Genetic Testing for Acute Myeloid Leukemia (AML)

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DESCRIPTION

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues. It is the most common form of acute leukemia among adults and accounts for the largest number of annual deaths from leukemias in the United States. In 2022, there will be an estimated 20,050 people diagnosed with AML, and 11,540 will die of the disease. According to the SEER Cancer Statistics Review, the median age at diagnosis is 68 years, other registries report 71 years, with approximately 54% of patients diagnosed at 65 years or older (and approximately a third diagnosed at $\geq$ 75 years of age). Thus, as the population ages, the incidence of AML, along with myelodysplastic syndromes (MDS), seems to be rising.

Environmental factors that have long been established to increase the risks of MDS and AML include prolonged exposure to petrochemicals, solvents such as benzene, pesticides and ionizing radiation.

Therapy related AML/MDS (secondary AML/MDS is a well-recognized consequence of cancer treatment in a proportion of patients receiving cytotoxic therapy for solid tumors or hematologic malignancies. Reports suggest that therapy related AML/MDS may account for 5% to 20% of patients with AML/MDS. The rate of therapy-related AML/MDS is higher among patients with certain primary tumors, including breast cancer, gynecological cancers, and lymphomas (such as non-Hodgkin lymphoma and Hodgkin lymphoma), largely owing to the more leukemogenic cytotoxic agents that are commonly used in the treatment of these tumors. Two well-documented categories of cytotoxic agents associated with development of therapy related AML/MDS are alkylating agents and topoisomerase inhibitors. Treatment with antimetabolites, such as purine analog fludarabine, has also been associated with therapy related AML/MDS in patients with lymphoproliferative disorders, particularly when administered in combination with alkylating agents. Radiotherapy especially in context of myeloablative therapy (e.g., total body irradiation or radioimmunotherapy) given before autologous hematopoietic cell transplantation (HCT) may also increase the risk for therapy related AML/MDS. The disease course for therapy related AML/MDS is generally progressive and may be more resistant to conventional cytotoxic therapies then de novo cases of AML/MDS. Importantly clinical outcomes in patients with therapy related AML have been shown to be significantly inferior (both in terms of relapse-free survival [RFS] and overall survival (OS) compared with patients with de novo cases, except those with a therapy related acute promyelocytic leukemia (APL) subtype or the favorable-risk core binding factor (CBF) translocations. The proportion of patients with unfavorable cytogenetics tends to be higher in the population with therapy-related AML. Even among the subgroup with favorable karyotypes, those with therapy related AML tend to do less well.

The initial evaluation of AML has two objectives. The first is to characterize the disease process based on factors such as prior toxic exposure, antecedent myelodysplasia, and karyotypic and molecular abnormalities, which may provide prognostics information that can impact responsiveness to chemotherapy and risk of relapse. The second objective focuses on patient-specific factors, including assessment of comorbid conditions, which may affect an individual's ability to tolerate chemotherapy. Both disease-specific and individual patient factors are taken into consideration when deciding treatment.

The evaluation and initial work-up for suspected AML consists of a comprehensive medical history and physical examination. Several gene mutations are associated with specific prognosis 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, ASKL1, TP53, BCR-ABL, and PML-RAR alphas are included in this group. All patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing 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 analysis of immediately actionable genes or chromosomal abnormalities (e.g., CBF, FLT3 [ITD or TKD], NPM1, IDH1 or IDH2) should be expedited. (NCCN AML Version 1.2022)

Gene Mutation	Description
NPM1	The NPM1 gene encodes a shuttle protein within the nucleolus of cells. Mutations in this gene occur in 28% to 35% of AML case. The NPM1 mutation has been shown to be associated with NK-AML with reported frequency of 48% to 53%. Isolated NPM1 mutation, which localizes to the cytoplasm confers a higher complete response (CR) rate and improved event-free survival (EFS) and OS compared with patients who are NK-AML and wild-type NPM1, resulting in outcomes similar to patients with faviral cytogenetics (e.g., CBF AML).
FLT3	The FLT3 gene encodes a receptor tyrosine kinase involved in hematopoiesis. Two major classes of activating FLT3 mutations have been identified in patients with AML, which include the internal tandem duplications (ITD) and tyrosine kinase domain (TKD) point mutations. FLT3-ITD mutations occur in approximately 30% of cases and are more common than FLT3-TKD mutations, which occur in approximately 10% of patients. Numerous studies have shown the negative prognostic influence of FLT3-ITD in patients with AML, resulting in shorter remission durations (e.g., decreased disease free-survival [DFS]) in patients with CR) and poorer survival outcomes compared with patients who have wild-type FLT3. Among patients with FLT3-ITD and NK-AML, median OS from the time of diagnosis ranged from 6 to 12 months.
CEBPA	Another mutation associated with prognosis is the CEBPA gene, a transcription factor that plays a key role in the differentiation of granulocytes. Mutations in CEBPA have been reported in 7% to 11% of patients with AML (or 13-15% of those with NK-AML) and have

	been associated with favorable outcome (similar to patients with CBF translocations) with regard to increased remission duration and OS outcome compare with a favorable outcome (similar to patients with CBF translocations) with regard to increased remission duration and OS outcome compared with wild-type CEBPA. The revised 2016 WHO classification of AML has redefined mutated CEBPA to indicate that biallelic (double) mutations (and not single CEBPA mutations) are associated with improved prognosis.
IDH1/2	Mutations in IDH1/2 have been reported in 6% to 9% of AML cases, with a higher frequency among patients with NK-AML (8%-16%). IDH1 mutations were found to occur concurrently with NK-AML and NPM1 mutations. Additionally, these mutations have been associated with wild-type CEBPA and the absence of FLT3 abnormalities. Findings from published reports on the prognostic effects of IDH1 mutations have been inconsistent, although some studies show no prognostic effect of IDH1 mutations on OS when considering IDH mutations (IDH1 and IDH2 combined) or in the overall patient population, IDH1 mutations correlated with significantly worse outcomes in the subgroup of NK-AML patients with favorable or intermediate – risk disease.
DNMT3A	The DNMT3A mutations have been reported in 18% to 22% of patients with AML, with a frequency of 29% to 34% in those with NK-AML. Data concerning the prognostic significance DNMT3A mutations on survival outcomes, whereas other studies have shown a negative prognostic effect in the overall population or specific subgroups. Studies have shown

	significantly decreased OS outcomes among patients with DNMT3A mutations compared with patients who have the wild-type gene (medial OS, 12-21 months versus 40-41 months). Significantly decreased OS with DNMT3A mutations has also been reported in the subgroup of patients with NK-AML who have wild-type NPM1 with or without FLT3-ITD, or NPM1 mutation in the presence of FLT3-ITD.
KIT	KIT mutations have been reported in approximately 20% of patients with CBF AML. Studies have shown that KIT mutations are associated with decreased remission duration (e.g., EFS and RFS) and decreased OS in patients with t(8;21).
KMT2A	The mixed lineage leukemia gene (MLL; also called HRX, ALL-1, or currently KMT2A), located on chromosome 11q23, was initially recognized as a recurrent locus of chromosomal translocation in AML and ALL. Depending on the fusion partner, the 11q23/KMTA2 rearrangement is associated with intermediate to poor prognosis. NK-AML can be characterized by partial tandem duplication in KMT2A gene (KMT2A-PTD), and KMT2A-PTD is associated with reduced OS.
RUNX1	The runt-related transcription factor 1 (RUNX1) gene, encoding a myeloid transcription factor, is mutated in approximately 10% of de novo AML cases and associated with adverse prognoses.
ASXL	The additional sex combs-like 1 (ASXL1) gene, located on chromosome band 20q11, encodes a protein in the enhancer of trithorax and polycomb (EPT) genes family, which have functions in transcription. ASX-L1 mutations have been reported in approximately 5% to 36% of de novo AML cases and are associated with poor outcomes.

TP53	TP53 mutations have been reported in approximately 12%-13% of AML cases, and are associated with unfavorable risk and poor outcomes.

The molecular markers discussed above provide prognostic information that aid in risk stratification and may influence subsequent treatment decisions.

AML has a highly heterogenous 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.

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 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. However, the role of MRD monitoring in AML is evolving and limited based on several factors. First, some patients may have relapse despite having no MRD, while others do not relapse despite being MRD positive. Additionally, more standardization is needed in identifying individual markers for MRD assessment as well threshold values to define MRD positive and MRD negative samples.

Clinical Context and Test Purpose

Optimal decisions regarding treatment intensity and chemotherapy-based consolidation therapy versus allogeneic transplantation remain unclear in cytogenetically normal acute myeloid leukemia (CN-AML). The purpose of genetic testing in patients who have CN-AML is to provide prognostic risk stratification information that may inform decisions regarding:

- whether to use standard or increased treatment intensity in induction therapy, consolidation therapy, or in relapsed/refractory acute myeloid leukemia (AML);
- whether to do allogeneic or autologous transplantation versus chemotherapy as consolidation therapy for an AML patient in the first remission;

- whether to use investigational therapies such as FLT3 inhibitors.

Genetic testing can be used during the initial evaluation of leukemia to provide prognostic information and guide treatment decisions. It also has an evolving role in the assessment of measurable residual disease (MRD) to assess the risk of relapse.

Induction therapy usually consists of 7 days of continuous infusion cytarabine at 100 to 200 mg/m^2 with 3 days of anthracycline. Studies have shown greater efficacy at higher doses but also increased toxicity.

Transplantation reduces the risk of recurrence but is typically associated with at least a 20% treatment-related mortality risk.

Populations
The population of interest is patients with newly diagnosed CN-AML, those in the first remission, and those who have relapsed.

Interventions
The intervention of interest is testing for FLT3, NMP1, or CEBPA variants. During initial assessment of AML, genetic testing provides prognostic risk assessment and helps guide treatment decisions.

Decisions about management of AML are generally made by patients and hematologists or oncologists in the secondary or tertiary care setting.

Comparators
The comparator of interest is risk stratification without FLT3, NMP1, or CEBPA genetic testing, either for initial evaluation or MRD.

Outcomes
Outcomes are focused on overall- and cancer-specific mortality, although treatment-related morbidity in the short- and long-term is also a focus.

The assays can be conducted during diagnostic evaluation, to aid in the treatment decision process.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect the presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops, or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predict response to therapy.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Prognosis of patients with *FLT3* internal tandem duplication (ITD), *NMP1*, or *CEBPA* variants compared with patients without *FLT3*-ITD, *NMP1*, or *CEBPA* variants are described in the Table below. Results from systematic reviews are presented when available and individual studies are included if they described a population not represented in the systematic reviews.

Survival Outcomes of Patients with FLT3-ITD, NMP1, or CEBPA Variants

Study	Design	Participants	Outcomes
Port et al (2014)	Systematic review of 19 studies published between 2000 and 2012, with 4 studies included in the meta-analysis	1942 patients with CN-AML <60 y in meta-analysis	*FLT3*-ITD WT vs *FLT3*-ITD variant: • OS HR=1.9 (95% CI, 1.6 to 22) • RFS HR=1.8 (95% CI, 1.5 to 2.2) *NPM1* WT vs *NPM1* variant: • OS HR=0.6 (95% CI, 0.5 to 0.7) • RFS HR=0.6 (95% CI, 0.5 to 0.6) *CEBPA* WT vs *CEBPA* variant: • OS HR=0.4 (95% CI, 0.3 to 0.5) • RFS HR=0.4 (95% CI, 0.3 to 0.6)
Li et al (2015)	Systematic review of 10 studies published before Aug 2014	6219 patients with AML	Any AML: • *CEBPA* monoallelic vs WT

			○ OS HR=1.1 (95% CI, 0.9 to 1.5) ○ EFS HR=1.1 (95% CI, 0.8 to 1.5) • *CEBPA* biallelic vs WT: ○ OS HR=0.4 (95% CI, 0.3 to 0.5) ○ EFS HR=0.4 (95% CI, 0.3 to 0.5) CN-AML: • *CEBPA* monoallelic vs WT: ○ OS HR=1.1 (95% CI, 0.9 to 1.5) ○ EFS HR=0.9 (95% CI, 0.7 to 1.2) • *CEBPA* biallelic vs WT: ○ OS HR=0.3 (95% CI, 0.2 to 0.4) ○ EFS HR=0.4 (95% CI, 0.3 to 0.5)
Dickson et al (2016	Retrospective analysis of patients enrolled in an RCT	662 AML patients >60 y	1-y OS: • *CEBPA*, biallelic: 75%

	between 1990 and 1998		• *NPM1* variant, *FLT3*-ITD WT: 54% • All others: 33% 3-y OS: • *CEBPA*, biallelic: 17% • *NPM1* variant, *FLT3-ITD* WT: 29% • All others: 12%
Wu et al (2016	Systematic review of 10 cohort studies published between 1995 and 2015	1661 pediatric patients with AML	*FLT3*-ITD WT vs *FLT3*-ITD variant: • OS HR=2.2 (95% CI, 1.6 to 3.0) • EFS HR=1.7 (95% CI, 1.4 to 2.1)
Kuwatsuka et al (2017	Retrospective analysis of patients enrolled in 2 clinical trials between 2001 and 2010	103 adolescent and young adults (age range, 15-39 y) with AML	*FLT3*-ITD WT vs *FLT3*-ITD variant: • OS HR=2.1 (95% CI, 1.1 to 4.1) • EFS HR=2.4 (95% CI, 1.3 to 4.2) *NPM1* WT vs *NPM1* variant: • OS HR=0.2 (95% CI, 0.06 to 1.0) • RFS HR=0.2 (95% CI, 0.09 to 0.7)
Rinaldi et al (2020)	Systematic review of 10 studies published between 1999 to 2020	1513 adult, non-transplant patients with AML	*FLT3-ITD WT vs FLT3-ITD variant:* • OS HR=1.91 (95% CI, 1.59 to 2.30) • EFS HR=1.64 (95% CI, 1.26 to 2.14)

AML: acute myeloid leukemia; CI: confidence interval; CN; cytogenetically normal; EFS: event-free survival; HR: hazard ratio; ITD: internal tandem duplication; OS, overall survival; RCT: randomized controlled trial; RFS: recurrence-free survival; WT; wild-type.

Section Summary
The *FLT3*-ITD variant is quite common in AML, particularly in patients with normal karyotypes, and has been associated with poorer survival (overall, event-free, and recurrence-free) in children, younger adults, and older adults. The prognostic effect of *FLT3* tyrosine kinase domain variants is uncertain. *NPM1* variants are found in approximately half of the patients with CN-AML. *NPM1* variants are associated with improved outcomes; however, the superior prognosis is limited to those with *NPM1* variants who do not have an *FLT3*-ITD variant. *CEBPA* variants are found in approximately 15% of patients with CN-AML. Patients with *CEBPA* variants have a favorable prognosis, although the effect may be limited to patients who carry 2 copies of the mutant allele (biallelic). The prognostic value of *NPM1* MRD evaluation has been evaluated retrospectively and found to be associated with higher risks for relapse and lower overall survival.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Randomized Controlled Trials
In 2020, Voso et. al. published a subgroup analysis of the trial evaluating outcomes in patients with the tyrosine kinase domain subtype. In this subgroup, 5-year event-free srvival was significantly better in the midostaurin group than in the placebo group (45.2% vs 30.1%; hazard ratio [HR], 0.66; 95% confidence interval [CI], 0.45 to 0.99; p=0.044), but 5-year overall survival was similar between the 2 treatment groups (65.9% vs 58.0%; HR, 0.74; 95% CI, 0.44 to 1.23; p=0.244).

In 2019, Cortes et. al. (2019) published results from an RCT evaluating patients with relapsed/refractory *FLT3*-mutated AML who were randomized to quizartinib (an FLT3 inhibitor) or salvage chemotherapy (see Tables 3 and 4). Only patients with the *FLT3* ITD subtype were included. One third of patients had refractory disease, while the rest had relapsed disease. Overall survival was improved with quizartinib compared to salvage chemotherapy.

In 2019 Perl et. al. published results from an RCT evaluating patients with relapsed/refractory *FLT3*-mutated AML who were randomized to gilteritinib (an FLT3 inhibitor) or salvage chemotherapy. Patients with the ITD subtype (88.4%), tyrosine kinase domain subtype (8.4%), and both subtypes (1.9%) were included. 60.6% of

patients had relapsed disease, with 39.4% had primary refractory disease. Median overall survival and percent of patients achieving complete remission was significantly better with gilteritinib.

In 2017, Knapper et. al. published results from 2 RCTs in which patients with previously untreated AML and confirmed *FLT3* variants were randomized to lestaurtinib (an FLT3 inhibitor) or a placebo following each of 4 cycles of induction and consolidation chemotherapy. Patients with ITD subtype (74%), tyrosine kinase domain subtype (23%), and both subtypes (2%) were included. There were no significant differences in remission or survival estimates between treatment groups

In 2017, Stone et.al. published results from an RCT in which patients with previously untreated AML and confirmed *FLT3* variants were randomized to standard chemotherapy with or without midostaurin. Patients with ITD (77%), and tyrosine kinase domain (23%) subtypes were included. The addition of midostaurin did not affect complete remission rates or time to complete remission in the overall cohort; however, overall and event-free survival was significantly better in the midostaurin group than in the placebo group

Section Summary
There are RCTs providing direct evidence of clinical utility, randomizing patients with AML and confirmed *FLT3* variants to different treatments. One RCT evaluated the addition of an FLT3 inhibitor, and 1 tested the addition of midostaurin to the chemotherapy regimen in patients with previously untreated AML. No significant difference between treatment groups was found with the addition of the FLT3 inhibitor, while the addition of midostaurin significantly improved OS and event-free survival compared with placebo. Another 2 RCTs evaluated comparative outcomes of treatment with a FLT3 inhibitor versus salvage chemotherapy in relapsed/refractory AML. Both gilteritinib and quizartinib prolonged survival compared to salvage chemotherapy in this population. Additionally, a chain of evidence for clinical utility can be constructed from retrospective analyses suggesting that risk stratification (favorable, intermediate, and poor) based on the presence of *NPM1*, *FLT3*-ITD, or *CEBPA* variants can help guide therapy decisions that are associated with improved outcomes. Patients with a favorable prognosis, including those who have *NPM*1 variants without *FLT3*-ITD variant or double-mutation *CEBPA*, may not derive an OS benefit with allo-HCT. Treatment of patients with intermediate or poor prognosis, including *FLT3*-ITD variant, depends on several risk factors but HCT may improve outcomes.

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 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 variants confer a poor prognosis, whereas *NPM1* (without the *FLT3* internal tandem duplication 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* internal tandem duplication, 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.

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 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. However, the role of MRD monitoring in AML is evolving and limited based on several factors. First, some patients may have relapse despite having no MRD, while others do not relapse despite being MRD positive. Additionally, more standardization is needed in identifying individual markers for MRD assessment as well threshold values to define MRD positive and MRD negative samples. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Panel Testing for AML
The evaluation and initial work-up for suspected AML consists of a comprehensive medical history and physical examination. Several gene mutations are associated with specific prognosis 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, ASKL1, TP53, BCR-ABL, and PML-RAR alphas are included in this group. All patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing 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 analysis of immediately actionable genes or chromosomal abnormalities (e.g., CBF, FLT3 [ITD or TKD], NPM1, IDH1 or IDH2) should be expedited. (NCCN AML Version 1.2022)

The MyAMLGene Panel Assay is a 194 targeted next generation sequencing (NGS) gene panel. Coding regions and potential genomic breakpoints within known somatic gene fusions are sequenced with 300bp paired end reads on an Illumina MiSeq instrument to an average depth of coverage >1000x. Using Invivoscribe's proprietary MyInformatics annotation and bioinformatics database, testing identifies single nucleotide variants (SNVs), indels, inversions and translocations. In addition, allelic frequencies can also be

used to investigate potential aneuploidy and clonality. The MyAML Gene Panel Assay may be utilized to determine relapsed disease in individual with acute myeloid leukemia (AML). However, utilization of expanded genetic panels (51 or more genes) for any indications related to AML based on the peer reviewed medical literature is insufficient in demonstrating the clinical utility and how this expanded genetic panel testing (51 or more genes) impacts patient management. Also, clinical validity of expanded genetic panels (51 or more genes) is incomplete and may be considered excessive because it is not possible to determine the clinical validity of the panel as a whole. The evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management

Messenger RNA (mRNA) is the product of RNA transcription, the firsts step in protein synthesis. Testing for DNA in combination with mRNA has been proposed as a method of detecting, diagnosing, and managing cancer. Currently, there is very limited data available to assess how messenger RNA (mRNA) testing operates outside a collaborative research setting, or how decision-making based on the results of such testing impacts health outcomes. Larger, well-designed prospective studies are needed which demonstrate the clinical utility of mRNA sequence analysis alone or in conjunction with DNA sequence analysis to aid in the classification of variations of uncertain significance or to otherwise detect, diagnose or manage cancer. Use of mRNA testing may be appropriate in the research setting, or to aid publicly available repositories of variant classifications; however, clinical application of the technology in the real world remains unclear. The evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management

Practice Guideline and Position Statements

National Comprehensive Cancer Network
Acute Myeloid Leukemia Version 1.2022

The evaluation and initial work-up for suspected AML consists of a comprehensive medical history and physical examination. Several gene mutations are associated with specific prognosis 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 alphas are included in this group. All patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing 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 analysis of immediately actionable genes or chromosomal abnormalities (e.g., CBF, FLT3 [ITD or TKD], NPM1, IDH1 or IDH2) should be expedited.

Risk Stratification by Genetics in Non-APL AML

Risk Category*	Genetic Abnormality
Favorable	T(8;21)(q22;q22.1); RUNX1-RUNX1T1 Inv916)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Biallelic mutated CEBPA NPM1 without FLT3-ITD or with FLT3-ITD^{low} • ***Note:*** *Low: low allelic ratio (<0.5)*
Intermediate	Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT-ITD^{low} (without adverse-risk genetic lesion) T(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favorable or adverse ***Notes****:* • *Low, low allelic ratio (<0.5)* • *High, high allelic ratio (≥0.5)* • *The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations*
Poor/Adverse	T(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3);KMT2A rearranged t(9;22)(q34.1q11.2); BCR-ABL1 inv(3)(q21.3q26.2) or t93;3)(q21.3;q26.2); GATA2,MECOM(EVl1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype (three or more unrelated chromosome abnormalities in the absence of 1 of the WHO-designated

	recurring translocations or inversions, that is, t98;210, inv(16) or t916;16), t(9,11), tv;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with BCR-ABL1), monosomal karyotype (defined by the presence of 1 single monosomy [excluding loss of X or Y] in association with at least 1 additional monosomy or structural chromosome abnormality (excluding CBF AML) Wild-type NPM1 and FLT3-ITD^{high} Mutated RUNX1 (should not be used as an adverse prognostic marker if the co-occur with favorable risk AML subtypes) Mutated ASXL1 (should not be used as an adverse prognostic marker if the co-occur with favorable risk AML subtypes) Mutated TP53 (are significantly associated with AML with complex and monosomal karyotype) • ***Note:*** *High, high allelic ratio (≥0.5)*

Monitoring During Therapy

Induction

- If cytogenetic were initially abnormal, include cytogenetics as part of remission documentation.

Response Criteria Definitions for Acute Myeloid Leukemia

Morphologic Leukemia-Free State

- BM <5% blasts in an aspirate with spicules; at least 200 cells must be enumerated
- No blasts with Auer rods or persistence of extramedullary disease
- If there is a question of residual leukemia, a BM aspirate/biopsy should be repeated in one week
- A BM biopsy should be performed if spicules are absent from the aspirate sample

Complete Response

- Morphologic CR- patient independent of transfusions
    - Absolute neutrophil count > 1000/mcL (blasts <5%)

    - Platelets $\geq$ 100,000/mcL (blasts <5%)
- CR without MRD (CR_{MRD})
    - If studied pretreatment, CR with negativity for a genetic marker by RQ-PCR or CR with negativity by MFC
    - Sensitivity varies by marker and method used; analyses should be done in experienced laboratoriesMolecular CR – moleculare studies negative
- CRh – partial hematological recovery defined as <5% blasts in the BM, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50 x 10^9/L and ANC > 0.5 x 10^9/L).
- CR with incomplete hematologic recovery (CRi0 – ALL CR criteria and transfusion dependence but with persistence of neutropenia (<1,000/mcL) or thrombocytopenia (<100,000/mcL).
- Responses less than CR may still be meaningful depending on the therapy

Partial Remission

- Decrease of at least 50% in the percentage of blasts to 5% to 25% in the BM aspirate and the normalization of blood counts, as noted above.

Relapse Following CR

- Defined as a reappearance of leukemia blasts in the peripheral blood or the finding of more than 5% blasts in the MB, not attributable to another cause (e.g., BM regeneration after consolidation therapy) or extramedullary relapse.

Induction Failure

- Failure to attain CR or CRi following exposure to at least 2 courses of intensive induction therapy.

The College of American Pathologists and American Society of Hematology

The College of American Pathologists and American Society of Hematology issued guidelines for the diagnostic work-up of AML which is also supported by the American Society of Clinical Oncology (ASCO) which includes the following:

- For pediatric and adult patients with suspected or confirmed AML of any type, the pathologist or treating clinician should ensure that testing for FLT3-ITD is performed. The pathologist or treating clinician may order mutational analysis that includes, but is not limited to, IDH1, IDH2, TET2, WT1, DNMT3A, and/or TP53 for prognostic and/or therapeutic purposes. (Strong recommendation)
- For patients other than those with confirmed core binding factor AML, APL, or AML with myelodysplasia-related cytogenetic abnormalities, the pathologist or treating clinician should also ensure that mutational analysis for NPM1, CEBPA, and RUNX1 is also performed. (Strong recommendation)

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, 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 FDA has chosen not to require any regulatory review of this test.

In May 2017, the FDA granted approval for midostaurin (Rydapt®, Novartis Pharmaceuticals). Rydapt® is a targeted therapy to be used in combination with chemotherapy when an FLT3 variant is detected by the LeukoStrat® CDx FLT3 Mutation Assay (Invivoscribe). In 2018, gilteritinib (Xospata®, Astellas Pharma US) was approved by the FDA for the treatment of relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test.

PRIOR APPROVAL

Not applicable.

POLICY

See Related Medical Policy

- 02.04.80 Next Generation Sequencing for the Assessment of Measurable Residual Disease (MRD)

The following genetic testing for acute myeloid leukemia (AML) may be considered **medically necessary** to guide management decisions:

- ASXL1
- CEBPA
- FLT3-ITD
- FLT3-TKD
- KIT
- IDH1
- IDH2
- NPM1
- RUNX1

The following genetic testing is considered **investigational** when the above criteria is not met and when utilized to detect minimal residual disease (MRD) for acute myeloid leukemia (AML) because the evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management.

- ASXL1
- CEBPA
- FLT3-ITD
- FLT3-TKD

- KIT
- IDH1
- IDH2
- NPM1
- RUNX1

Panel testing (51 or more genes) for acute myeloid leukemia (AML) including but not limited to myAML is considered **investigational** because the evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management.

The use of micro-RNA (miRNA) expression analysis including but not limited to MatePair Acute Myeloid Leukemia for diagnosis or prognosis in patients with confirmed or suspected acute myeloid leukemia (AML) is considered **investigational** because the evidence is insufficient in determining the technology improves net health outcomes to include changes in clinical management.

PROCEDURE CODES AND BILLING GUIDELINES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnosis codes.

- 81120 IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (e.g., glioma), common variants (e.g., R132H, R132C)
- 81121 IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (e.g., glioma), common variants (e.g., R140W, R172M)
- 81175 ASXL1 (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
- 81176 ASXL1 (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (e.g., exon 12)
- 81218 CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence
- 81245 FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
- 81246 FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)
- 81272 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8, 11,13, 17, 18)

- 81273 KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, D816 variant(s)
- 81310 NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, exon 12 variants
- 81334 RUNX1 (runt related transcription factor 1) (e.g., acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (e.g., exons 3-8)
- 81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
- 81456 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MET, MLL, NOTCH1, NPM1, NRAS, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
- 81479 Unlisted molecular pathology procedure (may be utilized for MatePair Acute Myeloid Leukemia)
- 0023U 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
- 0046U FLT3 (fms-related tyrosine kinase 3) e.g., acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative
  0049U NPM1 (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, quantitative
- 0050U Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements (MyAML NGS Invivoscribe)

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POLICY HISTORY		
Date	**Reason**	**Action**
January 2022	Annual Review	Policy Revised
May 2021	Annual Review	Policy Renew
May 2020	Annual Review	Policy Revised
May 2019	Annual Review	Policy Revised
May 2018	Annual Review	Policy Revised
May 2017	New Policy	New Policy

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

Wellmark Blue Cross and Blue Shield
Medical Policy Analyst
PO Box 9232
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