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Closing the gap between non-measurable residual disease and true absence of minimal residual disease

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The author declares no competing interests.

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Minimal residual disease (MRD) before allogeneic stem cell transplantation (alloSCT) is a known strong risk factor for relapse and mortality in patients with acute myeloid leukemia (AML), as has been demonstrated in numerous studies. Two methods are extensively used for MRD surveillance: flow cytometry and molecular testing by either polymerase chain reaction (PCR) or next generation sequencing (NGS). Molecular MRD testing offers enhanced sensitivity, up to 10^{-6}, albeit it can only be applied in selected cases, in which the presence of a mutated gene is *sine qua non* for residual leukemia.

Flow-based MRD detection using different-from-normal (DfN) and leukemia-associated immunophenotype (LAIP) approaches[1] has been adopted worldwide. It is applicable for the vast majority of patients with AML[2], although the sensitivity is 3 logs lower than that of PCR. It is also highly dependent on technical/operational variables, such as marrow dilution by blood, the number of cells/events collected, the type of antibodies used and the laboratory experience for interpretation. Hence, patients who are considered MRD-negative by flow cytometry before transplantation, still have a substantial risk of 20-25% for relapse[3]. This contrasts with the prognostic impact of molecular MRD negativity, which predicts for a relapse rate of less than 10%[4,5].

The current study by Tettero et al. puts in the spotlight the heterogeneity in flow-based MRD and its clinical applications in the real world[6]. Prior studies that reported a detrimental outcome for patients with MRD before alloSCT used centralized flow cytometry assessment for MRD detection[7,8]. The current article presents not only the largest study to date reporting the association of post-transplant outcomes and pre-alloSCT flow-based MRD results, but it also highlights that the prognostic value of MRD varies significantly between transplantation centers, even larger ones. Indeed, the prognostic impact of MRD in this cohort has been derived from only a limited number of centers, while in the majority of centers, the MRD detection before alloSCT has not predicted AML relapse or shorter survival. This heterogeneity is likely to reflect lower sensitivity of flow-based MRD in

multiple transplantation centers in the United States, potentially leading to false MRD-negative results. In line with this assumption, only 11% of patients in the analyzed cohort had detectable MRD before transplant as opposed to 20% and above in other reports[3]. Notably, although the flow cytometry equipment has improved over the years reported in the study, with the transition to 8-12 color platforms, the authors have not found either an increased MRD rate in the later study period, or a change in the prognostic impact of MRD detection. Yet, the study data reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) have not included the antibody panels applied, flow cytometry equipment, methods used for the interpretation of results (LAIP, DfN or both), the number of events or lower limit of detection in each sample. Thus, many parameters, determining the sensitivity of flow cytometry have been missing.

Tettero et al. demonstrate that even among large-volume transplantation centers in the United States, technology, methodology and interpretation issues vary significantly, decreasing the applicability of negative MRD for peri-transplantation decisions[6]. Indeed, even for research purpose, the European LeukemiaNet (ELN) discourages single-center studies "without relevant experience"[9]. In order to properly stratify the risk of patients when using flow-based MRD, it should be standardized and harmonized globally, allowing for its reproducibility, such as being done in European transplantation centers participating in the RESOLVE project. As an alternative to MRD estimation by flow cytometry, ultra-high sensitivity NGS panels offer broader applicability of molecular MRD testing for most AML cases and also might enable more standardized methods and reports[10]. All this with the realistic hope of being closer to reliably predicting for true absence of residual disease.

References

1. Wood BL. Acute myeloid leukemia minimal residual disease detection: the difference from normal approach. Curr Protoc Cytom. 2020;93(1):e73.
2. Cloos J, Valk PJM, Thiede C, et al. 2025 update on MRD in acute myeloid leukemia: a consensus document from the ELN-DAVID MRD Working Party. Blood. 2026;147(11):1147-1167.
3. Paras G, Morsink LM, Othus M, et al. Conditioning intensity and peritransplant flow cytometric MRD dynamics in adult AML. Blood. 2022;139(11):1694-1706.
4. Hu X, Zhao Y, Jiang C, et al. Peritransplant molecular MRD monitoring by targeted NGS in patients with FLT3-ITD-mutated acute myeloid leukemia. Blood Adv. 2026;10(16):5607-5619.
5. Dillon R, Hills R, Freeman S, et al. Molecular MRD status and outcome after transplantation in NPM1-mutated AML. Blood. 2020;135(9):680-688.
6. Tettero JM, Zhang MJ, Liu W, et al. Real-world heterogeneity in the prognostic value of pre-transplant flow cytometry measurable residual disease in acute myeloid leukemia in first complete remission: CIBMTR analysis . Haematologica. xxx
7. Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. Blood. 2019;134(12):935-945.
8. Terwijn M, van Putten WL, Kelder A ,et al. High prognostic impact of flow cytometric minimal residual disease detection in acute myeloid leukemia: data from the HOVON/SAKK AML 42A study. J Clin Oncol. 2013;31(31):3889-3897.
9. Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018;131(12):1275-1291.

10. Thol F, Gabdoulline R, Liebich A, et al. Measurable residual disease monitoring by NGS before allogeneic hematopoietic cell transplantation in AML. Blood. 2018;132(16):1703-1713.