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: 01/23/2019

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 (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.

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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 (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, three 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 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, vs 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
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Genetic testing for FLT3, NPM1, and CEBPA variants in cytogenetically normal acute myeloid leukemia (AML) patients 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 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 vs 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 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 (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 complete remission and overall 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 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 U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

In May 2017, the Food and Drug Administration 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).

**Centers for Medicare and Medicaid Services (CMS)**

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.

**Rationale/Source**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**TESTING FOR FLT3, NPM1, AND CEBPA VARIANTS TO RISK-STRATIFY ACUTE MYELOID LEUKEMIA**

**Clinical Context and Test Purpose**

Optimal decisions regarding treatment intensity and chemotherapy-based consolidation therapy vs allogeneic transplantation remain unclear in cytogenetically normal acute myeloid leukemia (CN-AML). The
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The purpose of genetic testing in patients who have CN-AML is to provide prognostic risk stratification information 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 vs 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 the risk of recurrence but is typically associated with at least a 20% treatment-related mortality risk.

Side effects of FLT3 inhibitors (eg, sorafenib, sunitinib, midostaurin, lestaurtinib, quizartinib) include QT prolongation, nausea, vomiting, diarrhea, anemia, abnormal liver function tests, increased bilirubin, fever, and fatigue. Currently the FLT3 inhibitor midostaurin has been approved by the Food and Drug Administration to be used in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. 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.

**Interventions**
The intervention of interest is testing for FLT3, NMP1, or CEBPA variants.

**Comparators**
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**
The assays can be conducted during diagnostic evaluation, to aid in the treatment decision process.
Setting
Decisions about management of AML are generally made by patients and hematologists or oncologists in the secondary or tertiary care setting.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Prognosis of patients with FLT3 internal tandem duplication (ITD), NMP1, or CEBPA variants compared with 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.
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## Table 1. Survival Outcomes of Patients With FLT3-ITD, NMP1, or CEBPA Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Port et al (2014)</td>
<td>Systematic review of 19 studies published between 2000 and 2012, with 4 studies included in the meta-analysis</td>
<td>1942 patients with CN-AML &lt;60 y in meta-analysis</td>
<td>FLT3-ITD WT vs FLT3-ITD variant:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• OS HR=1.9 (95% CI, 1.6 to 22)</td>
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<td></td>
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<td>• RFS HR=1.8 (95% CI, 1.5 to 2.2)</td>
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<td><strong>NPM1</strong> WT vs NPM1 variant:</td>
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<td></td>
<td>• OS HR=0.6 (95% CI, 0.5 to 0.7)</td>
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<td></td>
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<td></td>
<td>• RFS HR=0.6 (95% CI, 0.5 to 0.6)</td>
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<td><strong>CEBPA</strong> WT vs CEBPA variant:</td>
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<td></td>
<td>• OS HR=0.4 (95% CI, 0.3 to 0.5)</td>
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<td></td>
<td></td>
<td></td>
<td>• RFS HR=0.4 (95% CI, 0.3 to 0.6)</td>
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<td></td>
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<td></td>
<td>• CEBPA monoallelic vs WT</td>
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<td></td>
<td></td>
<td></td>
<td>• OS HR=1.1 (95% CI, 0.9 to 1.5)</td>
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<td></td>
<td></td>
<td></td>
<td>• EFS HR=1.1 (95% CI, 0.8 to 1.5)</td>
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<td></td>
<td></td>
<td></td>
<td>• CEBPA biallelic vs WT</td>
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<td></td>
<td></td>
<td></td>
<td>• OS HR=0.4 (95% CI, 0.3 to 0.5)</td>
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<td></td>
<td>• EFS HR=0.4 (95% CI, 0.3 to 0.5)</td>
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<td><strong>CN-AML:</strong></td>
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<td></td>
<td>• CEBPA monoallelic vs WT</td>
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<td></td>
<td></td>
<td></td>
<td>• OS HR=1.1 (95% CI, 0.9 to 1.5)</td>
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<td></td>
<td>• EFS HR=0.9 (95% CI, 0.7 to 1.2)</td>
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<td></td>
<td></td>
<td></td>
<td>• CEBPA biallelic vs WT</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• OS HR=0.3 (95% CI, 0.2 to 0.4)</td>
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<td></td>
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<td></td>
<td>• EFS HR=0.4 (95% CI, 0.3 to 0.5)</td>
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<tr>
<td>Dickson et al (2016)</td>
<td>Retrospective analysis of patients enrolled in an RCT between 1990 and 1998</td>
<td>662 AML patients &gt;60 y</td>
<td>1-y OS:</td>
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<tr>
<td></td>
<td></td>
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<td>• CEBPA, biallelic: 75%</td>
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<td>• NPM1 variant, FLT3-ITD WT: 54%</td>
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<td></td>
<td>• All others: 33%</td>
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<td>3-y OS:</td>
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<td></td>
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<td>• CEBPA, biallelic: 17%</td>
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<td>• NPM1 variant, FLT3-ITD WT: 29%</td>
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<td></td>
<td></td>
<td>• All others: 12%</td>
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<td></td>
<td></td>
<td></td>
<td>• OS HR=2.2 (95% CI, 1.6 to 3.0)</td>
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<td></td>
<td>• EFS HR=1.7 (95% CI, 1.4 to 2.1)</td>
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<tr>
<td>Kuwatsuka et al (2017)</td>
<td>Retrospective analysis of patients enrolled in 2 clinical trials between 2001 and 2010</td>
<td>103 adolescent and young adults (age range, 15-39 y) with AML</td>
<td>FLT3-ITD WT vs FLT3-ITD variant:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• OS HR=2.1 (95% CI, 1.1 to 4.1)</td>
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<td></td>
<td></td>
<td>• EFS HR=2.4 (95% CI, 1.3 to 4.2)</td>
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<td></td>
<td><strong>NPM1</strong> WT vs NPM1 variant:</td>
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<tr>
<td></td>
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<td></td>
<td>• OS HR=0.2 (95% CI, 0.06 to 1.0)</td>
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<tr>
<td></td>
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<td>• RFS HR=0.2 (95% CI, 0.09 to 0.7)</td>
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</tbody>
</table>
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Section Summary: Clinically Valid
The FLT3-ITD variant is quite common in AML, particularly in patients with normal karyotypes, and has been associated with poorer survival (overall, event-free, and recurrence-free) in children, younger adults, and older adults. The prognostic effect of FLT3 tyrosine kinase domain variants is uncertain. NPM1 variants are found in approximately half of the 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 an 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 (biallelic).

Clinically Useful
A test is clinically useful if use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The literature on the use of genetic markers consists mostly of retrospective analyses, with randomized controlled trials (RCTs) published in 2016 and 2017.

Retrospective Studies
Literature from retrospective analyses 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 the populations 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. Retrospective Analyses of Results by Treatment of Patients With and Without Genetic Variants

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlenk et</td>
<td>Retrospective</td>
<td>872 adults &lt;60 y with CN-AML, 53% NPM1 variant, 31% FLT3-ITD variant, 11% FLT3-TKD variant, 13% CEBPA variant</td>
<td>Allo-HCT vs other consolidation therapy:</td>
</tr>
<tr>
<td></td>
<td>analysis of patients in 4 AML therapy RCTs conducted between 1993 and 2004</td>
<td></td>
<td>• NPM1 without FLT3-ITD</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis of patients in 4 AML therapy RCTs conducted between 1993 and 2004</td>
<td></td>
<td>• Relapse rate HR=0.9 (0.5 to 1.8)</td>
</tr>
<tr>
<td></td>
<td>Retrospective analysis of patients in 4 AML therapy RCTs conducted between 1993 and 2004</td>
<td></td>
<td>Other genotypes (excluding CEBPA, NPM1 without FLT3-ITD):</td>
</tr>
<tr>
<td></td>
<td>124 adults &lt;60 y with</td>
<td></td>
<td>• Relapse rate HR=0.6 (0.4 to 0.9)</td>
</tr>
<tr>
<td>Schlenk et</td>
<td>Retrospective</td>
<td>Allo-HCT vs chemo:</td>
<td></td>
</tr>
<tr>
<td>et al (2008)</td>
<td>124 adults &lt;60 y with</td>
<td></td>
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</tbody>
</table>

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### Study Design Participants Outcomes Estimate (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>al (2013)</td>
<td>analysis of patients in 7 AML therapy RCTs conducted between 1987 and 2009</td>
<td>CN-AML who were CEBPA biallelic and had CR after induction therapy</td>
<td>RFS HR=0.2 (0.1 to 0.5) &lt;br&gt; OS HR=0.5 (0.2 to 1.2)  &lt;br&gt; Auto-HCT vs chemo:  &lt;br&gt; RFS HR=0.4 (0.2 to 0.8)  &lt;br&gt; OS HR=0.6 (0.2 to 1.4)</td>
</tr>
<tr>
<td>Willemze et al (2014)</td>
<td>Retrospective analysis of EORTC-GIMEMA AML-12 RCT conducted between 1999 and 2008</td>
<td>613 patients with AML, ages 15-60 y; 126 (21%) FLT3-ITD variant</td>
<td>Patients with FLT3-ITD variant categorized as very bad risk:  &lt;br&gt; OS at 6 y in patients at very bad risk 20% in standard cytarabine group vs 31% in high-dose group:  &lt;br&gt; HR=0.70 (0.47 to 1.04)</td>
</tr>
<tr>
<td>Chou et al (2014)</td>
<td>Retrospective analysis of patients from Taiwanese university hospital between 1995 and 2007</td>
<td>325 adults with AML who received conventional induction chemo; 81 (25%) FLT3-ITD, 69 (21%) NPM1, 33 (10%) NPM1 with FLT3-ITD WT, 42 (13%) CEBPA biallelic</td>
<td>Non-allo-HCT:  &lt;br&gt; CEBPA biallelic vs other:  &lt;br&gt; OS HR=0.5 (0.3 to 0.8)  &lt;br&gt; NPM1 variant with FLT3-ITD WT:  &lt;br&gt; OS HR=0.4 (0.2 to 0.7)  &lt;br&gt; Allo-HCT:  &lt;br&gt; CEBPA biallelic vs other:  &lt;br&gt; OS HR=0.3 (0.1 to 1.2)  &lt;br&gt; NPM1 variant with FLT3-ITD WT:  &lt;br&gt; OS HR=NR</td>
</tr>
<tr>
<td>Ma et al (2015)</td>
<td>Systematic review of 9 studies of chemo vs HCT published between 1989 and 2013</td>
<td>Patients with AML, FLT3-ITD variant</td>
<td>Allo-HCT vs chemo:  &lt;br&gt; OS OR=2.9 (2.0 to 4.1)  &lt;br&gt; DFS OR=2.8 (1.9 to 4.3)  &lt;br&gt; Relapse rate OR=0.1 (0.05 to 0.2)</td>
</tr>
<tr>
<td>Tarlock et al (2016)</td>
<td>Retrospective analysis of 2 AML RCTs conducted between 2003 and 2005</td>
<td>183 children with AML, FLT3-ITD variant who received standard chemo and HCT</td>
<td>Standard chemo with vs without gemtuzumab ozogamicin:  &lt;br&gt; Overall  &lt;br&gt; Relapse rate, 37% vs 59% (p=0.02)  &lt;br&gt; DFS=47% vs 41% (p=0.45)  &lt;br&gt; TRM=16% vs 0% (p=0.008)  &lt;br&gt; Patients with high FLT3-ITD allelic ratio  &lt;br&gt; Relapse rate, 15% vs 53% (p=0.007)  &lt;br&gt; DFS 65% vs 40% (p=0.08)  &lt;br&gt; TRM=19% vs 7% (p=0.08)</td>
</tr>
<tr>
<td>Ahn et al (2016)</td>
<td>Retrospective analysis of patients from 7 institutions in South Korea from 1998 to 2012</td>
<td>404 CN-AML patients ages ≥15 y treated with conventional induction chemo; 51 (13%) CEBPA biallelic</td>
<td>Overall, by CEBPA:  &lt;br&gt; 5-y OS biallelic, 62% (43% to 82%)  &lt;br&gt; 5-y OS monoallelic, 44% (19% to 69%)  &lt;br&gt; 5-y OS WT=26% (19% to 32%)  &lt;br&gt; Biallelic vs others:  &lt;br&gt; HR=0.4 (p=0.001)  &lt;br&gt; Among CEBPA biallelic:  &lt;br&gt; Chemo:</td>
</tr>
</tbody>
</table>
### Study Design Participants Outcomes Estimate (95% CI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>5-y OS=60% (40% to 81%)</th>
<th>5-y EFS=39% (15% to 64%)</th>
<th>5-y relapse incidence, 38% (17% to 59%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunner et al (2016)</td>
<td>Retrospective analysis of patients at 2 U.S. institutions between 2008 and 2014</td>
<td>81 consecutive AML patients who underwent FLT3-ITD testing who achieved CR with induction chemo followed by allo-HCT</td>
<td>Sorafenib maintenance therapy vs no sorafenib</td>
<td>2-y OS=81% vs 62%; HR=0.3 (0.1 to 0.8)</td>
<td>2-y PFS=82% vs 53%; HR=0.3 (0.1 to 0.8)</td>
</tr>
<tr>
<td>Versluis et al (2017)</td>
<td>Retrospective analysis of patients from 4 trials who achieved CR after 1 or 2 induction chemo cycles</td>
<td>Intermediate risk patients receiving the following postremission treatment: chemo (n=148); auto-HCT (n=168); allo-HCT with MAC (n=137); and allo-HCT with RIC (n=68)</td>
<td>Auto-HCT vs chemo: no difference in OS, RFS, relapse, or NRM</td>
<td>Allo-HCT with MAC vs chemo: no difference in OS</td>
<td>Allo-HCT with MAC vs auto-HCT: no difference in OS or RFS</td>
</tr>
</tbody>
</table>

Ma et al (2015) performed a systematic review including 7 studies published up to December 2012 that described use of HCT or chemotherapy in patients with AML in first complete remission who had FLT3-ITD

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variants. All studies were retrospective or nonrandomized controlled analyses. Allo-HCT was associated with a longer OS (OR=2.9; 95% CI, 2.0 to 4.1), longer disease-free survival (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 with chemotherapy. OS and disease-free survival 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; disease-free survival 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 complete remission 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 (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 benefited 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 (ie, 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 complete remission. In the non-allo-HCT patients, NPM1 variant/FLT3-ITD wild-type (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 wild-type 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).

**Prospective Studies**

In 2017, Knapper et al published results from 2 RCTs in which patients with previously untreated AML and confirmed FLT3 variants were randomized to lestaurtinib (an FLT3 inhibitor) or a placebo following each of 4 cycles of induction and consolidation chemotherapy (see Table 3). Patients with ITD subtype (74%), tyrosine kinase domain subtype (23%), and both subtypes (2%) were included. There were no significant differences in remission or survival estimates between treatment groups (see Table 4).
Genetic Testing for \textit{FLT3}, \textit{NPM1}, and \textit{CEBPA} Variants in Cytogenetically Normal Acute Myeloid Leukemia

Policy # 00459  
Original Effective Date: 01/21/2015  
Current Effective Date: 01/23/2019

In 2017, Stone et al published results from an RCT in which patients with previously untreated AML and confirmed \textit{FLT3} variants were randomized to standard chemotherapy with or without midostaurin (see Table 3). Patients with ITD (77%), and tyrosine kinase domain (23%) subtypes were included. The addition of midostaurin did not affect complete remission rates or time to complete remission; however, overall and event-free survival were significantly better in the midostaurin group than in the placebo group (see Table 4).

### Table 3. Summary of RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Active</th>
<th>Comparator</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knapper et al (2017)</td>
<td>England, Denmark, New Zealand</td>
<td>&gt;130</td>
<td>May 2002 to Dec 2014</td>
<td>Patients with previously untreated AML and confirmed \textit{FLT3} variants, mostly &lt;60 y</td>
<td>n=300</td>
<td>n=200</td>
<td>4 cycles of induction and consolidation chemotherapy, followed by lestaurtinib (\textit{FLT3} inhibitor)</td>
</tr>
</tbody>
</table>

Table 4. Summary of RCT Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Active</th>
<th>Control</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knapper et al (2017)</td>
<td>CR + CRi</td>
<td></td>
<td></td>
<td>1.4 (0.7 to 2.8)</td>
</tr>
<tr>
<td></td>
<td>5-y overall survival</td>
<td>NR</td>
<td>NR</td>
<td>0.9 (0.7 to 1.1)</td>
</tr>
<tr>
<td></td>
<td>5-y overall survival, censored at SCT</td>
<td>NR</td>
<td>NR</td>
<td>0.9 (0.7 to 1.3)</td>
</tr>
<tr>
<td></td>
<td>5-y cumulative incidence, relapse</td>
<td>NR</td>
<td>NR</td>
<td>0.9 (0.7 to 1.1)</td>
</tr>
<tr>
<td></td>
<td>5-y cumulative incidence, death in remission</td>
<td>NR</td>
<td>NR</td>
<td>1.1 (0.6 to 2.0)</td>
</tr>
<tr>
<td></td>
<td>5-y relapse-free survival</td>
<td>NR</td>
<td>NR</td>
<td>0.9 (0.7 to 1.1)</td>
</tr>
<tr>
<td>Stone et al (2017)</td>
<td>CR rate (95% CI)</td>
<td>59 (54 to 64)</td>
<td>54 (48 to 60)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Time to complete remission (range), median days</td>
<td>35 (20-60)</td>
<td>35 (20-60)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Overall survival (95% CI), median months</td>
<td>75 (31 to NR)</td>
<td>26 (19 to 43)</td>
<td>0.8 (0.6 to 1.0)</td>
</tr>
<tr>
<td></td>
<td>Event-free survival (95% CI), median months</td>
<td>8.2 (5 to 11)</td>
<td>3 (2 to 6)</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

CI: confidence interval; CR: complete remission; CRi: complete remission with incomplete peripheral blood count recovery; HR: hazard ratio; NR: not reported; NS: not significant; RCT: randomized controlled trial; SCT: stem cell transplantation.

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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: 01/23/2019

Section Summary: Clinically Useful
There are 2 RCTs providing direct evidence of clinical utility, randomizing patients with AML and confirmed FLT3 variants to different treatments. One RCT evaluated the addition of an FLT3 inhibitor, and one tested the addition of midostaurin to the chemotherapy regimen. No significant difference between treatment groups was found with the addition of the FLT3 inhibitor, while the addition of midostaurin significantly improved OS and event-free survival compared with placebo. Additionally, a chain of evidence for clinical utility can be constructed from retrospective analyses suggesting that risk stratification (favorable, intermediate, and poor) based on the presence of NPM1, FLT3-ITD, or CEBPA variants can help guide therapy decisions that are associated with improved outcomes. Patients with a favorable prognosis, including those who have NPM1 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.

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 randomized controlled trials, retrospective observational studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related mortality and morbidity. FLT3-ITD variants confer a poor prognosis, whereas NPM1 (without the FLT3-ITD 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-ITD, 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.

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

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Policy History
Original Effective Date: 01/21/2015
Current Effective Date: 01/23/2019
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

Next Scheduled Review Date: 01/2020

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<tr>
<th>Code Type</th>
<th>Code</th>
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<td>CPT</td>
<td>0023U, 81218, 81245, 81246, 81310, 81403, 81450</td>
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<td>Codes added eff date 07/01/2018: 0046U, 0049U, 0050U</td>
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<tr>
<td>HCPCS</td>
<td>No codes</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>C92.00-C92.02, C92.20-C92.22, C92.40-C92.42, C92.50-C92.52, C92.60-C92.62, C92.A0-C92.A2</td>
</tr>
</tbody>
</table>

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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

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