The Past, Present, and Future of Measurable Residual Disease (MRD) in Precision Oncology

The detection of residual cancer post-treatment has been one of oncology's most persistent challenges. Historically, MRD assessment relied on approaches such as imaging, cytomorphology, cytogenetics, and early molecular assays performed in specialized centers. Today, liquid biopsy–based approaches, including ctDNA analysis with highly sensitive molecular techniques such as ddPCR™ technology, enable detection and monitoring of tumor-derived signals in blood or tissue at lower levels than many conventional methods. What was once confined to specialized imaging and hematological testing centers has now evolved into a broad and rapidly expanding field spanning liquid biopsy approaches, including circulating tumor DNA (ctDNA) analysis, and real-time therapeutic decision-making across multiple cancer types. This article traces this journey, from the earliest feasibility studies of residual leukemic cells to today's sophisticated Droplet Digital™ PCR (ddPCR) workflows and explores where MRD monitoring is headed as it moves from research tool toward supporting clinical decision making.

Cancer treatment has evolved over the past two decades, progressing from cytotoxic strategies toward more personalized interventions tailored to the molecular characteristics of individual tumors. The study of MRD, which is defined as the persistence of tumor-derived molecular markers in blood or tissue following treatment, below the threshold of conventional clinical detection, has been instrumental to this transformation. Today, ctDNA MRD has become one of the most informative biomarkers available in oncology research, offering a real-time window into treatment response, relapse risk, and disease dynamics.[1]

The Past: From Concept to Feasibility

The origins of MRD monitoring lie in hematologic oncology, where leukemia research in the 1990s revealed that patients who achieved apparent clinical remission could still harbor residual leukemic cells capable of driving relapse.[2] Early methods, including conventional PCR and flow cytometry, enabled the detection of clonal immunoglobulin or T-cell receptor gene rearrangements and specific chromosomal translocations, providing, for the first time, molecular insights into the residual disease burden that imaging is unable to provide.[3]

However, these early approaches had important limitations. For example, conventional real-time quantitative PCR (qPCR) became the gold standard for MRD quantification in hematological malignancies.[4] Yet, its reliance on external reference standard curves derived from serial dilutions of diagnostic samples introduced variability and complicated cross-laboratory comparisons. Samples falling below the quantitative range posed interpretive challenges. Applying this technique to solid tumors, where circulating tumor DNA (ctDNA) constitutes a small fraction of total circulating cell-free DNA (cfDNA) (often below 0.01%), exceeded the sensitivity boundaries of early PCR-based approaches.[5]

Imaging techniques such as CT and MRI, while non-invasive, are limited in their ability to detect MRD as they rely on tumor dimensions and growth, and are incapable of detecting the cellular or molecular changes that precede cancer recurrence.[6] The rising need for a more sensitive, quantitative, reproducible, and scalable assay capable of detecting a single tumor-derived molecule within a complex sample, led to the emergence of ddPCR approaches.[7]

The Present: MRD Enters Clinical Reality

MRD monitoring is already reshaping clinical research design by enabling more nuanced treatment stratification. For example, patients who test ctDNA-negative following therapy may be candidates for de-escalation, sparing them unnecessary chemotherapy, while those who remain ctDNA-positive, or who become positive during MRD monitoring, may benefit from treatment intensification or early enrollment into continuing trials using alternative therapeutic modalities.[6,8]

Hematologic Malignancies

In hematological malignancies, where MRD monitoring has the longest track record, response-adapted therapy guided by MRD kinetics is already embedded in treatment protocols for acute lymphoblastic leukemia, and is currently being evaluated in chronic lymphocytic leukemia (CLL), multiple myeloma, and lymphoma.[7] In a retrospective study of juvenile myelomonocytic leukemia (JMML) patients following hematopoietic stem cell transplantation, ddPCR-based MRD monitoring detected molecular relapse earlier than conventional methods.[9] MRD levels at one month post-transplant proved prognostically significant with a defined cut-off effectively improving overall survival outcomes.[9]

Solid Tumors and ctDNA

MRD monitoring in solid tumors presents additional biological complexity, as ctDNA shedding into the bloodstream is fundamentally heterogeneous, tumor- and stage-dependent, and the analyte of interest may constitute a very small proportion of total cfDNA, particularly in early-stage or post-operative settings.[6] Nevertheless, growing evidence across colorectal, lung, and breast cancers has established ctDNA as a powerful marker used in MRD monitoring, with over 50 phase II/III trials using ctDNA-MRD as a primary endpoint or treatment decision trigger.[8,10]

Why ddPCR Technology Has Become Central to MRD Monitoring

The attributes that make ddPCR technology well suited to MRD monitoring, directly addressing the fundamental challenges of MRD detection, include its capacity for ultrasensitive, quantitative, and reproducible detection of rare targets in a high background, from limited and often precious sample volumes in research settings.[3]

Unlike qPCR, ddPCR technology requires no external calibration curves, and enables absolute quantification even when samples fall near or below the limit of quantification of conventional assays. This unique feature is particularly valuable in MRD settings, where the distinction between low positive and truly negative results carries direct clinical implications for treatment decisions, such as therapy de-escalation or cessation.[11,12] In a comparative study for MRD monitoring in multiple myeloma, mantle cell lymphoma, and follicular lymphoma, researchers demonstrated that ddPCR technology achieved sensitivity, accuracy, and reproducibility comparable to qPCR.[6] Among 69 patients with a documented molecular marker at diagnosis, ddPCR technology succeeded in all cases, while qPCR failed to produce a reliable standard curve in three patients. Of the 26 samples deemed positive but not quantifiable by qPCR, ddPCR technology reclassified 27% as quantifiable and 23% as negative, allowing for a clinically meaningful distinction.[6] More recently, the versatility of ddPCR technology for MRD monitoring has been demonstrated in rare and technically challenging hematological contexts.[13] Developing custom ddPCR assays targeting atypical leukemogenic *BCR::ABL1* fusion transcripts and uncommon mutations including *CBFB::MYH11* subtypes and *CEBPA* mutations, researchers demonstrated reliable serial MRD quantification at sensitivities below 0.01%, targets that would have been inaccessible to earlier molecular methods.[13]

ddPCR technology is also increasingly being used alongside next-generation sequencing (NGS) in a complementary research workflow, with NGS excelling at broad hypothesis-driven novel biomarker discovery, and ddPCR technology excelling at sensitive, cost-effective longitudinal monitoring in research settings.[14,15,16]

This division of labor is particularly suited for MRD workflows, where the monitoring phase may span months to years and require frequent, reproducible quantification from limited cfDNA inputs. Compared with repeated NGS runs, ddPCR technology offers a faster turnaround, a simpler data analysis pipeline, and lower per-sample costs, making it a practical choice for serial MRD monitoring in both research and emerging clinical settings.[7,17]

Addressing the need for standardized analytical validation frameworks that can support regulatory submissions and cross-institutional comparability, in May 2026 BLOODPAC's Analytical Validation Working Group published Version 2.0 of its Generic Protocols for the Analytical Validation of NGS-Based ctDNA Assays.[18] While analytical workflows are formally scoped to NGS-based assays for late-stage tumors, the resource recognizes digital PCR as a preferred orthogonal method for quantitative confirmation of NGS findings.[19,20] This indicates that as liquid biopsy moves toward clinical and regulatory adoption, the validation infrastructure being built around ctDNA assays is designed to be platform-inclusive, with ddPCR technology's established quantitative precision and sensitivity making a great fit within this framework. These analytical requirements align closely with the performance characteristics emphasized in international guidelines for tDNA testing, which stress the importance of sensitivity, specificity, and reproducibility when monitoring low-abundance targets such as ctDNA.[21,22]

The future of MRD monitoring

As MRD monitoring moves from research settings into clinical practice, the demand for platforms that are sensitive, reproducible, cost-effective, and simple to operate will only intensify. Demonstrating the need for analytical rigor in ctDNA-based decision-making, in April 2026 the FDA's Oncology Drugs Advisory Committee voted against endorsing AstraZeneca's camizestrant for HR-positive, HER2-negative metastatic breast cancer.[23] This decision was linked to a trial design that used ctDNA detection of *ESR1* mutations to trigger an early treatment switch before radiographic progression. The committee's main concern was not whether *ESR1* mutations could be detected in ctDNA, but whether the analytical confidence underpinning that detection was sufficient to justify making treatment decisions, particularly at the low allele fractions characteristic of early, preprogression monitoring.[23] As ctDNA moves from a research biomarker toward influencing treatment decisions, the testing standards are higher than ever and any lack of confidence in analytical rigor is no longer acceptable. This highlights a gap that ddPCR technology may help address in research settings. Unlike NGS, which excels at broad discovery but lacks the quantitative precision needed for reliable detection of low variant allele fractions,[24] ddPCR technology offers absolute quantification and can detect as little as a few molecules per sample.[25] Additionally, ddPCR technology's scalability, speed, and cost-effectiveness for serial monitoring further support its role in clinical research applications.

The next phase of MRD monitoring will be shaped by workflow standardization, clinical integration, and the adoption of reliable and scalable molecular platforms. The EuroMRD Consortium, comprising more than 60 laboratories worldwide, has played a central role in the harmonization of MRD assessment through standardized protocols and quality assurance frameworks. While primarily focused on qPCR approaches, these efforts highlight ongoing initiatives to assess emerging technologies, including ddPCR technology, for potential integration into clinically validated MRD workflows.[26,27]

These advances are enabling the development of personalized MRD approaches that integrate genomic profiling with sensitive, longitudinal monitoring in research settings. As ctDNA-directed MRD assessment continues to mature within clinical research, international guidelines increasingly emphasize the need for analytically robust platforms capable of sensitive and reproducible low variant allele fractions. When deployed in appropriately designed studies and integrated with complementary genomic technologies, such as NGS, ddPCR technology provides a strong analytical foundation for advancing MRD research toward future clinical adoption.

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