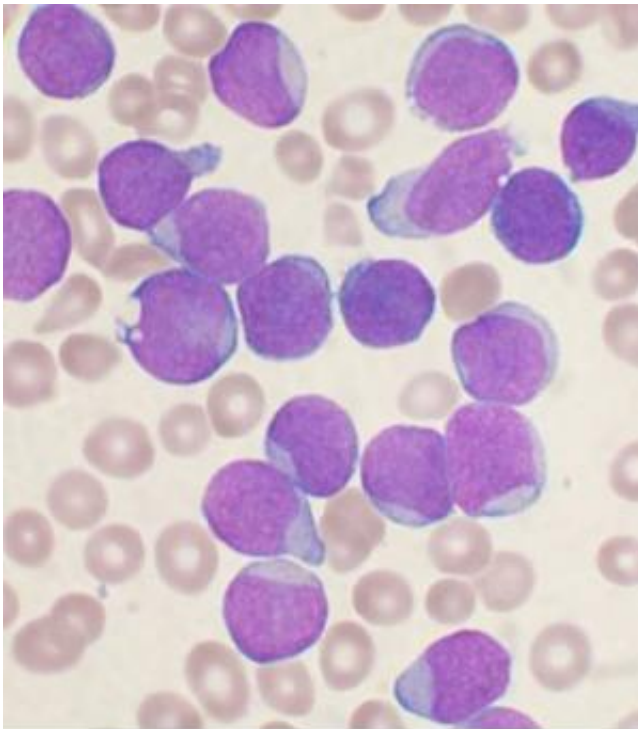


## New assay detects persistent disease in leukemia patients thought to be in remission

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A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

The outcomes of chronic myeloid leukemia (CML) have dramatically improved as the result of tyrosine kinase inhibitor (TKI) treatment. Use of a TKI regimen can lower the blood CML biomarker to levels imperceptible by current detection methods. For patients in "molecular remission," however, uncertainties remain regarding whether they will

relapse or if treatment should be discontinued. A study in *The Journal of Molecular Diagnostics* describes a new personalized DNA-based digital assay that detects persistent disease in 81% of samples taken from a group of patients thought to be in remission.

"If validated in clinical trials of stopping TKIs, this technique will permit a more personalized approach to recommendations for dose reduction or drug cessation in individual patients, ensuring that therapy is withdrawn only from patients with the highest chance of long-term remission," explained lead investigator and head of department Jane F. Apperley, MD, PhD, FRCPath, of the Centre for Haematology, Imperial College (London). Indeed, studies have shown that 60% of CML patients who achieve sustained undetectable levels of BCR-ABL1 transcripts—the hallmark biomarker of CML—experience disease recurrence after TKI [treatment](#) is withdrawn.

Investigators compared the sensitivity of the new technique, DNA-based digital PCR (dPCR) assay, to three other quantitative PCR methods currently used to measure residual CML, including reverse transcriptase-quantitative PCR (RT-qPCR), quantitative PCR (qPCR), and reverse transcriptase-digital PCR (RT-dPCR). RT-qPCR is currently the most widely used method for monitoring residual disease in CML patients.

Thirty-six samples were taken from six patients with early CML who were thought to be in deep molecular remission, as indicated by RT-qPCR results. Repeat analysis using dPCR with preamplification detected [persistent disease](#) in 81% of the samples. In comparison, the detection rate was 25% using RT-dPCR and 19% for qPCR. "We conclude that dPCR for BCR-ABL1 DNA is the most sensitive available method of residual disease detection in CML and may prove useful in the management of TKI withdrawal," stated Dr. Apperley.

The new assay has the potential to dramatically impact CML

management. Immediately after CML diagnosis, the patient's genomic breakpoints would be identified, enabling the design of a patient-specific assay. The patient's response to therapy would be monitored using standard RT-qPCR until reaching molecular remission. At that point, routine monitoring would be augmented with dPCR, allowing better-informed treatment decisions and improved patient management.

According to Dr. Apperley, the new method improves on previous methodologies in two key areas. First, dPCR is a DNA-based method that allows identification of BCR-ABL1 fusion junctions by targeted next-generation sequencing. This enables the rapid generation of high-performing DNA-based hydrolysis probe assays that are specific to the individual molecular footprint of each patient's CML clone, although the number and location of fusion junctions may vary among patients. The second advancement afforded by the new method relates to the greater sensitivity provided by the dPCR platform. "The technique we describe, with which we successfully mapped a disease-specific junction in all [patients](#) tested, is relatively simple, cost effective, and suited to a high-throughput laboratory," noted Dr. Apperley.

**More information:** "Next-generation sequencing-assisted DNA-based digital PCR for a personalized approach to the detection and quantification of residual disease in chronic myeloid leukaemia patients," by Mary Alikian, Peter Ellery, Martin Forbes, Gareth Gerrard, Dalia Kasperaviciute, Alona Sosinsky, Michael Mueller, Alexandra Whale, Dragana Milojkovic, Jane Apperley, Jim Huggett, Letizia Foroni, and Alistair G. Reid (DOI: [dx.doi.org/10.1016/j.jmoldx.2015.09.005](https://doi.org/10.1016/j.jmoldx.2015.09.005) ). Published online in advance of *The Journal of Molecular Diagnostics*, Volume 18, Issue 2 (March 2016)

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