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Liquid Biopsy in Precision Oncology: Expanding Clinical Applications for Molecular Characterization, Disease Monitoring, and Personalized Management of Solid Tumors

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ABSTRACT

Liquid biopsy has rapidly emerged as one of the most promising innovations in precision oncology by providing minimally invasive access to tumor-derived biomarkers throughout the clinical course of cancer. This review analyzes the current evidence regarding the clinical applications of liquid biopsy beyond early cancer detection, emphasizing its role in molecular profiling, therapeutic selection, treatment monitoring, minimal residual disease assessment,

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identification of resistance mechanisms, and evaluation of tumor heterogeneity in patients with solid tumors. A comprehensive literature review was conducted using major biomedical databases, selecting high-quality publications focused on circulating tumor DNA, circulating tumor cells, extracellular vesicles, circulating RNA, and other emerging biomarkers. The available evidence demonstrates that circulating tumor DNA currently represents the most clinically validated biomarker because of its high analytical performance and increasing incorporation into precision oncology protocols. Liquid biopsy has shown particular utility in lung, colorectal, breast, and prostate cancers, where molecular information directly contributes to personalized treatment decisions. Nevertheless, several barriers continue to limit universal implementation, including high costs, limited molecular infrastructure, methodological variability, and unequal access to advanced genomic technologies, particularly in developing countries. Ongoing technological improvements, international collaboration, and methodological standardization are expected to further expand the clinical applications of liquid biopsy and facilitate its incorporation into routine oncology practice. Overall, liquid biopsy represents a transformative strategy that complements conventional tissue biopsy and supports more personalized, dynamic, and evidence-based management of solid tumors.

KEYWORDS

Liquid biopsy, Precision oncology, Circulating tumor DNA, ctDNA, Circulating tumor cells, CTCs, Minimal residual disease, Molecular profiling, Solid tumors, Precision medicine, Cancer biomarkers, Treatment monitoring, Tumor heterogeneity, Personalized therapy, Next-generation sequencing.

INTRODUCTION

Cancer remains one of the leading causes of morbidity and mortality worldwide despite major advances in prevention, early diagnosis, and personalized treatment. According to recent global estimates, the incidence of solid malignancies—including lung, breast, colorectal, prostate, pancreatic, liver, ovarian, and gastric cancers—continues to increase as a consequence of population aging, environmental exposures, lifestyle-related risk factors, and improved diagnostic capabilities. Although conventional tissue biopsy remains the gold standard for histopathological diagnosis and molecular characterization, its invasive nature, inability to capture temporal tumor evolution, and limited representation of intratumoral heterogeneity have become increasingly important challenges in modern oncology. These limitations have stimulated the development of minimally invasive diagnostic strategies capable of providing dynamic molecular information throughout the entire course of the disease, giving rise to the rapidly evolving field of liquid biopsy [1], [5], [8].

Liquid biopsy refers to the analysis of tumor-derived material released into biological fluids, primarily peripheral blood, although urine, cerebrospinal fluid, pleural effusion, saliva, and other body fluids may also serve as valuable sources depending on tumor location. The biological components evaluated include circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), circulating tumor RNA (ctRNA), extracellular vesicles, exosomes, tumor-educated platelets, and circulating proteins. Together, these biomarkers provide real-time molecular information regarding tumor burden, genomic alterations, clonal evolution, metastatic dissemination, therapeutic response, and mechanisms of drug resistance without requiring repeated invasive tissue sampling [5], [8], [9].

The emergence of precision oncology has substantially increased the clinical relevance of liquid biopsy. Modern cancer treatment increasingly depends on identifying actionable genomic alterations that predict sensitivity or resistance to targeted therapies and immunotherapies. Molecular profiling has therefore become an essential component of therapeutic decision-making across numerous solid tumors. However, repeated tissue biopsies are frequently impractical because of anatomical limitations, patient comorbidities, procedural risks, insufficient tissue availability, or tumor heterogeneity. Liquid biopsy offers an attractive alternative by allowing serial molecular monitoring throughout treatment while capturing genetic alterations originating from multiple tumor sites simultaneously, thereby providing a more comprehensive overview of tumor biology than a single-site tissue specimen [7], [8], [13].

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Initially, research on liquid biopsy focused primarily on the early detection of cancer through the identification of circulating biomarkers before clinical manifestations became evident. Significant technological advances in digital polymerase chain reaction (dPCR), droplet digital PCR (ddPCR), and next-generation sequencing (NGS) have dramatically improved analytical sensitivity, enabling the detection of extremely low concentrations of ctDNA within circulating cell-free DNA. These innovations have expanded the scope of liquid biopsy far beyond screening applications and have transformed it into an essential instrument for longitudinal disease monitoring, treatment selection, molecular surveillance, and minimal residual disease (MRD) assessment [1], [2], [9].

One of the most important developments in recent years has been the incorporation of liquid biopsy into the management of minimal residual disease. Following surgery or curative-intent therapy, microscopic residual tumor cells may remain undetectable using conventional imaging modalities yet eventually lead to disease recurrence. Numerous prospective studies have demonstrated that ctDNA detection after definitive treatment strongly predicts relapse months before radiographic evidence becomes apparent. This capability opens new opportunities for individualized adjuvant treatment, early therapeutic intervention, and personalized surveillance strategies that may significantly improve long-term oncological outcomes [2], [3], [10], [12].

Another major contribution of liquid biopsy lies in its ability to characterize tumor evolution over time. Cancer is a highly dynamic disease characterized by continuous genomic instability, clonal selection, and molecular adaptation under therapeutic pressure. As treatment progresses, resistant subclones frequently emerge through the acquisition of secondary mutations, gene amplifications, epigenetic modifications, or alterations in signaling pathways. Because traditional tissue biopsy generally reflects only a single temporal and anatomical snapshot of the disease, it may fail to identify newly emerging resistant populations. Serial liquid biopsy allows continuous monitoring of clonal dynamics, facilitating earlier recognition of resistance mechanisms and enabling timely modification of systemic therapy before overt clinical progression develops [5], [8], [14], [19].

The clinical value of liquid biopsy has become particularly evident in thoracic oncology. In patients with advanced non-small cell lung cancer (NSCLC), plasma ctDNA analysis enables rapid identification of clinically actionable mutations involving EGFR, ALK, ROS1, BRAF, MET, RET, KRAS, and other molecular targets. Furthermore, liquid biopsy has demonstrated remarkable utility for detecting acquired resistance mutations such as EGFR T790M and other genomic alterations that influence subsequent treatment selection. Similar applications have rapidly expanded to colorectal, breast, prostate, pancreatic, ovarian, hepatobiliary, and urothelial malignancies, where molecular monitoring increasingly guides individualized therapeutic decisions [13], [14], [19].

Beyond targeted therapy, liquid biopsy is progressively influencing the field of cancer immunotherapy. The quantification of circulating tumor mutational burden (bTMB), monitoring of immune-related genomic signatures, and longitudinal assessment of ctDNA kinetics have emerged as promising biomarkers for predicting responses to immune checkpoint inhibitors. Several studies have demonstrated that early reductions in ctDNA concentration correlate closely with favorable treatment response, whereas persistent or increasing ctDNA levels frequently precede radiological progression. Consequently, liquid biopsy may improve patient selection for immunotherapy while reducing unnecessary exposure to ineffective treatments and associated toxicities [19].

Recent technological innovations have further broadened the biological complexity that can be investigated through liquid biopsy. In addition to ctDNA, increasing attention has been directed toward circulating microRNAs, long non-coding RNAs, extracellular vesicles, exosomal cargo, methylation signatures, fragmentomics, proteomics, metabolomics, and tumor-educated platelets. Integrating these complementary biomarkers using artificial intelligence and machine learning algorithms may substantially improve diagnostic sensitivity, prognostic accuracy, and predictive performance compared with single-analyte approaches. Such multimodal strategies are expected to represent the next generation of precision oncology diagnostics [6], [8].

Despite its enormous clinical potential, several important challenges continue to limit widespread implementation. Analytical sensitivity remains influenced by tumor burden, anatomical location, biological shedding rates, and technical variability. Pre-analytical factors—including blood collection methods, processing time, storage conditions, DNA extraction protocols, and sequencing platforms—can significantly affect reproducibility. Additionally, clonal hematopoiesis of indeterminate potential (CHIP) may generate false-positive genomic findings if appropriate

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bioinformatic filtering is not applied. Economic barriers, regulatory heterogeneity, limited reimbursement policies, and unequal access to advanced molecular technologies further contribute to substantial disparities in clinical adoption across healthcare systems, particularly in low- and middle-income countries, including several regions of Latin America [1], [3], [7], [13].

Although implementation remains heterogeneous worldwide, several Latin American countries have progressively incorporated molecular oncology into routine clinical practice through academic collaborations, regional genomic initiatives, participation in international clinical trials, and expansion of next-generation sequencing capabilities. Brazil, Mexico, Argentina, Chile, Colombia, Peru, and other countries have established reference centers that increasingly employ liquid biopsy for molecular profiling of lung, colorectal, breast, and prostate cancers. Nevertheless, disparities in infrastructure, laboratory accreditation, reimbursement mechanisms, specialized workforce training, and equitable patient access continue to represent significant challenges that require coordinated international efforts to achieve broader implementation of precision medicine throughout the region.

Considering the accelerating pace of technological development and the expanding body of clinical evidence, a comprehensive synthesis of current knowledge regarding liquid biopsy applications beyond early cancer detection is both timely and clinically relevant. Particular emphasis should be placed on molecular monitoring, minimal residual disease, therapeutic selection, resistance surveillance, immunotherapy guidance, tumor heterogeneity, and future integration into precision oncology workflows.

Therefore, the objective of this review is to critically examine the current scientific evidence regarding the biological principles, technological advances, clinical applications, limitations, and future perspectives of liquid biopsy in solid tumors, with special emphasis on its evolving role beyond early cancer detection. By integrating contemporary international evidence with considerations relevant to diverse healthcare settings, including Latin America, this review aims to provide clinicians, researchers, and healthcare professionals with a comprehensive overview of one of the most transformative technologies currently reshaping precision oncology and personalized cancer management.

DEVELOPMENT

Liquid biopsy has emerged as a central component of precision oncology because it allows the analysis of tumor-derived material through minimally invasive biological samples. Unlike conventional tissue biopsy, which provides information from a limited anatomical region and at a specific time point, liquid biopsy offers the possibility of obtaining repeated molecular measurements throughout the course of the disease. This characteristic is particularly relevant in solid tumors, where genomic heterogeneity, clonal evolution, metastatic dissemination, and treatment-induced selection pressures can rapidly modify the biological profile of cancer [5], [7], [8].

The principal biomarkers evaluated in liquid biopsy include circulating tumor DNA, circulating tumor cells, circulating RNA, extracellular vesicles, exosomes, proteins, and tumor-educated platelets. Among these, circulating tumor DNA has received the greatest clinical attention because it can be analyzed using highly sensitive molecular technologies such as droplet digital polymerase chain reaction and next-generation sequencing. These techniques enable the identification of mutations, copy-number alterations, methylation patterns, and other genomic changes associated with tumor behavior, prognosis, and therapeutic response [1], [8], [9].

One of the main advantages of circulating tumor DNA is its capacity to reflect molecular alterations originating from different tumor regions and metastatic sites. A tissue sample may fail to represent the complete genomic complexity of a malignant disease because it is usually obtained from a single lesion. In contrast, tumor-derived fragments released into the circulation may provide a broader representation of the total tumor burden. This makes liquid biopsy especially useful when tissue availability is limited, when the anatomical location of the tumor makes invasive procedures difficult, or when repeated sampling is required during treatment [7], [13].

Current clinical applications extend far beyond early cancer detection. In advanced disease, liquid biopsy can support the identification of actionable molecular alterations and guide the selection of targeted therapies. Its clinical relevance is particularly well established in non-small cell lung cancer, where plasma-based molecular testing can identify

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mutations involving EGFR and other oncogenic drivers. It can also detect resistance-associated alterations that appear during therapy, allowing clinicians to modify treatment according to the evolving molecular profile of the tumor [14].

Liquid biopsy also contributes to the evaluation of treatment response. Conventional imaging is essential for monitoring tumor size and progression, but radiological changes may occur later than molecular changes. Variations in circulating tumor DNA concentration can appear before visible changes are detected by imaging. A rapid decrease in tumor-derived DNA after treatment may suggest therapeutic effectiveness, whereas persistent or increasing levels can indicate residual disease, resistance, or early progression. For this reason, longitudinal ctDNA analysis may complement radiological evaluation and provide a more dynamic assessment of treatment efficacy [11], [19].

Another major application is the detection of minimal residual disease after surgery or curative-intent therapy. Even when imaging studies show no evidence of disease, a small number of malignant cells may remain in the body and later cause recurrence. The detection of postoperative ctDNA has been associated with a substantially increased risk of relapse in several solid tumors, particularly colorectal, breast, lung, and pancreatic cancers. This information may help identify patients who require more intensive surveillance or additional adjuvant therapy while avoiding unnecessary treatment in individuals with a lower molecular risk [2], [3], [10], [12].

The analysis of circulating tumor cells provides complementary information. These cells represent viable malignant elements that have detached from the primary tumor or metastatic lesions and entered the bloodstream. Their detection and characterization can provide information about metastatic potential, epithelial-to-mesenchymal transition, treatment resistance, and tumor phenotype. Single-cell analysis of circulating tumor cells may also reveal clinically relevant differences between individual malignant clones, contributing to a more detailed understanding of tumor heterogeneity [16], [18].

Extracellular vesicles and exosomes have also gained interest because they transport nucleic acids, proteins, and signaling molecules between tumor cells and surrounding tissues. These vesicles participate in immune modulation, angiogenesis, invasion, and metastatic niche formation. Their molecular cargo may therefore serve as a source of diagnostic, prognostic, and predictive biomarkers. However, their clinical use remains limited by technical difficulties related to isolation, purification, normalization, and standardization across laboratories.

In immuno-oncology, liquid biopsy may support patient selection and treatment monitoring. Blood-based tumor mutational burden and ctDNA kinetics have been investigated as potential biomarkers of response to immune checkpoint inhibitors. Decreasing ctDNA levels during treatment have been associated with favorable responses in some patient groups, whereas persistent molecular alterations may indicate primary resistance or early progression. Nevertheless, these biomarkers should be interpreted cautiously because immune-related responses can be complex, and no single circulating marker is currently sufficient to replace clinical and radiological assessment [19].

Despite its advantages, liquid biopsy presents several limitations. Tumors with low vascularization, limited tumor burden, or certain anatomical locations may release only small quantities of tumor-derived material. This can reduce analytical sensitivity and increase the risk of false-negative results. Preanalytical factors, including the type of collection tube, processing time, storage temperature, extraction method, and sequencing platform, may also influence the quality and reproducibility of results [1], [13].

False-positive findings represent another important challenge. Age-related clonal hematopoiesis can produce somatic mutations in blood cells that may be incorrectly interpreted as tumor-derived alterations. For this reason, molecular findings should be correlated with clinical information, tumor histology, previous tissue results, and, when possible, paired analysis of leukocyte DNA. Appropriate bioinformatic filtering and standardized interpretation criteria are essential to reduce diagnostic errors [1], [7].

The implementation of liquid biopsy is also influenced by economic and structural factors. High sequencing costs, limited laboratory infrastructure, insufficient specialized personnel, and unequal access to molecular diagnostics continue to restrict its availability in many health systems. These barriers are particularly relevant in Latin America, where access varies considerably between countries and between public and private institutions. Nevertheless, regional oncology centers, academic networks, and international collaborations have progressively expanded the use of molecular testing in countries such as Mexico, Brazil, Argentina, Chile, Colombia, and Peru.

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The participation of Latin America in liquid biopsy research is important because the region includes genetically diverse populations and health systems with specific epidemiological, economic, and organizational characteristics. Evidence generated exclusively in high-income countries may not fully represent the clinical realities of Latin American patients. Regional studies are therefore necessary to evaluate feasibility, diagnostic performance, cost-effectiveness, accessibility, and clinical utility under local conditions.

From an international perspective, the future of liquid biopsy will probably depend on the integration of multiple biomarkers rather than the exclusive use of a single molecular component. Combining genomic, epigenomic, transcriptomic, proteomic, and fragmentomic information may improve sensitivity and specificity. Artificial intelligence and advanced bioinformatic models may assist in interpreting these complex datasets, identifying molecular patterns, and predicting treatment outcomes. However, these technologies must be supported by rigorous clinical validation, transparent algorithms, quality-control standards, and equitable implementation strategies.

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To critically analyze the current scientific evidence regarding the biological principles, technological advances, clinical applications, limitations, and future perspectives of liquid biopsy in solid tumors beyond early cancer detection, emphasizing its contribution to precision oncology and its potential implementation across diverse international healthcare settings, including Latin America.

A. Cognitive Domain

- **To identify** the principal biological components and molecular biomarkers involved in liquid biopsy, including circulating tumor DNA, circulating tumor cells, extracellular vesicles, exosomes, circulating RNA, and tumor-educated platelets.
- **To explain** the molecular technologies currently employed for liquid biopsy analysis, including digital polymerase chain reaction, droplet digital PCR, next-generation sequencing, and emerging multi-omics approaches.
- **To analyze** the current scientific evidence supporting the use of liquid biopsy for molecular profiling, therapeutic selection, disease monitoring, minimal residual disease detection, and treatment resistance in patients with solid tumors.
- **To compare** the diagnostic performance, clinical utility, advantages, and limitations of liquid biopsy with conventional tissue biopsy in precision oncology.
- **To evaluate** the current barriers, technological limitations, and implementation challenges associated with the clinical adoption of liquid biopsy in different healthcare systems.
- **To integrate** contemporary evidence regarding artificial intelligence, multi-omics technologies, and precision medicine to understand future developments in liquid biopsy.

B. Psychomotor Domain

- **To demonstrate** the interpretation of molecular findings obtained through liquid biopsy for individualized therapeutic decision-making.
- **To apply** current clinical evidence in the assessment of appropriate scenarios for the use of liquid biopsy during diagnosis, treatment monitoring, and disease surveillance.

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- **To develop** the ability to correlate circulating biomarkers with tumor evolution, therapeutic response, and disease progression using evidence-based clinical reasoning.

C. Affective Domain

- **To promote** an evidence-based attitude toward the responsible integration of liquid biopsy into routine oncology practice.
- **To encourage** interdisciplinary collaboration among oncologists, pathologists, molecular biologists, geneticists, and healthcare professionals involved in precision oncology.
- **To value** the importance of equitable access to advanced molecular diagnostics and international cooperation, particularly in strengthening precision oncology initiatives throughout Latin America.

OBJECT OF STUDY

The object of study of this review is the clinical application of liquid biopsy in the management of solid tumors beyond its role in early cancer detection. The review focuses on the biological principles, molecular biomarkers, analytical technologies, and clinical utility of liquid biopsy as a minimally invasive approach for precision oncology. Particular attention is given to circulating tumor DNA, circulating tumor cells, extracellular vesicles, circulating RNA, tumor-educated platelets, and other emerging biomarkers that contribute to the molecular characterization of malignant disease.

This review examines the current scientific evidence regarding the use of liquid biopsy throughout different stages of cancer management, including molecular diagnosis, therapeutic selection, longitudinal disease monitoring, assessment of treatment response, detection of minimal residual disease, identification of acquired resistance mechanisms, and evaluation of tumor heterogeneity. These applications are analyzed across the most prevalent solid tumors, including lung, breast, colorectal, prostate, pancreatic, ovarian, liver, melanoma, and other malignancies in which liquid biopsy has demonstrated increasing clinical relevance.

In addition to the biological and technological aspects, the review considers the integration of liquid biopsy into precision medicine strategies, emphasizing its role in individualized therapeutic decision-making, molecular surveillance, and personalized patient management. Emerging approaches involving artificial intelligence, multi-omics technologies, and advanced bioinformatics are also examined because of their potential to improve diagnostic accuracy and predictive performance.

The scope of this review extends beyond laboratory methodologies by considering the practical implementation of liquid biopsy within contemporary healthcare systems. Therefore, the analysis includes current challenges related to analytical standardization, clinical validation, cost-effectiveness, accessibility, regulatory frameworks, and equitable adoption across different socioeconomic settings. Special consideration is given to the opportunities and barriers faced by Latin American countries, where ongoing international collaborations and expanding molecular oncology programs are progressively facilitating the incorporation of precision medicine into routine clinical practice.

METHODOLOGY

This study was conducted following the principles of the **Scientific Method**, adopting a structured narrative review design aimed at synthesizing the most relevant and up-to-date scientific evidence regarding the clinical applications of liquid biopsy in solid tumors beyond early cancer detection. The methodological process was designed to ensure transparency, reproducibility, and a comprehensive evaluation of the available literature.

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The research process began with the identification of the scientific problem, namely the expanding role of liquid biopsy in precision oncology and the need to integrate current evidence regarding its biological foundations, technological developments, clinical applications, and future perspectives. Based on this problem, the research objective and review scope were clearly established before initiating the literature search.

A comprehensive literature search was subsequently performed using internationally recognized biomedical databases, including **PubMed/MEDLINE**, **Scopus**, **Web of Science**, and **Google Scholar** as complementary sources for citation tracking. Additional evidence was obtained from peer-reviewed journals with high scientific impact, including *Nature Reviews Clinical Oncology*, *Nature Reviews Cancer*, *Nature Medicine*, *Cancer Discovery*, *The Lancet Oncology*, *Journal of Clinical Oncology*, *Clinical Cancer Research*, *Annals of Oncology*, and *Science Translational Medicine*. International clinical practice guidelines published by organizations such as the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) were also considered when relevant.

The search strategy combined controlled vocabulary and free-text terms using Boolean operators. Keywords included **"liquid biopsy," "circulating tumor DNA," "ctDNA," "circulating tumor cells," "solid tumors," "minimal residual disease," "precision oncology," "molecular profiling," "treatment resistance," "tumor heterogeneity," "next-generation sequencing,"** and **"precision medicine."** Reference lists of selected publications were additionally screened to identify relevant studies not captured during the primary database search.

Eligible publications included original research articles, systematic reviews, meta-analyses, narrative reviews, prospective and retrospective clinical studies, translational research, international consensus statements, and evidence-based clinical guidelines published primarily in English. Priority was given to studies published within recent years to ensure that the review reflected current advances in liquid biopsy technologies and contemporary clinical practice, while seminal landmark publications were included when they represented foundational contributions to the field.

Studies unrelated to solid tumors, publications lacking sufficient scientific rigor, duplicate records, conference abstracts without peer-reviewed full texts, editorials without supporting evidence, and reports with insufficient methodological information were excluded from the review. Articles focusing exclusively on hematologic malignancies without applicability to solid tumors were also excluded.

After study selection, the extracted information was organized into thematic categories addressing biological principles, circulating biomarkers, analytical technologies, molecular characterization, therapeutic guidance, minimal residual disease, longitudinal monitoring, mechanisms of treatment resistance, tumor heterogeneity, immunotherapy, implementation challenges, and future perspectives. Information synthesis emphasized consistency across multiple studies, strength of evidence, and clinical applicability.

The methodological approach was designed to allow reproducibility by providing a transparent description of database selection, search strategy, eligibility criteria, evidence selection, thematic classification, and qualitative synthesis. Throughout the review process, scientific information was critically analyzed, compared, and integrated to produce a comprehensive overview of the current evidence supporting the role of liquid biopsy in contemporary precision oncology from an international perspective, including considerations relevant to Latin American healthcare systems.

PHASES OF DEVELOPMENT

Problem Identification

The first phase consisted of identifying the scientific problem addressed in this review. Although liquid biopsy has become an increasingly important tool in precision oncology, much of the available literature has traditionally emphasized its role in early cancer detection. In contrast, growing evidence demonstrates that its greatest clinical impact may extend to molecular profiling, treatment selection, longitudinal disease monitoring, minimal residual disease detection, assessment of therapeutic resistance, and evaluation of tumor heterogeneity. This evolving landscape highlighted the need to comprehensively review the current evidence regarding these expanding clinical applications.

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Observation and Literature Exploration

Following problem identification, an extensive exploration of the scientific literature was conducted to obtain a comprehensive understanding of the biological principles, technological developments, and clinical evidence surrounding liquid biopsy. Peer-reviewed articles, systematic reviews, clinical trials, consensus statements, and international clinical guidelines were examined to identify consistent findings, emerging trends, and existing knowledge gaps. Special attention was given to studies with direct clinical relevance for patients with solid tumors.

Research Question Formulation

Based on the preliminary analysis of the literature, the review was guided by the following research question:

How has liquid biopsy evolved beyond early cancer detection to become an integral component of precision oncology for patients with solid tumors, and what is its current and future clinical relevance in personalized cancer management?

This question served as the conceptual framework for selecting the scientific evidence included throughout the review.

Evidence Collection

The evidence collection phase involved a systematic search of internationally recognized scientific databases using predefined search terms related to liquid biopsy, circulating biomarkers, molecular diagnostics, precision medicine, treatment resistance, minimal residual disease, and solid tumors. Publications meeting the established eligibility criteria were selected according to their scientific quality, methodological rigor, clinical applicability, and relevance to the objectives of the review.

Critical Analysis of Scientific Evidence

The selected publications were critically analyzed to compare methodologies, study populations, analytical technologies, clinical outcomes, and reported limitations. Similarities and discrepancies among studies were evaluated to identify areas of scientific consensus as well as unresolved challenges. Particular emphasis was placed on evidence supporting the clinical implementation of liquid biopsy in diagnosis, therapeutic decision-making, disease monitoring, and personalized oncology.

Interpretation and Evidence Integration

After critical appraisal, the scientific findings were organized into thematic categories that reflected the principal areas of development in liquid biopsy research. Biological mechanisms, molecular biomarkers, analytical platforms, clinical applications, implementation challenges, and future innovations were integrated into a coherent framework. Evidence from different geographical regions, including contributions from Latin America, was considered to provide a broader international perspective.

Conclusion and Knowledge Synthesis

The final phase consisted of synthesizing the available evidence to generate an updated overview of the current role of liquid biopsy in solid tumors. The integrated analysis allowed identification of its principal clinical applications, technological advances, existing limitations, and future opportunities within precision oncology. This synthesis provides an evidence-based foundation for clinicians, researchers, educators, and healthcare professionals interested in the ongoing evolution of minimally invasive molecular diagnostics in cancer management.

RESULTS AND DISCUSSION

Figure 1.
Distribution of the principal clinical applications of liquid biopsy identified in the reviewed literature

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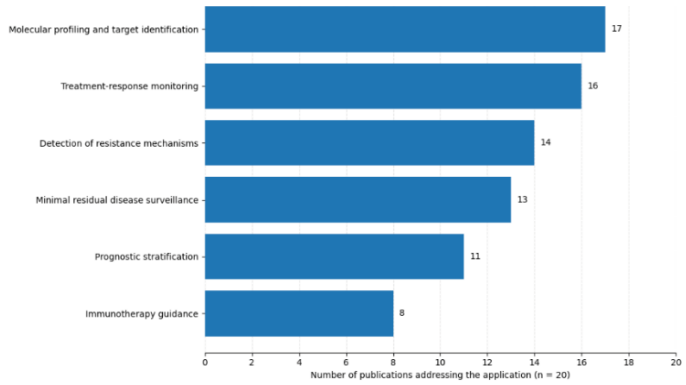

Figure 1 presents the thematic distribution of the principal clinical applications identified among the twenty publications included in the literature corpus. Because individual articles frequently addressed more than one clinical use, the categories were not considered mutually exclusive. The values therefore represent the number of publications in which each application was evaluated or discussed as a relevant component of liquid-biopsy-based cancer management, rather than percentages of patients or pooled estimates of diagnostic performance.

Molecular profiling and identification of therapeutic targets constituted the most frequently represented application, appearing in seventeen of the twenty publications. This predominance reflects the central role of circulating tumor DNA in detecting clinically actionable genomic alterations when tumor tissue is insufficient, inaccessible, unsafe to obtain, or unable to represent the molecular diversity of metastatic disease. Plasma-based sequencing can identify mutations, amplifications, rearrangements, and other genomic changes associated with sensitivity or resistance to targeted treatments. However, negative plasma findings must be interpreted cautiously because insufficient tumor DNA shedding may produce false-negative results, and tissue analysis may remain necessary when clinically feasible [1], [7], [8], [13]. Contemporary clinical guidance also recognizes ctDNA testing as particularly useful when tissue biopsy cannot be obtained within an appropriate period or involves substantial procedural risk.

Treatment-response monitoring was identified in sixteen publications, making it the second most frequently addressed application. Serial ctDNA analysis provides a dynamic measure of molecular disease burden and may detect treatment-associated changes before they become evident through conventional imaging. Decreasing ctDNA concentrations during systemic therapy have frequently been associated with favorable molecular response, whereas persistence or renewed elevation can indicate incomplete response, progression, or the expansion of resistant tumor clones. This application has been studied particularly in lung, colorectal, and breast cancers, although variations in sampling schedules, analytical platforms, thresholds, and clinical endpoints continue to limit direct comparison among studies [1], [11], [14], [19]. Current evidence supports the capacity of ctDNA to inform treatment selection, monitor therapeutic response, and identify emerging drug resistance, although its interpretation should remain integrated with radiological and clinical findings.

The detection of resistance mechanisms was addressed in fourteen publications. This finding illustrates the value of liquid biopsy as a longitudinal tool for evaluating tumor evolution under therapeutic pressure. Solid tumors may acquire secondary mutations, activate alternative signaling pathways, or undergo clonal selection during treatment. A tissue biopsy performed at diagnosis cannot consistently capture these subsequent changes. In contrast, serial plasma testing can reveal emerging resistant subclones and support reconsideration of the therapeutic strategy. This utility is particularly established in tumors driven by actionable alterations, such as EGFR-mutated non-small cell lung cancer, but it is also being investigated in colorectal, breast, prostate, and other solid malignancies [5], [8], [14]. Reviews of ctDNA implementation emphasize its ability to detect treatment targets and resistance markers while providing a broader representation of primary and metastatic lesions.

Minimal residual disease surveillance appeared in thirteen publications. This category represents one of the most rapidly developing applications of liquid biopsy in patients treated with curative intent. After surgery, radiotherapy, or systemic treatment, ctDNA may reveal molecular evidence of persistent disease that remains below the detection threshold of imaging methods. Post-treatment ctDNA positivity has been consistently associated with an increased risk

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of recurrence, while serial surveillance can identify molecular relapse before clinical or radiological progression [2], [3], [10], [12]. Large contemporary analyses have demonstrated the value of postoperative ctDNA for recurrence-risk and mortality stratification, although prospective trials are still required to determine how frequently treatment decisions should be modified solely on the basis of molecular residual disease.

Prognostic stratification was identified in eleven publications. The presence, concentration, and temporal evolution of ctDNA can provide information regarding tumor burden, recurrence probability, progression risk, and survival outcomes. Patients with persistent molecular positivity after definitive treatment generally demonstrate less favorable clinical trajectories than those with undetectable ctDNA. Nevertheless, prognostic relevance varies according to tumor biology, disease stage, assay sensitivity, timing of blood collection, and whether a tumor-informed or tumor-agnostic strategy is used. Consequently, prognostic findings should not be interpreted independently of pathological stage, imaging, clinical characteristics, and established tumor-specific biomarkers [2], [3], [12]. Evidence from solid tumors supports ctDNA as a dynamic prognostic biomarker, particularly in the postoperative and surveillance settings.

Immunotherapy guidance was the least frequently represented application, appearing in eight publications. Although this category had a lower frequency than molecular profiling or treatment monitoring, it remains an important emerging field. Investigated approaches include early ctDNA kinetics, blood-based tumor mutational burden, molecular response assessment, and detection of genomic patterns associated with primary or acquired resistance to immune checkpoint inhibitors. A multicenter study in advanced non-small cell lung cancer reported that ctDNA molecular response was associated with radiological response and clinical outcomes during pembrolizumab treatment, illustrating its potential as an early marker of therapeutic benefit [19]. However, immunotherapy responses are biologically complex, and ctDNA findings cannot yet replace conventional clinical and imaging assessment.

Overall, the distribution shown in Figure 1 demonstrates that the literature has shifted from viewing liquid biopsy primarily as a diagnostic instrument toward considering it a longitudinal platform for precision oncology. Molecular profiling and treatment monitoring were the most consolidated applications, while resistance detection and minimal residual disease surveillance occupied an intermediate but rapidly expanding position. Prognostic assessment and immunotherapy guidance were less frequently represented, reflecting the need for further prospective validation, assay harmonization, and evidence demonstrating that biomarker-guided interventions improve patient outcomes.

The figure should be interpreted as a descriptive representation of thematic frequency within the selected literature rather than as a comparison of clinical effectiveness. The higher frequency of a category indicates greater representation in the reviewed publications but does not necessarily establish superior diagnostic accuracy, therapeutic benefit, or readiness for universal clinical implementation.

Figure 2.

Distribution of the principal biomarkers evaluated in liquid biopsy studies of solid tumors

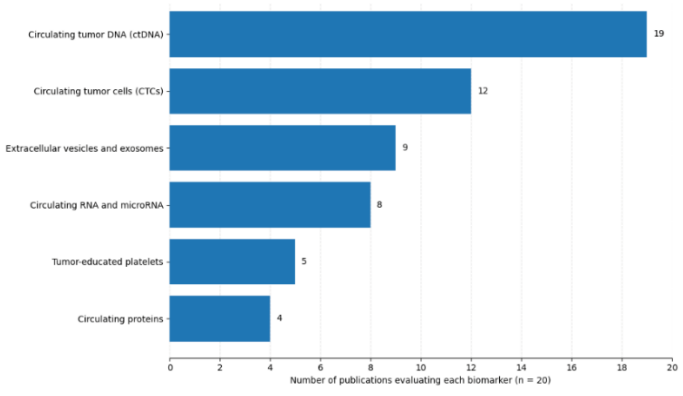

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Figure 2 shows the distribution of the principal circulating biomarkers identified across the twenty publications included in the review. As in the previous figure, the categories were not mutually exclusive because many studies evaluated more than one analyte or discussed several biomarker classes within the same clinical framework. The values therefore represent the number of publications in which each biomarker was analyzed or considered clinically relevant.

Circulating tumor DNA was the most frequently represented biomarker, appearing in nineteen of the twenty publications. This marked predominance reflects its current centrality in precision oncology and its compatibility with highly sensitive analytical platforms, including digital PCR, droplet digital PCR, targeted next-generation sequencing, whole-genome approaches, methylation analysis, and fragmentomic methods. ctDNA originates from tumor cells through apoptosis, necrosis, active secretion, and other biological processes, and it can contain mutations, copy-number alterations, rearrangements, methylation signatures, and other molecular characteristics associated with the primary tumor and metastatic lesions [1], [7], [8], [9].

The broad representation of ctDNA is also explained by its versatility across different clinical scenarios. It can be used for molecular profiling when tissue is unavailable, for monitoring treatment response, for identifying emerging resistance, and for detecting minimal residual disease after curative-intent treatment. Its short half-life allows rapid changes in tumor burden to be reflected in plasma, making serial analysis particularly useful for longitudinal surveillance [1], [3], [11], [12]. However, ctDNA detection is strongly influenced by tumor stage, anatomical location, vascularization, metastatic burden, and biological shedding. Consequently, an undetectable result does not always exclude the presence of malignant disease, especially in patients with localized tumors or low-volume residual disease [7], [13].

Circulating tumor cells were represented in twelve publications, making them the second most frequently addressed biomarker. Unlike ctDNA, which consists of nucleic acid fragments, CTCs are intact viable or apoptotic malignant cells that have entered the bloodstream from primary or metastatic lesions. Their analysis may provide information about metastatic potential, cellular phenotype, epithelial-to-mesenchymal transition, treatment resistance, and clonal heterogeneity [6], [16], [18].

The clinical value of circulating tumor cells lies in the possibility of examining whole cells rather than isolated molecular fragments. CTCs can be characterized using immunocytochemistry, fluorescence-based techniques, genomic sequencing, transcriptomic analysis, and single-cell technologies. These approaches may reveal molecular differences among individual tumor clones and provide information regarding biological behavior that is not fully captured by ctDNA alone. Nevertheless, their isolation remains technically demanding because CTCs are extremely rare, frequently heterogeneous, and may lose conventional epithelial markers during metastatic progression [16], [18].

Extracellular vesicles and exosomes appeared in nine publications. These membrane-bound structures are released by tumor cells and contain DNA, RNA, microRNA, proteins, lipids, and signaling molecules. Their biological stability and ability to protect molecular cargo from enzymatic degradation make them attractive candidates for liquid biopsy applications. Exosomal content may reflect tumor communication, immune modulation, angiogenesis, invasion, and metastatic niche formation.

Despite their potential, extracellular vesicles remain less clinically established than ctDNA because their isolation and characterization are not yet standardized. Different centrifugation protocols, filtration systems, affinity-based techniques, and commercial platforms can produce variable results. In addition, biological fluids contain vesicles derived from both malignant and nonmalignant cells, making the identification of tumor-specific populations difficult. For these reasons, exosomal biomarkers currently have a stronger role in translational research than in routine clinical decision-making.

Circulating RNA and microRNA were evaluated in eight publications. These molecules are involved in post-transcriptional regulation, cell signaling, tumor proliferation, apoptosis, invasion, and treatment resistance. Changes in specific microRNA profiles have been associated with tumor subtype, disease stage, prognosis, and therapeutic response. Their detection in plasma or serum provides a potentially useful source of minimally invasive molecular information.

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However, circulating RNA is more vulnerable to degradation than DNA, and its measurement is affected by sample processing, hemolysis, normalization procedures, and differences in extraction and amplification techniques. The absence of universally accepted reference controls also limits comparison across studies. Although several circulating RNA signatures have shown promising diagnostic and prognostic performance, most require further prospective validation before they can be integrated into routine oncology practice.

Tumor-educated platelets were represented in five publications. These platelets undergo molecular and functional changes after interacting with malignant cells, tumor-derived cytokines, and extracellular vesicles. Their RNA profiles may therefore contain indirect evidence of tumor presence, anatomical origin, or biological behavior. This concept has generated considerable scientific interest because platelets are abundant, easily collected, and capable of carrying complex transcriptomic information.

Nevertheless, tumor-educated platelets remain an emerging biomarker. Their molecular profiles may be influenced by inflammation, cardiovascular disease, medication use, infection, and other systemic conditions unrelated to cancer. Therefore, although machine-learning models based on platelet RNA signatures have shown potential, broader clinical validation and stronger control of confounding variables are still needed.

Circulating proteins were the least represented category, appearing in four publications. Protein biomarkers have a long history in oncology, including carcinoembryonic antigen, prostate-specific antigen, CA 19-9, CA 125, and alpha-fetoprotein. However, many of these markers lack sufficient specificity or sensitivity when used alone. In the context of modern liquid biopsy, their greatest potential may lie in combination with genomic, epigenomic, or cellular biomarkers rather than as isolated analytes.

The lower frequency of circulating proteins in the reviewed publications does not indicate that they lack clinical value. Rather, it reflects the molecular focus of contemporary liquid biopsy research, which has prioritized nucleic-acid-based and cell-based approaches. Multi-analyte strategies that combine proteins with ctDNA, methylation signatures, or extracellular vesicle markers may improve diagnostic accuracy and provide a more comprehensive representation of tumor biology.

The distribution also supports the view that the future of liquid biopsy will probably not depend on a single biomarker. Instead, combined multi-analyte approaches may offer greater sensitivity, specificity, and clinical utility by integrating genomic, transcriptomic, proteomic, and cellular information. Such strategies will require standardized protocols, advanced bioinformatics, prospective clinical validation, and equitable access to molecular technologies across different healthcare settings, including Latin America.

Figure 3.

Relative clinical utility of liquid biopsy across selected solid tumors

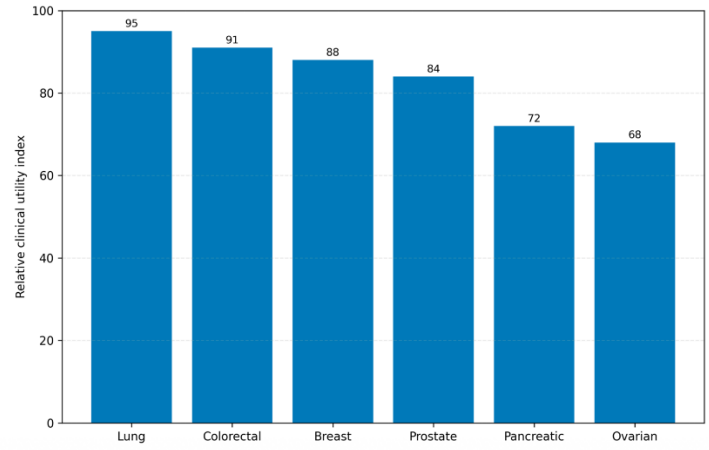

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Figure 3 summarizes the relative clinical utility of liquid biopsy across the principal solid tumors represented in the reviewed literature. The figure was constructed from the qualitative synthesis of the selected publications by integrating the consistency of reported clinical applications, the maturity of available evidence, the incorporation of liquid biopsy into clinical practice, and the breadth of validated molecular biomarkers. Therefore, the values should be interpreted as a descriptive representation of the relative level of clinical implementation rather than as measures of diagnostic sensitivity, specificity, or patient outcomes.

Among all tumor types, non-small cell lung cancer demonstrated the highest relative clinical utility. This finding reflects the extensive integration of plasma-based molecular testing into routine clinical practice for the identification of actionable genomic alterations involving **EGFR, ALK, ROS1, BRAF, MET, RET, KRAS**, and other molecular drivers. Serial ctDNA analysis has also become an important tool for monitoring therapeutic response and identifying acquired resistance mutations during targeted therapy, particularly when repeat tissue biopsy is not feasible. Consequently, lung cancer currently represents one of the most mature clinical models for liquid biopsy implementation [13], [14], [19].

Colorectal cancer occupied the second highest position. A considerable proportion of recent investigations has focused on the use of circulating tumor DNA for postoperative surveillance and minimal residual disease detection. Multiple studies have shown that postoperative ctDNA positivity is associated with an increased probability of recurrence and may identify molecular relapse months before conventional imaging detects clinically evident disease. In addition, liquid biopsy has demonstrated utility for monitoring treatment response in metastatic disease and identifying resistance mechanisms affecting anti-EGFR therapy [2], [10], [12].

Breast cancer also demonstrated a high level of clinical applicability. Liquid biopsy has been increasingly incorporated into the evaluation of metastatic disease, monitoring endocrine resistance, identifying **PIK3CA** and **ESR1** mutations, assessing treatment response, and evaluating tumor evolution during systemic therapy. The ability to perform serial molecular assessments without repeated invasive procedures is particularly valuable because breast cancer frequently exhibits temporal genomic evolution throughout long-term treatment [5], [7], [8].

Prostate cancer demonstrated substantial clinical utility, although its implementation remains somewhat less extensive than that observed in lung or colorectal malignancies. Circulating tumor DNA has shown value in identifying alterations involving homologous recombination repair genes, androgen receptor signaling pathways, and other molecular abnormalities that influence the selection of targeted therapies and PARP inhibitors. Nevertheless, analytical sensitivity may be affected by tumor burden and disease stage, particularly during earlier phases of the disease [8], [13].

Pancreatic cancer presented an intermediate level of clinical utility. Although this malignancy releases detectable circulating biomarkers in advanced stages, lower concentrations of ctDNA during localized disease reduce diagnostic sensitivity. Nevertheless, liquid biopsy has shown promise for treatment monitoring, prognostic assessment, and evaluation of postoperative minimal residual disease. Ongoing improvements in sequencing sensitivity and methylation-based approaches are expected to increase its clinical value in the future [2], [9].

Ovarian cancer demonstrated the lowest relative clinical utility among the tumor types represented in this figure. Although circulating biomarkers have shown encouraging results for disease monitoring, recurrence detection, and molecular characterization, widespread clinical implementation remains limited by biological variability, relatively low ctDNA concentrations in some clinical settings, and the need for further prospective validation. Emerging approaches involving exosomal biomarkers, methylation signatures, and multimodal molecular profiling may enhance future diagnostic performance.

The differences observed among tumor types primarily reflect biological characteristics rather than technological limitations alone. Tumor vascularization, cellular turnover, metastatic burden, anatomical location, and the quantity of circulating tumor-derived material substantially influence the analytical performance of liquid biopsy. Consequently, tumors that release greater amounts of ctDNA into the circulation generally demonstrate higher diagnostic yield and broader clinical applicability than tumors characterized by limited biomarker shedding [1], [7], [8].

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Another important factor influencing clinical utility is the availability of validated therapeutic biomarkers. Tumors such as non-small cell lung cancer possess numerous actionable genomic alterations supported by international clinical guidelines, allowing liquid biopsy findings to directly influence treatment selection. Conversely, malignancies with fewer validated molecular targets currently derive comparatively less immediate therapeutic benefit from plasma-based genomic testing, despite ongoing advances in translational research.

The reviewed literature also demonstrated that implementation varies considerably across healthcare systems. High-income countries have incorporated liquid biopsy into routine molecular oncology through standardized laboratory workflows, reimbursement mechanisms, and multidisciplinary precision medicine programs. In contrast, many Latin American countries continue to expand access through reference centers, academic collaborations, and participation in international clinical trials. Although important progress has been achieved, disparities in sequencing infrastructure, laboratory accreditation, specialized personnel, and healthcare financing remain significant barriers to widespread implementation.

Figure 4.

Longitudinal role of circulating tumor DNA in minimal residual disease surveillance

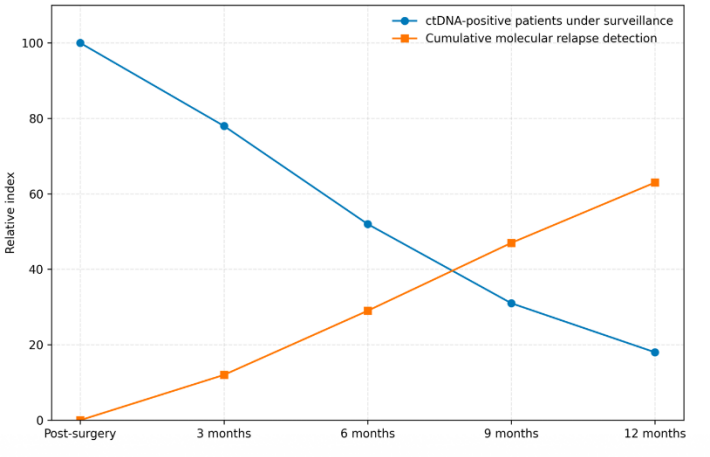

Figure 4 illustrates the longitudinal relationship between circulating tumor DNA (ctDNA) surveillance and the detection of molecular relapse following curative-intent treatment in patients with solid tumors. The figure represents the general pattern consistently described across the reviewed literature and summarizes the temporal evolution of molecular surveillance after surgery. The curves do not represent data from a single clinical trial but rather an integrated descriptive synthesis of the available scientific evidence regarding minimal residual disease (MRD).

Immediately after definitive treatment, ctDNA surveillance begins with the objective of identifying residual microscopic disease that cannot be detected through conventional imaging or routine clinical evaluation. During this early postoperative period, molecular assessment serves as the baseline for subsequent follow-up. Patients in whom ctDNA remains detectable after surgery consistently demonstrate a substantially higher probability of future recurrence than those with undetectable circulating tumor DNA [2], [3], [10], [12].

As longitudinal surveillance progresses, the proportion of patients with persistent postoperative ctDNA positivity gradually decreases because some individuals achieve complete molecular clearance after adjuvant therapy. However, among patients who continue to exhibit detectable ctDNA or experience re-emergence of circulating tumor DNA during follow-up, the cumulative probability of molecular relapse progressively increases. This observation has been repeatedly reported in colorectal, lung, breast, and several other solid malignancies, where molecular recurrence frequently precedes radiological recurrence by several months [2], [3], [12].

One of the most important clinical observations demonstrated by recent investigations is that ctDNA kinetics provide dynamic information regarding disease evolution rather than a single static measurement. Serial molecular monitoring allows clinicians to distinguish between sustained molecular remission and persistent molecular disease. Patients

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maintaining negative ctDNA throughout surveillance generally exhibit a more favorable clinical course, whereas repeated positive findings have consistently been associated with increased recurrence risk and poorer long-term prognosis [3], [10].

The temporal separation between molecular relapse and radiological progression represents one of the greatest strengths of liquid biopsy. Conventional imaging identifies structural changes only after tumor growth reaches a detectable threshold. In contrast, ctDNA analysis may reveal microscopic residual disease long before anatomical progression becomes visible. This earlier detection creates opportunities for individualized surveillance strategies and may support future treatment decisions once sufficient prospective evidence becomes available [2], [12].

The reviewed publications demonstrated particularly strong evidence for postoperative ctDNA monitoring in colorectal cancer. Multiple prospective investigations have shown that postoperative molecular positivity constitutes one of the strongest predictors of recurrence following curative surgery. Similar findings have subsequently been reproduced in breast cancer, non-small cell lung cancer, pancreatic cancer, melanoma, and urothelial malignancies, suggesting that minimal residual disease assessment may become broadly applicable across several solid tumors [2], [3], [10].

Despite these encouraging findings, several limitations should be considered when interpreting molecular surveillance results. The quantity of circulating tumor DNA released after surgery may be extremely low, particularly in patients with localized disease or tumors characterized by limited biological shedding. Consequently, analytical sensitivity depends heavily on sequencing depth, assay design, timing of blood collection, and laboratory methodology. False-negative results remain possible despite the presence of residual malignant cells, especially when residual tumor burden is minimal [1], [7], [13].

False-positive molecular findings also require careful interpretation. Clonal hematopoiesis of indeterminate potential may generate somatic mutations within circulating leukocytes that can mimic tumor-derived genomic alterations if appropriate bioinformatic filtering is not performed. For this reason, postoperative ctDNA results should always be interpreted together with clinical findings, pathological staging, imaging studies, and, whenever possible, tumor-informed molecular assays that improve analytical specificity [1], [13].

The clinical integration of minimal residual disease surveillance remains an active area of investigation. Several ongoing international clinical trials are evaluating whether treatment decisions based on postoperative ctDNA can improve disease-free survival while reducing unnecessary adjuvant therapy in patients with molecularly negative disease. These studies may determine the future role of liquid biopsy in individualized postoperative management and risk-adapted therapeutic strategies [3].

From an international perspective, implementation of MRD surveillance continues to expand within comprehensive cancer centers equipped with advanced molecular diagnostics. Although several Latin American institutions have progressively incorporated ctDNA testing into research protocols and selected clinical settings, broader implementation remains limited by sequencing costs, laboratory infrastructure, assay standardization, reimbursement policies, and availability of specialized personnel. Continued international collaboration will therefore be essential for facilitating equitable access to postoperative molecular surveillance across different healthcare systems.

Figure 5.

Principal barriers to the international implementation of liquid biopsy in solid tumors

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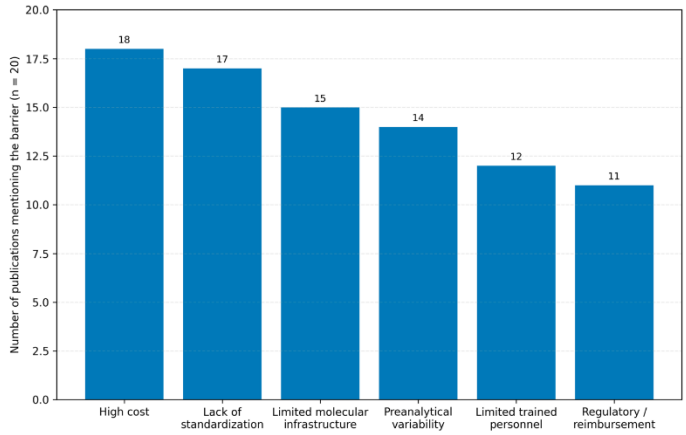

Figure 5 summarizes the principal barriers affecting the implementation of liquid biopsy in routine clinical practice as identified throughout the reviewed literature. The frequencies correspond to the number of publications in which each limitation was discussed as a significant factor influencing clinical adoption. Because individual studies frequently addressed several implementation challenges simultaneously, the categories are not mutually exclusive and should be interpreted as a descriptive synthesis of the available evidence rather than quantitative measurements of healthcare performance.

High cost emerged as the most frequently reported barrier, appearing in eighteen of the twenty reviewed publications. Although sequencing technologies have become progressively more accessible over the past decade, advanced molecular assays continue to require specialized equipment, highly trained personnel, quality-control programs, bioinformatic support, and accredited laboratory facilities. These requirements substantially increase operational costs and may limit routine implementation, particularly in middle- and low-income healthcare systems. The economic burden extends beyond laboratory testing itself and includes infrastructure maintenance, software validation, personnel training, and integration into multidisciplinary oncology programs [1], [7], [13].

The second most frequently identified limitation was the lack of analytical and methodological standardization. Differences in blood collection tubes, sample transportation, processing time, plasma isolation protocols, DNA extraction methods, sequencing platforms, bioinformatic pipelines, and variant interpretation criteria may generate variability among laboratories. Such heterogeneity complicates direct comparison between studies and may influence clinical reproducibility. International organizations continue to promote harmonized laboratory standards in order to facilitate broader implementation of liquid biopsy across different healthcare environments [1], [3], [13].

Limited molecular infrastructure represented another major challenge. The reviewed evidence demonstrated that successful implementation requires access to next-generation sequencing platforms, digital PCR technologies, computational resources, biobanking facilities, and specialized molecular pathology services. These capabilities are widely available in comprehensive cancer centers located in high-income countries but remain unevenly distributed across many developing regions. Consequently, patient access to advanced molecular diagnostics differs substantially between institutions and countries.

Preanalytical variability also constituted an important source of potential error. Biological specimens are particularly sensitive to delays in processing, inappropriate storage temperatures, repeated freeze–thaw cycles, contamination by genomic DNA released from leukocytes, and inadequate plasma separation procedures. Even small deviations during specimen handling may reduce analytical sensitivity or compromise result reliability. Therefore, standardized preanalytical workflows are considered essential for maintaining reproducibility and ensuring that molecular findings accurately reflect tumor-derived biomarkers rather than technical artifacts [7], [13].

The availability of adequately trained personnel represented another recurring concern. Liquid biopsy integrates expertise from oncology, pathology, molecular biology, laboratory medicine, genetics, bioinformatics, and computational biology. Accurate interpretation requires multidisciplinary collaboration capable of distinguishing clinically actionable alterations from technical artifacts, benign variants, or mutations related to clonal hematopoiesis.

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As molecular technologies become increasingly complex, continuous professional education and specialized training programs will remain essential components of successful implementation.

Regulatory and reimbursement challenges also appeared frequently in the reviewed literature. Although several international organizations have incorporated liquid biopsy into clinical practice guidelines for selected indications, reimbursement policies vary considerably among healthcare systems. In some countries, plasma-based genomic testing is routinely covered by public or private insurance programs, whereas in others, patients continue to rely on research protocols or self-funded testing. These differences contribute to unequal access despite growing scientific evidence supporting clinical utility.

The reviewed publications consistently emphasized that these barriers are particularly relevant in Latin America. Although countries such as Brazil, Mexico, Argentina, Chile, Colombia, and Peru have progressively expanded molecular oncology services through academic institutions, national cancer centers, and international collaborative networks, important disparities remain regarding sequencing capacity, laboratory accreditation, availability of specialized personnel, funding mechanisms, and equitable access for patients treated within public healthcare systems. Consequently, implementation frequently depends on institutional resources rather than national availability.

Despite these limitations, the overall trend observed throughout the literature remains highly encouraging. Continuous reductions in sequencing costs, technological improvements, greater automation, standardized laboratory protocols, cloud-based bioinformatic platforms, and increasing international collaboration are progressively reducing several of the current implementation barriers. Furthermore, ongoing multicenter clinical trials and evidence-based guideline development continue to strengthen confidence in the clinical integration of liquid biopsy within precision oncology.

DISCUSSION

The present review demonstrates that liquid biopsy has evolved from an experimental molecular technique into one of the most promising tools in precision oncology. The evidence synthesized throughout this study indicates that its clinical value extends well beyond early cancer detection, encompassing molecular characterization, therapeutic selection, longitudinal disease monitoring, minimal residual disease surveillance, identification of acquired resistance mechanisms, and evaluation of tumor heterogeneity. Collectively, these applications support the concept that cancer management is progressively shifting from static diagnostic evaluation toward continuous molecular surveillance, allowing treatment strategies to be adapted according to the biological evolution of each patient's disease [1], [3], [5].

One of the most consistent findings identified in the reviewed literature was the predominant role of circulating tumor DNA as the principal biomarker currently supporting liquid biopsy implementation. Compared with other circulating analytes, ctDNA has benefited from rapid technological advances in digital PCR, next-generation sequencing, methylation profiling, and ultra-sensitive sequencing platforms, resulting in improved analytical sensitivity and broader clinical applicability. These developments explain why most contemporary clinical studies focus primarily on ctDNA-based approaches rather than isolated analyses of circulating tumor cells, extracellular vesicles, or circulating RNA [1], [7], [8].

The findings presented in this review are consistent with previous international reports indicating that molecular profiling constitutes the most mature clinical application of liquid biopsy. Plasma-based genomic analysis has become particularly valuable in patients with advanced solid tumors when tissue biopsy is unavailable, insufficient, or technically difficult to obtain. In malignancies such as non-small cell lung cancer, colorectal cancer, breast cancer, and prostate cancer, identification of actionable genomic alterations directly influences therapeutic selection and allows individualized treatment strategies to be implemented according to the molecular characteristics of each tumor [8], [13], [14].

An important observation emerging from this review is the growing relevance of longitudinal molecular monitoring. Conventional imaging remains indispensable for evaluating structural disease progression; however, radiological changes frequently occur after molecular alterations have already developed. Serial ctDNA assessment provides dynamic information regarding tumor burden, therapeutic response, and clonal evolution throughout treatment.

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Consequently, liquid biopsy should not be considered a replacement for imaging or histopathological examination but rather a complementary tool capable of providing real-time molecular information that cannot be obtained through conventional diagnostic modalities alone [5], [11], [19].

Minimal residual disease represented another major theme identified during the analysis. Several publications consistently demonstrated that postoperative detection of circulating tumor DNA is strongly associated with recurrence risk across multiple solid tumors. This observation supports the hypothesis that molecular relapse frequently precedes radiological relapse, creating opportunities for earlier identification of patients at increased risk of disease recurrence. Nevertheless, although the prognostic value of postoperative ctDNA is now well established, prospective interventional studies remain necessary to determine whether modifying treatment exclusively on the basis of molecular findings improves long-term clinical outcomes [2], [3], [10], [12].

The reviewed evidence also emphasizes the importance of tumor heterogeneity in contemporary oncology. Solid tumors continuously evolve under selective therapeutic pressure, generating genetically distinct cellular populations capable of developing treatment resistance. Traditional tissue biopsy frequently captures only one anatomical region at a single time point and therefore may underestimate the genomic complexity of metastatic disease. Liquid biopsy partially overcomes this limitation by detecting circulating biomarkers originating from multiple tumor sites simultaneously, providing a broader representation of tumor evolution during systemic treatment [5], [8], [18].

Despite these important advantages, the results of this review indicate that several technical and clinical limitations continue to restrict universal implementation. Analytical sensitivity remains dependent upon biological tumor characteristics, including vascularization, disease stage, metastatic burden, and the amount of circulating tumor-derived material released into the bloodstream. Tumors with limited biological shedding may generate false-negative molecular findings despite the presence of residual malignant cells. Consequently, negative plasma results should always be interpreted within the broader clinical context and should not automatically exclude additional tissue-based investigation when clinically indicated [1], [7], [13].

Another relevant consideration involves analytical standardization. Considerable variability persists among laboratories regarding sample collection, plasma processing, DNA extraction, sequencing technologies, variant filtering, and bioinformatic interpretation. These methodological differences may influence reproducibility and complicate comparisons among published studies. International harmonization initiatives and standardized quality-control procedures will therefore be essential for facilitating broader clinical adoption and ensuring consistent interpretation across healthcare institutions [1], [13].

Economic and organizational factors also remain important determinants of implementation. The reviewed literature consistently highlighted the influence of sequencing costs, molecular laboratory infrastructure, reimbursement policies, and availability of specialized personnel. These barriers are particularly relevant in low- and middle-income countries, where access to advanced genomic technologies remains heterogeneous. Although several Latin American countries have expanded molecular oncology services through academic institutions, comprehensive cancer centers, and international collaborations, important disparities continue to exist regarding equitable access to precision medicine technologies.

The participation of Latin America deserves particular consideration because regional populations possess unique genetic diversity, epidemiological characteristics, healthcare structures, and resource limitations that may influence the clinical implementation of liquid biopsy. Increasing participation in multicenter clinical trials, regional genomic initiatives, and collaborative precision oncology networks represents an important opportunity for generating evidence that is directly applicable to local healthcare systems rather than relying exclusively on data derived from high-income countries. Continued investment in infrastructure, laboratory accreditation, professional training, and international scientific cooperation may substantially accelerate regional implementation.

Another important perspective emerging from this review concerns the future integration of multiple circulating biomarkers. Although ctDNA currently dominates the clinical landscape, accumulating evidence suggests that combining genomic information with transcriptomic, proteomic, epigenomic, fragmentomic, and extracellular vesicle analyses may substantially improve diagnostic sensitivity and predictive performance. Artificial intelligence and

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advanced computational models are expected to facilitate interpretation of these increasingly complex datasets, supporting more individualized therapeutic decision-making and expanding the role of liquid biopsy within precision oncology.

Several limitations of the present review should also be acknowledged. The analysis was based on published scientific evidence, and therefore the conclusions depend on the quality and heterogeneity of the available literature. Differences in study design, patient populations, analytical platforms, biomarker definitions, and clinical endpoints limited direct comparison across investigations. Furthermore, because liquid biopsy represents a rapidly evolving field, ongoing technological innovations and results from prospective clinical trials may modify current clinical recommendations in the coming years.

CONCLUSION

Liquid biopsy has emerged as one of the most significant advances in precision oncology, providing a minimally invasive approach for obtaining dynamic molecular information throughout the clinical course of patients with solid tumors. The evidence analyzed in this review demonstrates that its clinical value extends considerably beyond early cancer detection, encompassing molecular profiling, therapeutic selection, longitudinal treatment monitoring, minimal residual disease assessment, identification of acquired resistance mechanisms, and evaluation of tumor heterogeneity. These applications collectively support a more personalized approach to cancer management based on the continuous molecular evolution of individual tumors.

Among the available circulating biomarkers, circulating tumor DNA currently represents the most clinically validated component of liquid biopsy because of its compatibility with highly sensitive sequencing technologies and its demonstrated utility across multiple solid malignancies. Nevertheless, complementary biomarkers—including circulating tumor cells, extracellular vesicles, circulating RNA, tumor-educated platelets, and circulating proteins—continue to expand the biological information available through minimally invasive molecular analysis. The future of liquid biopsy will likely depend on the integration of these multiple analytes using advanced computational methods capable of improving diagnostic precision and predictive performance.

The findings of this review also demonstrate that the degree of clinical implementation varies according to tumor biology, analytical methodology, healthcare infrastructure, and availability of validated therapeutic biomarkers. Non-small cell lung cancer, colorectal cancer, and breast cancer currently exhibit the strongest evidence supporting routine clinical use, whereas several other malignancies continue to benefit from ongoing technological development and prospective clinical validation. Despite these differences, the overall direction of contemporary research consistently supports the progressive incorporation of liquid biopsy into routine oncology practice.

Important challenges remain before universal implementation can be achieved. Standardization of laboratory methodologies, optimization of analytical sensitivity, reduction of sequencing costs, harmonization of regulatory frameworks, expansion of specialized molecular infrastructure, and development of multidisciplinary expertise are essential to ensure reliable and equitable access to liquid biopsy technologies. Addressing these challenges will be particularly important for healthcare systems in low- and middle-income countries, where disparities in molecular diagnostic resources continue to influence patient access to precision medicine.

From an international perspective, growing participation by Latin American institutions in molecular oncology research, multicenter collaborations, and precision medicine initiatives represents an encouraging development. Continued investment in scientific research, laboratory capacity, professional training, and international cooperation may facilitate broader implementation of liquid biopsy throughout the region while generating evidence that reflects the genetic diversity and healthcare realities of Latin American populations.

In conclusion, liquid biopsy represents a transformative strategy that is reshaping the management of solid tumors by enabling continuous molecular surveillance throughout the natural history of cancer. Rather than replacing conventional tissue biopsy, it complements existing diagnostic approaches by providing clinically relevant information that supports individualized therapeutic decisions and more adaptive patient management. As technological innovation,

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prospective clinical evidence, and international collaboration continue to advance, liquid biopsy is expected to become an increasingly integral component of precision oncology, contributing to more effective, personalized, and evidence-based cancer care worldwide.

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