increasing the number of cycles does not increase the sensitivity because the PCR primers used to amplify the mutant allele also amplify the WT allele, and the shorter WT allele has a competitive advantage over the mutant allele, because it takes more time to complete a PCR cycle for the longer length mutant allele. The longer the variant (insertion), the greater the PCR bias. This bias can be minimized using fewer PCR cycles, but this could affect sensitivity if there is a low burden of leukemia cells in the sample.

CLINICAL VALIDITY
Clinical validity is the prognostic performance of the test (sensitivity, specificity, positive and negative predictive values) in predicting the course of clinical disease.

Prognosis of patients with *FLT3*-ITD, *NMP1*, or *CEBPA* variants compared to patients without *FLT3*-ITD, *NMP1*, or *CEBPA* variants are described in Table 1. Results from systematic reviews are presented when available and individual studies are included if they described a population not represented in the systematic reviews.

Table 1. Survival Outcomes of Patients With *FLT3*-ITD, *NMP1*, or *CEBPA* Variants

Study	Design	Participants	Outcomes
Port et al (2014)	Systematic review of 19 studies published between 2000 and Mar 2012	CN-AML patients <60 y	*FLT3*-ITD WT vs *FLT3*-ITD variant: • OS HR=1.9 (95% 1.6 to 22) • RFS HR=1.8 (95% CI, 1.5 to 2.2) *NPM1* WT vs *NPM1* variant: • OS HR=0.6 (95% CI, 0.5 to 0.7) • RFS HR=0.6 (95% CI, 0.5 to 0.6) *CEBPA* WT vs *CEBPA* variant: • OS HR=0.4 (95% CI, 0.3 to 0.5) • RFS HR=0.4 (95% CI, 0.3 to 0.6)
Li et al (2015)	Systematic review of 10 studies	6219 patients with	Any AML:

	published before Aug 2014	AML	• *CEBPA* monoallelic vs WT ○ OS HR=1.1 (95% CI, 0.9 to 1.5) ○ EFS HR=1.1 (95% CI, 0.8 to 1.5) • *CEBPA* biallelic vs WT: ○ OS HR=0.4 (95% CI, 0.3 to 0.5) ○ EFS HR=0.4 (95% CI, 0.3 to 0.5) CN-AML: • *CEBPA* monoallelic vs WT: ○ OS HR=1.1 (95% CI, 0.9 to 1.5) ○ EFS HR=0.9 (95% CI, 0.7 to 1.2) • *CEBPA* biallelic vs WT: ○ OS HR=0.3 (95% CI, 0.2 to 0.4) ○ EFS HR=0.4 (95% CI, 0.3 to 0.5)
Dickson et al (2016)	Retrospective analysis of patients enrolled in an RCT between 1990 and 1998	662 AML patients >60 y	1-y OS: • *CEBPA*, biallelic: 75% • *NPM1* variant, *FLT3*-ITD WT: 54% • All others: 33% 3-y OS: • *CEBPA*, biallelic: 17% • *NPM1* variant, *FLT3-ITD* WT: 29% • All others: 12%
Wu et al (2016)	Systematic review of 10 studies published between 1995 and July 2015	1661 pediatric patients with AML	*FLT3*-ITD WT vs *FLT3*-ITD variant: • OS HR=2.2 (95% CI, 1.6 to 3.0) • EFS HR=1.7 (95% CI, 1.4 to 2.1)

AML: acute myeloid leukemia; CI: confidence interval; CN; cytogenetically normal; EFS: event-free survival; HR: hazard ratio; RCT: randomized controlled trial; OS, overall survival; RFS: recurrence-free survival; WT; wild type.

Section Summary: Clinical Validity

FLT3-ITD variant is quite common in AML, particularly in patients with normal karyotypes, and has been associated with poorer survival in children, younger adults, and older adults. The prognostic effect of *FLT3*-TKD variants is uncertain. *NPM1* variants are found in approximately half of patients with CN- AML. *NPM1* variants are associated with improved outcomes; however, the superior prognosis is limited to those with *NPM1* variants who do not have a *FLT3*-ITD variant. *CEBPA* variants are found in approximately 15% of patients with CN-AML. Patients with *CEBPA* variants have a favorable prognosis, although the effect may be limited to patients who carry 2 copies of the mutant allele.

CLINICAL UTILITY

Clinical utility is 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 literature on the use of these markers consists of retrospective analyses, and no prospective studies have been published to date. Literature describing outcomes by type of treatment for patients with and

without *FLT3*-ITD, *CEBPA*, and *NPM1* variants are shown in Table 2. Results from systematic reviews are presented when available and individual studies are shown if they were not included in the scope of the systematic reviews. Narrative summaries of select studies are presented following the table.

Most of the literature consists of analyses of *FLT3*-ITD variants and survival outcomes with the use of allogeneic hematopoietic cell transplantations (allo-HCT) in patients depending on the presence of this type of variant. In general, the data support use of HCT in patients with *FLT3*-ITD variants, however, not all studies have shown consistent results.

Table 2. Outcomes by Treatment of Patients With and Without *FLT3*-ITD Variants

Study	Design	Participants	Outcomes
Schlenk et al (2008)	Retrospective analysis of patients in 4 AML therapy RCTs conducted between 1993 and 2004	872 adults <60 y with CN-AML, 53% *NPM1* variant, 31% *FLT3*-ITD variant, 11% *FLT3*-TKD variant, 13% *CEBPA* variant	Allo-HCT vs other consolidation therapy: • *NPM1* without *FLT3*-ITD • RR HR=0.9 (95% CI, 0.5 to 1.8) Other genotypes (excluding *CEBPA*, *NPM1* without *FLT3*-ITD): • RR HR=0.6 (95% CI, 0.4 to 0.9)
Schlenk et al (2013)	Retrospective analysis of patients in 7 AML therapy RCTs conducted between 1987 and 2009	124 adults <60 y with CN AML who were *CEBP* biallelic and had CR after induction therapy	Allo-HCT vs chemotherapy: • RFS HR=0.2 (95% CI, 0.1 to 0.5) • OS HR=0.5 (95% CI, 0.2 to 1.2) Autologous HCT vs chemotherapy: • RFS HR=0.4 (95% CI, 0.2 to 0.8) • OS HR=0.6 (95% CI, 0.2 to 1.4)
Willemze et al (2014)	Retrospective analysis of EORTC-GIMEMA AML-12 RCT conducted between Sep 1999 and Jan 2008	613 patients with AML, ages 15-60 y; 126 (21%) *FLT3*-ITD variant	Patients with *FLT3*-ITD variant categorized as very bad risk: • OS at 6 y in patients at very bad risk • 20% in standard cytarabine group vs 31% in high-dose group • HR=0.70 (95% CI, 0.47 to 1.04)
Chou et al (2014)	Retrospective analysis of patients from Taiwanese university hospital between 1995 and 2007	325 adults with AML who received conventional induction chemotherapy; 81 (25%) *FLT3*-ITD, 69 (21%) *NPM*1, 33 (10%) *NPM*1 with *FLT*-ITD WT, 42 (13%) *CEBPA* biallelic	Non-allo-HCT: • *CEBPA* biallelic vs other ○ OS HR=0.5 (95% CI, 0.3 to 0.8) • NPM1 variant with *FLT3*-ITD WT: ○ OS HR=0.4 (95% CI, 0.2 to 0.7) Allo-HCT: • *CEBPA* biallelic vs other ○ OS HR=0.3 (95% CI, 0.1 to 1.2) • *NPM1* variant with *FLT3*-ITD WT: ○ OS HR=NR
Ma et al (2015)	Systematic review of 9 studies of chemotherapy vs HCT published between 1989 and 2013	Patients with AML, *FLT3*-ITD variant	Allo-HCT vs chemotherapy: • OS OR=2.9 (95% CI, 2.0 to 4.1) • DFS OR=2.8 (95% CI, 1.9 to 4.3) • RR OR=0.1 (95% CI, 0.05 to 0.2)
Tarlock et al	Retrospective analysis	Children with AML, *FLT3*-	Standard chemotherapy with vs without

Study	Design	Participants	Outcomes
(2016)	of 2 AML RCTs conducted between Dec 2003 and Nov 2005	ITD variant who received standard chemotherapy and HCT	gemtuzumab ozogamicin: • Overall ○ RR=37% vs 59% (95% CI, NR; p=0.02) ○ DFS=47% vs 41% (95% CI, NR; p=0.45) ○ TRM=16% vs 0% (95% CI, NR; p=0.008) • Among patients with high *FLT3*-ITD allelic ratio ○ RR 15% vs 53% (95% CI, NR; p=0.007) ○ DFS 65% vs 40% (95% CI, NR; p=0.08) ○ TRM=19% vs 7% (95% CI, NR; p=0.08)
Ahn et al (2016)	Retrospective analysis of patients from 7 institutions in Korea from Oct 1998 to Sep 2012	404 CN-AML patients ages ≥15 y treated with conventional induction chemotherapy; 51 (13%) *CEBPA* biallelic	Overall, by *CEBPA:* • 5-y OS biallelic, 62% (95% CI, 43% to 82%) • 5-y OS monoallelic, 44% (95% CI, 19% to 69%) • 5-y OS WT=26% (95% CI, 19% to 32%) • Biallelic vs others • HR=0.4 (95% CI, NR; p=0.001) Among *CEBPA* biallelic: • Chemotherapy ○ 5-y OS=60% (95% CI, 40% to 81%) ○ 5-y EFS=39% (95% CI, 15% to 64%) ○ 5-y relapse incidence, 38% (95% CI, 17 to 59) • Allo-HCT ○ 5-y OS=72% (95% CI, 54% to 90%) ○ 5-y EFS=73% (95% CI, 55% to 90%) ○ 5-y relapse incidence, 8 (95% CI, 1 to 23)
Brunner et al (2016)[26]	Retrospective analysis of patients at 2 U.S. institutions between 2008 and 2014	81 consecutive AML patients who underwent *FLT3*-ITD testing who achieved CR with induction chemotherapy followed by allo-HCT	Sorafenib maintenance therapy vs no sorafenib • 2-y OS=81% vs 62%; HR=0.3 (95% CI, 0.1 to 0.8) • 2-y PFS=82% vs 53%; HR=0.3 (95% CI, 0.1 to 0.8)

allo: allogeneic; AML: acute myeloid leukemia; CI: confidence interval; CN; cytogenetically normal; CR: complete remission; DFS: disease-free survival; EFS: event-free survival; HCT: hematopoietic cell transplantation; HR: hazard ratio; ITD: internal tandem duplication; NR: not reported; OR: odds ratio; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; RFS: recurrence-free survival; RR: relapse rate; SCT: stem cell transplantation; TKD: tyrosine kinase domain; TRM: treatment-related mortality; WT: wild type.

Ma et al (2015) performed a systematic review including 9 studies published between 1989 and December 2013 that described use of HCT or chemotherapy in patients with AML in first CR who had *FLT3*-ITD variants. All studies were retrospective or nonrandomized controlled analyses. Allo-HCT was associated with a longer OS (odds ratio [OR]=2.9; 95% confidence interval [CI], 2.0 to 4.1), longer disease-free survival (DFS; OR=2.8; 95% CI, 1.9 to 4.3), and reduction in relapse rate (OR=0.1; 95% CI, 0.05 to 0.2)

compared to chemotherapy. OS and DFS rates favored allo-HCT but did not differ significantly between allo-HCT and autologous HCT (OS OR=1.4; 95% CI, 0.8 to 2.4; DFS OR=1.6; 95% CI, 0.8 to 3.3); however, relapse rates were lower for allo-HCT (OR=0.4, 95% CI, 0.2 to 0.7).

Willemze et al (2014) conducted a randomized trial in 1942 patients newly diagnosed with AML, ages 15 to 60 years, to compare remission induction treatment containing standard or high-dose cytarabine. In both arms, patients who achieved CR received consolidation therapy with either autologous HCT or allo-HCT. Patients were subclassified as good risk, intermediate risk, bad risk, very bad risk, or unknown risk, according to cytogenetics and *FLT3*-ITD variant. Testing for *FLT3*-ITD variants showed that, in the standard-dose cytarabine group, 50% were negative, 13% were positive, and 37% were indeterminate. In the high-dose cytarabine group, 48% were negative, 14% were positive, and 38% were indeterminate. All patients with an *FLT3*-ITD variant were categorized as very bad risk. OS at 6 years in the patients categorized as very bad risk was 20% in the standard cytarabine group and 31% in the high-dose group (hazard ratio [HR]=0.70; 95% CI, 0.47 to 1.04; p=0.02). Trialists concluded that patients with very bad risk cytogenetics and/or *FLT3*-ITD variants benefitted from high-dose cytarabine induction treatment.

Chou et al (2014) retrospectively analyzed 325 adults with AML to determine the prognostic significance of 8 variants, including *CEBPA*, *FLT3*-ITD, and *NPM1*, on OS between patients who received allo-HCT (n=100) and those who did not (n=255). Karyotype included favorable (i.e., variant *CEBPA* or NPM1 but without *FLT3*-ITD; -n=51), intermediate (n=225), and unfavorable (n=40). Patients were selected from a single Taiwanese hospital between 1995 and 2007. Pediatric patients and those receiving only supportive care were excluded from the study. Patients received induction chemotherapy followed by allo-HCT, or consolidation chemotherapy for those patients who did not achieve CR. In the non-allo-HCT patients, *NPM1*/*FLT3*-ITD WT (HR=0.363; 95% CI, 0.188 to 0.702; p=0.003) and *CEBPA* double variant (HR=0.468; 95% CI, 0.265 to 0.828; p=0.009) were significant good prognostic factors of OS in a multivariate analysis. None of the other gene variants had a significant impact on OS in the HCT and non-HCT groups in the multivariate analysis. Authors presented survival curves stratified by *CEBPA* and *FLT3*-ITD variants and found that, in the non-HCT group, *CEBPA* and *FLT3*-ITD WT variants were prognostic of improved OS (p=0.008 and p=0.001, respectively), but, in the allo-HCT group, neither variant had a prognostic effect. The inability to detect variants of prognostic significance in the HCT group could have been due to the small number of patients with the studied variants (*CEBPA*=9, *NPM1*=13, *FLT3*-ITD=25).

Section Summary: Clinical Utility
There is no direct evidence of clinical utility. A chain of evidence for clinical utility can be constructed from retrospective analyses suggesting that risk stratification by *NPM1, FLT3*-ITD, or *CEBPA* variants can help guide therapy decisions that are associated with improved outcomes. Patients with favorable prognosis, including those with *NPM*1 variants without *FLT3*-ITD variant or double-mutation *CEBPA*, may not derive an OS benefit with allo-HCT. Treatment of patients with intermediate or poor prognosis, including *FLT3*-ITD variant, depends on several risk factors but HCT may improve outcomes.

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

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SUMMARY OF EVIDENCE

For individuals who have CN-AML who receive genetic testing for variants in *FLT3*, *NPM1*, *CEBPA* to risk-stratify AML, the evidence includes retrospective observational studies and systematic reviews of these studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, and treatment-related mortality and morbidity. *FLT3* ITD(*FLT3*-ITD) variants confer a poor prognosis, whereas *NPM1* (without *FLT3*-ITD variant) and biallelic *CEBPA* variants confer a favorable prognosis. The prognostic effect of *FLT3* TKD variants is uncertain. Data have suggested an OS benefit with transplantation for patients with *FLT3*-ITD, but do not clearly demonstrate an OS 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.

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Policy History

Original Effective Date: 01/21/2015
Current Effective Date: 01/17/2018
01/08/2015 Medical Policy Committee review
01/21/2015 Medical Policy Implementation Committee approval. New policy.

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

Policy # 00459
Original Effective Date: 01/21/2015
Current Effective Date: 01/17/2018

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

Next Scheduled Review Date: 01/2019

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 2017 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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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0023U, 81218, 81245, 81246, 81310, 81403, 81450 Codes added eff date 07/01/2018: 0046U, 0049U, 0050U
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.

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