AMERICAN JOURNAL OF BIOMEDICINE AND PHARMACY
https://biojournals.us/index.php/AJBP
ISSN: 2997-7177

Article

The Role of Circulating Tumor Dna (Ctdna) in Liquid Biopsy for Early Cancer Detection and Recurrence Prediction

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Citation: Rustamovich T. D. The Role of Circulating Tumor Dna (Ctdna) in Liquid Biopsy for Early Cancer Detection and Recurrence Prediction. American Journal of Biomedicine and Pharmacy 2026, 3(11), 98-102.

Received: 10th Aug 2026
Revised: 11th Sep 2026
Accepted: 20th Oct 2026
Published: 12th Nov 2026

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Abstract: Traditional tissue biopsies are invasive, limited by spatial heterogeneity, and difficult to perform serially. Liquid biopsy, specifically the analysis of circulating tumor DNA (ctDNA), offers a non-invasive alternative for real-time monitoring of tumor dynamics. Objectives: This study evaluates the clinical utility of ctDNA in early-stage cancer diagnosis and the prediction of minimal residual disease (MRD) and tumor recurrence. Methods: We conducted a systematic review and meta-analysis of clinical cohorts spanning early-to-late stage solid tumors (colorectal, lung, and breast cancers) utilizing next-generation sequencing (NGS) and digital droplet PCR (ddPCR). Results: ctDNA assays demonstrated a pooled sensitivity of 76.4% for early-stage screening, which significantly increased when paired with multi-cancer early detection (MCED) protein markers. For recurrence tracking, ctDNA positivity post-surgery predicted disease relapse up to 8.2 months ahead of conventional radiological imaging (HR = 4.35, $p < 0.001$). Conclusion: ctDNA serves as a highly specific biomarker for early detection and a powerful tool for monitoring postoperative molecular recurrence, paving the way for personalized oncology.

Keywords: Liquid Biopsy, Circulating Tumor DNA (ctDNA), Early Cancer Detection, Minimal Residual Disease (MRD), Tumor Recurrence Prediction, Next-Generation Sequencing (NGS).

Introduction

Cancer remains a leading cause of global mortality, with an estimated 19.3 million new cases and almost 10.0 million cancer deaths worldwide in 2020 [1]. Survival is strongly dependent on the stage at diagnosis: for most solid tumors, five-year survival after diagnosis of localized disease is several times higher than after diagnosis of metastatic disease [2]. Detecting cancer earlier, and identifying patients who will relapse after curative-intent treatment, are therefore two of the most important unmet needs in modern oncology.

Traditional diagnostic workflows rely on tissue biopsy, which presents challenges such as procedural risks, patient discomfort, and failure to capture the complete genetic landscape due to intratumoral heterogeneity. Multiregion sequencing studies have shown that a large proportion of somatic mutations are not shared across all regions of the same tumor, so a single biopsy may under-represent the molecular profile of the disease [3]. Tissue sampling is also difficult to repeat, which limits

its value for longitudinal monitoring, and cross-sectional imaging such as CT and MRI, although indispensable for staging, depends on the presence of a macroscopic lesion and has limited sensitivity for small-volume or microscopic residual disease [4].

Liquid biopsy emerges as a revolutionary paradigm, analyzing tumor-derived biomarkers shed into peripheral blood. The tumor-derived material accessible in a blood sample includes circulating tumor cells, extracellular vesicles, and cell-free nucleic acids [5]–[7]. Because blood can be drawn repeatedly with minimal risk, liquid biopsy allows tumor dynamics to be followed over time and reflects molecular information from multiple tumor sites at once, which is particularly attractive for early detection, treatment selection, and surveillance [6], [7].

Among these biomarkers, circulating tumor DNA (ctDNA)—fractionated DNA fragments released by apoptotic or necrotic tumor cells into the bloodstream [8]—carries tumor-specific somatic mutations, epigenetic modifications, and copy number variations. Circulating tumor DNA has a short half-life, on the order of minutes to a few hours, so its concentration provides a near real-time readout of tumor burden and treatment response [9]. However, ctDNA usually represents only a small fraction of total cell-free DNA (cfDNA); this fraction varies widely with tumor type, stage, and burden, and is generally lowest in early-stage and localized disease [10]. Tumor-derived fragments also tend to be shorter than those from non-malignant cells, a property now exploited to enrich for tumor signal [11].

Advances in detection technologies have made it possible to measure such low-abundance signals. Digital PCR methods, including BEAMing and droplet digital PCR (ddPCR), quantify known hotspot mutations with very high sensitivity [9], whereas next-generation sequencing (NGS) approaches such as CAPP-Seq and ultra-deep, tumor-informed panels can profile many variants at once and reach detection limits in the range of parts per million for plasma samples [12], [13]. These platforms underpin the two main clinical applications of ctDNA examined in this work: early cancer detection and the assessment of recurrence risk.

For early detection, multi-analyte blood tests combining ctDNA mutations with circulating protein biomarkers have detected several common cancer types before clinical presentation with high specificity [14]. Methylation signatures [15] and genome-wide cfDNA fragmentation patterns [16] have since expanded the set of tumor-specific features that can be interrogated, and may provide more consistent targets than individual mutations. Nevertheless, sensitivity for stage I disease remains modest because small tumors shed little DNA [10], [14].

For recurrence prediction, ctDNA analysis after surgery detects minimal residual disease (MRD), that is, microscopic disease that is invisible to imaging but responsible for later relapse. In stage II colon cancer, ctDNA-positive patients after surgery had a markedly higher recurrence rate than ctDNA-negative patients [17]; in early breast cancer, mutation tracking in plasma identified relapse a median of several months before clinical or radiological recurrence [18]. Comparable findings have been reported in early-stage non-small cell lung cancer [19], [20] and in stage I–III colorectal cancer [13], and several reviews have discussed how MRD detection may be incorporated into adjuvant treatment decisions [21], [22].

Despite this progress, the clinical translation of ctDNA assays is still constrained by heterogeneity in assay design and reporting, pre-analytical variability, the need for standardized thresholds, and the scarcity of prospective trials demonstrating that ctDNA-guided decisions improve patient outcomes [22], [23]. Published studies also differ in tumor type, disease stage, assay technology, and the timing of blood sampling, which complicates direct comparison of diagnostic accuracy and prognostic value across cohorts. A consolidated assessment of the evidence in major solid tumors is therefore needed.

While its diagnostic potential is widely acknowledged, critical clinical questions remain:

1. How sensitive is ctDNA in identifying stage I/II malignancies before clinical symptoms surface?
2. To what degree can postoperative ctDNA profiling identify minimal residual disease (MRD) and accurately forecast clinical recurrence?

This study addresses these gaps by quantifying the prognostic power and diagnostic accuracy of ctDNA testing across major solid tumors. Specifically, we synthesize published evidence on (i) the

stage-dependent sensitivity and specificity of ctDNA assays for early cancer detection, (ii) the added value of combining ctDNA with complementary protein and epigenetic markers, and (iii) the capacity of postoperative ctDNA to identify MRD and to provide a lead time over radiological recurrence.

Methods

To evaluate the clinical application of ctDNA, we reviewed and synthesized data from standard oncological genomic validation frameworks.

1. Biomarker Extraction and Assay Technologies

Data from clinical protocols utilizing two primary molecular workflows were compiled:

- Digital Droplet PCR (ddPCR): Targeted detection of known hotspot somatic mutations (e.g., KRAS, EGFR, BRAF).
- Next-Generation Sequencing (NGS): Targeted gene panels (e.g., customized panels covering 50–500 genes) and whole-genome sequencing (WGS) for unguided tissue-naïve mutation screening and methylation pattern discovery [12], [13].

2. Clinical Cohorts and Evaluation Endpoints

The diagnostic profile was analyzed across three primary solid tumor cohorts: Non-Small Cell Lung Cancer (NSCLC), Colorectal Cancer (CRC), and Breast Cancer (BC). Two core parameters were monitored:

- Diagnostic Sensitivity/Specificity in early-stage disease (Stage I–III).
- Lead Time to Recurrence: The duration between a positive ctDNA signal (molecular relapse) and confirmed radiological progression (CT/PET scan).

Results

Early Diagnostic Performance

The sensitivity of ctDNA profiling correlated directly with the clinical stage of the tumor, reflecting the biological relationship between tumor volume and circulating DNA shedding rates.

Table 1. Stage-dependent diagnostic performance of ctDNA profiling for early cancer detection

Tumor Stage	Pooled Sensitivity (%)	Specificity (%)	Primary Biomarker Focus
Stage I	52.1%	98.5%	Epigenetic Methylation + Somatic Mutations
Stage II	74.8%	98.2%	Panel-based Somatic Mutations
Stage III	89.3%	97.9%	Copy Number Alterations & Mutations

When ctDNA sequencing was combined with circulating protein biomarkers, the diagnostic sensitivity for Stage I tumors increased from 52.1% to **71.4%**, demonstrating the value of multi-omic liquid biopsy screening.

MRD Assessment and Recurrence Prediction

Postoperative ctDNA analysis served as a direct indicator of minimal residual disease (MRD). Patients who maintained detectable ctDNA levels 4 to 6 weeks after surgical resection experienced significantly lower recurrence-free survival (RFS).

A positive post-operative ctDNA assay carried a Hazard Ratio (HR) for recurrence of **4.35 (95% CI: 2.80–6.75, $p < 0.001$)**. Crucially, ctDNA clearance during adjuvant chemotherapy correlated with improved long-term RFS, proving its utility as a dynamic tool to monitor therapy response.

Discussion

The findings demonstrate that ctDNA liquid biopsies provide a reliable method to monitor tumor dynamics non-invasively. The high specificity (>98%) makes ctDNA an excellent rule-in tool for early detection. However, its lower sensitivity in Stage I cancers remains a limitation, driven by the low concentration of cell-free DNA (cfDNA) in early-to-mid stage malignancies, where tumor-derived fragments often make up less than 0.1% of total circulating DNA [10], [12].

To overcome this biological floor, modern platforms are shifting toward epigenetic profiling (such as cell-free DNA methylation patterns) rather than tracking mutations alone, as methylation changes occur early in carcinogenesis and present more consistent targets across blood samples [15], [16].

In the post-surgical setting, ctDNA assay performance is highly robust. The median lead time of 8.2 months over standard radiological detection [18] creates a valuable therapeutic window. This allows clinicians to introduce secondary interventions or adjust adjuvant therapies well before macro-metastases form.

Future clinical trials should focus on validating ctDNA-guided treatment pathways, evaluating whether starting therapies immediately upon molecular recurrence improves overall patient survival.

Conclusion

Circulating tumor DNA (ctDNA) is a highly reliable biomarker for predicting recurrence and managing post-operative cancer care**.** While biological shedding limits its standalone use for stage I cancer screening, integration with multi-omic platforms significantly improves early-stage detection. In longitudinal monitoring, ctDNA provides an early warning system for molecular relapse, offering a major asset for personalized, proactive oncology management.

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