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Review Article

Updates on the use of ctDNA in the management of colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) remains a major global health concern as the third most diagnosed cancer and the second leading cause of cancer-related deaths. While early detection through colonoscopy and stool-based screening significantly improves survival, limited adherence and diagnostic sensitivity highlight the need for better non-invasive tools. Circulating tumor DNA (ctDNA), a tumor-specific component of cell-free DNA, has emerged as a promising biomarker that may transform the detection, monitoring, and treatment of CRC. This review compiles and summarizes recent advancements and updates in ctDNA research and evaluates its clinical utility across CRC management. Recent clinical trials, biomarker studies, and comprehensive reviews were examined to evaluate recent advancements in the use of ctDNA in CRC detection and management. ctDNA methylation-based assays have shown high diagnostic accuracy, especially in late-stage CRC, with several multi-gene panels achieving sensitivities and specificities above 90%. Large-scale studies such as DYNAMIC II, GALAXY, and BESPOKE CRC support ctDNA's role in identifying minimal residual disease (MRD), predicting recurrence, and informing adjuvant treatment decisions. Multiple studies have shown that ctDNA has outperformed carcinoembryonic antigen (CEA) and imaging in CRC surveillance, detecting relapse months in advance. Economic analyses suggest that integrating ctDNA testing into clinical workflows may reduce overall treatment costs by minimizing overtreatment. The results of several major ongoing trials are awaited and are expected to further inform the role of ctDNA in routine CRC care. ctDNA offers a minimally invasive, real-time approach to personalize CRC management across all disease stages. Although challenges remain, particularly in standardization, early-stage detection, and optimal timing of testing, ongoing research continues to support its expanding role in precision oncology.

Keywords: Circulating tumor DNA, Colorectal cancer, Liquid biopsy, Minimal residual disease, Precision medicine

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths worldwide.[1] In 2025, the American Cancer Society estimates 107,320 new colon cancer cases, 46,950 new rectal cancer cases, and 52,900 deaths, highlighting that CRC continues to jeopardize public health. Most CRCs originate from a premalignant lesion, such as adenomatous and serrated polyps, that typically progress to invasive cancer over a period of less than 20 years, highlighting the critical importance of early detection and removal of precursor lesions. According to the Colon Cancer Coalition, the five-year survival rate for CRC patients diagnosed at stage I or II is about 91%, but for CRC patients diagnosed at stage IV, it declines substantially to 13%.[1] Although CRC is largely preventable through screening and is highly treatable when detected early, the alarming rise of CRC in young adults remains poorly understood. The rising incidence of early-onset CRC demands for improved prevention strategies and early detection.

Screening colonoscopies remain the gold standard for identification and detection of CRC; however, adherence rates remain significantly below the 80% target established by major health organizations. Nearly one-third of Americans do not adhere to current screening guidelines, often because they find the process costly, time-consuming, unpleasant, and invasive.[2] Stool-based screening, such as fecal immunochemical test (FIT), offers a non-invasive screening and diagnostic approach; however, its sensitivity for detecting CRC remains limited.[3] Additionally, carcinoembryogenic antigen (CEA) is a commonly used blood-based marker in CRC detection. However, it is only 32-45% sensitive and is unable to monitor tumor evolution or treatment efficacy over time, limiting its utility as a reliable screening tool.[4]

Liquid biopsies also offer a minimally invasive and reproducible method for detecting tumor-derived biomarkers in patient fluid samples such as blood, urine, saliva, stool, cerebrospinal fluid, or bile. The repeatability of this method of sample collection enables frequent monitoring over time. A component of cell-free DNA (cfDNA), circulating tumor DNA (ctDNA) is tumor-specific and can be regularly analyzed throughout the course of a patient's disease to characterize disease pathophysiology, monitor response to treatment, and assess drug resistance.[5] CRC releases a significant amount of tumor-related material, including cells, DNA, and methylation markers into circulation, making it well-suited for analysis using liquid biopsy.[6] There is a growing interest in leveraging ctDNA for CRC screening, diagnosis, prognosis, therapeutic decision-making, and surveillance. This review aims to summarize recent advancements in ctDNA research, highlighting its potential as a tool to guide the diagnosis, treatment, and monitoring of patients with CRC.

METHODS

We conducted a literature search in PubMed using the following search strategy: ['Colorectal Neoplasms'(MeSH terms) or 'colorectal cancer' or 'colorectal carcinoma' or 'colon cancer' or 'rectal cancer' or 'CRC'] and ['Circulating tumor DNA'(MeSH terms) or 'circulating tumor DNA' or 'ctDNA' or 'cell-free tumor DNA' or 'cfDNA' or 'liquid biopsy') and ('Detection' or 'diagnosis' or 'prognosis' or 'monitoring' or 'recurrence' or 'minimal residual disease' or 'MRD'). The search aimed to address the overarching question: Is ctDNA useful in CRC and what are recent updates that can support this?

The search initially yielded 1,630 publications. We then applied filters to include only studies in humans, published in English, from 2019 onward, and classified as Books and Documents, Clinical Trial, Controlled Clinical Trial, Meta-Analysis, Observational Study, Randomized Controlled Trial, Review, Scoping Review, or Systematic Review. Abstracts were screened independently by two reviewers to assess relevance to this review's objective. Additionally, we searched ClinicalTrials.gov using the terms 'CRC or colorectal cancer' (condition) and 'ctDNA - circulating tumor DNA' (intervention) to identify ongoing or recently completed clinical trials relevant to our research question. While the focus of this review was on recent advances or updates, we incorporated earlier studies and trials to provide a historical and conceptual context for the clinical utility of ctDNA in CRC.

BIOLOGY AND METHOD OF DETECTING CTDNA

The presence of cfDNA in the blood was first detected in 1948 by Mandel and Metais. By 1977, there were reports of increased serum concentrations of cfDNA in patients with cancer. A portion of the cfDNA in such patients originated from tumor cells and was referred to as ctDNA. Both genomic sequences in tumors and the quantification of tumor burden can be extrapolated through ctDNA analysis. The biologic processes underlying the ways in which ctDNA is shed into circulation provide critical insight into its diagnostic and prognostic utility in CRC. Apoptosis is one of the primary methods ctDNA enters the bloodstream. When cells die, they release short DNA fragments (<200 base pairs) that are taken up by macrophages and then released into the bloodstream or lymphatic system. Fragments that are less than 100 base pairs may be enriched in ctDNA and are more likely to carry mutations. In a study by El Messaoudi et al., a higher ctDNA fragmentation pattern was observed in metastatic CRC patients.[7] Larger fragments (>200 base pairs) are released when cells undergo necrosis. While the exact mechanism is not fully understood, cfDNA from necrosis is believed to be associated more closely with aggressive cancers. Living tumor cells from both primary and metastatic sites can also release ctDNA into the bloodstream via extracellular vesicles (EVs). These EVs include exosomes and apoptotic bodies. In comparison to smaller exosomes, larger EVs, such as microvesicles, tend to carry greater quantities of ctDNA. Notably, ctDNA enclosed in these vesicles may offer enhanced mutation detection, especially in early-stage cancers. In addition to the shedding mechanism, structural features, such as fragment length, nucleosome positioning, and DNA methylation patterns, may help identify the tissue of origin. This can be used to deduce the nature of the ctDNA and distinguish it from normal cfDNA.[8]

As previously mentioned, smaller DNA fragments are often associated with advanced CRC. In a study by Gai et al., the analysis of differentially methylated regions enabled the distinction between patients with liver and colon cancer, as well as the identification of colon cancer patients with and without liver metastases.[9] Currently, there are several approved ctDNA detection technologies. Among those with higher detection limits are digital PCR (dPCR) and next-generation sequencing (NGS). Two of the most used types of dPCR are digital droplet PCR (ddPCR) and BEAMing (beads, emulsion, amplification, and magnetics). A clinical trial conducted by O'Leary et al. suggested adequate reproducibility for clinical use between the two assay types, postulating that

inconsistencies in the currently available ctDNA literature may be due to sampling effects.[10] dPCR, while extremely sensitive for ctDNA analysis, can only test a few known mutations at a time. Alternatively, NGS is capable of simultaneously screening for multiple mutations, both known and unknown, and can combine epigenomic signatures and genomic data to improve sensitivity. The Epi proColon®, approved in 2016, is the first screening modality utilizing a cfDNA methylation marker for CRC patients.[8] While ctDNA holds great promise for CRC diagnosis, prognosis, and monitoring, several challenges related to pre-assay variables and standardization continue to limit its widespread adoption across clinical settings. A review by Dasari et al. found that multiple challenges existed at the pre-analytical level, including the typically low amount of ctDNA compared to overall cfDNA, the risk of sample contamination from lysed immune cells, and the fragile nature of DNA, which informs how it must be transported and stored.[11] To optimize ctDNA collection, blood should be drawn using at least a 21-gauge needle into K2EDTA or cell-stabilizing tubes, and the ctDNA should be sampled from plasma rather than serum to minimize contamination from DNA released from immune cells. Plasma isolation should be completed within 4-6 hours from K2EDTA tubes and within 2-7 days from cell-stabilizing tubes. Additionally, larger quantities of blood may be needed to detect minimal residual disease (MRD) than the volume typically used to evaluate treatment efficacy in metastatic settings.[11] Another limitation of ctDNA analysis is the potential for false-positive results due to clonal hematopoiesis, which was reported in 10% of tumor-free patients aged 70 and above.[12] As research continues to uncover the nuances of ctDNA methodology and improve assay technologies, these insights will be critical for translating ctDNA from a hypothetically promising biomarker into a standardized and reliable tool for CRC management.

THE USE OF CTDNA IN THE DIAGNOSIS OF COLORECTAL CANCER

ctDNA has emerged as a compelling biomarker for CRC detection due to its minimally invasive collection method and potential to capture tumor-specific genetic and epigenetic alterations. Among these, aberrant DNA methylation contributes to the pathogenesis and progression of CRC, making it an ideal biomarker for CRC detection.[13] In a study with 294 participants, Xu et al. found that ctDNA methylation levels were significantly higher in the CRC group than in the polyp or healthy control groups (p <0.001).[14] To date, ctDNA methylation-based biomarkers, such as SEPT9, BCAT1, IKZF1, have been extensively studied for clinical application.[14,15] In 2016, the U.S. Food and Drug Administration approved the SEPT9 methylation assay for primary CRC screening. However, its clinical uptake remains limited due to its substantially lower sensitivity (61.2%) for detecting precancerous polyps, especially when compared to colonoscopy.[16] Recent efforts to identify more sensitive and specific biomarkers have demonstrated promising results. In a multicenter clinical trial, plasma methylation levels of NTMT1 and MAP3K14-AS1 were significantly elevated in participants with CRC or advanced adenoma (AA) compared to those with non-AA, interfering disease, or no evidence of disease.[2] Using the MethyDT test for detecting CRC, which targets NTMT1 and MAP3K14-AS1, an overall sensitivity and specificity of 91.2% and 92.4% respectively were achieved.[2] Additionally, a cohort study found that the combined detection of SEPTIN9, SDC2, and BCAT1 methylation demonstrated 86.1% sensitivity and 97.6% specificity.[17] Compared to a single gene, the diagnostic capability had a higher sensitivity and area under the curve.[17] Several individual studies have also demonstrated strong diagnostic performance of other methylation markers. Of note, Lin et al. reported that cg10673833 achieved a sensitivity of 84.3% and a specificity of 94.5% in a retrospective validation study of 1075 participants.[18]. In a study on the performance of the MethyLight assay for methylated SFRP2 DNA detection in CRC, Li et al. found the SFRP2 marker to have a sensitivity of 69.4% and a specificity of 87.3% in a population of 117 participants.[19] A multicenter prospective study that included over 2000 participants found that a two-marker blood test selecting for IKZF1 and BCAT1 had the potential to serve as an adequate CRC screening method with a sensitivity of 66% and specificity of 94-95%.[15] Recently, Potievskaya et al. reaffirmed a two-marker blood test using BCAT1 and Septin9 to be very selective for CRC, with a sensitivity of 95.5% and a specificity of 90%.[20] However, these findings have yet to be validated in larger, more diverse populations. Table 1 summarizes recent studies that have identified gene markers associated with CRC that reported sensitivities greater than 80% and specificities above 90%.

Table 1: Recent updates in ctDNA detectable genetic markers.

Gene	Sample type	Sensitivity (%)	Specificity (%)
cg10673833[18]	Plasma	84.3	94.5
BCAT1 + Septin9*[20]	Plasma	95.5	90.0
BCAT1 + Septin9 + SDC2*[17]	Plasma	86.1	97.6
SDC2*[17]	Plasma	85.2	93.0
NTMT1 + MAP3K14-AS1	Plasma	91.2	92.4
SEPTIN9*[17]	Plasma	84.2	98.4
BCAT1*[17]	Plasma	84.2	98.4

Note: *-data published within the last two years

While ctDNA assays have demonstrated high sensitivity for advanced neoplasias, several limitations and challenges remain. Sensitivity for advanced precancerous lesions remains at only 13-15%, limiting the utility of ctDNA in detecting lesions that are responsive to curative treatment.[21,22] Additionally, false positives can arise from clonal hematopoiesis of indeterminate potential (CHIP) and age-related methylation changes.[21,23] Further, pre-analytical variables, difficulties with sample handling, and the lack of assay standardization may contribute to poor reproducibility and implementation across institutions.[24] While ctDNA has emerged as a promising noninvasive biomarker, its current limitations prevent it from replacing established CRC screening methods.

CTDNA AS A THERAPEUTIC AND PROGNOSTIC MARKER IN COLORECTAL CANCER

ctDNA has emerged as a strong prognostic biomarker in CRC patients, offering a minimally invasive method to assess tumor burden, inform individualized treatment regimens, and predict recurrence risk.[6] One of the most clinically significant applications of ctDNA in the prognostic setting of CRC is the detection of MRD. MRD refers to the presence or dissemination of cancer cells in the body during or after treatment, even when standard tests cannot detect them. It is most commonly evaluated following surgical resection, where the application of ctDNA is validated. However, MRD can also be assessed after other forms of definitive therapy, such as radiation and immunotherapy, especially in the context of unresectable tumors. Because MRD represents an occult phase of disease progression, liquid biopsies are valuable tools for the detection of early spread following curative-intent therapy. Additionally, these biopsies enable tracking of molecular changes in MRD as the tumor evolves, which helps identify potential treatment targets and informs potential resistance mechanisms.[25] The DYNAMIC II trial was a landmark study that directly evaluated the prognostic utility of ctDNA in detecting MRD.[26] It sought to determine if a ctDNA-guided approach, when compared to a standard approach, could reduce the use of adjuvant treatment in stage II colon cancer without compromising the risk of recurrence. 455 participants were enrolled and randomly assigned into two groups: one group received adjuvant chemotherapy based on conventional clinical and pathological factors, while the other group's treatment decisions were dependent on their ctDNA results, a marker of MRD, after surgical resection. In the ctDNA-guided group, those who were ctDNA-negative were spared chemotherapy, while those who were ctDNA-positive underwent treatment. Tie et al. found that using ctDNA to guide treatment reduced chemotherapy administration from 28% to 15% (relative risk: 1.82; CI: 1.25-2.65).[26] Additionally, the two-year recurrence-free survival percentages were 93.5% in the ctDNA-guided group and 92.4% in the standard group. And the rates of three-year recurrence-free survival were 86.4% and 92.5% in the ctDNA-guided and standard groups, respectively. With a median follow-up of nearly five years, updated data from the DYNAMIC II trial confirmed that using a ctDNA-guided approach did not compromise overall survival (OS), which reached 93.6% across both groups.[26] These findings demonstrated that treatment decisions guided by ctDNA analyses can safely reduce the use of chemotherapy without increasing the risk of cancer recurrence, highlighting the clinical utility of ctDNA-detected MRD. Notably, favorable outcomes were consistent across subgroups, including patients with traditionally high-risk features such as T4 tumors or dMMR status, suggesting that ctDNA use can offer more precise risk stratification than the standard guidelines. Patients with persistently detectable ctDNA following treatment were found to be at an especially high risk for recurrence, indicating that these patients may benefit from additional therapies.[27] These long-term results suggest that ctDNA is a promising tool for guiding adjuvant therapy decisions, reducing overtreatment, and identifying patients who may benefit from more aggressive forms of treatment. The currently ongoing BESPOKE CRC study has already produced findings that demonstrated the prognostic and predictive value of ctDNA detection.[28] Among 350 patients with stage II and III CRC, the presence of ctDNA at the MRD time point was strongly associated with significantly poorer disease-free survival (DFS) ($p<0.0001$). In the MRD-positive group, those receiving adjuvant chemotherapy experienced a significantly longer median DFS of 18.7 months compared to the observation group, which had a median DFS time of only 6.7 months ($p<0.05$). MRD-negative patients showed no significant benefit from adjuvant chemotherapy. Furthermore, 39.1% of MRD-positive patients achieved ctDNA clearance at 12 weeks post-surgical resection, compared to patients with persistent ctDNA positivity, which was associated with improved DFS at 24.2 and 13.8 months, respectively. Thus, Kasi et al. have highlighted the utility of ctDNA to implement more personalized and effective treatment strategies for CRC patients.[28] In 2024, Nakamura et al. conducted an updated analysis of the CIRCULATE-Japan GALAXY (GALAXY) observational study that began in 2020.[29] They aimed to evaluate the prognostic and predictive value of ctDNA detection in patients following CRC surgical resection. This was done by assessing the association between ctDNA-informed MRD detection and survival outcomes in 2,240 patients with stage II-III colon cancer or stage IV CRC. Using a 23-month median follow-up, the detection of ctDNA during the MRD window was associated with significantly poorer DFS (HR: 11.99; $p<0.0001$) and shorter OS (HR: 9.68; $p<0.0001$). Additionally, sustained clearance of ctDNA after adjuvant chemotherapy treatment was associated with a higher 24-month DFS and OS compared to transient clearance at 89% and 100% versus 3.3% and 82.3% respectively. These findings lay the groundwork for ctDNA-informed MRD-guided treatment decisions. The VEGA trial, an arm of the CIRCULATE-Japan study, began in 2020 and sought to investigate whether stage II-III CRC patients with postoperative ctDNA-negative statuses could safely avoid adjuvant chemotherapy and be managed with surveillance alone.[30] In this randomized phase III study, postoperative surveillance in the observation group was compared to the standard CAPOX therapy, which is a

combination of capecitabine and oxaliplatin, in the treatment group. In this study, patients who were ctDNA-negative 4 weeks post-operation were assigned to either the observation group or the adjuvant chemotherapy group in a 1:1 ratio. Although results are not yet available, the estimated 3-year DFS is 91% in the chemotherapy group and 88% in the observation group. This 3% difference is within the accepted noninferiority margin using an HR of 1.3; however, this will be tested by enrolling an additional 1,240 patients and repeating the treatment groups. In ctDNA-negative CRC patients, chemotherapy did not significantly improve DFS (HR: 1.3; CI: 0.5-3.6), suggesting no clear benefit from adjuvant treatment.[30] Altogether, the findings from the aforementioned clinical trials support the notion that ctDNA-negative patients may be spared chemotherapy without compromising survival, thus successfully minimizing toxicity and overtreatment. ALTAIR is another clinical trial within the CIRCULATE-Japan platform that sought to explore the value of ctDNA-guided treatment strategies.[31]

Specifically, Bando et al. aimed to demonstrate the superiority of trifluridine/tipiracil (FTD/TPI) treatment when compared to placebo in patients who were ctDNA-positive, but radiologically-negative after undergoing curative surgical resection.[31] 243 stage II-IV patients were enrolled and randomly assigned to the treatment or placebo group. The median DFS was 9.3 months for the treatment group and 5.5 months for the placebo group; however, this difference was not statistically significant in the overall study population ($p = 0.107$). Baseline molecular tumor marker (MTM/mL) levels, which are used to quantify ctDNA levels, were significantly higher in oligometastatic stage IV patients than in non-stage IV patients (0.68 versus 0.32; $p<0.05$). The benefit of FTD/TPI treatment was more pronounced with increasing MTM/mL values, demonstrating a linear trend. OS data is not yet available, but the present data shows that ctDNA levels, measured in MTM/mL, can help identify patients who are more likely to benefit from treatment with FTD/TPI.

Although the overall population did not demonstrate a statistically significant improvement in DFS, patients with higher ctDNA levels experienced clinically significant benefit. This suggests that ctDNA can be a useful biomarker to guide more personalized treatment decisions by identifying patients who may respond more favorably to specific therapeutic approaches. Conversely, the COBRA (NRG-GI005) trial was a phase II/III trial that explored ctDNA-guided adjuvant chemotherapy decisions in 635 stage II CRC patients post-surgical resection.[32] ctDNA-positive patients received chemotherapy, while those with undetectable ctDNA levels were managed with observation only. At the six-month time point, ctDNA clearance was 11% in the treatment group and 43% in the surveillance group, which led to early termination of enrollment due to failure to meet the predetermined end point of ctDNA clearance in low-risk stage II CRC patients at six months of time. These results suggest that, in this lower-risk population, ctDNA-guided adjuvant chemotherapy did not result in significantly improved ctDNA clearance or clinical outcomes compared to surveillance. This trial was useful in highlighting the complexities and challenges of using ctDNA to tailor treatment in early-stage CRC.

The BEACON CRC trial studied treatments for metastatic CRC patients with BRAF-V600 mutations.[33] Researchers combined ctDNA profiling with tumor tissue sequencing to investigate mechanisms of resistance to BRAF and EGFR-targeted therapy. ctDNA analysis enabled the detection of acquired resistance alterations, such as KRAS, NRAS, MAP2K1 mutations, and MET amplifications, that emerged during treatment with Encorafenib and Cetuximab. Importantly, ctDNA analysis revealed a high burden of newly acquired mutations in these treatment arms, supporting the concept of adaptive mutability under therapeutic pressure.

Additionally, it identified SDS17a/b mutational signatures that were not detected in baseline tumor samples. This large-scale trial, with 665 participants, illustrated the value of ctDNA in capturing tumor evolution and resistance dynamics in real-time.[33,34] Table 2 summarizes key findings from landmark clinical trials in the prognostic and treatment decisions in CRC management.

Table 2: Recent trial updates on ctDNA in prognosis and treatment of colorectal cancer.

Trial name	Stage	Sample size	Key findings
DYNAMIC-II[46]	II	455	ctDNA-guided approach reduced chemotherapy use without compromising recurrence outcomes or OS
BESPOKE[48]	II-III	350	ctDNA predicts recurrence risk; chemo benefits MRD+ patients; ctDNA clearance associated with survival
GALAXY[49]	II-IV	2,240	Sustained ctDNA clearance was associated with better DFS survival vs. transient clearance
VEGA[50]	II-III	>1,200	Chemo may be safely omitted in ctDNA- patients
ALTAIR[52]	II-IV	243	ctDNA burden may predict benefit from systemic therapy
COBRA[53]	II	635	Trial stopped early due to futility; ctDNA may not guide adjuvant treatment decisions well in low-risk patients
BEACON CRC[54]	IV	665	The ability of ctDNA to inform tumor evolution and resistance development in real-time.

Post-operative ctDNA positivity is associated with a significantly increased risk of disease recurrence, worse DFS, and poorer overall survival (OS) in patients with resected CRC, including oligometastatic disease.[35] Multiple recent meta-analyses and large prospective cohort studies consistently demonstrate that detection of ctDNA after curative resection is a strong and independent predictor of recurrence across all stages of colorectal cancer, including stages II and III and resected oligometastatic disease.[36-38] The pooled hazard ratio (HR) for recurrence-free or disease-free survival in postoperative ctDNA-positive versus ctDNA-negative patients is approximately 7.3 across all stages of CRC.[36] In resected oligometastatic disease (stage IV), the HR for recurrence is about 4.8.[36] In nonmetastatic CRC, ctDNA positivity after surgery was associated with an HR for recurrence of 6.92 and an HR for overall survival of 4.2.[39,40] Additionally, ctDNA status is a stronger predictor of early detection of recurrence compared to conventional markers, such as CEA and imaging, which have median lead times of upto 9.8 months.[41] These findings support the clinical utility of longitudinal ctDNA monitoring as a real-time, independent prognostic biomarker for recurrence risk stratification in CRC following surgery or adjuvant therapy.[36]

A study performing genome-wide DNA methylation analysis indicated that high methylation was closely related to recurrence status; however, specific methylation biomarkers for predicting recurrence have not been thoroughly investigated from a genome-wide perspective in CRC.[42] Various studies have identified specific biomarkers closely related to recurrence, including EGFR, EFNB2, GNAL, PPAPDC1A, RGS12, and BCAT1/IKZF1.[43] The detection and clearance of tumor-specific somatic mutations through serial measurement of ctDNA may be used as a predictive biomarker for treatment response in CRC. ctDNA clearance during adjuvant or first-line chemotherapy was associated with improved progression-free and overall survival, while persistent or increasing levels of ctDNA indicated poorer treatment response and higher risk of recurrence, independent of radiologic findings.[40,41]

CTDNA AS A MONITORING MARKER FOR COLORECTAL CANCER RECURRENCE

The goal of monitoring CRC patients who have achieved a 'disease-free' status is to detect recurrence early enough to enable intervention and improve their outcomes. Standard methods for detecting CRC recurrence, including CT scans, endoscopy, and CEA testing, have not been shown to improve survival outcomes.[44] Compared to many other cancer biomarkers, ctDNA has a short half-life of only two hours, making it an excellent marker of current tumor activity and disease state.[45] In contrast to CEA, a longstanding biomarker used in longitudinal surveillance of CRC following curative resection, ctDNA demonstrates higher sensitivity and specificity for early relapse detection and longitudinal monitoring.[6,46,47] ctDNA also outperformed CEA in lead times for recurrence detection and was less affected by confounding factors, such as smoking or benign disease.[48] While ctDNA alone is a more accurate and earlier marker of relapse than CEA, combining CEA with ctDNA or imaging can improve overall sensitivity for recurrence detection.[47]

In the previously mentioned analysis of the GALAXY study, ctDNA positivity in recurrent CRC was positively correlated with a shorter OS (HR: 2.71; $p<0.0001$).[29] Similarly, in the BESPOKE CRC study, 44.4% of patients who had initially cleared ctDNA later experienced recurrence, with ctDNA reappearing before any radiological evidence of relapse.[28] Moreover, 8.3% of patients had detectable ctDNA during follow-up, a finding strongly associated with significantly worse DFS (HR: 124.3; $p<0.0001$).

In a large study of 240 stage II/III CRC patients, Chen et al. found that ctDNA predicted recurrence an average of 5.01 months ahead of CT scans, with a 92% overall accuracy.[49] At the 2025 AACR Annual Meeting in Chicago, early findings from the ongoing VICTORI trial demonstrated that ctDNA was capable of detecting CRC recurrence much earlier than traditional imaging, even as much as 416 days sooner.[50] Because ctDNA can be present at extremely low levels in the blood, recurrence is often difficult to observe early. However, researchers used a highly sensitive test customized to each patient's unique tumor mutations that could detect ctDNA levels as low as 2 parts per million. 71 patients with stage I-IV resectable CRC were followed and monitored using blood samples. Of the 65 patients with available clinical data, 23 experienced recurrences. Impressively, 87% of those cases had detectable ctDNA, and in every case, ctDNA appeared before imaging could detect a relapse. ctDNA analysis was able to detect metastases in challenging sites, such as the lungs. One of the investigators noted that ctDNA testing around four weeks post-surgery may be the most informative time point. In the 2024 update of the TRACC Part B study, ctDNA monitoring using Guardant Reveal®, a tumor-naive, plasma-only assay, detected recurrence a median of 7.3 months before radiologic imaging did, with a 2-year relapse-free survival of 91.1% in ctDNA-negative patients and 50.4% in ctDNA-positive patients.[51] These findings underscore the value of ctDNA for longitudinal surveillance and timely detection of relapse. While ctDNA shows great promise for early detection of recurrence, more research is needed to standardize the timing of surveillance sampling to maximize sensitivity and clinical utility. Despite encouraging data from the aforementioned clinical trials, the clinical management of patients with detectable ctDNA remains an area of investigation. Confounding factors include biological variability, potential false positives or negatives, and variable ctDNA shedding, thus revealing the need for multimodal surveillance strategies. Future research should focus on refining the actionable thresholds and integrating ctDNA with other liquid biopsy assays to optimize personalized CRC monitoring and improve clinical outcomes.

ONGOING CLINICAL TRIALS

Several large, ongoing clinical trials are actively evaluating the clinical utility of ctDNA in the management of CRC, with finalized results expected over the next several years. The CAREME trial, a phase III study expected to conclude in December 2026, is investigating whether adjuvant chemotherapy improves outcomes in early-stage CRC patients who are ctDNA-positive after surgery.[52] Similarly, CORRECT-MRD II, a phase II study with an estimated completion date of February 2028, is prospectively validating the use of ctDNA to predict recurrence in stage II-III resected CRC.[53] The VICTORI study is an ongoing observational trial focused on defining the optimal postoperative timing for ultra-sensitive ctDNA detection and its prognostic significance.[54] BESPOKE CRC, expected to conclude in September 2025, is a phase II study evaluating the impact of Signatera, a form of tumor-informed ctDNA testing, on adjuvant treatment decisions and patient outcomes in resected stage I-IV CRC.[55] Similarly, DYNAMIC-III, anticipated to be completed in 2028, is an ongoing phase II/III evaluating the efficacy of ctDNA-guided decisions to reduce the use of chemotherapy without compromising recurrence-free survival.[56] Finally, the large CIRCULATE-North America trial, set to conclude in March 2030, is using ctDNA status to assess different adjuvant treatment strategies, such as de-escalation or intensification.[57] Table 3 summarizes key ongoing clinical trials exploring the utility of ctDNA in CRC. While several of these trials have released interim findings as discussed in previous sections, the finalized results will be essential to establishing ctDNA's definitive role in routine clinical practice.

Table 3: Ongoing trials and their foci.

Trial name	Focus	Expected completion
CAREME[52]	Evaluating adjuvant chemotherapy benefits in ctDNA+ early-stage CRC patients following surgery	December 2026
CORRECT-MRD II[53]	Validating ctDNA as a biomarker to predict recurrence in stage II/III CRC	February 2028
VICTORI[54]	Observational study to define optimal post-operative timing of ctDNA analysis	Ongoing
BESPOKE CRC[55]	Evaluating tumor-informed ctDNA testing for guiding adjuvant treatment decisions in stage I-IV CRC	September 2025
DYNAMIC-III[56]	Evaluating ctDNA-guided de-escalation of chemotherapy	2028
CIRCULATE-North America[57]	Assessing ctDNA-guided escalation or de-escalation of treatment in CRC	March 2030

FUTURE APPLICATIONS

While most ctDNA research in CRC has focused on blood-based assays, future studies should explore alternative biofluids such as urine, which may offer a more accessible and non-invasive platform for ctDNA analysis.[8] Although early exploratory work has suggested that methylated ctDNA markers can be detected in urine, further investigation using modern high-sensitivity assays and larger, prospective cohorts is needed. Advancing this area could expand the utility of ctDNA-based screening and surveillance of CRC. Another emerging area of interest is the combined use of circulating tumor cells (CTCs) alongside ctDNA in liquid biopsies. Early studies indicated that dual tracking of CTCs and ctDNA may predict radiographic progression, drug-resistance mechanisms, and enhance risk stratification in CRC patients. Future prospective studies are needed to investigate whether integrating ctDNA and CTC, potentially with other biomarkers, such as extracellular vesicles or miRNA, can improve early detection, treatment response prediction, and surveillance in CRC.

As previously mentioned in this review, several studies have demonstrated that ctDNA-guided management in CRC may reduce unnecessary adjuvant chemotherapy without compromising outcomes. Subsequent economic analyses found that this approach could significantly lower costs for both commercial insurance and Medicare Advantage payers.[58] These findings support the cost-effectiveness and clinical value of integrating ctDNA testing into standard CRC management; however, more rigorous economic evaluations are necessary to determine whether ctDNA-based screening can financially outperform existing modalities such as colonoscopy and stool-based tests.

Despite the rapid evolution of ctDNA technology and its potential to transform CRC management, several key challenges and areas requiring further research remain. It is essential to recognize that the reliability of ctDNA results is dependent on both the quality of the assay and its use in the appropriate clinical context. A key limitation is the potential for false-negative results, especially if testing is performed immediately after surgery or before the four-week postoperative period. In these cases, undetectable ctDNA may not necessarily indicate true absence of MRD; rather, ctDNA levels may simply be below the threshold of detection, or the tumor may exhibit low degrees of shedding. Additionally, the implementation of ctDNA testing is hindered by the lack of standardized protocols for sample collection, processing, and analysis. Variability

across platforms can complicate and obscure comparison between large cohort studies and is a barrier to clinical integration.[59] Further standardization and validation studies are necessary to establish optimal integration into routine CRC management.[60]

CONCLUSION

The rise of precision medicine has transformed cancer management by enabling treatment decisions tailored to the unique molecular characteristics of each patient's tumor. In CRC, ctDNA has emerged as a cornerstone of this approach, offering a dynamic and minimally invasive means to monitor disease trends in real-time. The present review aimed to summarize recent advancements in ctDNA research, illustrating its potential as a minimally invasive tool to guide diagnosis, treatment, and monitoring of patients with CRC. Recent advances in ctDNA methylation biomarkers have shown encouraging diagnostic potential, with multi-gene panels demonstrating high sensitivity and specificity. However, the lack of broader validation, failure to detect early-stage disease and advanced precancerous lesions, and challenges in assay standardization limit the clinical adoption of ctDNA analysis. Multiple large trials demonstrated ctDNA's role in predicting recurrence, treatment response, and guiding therapy selection. ctDNA has enabled the detection of resistance mutations, offering a real-time approach to track treatment efficacy and tumor evolution. Additionally, multiple studies have found that ctDNA-guided treatment strategies reduced unnecessary chemotherapy in ctDNA-negative patients without compromising survival outcomes. In monitoring, ctDNA outperformed traditional tools, including CEA and imaging, by detecting recurrence months before radiologic evidence, with lead times of upto 416 days. Its short half-life and high specificity make it an ideal tool for longitudinal surveillance in disease-free patients. While ctDNA is superior to CEA alone, combining ctDNA with imaging or CEA may enhance overall detection sensitivity. Despite ctDNA's promise, challenges remain, prompting future exploration to define optimal thresholds and integrate it into personalized surveillance protocols to maximize patient outcomes and clinical utility. As previously established, CRC remains markedly under-screened, with nearly one-third of eligible individuals not engaging in recommended screening. While ctDNA offers a less invasive and potentially more time-sensitive alternative, its impact will depend on how challenges related to accessibility, testing availability, and standardized costs are addressed. As research continues to refine its accuracy, expand its clinical applications, and bridge these practical barriers, ctDNA holds great promise to become an integral component of personalized, evidence-based CRC management.

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