FEP 2.04.124 Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia

Effective Date: April 1, 2019

Related Policies:
5.21.93 Rydapt (midostaurin)

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

OBJECTIVE
The objective of this evidence review is to examine whether genetic testing for FLT3, NPM1, and CEBPA variants improve health outcomes in individuals with cytogenetically normal acute myeloid leukemia.

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

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

Genetic testing for FLT3 tyrosine kinase domain variants is considered investigational.

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

POLICY GUIDELINES
Genetic testing for cytogenetically normal acute myeloid leukemia is intended to guide management decisions in patients who would receive treatment other than low-dose chemotherapy or best supportive care.
FEP 2.04.124 Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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

Summary of Evidence

For individuals who have cytogenetically normal AML who receive genetic testing for variants in FLT3, NPM1, and CEBPA to risk-stratify AML, the evidence includes RCTs, retrospective observational studies, and systematic reviews of these studies. The relevant outcomes are OS, disease-specific survival, test validity, and treatment-related mortality and morbidity. FLT3-ITD variants confer a poor prognosis, whereas NPM1 (without the FLT3-ITD variant) and biallelic CEBPA variants confer a favorable prognosis. The prognostic effect of FLT3 TKD variants is uncertain. Data have suggested an OS benefit with transplantation for patients with FLT3-ITD, but do not clearly demonstrate an OS benefit of transplantation for patients with NPM1 and CEBPA variants. Major professional societies and practice guidelines have recommended testing for these variants to risk-stratify and to inform treatment management decisions, including possible hematopoietic cell transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements
National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (v.1.2019 provide the following recommendations: 14.

For the evaluation for acute leukemia, “bone marrow core biopsy and aspirate analysis, including immunophenotyping and cytochemistry.”

“A variety of gene mutations are associated with specific prognoses (category 2A) and may guide medical decision making (category 2B). Other mutations, such as FLT3-ITD, FLT3-TKD, IDH1/2, NPM1, and c-KIT may have therapeutic implications. This field of genomics in myeloid malignancies, and related implications in AML, are evolving rapidly. While the above mutations should be tested in all patients, multiplex gene panels and next generation sequencing analysis may be used to obtain a more comprehensive prognostic assessment.”

The guideline defined the following risk status based on molecular abnormalities:
FEP 2.04.124 Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia

- Mutated NPM1 without FLT3-ITD or with FLT3-ITD<sub>low</sub>: favorable risk
- Biallelic CEBPA: favorable risk
- Wild-type NPM1 and FLT3-ITD<sub>high</sub>: 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 1 outlines the risk stratification by genetic variants, and Table 2 summarizes recommended conventional care regimens based on risk category and age.

### Table 1. Risk Stratification by Genetic Variant

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

Table 2. 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><strong>Patients 18 to 60/65 years</strong></td>
<td></td>
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<tr>
<td>Favorable</td>
<td>• 2 to 4 cycles intermediate-dose cytarabine</td>
</tr>
<tr>
<td>Intermediate</td>
<td>• Allogeneic HCT from matched related or unrelated donor</td>
</tr>
<tr>
<td></td>
<td>• 2 to 4 cycles intermediate-dose cytarabine</td>
</tr>
<tr>
<td></td>
<td>• High-dose therapy and autologous HCT</td>
</tr>
<tr>
<td>Adverse</td>
<td>• Allogeneic HCT from matched related or unrelated donor</td>
</tr>
<tr>
<td><strong>Patients &gt;60/65 years</strong></td>
<td></td>
</tr>
<tr>
<td>Favorable</td>
<td>• 2 to 3 cycles intermediate-dose cytarabine</td>
</tr>
<tr>
<td>Intermediate/adverse</td>
<td>• Consider allogeneic HCT from matched related or unrelated donor</td>
</tr>
<tr>
<td></td>
<td>• Investigational therapy</td>
</tr>
</tbody>
</table>


U.S. Preventive Services Task Force Recommendations
Not applicable.

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

REFERENCES
9. Whitman SP, Maharry K, Radmacher MD, et al. FLT3 internal tandem duplication associates with adverse outcome and gene- and microRNA-expression signatures in patients 60 years of age or older with
FEP 2.04.124 Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia


POLICY HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>September 2014</td>
<td>New Policy</td>
<td>Policy updated with literature review; references 10-13 and 20-22 added. Title revised and medically necessary statement added for CEBPA mutation.</td>
</tr>
<tr>
<td>September 2015</td>
<td>Update Policy</td>
<td>Policy updated with literature review through November 6, 2017; references 2, 16-20, 23-26, 28, and 36-38 added. Policy statements unchanged. Title changed to “Genetic Testing for FLT3, NPM1, and CEBPA Variants in Cytogenetically Normal Acute Myeloid Leukemia”</td>
</tr>
<tr>
<td>March 2018</td>
<td>Update Policy</td>
<td>Policy updated with literature review through October 29, 2018; no references added. Policy statements unchanged.</td>
</tr>
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