Medical Policy

Genetic Testing for \textit{FLT3, and NPM1, and CEBPA} Mutations in Cytogenetically Normal Acute Myeloid Leukemia

Table of Contents

- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 693
BCBSA Reference Number: 2.04.124
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies

- Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia, #150

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Genetic testing for \textit{FLT3} internal tandem duplication (\textit{FLT3-ITD}), \textit{NPM1}, and \textit{CEBPA} variants may be considered \textbf{MEDICALLY NECESSARY} in cytogenetically normal acute myeloid leukemia.

Genetic testing for \textit{FLT3} internal tandem duplication (\textit{FLT3-ITD}), \textit{NPM1}, and \textit{CEBPA} variants is considered \textbf{INVESTIGATIONAL} in all other situations.

Genetic testing for \textit{FLT3} tyrosine kinase domain (\textit{FLT3-TKD}) variants is considered \textbf{INVESTIGATIONAL}.

Genetic testing for \textit{FLT3}, \textit{NPM1}, and \textit{CEBPA} variants to detect minimal residual disease is considered \textbf{INVESTIGATIONAL}.

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.

Medicare HMO Blue\textsuperscript{SM} and Medicare PPO Blue\textsuperscript{SM} Members

Medical necessity criteria and coding guidance for \textbf{Medicare Advantage members living in Massachusetts} can be found through the link below.

\url{Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)}
For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tr>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.
The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81245</td>
<td>FLT3 (fms-related tyrosine kinase 3)(eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)</td>
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<td>81218</td>
<td>CEBPA (CCAAT/enhancer binding protein [C/EBP], Alpha) (EG, acute myeloid leukemia), gene analysis, full gene sequence</td>
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<td>81310</td>
<td>NPM1 (nucleophosmin)(eg, acute myeloid leukemia) gene analysis, exon 12 variants</td>
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The following CPT code is considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

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<tr>
<td>81246</td>
<td>FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)</td>
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<td>0023U</td>
<td>Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin</td>
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Description
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. It was estimated that, in 2014, 18,860 people would be diagnosed with AML and 10,460 would die of the disease. Median age at diagnosis is 66 years, with approximately 1 in 3 patients diagnosed at 75 years of age or older.1

Diagnosis and Prognosis of AML
The most recent World Health Organization (WHO) 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, 3 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 WHO classification of acute leukemias. AML with FLT3 variants is not considered a distinct entity in the 2016 classification. The 2008 WHO classification recommends determining the presence of FLT3 variants because of the prognostic significance.3 Recent reviews (2012-2013) have highlighted the evolving classification of AML into distinct molecular subtypes.1,4-6

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 complete remission (CR) after induction treatment, possible postremission treatment options include intensive consolidation therapy, maintenance therapy, or autologous or allogeneic hematopoietic cell transplant.1

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 one of the most frequently encountered variants in AML, and approximately 30% of AML patients harbor some form of FLT3 variant.7 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 variants 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 25% of newly diagnosed adult cases of AML, versus FLT3-TKD variants, occurring in about 7% of patients. FLT3-ITD variants are a well-documented adverse prognostic marker, particularly in patients younger than 60 years of age and with normal- or intermediate-risk cytogenetics, and are associated with an increased risk of relapse and inferior overall survival (OS).7,9 Patients with FLT3-ITD variants have a worse prognosis when treated with conventional chemotherapy, compared with patients with wild-type (WT; ie, 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. Once FLT3-ITD AML relapses, the disease is rapidly fatal. Because of the high risk of relapse, HCT as consolidation therapy of a 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 (see the Clinical Validity section), 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 has only been studied in small numbers of patients. FLT3 tyrosine kinase inhibitors are under active clinical investigation.

NPM1 VARIANTS
The most common molecular aberration in AML is a variant of NPM1, which is found in 46% to 64% of patients with cytogenetically normal AML (CN-AML) and in 9% to 18% of patients with cytogenetically abnormal AML. Up to 50% of AML with mutated NPM1 also carry an FLT3-ITD. Mutated NPM1 confers an independent favorable prognosis for patients with CN-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 15% of AML patients with a normal karyotype. 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 CN-AML; double variants of CEBPA have shown a better prognosis with higher rates of CR and OS after standard induction chemotherapy.

Summary
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.

For individuals who have cytogenetically normal AML who receive genetic testing for variants in FLT3, NPM1, CEBPA to risk-stratify AML, the evidence includes 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 (FLT3-ITD) variants confer a poor prognosis, whereas NPM1 (without 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.

Policy History

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<tr>
<td>3/2017</td>
<td>BCBSA National medical policy review. Title updated to clarify that policy applies to cytogenetically normal AML. New references added. 3/1/2017</td>
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<td>1/2016</td>
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<td>6/2015</td>
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<td>1/2015</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:

- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References

10. Whitman SP, Ruppert AS, Radmacher MD, et al. FLT3 D835I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo


