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Genetic Testing for FLT3 and NPM1 Mutations in Acute Myeloid Leukemia

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Genetic Testing for FLT3 and NPM1 Mutations in 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) and NPM1 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) and NPM1 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 or NPM1 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

Treatment of acute myeloid leukemia (AML) is based upon risk stratification, mainly patient age and tumor cytogenetics. The identification of mutations in several genes, including *FLT3* and *NPM1*, have been proposed to allow for further segregation in the management of this heterogeneous disease.

Background

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 1/3 of patients diagnosed at 75 years of age or older.
(1)

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 (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 mutations). These cytogenetic and molecular changes form distinct clinical-pathologic-genetic entities with diagnostic, prognostic, and therapeutic implications. (2) Conventional cytogenetic analysis (karyotyping) is considered to be a mandatory component in the diagnostic evaluation of a patient with suspected acute leukemia, 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, 2 of the most frequent molecular changes with prognostic impact are 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” was included as a provisional entity 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. (2)

Recent reviews highlight the evolving classification of AML into distinct molecular subtypes. (1, 3-5)

Treatment

AML has a highly heterogeneous clinical course, and treatment generally depends on the different risk-stratification categories. (1) 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). (1)

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. (6) *FLT3* mutations are divided into 2 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 ~7% of patients. *FLT3/ITD* 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). (6-8). 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 patients, the remission durations are shorter and relapse rates are higher. The median time to relapse in patients with a *FLT3/ITD* mutation is 6 to 7 months compared with 9 to 11 months in patients with other AML subtypes. (6) 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. (6)
FLT3 tyrosine kinase inhibitors (TKIs) are under active clinical investigation.

The prognostic impact of *FLT3/TKD* mutations is less certain, and has only been studied in small numbers of patients. (6, 9)

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. (6)

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 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% to 15%) at diagnosis. (6) 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. (6)

Higher mutant to WT allelic ratios have been associated with worse outcomes. (6)

NPM1
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. (1) 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 negative prognostic effect of an *FLT3/ITD*, but possibly only if the *FLT3/ITD* to WT allelic ratio is low. (6)
The prognostic impact in patients with an abnormal karyotype is unclear. (1)

Regulatory Status
No U.S. food and Drug Administration (FDA) cleared genetic tests for *FLT3* or *NMP* were found. Thus, these genetic tests are offered as laboratory-developed tests. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

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 the blood or bone marrow. Testing for *FLT3* may involve a duplex assay which tests for both types of *FLT3* mutations (*ITD* and *TKD*), however, some laboratories only test for *ITD* mutations, as the prognostic effect of *TKD* mutations in uncertain. (6)

Several Laboratories offer these tests including Quest Diagnostics, Medical Genetic Laboratories of Baylor College, Geneva Labs of Wisconsin, LabPMM and ARUP Laboratories.

Rationale

Literature Review
This policy was created in 2014 and is based on a search of the MEDLINE database through June 11, 2014. Literature that describes the analytic validity, clinical validity, and clinical utility of genetic testing for *FLT3* and *NPM1* mutations was sought.

Analytic validity (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 *FLT3* or *NPM1* mutation testing is identified.

Clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

Published data on the clinical validity of *FLT3* testing is lacking, however, a review article highlights that a major limitation of most PCR assays for *FLT3/ITD* mutations is lack of sensitivity, compared with polymerase chain reaction (PCR) assays for other acute myeloid leukemia (AML)-associated genetic alterations. (6) 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. (6)

This bias can be minimized using fewer PCR cycles, but this could affect the sensitivity if there is a low burden of leukemia cells in the sample. (6)

Published data on the clinical validity of testing for *NPM1* mutations is not identified.

Clinical utility (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 clinical utility of molecular testing for *FLT3* and *NPM1* mutations is in whether such testing will change patient management and if this change in management will lead to improved patient outcomes.

The literature on the use of these markers consists of retrospective analyses, and no prospective studies have been published to date.

Most of the literature consists of analyses of *FLT3/ITD* mutations and survival outcomes with the use of allogeneic hematopoietic stem-cell transplantations (HSCT) in patients depending on the presence of this type of mutation. In general, the data support the use of HSCT in patients with *FLT3/ITD* mutations, however, not all studies have shown consistent results. (6)

Gale et al first reported the results of a retrospective analysis of *FLT3* status in patients enrolled in 2 trials in the United Kingdom. (10) The trials included 1135 adult patients with AML, of whom 141 received autologous HSCT and 170 an allogeneic HSCT in first complete remission (CR), based on donor availability. An *FLT3/ITD* was detected in 283 of the total study population of 1135. Of the patients who underwent autologous HSCT (n=141), 37 (26%) were *FLT3/ITD*-positive and among those who received an allogeneic HSCT (n=170), 35 (21%) were *FLT3/ITD*-positive. The clinical investigators were not aware of *FLT3/ITD* status and did not direct treatment based on *FLT3* mutation status. There was no difference in effect on relapse rate with the use of autologous versus allogeneic HSCT (OR=2.39; CI, 1.24 to 4.62 for autologous and OR=1.31; CI, 0.56 to 3.06 for allogeneic; p=0.3), nor between patients who did or did not receive a transplant (p=0.4).

They performed an additional analysis of the effect of allogeneic HSCT in *FLT3/ITD*-positive patients, by performing a donor versus no donor analysis of 683 patients in whom *FLT3/ITD* status was available. No difference in relapse rate was noted in *FLT3/ITD*-positive versus negative patients (OR=0.70, CI, 0.53 to 0.92 versus OR=0.59, CI, 0.40 to 0.87, respectively; p=.5).

The authors concluded that their results suggest that there is no strong evidence that *FLT3* status should influence the decision whether to proceed to transplant.

In 2012, Brunet et al retrospectively compared outcomes for *FLT3/ITD* AML patients registered in the European Group for Blood and Marrow Transplantation (EBMT) who underwent a myeloablative allogeneic HSCT in first remission, compared with patients without the mutation. (11) Of 1467 patients who met inclusion criteria (age 18 years or older, de novo AML, normal cytogenetics at diagnosis, myeloablative allogeneic HSCT performed between 2000 and 2008), 206 (14%) had *FLT/ITD* data. *FLT/ITD* was present in 120 patients, absent in 86. At 2 years, the relapse incidence was 30% +/- 5% versus 16% +/- 5% (p=0.006) in *FLT3/ITD*-positive versus *FLT3/ITD*-negative patients, and leukemia-free survival (LFS) 58% +/- 5% versus 71% +/- 6% (p=0.04), in *FLT3*-positive patients versus negative, respectively. Although the presence of *FLT3/ITD* led to a higher relapse risk and inferior LFS in this study when compared with the *FLT3*-negative patients, the observed 2-year LFS of 58% and the relapse risk of 30% in the patients with the *FLT3/ITD* mutation compares favorably with outcomes that have been reported in patients with *FLT3/ITD* mutations after post-remission chemotherapy (ie, that did not undergo transplant), which has been reported to have a median survival of 2.5 months.

Bornhäuser et al reported the results of the AML 96 study of the DSIL (German study initiative leukemia) in which 999 patients 60 years of age or younger were prospectively included between 1996 and 2003 and stratified according to cytogenetic risk category. (12) Of patients with intermediate-risk cytogenetics, 555 were available for evaluation of *FLT3* mutation status; 175 (31.5%) were *FLT3/ITD* positive. The rate of remission after 2 cycles of induction chemotherapy including high-dose Ara-C, was not different in patients with and without *FLT3/ITD* (68% vs 63%). The investigators decided to determine the impact of different consolidation therapies on overall survival (OS) and the probability of relapse with respect to *FLT3/ITD* mutation status. Patients underwent allogeneic HSCT (n=103), autologous HSCT (n=141) if no donor was available, or conventional consolidation chemotherapy consisting of high-dose Ara-c (n=132) if the patient could not mobilize autologous cells. After a median follow-up of 53 months, OS was not significantly different between *FLT3/ITD* positive and negative patients having undergone autologous or allogeneic HSCT. In the group that received conventional consolidation chemotherapy, *FLT3/ITD*-positive patients had an inferior probability of survival (21% vs 46%; hazard ratio [HR]=2.2; 95% CI, 1.4 to 3.5; p=0.001), and the relapse probability was significantly higher in *FLT3/ITD*-positive versus negative patients (94% vs 59%; HR=4.0; 95% CI, 2.5 to 6.6; p<0.001).

Dezern et al reviewed the clinical data from November 2004 to October 2008 of 133 consecutive patients with previously untreated AML. (13) Patients were between the ages of 20 and 59 and received induction and consolidation therapy at Johns Hopkins, and were followed through August 2010. Thirty-one patients (23%) harbored an *FLT3/ITD* mutation. Induction success was similar between the 2 groups with 20 of 31 (65%) of *FLT3/ITD* mutation patients and 52/85 (61%) of WT patients. Of the 20 *FLT3/ITD* patients in complete remission (CR1), 11 (55%) underwent allogeneic HSCT, 9 myeloablative and 2 nonmyeloablative. The *FLT3/ITD* patients who did not undergo HSCT either did not have a suitable donor or had precluding comorbidities. Seventeen (33%) of the WT patients underwent HSCT in CR1; 14 myeloablative, 1 syngeneic, 1 autologous and 1 nonmyeloablative allogeneic. In the *FLT3/ITD* nontransplant group, median relapse-free survival was 8.6 months (range 5.3-43.3 months) versus 54.1 months (range 6.4-69.9 months) in the *FLT3/ITD* transplant group (p=0.03). Median OS in the WT, nontransplant group versus the WT, transplant group was 57.3 months (range 3.9-64.4) versus 60 months, respectively (p=0.02).

The authors conclude that their study suggests an advantage of HSCT in patients with *FLT3/ITD* in early CR1. However, the number of patients transplanted was small

Willemze et al 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. (14) In both arms, patients who achieved CR received consolidation therapy with either an autologous or allogeneic HSCT. 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 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). The authors concluded that patients with very bad risk cytogenetics and/or *FLT3/ITD* mutation benefitted from high-dose cytarabine induction treatment.

Pratcorona et al reported on the outcomes of 303 patients with intermediate-risk cytogenetics AML who were treated with intensive chemotherapy. (15) They analyzed the effect of the ratio of *FLT3/ITD* to *FLT3* WT, depending on the presence of an *NPM1* mutation. *FLT3/ITD* mutations were identified in 94 (31%) of patients and *NPM1* mutations in 161 (53%) of patients (65 patients harbored both mutations). To further confirm the prognostic value of the *FLT3/ITD* mutations to WT ratio, the patients were also subdivided into *FLT*3wt, *FLT3-ITD*/wt, ratio <0.5 (low ratio) and *FLT3-ITD*/wt ratio ≥0.5 (high ratio). The 0.5 cutoff value was chosen based on maximum clinical prognostic impact derived at that threshold as, in this series, this cutoff showed the greatest difference in relapse rate in patients with *FLT3/ITD*. Among the patients with *NPM1* mutations, *FLT*wt and low ratio groups showed similar OS, relapse risk, and LFS. High ratio patients had a worse outcome. In patients without *NPM1* mutations, *FLT3/ITD* subgroups showed comparable outcomes, with a higher risk of relapse and shortened OS than WT *FLT3* patients.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers
None.

Clinical Trials:
No ongoing phase 3 trials comparing the outcomes of allogeneic or autologous HSCT depending upon *FLT3* or *NPM1* mutation status are identified.

Summary
Acute myeloid leukemia (AML) is a heterogeneous disease and treatment is based on risk stratification, mainly by patient age and tumor cytogenetics (karyotyping), which allow for patients to be divided into good, intermediate, and poor risk categories. The identification of mutations in several genes, including *FLT3* and *NPM*, have been proposed to allow for further segregation of prognostic categories in the cytogenetically normal group.

FLT/ITD mutations are known to confer a very poor prognosis, whereas *NPM1* mutations have been shown to confer an independently favorable prognosis, and limited data suggest that a coexistent *NPM1* mutation may mitigate the negative prognostic effect of an *FLT/ITD* mutation, if both mutations are present. The prognostic effect of *FLT/TKD* mutations is uncertain.

Data on the analytic and clinical validity of *FLT3* and *NPM1* mutation testing are lacking. Data on the clinical utility of testing for these mutations is limited to retrospective analyses, and consist predominantly of studies of the effect of the presence of a *FLT3/ITD* mutation in patients who underwent hematopoietic stem-cell transplant versus those who did not. Although some controversy exists as to the survival benefit in transplanting a patient with an *FLT3/ITD* mutation, retrospective studies, in general, have suggested a survival benefit in transplanting these poor risk patients, and major professional societies and guidelines recommend testing for these mutations for risk stratification and treatment management decisions, including possible hematopoietic stem-cell transplantation.

Therefore, genetic testing for *FLT3* internal tandem duplication (*FLT3/ITD*) and *NPM1* mutations may be considered medically necessary in cytogenetically normal AML, whereas genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations is considered investigational.

Practice Guidelines

The 2014 National Comprehensive Cancer Network guidelines for Acute Myeloid Leukemia (16)(16)(v 2.2014) 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.

Evaluation of several molecular markers (e.g., FLT3, NPM1, CEBPA, and c-KIT) may be important for risk assessment and prognostication, and may also guide treatment decisions.

The American Society of Clinical Oncology states that classification of AML increasing relies on genetic analysis and that broad-based mutation profiling of AML will be helpful in defining important prognostic subgroups and may contribute to the selection of patients for enrollment into trials with novel inhibitors.

The Alberta Provincial Hematology Tumour Team issued a 2009 guideline on acute myeloid leukemia that includes the 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 and NPM is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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Billing Coding/Physician Documentation Information

81245 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)
81310 NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants

Additional Policy Key Words

N/A

Policy Implementation/Update Information

9/1/14 New policy; considered investigational.
