

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

Effective Date: April 15, 2018

Related Policies:
5.21.93 Rydapt (midostaurin)

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

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.

FDA REGULATORY STATUS

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, are available under the auspices of the Clinical Laboratory Improvement Amendments. 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 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). FDA Premarket Approval was granted for the LeukoStrat® CDx *FLT3* Mutation Assay is a PCR-based, in vitro diagnostic test designed to detect internal tandem duplication (ITD) mutations and the tyrosine kinase domain mutations D835 and I836 in the *FLT3* gene in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with acute myelogenous leukemia (AML). The LeukoStrat® CDx *FLT3* Mutation Assay is used as an aid in the selection of patients with AML for whom RYDAPT (midostaurin) treatment is being considered. The LeukoStrat® CDx *FLT3* Mutation Assay is to be performed only at Laboratory for Personalized Molecular Medicine (LabPMM) LLC, a single site laboratory located at 6330 Nancy Ridge Dr., San Diego, CA 92121. (P160040)

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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.

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.² 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.³

Recent reviews (2012-2014) have highlighted the evolving classification of AML into distinct molecular subtypes.⁴⁻⁷

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

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BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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

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 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

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (3.2017) provide the following recommendations¹⁴:

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 2017.³⁹ The panel of 22 international experts on AML

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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

Genetic Variant	Risk Category
Biallelic <i>CEBPA</i>	Favorable
Mutated <i>NPM1</i> without <i>FLT3</i> -ITD	Favorable
Mutated <i>NPM1</i> with <i>FLT3</i> -ITD (low allelic ratio)	Favorable
Mutated <i>NPM1</i> with <i>FLT3</i> -ITD (high allelic ratio)	Intermediate
Wild-type <i>NPM1</i> without <i>FLT3</i> -ITD	Intermediate
Wild-type <i>NPM1</i> with <i>FLT3</i> -ITD (low allelic ratio)	Intermediate
Wild-type <i>NPM1</i> with <i>FLT3</i> -ITD (high allelic ratio)	Adverse

Adapted from Dohner et al (2017).³⁹
ITD: internal tandem duplication.

Table 2 Conventional Care Regimens by Risk and Age Categories

Risk and Age Categories	Conventional Care
Patients 18 to 60/65 years	
Favorable	<ul style="list-style-type: none"> • 2 to 4 cycles intermediate-dose cytarabine
Intermediate	<ul style="list-style-type: none"> • Allogeneic HCT from matched related or unrelated donor • 2 to 4 cycles intermediate-dose cytarabine • High-dose therapy and autologous HCT
Adverse	<ul style="list-style-type: none"> • Allogeneic HCT from matched related or unrelated donor
Patients >60/65 years	
Favorable	<ul style="list-style-type: none"> • 2 to 3 cycles intermediate-dose cytarabine
Intermediate/adverse	<ul style="list-style-type: none"> • Consider allogeneic HCT from matched related or unrelated donor • Investigational therapy

Adapted from Dohner et al (2017).³⁹
HCT: hematopoietic cell transplant.

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.

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POLICY HISTORY

Date	Action	Description
September 2014	New Policy	
September 2015	Update Policy	Policy updated with literature review; references 10-13 and 20-22 added. Title revised and medically necessary statement added for CEBPA mutation.
March 2018	Update Policy	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"

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