MEDICAL POLICY

POLICY TITLE	**GENETIC TESTING FOR FLT3, NPM1, AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA**
POLICY NUMBER	**MP 2.357**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**1/1/2025**

I. POLICY

Genetic testing for *FLT3, NPM1*, and *CEBPA* variants may be considered **medically necessary** in cytogenetically normal acute myeloid leukemia (see Policy Guidelines section).

Genetic testing for *FLT3*, *NPM1* and *CEBPA* variants is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Genetic testing for *FLT3*, *NPM1* and *CEBPA* variants to detect minimal residual disease is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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.

Cross-reference:

MP 2.379 Next Generation Sequencing for the Assessment of Measureable Residual Disease
MP 9.040 Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

POLICY TITLE	GENETIC TESTING FOR FLT3, NPM1, AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA
POLICY NUMBER	MP 2.357

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

Acute Myeloid Leukemia

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 20,250 new cases of AML and 11,540 deaths from AML in the United States in 2022.

Diagnosis and Prognosis of AML

The most recent World Health Organization classification (2022) 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 variants). These cytogenetic and molecular changes form distinct clinic 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 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 a variant of the *NPM1* gene, encoding a shuttle protein within the nucleolus. “AML with *NPM1* mutation” and "AML with *CEBPA* mutation" were included as categories in the 2022 World Health Organization classification of acute leukemias. AML with *FLT3* variants is not considered a distinct entity in the 2022 or prior 2016 classifications. The 2008 World Health Organization classification recommended determining the presence of *FLT3* variants because of the prognostic significance.

Treatment

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, enrollment in clinical trials with innovative compounds, palliative cytotoxic treatment, or supportive care only. For patients who achieve complete remission after induction treatment, possible post remission treatment options include intensive consolidation therapy, maintenance therapy, or autologous or allogeneic hematopoietic cell transplant.

Measurable (Minimal) Residual Disease Monitoring

Relapse in AML is believed to be due to residual clonal cells that remain following "complete response" after induction therapy but are below the limits of detection using conventional morphologic assessment. Residual clonal cells that can be detected in the bone marrow or blood are referred to as measurable residual disease (MRD), also known as minimal residual disease. MRD assessment is typically performed by multiparameter flow cytometry or polymerase chain reaction with primers for common variants. It is proposed that finding MRD at different time points in the course of the disease (e.g., after initial induction, prior to allogenic transplantation) may be able to identify patients at a higher risk for relapse. In those with a high risk of relapse during the first remission, stem cell transplantation may be more appropriate treatment approach. Studies in both children and adults with AML have demonstrated the correlation between MRD and risk for relapse. The role of MRD monitoring in AML is evolving, and important limitations remain. Some patients may have relapse despite having no MRD, while others do not relapse despite being MRD positive. Standards have recently been introduced for identifying certain individual markers for MRD assessment, and threshold values delineating MRD positivity and negativity have recently been defined for multiparameter flow cytometry and some variants detected by polymerase chain reaction or other methods.

FLT3 Variants

FMS-like tyrosine kinase (FLT3) plays a critical role in normal hematopoiesis and cellular growth in hematopoietic stem and progenitor cells. Variants in FLT3 are among the most frequently encountered in AML. FLT3 variants are divided into 2 categories: (1) internal tandem duplications (FLT3-ITD) variants, 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 variants are much more common than FLT3-TKD variants, occurring in 30 % of newly diagnosed adult cases of AML, versus FLT3-TKD variants, occurring in about 10 % of patients. FLT3-ITD variants are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age with normal- or intermediate-risk cytogenetics and are associated with an increased risk of relapse and inferior overall survival. Patients with FLT3-ITD variants have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild-type (WT; i.e., nonmutated) FLT3. Although remission can be achieved in patients with FLT3-ITD variants 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 an FLT3-ITD variant is 6 to 7 months compared with 9 to 11 months in patients with other AML subtypes.

Because of the high-risk of relapse, hematopoietic cell transplantations as consolidation therapy of the first remission for an FLT3-ITD AML patient is often considered. However, this treatment must be weighed against the treatment-related mortality associated with a transplant.

The clinical significance of an FLT3 variant varies by the nature of the variant and the context in which it occurs. Longer FLT3-ITD variants have been associated with reduced remission rates and/or worse survival in some studies.

For FLT3-ITD variants, the 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 variant detected at diagnosis is also present at relapse. However, in some cases, as FLT3/ITD positive AML evolves from diagnosis to relapse, the variant present at diagnosis may be absent (or undetectable) at relapse. This is most commonly seen where the mutant allele burden is low (5%-15%) at diagnosis. For this reason, and the overall lack of sensitivity of the assay, 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 variants is less certain and conflicting. Some studies have suggested a negative impact of tyrosine kinase domain variants on event-free survival and overall survival, while other studies have found no prognostic value, or potentially a benefit if a NPM1 mutation is also present. Next generation FLT3 tyrosine kinase inhibitors, with greater specificity for FLT3, have been under clinical investigation including gilteritinib, which was approved by the U.S. Food and Drug Administration (FDA) in 2018.

NPM1 Variants

A common molecular aberration in AML is a variant of NPM1, which is found in 28% to 35% of AML cases and is more common in cytogenetically normal AML.7, Up to 50% of AML with mutated NPM1 also carry an FLT3-ITD. Mutated NPM1 confers an independent favorable prognosis for patients with cytogenetically normal AML and either the presence or absence of an FLT3-ITD variant. Retrospective studies of banked clinical samples have suggested that an NPM1 variant may mitigate the negative prognostic effect of an FLT3-ITD variant, but possibly only if the FLT3-ITD-to-WT allelic ratio is low. The prognostic impact in patients with an abnormal karyotype is unclear.

CEBPA Variants

CEBPA (CCAAT/enhancer-binding protein) is a transcription factor gene that plays a role in cell cycle regulation and cell differentiation. Variants to CEBPA are found in approximately 7% to 11% of AML patients. CEBPA variants can be either biallelic (double variants) or monoallelic. Monoallelic variants are prognostically similar to CEBPA WT variant and do not confer a favorable prognosis in cytogenetically normal AML; double variants of CEBPA have shown a

better prognosis with higher rates of complete remission and overall survival after standard induction chemotherapy.

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 Sakyo) 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.

IV. RATIONALE

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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*-internal tandem duplication (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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AML with a genetic variant in FLT3, NPM1, and CEBPA, the evidence for measurable residual disease (MRD) monitoring of these genetic variants is limited to retrospective observational studies. 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; prospective evaluations using MRD results to direct prognostic evaluation and treatment

decisions are needed. 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.

V. DEFINITIONS TOP

NA

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes							
0046U	0049U	0050U	0171U				

Covered when medically necessary:

Procedure Codes							
81218	81245	81246	81310	0023U			

ICD-10-CM Diagnosis Code	Description
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.01	Acute myeloblastic leukemia, in remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.61	Acute myeloid leukemia with 11q23-abnormality in remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse

IX. REFERENCES

TOP

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X. POLICY HISTORY

TOP

MP 2.357	**04/30/2018 New Policy**. Adopting BCBSA criteria. Coding reviewed.
	03/25/2019 Consensus Review. No change to policy statements. Background, summary of evidence, and references reviewed.
	04/01/2020 Administrative Update. Coding update. New code 0171U added as investigational.
	04/01/2020 Consensus Review. Policy statements unchanged. Coding reviewed; references updated.
	03/16/2021 Consensus Review. Updated product variations, description/background, policy guidelines, summary of evidence, and references.
	03/23/2022 Minor Review. FLT3-TKD testing is now MN. Updated cross references, FEP, background, coding, and references.
	09/14/2022 Administrative Update. Removed code 0056U as of 10/1/2022.

POLICY TITLE	GENETIC TESTING FOR FLT3, NPM1, AND CEBPA VARIANTS IN CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA
POLICY NUMBER	MP 2.357

	04/21/2023 Consensus Review. Updated background and references. 0046U and 0049U moved to non-covered coding table as these tests are for MRD per the manufacturer.
	03/13/2024 Consensus Review. Updated background and references. No changes to coding.
	11/20/2024 Administrative Update. Removed NCCN statement.

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