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Perspective

Circulating Tumor DNA as a Predictive Biomarker in Colorectal Cancer Treatment

Emily R. Collins*

Division of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

DESCRIPTION

ColoRectal Cancer (CRC) ranks among the most common malignancies worldwide and remains a significant cause of cancer-related mortality. Despite advances in surgical techniques, chemotherapy and targeted therapies, treatment outcomes vary widely due to the heterogeneity of the disease and the emergence of resistance. In this evolving landscape, Circulating Tumor DNA (ctDNA) has emerged as a promising predictive biomarker that can guide treatment decisions, monitor therapeutic response and detect Minimal Residual Disease (MRD) in colorectal cancer patients. Circulating tumor DNA refers to small fragments of DNA released into the bloodstream by apoptotic or necrotic tumor cells, as well as by living cancer cells actively secreting nucleic acids. This tumor-derived DNA carries genetic and epigenetic alterations reflective of the primary tumor and metastatic sites. Unlike traditional tissue biopsies, ctDNA analysis offers a minimally invasive "liquid biopsy" that can be repeatedly sampled to provide real-time insights into tumor dynamics.

The use of ctDNA as a predictive biomarker in colorectal cancer is grounded in its ability to reveal actionable genetic mutations, track clonal evolution and identify resistance mechanisms. One of the earliest and most impactful applications of ctDNA in CRC is in monitoring mutations in the *KRAS*, *NRAS* and *BRAF* genes, which influence eligibility and responsiveness to anti Epidermal Growth Factor Receptor (EGFR) therapies. Patients harboring activating mutations in these genes typically do not benefit from EGFR inhibitors such as cetuximab and panitumumab. Therefore, detecting these mutations through ctDNA analysis allows clinicians to avoid ineffective treatments and tailor therapeutic regimens accordingly. Furthermore, ctDNA has proven invaluable in detecting minimal residual disease following surgery or adjuvant chemotherapy. Conventional imaging techniques and serum tumor markers often fail to identify microscopic disease that leads to relapse. Sensitive ctDNA assays, however, can detect tumor-specific mutations at very low allele frequencies, enabling earlier intervention. Several studies have demonstrated that postoperative ctDNA positivity strongly correlates with increased risk of recurrence, providing a compelling rationale for using ctDNA to stratify patients who may benefit from intensified adjuvant therapy.

The predictive potential of ctDNA also extends to monitoring response to systemic therapies in metastatic CRC. Dynamic changes in ctDNA levels during treatment reflect tumor burden and treatment efficacy more rapidly and accurately than radiologic assessments. Early clearance or reduction of ctDNA is associated with favourable outcomes, whereas persistence or increase signals resistance or progression. This real-time monitoring can guide timely modifications in therapeutic strategies, improving patient management. Technological advances have significantly enhanced the sensitivity and specificity of ctDNA detection. Techniques such as digital PCR, BEAMing (Beads, Emulsion, Amplification, Magnetics) and next-generation sequencing (NGS) allow for the identification of rare mutant alleles within a background of wild-type DNA. Additionally, multi-gene panels and whole-genome approaches provide comprehensive mutation profiles, capturing tumor heterogeneity and emerging resistance mutations.

Despite these promising developments, the clinical implementation of ctDNA assays in colorectal cancer faces several challenges. Standardization of assay methodologies, including sample collection, processing and analysis, is necessary to ensure reproducibility and comparability across laboratories. Additionally, establishing clinically relevant thresholds for ctDNA positivity and integrating results with existing diagnostic criteria require consensus.

Moreover, tumor shedding of ctDNA varies among patients and tumor types, influencing detection sensitivity. Some tumors, particularly those with low burden or specific anatomical sites, may release insufficient ctDNA into circulation for reliable analysis. These limitations underscore the need for combining ctDNA with other biomarkers or imaging modalities for comprehensive disease assessment. Cost and accessibility also impact widespread adoption, although costs are expected to decline as technology matures. Importantly, prospective clinical trials are underway to validate ctDNA-guided therapeutic strategies in colorectal cancer. These studies aim to define the

Correspondence to: Emily R. Collins, Division of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA, E-mail: emilycollins@harvard.edu

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role of ctDNA in selecting adjuvant therapy, guiding treatment escalation or de-escalation and improving patient outcomes.

CONCLUSION

Circulating tumor DNA represents a transformative predictive biomarker in colorectal cancer treatment, enabling precision oncology through non-invasive, real-time tumor profiling. By revealing actionable mutations, detecting minimal residual disease and monitoring treatment response, ctDNA facilitates personalized therapeutic decision-making that can improve survival and quality of life for CRC patients. While challenges remain in standardization, sensitivity, and clinical integration, ongoing research and technological progress continue to expand the utility of ctDNA. The incorporation of ctDNA analysis into routine clinical practice promises to refine treatment paradigms, minimize unnecessary toxicity and detect relapse earlier, ultimately advancing colorectal cancer management toward more effective and individualized care. As liquid biopsy technologies mature and clinical evidence accumulates, ctDNA is poised to become a cornerstone of colorectal cancer precision medicine, fulfilling its potential to transform outcomes for patients worldwide.