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

Policy Number: 2.04.124  Last Review: 09/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Genetic Testing for FLT3, NPM1, and CEBPA Mutations in Cytogenetically Normal Acute Myeloid Leukemia when it is determined to be medically necessary because the criteria shown below are met.

Note: This is a type of genetic testing that may be excluded in some contracts. Verify benefits prior to review for Medical Necessity.

When Policy Topic is covered
Genetic testing for FLT3 internal tandem duplication (FLT3/ITD), NPM1, and CEBPA mutations may be considered medically necessary in cytogenetically normal AML. (see Considerations)

When Policy Topic is not covered
Genetic testing for FLT3 internal tandem duplication (FLT3/ITD), NPM1, and CEBPA mutations is considered investigational in all other situations.

Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations is considered investigational.

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

Considerations
This testing is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.
### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
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</table>
| Individuals:  
• With cytogenetically normal acute myeloid leukemia | Interventions of interest are:  
• Genetic testing for variants in FLT3, NPM1, CEBPA to risk-stratify acute myeloid leukemia | Comparators of interest are:  
• Treatment based on conventional cytogenetics and patient characteristics | Relevant outcomes include:  
• Overall survival  
• Disease-specific survival  
• Test accuracy  
• Test validity  
• Treatment-related mortality  
• Treatment-related morbidity |

Treatment of acute myeloid leukemia (AML) is based on risk stratification, primarily related to patient age and tumor cytogenetics. In patients with cytogenetically normal AML, the identification of variants in several genes, including FLT3, NPM1, and CEBPA, has been proposed to allow for further segregation in the management of this heterogeneous disease.

For individuals who have cytogenetically normal AML who receive genetic testing for variants in FLT3, NPM1, and CEBPA to risk-stratify AML, the evidence includes 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 internal tandem duplication (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.

### Background

#### Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a group of diverse hematologic malignancies characterized by the clonal expansion of myeloid blasts in the bone marrow, blood, and/or other tissues. It is the most common type of leukemia in adults and is generally associated with a poor prognosis. The American Cancer Society has estimated there will be 21,380 new cases of AML and 10,590 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 (ie, at the level of the chromosome including chromosomal translocations or deletions) or molecular genetic abnormalities (ie, at
the level of the function of individual genes, including gene variants). These cytogenetic and molecular changes form distinct 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 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.\(^{12-14}\) *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 CN-AML; double variants of *CEBPA* have shown a better prognosis with higher rates of complete remission and overall OS after standard induction chemotherapy.\(^{15,16}\)

**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**

This evidence review was created in July 2014 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 6, 2017.

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 \textit{FLT3}, \textit{NPM1}, and \textit{CEBPA} variants to risk-stratify acute myeloid leukemia

\textbf{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 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 \textit{FLT3}, \textit{NMP1}, or \textit{CEBPA} genetic testing in patients with AML improve outcomes?

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

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

\textbf{Interventions}
The intervention of interest is testing for \textit{FLT3}, \textit{NMP1}, or \textit{CEBPA} variants.

\textbf{Comparators}
The comparator of interest is risk stratification without \textit{FLT3}, \textit{NMP1}, or \textit{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 \textit{FLT3} internal tandem duplication (ITD), \textit{NMP1}, or \textit{CEBPA} variants compared with patients without \textit{FLT3-ITD}, \textit{NMP1}, or \textit{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.

\textbf{Table 1. Survival Outcomes of Patients With \textit{FLT3-ITD}, \textit{NMP1}, or \textit{CEBPA} Variants}

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>\textit{Port et al (2014)}\textsuperscript{17}</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>\begin{itemize} \item \textit{FLT3-ITD} WT vs \textit{FLT3-ITD} variant: \begin{itemize} \item OS HR=1.9 (95% CI, 1.6 to 22) \item RFS HR=1.8 (95% CI, 1.5 to 2.2) \end{itemize} \item \textit{NPM1} WT vs \textit{NPM1} variant: \begin{itemize} \item OS HR=0.6 (95% CI, 0.5 to 0.7) \item RFS HR=0.6 (95% CI, 0.5 to 0.6) \end{itemize} \item \textit{CEBPA} WT vs \textit{CEBPA} variant: \begin{itemize} \item OS HR=0.4 (95% CI, 0.3 to 0.5) \item RFS HR=0.4 (95% CI, 0.3 to 0.6) \end{itemize} \end{itemize}</td>
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<tr>
<td>\textit{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>\begin{itemize} \item \textit{CEBPA} monoallelic vs WT: \begin{itemize} \item OS HR=1.1 (95% CI, 0.9 to 1.5) \item EFS HR=1.1 (95% CI, 0.8 to 1.5) \end{itemize} \item \textit{CEBPA} biallelic vs WT: \begin{itemize} \item OS HR=0.4 (95% CI, 0.3 to 0.5) \item EFS HR=0.4 (95% CI, 0.3 to 0.5) \end{itemize} \end{itemize} \textbf{CN-AML:} \begin{itemize} \item \textit{CEBPA} monoallelic vs WT: \begin{itemize} \item OS HR=1.1 (95% CI, 0.9 to 1.5) \item EFS HR=0.9 (95% CI, 0.7 to 1.2) \end{itemize} \item \textit{CEBPA} biallelic vs WT: \begin{itemize} \item OS HR=0.3 (95% CI, 0.2 to 0.4) \item EFS HR=0.4 (95% CI, 0.3 to 0.5) \end{itemize} \end{itemize}</td>
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<td>\textit{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>\begin{itemize} \item 1-y OS: \begin{itemize} \item \textit{CEBPA}, biallelic: 75% \item \textit{NPM1} variant, \textit{FLT3-ITD} WT: 54% \item All others: 33% \item 3-y OS: \item \textit{CEBPA}, biallelic: 17% \end{itemize} \end{itemize}</td>
</tr>
</tbody>
</table>
**Study** | **Design** | **Participants** | **Outcomes**
---|---|---|---
**Wu et al (2016)**<sup>19</sup> | Systematic review of 10 cohort studies published between 1995 and 2015 | 1661 pediatric patients with AML | • *NPM1* variant, *FLT3-ITD WT*: 29%
• All others: 12%

**Kuwatsuka et al (2017)**<sup>20</sup> | Retrospective analysis of patients enrolled in 2 clinical trials between 2001 and 2010 | 103 adolescent and young adults (age range, 15-39 y) with AML | *FLT3-ITD WT vs FLT3-ITD variant:*
• OS HR=2.2 (95% CI, 1.6 to 3.0)
• EFS HR=1.7 (95% CI, 1.4 to 2.1)

AML: acute myeloid leukemia; CI: confidence interval; CN: cytogenetically normal; EFS: event-free survival; HR: hazard ratio; 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 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.8

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>
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<tr>
<td>Schlenk et al (2008)21</td>
<td>Retrospective analysis of patients in 4 AML therapy RCTs conducted between 1993 and 2004</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>
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<td></td>
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<td></td>
<td>• NPM1 without FLT3-ITD</td>
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<td></td>
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<td>• Relapse rate HR=0.9 (0.5 to 1.8)</td>
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<td>Other genotypes (excluding CEBPA, NPM1 without FLT3-ITD):</td>
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<td>• Relapse rate HR=0.6 (0.4 to 0.9)</td>
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<tr>
<td>Schlenk et al (2013)22</td>
<td>Retrospective analysis of patients in 7 AML therapy RCTs conducted between 1987 and 2009</td>
<td>124 adults &lt;60 y with CN-AML who were CEBPA biallelic and had CR after induction therapy</td>
<td>Allo-HCT vs chemo:</td>
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<td>• RFS HR=0.2 0.1 to 0.5</td>
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<td>• OS HR=0.5 (0.2 to 1.2)</td>
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<tr>
<td>Willemze et al (2014)23</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:</td>
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<td>• OS at 6 y in patients at very bad risk 20% in standard cytarabine group vs 31% in high-dose group:</td>
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<td>• HR=0.70 (0.47 to 1.04)</td>
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<td>Chou et al (2014)24</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 FLT-ITD WT, 42 (13%) CEBPA biallelic</td>
<td>Non-allo-HCT:</td>
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<td>• CEBPA biallelic vs other</td>
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<td>o OS HR=0.5 (0.3 to 0.8)</td>
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<td>• NPM1 variant with FLT3-ITD WT:</td>
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<td>o OS HR=0.4 (0.2 to 0.7)</td>
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<td>• OS OR=2.9 (2.0 to 4.1)</td>
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<td>• DFS OR=2.8 (1.9 to 4.3)</td>
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<td>• Relapse rate OR=0.1 (0.05 to 0.2)</td>
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<tr>
<td>Tarlock et al (2016)26</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 vs with without gemtuzumab ozogamicin:</td>
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<td></td>
<td></td>
<td>• Overall</td>
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<td>o Relapse rate, 37% vs 59% (p=0.02)</td>
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<td>o DFS=47% vs 41% (p=0.45)</td>
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<td>o TRM=16% vs 0% (p=0.008)</td>
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<td></td>
<td>• Patients with high FLT3-ITD</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Outcomes Estimate (95% CI)</td>
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</table>
| Ahn et al (2016) | Retrospective analysis of patients from 7 institutions in South Korea from 1998 to 2012 | 404 CN-AML patients ages ≥15 y treated with conventional induction chemo; 51 (13%) CEBPA biallelic | 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 DFS=39% (15% to 64%)  
  • 5-y relapse incidence, 38% (17% to 59%)  
• Allo-HCT:  
  • 5-y OS=72% (54% to 90%)  
  • 5-y DFS=73% (55% to 90%)  
  • 5-y relapse incidence, 8% (1% to 23%) |
| Brunner et al (2016) | Retrospective analysis of patients at 2 U.S. institutions between 2008 and 2014 | 81 consecutive AML patients who underwent FLT3-ITD testing who achieved CR with induction chemo followed by allo-HCT | Sorafenib maintenance therapy vs no sorafenib:  
• 2-y OS=81% vs 62%; HR=0.3 (0.1 to 0.8)  
• 2-y PFS=82% vs 53%; HR=0.3 (0.1 to 0.8) |
| Versluis et al (2017) | Retrospective analysis of patients from 4 trials who achieved CR after 1 or 2 induction chemo cycles | 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) | Auto-HCT vs chemo: no difference in OS, RFS, relapse, or NRM  
Allo-HCT with MAC vs chemo: no difference OS  
• RFS: HR=0.7 (0.5 to 1.0)  
• Relapse: HR=0.2 (0.1 to 0.3)  
• NRM: HR=9.1 (2.7 to 30.4)  
Allo-HCT with RIC vs chemo: no difference in NRM  
• OS HR=0.5 (0.3 to 0.9)  
• RFS HR=0.5 (0.3 to 0.8)  
• Relapse HR=0.3 (0.2 to 0.6)  
Allo-HCT with MAC vs auto-HCT: no difference in OS or RFS  
• Relapse HR=0.3 (0.2 to 0.5)  
• NRM HR=5.7 (2.3 to 13.9)  
Allo-HCT with RIC vs auto-HCT: no difference in NRM:  
• OS HR=0.6 (0.4 to 1.0)  
• RFS HR=0.6 (0.4 to 1.0)  
• Relapse HR=0.5 (0.3 to 0.9) |

alo: allogeneic; AML: acute myeloid leukemia; auto: autologous; chemo: chemotherapy; CI: confidence interval; CN: cytogenetically normal; CR: complete remission; DFS: disease-free survival; EFS: event-free survival; HCT: hematopoietic cell transplantation; HR: hazard ratio; ITD: internal tandem duplication; MAC: myeloablative conditioning; NR: not reported; NRM: nonrelapse
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 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).

In 2017, Stone et al 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 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>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 $FLT3$ variants, mostly &lt;60 y</td>
<td>n=300 4 cycles of induction and consolidation chemotherapy, followed by lestaurtinib (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>NR</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>
</tbody>
</table>
### 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.

### Supplemental Information

#### Practice Guidelines and Position Statements

---

<table>
<thead>
<tr>
<th></th>
<th>CR rate (95% CI)</th>
<th>Time to complete remission (range), median days</th>
<th>Overall survival (95% CI), median months</th>
<th>Event-free survival (95% CI), median months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59 (54 to 64)</td>
<td>35 (20-60)</td>
<td>75 (31 to NR)</td>
<td>8.2 (5 to 11)</td>
</tr>
<tr>
<td></td>
<td>54 (48 to 59)</td>
<td>35 (20-60)</td>
<td>26 (19 to 43)</td>
<td>3 (2 to 6)</td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td>NS</td>
<td>0.8 (0.6 to 1.0)</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.
**National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (3.2017) provide the following recommendations:

For the evaluation for acute leukemia, “bone marrow with cytogenetics (karyotype ± FISH [fluorescence in situ hybridization]) and molecular analyses (KIT, FLT3-ITD [internal tandem duplication], NPM1, CEBPA, and other mutations).”

“Molecular abnormalities (KIT, FLT3-ITD, NPM1, CEBPA, and other mutations) are important for prognostication in a subset of patients (category 2A) and may guide therapeutic intervention (category 2B). These are useful for patients with normal karyotype (especially FLT3-ITD, NPM1 mutations) or core binding factor leukemia (especially KIT mutation).”

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 <strong>CEBPA</strong></td>
<td>Favorable</td>
</tr>
<tr>
<td>Mutated <strong>NPM1</strong> without <strong>FLT3-ITD</strong></td>
<td>Favorable</td>
</tr>
<tr>
<td>Mutated <strong>NPM1</strong> with <strong>FLT3-ITD</strong> (low allelic ratio)</td>
<td>Favorable</td>
</tr>
<tr>
<td>Mutated <strong>NPM1</strong> with <strong>FLT3-ITD</strong> (high allelic ratio)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Wild-type <strong>NPM1</strong> without <strong>FLT3-ITD</strong></td>
<td>Intermediate</td>
</tr>
<tr>
<td>Wild-type <strong>NPM1</strong> with <strong>FLT3-ITD</strong> (low allelic ratio)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Wild-type <strong>NPM1</strong> with <strong>FLT3-ITD</strong> (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>
</tbody>
</table>

ITD: internal tandem duplication.
- High-dose therapy and autologous HCT
- Allogeneic HCT from matched related or unrelated donor

**Patients >60/65 years**

**Adverse**

- Consider allogeneic HCT from matched related or unrelated donor
- Investigational therapy

**Favorable**

- 2 to 3 cycles intermediate-dose cytarabine

**Intermediate/adverse**

- Consider allogeneic HCT from matched related or unrelated donor


**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>
</tr>
</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 HSCT Consolidation</td>
<td>367</td>
<td>Sep 2018</td>
</tr>
<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 2018</td>
</tr>
<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>Dec 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>NCT No.</td>
<td>Trial Name</td>
<td>Planned Enrollment</td>
<td>Completion Date</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>--------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>NCT02668653</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>
</tr>
<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 2020</td>
</tr>
<tr>
<td>NCT02927262</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>Unpublished</td>
<td>Randomized Open Phase III Trial Testing Efficacy of Gemtuzumab Ozogamycin Associated to Intensive Chemotherapy for Patients Aged Between 18-60 Years and Presenting an AML With Intermediate Risk</td>
<td>327</td>
<td>Sep 2016 (completed)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*Denotes industry-sponsored or cosponsored trial.

References


Billing Coding/Physician Documentation Information

81218 CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81245 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81310 NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
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
0046U FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
0047U Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score

ICD-10 Codes
C92.00- Acute myeloblastic leukemia code range
C92.02
C92.60- Acute myeloid leukemia with 11q23-abnormality code range
C92.62
C92.A0- Acute myeloid leukemia with multilineage dysplasia code range
C92.A2

Additional Policy Key Words
N/A

Policy Implementation/Update Information
9/1/14 New policy; considered investigational.
9/1/15 Title revised and medically necessary statement added for CEBPA mutation testing. Added CPT codes 81246, 81403
9/1/16 Added CPT 81218. No policy statement changes.
9/1/17 Title updated to clarify that policy applies to cytogenetically normal AML. Policy statements unchanged.
9/1/18 Policy statements unchanged. Title changed to “Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia”

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