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Evolving Approaches in Tuberculosis Diagnostics: Present Insights and Future Perspectives

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ABSTRACT

TB is still a major public health problem and is responsible for substantial mortality and morbidity around the world. Timely and proper diagnosis is crucial for proper treatment and disease control. The review highlights the existing and new strategies used for TB diagnosis, such as conventional and molecular methods, immunological assays, biosensor-based platforms, and artificial intelligence (AI)-aided tools. New technologies like GeneXpert testing, NG sequencing, and non-sputum-based diagnostics have enhanced the timeliness and quality of TB diagnosis, especially drug-resistant TB. But problems associated with cost, infrastructure, and accessibility persist in preventing broad adoption. New diagnostic opportunities related to technologies that are faster, cheaper, and more user-friendly, developed at the point of care, could improve TB detection and help to contribute to global TB elimination.

Keywords: Tuberculosis, TB diagnostics, Molecular diagnostics, GeneXpert, Drug-resistant tuberculosis

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Introduction

Tuberculosis (TB) is an ancient disease that has afflicted humanity for more than 4,000 years [1]. It is caused by the bacterium *Mycobacterium tuberculosis* and spreads primarily through airborne transmission from person to person [2]. While TB most commonly affects the lungs (pulmonary TB), it can also involve other organs such as the brain, kidneys, intestines, and spine. Clinical manifestations vary depending on the site of infection; pulmonary TB typically presents with a persistent cough, chest pain, hemoptysis, fatigue, weight loss, fever, and night sweats. Despite being a preventable and treatable disease, TB remains one of the leading causes of morbidity and mortality, particularly in developing countries [3]. Globally, TB continues to pose a major public health challenge, with an estimated 10 million new cases and 1.2–1.7 million deaths reported annually between 2019 and 2021, making it the leading cause of death from a single infectious agent before the COVID-19 pandemic [4][5]. Prevalence estimates are similar to incidence, with about 10–11 million people living with active TB at any given time [5]. The burden is disproportionately concentrated in low- and middle-income countries, particularly in Southeast Asia, Africa, and the Western Pacific, which together account for over 80% of global cases and deaths [6][7]. While the overall global incidence, prevalence, and mortality rates have declined slowly over the past three decades, progress is uneven, with some regions and vulnerable populations (such as people living with HIV, children, and those with multidrug-resistant TB) experiencing higher rates and slower declines [8][9]. Notably, post-TB and latent TB infection represent additional, often underappreciated, components of the global disease burden [10][11]. The COVID-19 pandemic has further complicated TB control, disrupting diagnosis and treatment services and threatening to reverse recent gains [5][12].

Despite decades of global efforts, effective TB control continues to face major challenges. Delayed diagnosis remains a significant barrier, with diagnostic delays ranging from weeks to several months due to patient-related factors such as low awareness, stigma, and financial hardship, as well as health system barriers including inadequate laboratory capacity and poor referral mechanisms [13][14][15]. The growing burden of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB further complicates management, as treatment is longer, more toxic, less effective, and costly, with limited access to advanced diagnostics and newer drugs in resource-constrained regions [16][17][18]. In addition, TB control in high-burden countries is severely hindered by weak healthcare infrastructure, shortages of trained personnel, and the influence of social determinants such as poverty, malnutrition, and HIV co-infection [16][19]. Although recent innovations—including rapid molecular diagnostics, novel drug regimens, and digital health tools—offer promising opportunities, their implementation and equitable access remain restricted, underscoring the urgent need for sustainable solutions to overcome these persistent barriers [17][20].

Timely and accurate diagnosis is central to effective TB control, and recent diagnostic innovations have transformed the landscape of disease detection. Rapid molecular tools such as Xpert MTB/RIF and Xpert Ultra have significantly improved sensitivity, particularly among smear-negative and HIV-positive patients, while also enabling early drug resistance detection [21][22]. Emerging point-of-care and non-sputum-based diagnostics, including urine LAM, blood biomarkers, and CRISPR-based assays are expanding access for vulnerable populations such as children and people unable to produce sputum [23][33][34]. Advanced technologies like next-generation sequencing further enhance the detection of drug-resistant TB, supporting tailored treatment and reducing the risk of treatment failure [24]. Collectively, these innovations hold immense potential to accelerate case detection, enable earlier treatment initiation, and ultimately reduce TB incidence and mortality. However, their full impact depends on equitable access, integration into health systems, and investment in infrastructure and training.

This article aims to provide a comprehensive overview of current and emerging approaches in TB diagnostics, highlighting their strengths, limitations, and potential to address existing challenges. It discusses the impact of delayed diagnosis, drug resistance, and resource constraints, while examining how innovations such as rapid molecular tools, non-sputum-based assays, and next-generation sequencing can transform TB detection and management. The objective is to evaluate present insights, explore future perspectives, and identify key priorities for improving diagnostic accessibility and effectiveness in diverse healthcare settings.

Current Landscape of TB Diagnostics:

Conventional diagnostic approaches remain the cornerstone of tuberculosis (TB) detection in many high-burden, resource-limited settings. Microscopy—either Ziehl-Neelsen staining or fluorescence microscopy—provides a rapid and inexpensive means of identifying acid-fast bacilli in sputum, but its sensitivity is limited, particularly in HIV-positive, pediatric, and extrapulmonary TB cases [25][26]. Culture methods, including solid Lowenstein-Jensen media and liquid systems such as MGIT-960, serve as the gold standard due to their high specificity and capacity for drug susceptibility testing; however, they are constrained by long turnaround times (weeks for solid media, up to two weeks for liquid systems) and the need for laboratory infrastructure [26][27]. Radiological tools such as chest X-rays and CT scans are frequently employed for screening and assessment of lung pathology, yet they lack specificity and cannot definitively distinguish TB from other respiratory conditions [27][28]. Collectively, these conventional methods are hindered by sensitivity and specificity challenges, slow diagnostic timelines, and infrastructure dependence, underscoring the need to integrate them with rapid molecular and biomarker-based technologies for timely and accurate TB control [25][26].

Recent Innovations in TB Diagnostics

Molecular Diagnostics

Molecular diagnostics have revolutionized TB detection by enabling rapid identification of Mycobacterium tuberculosis and drug resistance. PCR-based assays provide substantially higher sensitivity than microscopy and can detect TB in smear-negative and extrapulmonary cases. Among these, GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra have transformed frontline TB diagnosis by delivering results within two hours while simultaneously identifying rifampicin resistance, with Ultra offering improved sensitivity in paucibacillary disease [27]. Line probe assays expand molecular capabilities by enabling rapid detection of resistance to first- and second-line drugs, facilitating early regimen optimization [28]. More recently, next-generation sequencing (NGS) has emerged as a powerful tool for comprehensive resistance profiling, outbreak investigation, and transmission surveillance, although its routine use remains limited by cost, data interpretation requirements, and laboratory capacity [29].

Immunological Diagnostics

Immunological diagnostics play an important complementary role in TB detection and screening. Interferon-gamma release assays (IGRAs) are widely used for diagnosing latent TB infection but lack the ability to reliably distinguish active disease from latent infection. Point-of-care lateral flow assays, particularly urine lipoarabinomannan (LAM) tests, have demonstrated clinical value in hospitalized and severely immunocompromised patients with HIV, where sputum-based diagnostics are often infeasible [30]. In parallel, emerging host biomarker-based assays, including transcriptomic and proteomic signatures, show promise for non-sputum-based diagnosis and treatment monitoring, although further validation is required before clinical implementation [31].

Biosensors and Nanotechnology-Based Diagnostics

Biosensors and nanotechnology-based diagnostic platforms represent an emerging frontier in TB diagnostics. Nanoparticle-based detection systems enhance analytical sensitivity by amplifying biological signals, enabling detection of low concentrations of TB biomarkers. Lab-on-a-chip platforms integrate sample preparation, amplification, and detection into compact, portable devices, offering the potential for rapid, decentralized testing in peripheral healthcare settings. Although largely in the developmental or early validation stages, these technologies may address key limitations of current diagnostics by combining speed, portability, and accuracy [34].

Digital and AI-Assisted Diagnostics

Digital health innovations and artificial intelligence (AI) are increasingly applied to TB diagnosis, particularly for image-based screening. AI-driven chest X-ray interpretation systems have demonstrated diagnostic performance comparable to expert radiologists and are being deployed for large-scale TB screening in high-burden settings [35]. Smartphone-based diagnostic tools and cloud-connected platforms facilitate remote interpretation and data sharing, expanding access to expert diagnostics. Additionally, the integration of big data analytics and predictive modeling supports identification of transmission hotspots and optimization of screening strategies, strengthening population-level TB control efforts [36].

Challenges and Barriers to Implementation

Despite significant progress, multiple barriers hinder widespread implementation of innovative TB diagnostics. High costs and limited affordability restrict access in low-income settings, while infrastructure and training requirements constrain decentralization. Policy, regulatory, and quality assurance gaps further delay adoption, and successful scale-up requires alignment with national TB programs and health system capacities. Acceptance and integration into routine practice depend on sustainable financing, workforce development, and political commitment [37].

Future Directions:

Future TB diagnostic strategies increasingly emphasize non-sputum-based diagnostics, including blood, urine, and breath-based assays, to overcome challenges associated with sputum collection. Multiplex diagnostics capable of detecting TB alongside co-infections such as HIV may improve efficiency and patient-centered care. Advances in portable, low-cost point-of-care devices, combined with precision diagnostics and personalized medicine, hold promise for tailoring therapy. Integration with digital health and telemedicine platforms will be critical to extending diagnostic reach and continuity of care.

Conclusion

Substantial progress has been achieved in TB diagnostic innovation across molecular, immunological, digital, and biosensor-based technologies. However, achieving meaningful public health impact requires balancing technological sophistication with affordability, feasibility, and health system readiness. Continued investment in context-appropriate diagnostics, coupled with strong policy support and global collaboration, will be essential to achieving TB elimination goals.

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