Measurable residual disease (MRD) and survival outcomes in patients with acute myeloid leukemia (AML)

MRD assessment

MRD assessment in AML can be used as a prognostic/predictive biomarker to inform treatment decision making and as a monitoring tool to identify impending relapse[1]

MRD positivity
Disease is still detected after treatment

MRD negativity
No detectable disease with current methods†
†An undetectable level of disease could still remain.

MRD assessments are employed to evaluate leukemic burden at diagnosis and following treatment in several hematologic diseases; this role is well established in ALL and CLL[2-4]

MRD assessments detect leukemic burden when there are too few leukemic cells to be identified through traditional morphologic detection[5]

~1:20
Sensitivity of morphology-based testing to determine CR[5]

FISH

~10^{-2} to ~10^{-6}
Sensitivity of assays to determine MRD negativity[5,6]

NGS

Current guidelines for MRD testing in AML clinical trials

US Food and Drug Administration (FDA)[10]:
Acknowledges the regulatory and clinical **uses of MRD as a biomarker for hematologic malignancies**

European LeukemiaNet (ELN)[11]:
Working Party recommends that **MRD monitoring should be part of AML standard of care**[a]

	FDA[10]	ELN[1]
Patient sample	Bone marrow is preferred; justification for peripheral blood should be provided	Bone marrow is used routinely to confirm remission. Peripheral blood is only recommended in specific molecular subgroups[a]
Time point	After patient achieves CR with recovery of blood counts	At diagnosis, after 2 cycles of chemotherapy, at the end of treatment, and (unless using MFC) during follow-up[b]

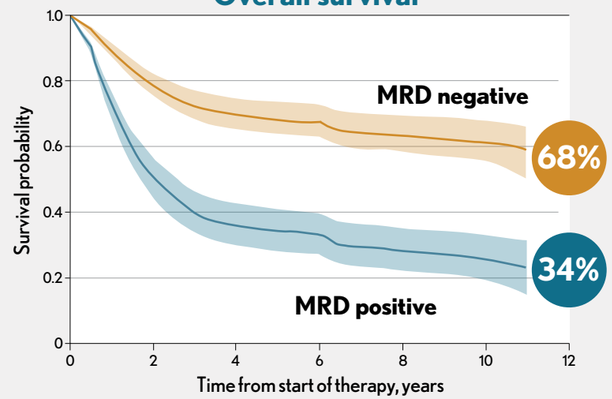
Common methods of assessing MRD in AML[5,6,12]

Method	Sensitivity	Strengths	Weaknesses
FISH	~1 to 10^{-2}	• Widely available • Detects numeric cytogenetic abnormalities	• Insensitive • Labor intensive • Expensive
MFC	Up to ~10^{-5}	• Applicable to most AML cases • Relatively quick • Highly sensitive and specific • Detects leukemia stem cell phenotype	• Challenging to perform • Dependent on antibody panel • Limited standardization • Phenotype is not always stable
RT-qPCR	Up to ~10^{-6}	• Widely available • Highly sensitive • Well standardized	• Time intensive • Expensive • Challenging to perform • Applicable to only ~50% of cases
NGS	Up to ~10^{-6}	• Relatively easy to perform • Sensitive	• Limited standardization • CHIP mutated genes • Persistent mutants in CR

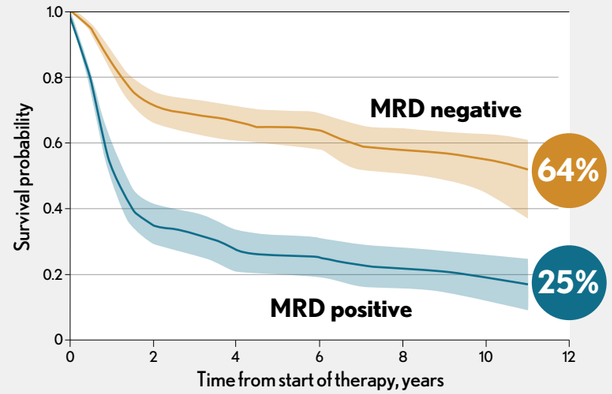
Predictive value of MRD in AML

MRD negativity in patients with AML is associated with **improved overall and disease-free survival, lower risk of relapse, and greater success of HCT[7-9]**

Overall survival[7]



Disease-free survival[7]



In a large meta-analysis, improved overall and disease-free survival was consistent across age groups, AML subtypes, and most MRD detection methods[7,c]

Abbreviations: MRD, measurable residual disease; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphoblastic leukemia; CR, complete remission; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing; RT-qPCR, quantitative reverse transcription polymerase chain reaction; CHIP, clonal hematopoiesis of indeterminate potential; APL, acute promyelocytic leukemia; HCT, hematopoietic cell transplantation; FDA, US Food and Drug Administration; ELN, European LeukemiaNet; MFC, multiparameter flow cytometry; PCR, polymerase chain reaction.

Footnotes: [a]Patients with mutant *NPM1*, CBF AML (*RUNX1-RUNX1T1* or *CBFB-MYH11*), or APL (*PML-RARA*) should have molecular assessment of MRD; AML patients not included in these molecularly defined subgroups should have MRD assessment using MFC.[1] [b]In APL, the most important MRD endpoint is PCR negativity for *PML-RARA* at the end of consolidation; for non-high-risk APL, MRD monitoring may be discontinued once MRD-negativity in bone marrow is achieved. [c]Except for cytogenetics and FISH.[7]

References: 1. Heuser M, et al. *Blood*. 2021;138(26):2753-2767. **2.** Brüggemann M, Kotrova M. *Blood Adv*. 2017;1(25):2456-2466. **3.** Jen EY, et al. *Clin Cancer Res*. 2019;25(2):473-477. **4.** Del Giudice I, et al. *Front Oncol*. 2019;9:689. **5.** Ravandi F, et al. *Blood Adv*. 2018;2(11):1356-1366. **6.** Jentzsch M, et al. *Cancers*. 2019;11(11):1625. **7.** Short NJ, et al. *JAMA Oncol*. 2020;6(12):1890-1899. **8.** Araki D, et al. *J Clin Oncol*. 2016;34(4):329-336. **9.** Ivey A, et al. *N Engl J Med*. 2016;374(5):422-433. **10.** US Food and Drug Administration. Hematologic malignancies: regulatory considerations for use of minimal residual disease in development of drug and biological products for treatment. January 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and. Accessed April 2022. **11.** Schuurhuis GJ, et al. *Blood*. 2018;131(12):1275-1291. **12.** Short NJ, Ravandi F. *Haematologica*. 2019;104(8):1532-1541.

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