Evaluating the Impact of Liquid Biopsies on Cancer Patient Survival: A Systematic Assessment of Efficacy

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Abstract

Background: Circulating tumor DNA (ctDNA) has emerged as a transformative biomarker for liquid biopsy, enabling real-time assessment of minimal residual disease (MRD), monitoring of treatment response, and early detection of recurrence. While ctDNA is established as a powerful prognostic marker, its true clinical utility lies in whether interventions guided by ctDNA status can improve survival. **Objective:** This review synthesizes evidence from existing clinical trials and protocols spanning colorectal, lung, and breast cancers to evaluate whether ctDNA-guided escalation, de-escalation, or adaptive therapy strategies translate into improved survival outcomes. **Methods:** A literature search was conducted in PubMed for interventional ctDNA-guided studies published between 2001 and 2025, including randomized controlled trials, single-arm interventional cohorts, large-scale registries, and prospective trial protocols. Data on study design, assay methodology, treatment strategy, endpoints, and survival outcomes were extracted. Studies were grouped into four categories: early-stage colorectal cancer, post-metastasectomy colorectal cancer, advanced/metastatic colorectal cancer, and non-colorectal solid tumors. **Results:** 16 eligible studies were identified and included. In early-stage colorectal cancer, the DYNAMIC trial(Tie et al., 2022; Tie et al., 2025) demonstrated that ctDNA-guided management halved chemotherapy use while preserving 5-year recurrence-free survival (88%) and overall survival (93.8%). Escalation strategies, such as REVISE and ALTAIR, are ongoing. In metastatic colorectal cancer, ctDNA-directed rechallenge (CHRONOS) and registry-based molecular matching (GOZILA) achieved improved outcomes, with GOZILA reporting an OS hazard ratio of 0.54 for matched therapy. In lung cancer, ctDNA-guided adaptive sequencing (APPLE) and tyrosine kinase inhibitor de-escalation(Dong et al., 2024) improved progression-free survival. In breast cancer, the PADA-1 protocol evaluates ctDNA-triggered endocrine switching, with results pending. **Conclusions:** ctDNA-guided strategies have shown definitive benefit for de-escalation in stage II colon cancer and predictive utility in metastatic precision oncology. Escalation strategies and applications in lung and breast cancers remain

promising but immature. Standardization of assays, demonstration of overall survival benefit, and incorporation into clinical guidelines will be critical for widespread adoption.

Keywords: circulating tumor DNA; ctDNA; liquid biopsy; minimal residual disease; colorectal cancer; lung cancer; breast cancer; survival; escalation; de-escalation; adaptive therapy

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Cancer remains one of the leading causes of mortality worldwide, with survival outcomes heavily dependent on the timing and accuracy of diagnosis, disease monitoring, and response to treatment. Traditional tissue biopsies, while considered the gold standard for cancer diagnosis and molecular profiling, are often invasive, costly, and limited in their ability to capture tumor heterogeneity or enable real-time disease monitoring. In recent years, liquid biopsies have emerged as a minimally invasive alternative that holds significant promise for transforming cancer care.

Liquid biopsy refers to the sampling and analysis of non-solid biological tissue, primarily blood, to detect and monitor cancer. It has emerged as one of the most promising innovations in modern oncology. The technique typically involves the detection of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), exosomes, and other tumor-derived biomarkers present in bodily fluids. These analytes offer valuable molecular insights into the genetic and epigenetic landscape of a tumor, enabling clinicians to track tumor evolution, detect minimal residual disease (MRD), and guide therapy decisions with greater precision. Compared to traditional biopsies, liquid biopsies offer several advantages: they are safer, allow for longitudinal sampling, and can provide a more comprehensive view of the tumor's molecular profile by capturing spatial and temporal heterogeneity.

Clinically, liquid biopsies are increasingly being integrated into cancer management across various tumor types, including lung, breast, colorectal, and prostate cancers. They are used for early detection, prognostic stratification, therapy selection based on actionable mutations, and surveillance for disease recurrence or resistance. The adoption of liquid biopsy technologies has been further accelerated by advances in next-generation sequencing (NGS) and digital PCR, which have significantly improved the sensitivity and specificity of detecting rare tumor-derived signals in blood.

Among the various analytes, ctDNA has reached the greatest level of clinical validation (Wan et al., 2017). ctDNA refers to short fragments of tumor-derived DNA released into the bloodstream by apoptotic and necrotic cancer cells. These fragments carry tumor-specific mutations, copy-number changes, methylation patterns, or fragmentomics signatures. Because ctDNA can represent <1% of total cell-free DNA, highly sensitive detection platforms — including digital droplet PCR (ddPCR), Safe-SeqS, and next-generation sequencing (NGS) — are required for reliable analysis (Merker et al., 2018).

Early studies established ctDNA as a prognostic marker. In colorectal cancer, postoperative ctDNA positivity was associated with recurrence rates exceeding 70%, compared with ~10% among ctDNA-negative patients (Tie et al., 2015; Wang et al., 2019). Similar findings have been demonstrated in lung cancer (Abbosh et al., 2017) and breast cancer (Rohanizadegan, 2018). However, prognostication alone is insufficient for clinical adoption; ctDNA must guide **actionable interventions** that improve survival.

The rationale for ctDNA-guided therapy lies in three strategies:

1. **De-escalation**: Sparing ctDNA-negative patients unnecessary adjuvant chemotherapy.
2. **Escalation**: Intensifying therapy for ctDNA-positive patients, aiming to eradicate minimal residual disease (MRD).
3. **Adaptive therapy**: Using ctDNA to detect resistance mutations in metastatic disease, enabling rechallenge or switching before clinical progression (Siravegna et al., 2019)

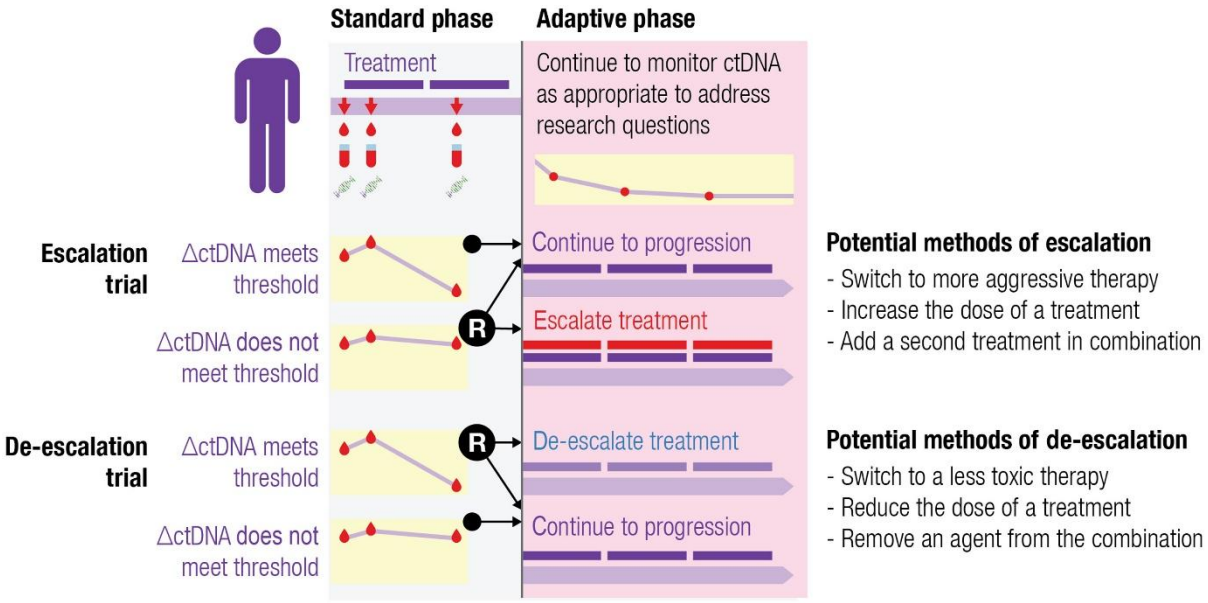

Figure 1: principles of adaptive clinical trials (Sanz-Garcia et al., 2022)

Despite these promising developments, a critical question remains: to what extent do liquid biopsies translate into improved survival outcomes for cancer patients? While many studies have demonstrated the diagnostic and predictive value of liquid biopsies, the evidence for the impact of treatment plans guided by liquid biopsies (such as escalation de-escalation studies) on long-term clinical endpoints, particularly overall survival (OS) and progression-free survival (PFS), remains fragmented and under-evaluated.

This review aims to assess the efficacy of approaches guided by liquid biopsies in improving survival outcomes in cancer patients. By synthesizing current clinical evidence across cancer types and different clinical trials, this review seeks to clarify the clinical value of liquid biopsies beyond diagnostic utility and to provide insights into their potential role in personalized oncology.

Methods

We conducted a comprehensive literature search on PubMed and Scopus, with the terms "circulating tumor DNA"OR "ctDNA"[Title/Abstract] AND "survival", for original peer-reviewed articles published between 2001 and 2025. Inclusion criteria were: (1) prospective use of ctDNA to guide

treatment allocation; (2) interventional intent (escalation, de-escalation, or adaptive switching); and (3) reported or planned survival outcomes (RFS/DFS/PFS/OS). Studies limited to analytical validation without therapy guidance were excluded.

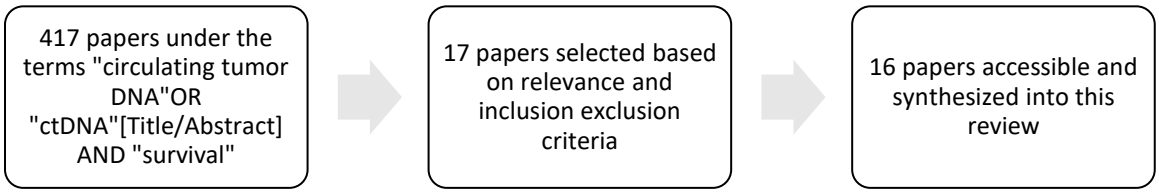

Figure 2: selection process for studies included in this review

Among the 417 results of the original literature search, we selected 17 eligible papers, one of which (Zatarain-Barrón et al., 2021) we could not access. We conducted a narrative synthesis of the sixteen interventional ctDNA-guided studies, encompassing completed RCTs, interventional cohorts, nationwide registries, and protocols.

For each study, we extracted author/year, cancer type, design, interventions, assay type (tumor-informed vs plasma-only; ddPCR vs NGS), timing of sampling (e.g., 4–7 weeks postsurgery; end-of-treatment; serial surveillance), endpoints, and survival outcomes. Given heterogeneity in assays, timelines, and endpoints, we present a narrative synthesis grouped into: early-stage CRC, post-metastasectomy CRC, metastatic CRC, and non-CRC solid tumors. Where helpful, we reference external context trials/registries (e.g., GALAXY, VEGA, ALTAIR, IMvigor010) to situate the findings.

Results

Early-Stage Colorectal Cancer

DYNAMIC trial: mature evidence of de-escalation without survival compromise

The most robust evidence for ctDNA-guided treatment comes from the DYNAMIC trial, which randomized 455 patients with resected stage II colon cancer to either ctDNA-guided adjuvant chemotherapy (ACT) or standard clinicopathologic decision-making (Tie et al., 2022). In the ctDNA-guided group, only patients with postoperative ctDNA positivity at 4 or 7 weeks received ACT, whereas all others underwent observation. This strategy reduced chemotherapy administration from 28% to 15%, while achieving noninferior 2-year recurrence-free survival (RFS) (93.5% vs. 92.4%).

Extended follow-up confirmed these findings. At five years, RFS remained virtually identical between arms (88% vs. 87%), as did overall survival (OS) (93.8% vs. 93.3%) (Tie et al., 2025). Importantly, ctDNA dynamics carried strong prognostic implications: patients with ctDNA clearance following ACT had estimated 5-year RFS of ~97%, whereas those with persistent ctDNA had near-universal relapse. These results firmly establish that ctDNA-guided de-escalation is oncologically safe and that ctDNA clearance may serve as a surrogate endpoint for long-term benefit.

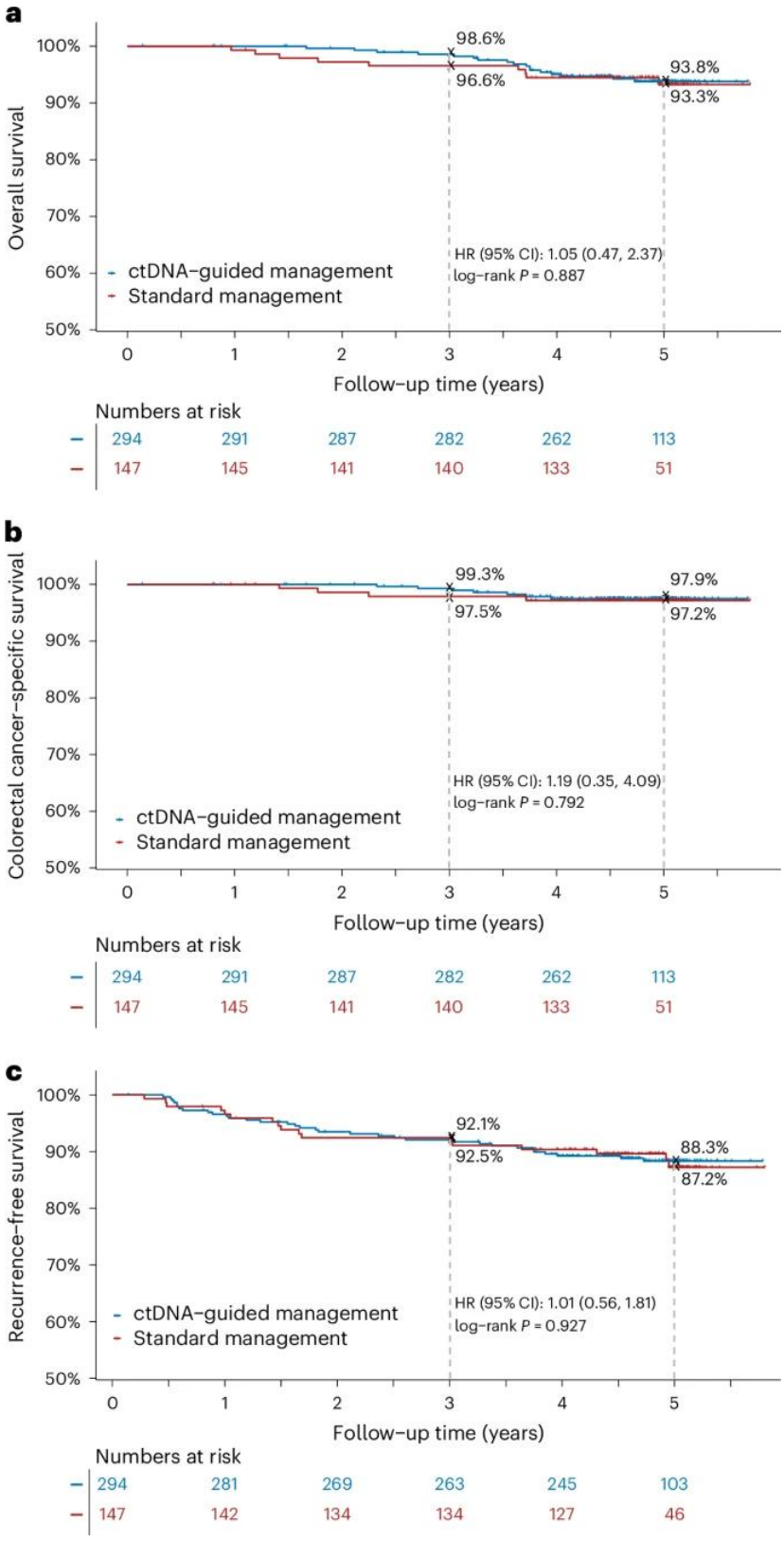

Figure 3: Kaplan-Meier estimates in the intention-to-treat population (Tie et al., 2025)

Ongoing randomised protocols: testing escalation and broader de-escalation

Several large-scale trials are underway to extend the paradigm of ctDNA-guided treatment beyond stage II disease:

- CIRCULATE (Folprecht et al., 2022) randomises ctDNA-positive patients with stage II colon cancer to ACT versus observation, aiming to demonstrate predictive benefit of chemotherapy in this group. Survival results are awaited.
- MEDOCC-CrEATE (Schraa et al., 2020) adopts a trial-within-cohort design in the Netherlands, comparing ctDNA-informed ACT allocation with standard follow-up. Two- and five-year DFS and OS are prespecified secondary endpoints.
- TRACC Part C (Slater et al., 2023) is a UK-based randomised noninferiority trial (N=1621 planned), testing whether ctDNA-guided de-escalation in ctDNA-negative stage II/III CRC is not inferior to standard ACT in terms of 3-year DFS.

Although survival results are not yet available, these trials will determine whether ctDNA-guided escalation and de-escalation translate into improvements in DFS and OS across broader patient populations.

Escalation and Adaptation in Colorectal and Rectal Cancer

REVISE: intensification in persistent ctDNA-positive stage III colon cancer

The REVISE trial is a multicentre phase II study that randomises stage III colon cancer patients who remain ctDNA-positive after two cycles of XELOX to either continue XELOX or intensify to FOLFOXIRI (Zhou, Huang, et al., 2025). Its primary endpoint is ctDNA clearance, with DFS and OS as key secondaries. As results are not yet reported, the trial remains hypothesis-generating but is designed to test whether treatment intensification for persistent MRD can alter survival trajectories.

CINTS-R: risk-adapted neoadjuvant therapy in rectal cancer

The CINTS-R trial is an open-label randomised study enrolling 470 patients with locally advanced rectal cancer (Zhou, Zhang, et al., 2025). The experimental arm uses ctDNA to stratify patients to total neoadjuvant therapy (TNT), modified chemoradiotherapy, or immunotherapy, while controls receive

standard chemoradiotherapy. The primary endpoint is 2-year disease-related treatment failure, with DFS and OS as secondary outcomes. No survival data are currently available.

OPTIMISE: ctDNA after resection of colorectal metastases

The OPTIMISE study investigates ctDNA-guided ACT following radical-intent treatment of colorectal metastases. Interim results reported feasibility of stratifying treatment by ctDNA status, but survival outcomes remain pending (Callesen et al., 2023). Given the high baseline recurrence risk after metastasectomy, ctDNA-guided escalation has the potential for significant survival impact once mature data are reported.

Metastatic Colorectal Cancer

CHRONOS: ctDNA-selected anti-EGFR rechallenge

The CHRONOS trial (Sartore-Bianchi et al., 2022) evaluated ctDNA as a selection tool for panitumumab rechallenge in RAS wild-type metastatic CRC patients who had previously benefited from EGFR blockade. By excluding patients with ctDNA-detected RAS/BRAF/EGFR-ECD resistance mutations, the study enriched for those likely to respond. Among 27 treated patients, the objective response rate (ORR) was 30%, with disease control in 63%. Median PFS and OS, while secondary outcomes, demonstrated clinically meaningful benefit compared with historical controls. This trial illustrates that ctDNA-guided rechallenge can restore sensitivity and confer survival benefit in a carefully selected population.

GOZILA: survival benefit from ctDNA-matched targeted therapy

The GOZILA study (Nakamura et al., 2025) is the largest real-world prospective ctDNA program, profiling more than 4,000 patients with gastrointestinal cancers. Approximately 24% received matched targeted therapy based on ctDNA findings, and survival outcomes significantly favoured the matched group. Median OS was 18.6 months with matched therapy versus 9.9 months with unmatched therapy (HR 0.54), and median PFS was 4.7 vs. 2.8 months (HR 0.65). Subgroups such as ERBB2-amplified and

MSI-high tumours had particularly high response rates (~50% and 47%, respectively). These findings provide direct population-level survival evidence that ctDNA-enabled molecular matching improves outcomes in advanced disease.

Non-Colorectal Solid Tumours

APPLE: early ctDNA-triggered switch in EGFR-mutant NSCLC

The APPLE trial (Remon et al., 2023) tested whether plasma EGFR T790M monitoring could inform early switching from gefitinib to osimertinib in EGFR-mutant NSCLC. Patients in Arm B (ctDNA-guided switch) achieved higher 18-month PFS on osimertinib (67.2% vs. 53.5%) and a trend towards improved OS (87% vs. 77%) compared with Arm C (switch at radiographic progression). Median PFS was also longer (22.0 vs. 20.2 months). These results demonstrate that molecularly guided adaptive sequencing can extend disease control and potentially improve survival compared with radiographic criteria alone.

Dong et al. (2024): ctDNA-guided tyrosine kinase inhibitor de-escalation

In a prospective study of advanced NSCLC, Dong et al. (2024) evaluated ctDNA- and CEA-guided discontinuation of EGFR-TKI after local consolidative therapy. Patients who stopped treatment while ctDNA- and CEA-negative achieved median PFS of 18.4 months, with a 96% response rate upon retreatment when ctDNA/CEA positivity recurred (Dong et al., 2024). These findings indicate that survival is not compromised by TKI breaks in molecularly defined patients and that retreatment can re-establish control, offering a model for ctDNA-guided de-escalation in advanced disease.

MRD-guided adjuvant osimertinib (protocol)

A phase III trial design described by Wang et al. (2024) randomises MRD-positive resected EGFR-mutant NSCLC to adjuvant osimertinib versus observation. The primary endpoint is PFS, with landmark 2- and 5-year rates specified (Wang et al., 2024). No results are yet reported, but the trial directly tests whether ctDNA-positivity predicts survival benefit from adjuvant targeted therapy.

CTONG 2201 (protocol): omission of adjuvant therapy in MRD-negative NSCLC

The CTONG 2201 trial (Zhang et al., 2024) is a prospective single-arm study in which patients with two consecutive MRD-negative ctDNA results post-resection omit adjuvant therapy. The primary endpoint is 2-year DFS, designed to validate the negative predictive value of ctDNA for safely sparing therapy. Results are pending.

PADA-1: ctDNA-triggered endocrine switching in breast cance***r***

The PADA-1 trial (Berger et al., 2022) is a phase III study in ER+/HER2− metastatic breast cancer, where ctDNA detection of emerging ESR1 mutations triggers randomisation to either continue aromatase inhibitor plus palbociclib or switch to fulvestrant plus palbociclib. The primary endpoint is PFS, with survival impact to be clarified upon trial completion.

Cross-Study Synthesis

- **Established benefit (survival-neutral de-escalation):** The DYNAMIC trial demonstrates that **omitting ACT in ctDNA-negative stage II colon cancer** does not compromise long-term RFS or OS, while halving chemotherapy use.
- **Emerging evidence (escalation):** Observational and mechanistic data indicate that **persistent ctDNA strongly predicts relapse**, but whether escalation improves survival is being tested in REVISE, CINTS-R, MEDOCC-CrEATE, TRACC Part C, and CTONG 2201.
- **Metastatic disease (survival benefit):** GOZILA provides robust evidence that **ctDNA-directed matched therapy improves OS**, while CHRONOS demonstrates that ctDNA-based selection can enable **clinically meaningful rechallenge**.
- **Non-colorectal tumours (promising signals):** APPLE and Dong et al. show that ctDNA-guided adaptive sequencing and de-escalation in NSCLC can **prolong PFS** and preserve retreatment efficacy, while PADA-1 explores similar adaptation in metastatic breast cancer.

Collectively, the evidence supports ctDNA as an **actionable biomarker** capable of influencing survival outcomes through de-escalation in early-stage disease, molecular matching in advanced disease, and adaptive strategies in lung and breast cancers. The next generation of randomised escalation and MRD-adaptive trials will determine whether ctDNA-guided therapy can **improve overall survival across solid tumours**.

Discussion

De-escalation is now evidence-based in stage II CRC. DYNAMIC demonstrated that withholding ACT in ctDNA-negative patients reduces toxicity and resource use without sacrificing survival over 5 years (Tie et al., 2022; Tie et al., 2025). This is a rare example of a biomarker-guided de-implementation that does not compromise oncologic outcomes and aligns with patient-centered care.

Escalation strategies remain to be proven in randomized settings. Observational analyses (e.g., GALAXY) identify ctDNA as the strongest post-operative predictor of relapse (Nakamura et al., 2020), and ctDNA clearance associates with favorable outcomes—yet causality (i.e., that escalating therapy because ctDNA is positive improves survival) requires trials like REVISE, ALTAIR, and CINTS-R. These studies will test whether acting on persistence or rise in ctDNA can convert poor-prognosis molecular positivity into durable disease control.

In metastatic disease, predictive utility is established. CHRONOS proves that ctDNA-negative for resistance mutations selects patients who benefit from anti-EGFR rechallenge; GOZILA shows that ctDNA-matched targeted therapies improve OS across GI cancers (Nakamura et al., 2025; Sartore-Bianchi et al., 2022). These results generalize a model wherein ctDNA guides who should receive what therapy and when.

Lung and breast cancers illustrate ctDNA's versatility. APPLE demonstrates earlier, ctDNA-triggered switching can improve PFS in EGFR-mutant NSCLC, while TKI de-escalation studies show that molecular surveillance can safely pause therapy with rapid recapture upon relapse signals (Dong et al., 2024; Remon et al., 2023). PADA-1 portends a future where endocrine therapy is routinely adapted to ctDNA-detected resistance (Berger et al., 2022).

Implementation challenges persist. Assay heterogeneity—tumor-informed (higher sensitivity, slower turnaround) vs plasma-only (rapid, potentially less sensitive)—complicates comparisons and guideline crafting (Merker et al., 2018). Sampling schedules are not standardized; postoperative

windows (e.g., 4–7 weeks) and end-of-therapy timepoints differ across trials and affect sensitivity for MRD detection. Endpoints vary (RFS/DFS vs OS), and many trials are underpowered for OS; GOZILA is a notable exception showing OS benefit with matched therapy. Cost-effectiveness and equitable access must be addressed to prevent disparities as ctDNA assays enter routine care. Finally, patient experience matters: negative ctDNA may reassure and support de-escalation; positive ctDNA without radiographic disease can induce anxiety—necessitating clear counseling and shared decision-making.

Future directions include assay harmonization and proficiency testing to enable cross-platform comparability; integration with methylation and fragmentomics (Klein et al., 2021) to improve sensitivity; and AI-driven models leveraging longitudinal ctDNA dynamics for individualized relapse risk and therapy timing. From a policy standpoint, phase III data will inform NCCN/ESMO recommendations, reimbursement, and broader adoption.

Conclusion

ctDNA-guided strategies have moved beyond prognostication to actionable interventions. De-escalation is validated in early-stage colorectal cancer. Predictive applications in metastatic disease are effective. Escalation trials and non-CRC applications are promising but immature.

ctDNA-guided strategies have already transformed management of early-stage colorectal cancer, proving safe de-escalation with preserved survival. In metastatic settings, ctDNA enables predictive therapy selection with measurable OS benefit. Escalation strategies, lung, and breast applications are promising but immature.

Over the next five years, results from TRACC, MEDOCC-CrEATE, REVISE, CINTS-R, PADA-1 and others will determine whether ctDNA-guided therapy becomes a universal standard of care.

List of abbreviations

- ACT – Adjuvant chemotherapy
- AI – Aromatase inhibitor

- APPLE – ctDNA-guided early switch trial in NSCLC
- CAPOX – Capecitabine plus oxaliplatin
- cfDNA – Cell-free DNA
- CHRONOS – ctDNA-guided panitumumab rechallenge in metastatic colorectal cancer
- ctDNA – Circulating tumor DNA
- DFS – Disease-free survival
- EGFR – Epidermal growth factor receptor
- ER – Estrogen receptor
- FOLFOXIRI – 5-fluorouracil, leucovorin, oxaliplatin, irinotecan
- GALAXY – CIRCULATE-Japan ctDNA registry
- GOZILA – Nationwide Japanese registry of ctDNA-guided precision oncology
- HR – Hazard ratio
- MRD – Minimal residual disease
- MSI – Microsatellite instability
- mCRC – Metastatic colorectal cancer
- NCCN – National Comprehensive Cancer Network
- NSCLC – Non-small cell lung cancer
- ORR – Objective response rate
- OS – Overall survival
- PADA-1 – ctDNA-guided endocrine therapy switch trial in ER+/HER2– metastatic breast cancer
- PFS – Progression-free survival
- RCT – Randomized controlled trial
- RFS – Recurrence-free survival
- TRACC – UK-based ctDNA-guided adjuvant trial in colorectal cancer
- TNT – Total neoadjuvant therapy

References

Abbosh, C., Birkbak, N. J., Wilson, G. A., Jamal-Hanjani, M., Constantin, T., Salari, R., Le Quesne, J., Moore, D. A., Veeriah, S., Rosenthal, R., Marafioti, T., Kirkizlar, E., Watkins, T. B. K., McGranahan, N., Ward, S., Martinson, L., Riley, J., Fraioli, F., Al Bakir, M.,…Swanton, C. (2017). Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*, *545*(7655), 446-451. https://doi.org/10.1038/nature22364

Berger, F., Marce, M., Delaloge, S., Hardy-Bessard, A. C., Bachelot, T., Bièche, I., Pradines, A., De La Motte Rouge, T., Canon, J. L., André, F., Arnould, L., Clatot, F., Lemonnier, J., Marques, S., & Bidard, F. C. (2022). Randomised, open-label, multicentric phase III trial to evaluate the safety and efficacy of palbociclib in combination with endocrine therapy, guided by ESR1 mutation monitoring in oestrogen receptor-positive, HER2-negative metastatic breast cancer patients: study design of PADA-1. *BMJ Open*, *12*(3), e055821. https://doi.org/10.1136/bmjopen-2021-055821

Callesen, L. B., Hansen, T. F., Andersen, R. F., Pallisgaard, N., Kramer, S., Schlander, S., Rafaelsen, S. R., Boysen, A. K., Jensen, L. H., Jakobsen, A., & Spindler, K. G. (2023). ctDNA-guided adjuvant treatment after radical-intent treatment of metastatic spread from colorectal cancer-the first interim results from the OPTIMISE study. *Acta Oncol*, *62*(12), 1742-1748. https://doi.org/10.1080/0284186X.2023.2259083

Dong, S., Wang, Z., Zhang, J. T., Yan, B., Zhang, C., Gao, X., Sun, H., Li, Y. S., Yan, H. H., Tu, H. Y., Liu, S. M., Gong, Y., Gao, W., Huang, J., Liao, R. Q., Lin, J. T., Ke, E. E., Xu, Z., Zhang, X.,…Wu, Y. L. (2024). Circulating Tumor DNA-Guided De-Escalation Targeted Therapy for Advanced Non-Small Cell Lung Cancer: A Nonrandomized Controlled Trial. *JAMA Oncol*, *10*(7), 932-940. https://doi.org/10.1001/jamaoncol.2024.1779

Folprecht, G., Reinacher-Schick, A., Weitz, J., Lugnier, C., Kraeft, A. L., Wisser, S., Aust, D. E., Weiss, L., von Bubnoff, N., Kramer, M., Thiede, C., & Tannapfel, A. (2022). The CIRCULATE Trial: Circulating Tumor DNA Based Decision for Adjuvant Treatment in Colon Cancer Stage II Evaluation (AIO-KRK-0217). *Clin Colorectal Cancer*, *21*(2), 170-174. https://doi.org/10.1016/j.clcc.2021.09.005

Klein, E. A., Richards, D., Cohn, A., Tummala, M., Lapham, R., Cosgrove, D., Chung, G., Clement, J., Gao, J., Hunkapiller, N., Jamshidi, A., Kurtzman, K. N., Seiden, M. V., Swanton, C., & Liu, M. C. (2021). Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. *Ann Oncol*, *32*(9), 1167-1177. https://doi.org/10.1016/j.annonc.2021.05.806

Merker, J. D., Oxnard, G. R., Compton, C., Diehn, M., Hurley, P., Lazar, A. J., Lindeman, N., Lockwood, C. M., Rai, A. J., Schilsky, R. L., Tsimberidou, A. M., Vasalos, P., Billman, B. L., Oliver, T. K., Bruinooge, S. S., Hayes, D. F., & Turner, N. C. (2018). Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol*, *36*(16), 1631-1641. https://doi.org/10.1200/JCO.2017.76.8671

Nakamura, Y., Ozaki, H., Ueno, M., Komatsu, Y., Yuki, S., Esaki, T., Taniguchi, H., Sunakawa, Y., Yamaguchi, K., Kato, K., Denda, T., Nishina, T., Takahashi, N., Satoh, T., Yasui, H., Satake, H., Oki, E., Kato, T., Ohta, T.,…Yoshino, T. (2025). Targeted therapy guided by circulating tumor DNA

analysis in advanced gastrointestinal tumors. *Nat Med*, *31*(1), 165-175. https://doi.org/10.1038/s41591-024-03244-8

Nakamura, Y., Taniguchi, H., Ikeda, M., Bando, H., Kato, K., Morizane, C., Esaki, T., Komatsu, Y., Kawamoto, Y., Takahashi, N., Ueno, M., Kagawa, Y., Nishina, T., Kato, T., Yamamoto, Y., Furuse, J., Denda, T., Kawakami, H., Oki, E.,…Yoshino, T. (2020). Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan GI-SCREEN and GOZILA studies. *Nat Med*, *26*(12), 1859-1864. https://doi.org/10.1038/s41591-020-1063-5

Remon, J., Besse, B., Aix, S. P., Callejo, A., Al-Rabi, K., Bernabe, R., Greillier, L., Majem, M., Reguart, N., Monnet, I., Cousin, S., Garrido, P., Robinet, G., Garcia Campelo, R., Madroszyk, A., Mazieres, J., Curcio, H., Wasag, B., Pretzenbacher, Y.,…Dziadziuszko, R. (2023). Osimertinib treatment based on plasma T790M monitoring in patients with EGFR-mutant non-small-cell lung cancer (NSCLC): EORTC Lung Cancer Group 1613 APPLE phase II randomized clinical trial. *Ann Oncol*, *34*(5), 468-476. https://doi.org/10.1016/j.annonc.2023.02.012

Rohanizadegan, M. (2018). Analysis of circulating tumor DNA in breast cancer as a diagnostic and prognostic biomarker. *Cancer Genet*, *228-229*, 159-168. https://doi.org/10.1016/j.cancergen.2018.02.002

Sanz-Garcia, E., Zhao, E., Bratman, S. V., & Siu, L. L. (2022). Monitoring and adapting cancer treatment using circulating tumor DNA kinetics: Current research, opportunities, and challenges. *Sci Adv*, *8*(4), eabi8618. https://doi.org/10.1126/sciadv.abi8618

Sartore-Bianchi, A., Pietrantonio, F., Lonardi, S., Mussolin, B., Rua, F., Crisafulli, G., Bartolini, A., Fenocchio, E., Amatu, A., Manca, P., Bergamo, F., Tosi, F., Mauri, G., Ambrosini, M., Daniel, F., Torri, V., Vanzulli, A., Regge, D., Cappello, G.,…Bardelli, A. (2022). Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial. *Nat Med*, *28*(8), 1612-1618. https://doi.org/10.1038/s41591-022-01886-0

Schraa, S. J., van Rooijen, K. L., van der Kruijssen, D. E. W., Rubio Alarcon, C., Phallen, J., Sausen, M., Simmons, J., Coupe, V. M. H., van Grevenstein, W. M. U., Elias, S., Verkooijen, H. M., Lacle, M. M., Bosch, L. J. W., van den Broek, D., Meijer, G. A., Velculescu, V. E., Fijneman, R. J. A., Vink, G. R., Koopman, M., & group, P.-M. (2020). Circulating tumor DNA guided adjuvant chemotherapy in stage II colon cancer (MEDOCC-CrEATE): study protocol for a trial within a cohort study. *BMC Cancer*, *20*(1), 790. https://doi.org/10.1186/s12885-020-07252-y

Siravegna, G., Mussolin, B., Venesio, T., Marsoni, S., Seoane, J., Dive, C., Papadopoulos, N., Kopetz, S., Corcoran, R. B., Siu, L. L., & Bardelli, A. (2019). How liquid biopsies can change clinical practice in oncology. *Ann Oncol*, *30*(10), 1580-1590. https://doi.org/10.1093/annonc/mdz227

Slater, S., Bryant, A., Chen, H. C., Begum, R., Rana, I., Aresu, M., Peckitt, C., Zhitkov, O., Lazaro-Alcausi, R., Borja, V., Powell, R., Lowery, D., Hubank, M., Rich, T., Anandappa, G., Chau, I., Starling, N., & Cunningham, D. (2023). ctDNA guided adjuvant chemotherapy versus standard of care adjuvant chemotherapy after curative surgery in patients with high risk stage II or stage III colorectal cancer: a multi-centre, prospective, randomised control trial (TRACC Part C). *BMC Cancer*, *23*(1), 257. https://doi.org/10.1186/s12885-023-10699-4

Tie, J., Cohen, J. D., Lahouel, K., Lo, S. N., Wang, Y., Kosmider, S., Wong, R., Shapiro, J., Lee, M., Harris, S., Khattak, A., Burge, M., Harris, M., Lynam, J., Nott, L., Day, F., Hayes, T., McLachlan, S. A., Lee, B.,…Investigators, D. (2022). Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. *N Engl J Med*, *386*(24), 2261-2272. https://doi.org/10.1056/NEJMoa2200075

Tie, J., Kinde, I., Wang, Y., Wong, H. L., Roebert, J., Christie, M., Tacey, M., Wong, R., Singh, M., Karapetis, C. S., Desai, J., Tran, B., Strausberg, R. L., Diaz, L. A., Jr., Papadopoulos, N., Kinzler, K. W., Vogelstein, B., & Gibbs, P. (2015). Circulating tumor DNA as an early marker of therapeutic response in patients with metastatic colorectal cancer. *Ann Oncol*, *26*(8), 1715-1722. https://doi.org/10.1093/annonc/mdv177

Tie, J., Wang, Y., Lo, S. N., Lahouel, K., Cohen, J. D., Wong, R., Shapiro, J. D., Harris, S. J., Khattak, A., Burge, M. E., Lee, M., Harris, M., McLachlan, S. A., Horvath, L., Karapetis, C., Shannon, J., Singh, M., Yip, D., Ananda, S.,…Gibbs, P. (2025). Circulating tumor DNA analysis guiding adjuvant therapy in stage II colon cancer: 5-year outcomes of the randomized DYNAMIC trial. *Nat Med*, *31*(5), 1509-1518. https://doi.org/10.1038/s41591-025-03579-w

Wan, J. C. M., Massie, C., Garcia-Corbacho, J., Mouliere, F., Brenton, J. D., Caldas, C., Pacey, S., Baird, R., & Rosenfeld, N. (2017). Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer*, *17*(4), 223-238. https://doi.org/10.1038/nrc.2017.7

Wang, K., Ma, J., Luo, W., Yin, Q., Zhang, X., Li, Y., & Zhang, H. (2024). Adjuvant osimertinib therapy guided by ctDNA-assessed MRD in resected EGFR-mutated stage IA-IIA non-small-cell lung cancer: a randomized clinical trial study protocol. *Am J Cancer Res*, *14*(11), 5427-5433. https://doi.org/10.62347/ifrh7248

Wang, Y., Li, L., Cohen, J. D., Kinde, I., Ptak, J., Popoli, M., Schaefer, J., Silliman, N., Dobbyn, L., Tie, J., Gibbs, P., Tomasetti, C., Kinzler, K. W., Papadopoulos, N., Vogelstein, B., & Olsson, L. (2019). Prognostic Potential of Circulating Tumor DNA Measurement in Postoperative Surveillance of Nonmetastatic Colorectal Cancer. *JAMA Oncol*, *5*(8), 1118-1123. https://doi.org/10.1001/jamaoncol.2019.0512

Zatarain-Barrón, Z. L., Cardona, A. F., Díaz-García, D., Trejo Rosales, R., Rojas, L., Cruz-Rico, G., Nagy, R., Cabrera, L., Vargas, C., Saam, J., Barrón, F., & Arrieta, O. (2021). Cell-Free Circulating Tumor DNA Improves Standard Genotyping of Non-Small-Cell Lung Cancer and Increases Detection of Targetable Alterations in a Selected Hispanic Cohort. *Oncology*, *99*(8), 539-546. https://doi.org/10.1159/000514648

Zhang, J. T., Dong, S., Gu, W. Q., Zhao, N., Liang, Y., Tang, W. F., Liu, S. Y., Wang, F., Wang, G. S., Peng, B., Wu, N., Yan, S., Geng, G. J., Xie, Z. F., Yang, Y. L., Zhang, J. H., Zhang, T., Yang, N., Jiao, W. J.,…Wu, Y. L. (2024). Adjuvant Therapy-Free Strategy for Stage IB to IIIA Non-Small-Cell Lung Cancer Patients After Radical Resection Based on Longitudinal Undetectable Molecular Residual Disease: Prospective, Multicenter, Single-Arm Study (CTONG 2201). *Clin Lung Cancer*, *25*(1), e1-e4. https://doi.org/10.1016/j.cllc.2023.09.008

Zhou, J., Huang, J., Zhou, Z., Fan, R., Deng, X., Qiu, M., Wu, Q., & Wang, Z. (2025). Value of ctDNA in surveillance of adjuvant chemosensitivity and regimen adjustment in stage III colon cancer: a

protocol for phase II multicentre randomised controlled trial (REVISE trial). *BMJ Open*, *15*(1), e090394. https://doi.org/10.1136/bmjopen-2024-090394

Zhou, J., Zhang, X., Liu, Q., Li, Y., Wu, G., Fu, W., Yao, H., Wang, Z., Xue, H., Xu, T., Chen, W., Lu, J., Zhang, G., Wu, B., An, Y., Qiu, X., Xiao, Y., & Lin, G. (2025). Rationale and design of a multicentre randomised controlled trial on circulating tumour DNA-guided neoadjuvant treatment strategy for locally advanced rectal cancer (CINTS-R). *BMJ Open*, *15*(1), e090765. https://doi.org/10.1136/bmjopen-2024-090765