Corporate Medical Policy

Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia

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Description of Procedure or Service

Treatment of acute myeloid leukemia (AML) is based on 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, have been proposed to allow for further segregation in the management of this heterogeneous disease.

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 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017.

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, as 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 3 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, 3 of the most frequent molecular changes with prognostic impact are mutations of CEBPA encoding 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
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Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia

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 postremission treatment options include intensive consolidation therapy, maintenance therapy or autologous or allogeneic hematopoietic stem-cell transplantation (HSCT).

**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 2 categories: internal tandem duplications (FLT3/ITD) mutations, which occur in or near the juxtamembrane domain of the receptor, and 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 is 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 (ie, nonmutated) FLT3. Although remission can be achieved in patients with FLT3/ITD mutations using conventional induction chemotherapy at a frequency similar to other AML subtypes. Once FLT3/ITD AML relapses, the disease is rapidly fatal.

Because of the high risk of relapse, hematopoietic stem-cell transplantation (HSCT) 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 (non-mutated) alleles. This ratio is influenced by the number of malignant versus benign cells in the sample tested and by the percentage of cells with 0, 1 or 2 mutated alleles. In most cases, the 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 in cases in which the mutant allele burden is low (5%-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 FLT3/TKD mutations is less certain, and has only been studied in small numbers of patients.

**NPM1 Mutations**

The most common molecular aberration in AML is a mutation of NPM1, which is found in 46% to 64% of cytogenetically normal AML (CN-AML) and 9% to 18% of cytogenetically abnormal AML. Up to 50% of AML with mutated NPM1 also carry a FLT3/ITD. Mutated NPM1 confers an independent favorable prognosis for patients with CN-AML and either the presence or absence of a FLT3/ITD. Retrospective studies of banked clinical samples suggest that a NPM1 mutation may mitigate the
Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia

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.

**CEBPA Mutations**

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

**Related Policies:**

Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

**Policy**

BCBSNC will provide coverage for Genetic Testing for FLT3, NPM1, and CEBPA Mutations in Acute Myeloid Leukemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

**Benefits Application**

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**When Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia is covered**

Genetic testing for FLT3 internal tandem duplication (FLT3/ITD), NPM1, and CEBPA mutations may be considered medically necessary in cytogenetically normal AML.

**When Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia 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) mutations is considered investigational.

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

Genetic testing for ASXL1 and RUNX1 mutations are considered investigational.

**Policy Guidelines**
Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia

Treatment of acute myeloid leukemia (AML) is based on 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, have 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, 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 mortality and morbidity. FLT3 internal tandem duplication (FLT3-ITD) variants confer a poor prognosis, whereas NPM1 (without FLT3-ITD variant) and biallelic CEBPA variants confer a favorable prognosis. The prognostic effect of FLT3 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0023U, 81175, 81176, 81218, 81245, 81246, 81272, 81273, 81310, 81334, 81403

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director review 8/2014

Medical Director review 11/2014


Senior Medical Director review 7/2015

Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia


Specialty Matched Consultant Advisory Panel 11/2017


Policy Implementation/Update Information

For Policy titled “Genetic Testing for FLT3 and NPM1 Mutations in Acute Myeloid Leukemia”

11/11/14 Evidence Based Guideline converted to Corporate Medical Policy. Genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations may be medically necessary in cytogenetically normal AML. Genetic testing for FLT3 internal tandem duplication (FLT3/ITD) and NPM1 mutations is considered investigational in all other situations. Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations and genetic testing for FLT3 or NPM1 mutations to detect minimal residual disease is considered investigational. Added CPT 81246 to “Billing/Coding section for 2015 code update. Medical director review 11/2014. Policy noticed 11/11/14 for effective date 1/13/15. (lpr)

1/13/15 Specialty Matched Consultant Advisory Panel review 11/24/14. No change to policy intent. (lpr)

For Policy re-titled “Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia”

9/1/15 Policy re-titled “Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia.” Updated the Description and Policy Guidelines sections. Under “When Covered” section added medically necessary indication for CEBPA mutation testing. Reference added. Senior medical director review 7/2015. (lpr)

12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. Added CPT codes 81218, 81272, 81273 to Billing/Coding section for effective date 1/1/2016. (lpr)

12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

2/24/17 Revised Policy Guidelines section. Reference added. No change to policy intent. (lpr)

9/29/17 CPT 0023U added to Billing/Coding section for effective date 10/1/17. (lpr)

Genetic Testing for FLT3, NPM1 and CEBPA Mutations in Acute Myeloid Leukemia

3/29/18  Reference added. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.