MEASURABLE RESIDUAL DISEASE HAS PROGNOSTIC AND THERAPEUTIC IMPLICATIONS IN ACUTE MYELOID LEUKEMIA

AML is the most common form of acute leukemia in adults, with an estimated age-standardized global median incidence of 2.28 cases per 100,000 persons.[1,2] AML is a complex hematologic malignancy that remains largely incurable, with the majority of patients relapsing with current SOC therapy.[3]

68%–74%
of patients relapse within 3 years[4]

AML survival rates are the lowest among all leukemias in the US[5,6]

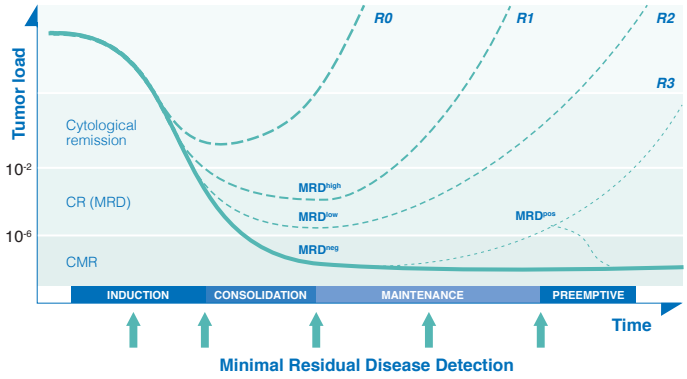
5-year survival rate of 29.5%[7]

MRD is the persistence of leukemic cells after treatment at levels below morphologic detection in patients in CR and is a risk factor for relapse[8,9]

Following treatment, patients may still have residual disease, or MRD, that is undetectable with standard morphologic assessment used to determine CR.[8,9]

- CR does not provide adequate insight into the true quality of response, as the majority of patients who achieve CR relapse within 3–5 years of diagnosis[10]
- MRD negativity may indicate undetectable levels of residual disease based on the sensitivity of the method used[3,8]

Evolution of tumor load and MRD before, during, and after chemotherapy[10]



CR without MRD was added to the AML 2017 ELN response criteria as a grade of response deeper than morphologic CR[3,4]

A patient who did not achieve MRD-negative status will relapse very quickly ***R0***. Depending on the level of MRD present, relapse will occur sooner or later ***R1, R2, R3***.[10]

MRD-negative status is a prognostic factor for longer survival in AML and decreased risk of relapse post-HSCT[11,12,*]

5-Year Overall Survival:[11]

34% for patients who are MRD(+) **vs** **68%** for patients who are MRD(–)

3-Year Relapse Estimates:[12]

67% for patients in MRD(+) **remission** **vs** **22%** for patients in MRD(–) **remission**

Early MRD assessment and MRD-driven treatment strategies can improve outcomes in patients with AML, including those with favorable cytogenetic risk factors[13-15]

*In a meta-analysis of 81 publications with over 11,000 patients.[11]

AML, acute myeloid leukemia; CMR, complete molecular remission; CR, complete remission; ELN, European LeukemiaNet; HSCT, allogeneic hematopoietic stem cell transplantation; MRD, measurable (minimal) residual disease; SOC, standard-of-care.

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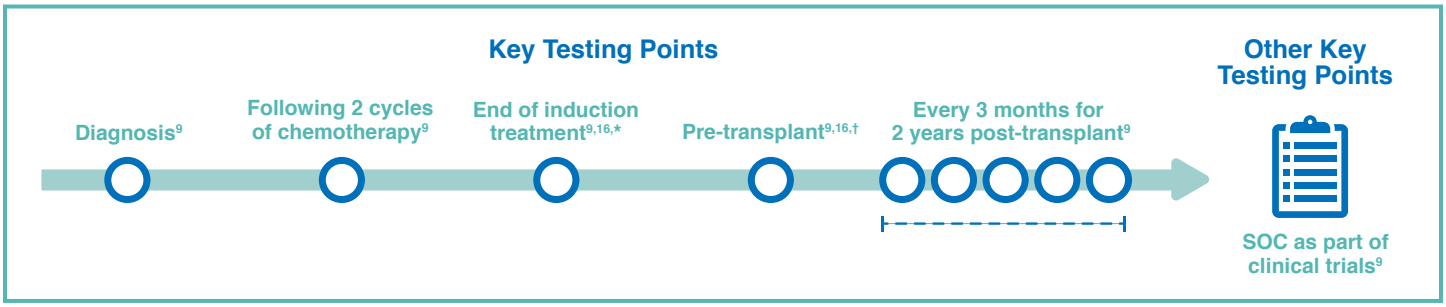
Clinical guidelines recommend patients with AML undergo MRD testing throughout the course of the disease[9,16]



*MRD can be evaluated from peripheral blood or bone marrow samples.[9] †For patients undergoing HSCT, MRD should be assessed from peripheral blood or bone marrow after the last conventional chemotherapy treatment but not earlier than 4 weeks before conditioning treatment.[9]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for AML provide guidance on defining molecular relapse by MRD status and the implications of MRD status.[16]

- NCCN Guidelines® state that MRD(–) after induction predicts a lower incidence of relapse and MRD(+) is not proof of relapse. However, a persistently positive MRD result after induction is associated with an increased risk of relapse. For favorable-risk patients, NCCN Guidelines recommend considering a clinical trial or alternative therapy if persistently MRD(+) after induction and/or consolidation[16]

Assessing MRD in AML

The molecular and immunological heterogeneity of AML requires various MRD platforms for different patient populations[9]

Method	Sensitivity	Target	Advantages and Disadvantages
MFC[9,17]	~10^{-4}–10^{-5}	• LAIP • DfN	Broadly applicable Limited standardization and subjective interpretation
NGS[17-19]	~10^{-3}–10^{-6}	• Recurrent myeloid gene mutations (eg, *NPM1*, *RUNX1*, *IDH1/IDH2*, etc)	Sensitive and relatively easy to perform Limited standardization and undefined role
RT-qPCR[9,17,18]	~10^{-3}–10^{-5}	• Fusion gene transcripts (eg, *PML-RARA*, *RUNX1-RUNX1T1*, and *CBFB-MYH11*) • Recurrent gene mutations (eg, *NPM1*) • Overexpressed genes (eg, *WT1*)	Most established method for clinical care (APL and CBF AML) Overall, 50% of patients have a target mutation that can be potentially used to measure MRD (in older patients, target mutations are < 35%)

MFC detects aberrant phenotypes applicable to the majority of patients with AML, while molecular techniques such as NGS and RT-qPCR identify leukemia-specific genetic targets.[9,17]

While karyotyping and/or FISH methods play an important role at diagnosis, they have limited sensitivity for MRD detection.[3]

Clinical guideline recommendations exist for MRD evaluation in AML, which can be performed by CLIA-certified facilities[9,16]

APL, acute promyelocytic leukemia; CBF AML, core-binding factor acute myeloid leukemia; CBFB-MYH11, core-binding factor subunit beta myosin heavy chain 11; CLIA, Clinical Laboratory Improvement Amendments; DfN, different from normal; FISH, fluorescence in situ hybridization; IDH1, isocitrate dehydrogenase-1; IDH2, isocitrate dehydrogenase-2; LAIP, leukemia-associated immunophenotype; MFC, multiparameter flow cytometry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NPM1, nucleophosmin 1; PML-RARA, promyelocytic leukemia gene retinoic acid receptor-alpha; RT-qPCR, real-time quantitative polymerase chain reaction; RUNX1, runt-related transcription factor 1; RUNX1-RUNX1T1, RUNX1 translocated to 1; WT1, Wilms' tumor gene.

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