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# MRD assessment in AML – Recommendations from the ELN MRD Working Party

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Measurable Residual Disease (MRD) is an independent prognostic factor for outcomes in Acute Myeloid Leukemia (AML). At present, there are several methods used to evaluate MRD in various settings including Multiparameter Flow Cytometry (MFC), Real-time Quantitative Polymerase Chain Reaction (RQ-PCR), Next Generation Sequencing (NGS) and Digital PCR. However, there are currently no standardized guidelines on how or when to measure MRD and its application in clinical practice.

On behalf of the European LeukemiaNet (ELN), a group of 24 international experts in the field of Acute Myeloid Leukemia (AML) particularly in the research, clinical and translational knowledge in MRD in AML have published a consensus document on MRD assessment in AML in Blood on 12 January 2018. The expert panel included many members of the AML Global Portal (AGP) European and North American Steering Committees. The ELN partners with the AGP Steering Committee and the AGP Secretariat to provide a unique online educational platform for academic researchers and clinicians treating AML patients worldwide.

The recommendations by the ELN MRD Working Party on MRD assessment were subdivided into three categories including MFC MRD, molecular MRD and clinical MRD and are discussed below.

**MFC MRD assessment**

Two different approaches have been used to assess MFC MRD including the Leukemia-Associated Immunophenotype (LAIP) and the Different-from-Normal (DfN) approach. LAIP approach enables a more reliable definition at follow-up of aberrancies already present at diagnosis (identifies immunophenotypic shifts), while the DfN approach measures aberrancies present at follow-ups.

***Key recommendations***

To best define MFC MRD, the ELN MRD Working Party recommends that these two approaches should be combined and termed this combination, **LAIP-based DfN** approach. This approach would enable the detection of new aberrancies emerging at follow-up and monitor patients in cases where there is an absence of diagnostic information. They further noted that this approach could be used separately to validate the prognostic impact of unknown aberrancies.

**Molecular MRD assessment**

Real-time PCR-based and sequencing approaches are the two common molecular methods for MRD assessment. At present, the RQ-PCR approach is “highly sensitive” and thus regarded as the “gold standard”. NGS can be used to detect all leukemia specific abnormalities but it is an emerging technique for MRD assessment.

**Key recommendations**

The ELN MRD Working Party recommends that RQ-PCR platforms should be used for MRD assessment based on the established high sensitivity. Heparin and ethylenediaminetetraacetic acid (EDTA) can be used as anti-coagulants.

**Clinical application of MRD**

The ELN MRD Working Party recommends that in the clinical setting, morphology-based CR should be refined by assessment of MRD. Additionally, MRD should be used to refine risk assessment prior to consolidation treatment and the post-induction time point closer to consolidation.

According to the experts, MRD monitoring should be considered part of the standard of care for AML patients. Molecular MRD assessment should be limited to APL, *CBF-AML* and *NPM1* mutated AML while MFC MRD assessment should be used for other patients who are not molecularly defined.

The experts also recommend that MRD should be assessed at both pre-transplant and post-transplant settings. During prospective clinical trials, the authors recommend that molecular and/or MFC assessment of MRD should be performed as part of response evaluation.

**References**

1. Schuurhuis G. J. *et al*. Minimal/measurable residual disease in AML: consensus document from ELN MRD Working Party. Blood. 2018 Jan 12. DOI: 10.1182/blood-2017-09-801498. [Epub ahead of print].