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Review article

Evaluating the diagnostic power of liquid biopsy in precision Oncology: A narrative review of progress, limitations, and perspectives.

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ABSTRACT

In our world today, cancer is one of the most significant challenges to global health, with high morbidity rates. The emergence of liquid biopsy has fundamentally redefined the landscape of precision oncology, transitioning from a theoretical blood-based alternative to an essential clinical tool in precision oncology. where its utility offered a minimally invasive technique in cancer analysis through tumor markers. Liquid biopsy is a minimally invasive procedure used in cancer analysis to detect specific tumor biomarkers, specifically tracing the path of these biomarkers from benchtop discovery to their current status as FDA-cleared companion diagnostics.

The primary objective of the review is to provide a comprehensive synthesis of the technological, clinical, and regulatory evolution of liquid biopsy over the past quarter century, and to synthesize recent evidence regarding its role in early cancer detection and therapy response prediction. This review emphasizes the transformative impact of ctDNA in detecting minimal residual disease (MRD) and monitoring real-time clonal evolution, which has enabled clinicians to pivot therapies before radiographic progression.

However, to transition this technology from a secondary monitoring tool to a primary screening tool, future research must prioritize the standardization of the pre-analytical protocols and multiple trials so that by bridging the gap between high-tech research and global accessibility, liquid biopsy will have the potential to democratize precision medicine and significantly improve survival outcomes on a global scale.

Keywords: *Liquid biopsy, circulating tumor DNA, circulating tumor cells, cancer diagnostics, cancer, breast cancer, precision oncology.*
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INTRODUCTION

Cancer remains a major global health challenge, accounting for nearly 10 million deaths in 2020 — about one in six deaths worldwide. [1] With millions of new cancer cases diagnosed each year, early detection and timely treatment can make a significant difference in saving lives and improving outcomes.[2]

Conventional diagnostic methods such as imaging (CT, PET-CT, MRI) and tissue biopsies remain essential for cancer detection, staging, and monitoring [3,4]. Tissue biopsies provide histopathologic confirmation and enable detailed molecular characterization, but they are invasive, often risky, and sometimes unfeasible due to anatomical constraints or poor patient condition [5]. Imaging modalities, while useful for assessing disease burden, are limited by radiation exposure, restricted sensitivity in detecting minimal residual disease, and inability to capture tumor molecular evolution [6]

The implementation of precision oncology highlighted the need for less invasive approaches that can detect tumor heterogeneity and dynamic changes over time. This paved the way for liquid biopsy, a minimally invasive technique analyzing tumor-derived material such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), and exosomes in body fluids [7].

One notable approach is liquid biopsy, a minimally invasive and easily repeatable test that involves the cytological and molecular analysis of cancer markers released by tumors into body fluids. Blood is the most commonly used source for liquid biopsy, as it offers a wide range of biological analytes — including circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), tumor-educated platelets (TEPs), circulating exosomes, DNA methylation patterns, as

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well as metabolomic and proteomic markers. Liquid biopsy analyzes circulating tumor DNA (ctDNA) in blood plasma, has been reported to be less invasive and effective for comprehensive genetic analysis of heterogeneous solid tumors, offering a promising alternative to traditional tissue biopsy. By capturing tumor-derived genetic alterations shed into the bloodstream, liquid biopsy shows high concordance with histologic analysis for detecting EGFR mutations in NSCLC, providing an alternative technology for individualized treatment and monitoring. [14,15].

Main Components & Examples: Circulating tumor DNA (ctDNA), Circulating tumor cells (CTCs), Tumor-educated platelets (TEPs), Exosomes, DNA methylation markers, Proteomic and metabolomic markers. These components provide valuable insights into tumor genetics, progression, and response to treatment.

This review aims to evaluate how liquid biopsy addresses the limitation of tissue sampling, its efficacy in monitoring, its limitations, and its future prospects in clinical oncology. This review identifies the following key questions :

- How does a liquid biopsy reveal targetable genes?
- Clinical evidence.
- Prognostic values in identifying minimal residual disease.
- Implementation and limitations.

METHODS

Research selection: A targeted literature search was conducted to identify relevant studies for this review. The selection process was based on the following criteria:

Databases: PubMed and Google Scholar.

Search Terms: 'liquid biopsy',"ctDNA,' circulating tumor cells', "exosomes", and 'precision oncology'.

Years Considered: 2004 to 2025.

Language: Only English-language publications were included.

Study Types: Systematic reviews, meta-analyses, Peer-reviewed articles, clinical trials, and reports on FDA-approved assays.

Selection Criteria: Articles were chosen based on their clinical relevance to tumor genetics and disease monitoring.

DISCUSSION

1. Current applications

To date, the most established role of liquid biopsy application in the clinic is in guiding treatment selection by identifying targetable variants within a patient's tumor.

Circulating tumor DNA (ctDNA) testing has proven to be an effective alternative for tumor genomic profiling, especially when tissue samples are unavailable."[16]

The landmark FDA approval of the cobas® EGFR v2 test for detecting EGFR mutations in plasma cell-free DNA (cfDNA) from patients with advanced non-small cell lung cancer (NSCLC) paved the way for the approval of several other ctDNA-based companion diagnostic tests, including Guardant360 CDx and FoundationOne Liquid CDx. [17,18,19]

"In addition, strong evidence supports the use of ctDNA to identify resistance mechanisms to targeted therapies in solid tumors. [20,21,22,23,24,25].

For example, liquid biopsy shows high sensitivity in detecting estrogen receptor 1 (ESR1) mutations in metastatic estrogen receptor–positive breast cancer. These mutations are strongly associated with endocrine resistance, and patients harboring them may benefit from treatment with elacestrant. [26,27].

Longitudinal ctDNA can be used to guide treatment decisions in patients with metastatic colorectal cancer by capturing tumor heterogeneity and resistance to targeted agents. Recent evidence supports ctDNA-based strategies for selecting patients eligible for anti-EGFR rechallenge. [28,29]

Circulating tumor cells (CTCs) are cancer cells that circulate in the bloodstream, representing the metastatic process of cancer and serving as important analytes in liquid biopsies.[30]

Since the landmark 2004 publication by Cristofanilli and colleagues, which demonstrated the prognostic significance of CTC detection in metastatic breast cancer [31]

Multiple studies in breast, prostate, and colorectal cancers have shown that CTC detection is linked to poorer prognosis. [32,33,34].

Consequently, the Cell Search platform, which enumerates CTCs in the peripheral blood of cancer patients through EpCAM-based capture and fluorescent labeling [62], has received FDA approval for clinical use in metastatic breast, colorectal, and prostate cancers. At present, only blood-based CTC and ctDNA assays are approved for routine clinical application, whereas other liquid biopsy assays remain investigational and should be limited to research settings.[35]

Patients with locally advanced rectal cancer (LARC) are currently managed with a trimodality approach consisting of neoadjuvant chemoradiation therapy (nCRT), surgery with total mesorectal excision, and adjuvant chemotherapy when indicated. [36,37]

The cost-effectiveness of liquid biopsies (LBs) has been demonstrated in guiding treatment selection for lung cancer patients, as well as in the screening and early detection of colorectal, gastric, breast, brain, and several other cancers.

Tissue biopsy remains the gold standard for pathological diagnosis, tissue genotyping, and treatment planning in

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NSCLC [38,39,40]. However, this approach is limited by its inability to capture the clonal heterogeneity of the disease [40]. Moreover, the growing number of treatment-guiding biomarkers often requires multiple biopsies and repeated sampling to guide subsequent therapies, which is frequently unfeasible or poses risks due to the anatomical location of primary or metastatic lesions, or because of the patient's declining overall condition [61].

1. How liquid biopsy reveals targetable and actionable genes

What liquid biopsy measures and how it detects genomic alterations

Liquid biopsy specimens contain circulating tumor DNA (ctDNA), circulating tumor cells, extracellular vesicles, and cell-free RNA; among these, ctDNA is the most extensively studied analyte for clinical applications because it carries tumor-derived genetic material that can be evaluated for genomic alterations [46]. ctDNA assays can detect a broad spectrum of genomic changes, including single-nucleotide variants, insertions/deletions, copy-number alterations, and gene fusions, and emerging platforms can also assess DNA methylation signatures [45]. Detection technologies include droplet digital PCR for focused testing of known variants and next-generation sequencing approaches — targeted, whole exome, or whole genome for broad molecular profiling [45,46].

How liquid biopsy identifies targetable and actionable genes

Actionable alterations are defined as those that can be matched to an approved targeted therapy or a clinical trial option. ctDNA analysis can identify actionable oncogenic drivers, including EGFR mutations, ALK and ROS1 rearrangements, BRAF V600E, MET exon 14 alterations, PIK3CA mutations, HER2 amplifications, RET and NTRK fusions, and KRAS G12C [45]. Detection of such alterations in plasma can guide the selection of targeted therapy when tissue is inadequate or unobtainable [45]. Comprehensive cfDNA analysis has detected guideline-recommended biomarkers with high concordance to tissue genotyping [47], and plasma-based genotyping has also identified additional actionable alterations not captured by tissue genotyping alone, thereby expanding the number of patients eligible for targeted therapies [48]

How does that information guide therapy selection (treatment):

- Initial matching to targeted therapy

Comprehensive cfDNA analysis detected all guideline-recommended biomarkers with high concordance to tissue genotyping and was clinically useful for identifying patients eligible for targeted therapy [47]. In addition, plasma genotyping for EGFR sensitizing mutations was associated with outcomes to first-line EGFR-TKIs that were similar to those based on tissue genotyping. Plasma genotyping identified patients with EGFR T790M who benefited from osimertinib [49].

- Finding resistance mechanisms

An acquired EGFR C797S mutation mediates resistance to AZD9291 in NSCLC harboring EGFR T790M. The study further showed that ctDNA analysis identified C797S mutations… demonstrating the potential of plasma genotyping to detect emergent resistance mechanisms [50].

- Broad matchmaking/trial enrollment

Plasma-based genotyping identified additional actionable alterations not captured by tissue genotyping alone, thereby expanding the number of patients eligible for targeted therapies.[48]

Similarly, molecular profiling of advanced solid tumors improved the assignment of patients to genotype-matched clinical trials and was associated with improved outcomes in those who received matched treatment.[51]

2. The role in Monitoring Treatment Response and Detecting Relapse

Liquid biopsy enables real-time assessment of tumor response to therapy. Following treatment initiation, ctDNA levels typically decline if the tumor is regressing, whereas an increase in ctDNA may signal treatment resistance or disease progression earlier than conventional imaging [41].

In breast cancer, ctDNA analysis has demonstrated the ability to detect minimal residual disease (MRD) months before clinical relapse becomes apparent on imaging, providing an opportunity to adjust therapy proactively [42]. Similarly, in colorectal and lung cancers, serial ctDNA testing facilitates the early identification of emerging resistance mutations, enabling timely modifications to treatment strategies [43,44].

Thus, liquid biopsy serves as a powerful tool for long-term monitoring and early relapse detection across multiple cancer types.

3. Prognostic value and treatment monitoring

5.1) Tumor burden and dynamics

The amount of ctDNA correlates with tumor burden, and a decrease in ctDNA levels during treatment correlates with response, whereas an increase predicts resistance and disease progression; moreover, changes in ctDNA levels can anticipate radiographic response or progression.[52]

5.2) Minimal residual disease (MRD) and recurrence prediction

Detection of ctDNA after surgery was strongly associated with risk of recurrence, and patients with detectable ctDNA after adjuvant chemotherapy had significantly shorter

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relapse-free survival compared with those without detectable ctDNA. Furthermore, ctDNA detection preceded radiologic recurrence by a median of 8.7 months.[53]

4. Evidence that ctDNA-guided decisions affect outcomes.

Molecular profiling of advanced solid tumors improved the assignment of patients to genotype-matched clinical trials, and patients who received matched treatment had improved outcomes compared with those who did not receive matched therapy [51].

Nevertheless, the clinical utility of cfDNA testing depends on assay sensitivity and specificity, tumor type, and the clonal status of detected alterations [47].

5. Limitations and interpretive caveats

Low tumor fraction / false negatives: A negative plasma result does not exclude the presence of a mutation because some tumors shed little or no ctDNA into the circulation.[46]

Clonal hematopoiesis (CHIP) and non-tumor sources: The majority of variants detected in cfDNA from patients without detectable tumors were derived from clonal hematopoiesis. Common CHIP-associated genes included DNMT3A, TET2, and JAK2.[54]

Assay variability and coverage: Different ctDNA assays vary in gene coverage, analytic sensitivity, and their ability to detect copy-number alterations or gene fusions.[45]

Biological heterogeneity: Plasma genotyping reflects the mixture of tumor-derived variants shed from multiple metastatic sites [5]; therefore, distinguishing driver mutations from subclonal or CHIP-related events requires orthogonal confirmation and careful interpretation.[54]

6. Practical clinical workflow:

1. Plasma ctDNA analysis can be considered at the time of diagnosis when tumor tissue is unavailable or when biopsy is medically contraindicated, or when results are delayed [46].
2. If an actionable mutation is detected in plasma, this result can be used to guide therapy, with tissue confirmation pursued when required for regulatory or companion-diagnostic purposes [46].
3. If the plasma test is negative, tumor tissue genotyping should be performed whenever feasible.[46]
4. For follow-up, serial ctDNA analysis may be useful for monitoring treatment and minimal residual disease, and ctDNA detection preceded radiologic recurrence by a median of 8.7 months [53].

7. Prognostic Value:

Liquid biopsy also provides important prognostic insights, offering indications of cancer aggressiveness. In breast cancer, elevated ctDNA levels have been shown to correlate with poorer overall survival [41], while higher counts of CTCs consistently predict progression-free and overall survival [35]. Additionally, specific mutations detected in ctDNA, such as TP53, have been linked to relapse and may reflect a more aggressive tumor phenotype [42].

Comparable observations have been made in prostate and colorectal cancers, where higher ctDNA burden correlates with tumor stage, recurrence risk, and reduced survival [55,56]. Therefore, beyond its role in diagnosis and treatment guidance, liquid biopsy can aid in patient risk stratification and inform the intensity of follow-up care.

8. Liquid Biopsy and Reduced Need for PET-CT / Re-biopsies

Liquid biopsy offers an opportunity to decrease reliance on repeated tissue biopsies and imaging procedures by providing molecular insights through a simple blood draw. For instance, in metastatic colorectal cancer, ctDNA analysis has detected recurrence several months before conventional imaging modalities [8]. Similarly, in lung cancer, ctDNA-based minimal residual disease (MRD) testing has demonstrated high specificity (up to 87%) for relapse prediction after definitive therapy [9]. Tissue tumor profiles are subject to sampling bias, limited in capturing tumor heterogeneity, and cannot be obtained repeatedly; by contrast, ctDNA-based liquid biopsy allows repeated, less invasive sampling, enabling monitoring of treatment response and detection of emerging resistance mutations over time [10]. By complementing, and in some cases replacing, conventional imaging and biopsy procedures, liquid biopsy has the potential to reduce patient burden and healthcare costs while improving early detection of relapse.

9. Limitations: Sensitivity, Specificity, PPV, NPV, and False Negatives:

Despite its advantages, liquid biopsy has important limitations. The sensitivity of ctDNA analysis is reliant on biological and technical factors; the abundance of tumor cells, reflected by tumor stage or overall tumor burden, can dictate sensitivity, and lower-stage tumors have lower numbers of ctDNA fragments.[11]. Specificity, although generally high in Cfdna assays, can be compromised by non-tumor sources of cfDNA, such as clonal hematopoiesis [12].

The clinical utility of liquid biopsy also depends on predictive values. In lung cancer, it's reported that 'the specificity of ctDNA MRD in predicting recurrence is high (0.86–0.95) with moderate sensitivity (0.41–0.76), whether shortly after treatment or during the surveillance,' noting that this moderate sensitivity highlights the challenge of false-negative results in ctDNA-negative patients. [9] Also, it's found that the majority of variants detected in cfDNA

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were derived from clonal hematopoiesis (CHIP) rather than tumor, and emphasized that 'these CHIP-derived variants represent a major source of false-positive results in cfDNA analyses, showing how non-tumor sources can compromise specificity and positive predictive value. [11].

False negatives are a critical concern. False-negative results in ctDNA testing may arise from low levels of circulating tumor DNA, technical detection limits of current assays, pre-analytical issues such as sample handling or degradation, and tumor heterogeneity not captured by the specific assay used [13] As they emphasize, 'a single biopsy can provide only a snapshot of the molecular profile of a heterogeneous tumor, and may therefore miss clinically relevant subclones,' while ctDNA has the advantage of capturing DNA shed from multiple tumor sites, potentially offering a more comprehensive view of heterogeneity. Nevertheless, 'some tumor subclones may not shed sufficient DNA into the circulation to be detected, resulting in false-negative findings [13]. Clinically, this limitation is illustrated by [9], who reported that landmark MRD detection in non-small cell lung cancer achieved a pooled specificity of 0.95 but a sensitivity of only 0.32, underscoring the need for methodological improvements and cautious interpretation of negative results in practice.[9].

10. Implementation and Cost Considerations

Although liquid biopsy shows great promise, its clinical adoption faces major barriers. Lack of assay standardization and variability in test sensitivity hinder reproducibility [46]. High costs of NGS-based assays restrict access, especially in low- and middle-income countries [59]. Even in high-income settings, insurance coverage and reimbursement remain inconsistent, creating disparities [60]. Moreover, regulatory validation and quality-control frameworks are still evolving, delaying widespread implementation [7]. Overcoming these issues is critical for translating liquid biopsy into routine oncology practice.

11. Future Perspectives

Liquid biopsy is advancing rapidly with the development of highly sensitive technologies such as digital PCR and next-generation sequencing (NGS) [11]. Future approaches that integrate multiple biomarkers—ctDNA, CTCs, exosomes, and microRNAs—have the potential to enhance early detection sensitivity and provide a more comprehensive understanding of tumor biology [57].

Incorporating liquid biopsy into routine screening, particularly for high-risk populations, could allow earlier diagnosis, more personalized treatment, and improved survival outcomes [58]. Ongoing clinical trials are also evaluating its role in detecting minimal residual disease (MRD), which may transform how cancer remission is monitored [56]. Nonetheless, further progress in standardization, cost reduction, and validation through large-scale clinical studies is essential before liquid biopsy can replace traditional tissue biopsy [46].

Summary

Liquid biopsy represents a rapidly evolving approach in oncology, offering a non-invasive window into tumor biology through analysis of circulating biomarkers such as ctDNA and CTCs. It has proven its value for monitoring treatment response, detecting relapse earlier than imaging, and providing prognostic insights by linking biomarker burden and specific mutations to survival outcomes. Beyond guiding therapy decisions, liquid biopsy supports risk stratification and individualized follow-up strategies across multiple cancer types.

With advances in sensitive technologies and multi-marker integration, its potential extends to early detection and minimal residual disease assessment, opening new frontiers in precision medicine. While challenges remain in standardization, validation, and accessibility, liquid biopsy is steadily shaping the future of cancer diagnosis, management, and long-term surveillance.

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List of abbreviations:

ctDNA: Circulating Tumor DNA
CTCs: Circulating Tumor Cells
TEPs: Tumor-educated platelets
ALK: Anaplastic Lymphoma Kinase
C797S: A resistance mutation at the 797th position of the EGFR protein
cfDNA: Cell-free DNA
CHIP: Clonal Hematopoiesis of Indeterminate Potential
DNMT3A: DNA Methyltransferase 3 Alpha
EGFR: Epidermal Growth Factor Receptor
EGFR-TKIs: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors
EpCAM: Epithelial Cell Adhesion Molecule
ESR1: Estrogen Receptor 1
FDA: Food and Drug Administration
HER2: Human Epidermal Growth Factor Receptor 2
JAK2: Janus Kinase 2
KRAS: Kirsten Rat Sarcoma Virus
LARC: Locally Advanced Rectal Cancer
MRD: Minimal Residual Disease

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nCRT: Neoadjuvant Chemoradiation Therapy
NGS: Next-Generation Sequencing
NPV: Negative Predictive Value
NSCLC: Non-Small Cell Lung Cancer
PCR: Polymerase Chain Reaction
PET-CT: Positron Emission Tomography-Computed Tomography
PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PPV: Positive Predictive Value
ROS1: c-ros Oncogene 1
T790M: A specific resistance mutation in the EGFR gene
TET2: Tet Methylcytosine Dioxygenase 2
TP53: Tumor Protein P53

Author contribution:

Sara Sayed Ahmed (First author): Conceptualization, Data Curation, Investigation, Methodology, Writing Original Draft, Review & editing.
Shaifalika Thakur (second author): Conceptualization, Supervision, Validation, Review & Editing.

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The authors declare no conflict of interest**.**

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Data sharing is not applicable to this article, as no new datasets were created or analyzed. All data analyzed during this review are available within the article and its cited references.

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