Received: 30 September 2025 | Revised: 23 December 2025 | Accepted: 7 January 2026

DOI: 10.1002/cncr.70286

REVIEW ARTICLE

Minimal residual disease in solid tumors: Clinical applications and future directions

Theresa Abdo MD[1] | **Ahmad Alhalabi MD**[1] | **Sacha Yaghi BS**[2] | **Mohammad Aloran MD**[3] | **You Li MD**[1] | **María Herrán MD**[1] | **Rami Tfayli MD**[1] | **Thomas A. Samuel MD**[1] | **Zeina Nahleh MD, FACP**[1]

[1]Department of Hematology and Oncology Cleveland Clinic Florida, Maroone Cancer Center, Weston, Florida, USA

[2]Faculty of Medicine American University of Beirut, Beirut, Lebanon

[3]Faculty of Medicine, Yarmouk University, Irbid, Jordan

Correspondence
Theresa Abdo, Department of Hematology and Oncology Cleveland Clinic Florida, Maroone Cancer Center, 2950 Cleveland Clinic Blvd, Weston, FL 33331, USA.
Email: Theresa7abdo@gmail.com

Abstract

Minimal residual disease (MRD) refers to the presence of residual cancer cells or tumor-derived fragments that persist after treatment and remain undetectable by conventional imaging or protein-based assays. Circulating tumor DNA (ctDNA) has emerged as a dynamic biomarker for MRD detection. It enables real-time disease monitoring, prognostication, and often therapeutic decision-making. Two major ctDNA approaches exist, tumor-informed and tumor-agnostic, and they differ in sensitivity, specificity, and clinical feasibility. Recent clinical trials have supported a prognostic and predictive utility of ctDNA MRD in gastrointestinal, lung, breast, and other malignancies, with positive postoperative or post-treatment MRD status correlating with higher recurrence risk and inferior survival outcomes. However, integration into clinical practice remains limited by challenges, including tumor heterogeneity, variable ctDNA shedding across tumor stage, location and timing, lack of standardized assay interpretation, and cost-effectiveness concerns. Emerging technologies such as methylation-based sequencing, ultra-deep next-generation sequencing, and machine learning–driven risk models hold promise for improving detection accuracy and clinical applicability. Ongoing clinical trials are expected to determine the impact of earlier MRD detection and intervention on patient outcomes, potentially supporting the broader adoption of ctDNA MRD. In this article, the authors reviewed the recent clinical applications, limitations and future directions of MRD in solid tumors.

KEYWORDS
cancer monitoring, circulating tumor DNA, clinical applications, minimal residual disease, prognostic and predictive biomarker, solid tumors

INTRODUCTION

Minimal residual disease or molecular residual disease (MRD) refers to the cancer cells or their fragments that remain in the body after treatment completion. These cells or fragments are not detectable by the traditional imaging or protein methods but can be indicators of persistence, recurrence or metastasis of the cancer.[1] Unlike histology and stage that predict the risk of recurrence, MRD could directly identify the presence of residual cancer.[2]

Circulating tumor DNA (ctDNA) has emerged as a dynamic biomarker of MRD that enables real-time tracking of the cancer as opposed to a static biopsy, and monitoring treatment response as well as potentially identifying drug resistance.[3] CtDNA is a component of cell-free DNA that originates from tumor tissue in the patient's plasma.[4] It can be detected by methods such as polymerase chain reaction (PCR), and next-generation sequencing.[5] Current ctDNA genotype assays have not reached optimal clinical sensitivity, especially in patients with early-stage disease or in immediate post-treatment settings, due to lower tumor shedding compared to patients with advanced-stage disease.[4] Thus, there is a need for more sensitive assays for detecting tumor ctDNA.

There are currently two main types of ctDNA testing: tumor-informed and tumor-agnostic. Tumor-informed testing (e.g., Signatera assay[6]) employs a personalized approach that uses the patient's cancer tissue (following biopsy or surgery) to create a panel of mutations specific to the individual tumor.[6] It is reported to be highly sensitive and specific,[6] but it can be costly, time-consuming and requires a prior invasive procedure to obtain the tissue sample. In contrast, tumor-agnostic testing (like Guardant360 assay) is done via pre-made panels, which do not require tissue sampling, have lower sensitivity and specificity, but are more likely to be cost-effective with a rapid tunnaround.[7] Additionally, they have demonstrated utility for MRD detection in multiple cancers, such as NSCLC and colorectal cancer, supporting broader pan-tumor application.[7] Test selection should be based on the clinical context.[8] Table 1 presents a list of some of the ctDNA assays used in the adjuvant setting.

One of the main clinical applications of ctDNA MRD is its potential use as a prognostic and predictive marker for patients with cancer to further estimate a patient's outcome and help assess the patient's likeliness to benefit from treatment, respectively.[9] Although MRD is currently used as a prognostic and predictive marker to guide treatment decisions, and as a surrogate end point for clinical trials in hematologic malignancies (acute lymphoblastic leukemia, acute myeloid leukemia, multiple myeloma, etc.),[10,11] it is not widely integrated into standard-of-care clinical practices in solid tumors. One of the major controversies surrounding MRDs use is that it could allow the detection of tumors in advance of clinical symptoms (longer lead time), without evidence showing this can lead to better outcomes for the patients.[12] Furthermore, it can lead to potential harm including added costs, increased diagnostic procedures, patient anxiety and although rare, potential exposure to toxic unnecessary therapies in case of false-positive findings.[12] Several trials are currently examining the clinical utility of MRD testing including ASPIRA[13] and ALTAIR[14] that are included in Tables 2, 3, and 4. Hence, the main benefits of MRDs thus far have been in approximating recurrence rate and likelihood of cure that can be communicated to the patients.[15]

In this comprehensive review article, we explore the recent literature on the topic and provide practical updates on the clinical applications, limitations and future directions of MRD in solid tumors.

ctDNA and MRD in gastrointestinal cancers

One of the largest studies exploring the clinical utility of ctDNA MRD in gastrointestinal (GI) tumors, particularly in colorectal cancer (CRC) is the CIRCULATE-JAPAN multinational initiative, which includes three trials: the GALAXY, VEGA, and the ALTAIR trials.[16] The GALAXY trial consisted of monitoring MRD status in patients with stage II–IV CRC after surgery with ctDNA. An interim analysis of this arm showed that ctDNA positivity during a 60-day postoperative window was associated with inferior disease-free survival (DFS; Hazard Ratio (HR), 11.99; $p < .0001$) and overall survival (OS; HR, 9.68; $p < .0001$)

TABLE 1 MRD assays: regulatory status and cancer coverage.

Assay name	Cancer types	Regulatory/FDA status
clonoSEQ (Adaptive Biotechnologies)	Hematologic malignancies (multiple myeloma, B-cell ALL, CLL)	FDA approved
Signatera (Natera)	Solid tumors (e.g., colorectal, breast, bladder, lung, other)	Not FDA approved; BDD granted
Guardant Reveal (Guardant Health)	Solid tumors (colorectal, breast, lung)	Not FDA approved
Haystack MRD (Quest Diagnostics)	Multiple solid tumors including breast and colorectal	Not FDA approved; BDD granted (August 2025)
RaDaR (Inivata/NeoGenomics)	Multiple solid tumors including breast and lung	Not FDA approved
FoundationOne Tracker (Foundation Medicine)	All solid tumors including muscle-invasive bladder cancer	Not FDA approved

Abbreviations: BDD, breakthrough device designations from FDA for certain intended uses, which is a pathway to expedite review; FDA, Food and Drug Administration; MRD, minimal residual disease.

TABLE 2 Ongoing ctDNA trials in gastrointestinal cancers.

Trial name	NCT no.	Cancer type	Phase	Assay	Design	Preliminary results
CIRCULATE-US	NCT05174169	Stage II–III colon cancer (post-resection)	Phase 2/3	Signatera ctDNA	Prospective trial using postoperative ctDNA (via Signatera) to risk-stratify adjuvant therapy	NA
GALAXY	Japan registry (UMIN000039205)	Resectable colorectal cancer (stage II–IV or recurrent)	Observational	Signatera ctDNA	Large-scale prospective registry monitoring ctDNA pre-/post-surgery	Sustained ctDNA clearance associated with better outcomes (24-month DFS 89% vs. 3.3%; 24-month OS 100% vs. 82.3%)
VEGA	Japan registry (jRCT1031200006)	Resectable colorectal cancer (stage II–IV or recurrent)	Phase 3	Signatera ctDNA	ctDNA-negative patients randomized: standard adjuvant CAPOX (capecitabine + oxaliplatin) vs. observation only (de-escalation)	NA
ALTAIR[14]	NCT04457297	Resectable colorectal cancer (stage II–IV or recurrent)	Phase 3	Signatera ctDNA	ctDNA-positive patients randomized to TAS-102 (trifluridine/tipiracil) vs. placebo (escalation)	NA
DYNAMIC-III	ACTRN12617001566325	Stage III colon cancer	Phase 2/3	Tumor-informed ctDNA assay	Randomized trial where postoperative ctDNA guides adjuvant therapy	Noninferiority for 3-year RFS not yet fully met
BESPOKE CRC	NCT04264702	Resected colorectal cancer (stages I–IV)	Observational	Signatera ctDNA	Multicenter, assess how ctDNA influences adjuvant chemotherapy decisions and detect asymptomatic recurrence	ctDNA positivity associated with inferior DFS
COBRA[21]	NCT04068103	Low-risk stage II colon cancer	Phase 2/3	Guardant LUNAR-1	Randomized trial comparing ctDNA-guided chemotherapy vs surveillance	No benefit from ctDNA guided chemotherapy.
ARTEMIS-PC	NCT06043921	Pancreatic cancer (resectable and unresectable)	Observational	Invitae	Multicenter Japanese study using customized ctDNA panels derived from tumor tissue to monitor MRD over time	NA
MRD-GC	NCT06893133	Gastric or gastroesophageal junction adenocarcinoma (stage II–III post-neoadjuvant)	Observational	Combination of personalized and fixed ctDNA-MRD panels	Aims to assess ctDNA-MRD's predictive power and lead-time advantage over imaging in recurrence detection	NA
TRACC Part C	NCT04050345	High-risk stage II and III CRC	Phase 3	Guardant Reveal	Multicenter UK study evaluating whether ctDNA-guided de-escalation of ACT is noninferior to standard ACT	NA

Abbreviations: ACT, adjuvant chemotherapy; CRC, colorectal cancer; ctDNA, circulating tumor DNA; DFS, disease-free survival; MRD, minimal residual disease; NA, not applicable; OS, overall survival; RFS, recurrence-free survival; UK, United Kingdom.

compared to ctDNA-negative patients.[17] Notably, patients with positive ctDNA results who received adjuvant chemotherapy had sustained ctDNA clearance that correlated with statistically significant improvement in DFS and OS compared to patients with positive ctDNA results who did not receive adjuvant chemotherapy, whereas no significant benefit to adjuvant chemotherapy was observed in patients with ctDNA-negative results,[17] supporting the role of ctDNA as a stratification tool for adjuvant treatment. The VEGA arm is

TABLE 3 Ongoing ctDNA trials in lung cancers.

Trial name	NCT no.	Cancer type	Phase	Assay	Design	Preliminary results
MERMAID 1	NCT04385368	NSCLC	Phase 3	NA	Evaluating adjuvant durvalumab plus chemotherapy in MRD-positive patients after complete resection	NA
MERMAID 2	NCT04642469	NSCLC	Phase 3	NA	Assessing durvalumab vs. placebo in MRD-positive patients during surveillance after surgery	NA
ADAPT-E	NCT04585477	Early-stage NSCLC (stages I–III)	Phase 2	NA	Testing adjuvant durvalumab with or without chemotherapy based on ctDNA MRD status	NA

Abbreviations: ctDNA, circulating tumor DNA; MRD, minimal residual disease; NA, not applicable; NSCLC, non–small cell lung cancer.

TABLE 4 Ongoing ctDNA trials in breast cancers.

Trial name	NCT no.	Cancer type	Phase	Assay	Notes	Preliminary results
DARE	NCT04567420	ER+/HER2− breast cancer	2	Signatera	Evaluates ctDNA-guided adjuvant therapy in high-risk patients	High sensitivity and negative predictive value of test
TRAK-ER	NCT04985266	ER+/HER2− breast cancer	2	NA	Investigates early detection of molecular relapse using ctDNA tracking and treatment with palbociclib plus fulvestrant	NA
ASPIRA[13]	NCT04434040	TNBC	2	NA	Assesses combination of atezolizumab and sacituzumab govitecan in patients with residual disease post-neoadjuvant therapy	NA
LEADER	NCT03285412	ER+/HER2− early-stage breast cancer	2	Signatera	Compares ribociclib dosing schedules in combination with endocrine therapy for ctDNA MRD-positive patients	MRD positive + treatment: high ctDNA clearance and delayed recurrence; MRD negative: 12-month RFS = 99%
EXActDNA-003	NCT06401421	High-risk early breast cancer	Observational	NA	Clinical validation study using bespoke ctDNA assays to predict recurrence post-neoadjuvant therapy	NA
CIPHER	NCT05333874	Early-stage breast cancer	1	Signatera	Pilot study evaluating ctDNA dynamics during neoadjuvant therapy and patient attitudes toward ctDNA testing	NA

Abbreviations: ctDNA, circulating tumor DNA; MRD, minimal residual disease, NA, not applicable; RFS, recurrence-free survival; TNBC, triple-negative breast cancer.

currently assessing the noninferiority of observation alone compared to standard adjuvant chemotherapy in ctDNA-negative patients, whereas the ALTAIR arm is assessing the superiority of adjuvant chemotherapy compared to no treatment in ctDNA-positive patients.[16,18] No results have been published yet for the later arms. The CIRCULATE-US (NCT05174169) is an ongoing trial exploring ctDNA-guided escalation and de-escalation of adjuvant chemotherapy in stage II–III colon cancer, comparing surveillance versus immediate therapy in ctDNA-negative patients and standard versus intensified regimens in ctDNA-positive patients.[19] Notably, optimizing ctDNA positivity thresholds for sensitivity and specificity proved more effective for guiding adjuvant chemotherapy and de-escalation decisions than a simple binary cutoff.[20] The COBRA trial (NCT04068103),[21] a multicenter, randomized phase 2/3 study, was discontinued early, after showing that ctDNA-positive patients post-resection did not derive benefit from adjuvant chemotherapy,[22] highlighting that the routine use of MRD testing to guide treatment decisions remains controversial and underscoring the need for further research to define the appropriate clinical context for its implementation. It is important to note that many of the mentioned trials were conducted outside the United States and therefore clinicians and researchers should interpret the results within their specific clinical and health care setting. Accordingly, Table 5 highlights ongoing observational and interventional studies within the United States.

Other ongoing trials include the DYNAMIC-I trial (ACTRN126 15000381583), which explores how ctDNA status (positive or negative) can guide adjuvant chemotherapy in stage II colon cancer patients (i.e., by not giving adjuvant chemotherapy to patients with ctDNA negative results). Initial results indicated a noninferior 2-year

TABLE 5 Ongoing interventional and observational ctDNA MRD trials for solid tumors in the United States.

Trial name	NCT no.	Cancer type	Phase	Assay	Design	Preliminary results
CORRECT-MRD II	NCT05210283	Resected stage II or III colorectal cancer	Observational	Tumor-informed ctDNA	Validates the association of ctDNA with recurrence-free interval	NA
CORRECT-MRD I	NCT06398743	Resected stage II or III colorectal cancer	Observational	Tumor-informed ctDNA	Validates the association of post-definitive therapy and pre-recurrence ctDNA positivity	NA
ADAPT-E	NCT04585477	Early stage lung cancer	2	AVENIO ctDNA surveillance kit	Evaluates ctDNA changes in durvalumab treated vs. standard management	NA
EXActDNA-003	NCT06401421	High-risk early breast cancer	Observational	NA	Clinical validation study using bespoke ctDNA assays to predict recurrence post-neoadjuvant therapy	NA
LEADER	NCT03285412	ER+/HER2− early-stage breast cancer	2	Signatera	Compares ribociclib dosing schedules in combination with endocrine therapy for ctDNA MRD-positive patients	MRD positive + treatment: high ctDNA clearance and delayed recurrence; MRD negative: 12−month RFS = 99%
DARE	NCT04567420	ER+/HER2− breast cancer	2	Signatera	Evaluates ctDNA-guided adjuvant therapy in high-risk patients	High sensitivity and negative predictive value of test
TRAK-ER	NCT04985266	ER+/HER2− breast cancer	2	NA	Investigates early detection of molecular relapse using ctDNA tracking and treatment with palbociclib plus fulvestrant	NA
ASPIRA13	NCT04434040	TNBC	2	NA	Assesses combination of atezolizumab and sacituzumab govitecan in patients with residual disease post-neoadjuvant therapy	NA
ORACLE	NCT05059444	Multiple solid tumors	Observational	Guardant Reveal	Distant recurrence-free interval	NA
TEMPUS ARIES	NCT06207032	Pan-cancer solid tumors	Registry	NA	Longitudinal ctDNA biobank	NA

Abbreviations: ctDNA, circulating tumor DNA; MRD, minimal residual disease, NA, not applicable; RFS, recurrence-free survival; TNBC, triple-negative breast cancer.

recurrence-free survival (RFS) among patients with ctDNA-guided management compared to standard risk-based (non-ctDNA guided) management.[23] Long-term follow-up demonstrated a noninferior 5-year RFS and OS with ctDNA-guided versus standard management (88% and 93.8% vs. 87% and 93.3%, respectively).[24] Interestingly, a post hoc analysis of ctDNA clearance predicted a 5-year recurrence-free probability of 97% versus 0% for ctDNA persistence ($p < .001$).[24] A follow-up study, DYNAMIC-III, explored the impact of ctDNA-guided de-escalation or escalation of adjuvant chemotherapy in patients with resected stage III colon cancer. This study was presented at the American Society of Clinical Oncology (ASCO) 2025 meeting, suggesting that the recurrence risk increased with increasing post-operative ctDNA levels; further analysis of post-adjuvant chemotherapy ctDNA status are currently ongoing.[25]

Several other recent trials have reported on the role ctDNA as a prognostic and predictive marker in CRC, including the COSMOS-CRC-01 trial including patients with stage I–III CRC. The study concluded that the presence of postoperative ctDNA was significantly associated with recurrence risk, with a median lead time of 5.3 months before radiographic detection.[26] Similarly, in a large Danish cohort of 851 patients with stage II–III CRC treated with curative intent, a tumor-informed test showed that both postoperative and serial ctDNA detection were strongly prognostic for cancer recurrence rates (HR, 11.3 and 30.7, respectively; $p < .001$).[20] This study also highlighted the challenges in detecting postoperative ctDNA in metastatic CRC based on different locations of metastasis. For example, ctDNA positivity was lower in lung metastases and peritoneal metastases compared to metastasis to lymph nodes, liver, other

sites and multiple sites,[20] which argues the need for higher sensitivity of MRD tests when used in disease monitoring.[27] Another report from The TRACC part B trial in the United Kingdom demonstrated that postoperative ctDNA detection was the strongest independent predictor of recurrence in multivariable analysis.[28] Discordant results were attributed to sampling frequency, low-shedding tumors, or immune-mediated disease control in ctDNA-negative individuals whose cancer recurred and second primaries or misclassification of clonal hematopoiesis variants in ctDNA-positive variants that remained disease free. Part C of this trial is actively evaluating ctDNA-guided ACT treatment de-escalation.[28]

Currently, the use of ctDNA is a standard clinical practice for CRC in the adjuvant setting. Although there is no consensus on the optimal time and frequency to test for ctDNA in CRC, real-world reports indicated that ctDNA is commonly tested for in the immediate postoperative setting and every 3 to 6 months afterward.[29]

Similar to CRC, MRD has been explored in rectal cancer and other GI tumors. In locally advanced rectal cancer (LARC), where the primary cause of treatment failure is generally due to distant metastasis,[30] early identification of high-risk individuals is prioritized. A multicenter study of LARC patients from China found that ctDNA levels correlated with size and stage of the tumor, and that ctDNA clearance following neoadjuvant chemoradiotherapy (CRT) predicted improved survival outcomes.[31] Additionally, a report from the DYNAMIC-rectal study recently showed that the recurrence rate in treated ctDNA-positive patients was lower when compared to untreated historical controls.[32]

Other studies in different GI tumors[33,34] have reinforced the role of MRD in both outcome prognosis and guiding treatment decisions. In metastatic GI tumors, ctDNA was reported to predict treatment response by detecting mutations like BRAF V600E post-chemotherapy[35] and tracking tumor evolution through RAS status.[36,37] Similarly in advanced gastrointestinal stromal tumor (GIST), ctDNA next-generation sequencing (NGS) identified imatinib-resistant mutations missed by tissue testing, enabling personalized second-line therapy and patients with KIT exons 13/14 benefited from sunitinib, whereas those with exons 17/18 responded better to ripretinib.[38] Ongoing GI trials examining the role of CT DNA in the adjuvant setting are listed in Table 2.

ctDNA and MRD in lung cancer

In the landmark Checkmate 816 phase 3 trial, increased event-free survival (EFS) and pathological complete responses (pCR) were reported following neoadjuvant nivolumab plus chemotherapy compared to chemotherapy alone for resectable lung cancer.[39] A notable exploratory analysis revealed that EFS and pCR were correlated with ctDNA clearance in both treatment groups, highlighting the prognostic potential of ctDNA in lung cancer.[39] This was followed by a recent report from the Checkmate 77T trial in which ctDNA clearance following treatment was identified as an independent predictor of treatment response.[40] Similar results were also seen in the phase 3 AEGEAN trial where overall DFS rates at 12 months were worse in MRD-positive (14.3%; 95% CI, 2.4–36.3) versus MRD-negative patients (89.3%; 95% CI, 82.6–93.5).[41] Other studies have also noted the prognostic[42,43] and predictive[44–46] potential of ctDNA in lung cancers. In addition, Tan et al.[47] used a TI-assay to risk-stratify patients with early-stage non–small cell lung cancer (NSCLC).

Other studies evaluated the role of ctDNA at baseline and suggested that positive ctDNA after surgical resection was strongly associated with a high risk of relapse. The authors also remarked that detection in early-stage NSCLC is difficult, with a limited sensitivity and variable performance across different NSCLC subtypes.[47] Another study by Herbst et al.[48] in a post hoc analysis of the ADAURA trial noted that at randomization, ctDNA detection rates correlated with disease advancement: ctDNA was detected in 0% of stage IB disease, 39% of stage II disease, and 61% of stage III disease. As well, MRD detection preceded imaging-based DFS events by a median of 4.7 months.

Currently, there are no Food and Drug Administration (FDA)-approved MRD tests for lung cancer. However, ongoing and future trials are expected to help establish a standardized usage and interpretation of the ctDNA testing in lung cancer. The MERMAID trials 1 and 2 will assess the benefits of adjuvant therapy in patients with resected, stage II–III MRD-positive NSCLC,[49] and the efficacy and safety of durvalumab versus placebo in patients with resected, stage II-III NSCLC who become MRD-positive after curative-intent therapy,[50] respectively. Ongoing lung cancer trials examining the role of CT DNA in the adjuvant setting are listed in Table 3.

ctDNA and MRD in breast tumors

The role of ctDNA is currently established in advanced breast cancer and originated with ctDNA testing for actionable mutations in metastatic cancer.[51] Most notably, the FDA approved elacestrant for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer with a companion ctDNA assay Guardant360 CDx,[52] following results from the EMERALD trial (NCT03778931) that demonstrated significantly improved progression-free survival (PFS) with elacestrant for people with ctDNA detected ESR1 mutations.[53] A subsequent meta-analysis of metastatic breast cancer studies identified significant associations of ctDNA detection of TP53 and ESR1 alterations with worse survival, further highlighting the prognostic value of ctDNA.[54] In the phase 3 double-blinded randomized SERENA-6 trial, patients with hormone receptor–positive, HER2-negative advanced breast cancer who developed an emergent ESR1 mutation detected by ctDNA experienced a 56% reduction in risk of progression or death when switched to camizestrant (a selective estrogen receptor degrader) plus a CDK4/6 inhibitor compared with continuing an aromatase inhibitor regimen (HR, 0.44; 95% CI, 0.31–0.60; $p < .00001$).[55] Median PFS was prolonged to 16.0 months in the camizestrant arm versus 9.2 months, with consistent benefit across all subgroups.[55]

The role of ctDNA in metastatic breast cancer is currently being assessed in early-stage breast cancer. A pilot study, including 30 patients with primary breast cancer who were monitored with ctDNA for up to 12 years following surgery and adjuvant chemotherapy, suggested that ctDNA could be detected ahead of clinical or radiologic relapse with a lead interval of up to 38 months.[56] More recently, a patient-informed ctDNA assay (CloneSight) was reported to detect ctDNA positivity in 50% of recurred patients with hormone receptor-positive early breast cancer up to 68 months in advance of recurrence, while it remained negative in 93% of patients who did not recur.[57] A study using a NGS panel was able to detect distant recurrence with a lead time of 3.4–18.5 months in 79% of patients with early-stage breast cancer, whereas ctDNA was negative in patients who did not recur.[58] Another study reported a clinical sensitivity of 76.9%, specificity of 100%, and a median lead time of 11.7 months from clinical relapse for patients with early-stage breast cancer using the ctDNA-based MRD personalized cancer monitoring (PCM) assay.[59]

The c-TRAK-TN trial employed a tumor-informed Signatera assay to assess ctDNA-based MRD detection in triple-negative breast cancer (TNBC) and evaluated the addition of pembrolizumab in patients who were ctDNA-positive. However, the trial failed to achieve its goal because 72% of patients already had metastatic diseases on ctDNA detection.[60] A recent systematic review and meta-analysis showed that post-neoadjuvant (before or after surgery) ctDNA positivity is associated with higher recurrence rates and worsened overall survival.[61] However, many of these patients receive several adjuvant therapies that can affect long-term outcomes, therefore, it remains unclear if therapeutic intervention for patients with ctDNA positive testing can improve outcomes.[61]

In summary, despite the interesting results on the prognostic ability of ctDNA in breast cancer, no clear association between its monitoring and improved patient outcomes has been established yet, nor has strong evidence supported its role in guiding treatment escalation or de-escalation.[62,63] Ongoing and future trials should help further guide the clinical application of ctDNA in early-stage breast cancer. Promising results from the PRE-PHENIX trial, a multicenter observational study that explores the prevalence of MRD measured by Guardant Reveal in patients with HER2-positive metastatic breast cancer on long-term first-line trastuzumab-pertuzumab maintenance, were presented at the 2025 ASCO meeting. Guardant Reveal identified that 10 of the 11 patients (91%) with disease progression had MRD, whereas no MRD was found among the 32 patients with Complete Response.[64] A prospective study (PHENIX) to investigate trastuzumab-pertuzumab maintenance interruption by ctDNA monitoring is planned.[64] Table 3 presents a list of ongoing examining ctDNA utility in the adjuvant setting.

ctDNA and MRD In other solid tumors

In glioblastoma multiforme, efforts are currently being made to detect MRD in cerebrospinal fluid (CSF) postoperatively.[65] A recent trial examined the feasibility of using dynamic tumor in situ fluid ctDNA (TISF-DNA) to monitor MRD and evaluate postsurgical treatment response.[66] Patients with positive TISF-ctDNA ($n = 62.2\%$) showed a significantly higher risk of recurrence (HR, 2.512; 95% CI, 1.264–4.993, $p = .0054$). Importantly, TISF-ctDNA positivity preceded imaging signs of recurrence by a median of 71 days.[66] In two other studies, TISF-ctDNA MRD status was strongly correlated with clinical outcomes,[67,68] highlighting the potential to use TISF-ctDNA as a more accurate monitoring tool for tumor recurrence and treatment efficacy in glioblastoma. However, the challenge that presents with CSF MRD is the feasibility and invasiveness of obtaining CSF for repeated analysis compared to standard imaging monitoring.[69]

In ovarian cancer, an ancillary analysis of the CHIVA phase 2 GINECO trial analyzed the ctDNA of patients with advanced epithelial ovarian cancer at diagnosis and after each neoadjuvant chemotherapy (NACT).[62] The results suggested that a significant decrease in ctDNA positivity after one NACT cycle was independently associated with improved PFS, OS, and higher eligibility for interval cytoreductive surgery.[70] In locally advanced cervical cancer, a recent analysis of a large global patient population from the CALLA trial presented at the 2025 ASCO meeting showed that high baseline ctDNA was associated with increased risk of progression or death. Interestingly, lower levels of ctDNA following treatment with durvalumab plus chemoradiotherapy (CRT) compared to CRT alone correlated with improved survival, particularly among patients with PD-L1 tumor-associated positivity ≥20%.[71] This analysis supports the potential utility of using ultrasensitive ctDNA analysis to guide future treatment decisions in cervical cancer.

In genitourinary cancer, the prognostic role of ctDNA in advanced prostate cancer was recently evaluated. In metastatic castration-resistant prostate cancer, ctDNA measured at baseline and during treatment independently predicted poorer outcomes with enzalutamide, providing robust prognostic value than traditional biomarkers.[72] Those results were further are corroborated by Knuston et al.[73] Interestingly, a similar outcome was observed in muscle-invasive bladder cancer, where the detection of ctDNA post–radical cystectomy was strongly associated with shorter DFS, comparing to patients with undetectable ctDNA with better outcomes and did not benefit from adjuvant therapy. This suggests a potential therapeutic role in bladder cancer, beyond prognostic implications.[74] Several additional studies have further demonstrated the prognostic and predictive potential of MRD detection in genitourinary cancers.[75,76] Importantly, urinary tumor DNA profiling, which identifies mutations associated with urothelial carcinoma, alternative to ctDNA (blood), has also been successful in predicting recurrence, and enhancing personalized treatment strategies.[77,78] Although plasma ctDNA allows minimally invasive serial monitoring, it may miss site-specific tumors that urine or CSF ctDNA could detect; thus, analyte choice should be guided by clinical context.

In addition, recent studies have emerged recently with similar results on the predictive and prognostic value of ctDNA-MRD in melanoma,[79] endometrial cancer,[80] and soft tissue sarcomas.[81]

Limitations of ctDNA MRD In solid tumors

ctDNA-based MRD testing in solid tumors has demonstrated significant prognostic and predictive value, but several limitations must be addressed before it can be widely adopted in clinical practice. This methodology is particularly important in the setting of tumor heterogeneity. Single-site biopsies may miss the full genomic profile of a tumor (spatial heterogeneity) and fail to capture subsequent clonal evolution, especially in advanced or previously treated disease.[82,83] The addition of liquid biopsy assays has been revolutionary in addressing this issue by providing a noninvasive, dynamic method of studying whole tumor genomics, albeit with limitations[82–85] Some of these limitations were discussed above. A notable limitation is that ctDNA assays typically targeting a limited set of known mutations, might miss novel subclones that drive relapse, even in tumor-informed assays, potentially leading to false-negative results.[86] The novel technologies that are currently in development, such as methylation pattern-based sequencing and novel ultra-sensitive mutation detection methods could further refine and improve these assays.[28,48,87,88]

Another limitation is the variable tumor shedding, or release of tumor fragments including ctDNA into the bloodstream,[89] based on stage, location, and timing of the assay. Early-stage tumors, brain tumors, and certain solid tumors with metastasis to the lungs or peritoneum tend to have lower ctDNA shedding, which can yield false-negative results.[20,90–92] Conversely, perioperative complications may elevate MRD levels, and subsequently confound assessment.[93] Furthermore, the lack of standardization across assays, such as variations in sample collection, processing, sequencing depth, and mutation panels, limits results generalizability for clinical use.[94] In addition, the variability in currently available assays makes it difficult to compare results from different studies and consequently to have standardized guidelines for interpretation of MRD assays and subsequent management.[95–97]

Another potential limitation of the frequent use of ctDNA is the high cost of ctDNA testing and could be one of the major obstacles to its adoption into standard of care usage. Kramer et al.[98] examined the cost-effectiveness of ctDNA-guided treatment by simulating 1000 stage II colon cancer patients in the Netherland. They measured costs, life years, quality-adjusted life years (QALYs), recurrences, and cancer-related deaths. Although the study concluded that the most clinically beneficial strategy is combining MRD testing with standard of care: mismatch repair status (MMR) and pathological tumor stage (PT), to determine the need for adjuvant chemotherapy, it noted that this is not currently cost-effective under the Dutch willingness-to-pay (WTP) threshold (€50,000 per QALY) as it resulted in an incremental cost-effectiveness ratio (ICER) of €67,413 per QALY.[98] Notably, the study mentioned that this combination strategy could be cost-effective if the costs of ctDNA testing were lower than €1500 per patient, or if ctDNA-positive patients respond substantially better to ACT than ctDNA-negative patients, or if the ctDNA test performance improves substantially.[98]

In contrast, a budget impact analysis conducted in the United States incorporating age-specific incidence of colon cancer, use of adjuvant chemotherapy, costs associated with ctDNA testing, drug acquisition, administration, surveillance, and adverse events, concluded that ctDNA testing led to cost savings for both commercial and Medicare Advantage payers.[99] The cost savings increased with higher test adoption rates and were mainly driven by reduced adjuvant chemotherapy use in ctDNA-guided treatment compared to standard clinical evaluation.[99] It is important to know that cost-effectiveness may vary substantially between health systems and require further evaluation.

CONCLUSION

In conclusion, ctDNA-based MRD detection is reshaping cancer care by identifying high-risk patients, guiding personalized treatment, and monitoring treatment response. Current evidence supports the clinical use of ctDNA most strongly in colorectal cancer, with consistent prognostic and emerging predictive utility, whereas in lung, breast, and other solid tumors ctDNA primarily serves as a prognostic biomarker, with treatment-guiding applications remaining investigational. Ongoing trials in the United States (Table 5) and worldwide (Tables 2–4) seek to explore ctDNA guided interventions and whether these can be translated to better patient outcomes Although standardization, sensitivity, and cost remain a challenge, this field is rapidly evolving with ongoing and future clinical trials expected to further establish its value and guide its safe implementation in everyday clinical settings. As research continues to unfold, the insights gained from ctDNA will undoubtedly shape the future of personalized cancer treatment.

FUTURE RESEARCH DIRECTION

Future research efforts should aim to enhance the sensitivity and specificity of ctDNA assays to improve their clinical utility. Advances in sequencing technologies, including ultra-deep sequencing and whole genome sequencing, enable more reliable detection in early-stage and low-shedding tumors.[88,100,101] Additionally, the development of comprehensive genomic panels that include noncanonical variants and epigenetic markers, such as DNA methylation, could potentially increase detection sensitivity and broaden the applicability of ctDNA assays across diverse tumor types.[28,87] Machine learning algorithms may improve predictive accuracy and enable more precise risk stratification, thereby supporting the advancement of personalized treatments.[102,103]

Another focus of future research is optimizing ctDNA monitoring schedules

Longitudinal sampling, where ctDNA is measured at multiple time points during treatment or follow-up, has demonstrated greater consistency and clinical relevance than single time-point

measurements.[59,104 97] Accordingly, standardizing sampling schedules would be critical to ensure accurate detection and effective disease monitoring.[47,48] Admittedly, these trials are difficult and costly to conduct, due to three major challenges: the high level of variability in ctDNA detection, the extensive costs associated with trial requirements, and the complex logistics and ethical considerations involved.[105] Finally, future research should clearly determine whether earlier detection of recurrence or metastasis and subsequent management changes using MRD would actually improve patient outcomes and survival.[62]

AUTHOR CONTRIBUTIONS

Theresa Abdo: Conceptualization; investigation; methodology; project administration; resources; writing—original draft; writing—review and editing. **Sacha Yaghi**: Writing—original draft. **Ahmad Alhalabi**: Writing—original draft; writing—review and editing. **Mohammad Aloran**: Writing—original draft. **You Li**: Writing—review and editing. **María Herrán**: Writing—review and editing. **Rami Tfayli**: Writing—review and editing. **Thomas A. Samuel**: Supervision; writing—review and editing. **Zeina Nahleh**: Supervision; writing—review and editing.

ACKNOWLEDGMENTS

No copyrighted material or patient data were reproduced in this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Theresa Abdo https://orcid.org/0009-0007-0703-1319
Mohammad Aloran https://orcid.org/0009-0005-8365-787X
Zeina Nahleh https://orcid.org/0000-0002-2489-1501

REFERENCES

1. Liu M, Mu T, Gu J, Xu M, Chen S. The method of minimal residual disease detection with circulating tumor DNA and its clinical applications in colorectal cancer. *Cancer Rep (Hoboken)*. 2025;8(3):e70167. doi:10.1002/cnr2.70167
2. Mannucci A, Goel A. From treating risk to treating disease: response, remission, and cure in the MRD era of colon cancer. ASCO Daily News. December 18, 2024. doi:10.1200/adn.24.300035
3. Bartolomucci A, Nobrega M, Ferrier T, et al. Circulating tumor DNA to monitor treatment response in solid tumors and advance precision oncology. *NPJ Precis Oncol*. 2025;9(1):84. doi:10.1038/s41698-025-00876-y
4. Stetson D, Labrousse P, Russell H, et al. Next-generation molecular residual disease assays: do we have the tools to evaluate them properly? *J Clin Oncol*. 2024;42(23):2736-2740. doi:10.1200/jco.23.02301
5. Song M, Pan W, Yu X, et al. Minimal residual disease detection: implications for clinical diagnosis and cancer patient treatment. *MedComm*. 2025;6(6):e70193. doi:10.1002/mco2.70193
6. George MA, Schwartz G, McHayleh W, et al. Clinical performance of Signatera Genome assay in a cohort of patients (pts) with solid tumors. *J Clin Oncol*. 2025;43(suppl 16):3142. doi:10.1200/jco.2025.43.16_suppl.3142
7. Martínez-Castedo B, Camblor DG, Martín-Arana J, et al. Minimal residual disease in colorectal cancer. Tumor-informed versus tumor-agnostic approaches: unraveling the optimal strategy. *Ann Oncol*. 2025;36(3):263-276.
8. Camblor DG, Martínez-Castedo B, Martín-Arana J, et al. Clinical performance of tumor-informed versus tumor-agnostic ctDNA assays for colorectal cancer recurrence: a systematic review and diagnostic accuracy meta-analysis. *Cancer Treat Rev*. 2026;142:103066.
9. FDA-NIH Biomarker Working Group. Understanding prognostic versus predictive biomarkers. National Institutes of Health (US). 2016.
10. Chandhok NS, Sekeres MA. Measurable residual disease in hematologic malignancies: a biomarker in search of a standard. *eClinicalMedicine*. 2025;86:103348. doi:10.1016/j.eclinm.2025.103348
11. Wallington-Beddoe CT, Mynott RL. Prognostic and predictive biomarker developments in multiple myeloma. *J Hematol Oncol*. 2021;14(1):151. doi:10.1186/s13045-021-01162-7
12. Pusztai LRM. *Balancing the Benefits and Harms of ctDNA Surveillance in Early-Stage Breast Cancer*. ASCO Daily News; 2024.
13. Genentech I, Up S, To C, eds. *A Single Arm Phase 2 Trial of Atezolizumab With Sacituzumab Govitecan to Prevent Recurrence in Triple Negative Breast Cancer (ASPRIA)*; 2020.
14. Shirasu H, Taniguchi H, Matsuhashi N, et al. A randomized, double-blind, phase III study comparing trifluridine/tipiracil hydrochloride versus placebo in resected colorectal cancer patients with positive circulating tumor DNA after standard adjuvant therapy (EPOC 1905): the ALTAIR trial in CIRCULATE-Japan (trial in progress). *J Clin Oncol*. 2022;40(4_suppl):TPS215. doi:10.1200/JCO.2022.40.4_suppl.TPS215
15. Sorscher S. Circulating tumor DNA for solid tumor minimal/molecular residual disease detection in cancer survivors. *Am J Med*. 2024;137(12):1168-1169. doi:10.1016/j.amjmed.2024.08.014
16. Taniguchi H, Nakamura Y, Kotani D, et al. CIRCULATE-Japan: circulating tumor DNA-guided adaptive platform trials to refine adjuvant therapy for colorectal cancer. *Cancer Sci*. 2021;112(7):2915-2920. doi:10.1111/cas.14926
17. Nakamura Y, Watanabe J, Akazawa N, et al. ctDNA-based molecular residual disease and survival in resectable colorectal cancer. *Nat Med*. 2024;30(11):3272-3283. doi:10.1038/s41591-024-03254-6
18. Shirasu H, Taniguchi H, Matsuhashi N, et al. A randomized, double-blind, phase III study comparing trifluridine/tipiracil hydrochloride therapy versus placebo in resected colorectal cancer patients who are positive for blood circulating tumor DNA after standard adjuvant therapy (EPOC 1905): ALTAIR trial in CIRCULATE-Japan (trial in progress). *J Clin Oncol*. 2022;40(suppl 4):TPS215. doi:10.1200/jco.2022.40.4_suppl.tps215
19. Sahin IH, Lin Y, Yothers G, et al. Minimal residual disease-directed adjuvant therapy for patients with early-stage colon cancer: CIRCULATE-US. *Oncology (Williston Park)*. 2022;36(10):604-608. doi:10.46883/2022.25920976
20. Henriksen TV, Demuth C, Frydendahl A, et al. Unraveling the potential clinical utility of circulating tumor DNA detection in colorectal cancer—evaluation in a nationwide Danish cohort. *Ann Oncol*. 2024;35(2):229-239. doi:10.1016/j.annonc.2023.11.009
21. Morris VK II, Yothers G, Kopetz S, et al. Phase II/III study of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA). *J Clin Oncol*. 2020;38(15_suppl):TPS4121. Presented at the 2020 ASCO Virtual Scientific Program. doi:10.1200/JCO.2020.38.15_suppl.TPS4121

22. Morris VK, Yothers G, Kopetz S, et al. Phase II results of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA) phase II/III study. *J Clin Oncol*. 2024;42(suppl 3):5. doi:10.1200/jco.2024.42.3_suppl.5
23. Tie J, Cohen JD, Lahouel K, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer. *N Engl J Med*. 2022;386(24):2261-2272. doi:10.1056/nejmoa2200075
24. Tie J, Wang Y, Lo SN, et al. Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial. *Nat Med*. 2025;31(5):1509-1518. doi:10.1038/s41591-025-03579-w
25. Tie J, Wang Y, Loree JM, et al. ctDNA-guided adjuvant chemotherapy escalation in stage III colon cancer: Primary analysis of the ctDNA-positive cohort from the randomized AGITG dynamic-III trial (intergroup study of AGITG and CCTG). *J Clin Oncol*. 2025;43(suppl 16):3503. doi:10.1200/jco.2025.43.16_suppl.3503
26. Nakamura Y, Tsukada Y, Matsuhashi N, et al. Colorectal cancer recurrence prediction using a tissue-free epigenomic minimal residual disease assay. *Clin Cancer Res*. 2024;30(19):4377-4387. doi:10.1158/1078-0432.ccr-24-1651
27. Bando H, Nakamura Y, Taniguchi H, et al. Effects of metastatic sites on circulating tumor DNA in patients with metastatic colorectal cancer *JCO Precis Oncol* 2022;6:e2100535. doi:10.1200/po.21.00535
28. Slater S, Bryant A, Aresu M, et al. Tissue-free liquid biopsies combining genomic and methylation signals for minimal residual disease detection in patients with early colorectal cancer from the UK TRACC Part B study. *Clin Cancer Res*. 2024;30(16):3459-3469. doi:10.1158/1078-0432.ccr-24-0226
29. Nguyen HV-A, Nguyen N, Le DN, et al. Real-world utilization and performance of circulating tumor DNA monitoring to predict recurrence in solid tumors. *JCO Oncol Adv*. 2025(2):e2400084. doi:10.1200/oa-24-00084
30. Tang C, Xu J, Lin M, et al. Risk factors for distant metastasis in T3 T4 rectal cancer. *Clin Med Insights Oncol*. 2024;18:11795549241227423. doi:10.1177/11795549241227423
31. Zhou J, Li L, Liu Y, et al. Circulating tumour DNA in predicting and monitoring survival of patients with locally advanced rectal cancer undergoing multimodal treatment: long-term results from a prospective multicenter study. *EBioMedicine*. 2025;112:105548. doi:10.1016/j.ebiom.2024.105548
32. Tie J, Cohen JD, Wang Y, et al. Circulating tumor DNA analysis informing adjuvant chemotherapy in locally advanced rectal cancer: the randomized AGITG DYNAMIC-Rectal study. *J Clin Oncol*. 2024;42(suppl 3):12. doi:10.1200/jco.2024.42.3_suppl.12
33. Yang Y, Liu Z, Wong I, et al. Detecting residual disease after neoadjuvant chemoradiotherapy for oesophageal squamous cell carcinoma: the prospective multicentre preSINO trial. *Br J Surg*. 2025;112(2):znaf004. doi:10.1093/bjs/znaf004
34. Feng J, Liu W, Wang W, et al. Comparative analysis of ctDNA-MRD and MVI in predicting postoperative recurrence of hepatocellular carcinoma. *J Clin Oncol*. 2025;43(suppl 16):4128. doi:10.1200/jco.2025.43.16_suppl.4128
35. Iwai T, Yamada T, Uehara K, et al. Clinical implications of cell-free DNA in managing BRAF V600E mutation-positive colorectal cancer. *Genes*. 2025;16(3):275. doi:10.3390/genes16030275
36. Valladares-Ayerbes M, Safont MJ, González Flores E, et al. Sequential RAS mutations evaluation in cell-free DNA of patients with tissue RAS wild-type metastatic colorectal cancer: the PERSEIDA (Cohort 2) study. *Clin Transl Oncol*. 2024;26(10):2640-2651. doi:10.1007/s12094-024-03487-4
37. Wu FTH, Topham JT, O'Callaghan CJ, et al. Kinetic profiling of RAS mutations with circulating tumor DNA in the Canadian Cancer Trials Group CO.26 Trial suggests the loss of RAS mutations in neo-RAS-wildtype metastatic colorectal cancer is transient. *JCO Precis Oncol*. 2024;8:e2400031. doi:10.1200/po.24.00031
38. Heinrich MC, Jones RL, George S, et al. Ripretinib versus sunitinib in gastrointestinal stromal tumor: ctDNA biomarker analysis of the phase 3 INTRIGUE trial. *Nat Med*. 2024;30(2):498-506. doi:10.1038/s41591-023-02734-5
39. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973-1985. doi:10.1056/nejmoa2202170
40. Cascone T, Awad MM, Spicer J, et al. Perioperative nivolumab (NIVO) vs placebo (PBO) in patients (pts) with resectable NSCLC: updated survival and biomarker analyses from CheckMate 77T. *J Clin Oncol*. 2025;43(suppl 17):LBA8010. doi:10.1200/jco.2025.43.17_suppl.lba8010
41. Reck M, Gale D, Zhu Z, et al. Association of post-surgical MRD status with neoadjuvant ctDNA dynamics, genomic mutations, and clinical outcomes in patients with resectable NSCLC (R-NSCLC) from the phase 3 AEGEAN trial. *J Clin Oncol*. 2025;43(suppl 16):8009. doi:10.1200/jco.2025.43.16_suppl.8009
42. Horndalsveen H, Haakensen VD, Madebo T, et al. ctDNA-based MRD detection in unresectable NSCLC undergoing curatively intended chemoradiotherapy and durvalumab. *J Clin Oncol*. 2025;43(suppl 16):8011. doi:10.1200/jco.2025.43.16_suppl.8011
43. Gray JE, Markovets A, Reungwetwattana T, et al. Longitudinal analyses of circulating tumor DNA for the detection of EGFR mutation-positive advanced NSCLC progression during treatment: data from FLAURA and AURA3. *J Thorac Oncol*. 2024;19(11):1525-1538. doi:10.1016/j.jtho.2024.07.008
44. Hong Y, Zhuang W, Lai J, et al. Plasma EGFR mutation ctDNA dynamics in patients with advanced EGFR-mutated NSCLC treated with Icotinib: phase 2 multicenter trial result. *Sci Rep*. 2024;14(1):23115. doi:10.1038/s41598-024-73749-2
45. Jun S, Shukla NA, Durm G, et al. Analysis of circulating tumor DNA predicts outcomes of short-course consolidation immunotherapy in unresectable stage III NSCLC. *J Thorac Oncol*. 2024;19(10):1427-1437. doi:10.1016/j.jtho.2024.06.024
46. Tamiya A, Mizumori Y, Osuga M, et al. Circulating tumour DNA in patients with EGFR-mutated non-small-cell lung cancer and early disease progression after first-line osimertinib treatment: the ELUCIDATOR Multicentre Prospective Observational Study. *Cancer Med*. 2025;14(7):e70861. doi:10.1002/cam4.70861
47. Tan AC, Lai GGY, Saw SPL, et al. Detection of circulating tumor DNA with ultradeep sequencing of plasma cell-free DNA for monitoring minimal residual disease and early detection of recurrence in early-stage lung cancer. *Cancer*. 2024;130(10):1758-1765. doi:10.1002/cncr.35263
48. Herbst RS, John T, Grohé C, et al. Molecular residual disease analysis of adjuvant osimertinib in resected EGFR-mutated stage IB–IIIA non-small-cell lung cancer. *Nat Med*. 2025;31(6):1958-1968. doi:10.1038/s41591-025-03577-y
49. Peters S, Spigel D, Ahn M, et al. P03.03 MERMAID-1: a phase III study of adjuvant durvalumab plus chemotherapy in resected NSCLC patients with MRD+ post-surgery. *J Thorac Oncol*. 2021;16(3):S258-S259. doi:10.1016/j.jtho.2021.01.376
50. Spigel DR, Peters S, Ahn MJ, et al. 93TiP MERMAID-2: phase III study of durvalumab in patients with resected, stage II-III NSCLC who become MRD+ after curative-intent therapy. *J Thorac Oncol*. 2021;16(4):S745-S746. doi:10.1016/s1556-0864(21)01935-3
51. Croessmann S, Park BH. Circulating tumor DNA in early-stage breast cancer: new directions and potential clinical applications. *Clin Adv Hematol Oncol*. 2021;19(3):155-161.
52. Shah M, Lingam H, Gao X, et al. US food and drug administration approval summary: elacestrant for estrogen receptor-positive,

human epidermal growth factor receptor 2-negative, ESR1-mutated advanced or metastatic breast cancer. *J Clin Oncol*. 2024;42(10):1193-1201. doi:10.1200/JCO.23.02112
53. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: results from the randomized phase III EMERALD Trial. *J Clin Oncol*. 2022;40(28):3246-3256. doi:10.1200/jco.22.00338
54. Dickinson K, Sharma A, Agnihotram R-KV, et al. Circulating tumor DNA and survival in metastatic breast cancer: a systematic review and meta-analysis. *JAMA Netw Open*. 2024;7(9):e2431722. doi:10.1001/jamanetworkopen.2024.31722
55. Turner NC, Mayer EL, Park YH, et al. Camizestrant + CDK4/6 inhibitor (CDK4/6i) for the treatment of emergent ESR1 mutations during first-line (1L) endocrine-based therapy (ET) and ahead of disease progression in patients (pts) with HR+/HER2– advanced breast cancer (ABC): Phase 3, double-blind ctDNA-guided SERENA-6 trial. *J Clin Oncol*. 2025;43(suppl 17):LBA4. doi:10.1200/jco.2025.43.17_suppl.lba4
56. Shaw JA, Page K, Wren E, et al. Serial postoperative circulating tumor DNA assessment has strong prognostic value during long-term follow-up in patients with breast cancer *JCO Precis Oncol* 2024;8:e2300456. doi:10.1200/po.23.00456
57. Comino-Méndez I, Velasco-Suelto J, Pascual J, et al. Identification of minimal residual disease using the clonesight test for ultrasensitive ctDNA detection to anticipate late relapse in early breast cancer. *Breast Cancer Res*. 2025;27(1):65.
58. Janni W, Rack B, Friedl TWP, et al. Detection of minimal residual disease and prediction of recurrence in breast cancer using a plasma-only circulating tumor DNA assay. *ESMO Open*. 2025;10(4):104296. doi:10.1016/j.esmoop.2025.104296
59. Yoo T-KR, Lee J-Y, Park H, et al. Longitudinal dynamics of circulating tumor DNA for treatment monitoring in patients with breast cancer recurrence. *Sci Rep*. 2024;14(1):20252. doi:10.1038/s41598-024-70887-5
60. Turner NC, Swift C, Jenkins B, et al. Results of the c-TRAK TN trial: a clinical trial utilising ctDNA mutation tracking to detect molecular residual disease and trigger intervention in patients with moderate- and high-risk early-stage triple-negative breast cancer. *Ann Oncol*. 2023;34(2):200-211. doi:10.1016/j.annonc.2022.11.005
61. Zhang D, Jahanfar S, Rabinowitz JB, et al. Role of circulating tumor DNA in early-stage triple-negative breast cancer: a systematic review and meta-analysis. *Breast Cancer Res*. 2025;27(1):38. doi:10.1186/s13058-025-01986-y
62. Chen JH, Geng Y, Lucci A. Applications of ctDNA testing to monitor and detect residual disease in breast cancer. *Expert Rev Mol Diagn*. 2025;25(6):263-274. doi:10.1080/14737159.2025.2498545
63. Elliott MJ, Echelard P, Pipinikas C, et al. Longitudinal evaluation of circulating tumor DNA in patients undergoing neoadjuvant therapy for early breast cancer using a tumor-informed assay. *Nat Commun*. 2025;16(1):1837. doi:10.1038/s41467-025-56658-4
64. Llombart-Cussac A, Fernandez-Murga L, Martinez E, et al. Circulating tumor DNA (ctDNA)-based minimal residual disease (MRD) measured by Guardant Reveal in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with long-term disease control on first-line trastuzumab-pertuzumab. *J Clin Oncol*. 2025;43(suppl 16):1052. doi:10.1200/jco.2025.43.16_suppl.1052
65. Riviere-Cazaux C, Dong X, Mo W, et al. Longitudinal glioma monitoring via cerebrospinal fluid cell-free DNA. *Clin Cancer Res*. 2025;31(5):881-889. doi:10.1158/1078-0432.ccr-24-1814
66. Zhang J, Liu G, Wang D, et al. Dynamic tumor in situ fluid circulating tumor DNA postsurgery effectively predicts recurrence and clinical benefits for glioblastomas. *Neurosurgery*. 2025;97(3):671-680. doi:10.1227/neu.0000000000003384
67. Wang D, Zhang J, Bu C, et al. Dynamics of tumor in situ fluid circulating tumor DNA in recurrent glioblastomas forecasts treatment efficacy of immune checkpoint blockade coupled with low-dose bevacizumab. *J Cancer Res Clin Oncol*. 2024;150(10):466. doi:10.1007/s00432-024-05997-8
68. Guo G, Zhang Z, Zhang J, et al. Predicting recurrent glioblastoma clinical outcome to immune checkpoint inhibition and low-dose bevacizumab with tumor in situ fluid circulating tumor DNA analysis. *Cancer Immunol Immunother*. 2024;73(10):193. doi:10.1007/s00262-024-03774-7
69. Fischer TT, Maaß KK, Puranachot P, et al. Ultra-low-input cell-free DNA sequencing for tumor detection and characterization in a real-world pediatric brain tumor cohort. *Acta Neuropathol Commun*. 2025;13(1):134. doi:10.1186/s40478-025-02024-w
70. Azaïs H, Brochard C, Taly V, et al. Prognostic value of circulating tumor DNA at diagnosis and its early decrease after one cycle of neoadjuvant chemotherapy for patients with advanced epithelial ovarian cancer. An ancillary analysis of the CHIVA phase II GINECO trial. *Gynecol Oncol*. 2025;192:145-154.
71. Mayadev J, Limón JCV, Godinez FJR, et al. Ultrasensitive detection and tracking of circulating tumor DNA (ctDNA) and association with relapse and survival in locally advanced cervical cancer (LACC): phase 3 CALLA trial analyses. *J Clin Oncol*. 2025;43(suppl 16):5502. doi:10.1200/jco.2025.43.16_suppl.5502
72. Sweeney CJ, Petry R, Xu C, et al. Circulating tumor DNA assessment for treatment monitoring adds value to PSA in metastatic castration-resistant prostate cancer. *Clin Cancer Res*. 2024;30(18):4115-4122. doi:10.1158/1078-0432.ccr-24-1096
73. Knutson TP, Luo B, Kobilka A, et al. AR alterations inform circulating tumor DNA detection in metastatic castration resistant prostate cancer patients. *Nat Commun*. 2024;15(1):10648. doi:10.1038/s41467-024-54847-1
74. Sfakianos JP, Basu A, Laliotis G, et al. Association of tumor-informed circulating tumor DNA detectability before and after radical cystectomy with disease-free survival in patients with bladder cancer. *Eur Urol Oncol*. 2025;8(2):306-314. doi:10.1016/j.euo.2024.07.001
75. Ayanambakkam A, Laliotis G, Reyes KR, et al. Association of tumor-informed ctDNA-based molecular residual disease (MRD) with clinical outcomes for upper tract urothelial cancer (UTUC). *J Clin Oncol*. 2025;43(suppl 16):4565. doi:10.1200/jco.2025.43.16_suppl.4565
76. Powles T, Chang YH, Yamamoto Y, et al. Pembrolizumab for advanced urothelial carcinoma: exploratory ctDNA biomarker analyses of the KEYNOTE-361 phase 3 trial. *Nat Med*. 2024;30(9):2508-2516. doi:10.1038/s41591-024-03091-7
77. Narayan VM, Tholomier C, Mokkapati S, et al. Minimal residual disease detection with urine-derived DNA is prognostic for recurrence-free survival in bacillus Calmette-Guérin-unresponsive non-muscle-invasive bladder cancer treated with nadofaragene firadenovec. *Eur Urol Oncol*. 2025;8(2):425-434. doi:10.1016/j.euo.2024.09.016
78. Yang K, Hu H, Wu J, et al. Letter to the Editor: clinical utility of urine DNA for noninvasive detection and minimal residual disease monitoring in urothelial carcinoma. *Mol Cancer*. 2023;22(1):25. doi:10.1186/s12943-023-01729-7
79. Long GV, Tang H, Desai K, et al. Pretreatment and on-treatment ctDNA and tissue biomarkers predict recurrence in patients with stage IIIB-D/IV melanoma treated with adjuvant immunotherapy: CheckMate 915. *J Immunother Cancer*. 2025;13(7):e012034. doi:10.1136/jitc-2025-012034

80. Latham A, Mueller JJ, Charalambous K, et al. Feasibility of Pap-derived ctDNA for detection of sporadic and Lynch-associated endometrial cancer. *J Clin Oncol*. 2025;43(suppl 16):10503. doi:10.1200/jco.2025.43.16_suppl.10503
81. Park CL, Demicco E, Howarth K, et al. Detecting ctDNA using personalized structural variants to forecast recurrence in localized soft tissue sarcoma (STS). *J Clin Oncol*. 2025;43(suppl 16):11511. doi:10.1200/jco.2025.43.16_suppl.11511
82. Mazouji O, Ouhajjou A, Anouar N, Nejjari C, Incitti R, Mansour H. Mutational profiling using liquid biopsy to guide targeted therapy in patients with metastatic cancer. *Sci Rep*. 2025;15(1):11135. doi:10.1038/s41598-025-88094-1
83. Al Bakir M, Huebner A, Martínez-Ruiz C, et al. The evolution of non-small cell lung cancer metastases in TRACERx. *Nature*. 2023;616(7957):534-542. doi:10.1038/s41586-023-05729-x
84. Ma L, Guo H, Zhao Y, et al. Liquid biopsy in cancer: current status, challenges and future prospects. *Signal Transduct Targeted Ther*. 2024;9(1):336. doi:10.1038/s41392-024-02021-w
85. Lv D, Lan B, Guo Q, et al. Exploration of the clonal evolution and construction of the tumor clonal evolution rate as a prognostic indicator in metastatic breast cancer. *BMC Med*. 2025;23(1):122. doi:10.1186/s12916-025-03959-6
86. Nakamura Y, Ozaki H, Ueno M, et al. Targeted therapy guided by circulating tumor DNA analysis in advanced gastrointestinal tumors. *Nat Med*. 2025;31(1):165-175. doi:10.1038/s41591-024-03244-8
87. Mo S, Ye L, Wang D, et al. Early detection of molecular residual disease and risk stratification for stage I to III colorectal cancer via circulating tumor DNA methylation. *JAMA Oncol*. 2023;9(6):770-778. doi:10.1001/jamaoncol.2023.0425
88. Chen K, Yang F, Shen H, et al. Individualized tumor-informed circulating tumor DNA analysis for postoperative monitoring of non-small cell lung cancer. *Cancer Cell*. 2023;41(10):1749-1762e1746. doi:10.1016/j.ccell.2023.08.010
89. Sánchez-Herrero E, Serna-Blasco R, Robado de Lope L, et al. Circulating tumor DNA as a cancer biomarker: an overview of biological features and factors that may impact on ctDNA analysis. *Front Oncol*. 2022;12:943253.
90. Efthymiou V, Queenan N, Haas M, Naegele S, Goss D, Faden DL. Circulating tumor DNA in the immediate postoperative setting. *Ann Surg Oncol*. 2024;31(4):2319-2325. doi:10.1245/s10434-023-14860-y
91. Zhang X, Zhang Y, Zhang S, Wang S, Yang P, Liu C. Investigate the application of postoperative ctDNA-based molecular residual disease detection in monitoring tumor recurrence in patients with non-small cell lung cancer--a retrospective study of ctDNA. *Front Oncol*. 2023;13:1098128. doi:10.3389/fonc.2023.1098128
92. Rhrissorrakrai K, Utro F, Levovitz C, Parida L. Lesion shedding model: unraveling site-specific contributions to ctDNA. *Briefings Bioinf*. 2023;24(2):bbad059. doi:10.1093/bib/bbad059
93. Oki E, Sato S, Ando K, et al. Impact of perioperative complications on ctDNA-based MRD detection and prognosis: insights from the GALAXY study. *J Clin Oncol*. 2025;43(suppl 16):3600. doi:10.1200/jco.2025.43.16_suppl.3600
94. Zhu L, Xu R, Yang L, et al. Minimal residual disease (MRD) detection in solid tumors using circulating tumor DNA: a systematic review. *Front Genet*. 2023;14:1172108. doi:10.3389/fgene.2023.1172108
95. Chan HT, Chin YM, Low SK. Circulating tumor DNA-based genomic profiling assays in adult solid tumors for precision oncology: recent advancements and future challenges. *Cancers (Basel)*. 2022;14(13):3275. doi:10.3390/cancers14133275
96. Chidharla A, Rapoport E, Agarwal K, et al. Circulating tumor DNA as a minimal residual disease assessment and recurrence risk in patients undergoing curative-intent resection with or without adjuvant chemotherapy in colorectal cancer: a systematic review and meta-analysis. *Int J Mol Sci*. 2023;24(12):10230. doi:10.3390/ijms241210230
97. Ding H, Yuan M, Yang Y, Xu XS. Identifying key circulating tumor DNA parameters for predicting clinical outcomes in metastatic non-squamous non-small cell lung cancer after first-line chemo-immunotherapy. *Nat Commun*. 2024;15(1):6862. doi:10.1038/s41467-024-51316-7
98. Kramer A, Greuter MJE, Schraa SJ, et al. Early evaluation of the effectiveness and cost-effectiveness of ctDNA-guided selection for adjuvant chemotherapy in stage II colon cancer. *Ther Adv Med Oncol*. 2024;16:17588359241266164. doi:10.1177/17588359241266164
99. Li Y, Heer AK, Sloane HS, et al. Budget impact analysis of circulating tumor DNA testing for colon cancer in commercial health and Medicare Advantage plans. *JAMA Health Forum*. 2024;5(5):e241270. doi:10.1001/jamahealthforum.2024.1270
100. Tran I, Galbraith K, Gardner SL, et al. Ultrasensitive detection and monitoring of central nervous system tumors from plasma using personalized whole-genome ctDNA profiling. *J Clin Oncol*. 2023;41(suppl 16):2064. doi:10.1200/jco.2023.41.16_suppl.2064
101. Hashimoto T, Kobayashi S, Oki E, et al. Ultra-sensitive pan-cancer molecular residual disease assessment using whole-genome sequencing-based personalized ctDNA panel: initial results from the MONSTAR-SCREEN-3 project. *J Clin Oncol*. 2025;43(suppl 16):3007. doi:10.1200/jco.2025.43.16_suppl.3007
102. Wu Y, Li C, Yang Y, et al. Predicting disease progression in inoperable localized NSCLC patients using ctDNA machine learning model. *Cancer Med*. 2024;13(20):e70316. doi:10.1002/cam4.70316
103. Widman AJ, Shah M, Frydendahl A, et al. Ultrasensitive plasma-based monitoring of tumor burden using machine-learning-guided signal enrichment. *Nat Med*. 2024;30(6):1655-1666. doi:10.1038/s41591-024-03040-4
104. Lv J, Xu LX, Li ZX, et al. Longitudinal on-treatment circulating tumor DNA as a biomarker for real-time dynamic risk monitoring in cancer patients: the EP-SEASON study. *Cancer Cell*. 2024;42(8):1401-1414e1404. doi:10.1016/j.ccell.2024.07.001
105. Fusco N, Venetis K, Pepe F, et al. International society of liquid biopsy (ISLB) perspective on minimal requirements for ctDNA testing in solid tumors. *J Liq Biopsy*. 2025;8:100301. doi:10.1016/j.jlb.2025.100301

How to cite this article: Abdo T, Alhalabi A, Yaghi S, et al. Minimal residual disease in solid tumors: clinical applications and future directions. *Cancer*. 2026;e70286. doi:10.1002/cncr.70286