Corporate Medical Policy

Genetic Testing for Acute Myeloid Leukemia AHS-M2062

Description of Procedure or Service

Acute myeloid leukemia (AML) is characterized by large numbers of abnormal, immature myeloid cells in the bone marrow and peripheral blood resulting from genetic changes in hematopoietic precursor cells which disrupt normal hematopoietic growth and differentiation (Stock, 2017).

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for acute myeloid leukemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Acute Myeloid Leukemia is covered

The use of genetic testing for acute myeloid leukemia is considered medically necessary for the following:

A. Genetic testing for FLT3 internal tandem duplication (FLT3/ITD), IDH1, IDH2, TET2, WT1, DNMT3A, ASXL1 and/or TP53 MEETS COVERAGE CRITERIA in adult and pediatric patients with suspected or confirmed AML of any type for prognostic and/or therapeutic purposes.

B. Genetic testing for KIT mutations for adult and pediatric patients with confirmed core-binding factor (CBF) AML (AML with t(8;21)(q22;q22.1); RUNX1-RUNXIT1 or inv(16)(p13.1q22); CBFB-MYH11).

C. Genetic testing for NPM1, CEBPA, and RUNX1 mutations for patients other than those with confirmed core binding factor AML or AML with myelodysplasia-related cytogenic abnormalities.

When Genetic Testing for Acute Myeloid Leukemia is not covered
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The use of genetic testing for acute myeloid leukemia is considered **investigational** in all other situations of the FLT3 and NPM1, including, but not limited to the following:

A. Genetic testing for FLT3 tyrosine kinase domain (FLT3/TKD) mutations;
B. Genetic testing for FLT3, NPM1, CEBPA, IDH ½, and KIT mutations to detect minimal residual disease

The use of global/gene specific methylation, micro RNA (miRNA) expression, or gene expression analysis for diagnosis or prognosis in patients with confirmed acute leukemia is considered **investigational**.

**Policy Guidelines**

AML is the most common acute leukemia in adults (80%), with a median age at diagnosis of 65 years, and generally associated with a poor prognosis. It is much less common in children less than 10 years of age, where less than 10 percent of acute leukemias are diagnosed as AML (C. A. Schiffer, John, 2017; Siegel, Miller, & Jemal, 2017; J. F. Yamamoto & Goodman, 2008).

Clinical presentation includes symptoms related to complications of pancytopenia, including weakness and fatigability (Meyers, Albitar, & Estey, 2005), infections of variable severity, and hemorrhagic findings (Nebgen, Rhodes, Hartman, Munsell, & Lu, 2016); (C. Schiffer, 2017).

Analysis of gene sequencing of AML cases generally reveal more than 10 significant gene mutations, many of which are thought to participate in leukemogenesis (CGARN, 2013). Mutations impacting signal activation are frequent (60 percent of cases) the most common of which are mutations in FLT3 (28 percent)(Stock, 2017). FLT3 is a transmembrane tyrosine kinase receptor that stimulates cell proliferation upon activation. Both internal tandem duplications of different lengths and point mutations in the activating loop of the kinase domain result in ligand-independent activation of the FLT3 receptor and a proliferative signal (Bacher, Haferlach, Kern, Haferlach, & Schnittger, 2008; Y. Yamamoto et al., 2001). The second most common mutation in AML (27 percent) is of nucleophosmin (NPM1), a ubiquitously expressed phosphoprotein that normally shuttles between the nucleus and cytoplasm, which prevents its transport to the nucleus (Falini et al., 2005; Stock, 2017). NPM1 mutations are associated with improved outcomes, although the mechanism is not known (C. Schiffer, 2017).

Analytic Validity

There is very limited published literature on the analytic validity and clinical validity of genetic testing for FLT3 and NPM1 mutations in AML. However, the analytic validity of PCR in general is extremely high (Molecular Pathology in Clinical Practice, 2016). The clinical utility of testing is to allow for further risk stratification, prognostication, and guide management decisions in patients with AML. Several studies have concluded that testing for FLT3 and NPM1 mutation testing in cytogenetically normal AML is useful for prognosis and treatment decision making (DeZern et al., 2011; Pastore et al., 2014; Willemze et al., 2014).

Clinical Validity and Utility

Dohner et al (2010) note that “AML with FLT3 mutations are not considered a distinct entity, although determining the presence of such mutations is recommended by WHO because they have prognostic significance.” The authors further state that “while testing for NPM1, CEBPA, and FLT3 is currently not considered mandatory outside clinical trials, the panel recommends that these 3 mutations be analyzed at least in patients with cytogenetically normal AML (CN-AML) who will receive treatment other than low-dose chemotherapy or best supportive care” (Dohner et al, 2010)

Devillier et al (2015) sought to “identify distinct biological and prognostic subgroups based on mutations of ASXL1, RUNX1, DNMT3A, NPM1, FLT3 and TP53 in 125 AML-MRC patients according to the presence of MLD, cytogenetics and outcome. ASXL1 mutations (n=26, 21%) were associated with a higher proportion of marrow dysgranulopoiesis (mutant vs. wild-type: 75% vs. 55%, p=0.030) and were mostly found in intermediate cytogenetic AML (23/26) in which they predicted inferior 2-year overall
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survival (OS, mutant vs. wild-type: 14% vs. 37%, p=0.030). TP53 mutations (n=28, 22%) were mostly found in complex karyotype AML (26/28) and predicted poor outcome within unfavorable cytogenetic risk AML (mutant vs. wild-type: 9% vs. 40%, p=0.040). In multivariate analysis, the presence of either ASXL1 or TP53 mutation was the only independent factor associated with shorter OS (HR, 95%CI: 2.53, 1.40-4.60, p=0.002) while MLD, MDS-related cytogenetics and previous MDS history did not influence OS. We conclude that ASXL1 and TP53 mutations identify two molecular subgroups among AML-MRCs, with specific poor prognosis. This could be useful for future diagnostic and prognostic classifications.”

According to Schiffer and Anastasi (2017), “abnormalities in certain genes, such as mutations in FLT3, nucleophosmin (NPM1), KIT, CEBPA, or RUNX1 as well as gene expression profiles confer prognostic significance in adult patients with AML.” They further recommend that “patients with newly diagnosed AML, particularly younger patients, should have these molecular genetic factors analyzed because they have prognostic importance, already have therapeutic implications with respect to post-remission therapy choices (transplant versus chemotherapy), and might become targets of agents undergoing development and study”(C. A. Schiffer, John, 2017).

Bolouri et al analyzed the “molecular landscape of pediatric acute myeloid leukemia (AML) and characterize nearly 1,000 participants in Children's Oncology Group (COG) AML trials. The COG-National Cancer Institute (NCI) TARGET AML initiative assessed cases by whole-genome, targeted DNA, mRNA and microRNA sequencing and CpG methylation profiling.” They found that “Validated DNA variants corresponded to diverse, infrequent mutations, with fewer than 40 genes mutated in >2% of cases. In contrast, somatic structural variants, including new gene fusions and focal deletions of MBNL1, ZEB2 and ELF1, were disproportionately prevalent in young individuals as compared to adults. Conversely, mutations in DNMT3A and TP53, which were common in adults, were conspicuously absent from virtually all pediatric cases. New mutations in GATA2, FLT3 and CBL and recurrent mutations in MYC-ITD, NRAS, KRAS and WT1 were frequent in pediatric AML. Deletions, mutations and promoter DNA hypermethylation convergently impacted Wnt signaling, Polycomb repression, innate immune cell interactions and a cluster of zinc finger-encoding genes associated with KMT2A rearrangements. These results highlight the need for and facilitate the development of age-tailored targeted therapies for the treatment of pediatric AML.”

Jongen-Lavrencic et al (2018) conducted a study of 482 patients 18 to 65 years with newly diagnosed AML. Targeted next-generation sequencing was carried out at diagnosis and after induction therapy (during complete remission). They found that “A comparison of sequencing with flow cytometry for the detection of residual disease showed that sequencing had significant additive prognostic value. Conclusions Among patients with AML, the detection of molecular minimal residual disease during complete remission had significant independent prognostic value with respect to relapse and survival rates, but the detection of persistent mutations that are associated with clonal hematopoiesis did not have such prognostic value within a 4-year time frame.”

State and Federal Regulations, as applicable

On April 28, 2017 the FDA approved the LeukoStrat® CDx FLT3 Mutation Assay as 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.”
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On August 1, 2017 the FDA approved the Abbott RealTime IDH2 as an “in vitro polymerase chain reaction (PCR) assay for the qualitative detection of single nucleotide variants (SNVs) coding nine IDH2 mutations (R140Q, R140L, R140G, R140W, R172K, R172M, R172G, R172S, and R172W) in DNA extracted from human blood (EDTA) or bone marrow (EDTA). Abbott RealTime IDH2 is for use with the Abbott m2000rt System.

Abbott RealTime IDH2 is indicated as an aid in identifying acute myeloid leukemia (AML) patients with an isocitrate dehydrogenase-2 (IDH2) mutation for treatment with IDHIFA® (enasidinib).”

**The 2016 World Health Organization classification of myeloid neoplasms and acute leukemia**

In the recent revision of the 4th edition on Classification of Tumors of Hematopoietic and Lymphoid Tissues, World Health Organization (WHO) incorporated new molecular genetic findings and clinical data into its classification of acute leukemias. WHO expanded on the prognostic significance of various gene mutations for each AML subtype. For example, for the AML with recurrent genetic abnormalities, inv (3) (q21.3; q26.2) doesn’t represent a fusion gene anymore, but rather a repositioning of a distal GATA2 enhancer leading to activation of MECOM (EV11) expression and GATA2 haploinsufficiency. The AML with CEBPA mutation is defined on the basis of biallelic mutation instead of single mutations because of prognostic significance. The provisional two categories are also added such as AML with RUNX1 for de novo AML without preexisting cytogenetic abnormalities associated with MDS and AML with BCR-ABL1 fusion gene. AML with NPM1 or biallelic CEBPA mutations and multilineage dysplasia are now considered separately instead of being a part of AML with myelodysplasia-related changes because of a lack of prognostic significance. The complete list for acute myeloid neoplasms 2016 WHO classification is shown in Figure 1 (Arber et al, 2016).

In the absence of JAK2, CALR, and MPL mutations, the presence of another clonal marker is included as one of the major diagnostic criteria for PMF. Additional mutation in ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2 and SF3B1 genes are noted to be of use in determining the clonal nature of the disease.
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Following recent progress in molecular genetic findings and 2016 WHO classification of acute leukemias, the College of American Pathologists (CAP) and the American Society of Hematology (ASH) have formed an expert panel to review and establish guidelines for appropriate laboratory testing. The published guideline provides twenty-seven guideline statements ranging from recommendations on what testing is appropriate for the diagnostic and prognostic evaluation of leukemias to where the testing should be performed and how results should be reported. The appropriate molecular genetic testing for AML is discussed starting from 16th guideline statement.

Expert panel strongly recommends testing for FLT3-ITD in adult and pediatric patients with suspected or confirmed AML of any type. They also recommend testing for other mutational analysis that could include, but not limited to, IDH1, IDH2, TET2, WT1, DNMT3A, and/or TP53 for prognostic and/or therapeutic purposes (Statement 16).

In the 17th guideline statement, expert panel strongly recommends testing for KIT mutation in adult patients with confirmed core-binding factor (CBF) AML (AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1 or inv(16)(p13.1q22)/t(16;16)(p13.1q22); CBFB-MYH11). It is only an expert consensus opinion for testing KIT mutation in pediatric patients with confirmed core binding factor AML (AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1 or inv(16)(p13.1q22)/t(16;16)(p13.1q22); CBFB-MYH11) which is not a strong recommendation (Statement 17).

The strong recommendation is also given for patients other than those with confirmed core binding factor AML, APL, or AML with myelodysplasia-related cytogenetic abnormalities that testing is needed for mutational analysis for NPM1, CEBPA, and RUNXI (Statement 19).

In the 20th guideline statement, expert panel is providing no recommendation on either for or against the use of global/gene specific methylation, micro RNA (miRNA) expression, or gene expression analysis for diagnosis or prognosis in patients with confirmed acute leukemia.

Finally, in their last statement, expert panel strongly recommends the use of current WHO terminology for the final diagnosis and classification of acute leukemias.


The NCCN Guidelines on Acute Myeloid Leukemia (2018), recommend bone marrow core biopsy and aspirate analysis including immunophenotyping and cytochemistry, cytogenetic analysis with karyotype with or without FISH, molecular analysis (KIT, FLT3 [ITD and TKD], NPM1, CEBPA, IDH1, IDH2, TP53 and other mutations) in the initial evaluation for Acute Leukemia:

NCCN also states that “A variety of gene mutations are associated with specific prognosis and may guide medical decision making. Currently, c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1/IDH2, and TP53 are included in this group; however, this field is 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(Papaemmanuil et al., 2016). The information obtained may have prognostic impact in AML, may influence medical decision making regarding consolidation with chemotherapy versus an allogeneic hematopoietic stem cell transplant, or determination for clinical trial participation.”

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.

NOTE: For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.
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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81120, 81121, 81175, 81176, 81218, 81245, 81246, 81272, 81273, 81310, 81334, 81403, 81404, 81405, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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Medical Director review 8/2019


Policy Implementation/Update Information

1/1/2019 New policy developed. BCBSNC will provide coverage for genetic testing for acute myeloid leukemia when it is determined to be medically necessary and criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
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<tr>
<th>Date</th>
<th>Description</th>
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<tr>
<td>9/10/19</td>
<td>Reviewed by Avalon 2nd Quarter 2019 CAB. Deleted coding table from Billing/Coding section. Added statement under Policy Guidelines for clarity “NOTE: For 5 or more gene tests being run on a tumor specimen (i.e. non-liquid biopsy) on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.” Medical Director review 8/2019. (lpr)</td>
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<tr>
<td>10/29/19</td>
<td>Wording in the Policy, When Covered, and/or Not Covered section (s) changed from Medical Necessity to Reimbursement language, where needed. (hb)</td>
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<tr>
<td>12/31/19</td>
<td>Specialty Matched Consultant Advisory Panel review 11/20/2019. No change to policy statement. (lpr)</td>
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