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

MRD is the persistence of leukemic cells after treatment at levels below morphologic detection in patients in CR and is a risk factor for relapse8,9

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 diagnosis10

• MRD negativity may indicate undetectable levels of residual disease based on the sensitivity of the method used3,8

Evolution of tumor load and MRD before, during, and after chemotherapy10

CR without MRD was added to the AML 2017 ELN response criteria as a grade of response deeper than morphologic CR3,4

MRD-negative status is a prognostic factor for longer survival in AML and decreased risk of relapse post-HSCT11,12,*

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 factors13-15

*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.
**Clinical guidelines recommend patients with AML undergo MRD testing throughout the course of the disease**

- MRD can be evaluated from peripheral blood or bone marrow samples. 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.

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.

- 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.

### Assessing MRD in AML

**The molecular and immunological heterogeneity of AML requires various MRD platforms for different patient populations**

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Target</th>
<th>Advantages and Disadvantages</th>
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<tbody>
<tr>
<td><strong>MFC</strong></td>
<td>~10^-6–10^-4</td>
<td>LAIP, DIN</td>
<td>Broadly applicable, Limited standardization and subjective interpretation</td>
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<tr>
<td><strong>NGS</strong></td>
<td>~10^-5–10^-4</td>
<td>Recurrent myeloid gene mutations (eg, NPM1, RUNX1, IDH1/IDH2, etc)</td>
<td>Sensitive and relatively easy to perform, Limited standardization and undefined role</td>
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<tr>
<td><strong>RT-qPCR</strong></td>
<td>~10^-5–10^-6</td>
<td>Fusion gene transcripts (eg, PML-RARA, RUNX1-RUNX1T1, and CBFB-MYH11)</td>
<td>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 &lt; 35%)</td>
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</table>

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.

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

### Clinical guideline recommendations exist for MRD evaluation in AML, which can be performed by CLIA-certified facilities

- 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; DIN, 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; SOCl, Clinical Laboratory Improvement Amendments; 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.

### Key Testing Points

- **Diagnosis**
- Following 2 cycles of chemotherapy
- End of induction treatment
- Pre-transplant
- Every 3 months for 2 years post-transplant
- After HSCT evaluation
- SOC as part of clinical trials

### Other Key Testing Points

- Diagnosis
- Following 2 cycles of chemotherapy
- End of induction treatment
- Pre-transplant
- Every 3 months for 2 years post-transplant
- After HSCT evaluation
- SOC as part of clinical trials

**References:**