Acute Myeloid Leukemia Molecular Genetic Testing

Acute myeloid leukemias (AMLs) are a heterogeneous group of disorders characterized by the clonal expansion of myeloid precursors in the peripheral blood, bone marrow, and/or other tissues, which results in impaired hematopoiesis and bone marrow failure.[1,2,3,4] AML is the most common acute leukemia in adults (~80% of leukemia cases) and accounts for the largest number of annual deaths from leukemia in the United States.[2,4] Gene alterations, along with translocations and inversions, carry prognostic importance in AML. In addition to large chromosomal rearrangements, molecular changes have also been implicated in the development of AML. A comprehensive evaluation of several molecular markers, including *FLT3*, *NPM1*, *CEBPA*, *KIT*, *IDH1*, and *IDH2*, is important for risk assessment and prognostication in certain patients with AML, and may guide treatment decisions.[2]

For more information on next generation sequencing testing for AML, see Myeloid Malignancies Mutation Panel by Next Generation Sequencing. For information on cytogenetic testing related to AML, see Acute Myeloid Leukemia Panel by FISH, Acute Myeloid Leukemia with Myelodysplastic Syndrome (MDS) or Therapy-Related MDS Panel by FISH and Acute Promyelocytic Leukemia Molecular Testing.

Testing Strategy

At diagnosis, the minimum AML workup includes a bone marrow aspirate for morphology, flow cytometric immunophenotyping, cytogenetics (eg, karyotyping and fluorescence in situ hybridization [FISH]), and appropriate molecular genetic testing.[1,2,3]

Disease Overview

Incidence

>20,0000 cases/year in the U.S.[4]

Tests to Consider

Detect and quantitate gene alterations/translocations/inversions. Use for minimal residual disease (MRD) and relapse risk monitoring.

CBFB-MYH11 inv(16) Detection, Quantitative 2011114

Method: Reverse Transcription Quantitative Polymerase Chain Reaction

NPM1 Mutation Detection by RT-PCR, Quantitative 3000066

Method: Quantitative Reverse-Transcription Polymerase Chain Reaction

PML-RARA Translocation, t(15;17) by RT-PCR, Quantitative 2002871

Method: Reverse Transcription Polymerase Chain Reaction

RUNX1-RUNX1T1 (AML1-ETO) t(8;21) Detection, Quantitative 2010138

Method: Quantitative Reverse Transcription Polymerase Chain Reaction

Use for diagnosis, prognosis, and management. Not intended for MRD monitoring.

FLT3 ITD and TKD Mutation Detection 3001161

Method: Polymerase Chain Reaction

IDH1 and IDH2 Mutation Analysis, exon 4 2006444

Method: Polymerase Chain Reaction/Sequencing

Age of Onset

Median is 67 years[2]

Symptoms

- Symptoms resulting from thrombocytopenia, neutropenia, and anemia due to the accumulation of blasts in the marrow[2]
- Morphologic hallmark: excessive accumulation of blasts (typically >20%) and other defined immature cells which affect one or more myeloid lineage[2]

Test Interpretation

For more detailed information on the prognostic significance of molecular markers in AML, see the ARUP Consult Acute Myeloid Leukemia topic.

Use for prognostication of cytogenetically normal AML (CN-AML).

CEBPA Mutation Detection 2004247

Method: Polymerase Chain Reaction/Sequencing

Prognostication in core-binding factor-related (CBF) AML.

KIT Mutations in AML by Fragment Analysis and Sequencing 2002437

Method: Polymerase Chain Reaction/Fragment Analysis/Sequencing

Related Next Generation Sequencing Test.

Myeloid Malignancies Mutation Panel by Next Generation Sequencing 2011117

Method: Massively Parallel Sequencing

Recurrent Genetic Abnormalities in AML[2,4,5]

Molecular Genetic Alteration	Prognostic Significance
CEBPA	Biallelic mutations confer favorable prognosis
FLT3 ITD and TKD	Poor prognosis associated with *FLT3* ITD mutation; *FLT3* TKD mutation has unclear prognosis
IDH1 and *IDH2*	Unfavorable prognosis; targeted therapy is available for AML with IDH1 or IDH2 mutation
KIT	Poor prognosis, usually associated with core binding factor leukemias; increased risk of relapse
NPM1	Favorable prognosis in patients with normal karyotype and without *FLT3* ITD mutation; poor prognosis if present with *FLT3* ITD and *DNMT3A* mutations

[a]These fusions can initially be screened by FISH, but are also useful in monitoring for MRD.

CR, complete remission

Sources: NCCN, 2019[2]; De Kouchkovsky, 2016[4]; WHO, 2017[5]

Molecular Genetic Alteration	Prognostic Significance
CBFB-MYH11[a]	Usually associated with high rate of complete remission (CR) and long-term, disease-free survival when treated with intensive consolidation therapy
PML-RARA[a]	More favorable prognosis than any other AML cytogenetic subtype when treated appropriately
RUNX1-RUNX1T1[a]	Usually associated with a high rate of CR and long-term, disease free survival when treated with intensive consolidation therapy

[a]These fusions can initially be screened by FISH, but are also useful in monitoring for MRD.

CR, complete remission

Sources: NCCN, 2019[2]; De Kouchkovsky, 2016[4]; WHO, 2017[5]

Sensitivity/Specificity

Gene	Methodology	Analytical Sensitivity	Analytical Specificity
CEBPA	PCR/sequencing	40% mutated cells	100%
FLT3 ITD and TKD	PCR/CE	Signal ratio of 0.05 for ITD and 0.05 for TKD D835	100%
IDH1 and *IDH2*	PCR/sequencing	40% mutated cells	100%
KIT	PCR/fragment analysis/sequencing	30% mutated cells for exon 17 5% mutated cells for exon 8	100%
NPM1	Quantitative reverse transcription PCR	1:100,000	100%
CBFB-MYH11[a]	Quantitative reverse transcription PCR)	1:10,000	100%
PML-RARA[a]	Quantitative reverse transcription PCR	1:10,000	85%
RUNX1-RUNX1T1[a]	Quantitative reverse transcription PCR	1:100,000	100%

[a]These fusions can initially be screened by FISH, but are also useful in monitoring for MRD.

CE, capillary electrophoresis; PCR, polymerase chain reaction

Limitations

- Variants outside the targeted regions or below the limit of detection will not be identified

- Results must always be interpreted within the patient's clinical context and in conjunction with other relevant data and should not be used alone for a diagnosis of malignancy

References

1. Arber DA, Borowitz MJ, Cessna M, et al. Initial Diagnostic Workup of Acute Leukemia: Guideline From the College of American Pathologists and the American Society of Hematology. Arch Pathol Lab Med. 2017; 141 (10): 1342-1393. PubMed

2. NCCN Clinical Practice Guidelines in Oncology, Acute Myeloid Leukemia. National Comprehensive Cancer Network. Mar 2019; [Last update: Mar 2019; Accessed: May 2019]

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4. De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. Blood Cancer J. 2016; 6 (7): e441. PubMed

5. Swerdlow S, Campo E, Jaffe E, Pileri S, Stein H, Thiele J, Arber D, Hasserjian R, Le Beau M. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Revised 4th Ed.. Lyon, France: International Agency for Research on Cancer, 2017.

Related Information

Acute Myeloid Leukemia - AML

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