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**Review Paper**

# Liquid Biopsy for Pathogen Detection in Precision Infectious Disease Diagnostics

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## ABSTRACT

Background : Infectious diseases remain a global health challenge, where timely and accurate diagnosis is critical for effective treatment. Conventional pathogen detection methods, while reliable, are often slow, invasive, and limited in detecting subtle or deep-seated infections. Unlike conventional diagnostics, liquid biopsy enables pathogen detection independent of microbial viability, positioning it as a potential paradigm shift in precision infectious disease management.Objective : This review aims to explore liquid biopsy as a non-invasive approach for pathogen detection and to evaluate its applications in precision infectious disease diagnostics, including pathogen identification, treatment guidance, and disease monitoring.Methods:This review analyzed scientific literature from PubMed and PubMed Central (PMC), focusing on studies reporting the diagnostic performance, clinical utility, and technological advancements of liquid biopsy-based pathogen detection, including metagenomic next-generation sequencing (mNGS), digital PCR (dPCR), and extracellular vesicle analysis.Conclusion: Liquid biopsy offers a promising, non-invasive, and rapid diagnostic modality for complex and culture-negative infectious diseases, enabling precision antimicrobial guidance; however, its clinical adoption remains constrained by the need for assay standardization, robust contamination control, and large-scale validation...

## INTRODUCTION

Accurate and timely detection of pathogenic microorganisms is a cornerstone of infectious disease management and clinical microbiology. Conventional diagnostic approaches, including culture, microscopy, serology, and targeted molecular assays, remain widely used but are often limited by prolonged turnaround times, reduced sensitivity following antimicrobial exposure, and difficulty in detecting fastidious or unculturable pathogens [1,2,9]. These limitations are

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particularly evident in critically ill patients and in cases of sepsis, culture-negative infections, and deep-seated infections, where delayed diagnosis can negatively impact clinical outcomes [1,2].

Liquid biopsy emerged as a minimally invasive diagnostic strategy in oncology, where early studies demonstrated that circulating tumor DNA, circulating tumor cells, extracellular vesicles, and tumor-associated RNA present in body fluids reflect tumor burden, molecular heterogeneity, and therapeutic response [3,4,10]. These findings established the fundamental theory that disease-specific molecular material released into circulation can serve as reliable non-invasive diagnostic biomarkers [3,4].

This concept has since been extended to infectious diseases, where pathogenic microorganisms release microbial cell-free DNA into host biofluids during replication, tissue invasion, and immune-mediated lysis [5,6]. Advances in metagenomic next-generation sequencing and cell-free DNA–based assays now enable unbiased detection of bacterial, viral, fungal, and parasitic pathogens directly from plasma, supporting precision infectious disease diagnostics in conditions such as invasive fungal infections, transplant-associated infections, and complex pulmonary diseases [5,6,7,11]. Experimental studies also suggest that abnormal circulating protein signatures associated with prion diseases may be detectable using liquid biopsy approaches [8]. However, challenges related to assay standardization, contamination control, data interpretation, and large-scale clinical validation remain significant barriers to routine clinical implementation [5,7].

Despite increasing research interest, a consolidated evaluation of liquid biopsy technologies within the framework of precision infectious disease diagnostics remains limited.

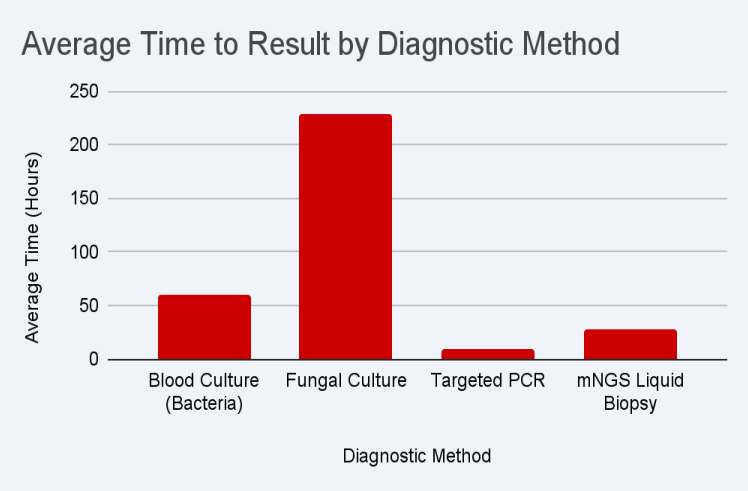


***Figure 1: Turnaround time (TAT) comparison from sample collection to result. Liquid biopsy demonstrates a standardized TAT regardless of pathogen growth rate, whereas conventional methods are limited by microbial doubling time.***

***(Source: Adapted from Chiu & Miller, 2019).***

**Review of Literature**

Liquid biopsy refers to the analysis of disease-derived molecular components present in body fluids, enabling non-invasive diagnosis and monitoring of pathological states. This facilitates clinical diagnosis and monitoring illness without needing invasive procedures [11,19]. It started in the field of cancer, where pieces of DNA from tumors, RNA from tumor cells, extracellular vesicles, and proteins linked to the tumor were found to reflect tumor burden, molecular heterogeneity, and treatment response [11]. These disease-derived molecular markers are released naturally into circulation and can be used for non-

invasive health assessment [19]. Microbial cell-free DNA (mcfDNA) serves as the primary biomarker for liquid biopsy in infectious diseases. Originating from microbial replication, tissue invasion, and immune-mediated lysis, these fragments provide a real-time molecular snapshot of infection [19, 18]. Unlike host-derived cfDNA, mcfDNA provides a molecular signature of active or recent infection independent of the pathogen's ability to grow in vitro [11,17].

Microbial cell-free DNA (cfDNA) refers to small fragments of genetic material released by pathogens into body fluids such as blood, plasma, or urine during infection [11,19]. This release occurs through several biological processes, including microbial replication, tissue invasion, immune-mediated destruction, and natural microbial death [11,19].

One of the primary sources of microbial cfDNA is microbial lysis. Pathogens can break apart when attacked by host immune cells such as neutrophils and macrophages or following exposure to antimicrobial therapy, leading to the release of DNA fragments into the circulation [17,18]. Importantly, microbial cfDNA may remain detectable even when viable organisms are no longer present, such as after antibiotic treatment or in deep-seated infections where pathogens are not directly accessible [11].

Microbial cfDNA differs from host-derived cfDNA in both size and dynamics. It is typically shorter, often ranging between 100 and 200 base pairs, and has a short half-life due to rapid clearance by nucleases and renal filtration [19]. Nevertheless, advanced molecular techniques such as metagenomic next-generation sequencing (mNGS) and digital PCR enable highly sensitive detection of these fragments, providing real-time insights into active or recent infections [17,18].

The presence of microbial cfDNA in circulation does not necessarily indicate bloodstream infection but rather reflects microbial activity somewhere in the body. This feature is particularly valuable in diagnosing culture-negative infections, infections caused by fastidious organisms, or conditions where invasive sampling is difficult or risky [11,17].In addition to free DNA fragments, some pathogens release extracellular vesicles containing microbial DNA and RNA. These vesicles protect nucleic acids from rapid degradation, increasing their stability in circulation and enhancing detectability [11,19]. When combined with host-response biomarkers, microbial cfDNA analysis contributes to a comprehensive molecular profile of infection.

Overall, microbial cfDNA originates from immune-mediated killing, antimicrobial exposure, and pathogen-derived vesicle release. Its detectability using modern molecular platforms forms the biological foundation of liquid biopsy–based diagnostics, offering a non-invasive and sensitive approach for identifying and monitoring infectious diseases [11,18].

## Methodology

This review focused on current scientific literature to evaluate the comparative performance and technical frameworks of liquid biopsy-based diagnostic modalities for infectious diseases. A systematic search was performed across PubMed and PubMed Central (PMC) databases to identify studies addressing advanced molecular tools used for pathogen detection in host biofluids, with particular emphasis on studies reporting the real-world diagnostic performance of metagenomic next-generation sequencing (mNGS), digital PCR (dPCR), quantitative PCR (qPCR), and extracellular vesicle analysis.

The review followed a structured narrative synthesis approach, prioritizing studies reporting diagnostic performance, clinical utility, and technological advancements in liquid biopsy for infectious diseases.

**Search Strategy:**

Keywords used included: "liquid biopsy", "microbial cell-free DNA", "infectious diseases", "metagenomic next-generation sequencing", "digital PCR", and "pathogen detection".

**Inclusion Criteria:**

- Studies focusing on liquid biopsy applications in infectious disease diagnostics
- Articles reporting diagnostic performance, clinical utility, or technological advancements
- Peer-reviewed original research and review articles

**Exclusion Criteria:**

- Non-English publications
- Studies lacking clinical or diagnostic relevance
- Case reports with limited generalizability

A total of **56 studies** were initially identified, of which **29 relevant studies** were included after screening titles, abstracts, and full texts based on relevance and quality.

**Technologies Used in Liquid Biopsy for Pathogen Detection**

Liquid biopsy uses special tools that find pathogen materials, like DNA, RNA, and extracellular vesicles from microbes, directly in body fluids. These tools help find infections without needing to take tissue samples, and they work quickly and accurately, even when regular tests don't find anything [11,18].

1. **Metagenomic Next-Generation Sequencing (mNGS):**
   This approach enables unbiased sequencing of total nucleic content within a sample, facilitating comprehensive pathogen detection. It can find bacteria, viruses, fungi, and parasites. It's especially useful for serious or hard-to-find infections and can check for many different germs at the same time [11,17].
2. **Digital PCR (dPCR):**
   This technique divides DNA into many small parts and measures each part separately. It helps find very small amounts of microbial DNA that might be broken or hard to detect. This is useful for tracking how much of a pathogen is in the body during treatment [17,18].
3. **qPCR and Targeted Panels:**
   qPCR is a quick way to find specific known germs. It works well for confirming results from other tests like mNGS or dPCR. Although it can't find new or unknown germs, it is cheaper and easier to use [11].
4. **Extracellular Vesicle and RNA Analysis:**
   Some germs release extracellular vesicles called extracellular vesicles that carry their genetic material into the blood. These packages protect the genetic material from being broken down. Studying these vesicles can show if an infection is active and can support findings from other DNA tests [11,19].
5. **New and Upcoming Technologies:**
   New methods like CRISPR-based tests and nanopore sequencing are being developed for faster, more accurate, and real-time pathogen detection. These could be used in doctors' offices or at the bedside, making testing easier and quicker [11, 18].

By combining mNGS, dPCR, qPCR, and extracellular vesicle analysis, liquid biopsy allows **rapid, sensitive, and non-invasive pathogen detection**, forming the foundation for precision infectious disease diagnostics [11,17,18,19]. Among these platforms, mNGS enables hypothesis-free pathogen detection, whereas dPCR offers superior analytical sensitivity in low-burden infections, and qPCR remains advantageous for rapid targeted confirmation.

The Advantage of liquid biopsy over conventional diagnostics is summarized in Table 1

**Table 1. Comparison of Liquid Biopsy–Based Pathogen Detection and Conventional Diagnostic Methods**

| Feature / Parameter | Liquid Biopsy (cfDNA / mNGS-based methods) | Conventional Diagnostics (Culture / CMT) |
|---|---|---|
| **Invasiveness** | Minimally invasive (blood or other body fluids) | Often invasive (tissue biopsy, repeated sampling) |
| **Turnaround Time** | Rapid to moderate (hours to days, depending on platform) | Slow (days to weeks, especially for fastidious organisms) |
| **Detection of Fastidious / Unculturable Pathogens** | High capability; detects organisms independent of viability | Limited or absent detection |
| **Performance After Antibiotic Exposure** | Less affected; detects residual microbial cfDNA | Markedly reduced sensitivity |
| **Pathogen Spectrum** | Broad, hypothesis-free detection (bacteria, viruses, fungi, parasites) | Limited to targeted organisms |
| **Utility in Culture-Negative Infections** | High diagnostic yield in culture-negative and deep-seated infections | Poor diagnostic yield |
| **Detection of Polymicrobial Infections** | Effective detection of multiple pathogens simultaneously | Often misses co-infections |
| **Quantitative Monitoring** | Enables longitudinal monitoring of pathogen burden | Limited or not feasible |
| **Assessment of Pathogen Viability** | Cannot distinguish live vs dead organisms | Confirms viable organisms |
| **Antimicrobial Resistance Information** | Limited and incomplete due to fragmented cfDNA | Direct phenotypic susceptibility testing possible |
| **Risk of Contamination** | Susceptible to environmental and reagent DNA contamination | Lower contamination risk |
| **Clinical Impact on Management** | Supports early diagnosis and targeted therapy in complex cases | Standard reference method but limited in difficult cases |
| **Cost and Infrastructure** | High cost; requires sequencing platforms and bioinformatics expertise | Lower cost; widely available |

*As summarized in Table 1, liquid biopsy-based approaches demonstrate significant advantages over conventional diagnostic methods in terms of speed, pathogen diversity, and diagnostic yield, particularly in culture-negative and complex infections. However, limitations related to cost,*

*contamination risk, antimicrobial resistance profiling, and inability to assess pathogen viability highlight the need for liquid biopsy to be used as a complementary rather than replacement diagnostic tool.*


**Figure 2: Integrated Liquid Biopsy Workflow for Precision Infectious Disease Diagnostics.**

*This process illustrates the transition from minimally invasive sample collection and molecular processing to hypothesis-free detection and clinical decision-making. Unlike conventional culture, this workflow enables rapid pathogen identification and antimicrobial stewardship within a standardized timeframe. Source: Compiled by authors based on published literature ( Zhang et al., 2024; Duan et al., 2021; Sun et al., 2026; Yang et al., 2024; Lai et al., 2025; Lin et al., 2023; Yu et al., 2024)*

## RESULTS

Analysis of the reviewed literature demonstrates that liquid biopsy in infectious diseases is primarily driven by advanced molecular technologies capable of detecting circulating microbial components in body fluids. Metagenomic next-generation sequencing (mNGS) consistently emerged as a cornerstone platform, offering unbiased, hypothesis-free detection of bacterial, viral, fungal, and parasitic pathogens within a single assay. This approach is

particularly valuable in critically ill patients, deep-seated infections, and culture-negative clinical scenarios. Digital PCR (dPCR) enhances analytical sensitivity through sample partitioning, enabling accurate detection and quantification of low-abundance or fragmented microbial cell-free DNA (cfDNA). This makes it highly suitable for therapeutic monitoring and assessment of pathogen burden dynamics. In contrast, quantitative PCR (qPCR) and targeted multiplex panels provide rapid and cost-effective detection of predefined pathogens, often serving as confirmatory or complementary tools to sequencing-based methods.

Additionally, extracellular vesicle–associated nucleic acid analysis offers insight into active infection states by detecting protected microbial genetic material circulating in plasma. Emerging innovations, including CRISPR-based diagnostics and nanopore sequencing technologies, indicate a shift toward faster, real-time, and potentially point-of-care pathogen detection platforms. Compared with conventional culture-based diagnostics, liquid biopsy demonstrates several clinically meaningful advantages. It is minimally invasive, requiring only blood or other accessible body fluids, thereby reducing procedural risk and improving patient compliance. The reviewed evidence highlights superior diagnostic yield in culture-negative infections, infections occurring after antibiotic exposure, and cases involving fastidious or unculturable organisms.

Liquid biopsy approaches enable broad-spectrum pathogen detection independent of organism viability, facilitating identification of polymicrobial infections that may be underrecognized by standard culture methods. Furthermore, quantitative assessment of circulating microbial DNA supports longitudinal monitoring of treatment response, offering a dynamic biomarker of disease progression and therapeutic efficacy. Despite its diagnostic potential, several limitations remain. Liquid biopsy cannot reliably differentiate between viable and non-viable organisms, which may complicate interpretation in treating or resolving infections. Antimicrobial resistance profiling remains incomplete, particularly when relying on fragmented cfDNA rather than phenotypic susceptibility testing.

Technical challenges include susceptibility to environmental and reagent contamination, requirement for advanced sequencing infrastructure, high operational costs, and dependence on specialized bioinformatics expertise. These barriers currently limit universal clinical implementation but also delineate clear areas for methodological refinement and standardization.

Collectively, these findings highlight the complementary roles of sequencing-based and amplification-based technologies in advancing non-invasive pathogen detection.

## DISCUSSION

Based on the collective evidence analyzed in this review, several developmental trajectories are poised to shape the advancement of liquid biopsy in accurate infectious disease diagnostics. A primary challenge highlighted over studies is the variability in pre-analytical and analytical strategies, which hampers reproducibility and cross-institutional comparability; subsequently, future advancement will depend on the standardization of sample collection, cfDNA extraction, sequencing stages, and bioinformatic pipelines [1,2,3]. While early clinical applications demonstrate strong performance in systemic diseases, sensitivity is decreased in low microbial load states, emphasizing the need for enhanced microbial cfDNA improvement and host-background suppression to improve detection in localized, early-stage, or partially treated diseases

[4,5]. The non-invasive utility of microbial cell-free DNA (mcfDNA) analysis presents a significant clinical advantage for vulnerable patient cohorts, such as transplant recipients and neonates, in whom invasive tissue sampling is frequently contraindicated due to procedural risks. In scenarios involving suspected invasive fungal disease, liquid biopsy facilitates the expedited identification of *Aspergillus* species while circumventing the morbidity associated with lung biopsy, thereby optimizing both patient safety and diagnostic compliance. [6,7]. Serial cfDNA estimations advance offer dynamic monitoring of infection dynamics, providing real-time insights into treatment response, persistence, and early relapse detection compared with conventional diagnostics [8,9]. Recognizing the limitations of cfDNA alone in distinguishing colonization from active infection, future diagnostic frameworks are likely to adopt multi-omic approaches, integrating circulating RNA, proteins, extracellular vesicles, and host-response biomarkers for more biologically instructive interpretations [10,11]. Large-scale, multicenter clinical validation remains essential to demonstrate utility, cost-effectiveness, and effect on persistent outcomes [12]. The non-invasive nature of liquid biopsy is especially beneficial for high-risk populations, including immunocompromised patients, transplant recipients, neonates, and critically ill individuals, justifying targeted validation in these groups [13,14]. Beyond clinical validation, the adoption of liquid biopsy is driven by **diagnostic stewardship**. While mNGS has higher upfront costs than culture, it provides a definitive diagnosis within 24–48 hours. This drastically reduces the 'Average Time to Result' compared to fungal cultures, which can exceed 200 hours. By delivering faster results, liquid biopsy allows for earlier targeted therapy, shorter hospital stays, and reduced use of expensive, unnecessary broad-spectrum antibiotics. Finally, expanding the detectable pathogen spectrum beyond conventional infectious agents including prion-associated biomarkers and rising pathogens may significantly broaden the clinical and epidemiological applications of this technology [15,16].

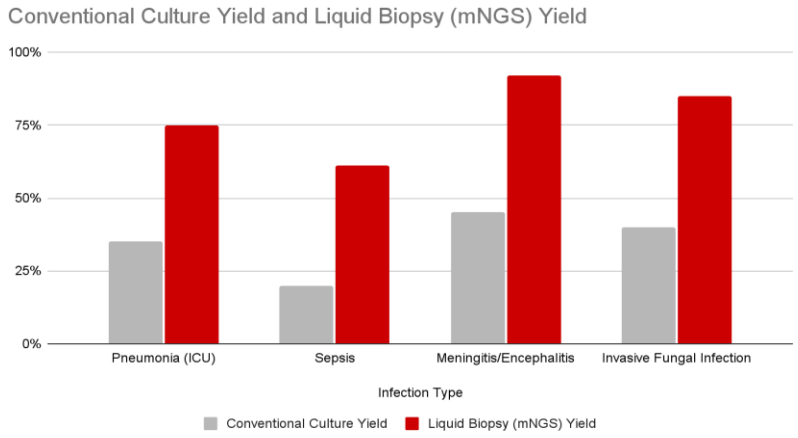


***Figure 1: Comparative Diagnostic Yield of mNGS vs. Conventional Culture. The bar graph illustrates the superior sensitivity of metagenomic next-generation sequencing (mNGS) over conventional culture-based methods across four critical infection categories. The diagnostic gap is most pronounced in invasive fungal infections and sepsis, where traditional methods often yield negative results due to low pathogen burden or prior antimicrobial exposure.***

***(Compiled by authors based on the published literature from Blauwkamp et al., 2019 and Miao et al., 2018).***

## CONCLUSION

Liquid biopsy, particularly the analysis of circulating microbial cell-free DNA using advanced molecular technologies such as metagenomic next-generation sequencing (mNGS), represents a promising complementary tool in infectious disease diagnostics [11,18,21]. It enables rapid, non-invasive, and unbiased detection of a broad spectrum of pathogens, including fastidious, deep-seated, and culture-negative infections, and facilitates precision-guided antimicrobial therapy and longitudinal monitoring [18,20,22,23,24,25,26]. Despite these advantages, limitations related to assay standardization, contamination risk, inability to assess pathogen viability, and incomplete antimicrobial resistance profiling highlight the need for careful integration alongside conventional diagnostics [11,21,22]. Future research should focus on large-scale clinical validation, standardization of workflows, and incorporation of multi-omic approaches to maximize diagnostic accuracy and clinical utility, particularly in high-risk populations [18,22,24]. Future integration with artificial intelligence-driven interpretation platforms may further enhance diagnostic accuracy and clinical decision support.

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