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FEP Medical Policy Manual

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

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2.04.147 - Next-Generation Sequencing for the Assessment of Measurable Residual Disease

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

Description

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Treatment of acute myeloid leukemia (AML) is based on risk stratification, primarily related to age and tumor cytogenetics. In individuals 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 the net health outcome 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-ITD*, *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 individuals who would receive treatment other than low-dose chemotherapy or best supportive care.

BENEFIT APPLICATION

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

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.

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, and they 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.

The FDA has granted approval for midostaurin (Rydapt, Novartis Pharmaceuticals), gilteritinib (Xospata, Astellas Pharma US), and quizartinib (Vanflyta, Daiichi Sankyo) for the treatment of acute myeloid leukemia with a *FLT3* mutation as detected by an FDA-approved test. A list of cleared or approved companion diagnostic devices can be found at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

RATIONALE

Summary of Evidence

For individuals who have cytogenetically normal acute myeloid leukemia (AML) who receive genetic testing for variants in *FLT3*, *NPM1*, and *CEBPA* to risk-stratify AML, the evidence includes randomized controlled trials (RCTs), retrospective observational studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related mortality and morbidity. *FLT3*-internal tandem duplication (ITD) variants confer a poor prognosis, whereas *NPM1* (without the *FLT3*-ITD variant), biallelic *CEBPA*, and single basic leucine zipper region-mutant *CEBPA* variants confer a favorable prognosis. The prognostic effect of *FLT3*-tyrosine kinase domain (TKD) 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have AML with a genetic variant in *FLT3*, *NPM1*, or *CEBPA,* the evidence for measurable residual disease (MRD) monitoring of these genetic variants is limited to mostly retrospective observational studies and a pooled analysis of 2 open-label, randomized controlled trials. Relevant outcomes are overall survival, disease-specific survival, test validity, and treatment-related mortality and morbidity. Detection of MRD based on *NPM1* variant presence is associated with higher risks for relapse and lower overall survival. In a pooled analysis of 2 open-label RCTs using MRD assessments of genetic variants to guide treatment decisions, a survival benefit was observed in the subgroup of patients with baseline *NPM1* and *FLT3*-ITD mutations, but not in the subgroup with baseline *NPM1* mutations without *FLT3*-ITD. For the use of genetic variants to detect MRD, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines for acute myeloid leukemia (AML) (v.3.2026) provide the following recommendations:[9,]

For the evaluation for acute leukemia, bone marrow core biopsy and aspirate analyses (including immunophenotyping by immunohistochemistry (IHC) stains with flow cytometry) and cytogenetic analyses are needed to risk stratify patients and potentially guide therapy of AML.

"Several gene mutations are associated with specific prognoses in a subset of patients (category 2A) and may guide treatment decisions (category 2B). Molecular analyses for lesions that allow risk stratification per ELN 2022 are recommended for all patients at diagnosis." All patients should be tested for mutations, and multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML in various phases of treatment." "To appropriately stratify therapy options, test results of molecular and cytogenetic analyses of immediately actionable genes or chromosomal abnormalities should be expedited."

The guideline defined the following risk status based on molecular abnormalities:

Table 1. Risk Factors Based on Genetic Abnormalities

Risk Category	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1); *RUNX 1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB::MYH11* • bZIP in-frame mutated *CEBPA* • Mutated *NPM1* without *FLT3*-ITD

Intermediate	• Mutated *NPM1* with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor/Adverse	• t(6;9)(p23.3;q34.1); *DEK::NUP214* • t(v;11q23.3); *KMT2A* rearranged • t(9;22)(q34.1;q11.2); *BCR::ABL*1 • t(8;16)(p11.2;p13.3); *KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* • t(3q26.2;v); *MECOM(EVI1)*-rearranged • -5 or del(5q); -7; -17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2* • Mutated *TP53*

Adapted from NCCN guidelines for AML (v.3.2026).
ITD: internal tandem duplication

The role of measurable (minimal) residual disease (MRD) assessment for prognosis and treatment is evolving. Per the NCCN:

- "There is compelling evidence in both children and adults with AML that detectable MRD following achievement of remission is associated with an increased risk of relapse."
- "The threshold to define MRD+ and MRD- samples depends on the technique and subgroup of AML."
- "The most frequently used methods for MRD assessment include quantitative molecular assays such as real-time quantitative PCR (RQ-PCR) and multicolor flow cytometry (MFC) assays specifically designed to detect abnormal MRD immunophenotypes."
- "The optimal sample for initial MRD assessment is a first, dedicated pull of the BM aspirate. The quality of the sample is of paramount importance to have reliable evaluation. Once MRD-negative remission by BM is achieved, peripheral blood can be utilized for surveillance of MRD for PML::RAR alpha, NPM1, CBFB::MYH11, and RUNX1::RUNX1T1."
- "The Panel recommends RQ-PCR for detection of PML::RAR alpha, NPM1, CBFB::MYH11, and RUNX1::RUNX1T1. Utilization of an assay with a minimum limit of detection of ≤10^-4 is recommended."
- "For detection of FLT3-ITD, the Panel recommends a highly sensitive, NGS-based, targeted, deep-sequencing assay with a sensitivity level of ≤10^-5."

In a section on the management of MRD positivity, the NCCN notes:

- "For NPM1, CBFB::MYH11, and RUNX1::RUNX1T1-mutated AML, if MRD is persistently positive after induction and/or consolidation, consider a clinical trial or alternative therapies, including HCT."
- "As there is no clear optimal management of MRD positivity, the Panel favors a clinical trial for MRD positivity if available."

European LeukemiaNet

The European LeukemiaNet international expert panel recommendations for the diagnosis and management of adults with AML were updated in 2017 and again in 2022.[61,62,] The most recent update reflects the 2022 changes to the World Health Organization classification of AML. The panel 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 2 outlines the risk stratification by genetic variants, and Table 3 summarizes recommended conventional care regimens based on patient fitness and risk characteristics, including mutations and other considerations.

The European LeukemiaNet MRD Working Party is an international expert panel convened with the objective of providing guidelines for technical assessment and clinical use of immunophenotypic and molecular MRD testing in AML; the panel's first consensus recommendations were published in 2018, and updated recommendations were published in 2021.[63,7,] In the 2021 update, the panel recommended that molecular MRD be assessed by real-time quantitative or digital polymerase chain reaction in patients with *NPM1*, *CBFB-MYH11*, or *RUNX1-RUNX1T1* mutations, and by MFC in all other patients. NGS-based MRD monitoring is considered by the panel to be "useful to refine prognosis in addition to MFC but, to date, there are insufficient data to recommend NGS-MRD as a stand-alone technique." The panel also defined MRD positivity thresholds according to whether <FC or polymerase chain reaction techniques were used, and provisional MRD positivity thresholds for NGS techniques.

Table 2. Risk Stratification by Genetic Variant

Risk Category	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • *inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11* • *Mutated NPM1 without FLT3-ITD* • *Basic leucine zipper in-frame mutated CEBPA*
Intermediate	• *Mutated NPM1 with FLT3-ITD* • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP* • *inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1)* • *t(3q26.2;v)/MECOM(EVI1)-rearranged* • *−5 or del(5q); −7; −17/abn(17p)* • *Complex karyotype, monosomal karyotype* • *Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* and/or *ZRSR2* • *Mutated TP53*

Adapted from Dhner et al (2022).[62,]
ITD: internal tandem duplication.

Table 3. Selected Conventional Care Regimens by Fitness and Risk Characteristics

Patient Characteristics	Induction Therapy	Consolidation Therapy	Maintenance Therapy	Salvage therapy
Considered fit for intensive therapy				
With *FLT3* mutation	Anthracycline plus cytarabine ("7 + 3") plus midostaurin	• Intermediate-dose cytarabine plus midostaurin and/or • If relapse probability with chemotherapy alone >35% to 40%*: allo-HCT	Midostaurin	Gilteritinib or options for other fit patients listed below
Without *FLT3* mutation	"7 + 3"	• Intermediate-dose cytarabine and/or • If relapse probability with chemotherapy alone >35% to 40%*: allo-HCT	Oral azacitidine	• Intermediate-dose cytarabine with or without anthracycline • FLAG-IDA chemotherapy • MEC chemotherapy
CD33-positive AML with favorable- or intermediate-	"7 + 3" with ("other" option) or without gemtuzumab	• Intermediate-dose cytarabine with ("other" option) or without	--	

risk disease	ozogamicin	gemtuzumab ozogamicin, and/or • If relapse probability with chemotherapy alone >35% to 40%*: allo-HCT		• CLAG-M chemotherapy • allo-HCT
AML with myelodysplasia-related changes or therapy-related AML	"7 + 3" or liposomal-coformulated daunorubicin and cytarabine ("other" option)	• Intermediate-dose cytarabine or liposomal-coformulated daunorubicin and cytarabine ("other" option), and/or • If relapse probability with chemotherapy alone >35% to 40%*: allo-HCT	--	
Not considered fit for intensive therapy				
With *FLT3* mutation	• Venetoclax plus either azacitidine or decitabine • Venetoclax plus low-dose cytarabine • *IDH1* mutation: ivosidenib with or without azacitidine • Best supportive care			Gilteritinib
Without *FLT3* mutation				• *IDH1* mutation: ivosidenib • *IDH2* mutation: enasidenib

Adapted from Dhner et al (2022).[62,]
*Examples include intermediate- or adverse-risk disease and/or inadequate clearance of measurable residual disease.
allo: allogeneic, AML: acute myeloid leukemia, HCT: hematopoietic cell transplant.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2014	New policy	
September 2015	Replace 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	Replace 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,
March 2019	Replace policy	Policy updated with literature review through October 29, 2018; no references added. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through November 11, 2019; reference on NCCN guidelines updated. Policy statements unchanged.
March 2021	Replace policy	Policy updated with literature review through November 22, 2020; references added. Policy statements unchanged.
March 2022	Replace policy	Policy updated with literature review through November 15, 2021; references added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through November 15, 2022; references added. Minor editorial refinements to policy statements; intent unchanged.
March 2024	Replace policy	Policy updated with literature review through December 4, 2023; no references added. Policy statements unchanged.
March 2025	Replace policy	Policy updated with literature review through November 27, 2024; references added. Policy statements unchanged.
March 2026	Replace policy	Policy updated with literature review through November 26, 2025; references added. Policy statements unchanged.