Corporate Medical Policy

Genetic Testing for Acute Myeloid Leukemia AHS-M2062

File Name: genetic_testing_for_acute_myeloid_leukemia
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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, 2020).

Related Policies:
Genetic Cancer Susceptibility Using Next Generation Sequencing AHS-M2066
Serum Tumor Markers for Malignancies AHS-G2124
Minimal Residual Disease (MRD) AHS- M2175

******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 and tyrosine kinase domain mutations (*ITD and TKD*), *IDH1, IDH2, TET2, WT1, DNMT3A, ASXL1* and/or *TP53* in adult and pediatric patients with suspected or confirmed acute myeloid leukemia 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-RUNX1T1* or inv(16)(p13.1q22) /t(16;16)(p13.1;q22); *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

Genetic testing for acute myeloid leukemia is considered investigational in 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.

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.

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.

AML is the most common acute leukemia in adults (80%), with a median age at diagnosis of 65 years. An AML diagnosis in adults is generally associated with a poor prognosis. This disease is much less common in children younger than 10 years of age, as less than 10 % of acute leukemias are diagnosed as AML (Schiffer & Gurbaxani, 2022; John, 2017; Siegel et al., 2017; Yamamoto & Goodman, 2008).

A clinical presentation of AML includes symptoms related to complications of pancytopenia, including weakness and fatigability, infections of variable severity, and hemorrhagic findings (Schiffer & Gurbaxani, 2022). 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). The most common gene mutations are as follows: *FLT3* (28%), *NPM1* (27%), *DNMT3A* (26%), *IDH1* or *IDH2* (20%), *NRAS* or *KRAS* (12%), *RUNX1* (10%), *TET2* (8%), *TP53* (8%), *CEBPA* (6%), and *WT1* (6%). Mutations impacting signal activation are frequent (60% of cases); the most common of which are mutations in *FLT3* (Stock, 2020).

FMS-like tyrosine kinase 3 (FLT3) is a transmembrane tyrosine kinase receptor that stimulates cell proliferation upon activation. Both internal tandem duplications (ITDs) 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. A *FLT3-ITD* mutation has been shown to have a poor prognosis in contrast to *FTL3* point mutations in the activation loop of the kinase domain. Higher ratios of mutated alleles compared to wild-type alleles confer worse prognoses (Schiffer, 2021).

The second most common mutation in AML (27%) is of nucleophosmin (NPM1), a ubiquitously expressed phosphoprotein that normally shuttles between the nucleus and cytoplasm (Falini et al., 2005; Stock, 2020). *NPM1* mutations are associated with improved outcomes although the mechanism is not known. Concurrent mutations (such as an *FTL3* mutation) may influence prognosis, but generally *NPM1* patients without concurrent mutations have better prognoses (Schiffer, 2021).

The *CCAAT/enhancer binding protein alpha* (*CEBPA*) gene mutation is also common in AML. *CEBPA* encodes a transcription factor necessary for myeloid differentiation. This mutation is one of the two mutations associated with familial leukemia and consists of about 10% of AML cases. Familial AML with a *CEBPA* mutation has a phenotype similar to those of "sporadic AML with biallelic *CEBPA* mutations," but most of the current data revolves around the assessment of *CEBPA* double mutations. *CEBPA* single mutations and hypermethylated *CEBPA* requires further study (Schiffer, 2021).

Isocitrate dehydrogenase (IDH) 1 and 2 mutations comprise approximately 15% of AML cases. These mutations are mutually exclusive with *Tet Methylcytosine Dioxygenase 2* (*TET2*) and *Wilms' tumor 1*

(*WT1*) mutations but are commonly seen with *NPM1* and DNA *methyltransferase 3A* (*DNMT3A*) mutations. Data on the prognoses of these mutations is varied (C. Schiffer, 2021).

KIT mutations also comprise about 6% of AML cases. *KIT* encodes the receptor for a stem cell factor, and prognoses are varied (Castells, 2021; Schiffer, 2021). Some researchers suggest that of all *KIT* mutations, the D816 mutation is the most unfavorable prognostic factor in AML patients (Yui et al., 2017).

Approximately 8 percent of AML cases consist of *WT1* gene mutations. *WT1* encodes a transcriptional regulator for genes involved in maturation and growth. Again, the prognosis of this mutation is mixed (Schiffer, 2021), although some researchers strongly support the theory that *WT1* mutations are associated with poor AML prognoses (Hou et al., 2010). The *WT1* mutation status of AML patients may also change during disease progression. New research has suggested that after allogenic stem cell transplantation, AML relapse could be due to a gain in *WT1* gene alterations and a "high mutation load" (Vosberg et al., 2018).

ASXL *Transcriptional Regulator 1 (ASXL1)* and ASXL *Transcriptional Regulator 2* (*ASXL2)* may also be mutated in AML cases. *ASXL1* has an unclear function, but it is speculated to be related to histone post-translational modifications. The frequency of *ASXL1* is varied, as estimates range from 6% to 30%. Furthermore, *ASXL1* mutations are mutually exclusive with *NPM1* mutations, and *ASXL2* mutations are associated with *RUNX1* mutations (also known as *AML1* or *CBFA2*) (Schiffer, 2021).

The *DNMT3A* gene amounts to 20%-22% of AML cases. This gene plays a role in epigenetic modifications for development and differentiation. Mutations in this gene affect hematopoietic stem cell differentiation. Prognoses of this gene mutation have been mixed (Schiffer, 2021).

Tumor protein 53 (*TP53*) and RAS and may also be present in AML cases and may be accompanied by other genetic abnormalities. RAS regulates cell signal transduction, and its mutation leads to a constitutionally active growth stimulus whereas *TP53* encodes a transcriptional activator of growth inhibitory genes (Frucht & Lucas, 2022; Rai & Stilgenbauer, 2021).

Gene expression profiling and microRNA expression profiling may also contribute to assessment and management of AML. Gene expression profiling has been used to differentiate between risk groups based on cytogenetic evaluation whereas microRNA profiling evaluates the regulation of gene expression. However, neither technique is used regularly in clinical practice as these techniques have yet to be widely validated (Schiffer, 2021).

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 (Leonard, 2016). Other tools, such as flow cytometry and next generation sequencing (NGS) have also been used for AML prognostic and diagnostic purposes.

Ampasavate et al. (2019) have developed a quantitative protocol and flow cytometry-based method for monitoring an anti-FLT3 interaction. The FLT3 biomarker has been previously identified as a poor prognostic marker for AML patients. This method can rapidly identify intact FLT3 on the leukemic cell surface. "The results demonstrated good linearity ($r2 > 0.99$)"; further, "When compared with Western blotting results, FLT3 protein expression levels in leukemia patient's bone marrow samples were demonstrated in the same trend" (Ampasavate et al., 2019). The researchers state that this technique is reliable, rapid, effective and "provided a practical analysis of FLT-3 biomarker levels which is valuable for physician decision in acute leukemia treatment" (Ampasavate et al., 2019).

Alonso et al. (2019) have researched the utility of a 19-gene NGS panel for AML diagnostic purposes. This targeted NGS panel was studied in a cohort of 162 patients with AML. The authors note that "The assay yielded a median read depth >2000×, with 88% of on-target reads and a mean uniformity >93% without significant global strand bias. The method was sensitive and specific, with a valid performance at

the clinical variant allele frequency cutoff of 3% for point mutations and 5% for insertions or deletions (Alonso et al., 2019).” The researchers conclude that this is a “reliable and reproducible method” for AML diagnoses.

Clinical Utility and Validity

The clinical utility of testing fallows for further risk stratification, prognostication, and guide management decisions in patients with AML. Several studies have concluded that *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).

Devillier et al. (2015) sought to identify biological and prognostic subgroups based on genetic mutations in AML patients. A total of 125 AML patients with myelodysplasia-related changes (“MRC”) were evaluated. The authors focused on the 26 patients with *ASXL1* mutations and 28 with *TP53* mutations. The *ASXL1* mutation cohort was found to have a higher proportion of marrow dysgranulopoiesis and an overall survival (OS) rate that was below average for wild-types (14% for *ASXL1* mutants, 37% for wild-types). The *TP53* cohort was found to have a “complex karyotype” and predicted a poor outcome with unfavorable cytogenetic risk AML. Both mutations were found to be an independent factor associated with shorter OS (Devillier et al., 2015).

Bolouri et al. (2018) examined 993 children’s genetic data from the Children's Oncology Group (COG) AML trials to characterize the molecular landscape of AML. The authors found that certain somatic variants, such as *MBNL1,* were “disproportionately prevalent” in children compared to adults. However, certain variants common in adults such as *TP53*, were not found in children. Other mutations such as *NRAS* and *KRAS* were “frequent” in pediatric AML. The authors concluded that their results “highlight the need for and facilitate the development of age-tailored targeted therapies for the treatment of pediatric AML” (Bolouri et al., 2018).

Jongen-Lavrencic et al. (2018) conducted a study of 482 patients 18 to 65 years with newly diagnosed AML. Targeted next-generation sequencing (NGS) was carried out at diagnosis and after induction therapy (during complete remission). At least one mutation was detected in 430 (89.2%) patients, and mutations persisted in 51.4% of those patients during complete remission. The detection of minimal residual disease was associated with a significantly increased relapse rate than no detection. Persistent DTA mutations (mutations in *DNMT3A*, *TET2*, and *ASXL1*) were not correlated with an increased relapse rate. Overall, the authors concluded, “A comparison of sequencing with flow cytometry for the detection of residual disease showed that sequencing had significant additive prognostic value. 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” (Jongen-Lavrencic et al., 2018).

Kuwatsuka et al. (2018) evaluated the genetic background of 103 young adults and their subsequent clinical outcomes. The 103 cases included mutations in *FLT3-ITD, KIT, CEBPA, NRAS, KRAS, WT1, MLL-PTD*, and *NPM1*. Overall, *FLT3-ITD* and *NPM1* mutations were associated with a greater mortality risk. *NPM1* mutations conferred a 100% survival rate in the absence of *FLT3-ITD* mutations, but *FLT3-ITD* conferred only a 35% survival without *NPM1* mutations (Kuwatsuka et al., 2018).

Zhu et al. (2017) assessed the effect of gene mutations on the subsequent cytogenetic aberrations. A total of 560 patients were enrolled, and the authors examined the following alterations: “*CEBPA*, *NPM1, FLT3, C-KIT, NRAS, WT1, DNMT3A, MLL-PTD* and *IDH1/2*, as well as expression levels of MECOM, ERG, GATA2, WT1, BAALC, MEIS1 and SPI1.” The investigators found that the expression levels of MECOM, MEIS1, and BAALC influenced cytogenetic aberration. Further, *FLT3*, *C-KIT*, and *NRAS* mutations all contained a “conversed” expression profile of MEIS1, WT1, GATA2, and BAALC expression. The investigators also noted “*FLT3, DNMT3A, NPM1* and biallelic *CEBPA* represented the mutations associated with the prognosis of AML in our group” (Zhu et al., 2017).

Papaemmanuil et al. (2016) examined the relationship between genotype and pathophysiology in AML. A total of 1540 patients with 5234 driver mutations across 76 genes were studied. The authors found three genomic subcategories in addition to the currently defined AML subgroups; mutations in genes encoding chromatin, RNA splicing regulators or both (such as *ASXL1* or *RUNX1*), *TP53* mutations, chromosomal aneuploidies or both (unusual karyotypes and *TP53*), and *IDH2* mutations. The authors noted that "patients with chromatin–spliceosome and *TP53*–aneuploidy AML had poor outcomes." The *NPM1* cohort was the largest of the sample (27%, 436 patients) and 319 of those patients also carried a DNA methylation or hydroxylmethylation gene, such as *IDH1/2* or *TET2*. The authors also noted that *NPM1-DNMT3A–NRASG12/13* had an "unexpectedly benign" prognosis, and the *NPM1* subgroup's prognoses were largely determined by the context in which the NPM1 mutation occurred (such as in *NRAS, IDH*, and so on) (Papaemmanuil et al., 2016).

Sperr et al. (2016) evaluated the effect of a genetic mutation and karyotype on the efficacy of treatment for elderly patients. A total of 192 patients over 60 years old were enrolled, and 115 of these patients achieved "complete hematologic remission (CR)." The authors stated that *NPM1* mutations (*NPM1*mut) and karyotype were the only independent predictors of survival, also noting that *NPM1*mut showed a prognostic impact on both normal (CN) and non-chromosomal (Mkneg) karyotypes. The authors concluded that "elderly patients with CN/Mkneg-*NPM1*mut or core binding factor AML can achieve long term median continuous CR when treated with intensive induction and consolidation therapy whereas most elderly patients with CN/Mkneg-NPM1wild-type or CN/Mkpos AML may not benefit from intensive chemotherapy" (Sperr et al., 2016).

Heiblig et al. (2019) assessed the impact of *NPM1* subtypes on treatment outcomes. One hundred seventy-five patients were examined. The authors found that out of the *NPM1* AML cases, 73% (128) were "Type A" mutations (TCTG at exon 12) and 27% (47) were "Non Type-A mutations" (Type B: CATG and Type D: CGTG). The Type-A mutations were found to achieve minimal residual disease (MRD) earlier than non Type-A mutations. However, non-type A mutations achieved better rates of medial survival (Heiblig et al., 2019).

Xu et al. (2020) have analyzed data from 220 normal karyotype AML pediatric patients. Participants were selected from the Cancer Genome Atlas database. It was found that 12.7% of these patients had *WT1* mutations, and that "the *WT1*-mutated group suffered lower rates of complete remission (CR) ($P < 0.001$ and $P < 0.001$, respectively) but higher rates of minimal residual disease (MRD) ($P = 0.003$ and $P = 0.021$, respectively) after both one and two courses of induction chemotherapy" (Xu et al., 2020). Patients with *WT1* mutations also had significantly worse event-free and overall survival rates ($P=0.007$ and $P<0.001$, respectively) (Xu et al., 2020).

Sasaki et al. (2020) studied the impact of *ASXL1, DNMT3A, JAK2, TET2*, and *TP53* mutations on survival in newly diagnosed acute myeloid leukemia (AML) patients. 421 bone marrow aspirates were studied using NGS for these mutations with a minimum variant allele frequency (VAF) of 5%. "A total of 71 patients (17%) had *ASXL1* mutations, 104 patients (25%) had *DNMT3A* mutations, 16 patients (4%) had *JAK2* mutations, 82 patients (20%) had *TET2* mutations, and 86 patients (20%) had *TP53* mutations." The median VAF of *ASXL1* was 34.31% (range, 1.17%-58.62%), *DNMT3A* was 41.76% (range, 1.02%-91.66%), *JAK2* was 46.70% (range, 10.4%-71.7%), *TET2* was 42.78% (range, 2.26%-95.32%), and *TP53* was 45.47% (range, 1.15%-93.74%). In patients with these mutations, the median overall survival was 11 months. In patients without these mutations, the overall survival was 27 months. The authors conclude that "The VAF of *ASXL1, DNMT3A, JAK2, TET2, TP53*, and *NPM1* mutations is associated with worse prognosis in patients with newly diagnosed AML." (Sasaki et al., 2020).

Duncavage et al. (2021) investigated the clinical utility and accuracy of whole-genome sequencing (WGS) for the purpose of risk stratification in patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). The results from 263 patients were compared with findings from cytogenetic analysis and targeted sequencing. When conducting the WGS, they found that all 40 recurrent translocations and 91 copy-number alterations found on cytogenetic analysis were identified on WGS. There were also new clinically reportable genomic events among 17.0% of the patient sample. The standard AML risk groups, "as defined by sequencing results instead of cytogenetic analysis, correlated with clinical outcomes."

WGS was also able to classify patients with inconclusive cytogenetic analysis results into risk groups. This demonstrates that WGS could increase the diagnostic yield of AML and MDS and supplement the accuracy of cytogenetic analysis (Duncavage et al., 2021).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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."

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® (enasidenib)."

Guidelines and Recommendations

World Health Organization (WHO)

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 (EVI1) expression and GATA2 haploinsufficiency. The AML with CEBPA mutation is defined based on 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.

Figure 1: WHO classification of AML and related neoplasms from Arber et al. (2016)

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

College of American Pathologists (CAP) and American Society of Hematology (ASH)

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)(p13.1;q22); 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)(p13.1;q22); 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 *RUNX1* (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.

American Society of Clinical Oncology (ASCO)

The ASCO has announced an endorsement of the 2017 CAP and ASH guideline regarding the initial diagnostic work-up of acute leukemia. The ASCO supports all twenty-seven guideline statements. The statements relevant to this policy are noted in the 2017 CAP and ASH guidelines above.

National Comprehensive Cancer Network (NCCN)

For the initial evaluation of AML, the NCCN guidelines recommend bone marrow core biopsy and aspirate analyses "(including immunophenotyping by immunohistochemistry stains with flow cytometry)" and cytogenetic analyses (karyotype + FISH), molecular analyses (ASXL1, c-KIT, *FLT3 [ITD and TKD], NPM1, CEBPA* (biallelic)*, IDH1, IDH2, RUNX1, TP53* and other mutations) (NCCN, 2021).

EUROPEAN LEUKEMIANET RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

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 or with *FLT3*-ITD^{low}† Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic le t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

The NCCN also states that "Several gene mutations are associated with specific prognoses in a subset of patients (category 2A); and may guide treatment decisions (category 2B). Presently, *c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA (biallelic), IDH1/IDH2, RUNX1, ASXL1*, *TP53, BCR-ABL, and PML-RAR alpha* are included in this group (NCCN, 2021)."

European LeukemiaNet (ELN) Working Party

The ELN expert panel released guidelines for the assessment of measurable residual disease (MRD) of AML that were updated in 2021. First, for molecular MRD recommendations, "techniques for molecular MRD assessment should reach an LOD [limit of detection] of 10^{-3} or lower. To achieve this LOD, qPCR, dPCR, or error-corrected NGS using UMIs [unique molecular identifiers] is recommended (Grade of Recommendation: B)."

Other recommendations for molecular MRD testing included:

- "For patients with mutant *NPM1*, CBF AML (*RUNX1-RUNX1T1* or *CBFB-MYH11*), or APL (*PML-RARA*), we recommend molecular MRD assessment by qPCR or dPCR. (Grade of Recommendation: A)"
- "Leukemia-specific PCR assays (eg, for *NPM1, PML-RARA,* or *CBF* AML) are preferred over fewer specific markers, such as *WT1* or *EV11* expression (Grade of Recommendation: B)"
- "Targeted NGS-MRD using specific mutations identified at diagnosis vs agnostic panel approaches has different strengths and limitations, but both approaches can be considered, depending on sensitivity, turnaround time, resource use, setting (research, clinical trial, or clinical routine), and ability to standardize methodology and reporting. (Grade of Recommendation: B)"
- "If a panel approach is used for NGS-MRD, emerging variants not found at diagnosis should be reported only if confidently detected above background noise. (Grade of Recommendation: B)"
- "For NGS-MRD, we recommend considering all detected mutations as potential MRD markers, with the limitations detailed in recommendations B9 to B11 (listed below) (Grade of Recommendation: B)"
    - "Germline mutations (VAF of ~50 in genes *ANKRD26*, *CEBPA*, *DDX41*, *ETV6*, *GATA2*, *RUNX1*, and *TP53*) should be excluded as NGS-MRD markers, as they are noninformative for MRD. (Grade of Recommendation: A)"
    - "Mutations in *DNMT3A*, *TET2*, and *ASXL1* (DTA) can be found in age-related clonal hematopoiesis and should be excluded from MRD analysis. (Grade of Recommendation: A)"
    - "Mutations in signaling pathway genes (*FLT3-ITD*, *FLT3-TKD*, *KIT*, and *RAS*, among others) most likely represent residual AML when detected, but are often subclonal and have a low negative predictive value. These mutations are best used in combination with additional MRD markers. (Grade of Recommendation: B)" (Heuser et al., 2021).

The ELN also released guidelines for the diagnosis and management of AML. Their genetic test battery includes cytogenetics, screening for gene mutations in *NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1*, and screening for gene rearrangements in *PML-RARA, CBFB-MYH11, RUNX1-RUNX1T1, BCR-ABL1*, other fusion genes (if available) (Döhner et al., 2017).

EUROPEAN LEUKEMIANET RISK STRATIFICATION BY GENETICS IN NON-APL AML[1,2]

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 or with *FLT3*-ITD^{low}† Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}† Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adverse
Poor/Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; -17/abn(17p) Complex karyotype,§ monosomal karyotype‖ Wild-type *NPM1* and *FLT3*-ITD^{high}† Mutated *RUNX1*¶ Mutated *ASXL1*¶ Mutated *TP53*#

British Committee for Standards in Haematology (BCSH)

The BCSH has published guidelines for the diagnosis and management of AML in pregnancy. These guidelines state that "The diagnostic criteria for AML are the same in a pregnant patient as in non-pregnant women. These criteria are defined in the World Health Organization (WHO) classification of the myeloid

neoplasms. Where a diagnosis of leukemia is suspected, care must be taken to ensure that marrow samples are directed for immunophenotypic, cytogenetic and molecular analysis to allow accurate sub-typing and understanding of prognostic features (Ali et al., 2015)."

Canadian Consensus Guidelines

Revised Canadian consensus guidelines for the treatment of older patients with AML were published in 2017. The guidelines included the following recommendation:

- "For older patients who are candidates for intensive chemotherapy, *FLT-ITD* and *TKD* mutation testing results should be provided within one week. For patients up to age 70 with a *FLT3-ITD* or *TKD* mutation, midostaurin, if available, should be added to induction and consolidation, and continued as maintenance therapy if not transplanted, in the schedule used in the RATIFY and German AMLSG studies (Brandwein et al., 2017)."

European Society For Medical Oncology (ESMO)

ESMO released guidelines for the diagnosis of acute myeloid leukemia in adult patients. They recommend molecular testing for *c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1, IDH2,* and *TP53* mutations. They state that "next-generation sequencing (NGS) of a panel of genes commonly mutated in AML provides important additional prognostic and therapeutic information (Heuser et al., 2020)."

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, 81405, 81479, 0023U, 0046U, 0049U

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

Specialty Matched Consultant Advisory Panel 11/2019

Medical Director review 8/2020

Specialty Matched Consultant Advisory Panel 11/2020

Medical Director review 11/2020

Specialty Matched Consultant Advisory Panel 8/2021

Medical Director review 8/2022

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)

9/10/19 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)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section (s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

12/31/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. No change to policy statement. (lpr)

10/1/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Updated "When Covered" section to include medical necessity coverage for tyrosine kinase domain mutations (TKD). Extensive updates to policy guidelines section. References added. CPT codes 0023U, 0046U, 0049U added to Billing/Coding section for effective date 10/1/20. Added related policies. Medical Director review 8/2020. (lpr)

12/8/20 Specialty Matched Consultant Advisory Panel review 11/18/2020. No change to policy statement. (lpr)

9/7/21 Specialty Matched Consultant Advisory Panel review 8/18/2021. Reviewed by Avalon 2nd Quarter 2021 CAB. Updated policy guidelines and added references. Under "When Not Covered section: removed Item A: "Genetic testing for FLT3, NPM1, CEBPA, IDH ½, KIT and other mutations to detect minimal residual disease." Please see CMP Minimal Residual Disease AHS-M2175. Medical Director review 7/2021. (lpr)

9/13/22 Reviewed by Avalon 2nd Quarter 2022 CAB. Updated policy guidelines and references. Removed CPT code 81404 from Billing/Coding section. (lpr)