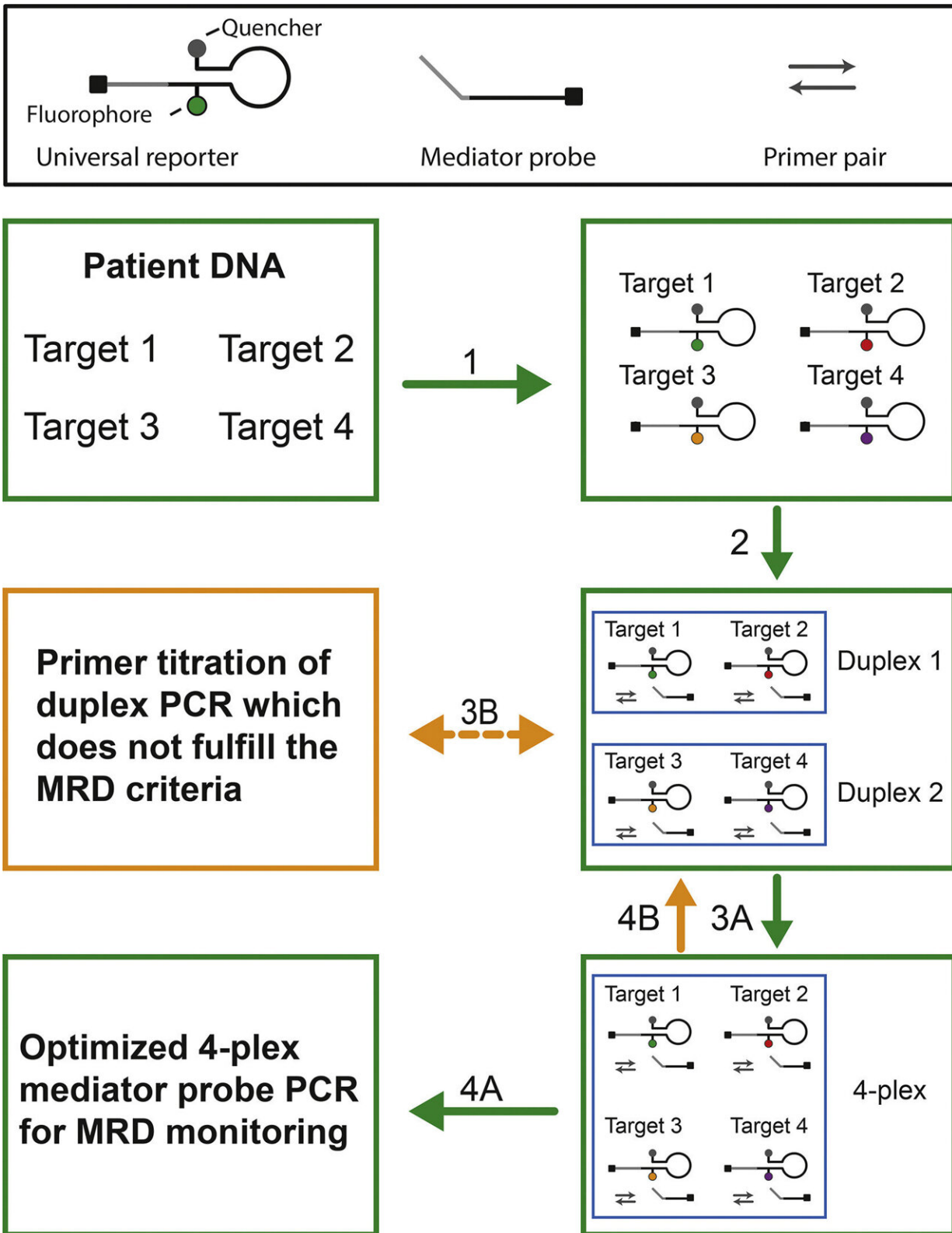


New personalized test for an earlier and more accurate prediction of cancer relapse for children with ALL

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MRD-multiplex workflow for the development of patient-specific 4-plex MP

PCR assays through an iterative process. MP PCR-design and -analysis can be done with different software tools already available. In addition, specialized software for multiplex MRD-PCR-design (Assay Manager GNWI mbH, Germany) and standardized analysis (ValidScale Hahn-Schickard e.V., Germany) have been under clinical validation. Credit: *The Journal of Molecular Diagnostics*

Researchers have developed a new protocol for monitoring acute lymphoblastic leukemia (ALL), the most common cancer in children, to inform more effective treatment strategies and detect disease recurrence. The personalized mediator probe PCR (MP PCR) uses multiple genomic cancer cell markers in a single assay and is simpler than current techniques. It improves monitoring clonal tumor evolution to detect a relapse sooner and avoid false negative results. Their protocol is detailed in the *Journal of Molecular Diagnostics*.

The survival rate for children with ALL has increased impressively to over 80% over the last several decades. However, the prognosis for children whose cancer recurs remains unfavorable. Therefore, minimal residual disease (MRD) [monitoring](#) is an important prognostic factor for treatment response and patient stratification. MRD monitoring uses highly sensitive real-time PCR to measure the amount of cancer cells among normal cells.

"MRD markers can disappear during treatment, which can lead to false-negative results and poor decision-making in personalized treatments," explains Principal investigator Cornelia Eckert, Ph.D., Department of Pediatric Oncology/Hematology, Charité—Universitätsmedizin Berlin, German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ). Consequently, monitoring at least two independent markers per patient is recommended. Dr. Eckert continues, "The current gold standard EuroMRD consortium guidelines call for amplification

using singleplex real-time PCR quantification, making testing additional markers more laborious and expensive. They also lead to a higher consumption of patient material."

To overcome these limitations, Dr. Eckert and co-investigators established the personalized MP PCR, an iterative workflow and guidelines for designing multiplex real-time PCRs to monitor up to four MRD markers for ALL simultaneously in one assay. When tested on DNA in bone marrow samples from patients with ALL, the MP PCRs met the EuroMRD gold standard guidelines and level of sensitivity for clinical decision-making.

Co-investigator Michael Lehnert, Ph.D., Hahn-Schickard Freiburg, states, "Multiplexing can significantly improve personalized MRD monitoring of patients, because a higher number of MRD markers per patient can be analyzed at the same time. Even though these patient-specific sequences of [cancer](#) cells only differ in a few DNA nucleotides from healthy cells, our multiplex assay can still distinguish between these DNA sequences. Therefore, a broader range of patient-specific sequences can be included in the assay."

The MRD-MP guidelines are simple and may allow assay standardization across different laboratories. To demonstrate the potential transfer of the duplex MP PCR into a routine diagnostic setting, the new assay was applied in a prospectively assessed patient case in comparison with the gold standard singleplex test. Both fulfilled the EuroMRD guidelines and led to a similar quantitative range and sensitivity.

In order to deal with challenges inherent to multiplex PCR, the researchers developed an efficient iterative workflow for PCR design and optimization. DNA primer titration is only involved and extended if the assay performance is not sufficient in the first step, so that the

number of iterations is minimized.

"There is a vast variety of DNA marker sequences unique to each leukemia," adds first author Elena Kipf, Ph.D., Hahn-Schickard Freiburg. "The MRD-multiplex workflow provides a systematic and reliable way of effective MRD-MP PCR design and optimization and helps the standardization of personal diagnostics."

While their work demonstrates that multiplex MP PCR has the potential to set a new standard in personalized MRD monitoring, the researchers note it must be clinically validated in a representative cohort of ALL patients. "Cancer is a fatal disease from which not every patient can be cured," Dr. Eckert stresses. "After successful clinical validation, patients could benefit from extended MRD monitoring, leading to more precise predictions of therapy response and better patient stratification and outcomes."

More information: Elena Kipf et al, Advanced Minimal Residual Disease Monitoring for Acute Lymphoblastic Leukemia with Multiplex Mediator Probe PCR, *The Journal of Molecular Diagnostics* (2021).
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