Policy Statement

Genetic testing for FLT3 internal tandem duplication (FLT3-ITD), NPM1, and CEBPA variants may be considered **medically necessary** in cytogenetically normal acute myeloid leukemia (see Policy Guidelines section).

Genetic testing for FLT3 internal tandem duplication (FLT3-ITD), NPM1, and CEBPA variants is considered **investigational** in all other situations.

Genetic testing for FLT3 tyrosine kinase domain (FLT3-TKD) variants is considered **investigational**.

Genetic testing for FLT3, NPM1, and CEBPA variants to detect minimal residual disease is considered **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.

**Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Coding**

There is specific CPT coding for the following testing:

- **0023U**: Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin (New code effective 10/01/17)
- **81218**: CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence
- **81245**: FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)
- **81246**: FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)
- **81310**: NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants

Effective July 1, 2018, there are several new PLA codes established for this type of testing:

- **0046U**: FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative. This code is for FLT3 ITD MRD by NGS, LabPMM LLC.
• **0049U**: NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, quantitative. This code is for NPM1 MRD by NGS by LabPMM LLC

• **0050U**: Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements. This code is for MyAML NGS Panel by LabPMM LLC

• **0056U**: Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s). This code is for MatePair Acute Myeloid Leukemia Panel by Mayo Clinic

**Description**

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.

**Related Policies**

• Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

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).
Rationale

Background
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 21380 new cases of AML and 10590 deaths from AML in the United States in 2017.1,

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 clinicopathologic-genetic entities with diagnostic, prognostic, and therapeutic implications.2 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 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.3.

Recent reviews (2012-2014) have highlighted the evolving classification of AML into distinct molecular subtypes.4,5,6,7,

Treatment
AML has a highly heterogeneous clinical course, and treatment generally depends on the different risk stratification categories.4 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.4,

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.8, FLT3 variants are divided into two 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 normal- or intermediate-risk cytogenetics, and are associated with an increased risk of relapse and inferior overall survival.8,9,10. 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.8. 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.8

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.8

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 zero, one, or two 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.8 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.8. Higher mutant-to-WT allelic ratios have been associated with worse outcomes.8

The prognostic impact of FLT3-TKD variants is less certain and has only been studied in small numbers of patients.8,11. 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.4 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.8 The prognostic impact in patients with an abnormal karyotype is unclear.4

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.12,13,14. 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.15,16.
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 (CN-AML). 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 the 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/m² 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 (e.g., 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 the 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 three 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 the 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 the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predict 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.

**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>FLT3-ITD WT vs FLT3-ITD variant:</th>
</tr>
</thead>
</table>
| Port et al (2014)¹⁷ | Systematic review of 19 studies published between 2000 and 2012, with 4 studies included in the meta-analysis | 1942 patients with CN-AML <60 y in meta-analysis | OS HR=1.9 (95% CI, 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)  

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al (2015)\textsuperscript{16}</td>
<td>Systematic review of 10 studies published before Aug 2014</td>
<td>6219 patients with AML</td>
<td>Any AML:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• CEBPA monoallelic vs WT</td>
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<td></td>
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<td></td>
<td>o OS HR=1.1 (95% CI, 0.9 to 1.5)</td>
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<td>o EFS HR=1.1 (95% CI, 0.8 to 1.5)</td>
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<td>• CEBPA biallelic vs WT:</td>
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<td>o OS HR=0.4 (95% CI, 0.3 to 0.5)</td>
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<td>o EFS HR=0.4 (95% CI, 0.3 to 0.5)</td>
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<td>CN-AML:</td>
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<td></td>
<td></td>
<td></td>
<td>• CEBPA monoallelic vs WT:</td>
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<tr>
<td></td>
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<td></td>
<td>o OS HR=1.1 (95% CI, 0.9 to 1.5)</td>
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<td>o 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>
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<td></td>
<td>o 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>o EFS HR=0.4 (95% CI, 0.3 to 0.5)</td>
</tr>
<tr>
<td>Dickson et al (2016)\textsuperscript{18}</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>
<td></td>
<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>• 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></td>
<td>• All others: 12%</td>
</tr>
<tr>
<td>Wu et al (2016)\textsuperscript{19}</td>
<td>Systematic review of 10 cohort studies published between 1995 and 2015</td>
<td>1661 pediatric patients with AML</td>
<td>FLT3-ITD WT vs FLT3-ITD variant:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• OS HR=2.2 (95% CI, 1.6 to 3.0)</td>
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<td>• EFS HR=1.7 (95% CI, 1.4 to 2.1)</td>
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<tr>
<td>Kuwatsuka et al (2017)\textsuperscript{20}</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>• EFS HR=2.4 (95% CI, 1.3 to 4.2)</td>
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<td>• NPM1 WT vs NPM1 variant:</td>
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<td></td>
<td>o OS HR=0.2 (95% CI, 0.06 to 1.0)</td>
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<td>o RFS HR=0.2 (95% CI, 0.09 to 0.7)</td>
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</tbody>
</table>

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

**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 two copies of the mutant allele (biallelic).

**Clinically Useful**

A test is clinically useful if the use of the results informs 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 RCTs published in 2016 and 2017.

**Randomized Controlled Trials**

Knapper et al (2017) 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).

Stone et al (2017) published results from an RCT in which patients with previously untreated AML and confirmed FLT3 variants were randomized to standard chemotherapy with or without midostaurin (see Table 2). 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 was significantly better in the midostaurin group than in the placebo group (see Table 3).

### Table 2. Summary of RCT Characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knapper et al(2017)²¹</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 FLT3 variants, mostly &lt;60 y</td>
<td>• n=300&lt;br&gt;• 4 cycles of induction and consolidation chemotherapy, followed by lestaurtinib (FLT3 inhibitor)</td>
<td>• n=200&lt;br&gt;• 4 cycles of induction and consolidation chemotherapy, followed by placebo</td>
</tr>
<tr>
<td>Stone et al (2017)²²</td>
<td>17 in North America, Europe, Australia</td>
<td>225</td>
<td>May 2008 to Oct 2011</td>
<td>Patients with previously untreated AML and confirmed FLT3 variants, 18-59 y</td>
<td>• n=360&lt;br&gt;• Standard chemotherapy plus midostaurin (kinase inhibitor)</td>
<td>• n=357&lt;br&gt;• Standard chemotherapy plus placebo</td>
</tr>
</tbody>
</table>

AML: acute myeloid leukemia; RCT: randomized controlled trial.

### Table 3. 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)²¹</td>
<td>CR + CRi</td>
<td>1.4 (0.7 to 2.8)</td>
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<tr>
<td></td>
<td>5-y overall survival</td>
<td>NR</td>
<td>NR</td>
<td>0.9 (0.7 to 1.1)</td>
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<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>
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<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>
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<tr>
<td>Stone et al (2017)²²</td>
<td>CR rate (95% CI)</td>
<td>59 (54 to 64)</td>
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<tr>
<td></td>
<td>Time to complete remission (range), median days</td>
<td>35 (20-60)</td>
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<td>Overall survival (95% CI), median months</td>
<td>75 (31 to NR)</td>
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<tr>
<td></td>
<td>Event-free survival (95% CI), median months</td>
<td>8.2 (5 to 11)</td>
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</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.

### 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 4. 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.⁸
Table 4. 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>
</table>
| Schlenk et al (2008)²³       | 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  
  - Relapse rate HR=0.9 (0.5 to 1.8)  
  Other genotypes (excluding CEBPA, NPM1 without FLT3-ITD):  
  - Relapse rate HR=0.6 (0.4 to 0.9) |
| Schlenk et al (2013)²⁴       | Retrospective analysis of patients in 7 AML therapy RCTs conducted between 1987 and 2009 | 124 adults <60 y with CN-AML who were CEBPA biallelic and had CR after induction therapy | Allo-HCT vs chemo:  
  - RFS HR=0.2 (0.1 to 0.5)  
  - OS HR=0.5 (0.2 to 1.2)  
  Auto-HCT vs chemo:  
  - RFS HR=0.4 (0.2 to 0.8)  
  - OS HR=0.6 (0.2 to 1.4) |
| Willemze et al (2014)²⁵      | Retrospective analysis of EORTC-GIMEMA AML-12 RCT conducted between 1999 and 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 (0.47 to 1.04) |
| Chou et al (2014)²⁶          | Retrospective analysis of patients from Taiwanese university hospital between 1995 and 2007 | 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 | Non-allo-HCT:  
  - CEBPA biallelic vs other  
  - OS HR=0.5 (0.3 to 0.8)  
  - NPM1 variant with FLT3-ITD WT:  
  - OS HR=0.4 (0.2 to 0.7)  
  Allo-HCT:  
  - CEBPA biallelic vs other:  
  - OS HR=0.3 (0.1 to 1.2)  
  - NPM1 variant with FLT3-ITD WT:  
  - OS HR=NR |
  - OS OR=2.9 (2.0 to 4.1)  
  - DFS OR=2.8 (1.9 to 4.3)  
  - Relapse rate OR=0.1 (0.05 to 0.2) |
| Tarlock et al (2016)²⁸       | Retrospective analysis of 2 AML RCTs conducted between 2003 and 2005 | 183 children with AML, FLT3-ITD variant who received standard chemo and HCT | Standard chemo with vs without gemtuzumab ozogamicin:  
  - Overall  
  - Relapse rate, 37% vs 59% (p=0.02)  
  - DFS=47% vs 41% (p =0.45)  
  - TRM=16% vs 0% (p=0.008)  
  - Patients with high FLT3-ITD allelic ratio  
  - Relapse rate, 15% vs 53% (p=0.007)  
  - DFS 65% vs 40% (p=0.08)  
  - o TRM=19% vs 7% (p=0.08)  
  Overall, by CEBPA:  
  - 5-y OS biallelic, 62% (43% to 82%)  
  - 5-y OS monoallelic, 44% (19% to 69%)  
  - 5-y OS WT=26% (19% to 32%)  
  Biallelic vs others:  
  - HR=0.4 (p =0.001)  
  Among CEBPA biallelic:  
  - Chemo:  
    - 5-y OS=60% (40% to 81%)  
    - 5-y EFS=39% (15% to 64%)  
    - 5-y relapse incidence, 38% (17% to 59%)  
  - Allo-HCT:  
    - 5-y OS=72% (54% to 90%) |
Ma et al (2015)\(^{27}\) performed a systematic review including 7 studies\(^{22,32,33,34,35,36,37,38}\) published up to December 2012 that described the use of HCT or chemotherapy in patients with AML in the first complete remission who had FLT3-ITD 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 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 with 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).

Willemsen 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.\(^{25}\) In both arms, patients who achieved complete remission received consolidation therapy with either autologous HCT or allo-HCT. Patients were subclassified as a 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 30% were indeterminate. All patients with an FLT3-ITD variant were categorized as a 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 (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 complete remission. In the non-allo-HCT patients, NPM1 variant/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: Clinically Useful
There are two 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 RCTs, retrospective observational studies, and systematic reviews of these studies. The relevant outcomes are OS, disease-specific survival, test 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 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.

Supplemental Information
Practice Guidelines and Position Statements

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (v.1.2018) provide the following recommendations¹:
  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). Currently, c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1/IDH2, and TP53 are included in this group; however, this field is evolving rapidly. While the above mutations should be tested in all patients, multiplex gene panels and next generation sequencing analysis may be used to obtain a more comprehensive prognostic assessment."

The guideline defined the following risk status based on molecular abnormalities:
- NPM1 without FLT3-ITD: favorable risk
- Isolated biallelic CEBPA: favorable risk
- FLT3-ITD: poor risk.

**European LeukemiaNet**

The 2010 European LeukemiaNet 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 5 outlines the risk stratification by genetic variants, and Table 6 summarizes recommended conventional care regimens based on risk category and age.

**Table 5. Risk Stratification by Genetic Variant**

<table>
<thead>
<tr>
<th>Genetic Variant</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biallelic CEBPA</td>
<td>Favorable</td>
</tr>
<tr>
<td>Mutated NPM1 without FLT3-ITD</td>
<td>Favorable</td>
</tr>
<tr>
<td>Mutated NPM1 with FLT3-ITD (low allelic ratio)</td>
<td>Favorable</td>
</tr>
<tr>
<td>Mutated NPM1 with FLT3-ITD (high allelic ratio)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Wild-type NPM1 without FLT3-ITD</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Wild-type NPM1 with FLT3-ITD (low allelic ratio)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Wild-type NPM1 with FLT3-ITD (high allelic ratio)</td>
<td>Adverse</td>
</tr>
</tbody>
</table>


**Table 6. Conventional Care Regimens by Risk and Age Categories**

<table>
<thead>
<tr>
<th>Risk and Age Categories</th>
<th>Conventional Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients 18 to 60/65 years</td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>2 to 4 cycles intermediate-dose cytarabine</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Allogeneic HCT from matched related or unrelated donor</td>
</tr>
<tr>
<td></td>
<td>2 to 4 cycles intermediate-dose cytarabine</td>
</tr>
<tr>
<td></td>
<td>High-dose therapy and autologous HCT</td>
</tr>
<tr>
<td>Adverse</td>
<td>Allogeneic HCT from matched related or unrelated donor</td>
</tr>
<tr>
<td>Patients &gt;60/65 years</td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>2 to 3 cycles intermediate-dose cytarabine</td>
</tr>
<tr>
<td>Intermediate/adverse</td>
<td>Consider allogeneic HCT from matched related or unrelated donor</td>
</tr>
<tr>
<td></td>
<td>Investigational therapy</td>
</tr>
</tbody>
</table>


**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 7.

Table 7. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>NCT02474290</td>
<td>Sorafenib for Prophylaxis of Leukemia Relapse in Allogeneic Hematopoietic Stem Cell Transplant Recipients With FLT3-ITD Positive Acute Myeloid Leukemia</td>
<td>196</td>
<td>Aug 2018</td>
</tr>
<tr>
<td>NCT02039726a</td>
<td>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 HSC/T consolidation</td>
<td>367</td>
<td>Jul 2019</td>
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<tr>
<td>NCT01296178</td>
<td>First Line Treatment Adapted To Risk Of Acute Myeloblastic Leukemia In Patients Less Than Or Equal To 65 Years</td>
<td>200</td>
<td>Dec 2019</td>
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<tr>
<td>NCT01237808</td>
<td>Study of Low-Dose Cytarabine and Etoposide With or Without All-Trans Retinoic Acid in Older Patients Not Eligible for Intensive Chemotherapy With Acute Myeloid Leukemia and NPM1 Mutation</td>
<td>144</td>
<td>Jul 2018</td>
</tr>
<tr>
<td>NCT02156297</td>
<td>Sorafenib to Treat AML Patients with FLT3-ITD Mutation, a Non-interventional Cohort Study</td>
<td>100</td>
<td>Aug 2019</td>
</tr>
<tr>
<td>NCT01477606a</td>
<td>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 a FLT3 internal Tandem Duplication</td>
<td>440</td>
<td>Jun 2020</td>
</tr>
<tr>
<td>NCT00893399</td>
<td>Phase III Study of Chemotherapy in Combination With ATRA With or Without Gemtuzumab Ozogamicin in Patients With Acute Myeloid Leukemia and NPM1 Gene Mutation</td>
<td>588</td>
<td>Jul 2020</td>
</tr>
<tr>
<td>NCT02668653a</td>
<td>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 (+) AML</td>
<td>536</td>
<td>Nov 2020</td>
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<tr>
<td>NCT03031249</td>
<td>Efficacy and Safety of ATO Plus ATRA in Nucleophosmin-1 Mutated Acute Myeloid Leukemia</td>
<td>250</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT02927262a</td>
<td>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</td>
<td>354</td>
<td>Mar 2024</td>
</tr>
<tr>
<td>NCT00860639a</td>
<td>Randomized Open Phase III Trial Testing Efficacy of Gemtuzumab Ozogamicin Associated to Intensive Chemotherapy for Patients Aged Between 18-60 Years and Presenting an AML With Intermediate Risk</td>
<td>327</td>
<td>Sep 2016 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a Denotes industry-sponsored or cosponsored trial.

References


NPM1 and CEBPA without FLT3-ITD. Biol Blood Marrow Transplant. Dec 2012;18(12):1845-1850. PMID 22766221

Documentation for Clinical Review

Please provide the following documentation (if/when requested):
- History and physical, including:
  - Reason for testing
  - Lab reports, demonstrating:
    - Cytogenetic analysis
    - NMP mutation
    - Determined FLT3/ITD mutations

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE
The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>0023U</td>
<td>Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin</td>
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<tr>
<td></td>
<td>0046U</td>
<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative (Code effective 7/1/2018)</td>
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<tr>
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<td>0049U</td>
<td>NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, quantitative (Code effective 7/1/2018)</td>
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<tr>
<td></td>
<td>0050U</td>
<td>Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements (Code effective 7/1/2018)</td>
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<td>0056U</td>
<td>Hematology (acute myelogenous leukemia), DNA, whole genome next-generation sequencing to detect gene rearrangement(s), blood or bone marrow, report of specific gene rearrangement(s) (Code effective 7/1/2018)</td>
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<td></td>
<td>81218</td>
<td>CEBPA (CCAAT enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence</td>
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<tr>
<td>Type</td>
<td>Code</td>
<td>Description</td>
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<tr>
<td>-------</td>
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<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>81245</td>
<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)</td>
</tr>
<tr>
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<td>81246</td>
<td>FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)</td>
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<tr>
<td></td>
<td>81310</td>
<td>NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants</td>
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<td>HCPCS</td>
<td>None</td>
<td>None</td>
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<tr>
<td>ICD-10</td>
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<td>None</td>
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</tbody>
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**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>09/30/2014</td>
<td>BCBSA Policy Adoption</td>
<td>Medical Policy Committee</td>
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<tr>
<td>01/01/2015</td>
<td>Coding update</td>
<td>Administrative Review</td>
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<tr>
<td>01/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy title change from Genetic Testing for FLT3, NPM1, and CEBPA Mutations in Acute Myeloid Leukemia Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2018</td>
<td>Policy title change from Genetic Testing for FLT3, NPM1, and CEBPA Mutations in Cytogenetically Normal Acute Myeloid Leukemia Policy revision without position change</td>
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<td>08/01/2018</td>
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<tr>
<td>04/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.
Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.