Name of Policy: Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Cytogenetically Normal Acute Myeloid Leukemia

Policy #: 583
Category: Laboratory

Latest Review Date: February 2017
Policy Grade: D

Background/Definitions: As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Treatment of acute myeloid leukemia (AML) is based upon risk stratification, mainly patient age and tumor cytogenetics. In patients with cytogenetically normal AML, the identification of mutations in several genes, including FLT3, NPM1, and CEBPA, has been proposed to allow for further segregation in the management of this heterogeneous disease.

Acute Myeloid Leukemia
Acute myeloid leukemia (AML) is a group of diverse hematologic malignancies characterized by the clonal expansion of myeloid blasts in the bone marrow, blood and/or other tissues. It is the most common type of leukemia in adults, and is generally associated with a poor prognosis. It is estimated that, in 2014, 18,860 people will be diagnosed with AML and 10,460 will die of the disease. The median age at diagnosis is 66 years, with approximately one in three patients diagnosed at 75 years of age or older.

Diagnosis and Prognosis of AML
The most recent World Health Organization (WHO) classification (2008) 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 mutations). These cytogenetic and molecular changes form distinct clinical-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. Younger adult patients are usually categorized into three different risk groups based on cytogenetics (good, intermediate, poor risk).

Molecular mutations 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 mutations of the CEBPA encoding a transcription factor, mutations of the FLT3 gene, encoding a receptor of tyrosine kinase involved in hematopoiesis and mutation of the NPM1 gene, encoding a shuttle protein within the nucleolus. “AML with mutated NPM1 or CEBPA” were included as provisional entities in the 2008 WHO classification of acute leukemias. AML with FLT3 mutations is not considered a distinct entity in the 2008 classification, although the WHO recommends determining the presence of FLT3 mutations because of the prognostic significance.

Recent reviews highlight the evolving classification of AML into distinct molecular subtypes.

Treatment
AML has a highly heterogeneous clinical course, and treatment generally depends on the different risk-stratification categories. Depending on the risk-stratification category, treatment modalities may include intensive remission induction chemotherapy, hypomethylating agents, clinical trials with innovative compounds, palliative cytotoxic treatment or supportive care only. For patients who achieve a complete remission (CR) after induction treatment, possible post-
remission treatment options include intensive consolidation therapy, maintenance therapy or autologous or allogeneic hematopoietic cell transplantation (HCT).

**FLT3 Mutations**

FMS-like tyrosine kinase (FLT3) plays a critical role in normal hematopoiesis and cellular growth in hematopoietic stem and progenitor cells. Mutations in FLT3 are one of the most frequently encountered mutations in AML, and approximately 30% of AML patients harbor some form of FLT3 mutation. FLT3 mutations are divided into two categories:

1. Internal tandem duplications (FLT3/ITD) mutations, 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 mutations are much more common than FLT3/TKD mutations, occurring in 25% of newly diagnosed adult cases of AML, versus FLT3/TKD mutations, occurring in about 7% of patients. FLT3/ITD mutations are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age and with normal or intermediate risk cytogenetics, and are associated with an increased risk of relapse and inferior overall survival (OS). Patients with FLT3/ITD mutations have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild type (i.e., nonmutated) FLT3. Although remission can be achieved in patients with FLT3/ITD mutations 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 a FLT3/ITD mutation is six to seven months compared with nine 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 transplantation (HCT) as consolidation of a first remission for a FLT3/ITD AML patient is often a consideration. However, this must be weighed against the treatment-related mortality associated with a transplant.

The clinical significance of an FLT3 mutation varies according to the nature of the mutation and the context in which it occurs. Longer FLT3/ITD mutations have been associated with reduced remission rates and/or worse survival in some studies.

For FLT3/ITD mutations, allelic ratio refers to the number of ITD-mutated alleles compared with the number of WT (nonmutated) alleles. This ratio is influenced by the number of malignant versus benign cells in the sample tested and by the percentage of cells with zero, one or two mutated alleles. In most cases, the mutation detected at diagnosis is also present at relapse. However, in some cases, as FLT3/ITD-positive AML evolves from diagnosis to relapse, the mutation present at diagnosis may be absent (or undetectable) at relapse. This is most commonly seen where the mutant allele burden is low (5% to 15%) at diagnosis. For this reason, and the overall lack of sensitivity of the assay (see Clinical Validity), 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 \textit{FLT3-TKD} mutations is less certain, and has only been studied in small numbers of patients. \textit{FLT3} tyrosine kinase inhibitors are under active clinical investigation.

\textbf{NPM1 Mutations}

The most common molecular aberration in AML is a mutation of \textit{NPM1}, which is found in 46\% to 64\% of cytogenetically normal AML (\textit{CN-AML}) and 9\% to 18\% of cytogenetically abnormal AML. Up to 50\% of AML with mutated \textit{NPM1} also carry a \textit{FLT3/ITD}. Mutated \textit{NPM1} confers an independent favorable prognosis for patients with \textit{CN-AML} and either the presence or absence of a \textit{FLT3/ITD}. Retrospective studies of banked clinical samples suggest that a \textit{NPM1} mutation may mitigate the negative prognostic effect of an \textit{FLT3/ITD}, but possibly only if the \textit{FLT3/ITD} to WT allelic ratio is low. The prognostic impact in patients with an abnormal karyotype is unclear.

\textbf{CEBPA Mutations}

\textit{CEBPA} (CCAAT/enhancer binding protein) is a transcription-factor gene that plays a role in cell cycle regulation and cell differentiation. Mutations to \textit{CEBPA} are found in approximately 15\% of AML patients with a normal karyotype. \textit{CEBPA} mutations can be either biallelic (double mutations) or monoallelic. Monoallelic mutations are prognostically similar to \textit{CEBPA} WT and do not confer a favorable prognosis in cytogenetically normal AML; double mutations of \textit{CEBPA} have shown a better prognosis with higher rates of CR and OS after standard induction chemotherapy.

\textbf{Policy:}

\textbf{Effective for dates of service on or after August 18, 2015:}

Genetic testing for \textit{FLT3 internal tandem duplication (FLT3/ITD), NPM1, and CEBPA mutations for patients with cytogenetically normal AML meets} Blue Cross and Blue Shield of Alabama’s medical criteria for coverage. *This testing is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.

Genetic testing for \textit{FLT3 internal tandem duplication (FLT3/ITD), NPM1, and CEBPA mutations does not meet} Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered \textit{investigational} in all other situations.

Genetic testing for \textit{FLT3 tyrosine kinase domain (FLT3/TKD) mutations does not meet} Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered \textit{investigational}.

Genetic testing for \textit{FLT3, NPM1, and CEBPA mutations to detect minimal residual disease does not meet} Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered \textit{investigational}. 

---

\textbf{Proprietary Information of Blue Cross and Blue Shield of Alabama}
\textbf{An Independent Licensee of the Blue Cross and Blue Shield Association}
\textbf{Medical Policy #583}
Effective for dates of service prior to August 18, 2015:
Genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations for patients with cytogenetically normal AML meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage. *This testing is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.

Genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational in all other situations.

Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Genetic testing for FLT3 or NPM1 mutations to detect minimal residual disease does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
This evidence review was originally created in July 2014 and the most recent update is based on a search of the MEDLINE database through November 7, 2016.

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

Clinical Context and Test Purpose
Optimal decisions regarding treatment intensity and chemotherapy-based consolidation therapy versus allogeneic transplantation remains unclear in cytogenetically normal acute myeloid leukemia (CN-AML). The purpose of genetic testing is to provide prognostic risk stratification information in patients who have CN-AML which may inform decisions regarding.
• whether to use standard or increased treatment intensity in induction therapy, consolidation therapy or in relapsed/refractory AML;
• whether to do allogeneic or autologous transplantation versus chemotherapy as consolidation therapy for an AML patient in first remission;
• whether to use investigational therapies such as FLT3 inhibitors.

Induction therapy usually consists of seven days of continuous infusion cytarabine at 100 to 200 mg/m2 with three days of anthracycline. Studies have shown greater efficacy at higher doses but along with the added benefit there is increased toxicity.

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

Side effects of FLT3 inhibitors (e.g., sorafenib, sunitinib, midostaurin, lestaurtinib, quizartinib) include QT prolongation, nausea, vomiting, diarrhea, anemia, abnormal liver function tests, increased bilirubin, fever, and fatigue. Currently no FLT3 inhibitor is approved for this indication although midostaurin is under priority review at the Food and Drug Administration. 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 relevant populations of interest are patients with newly diagnosed CN-AML, those in first remission or those who have relapsed.

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

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

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

Analytic Validity
Analytic Validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent.

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

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

Clinical Validity
Clinical validity is the prognostic performance of the test [sensitivity, specificity, positive and negative predictive values] in predicting the course of clinical disease.

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

Table 1 Survival Outcomes of Patients With FLT3-ITD, NMP1, or CEBPA Mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
  - OS HR=1.9 (95% CI, 1.6 to 22)  
  - RFS HR=1.8 (95% CI, 1.5 to 2.2)  

  **NMP1 WT vs NMP1 mutation**  
  - OS HR=0.6 (95% CI, 0.5 to 0.7)  
  - RFS HR=0.6 (95% CI, 0.5 to 0.7)  

  **CEBPA WT vs CEBPA mutation**  
  - OS HR=0.4 (95% CI, 0.3 to 0.5)  
  - RFS HR=0.4 (95% CI, 0.3 to 0.5)  

  - *CEBP4 monoallelic vs WT*  
    - OS HR=1.1 (95% CI, 0.9 to 1.5)  
    - EFS HR=1.1 (95% CI, 0.8 to 1.5)  
  - *CEBP4 biallelic vs WT*  
    - OS HR=0.4 (95% CI, 0.3 to 0.5)  

Proprietary Information of Blue Cross and Blue Shield of Alabama  
An Independent Licensee of the Blue Cross and Blue Shield Association  
Medical Policy #583
<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Patients</th>
<th>OS &amp; EFS Details</th>
</tr>
</thead>
</table>
| Dickson et al (2016) | Retrospective analysis of patients enrolled in an RCT between 1990 and 1998  | 662 AML patients older than 60 years | 1-year OS: • **CEBPA** monoallelic vs WT: HR = 1.1 (95% CI, 0.9 to 1.5)  
• OS HR = 0.9 (95% CI, 0.7 to 1.2)  
• EFS HR = 0.9 (95% CI, 0.7 to 1.2)  

3-year OS: • **CEBPA** monoallelic vs WT: HR = 1.1 (95% CI, 0.9 to 1.5)  
• OS HR = 0.9 (95% CI, 0.7 to 1.2)  
• EFS HR = 0.9 (95% CI, 0.7 to 1.2)  

1661 pediatric patients with AML  

1-year OS: • **CEBPA** biallelic: 75%  
• **NPM1** mutation, **FLT3-ITD** WT: 54%  
• All others: 33%  

3-year OS: • **CEBPA** biallelic: 17%  
• **NPM1** mutation, **FLT3-ITD** WT: 29%  
• All others: 12%  

• OS HR = 2.2 (95% CI, 1.6 to 3.0)  
• EFS HR = 1.7 (95% CI, 1.4 to 2.1)  

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

**Section Summary: Clinical Validity**

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

**Clinical Utility**

Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

The literature on the use of these markers consists of retrospective analyses, and no prospective studies have been published to date. Literature describing outcomes by type of treatment for
patients with and without FLT3-ITD, CEBPA4, and NPM1 mutations are shown in Table 2. Results from systematic reviews are presented when available and individual studies are shown if they are 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 mutations and survival outcomes with the use of allogeneic hematopoietic cell transplantations (HCT) in patients depending on the presence of this type of mutation. In general, the data support the use of HCT in patients with FLT3/ITD mutations; however, not all studies have shown consistent results.

Table 2 Outcomes by Treatment of Patients With And Without FLT3-ITD Mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Schlenk et al (2008)   | Retrospective analysis of patients in 4 AML therapy RCTs conducted between 1993 and 2004 | 872 adults <60 y with CN-AML, 53% NPM1 mut, 31% FLT3-ITD mut, 11% FLT3-TKD mut, 13% CEBPA mut | **Allo-HCT vs other consolidation therapy**  
  • NPM1 without FLT3-ITD  
  • RR HR=0.9 (95% CI, 0.5 to 1.8)  
  **Other genotypes (excluding CEBPA, NPM1 without FLT3-ITD)**  
  • RR HR=0.6 (95% CI, 0.4 to 0.9) |
| Schlenk et al (2013)   | Retrospective analysis of patients in 7 AML therapy RCTs conducted between 1987 and 2009 | 124 adults <60 y with CN-AML who were CEBPA biallelic and had CR after induction therapy | **Allo-HCT vs chemotherapy**  
  • RFS HR=0.2 (95% CI, 0.1 to 0.5)  
  • OS HR=0.5 (95% CI, 0.2 to 1.2)  
  **Auto-HCT vs chemotherapy**  
  • RFS HR=0.4 (95% CI, 0.2 to 0.8)  
  • OS HR=0.6 (95% CI, 0.2 to 1.4) |
| Willemze (2014)        | Retrospective analysis of EORTC-GIMEMA AML-12 RCT conducted between Sep 1999 and Jan 2008 | 613 patients with AML, ages 15-60 y; 126 (21%) FLT3-ITD mut | **Patients with FLT3-ITD mut categorized as very bad risk**  
  • OS at 6 y in patients at very bad risk  
  • 20% in standard cytarabine group vs 31% in high-dose group  
  • HR=0.70 (95% CI, 0.47 to 1.04) |
| Chou et al (2014)      | Retrospective analysis of patients from National Taiwan University Hospital between 1995 and 2007 | 325 adults with AML who received conventional induction chemotherapy: 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  
  o OS HR=0.5 (95% CI, 0.3 to 0.8)  
  • NPM1 mut with FLT3-ITD WT  
  o OS HR=0.4 (95% CI, 0.2 to 0.7)  
  **Allo-HCT** |
- **CEBP4** biallelic vs other
  - OS HR=0.3 (95% CI, 0.1 to 1.2)
  - NPM1 mut with FLT3-ITD WT
  - OS HR=NR

**Allo-HCT vs chemotherapy**
- OS OR=2.9 (95% CI, 2.0 to 4.1)
- DFS OR=2.8 (95% CI, 1.9 to 4.3)
- RR OR=0.1 (95% CI, 0.05 to 0.2)

**Standard chemotherapy with vs without gemtuzumab ozogamicin**
- Overall
  - RR=37% vs 59% (95% CI, NR; p=0.02)
  - DFS=47% vs 41% (95% CI, NR; p=0.45)
  - TRM=16% vs 0% (95% CI, NR; p=0.008)
- Among patients with high FLT3-ITD allelic ratio
  - RR 15% vs. 53% (95% CI, NR; p=0.007)
  - DFS 65% vs 40% (95% CI, NR; p=0.08)
  - TRM=19% vs. 7% (95% CI, NR; p=0.08)

**Ahn et al (2016)**
- Retrospective analysis of patients from 7 institutions in Korea from Oct 1998 to Sep 2012
- 404 CN-AML patients ages ≥15 y treated with conventional induction chemotherapy; 51 (13%) CEBPA1 biallelic

**Overall, by CEBPA**
- 5-y OS biallelic, 62% (95% CI, 43% to 82%)
- 5-y OS monoallelic, 44% (95% CI, 19% to 69%)
- 5-y OS WT=26% (95% CI, 19% to 32%)
- Biallelic vs others
- HR = 0.4 (95% CI NR; p=0.001)

**Among CEBPA biallelic**
- Chemotherapy
  - 5-y OS=60% (95% CI, 40% to 81%)
  - 5-y EFS=39% (95% CI, 15% to 64%)
  - 5-y relapse incidence, 38%
Medical Policy #583

(95% CI, 17 to 59)
- Allo-HCT
  - 5-y OS=72% (95% CI, 54% to 90%)
  - 5-y EFS=73% (95% CI, 55% to 90%)
  - 5-y relapse incidence, 8
    (95% CI, 1 to 23)

81 consecutive AML patients who underwent FLT3-ITD testing who achieve CR with induction chemotherapy followed by allo-HCT

Sorafenib maintenance therapy vs no sorafenib
- 2-y OS=81% vs 62%; HR=0.3 (95% CI, 0.1 to 0.8)
- 2-y PFS=82% vs 53%; HR=0.3 (95% CI, 0.1 to 0.8)

allo: allogeneic; AML: acute myeloid leukemia; auto: autologous; 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; mut: mutation; NR: not reported; OR: odds ratio; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial; RR: relapse rate; SCT: stem cell transplantation; TRM: treatment-related mortality; WT: wild type.

Ma et al (2015) performed a systematic review and meta-analysis including 9 studies published between 1989 and December 2013 that described use of HCT or chemotherapy in patients with AML in first complete remission who were FLT3-ITD mutation. All studies were either 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 to chemotherapy. The OS and DFS favored allo-HCT but did not differ significantly between allo-HCT and autologous HCT (OS OR=1.4; 95% CI, 0.8 to 2.4; DFS OR=1.6; 95% CI, 0.8 to 3.3); however, relapse rates were lower for allo-HCT (OR=0.4, 95% CI, 0.2 to 0.7).

Willemze et al (2014) conducted a randomized trial in 1942 newly diagnosed patients with AML, age 15 to 60 years to compare remission induction treatment containing either standard or high-dose cytarabine. In both arms, patients who achieved CR received consolidation therapy with either an autologous or allogeneic HCT. Patients were subclassified as good risk, intermediate risk, bad risk, very bad risk or unknown risk, according to cytogenetics and FLT3/ITD mutation. Testing for FLT3/ITD mutation showed that in the standard dose cytarabine group, 50% were negative, 13% were positive, and 37% were unknown. In the high-dose cytarabine group, 48% were negative, 14% were positive, and 38% were unknown. All patients with a FLT/ITD mutation were categorized as very bad risk. OS at six 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). The authors concluded that patients with very bad risk cytogenetics and/or FLT3/ITD mutation benefitted from high-dose cytarabine induction treatment.

Chou et al (2014) conducted a retrospective analysis of 325 adult AML patients to determine the prognostic significance of eight mutations, including CEBPA, FLT3-ITD, and NPM1, on OS between patients who received allogeneic HCT (n=100) and those who did not (n=255). Karyotype included favorable (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 allogeneic stem cell transplant, or consolidation chemotherapy for those patients who did not achieve CR. In the non-allogeneic HCT patients, \( NPM1/FLT3-ITD^{wt} \) (HR=0.363; 95% CI, 0.188 to 0.702; p=0.003) and \( CEBPA \) double mutation (HR=0.468; 95% CI, 0.265 to 0.828; p=0.009) were significant good prognostic factors of OS in a multivariate analysis. All other gene mutations failed to have a significant impact on OS in the HCT and non-HCT groups in the multivariate analysis. The authors presented survival curves stratified by \( CEBPA \) and \( FLT3-ITD \) mutations and found that, in the non-HCT group, \( CEBPA \) and \( FLT3-ITD^{wt} \) mutations were prognostic of improved OS (p=0.008 and p=0.001, respectively), but, in the allogeneic HCT group, neither mutation had a prognostic effect. The inability to detect mutations of prognostic significance in the HCT group could be due to the small number of patients with the studied mutations (\( CEBPA=9, NPM1=13, FLT3-ITD=25 \)).

**Section Summary: Clinical Utility**

There is no direct evidence of clinical utility. Indirect evidence of utility is available from retrospective analyses suggesting that risk stratification by \( NPM1, FLT3-ITD, \) or \( CEBPA \) can help guide therapy decisions that are associated with improved outcomes. Patients with favorable prognosis, including \( NPM1 \) gene mutations without \( FLT3-ITD \) mutation or double mutant \( CEBPA \), may not derive benefit in OS with use of allo-HCT instead of consolidation chemotherapy. Treatment of patients with intermediate or poor prognosis, including \( FLT3-ITD \) mutation, 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 mutations in \( FLT3, NPM1, CEBPA \) to risk-stratify AML, the evidence includes retrospective observational studies and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related morbidity and mortality. \( FLT3 \) internal tandem duplication (\( FLT3-ITD \)) mutations confer a poor prognosis, whereas \( NPM1 \) (without \( FLT3-ITD \) mutation) and biallelic \( CEBPA \) mutations confer a favorable prognosis. The prognostic effect of \( FLT3 \) tyrosine kinase domain (\( FLT3-TKD \)) mutations is uncertain. Data suggest an overall survival benefit with transplantation for patients with \( FLT3-ITD \), but perhaps no overall survival benefit of transplantation for patients with \( NPM1 \) and \( CEBPA \) mutations. Major professional societies and guidelines recommend testing for these mutations 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.

**Practice Guidelines and Position Statements**

National Comprehensive Cancer Network

The National Comprehensive Cancer Network guidelines for Acute Myeloid Leukemia (v.2.2016) provide the following recommendations:

- For the evaluation and initial workup for suspected acute leukemias, bone marrow analysis with cytogenetics (karyotype) with or without fluorescence in situ hybridization
(FISH) is necessary to establish the diagnosis of AML; cryopreservation of samples for evaluation of other markers, including FLT3-ITD and NPM1 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).”

European LeukemiaNet
The 2010 European LeukemiaNet international expert panel recommendations for the diagnosis and management of adult patients with AML suggested that NPM1, CEBPA, and FLT3 mutations should be analyzed at least in patients with cytogenetically normal AML who will receive treatment other than low-dose chemotherapy or best supportive care.

Alberta Provincial Hematology Tumour Team
The Alberta Provincial Hematology Tumour Team issued 2009 guidelines on AML that included a recommendation for molecular analysis in cases with normal karyotypes, including FMS-like tyrosine kinase 3 (FLT3).

U.S. Preventative Services Taskforce
Genetic testing for FLT3, NPM1 and CEBPA is not a preventive service.

Key Words:
Acute Myeloid Leukemia, AML, FLT3, NPM1, ITD, TKD, CEBPA

Approved by Governing Bodies:
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Several laboratories offer these tests, including Quest Diagnostics, Medical Genetic Laboratories of Baylor College, Geneva Labs of Wisconsin, LabPMM, and ARUP Laboratories, available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

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

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**

**CPT Codes:**

81218  
**CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) gene analysis, full gene sequence (Effective 1/1/2016)**

81245  
**FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15) (Effective 1/1/2012)**

81246  
**FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836) (Effective 1/1/2015)**

81310  
**NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants (Effective 1/1/2012)**

**Previous Coding:**

**CPT Codes:**

81403  
**CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), full gene sequence. (deleted effective 1/1/2016)**

**References:**


Policy History:
Medical Policy Group, December 2011 (1): 2012 Coding Update –added codes 81245 and 81310
Medical Policy Panel, July 2014
Medical Policy Group, January 2015 (3): Added new code 81246
Medical Policy Group, February 2015 (3): Created individual policy with all references related to genetic testing for FLTE and NPM1 Mutations in Acute Myeloid Leukemia removed from medical policy #133; Update to Key Points, Key Words and References; no change in policy statement.
Medical Policy Panel, July 2015
Medical Policy Group, August 2015 (3): 2015 updates to the Title, Description, Key Points, Approved Governing Bodies, Coding & References; added CEBPA to Policy statements.
Available for comment August 19 through October 2, 2015
Medical Policy Group, November 2015: 2016 Annual Coding Update; added new CPT code 81218 to current coding; created previous coding section and moved cpt code 81403 from current coding to previous coding.

Medical Policy Panel, January 2017

Medical Policy Group, February 2017 (3): 2017 Updates to Title, Description, Key Points. Approved by Governing Bodies & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.