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Review Article

Advances in tuberculosis diagnostics: From molecular innovations to AI-driven solutions

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Abstract

Tuberculosis (TB) continues to pose a serious threat to world health, improvements in diagnostic technologies are essential for both early identification and successful treatment. The sensitivity, rapidity, and accessibility of traditional diagnostic procedures, such as sputum smear microscopy and culture methods, are limited. Accuracy, turnaround time, and scalability have all increased with recent advancements in TB tests. Mycobacterium tuberculosis and medication resistance can be quickly identified thanks to molecular diagnostics like GeneXpert MTB/RIF and Truenat. TB strains and resistance mutations can be accurately identified using next-generation sequencing (NGS) and CRISPR-based diagnostics. Early screening is improved by artificial intelligence (AI)-assisted imaging methods, such as automated chest X-ray interpretation, especially in environments with limited resources. The sensitivity and specificity of point-of-care diagnostics are enhanced by biosensors and nanotechnology-based methods. Latent TB infection diagnosis is also made easier by immunodiagnostic procedures such host biomarker-based tests and interferon-gamma release assays (IGRAs). Personalized TB diagnostics may be developed by the use of multi-omics techniques that combine transcriptomics, proteomics, and metabolomics. Additionally, new wearable and non-invasive breath-based detection techniques are becoming more popular. Cost, accessibility, and integration into healthcare systems are still issues in spite of these developments. Future studies should concentrate on integrating digital health to improve real-time surveillance, scalability, and affordability. By guaranteeing prompt and precise detection, the ongoing development of TB diagnostics will be essential to reaching the worldwide TB elimination targets.

Keywords: Tuberculosis, Molecular diagnostics, Artificial intelligence, Biosensors, Next-generation sequencing.

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1. Introduction

1.1. Overview of TB as a Global health burden

Due to its high rates of morbidity and mortality, especially in low- and middle-income countries (LMICs), tuberculosis (TB) continues to be a major worldwide health concern. According to estimates from the World Health Organization (WHO), TB is the second most common infectious agent-related cause of death after COVID-19, accounting for around 1.5 million fatalities and almost 10 million new cases every year. The rise of extensively drug-resistant (XDR-TB) and multidrug-resistant (MDR-TB) strains of the disease, which make treatment more difficult and raise the risk of transmission, contributes to the ongoing burden of TB. Reducing the spread of disease, starting treatment on time, and enhancing patient outcomes all depend on early detection and precise diagnosis. To improve detection capacities, technical breakthroughs are necessary due to the considerable obstacles facing the global TB diagnostic scenario.[1,2]

1.2. Limitations of conventional TB diagnostic methods

Conventional diagnostic techniques like mycobacterial culture and sputum smear microscopy, which have been the mainstay of TB detection for decades, have significant shortcomings in terms of sensitivity, specificity, and turnaround time. Despite being often employed in environments with limited resources, smear microscopy has

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a sensitivity of just 50% in HIV-co-infected patients and is unable to identify paucibacillary infections. Although culture-based techniques, such as the use of liquid culture systems (e.g., MGIT) and Lowenstein-Jensen (LJ) media, are thought to be the gold standard, they take weeks for bacteria to develop, which causes delays in the start of treatment.[3] Clinical decision-making is further complicated by the intrinsic limitations of interferon-gamma release assays (IGRAs) and tuberculin skin testing (TST), which are unable to differentiate between latent TB infection (LTBI) and current TB disease. These drawbacks underscore the pressing need for cutting-edge diagnostic tools that provide quick, accurate, and easily accessible TB screening.[4]

1.3. Need for rapid, accurate, and accessible diagnostics

The need for point-of-care (POC) devices that offer real-time, highly sensitive, and specific TB detection is urgent due to the limitations of traditional diagnostic methods. Deployable in high-burden and resource-constrained environments, effective diagnostic techniques should evaluate medication resistance patterns and allow early illness detection. By providing quick results and automated procedures, the introduction of molecular diagnostics—including nucleic acid amplification tests (NAATs) like GeneXpert MTB/RIF and Truenat—has greatly enhanced TB identification. But obstacles like costly prices, infrastructure needs, and technological know-how prevent them from being widely used. Next-generation sequencing (NGS), AI-driven diagnostics, and CRISPR-based biosensors are examples of emerging technologies that present new opportunities to transform TB detection and go past current obstacles.[5,6]

1.4. Scope and objectives

With an emphasis on molecular breakthroughs and AI-driven solutions, this study offers a thorough examination of current developments in TB diagnosis. The scope includes a thorough examination of cutting-edge digital diagnostic techniques, innovative biosensing platforms, and molecular tests. In order to increase the precision and effectiveness of diagnosis, AI-based approaches being investigated, such as deep learning algorithms for digital radiography and automated microscopy. This study also critically assesses the difficulties, accessibility, and clinical value of new diagnostic technology. This analysis attempts to close the gap between technological discoveries and practical application in international TB control efforts by identifying recent developments, constraints, and potential paths forward.The end strategy for tb as shown in tb report of United Nations in **Figure 1**.[7,8,9,10]

2. Traditional TB Diagnostic Methods and Their Limitations

TB control efforts depend heavily on quick and accurate diagnosis since early discovery lowers disease transmission and allows for prompt treatment initiation. Despite their widespread use, traditional TB diagnostic techniques have a number of intrinsic drawbacks, such as poor sensitivity, slow turnaround times, and an inability to differentiate between latent and active infections. In areas where tuberculosis is endemic, when prompt and accurate diagnosis is essential for efficient disease management, these drawbacks present serious difficulties. The main traditional TB diagnostic techniques are covered in this section, along with their historical significance, diagnostic capabilities, and limitations. These include sputum smear microscopy, culture-based methods, and immunological tests like the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs).[11]

2.1. Sputum smear microscopy

Historically, sputum smear microscopy has been one of the most used methods for diagnosing tuberculosis, especially in environments with low resources. The Ziehl-Neelsen (ZN) staining method was first used in the late 19th century after Robert Koch discovered Mycobacterium tuberculosis. Because of its ease of use, affordability, and low infrastructure needs, it has remained a mainstay of TB detection. To see acid-fast bacilli (AFB) under a light microscope, sputum samples are stained with carbol fuchsin, decolored with acid-alcohol, and then counterstained with methylene blue. Even though auramine-rhodamine staining in fluorescence microscopy has increased detection rates when compared to traditional ZN staining, overall diagnostic sensitivity is still a significant drawback.[12] Smear microscopy has a wide range of sensitivity, from 20 to 80%. Patients with a high bacillary burden (>10,000 bacilli/mL of sputum) had greater detection rates. Smear microscopy, however, has low sensitivity in paucibacillary instances, such as in children with co-infected HIV and TB, which results in a high number of false-negative readings. Furthermore, non-tuberculous mycobacteria (NTM) can also have acid-fast characteristics, which could result in a misdiagnosis, limiting the specificity of AFB microscopy. The method cannot identify patterns of antibiotic resistance, hence additional molecular or culture-based testing is required for antimicrobial susceptibility profiling & a conclusive TB diagnosis.[13]

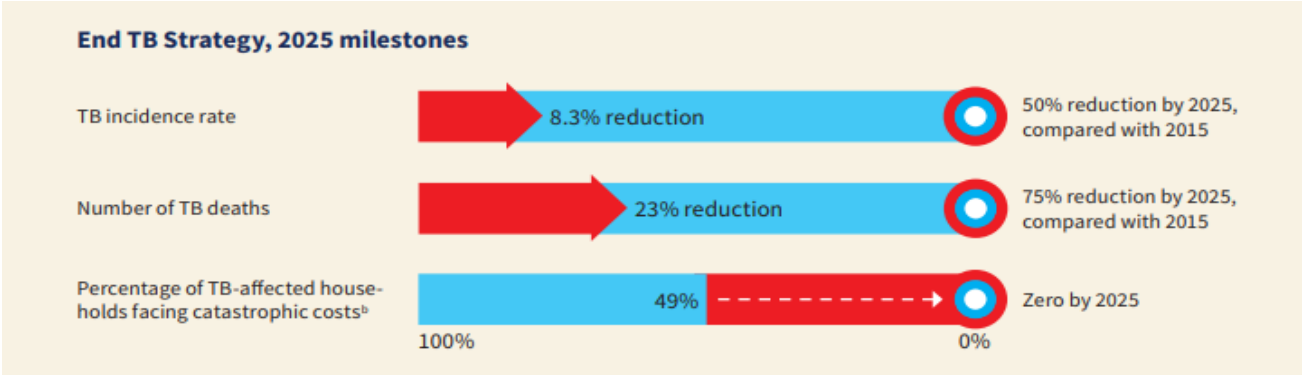

Figure 1: End TB strategy[10]

2.2. Culture-based techniques

Because of their higher sensitivity and capacity to confirm M, culture-based methods are considered the gold standard for diagnosing tuberculosis. Infection from tuberculosis with good specificity. By isolating and cultivating mycobacteria from clinical specimens in solid or liquid medium, these techniques enable drug susceptibility testing (DST) and conclusive identification. For the detection of tuberculosis, solid culture techniques like Löwenstein-Jensen (LJ) medium have been widely employed and are still a vital tool in reference labs. Glycerol, malachite green, and coagulated egg make up the LJ medium, which offers a specific environment for mycobacterial growth. This approach has a long incubation period, usually taking 3–8 weeks for visible colony formation, which delays diagnosis and therapy initiation even though it is very specific.[14]

Liquid culture technologies, including the Mycobacteria Growth Indicator Tube (MGIT) system, have been created to overcome this restriction and speed up mycobacterial identification. To identify mycobacterial metabolism, MGIT, an automated fluorescence-based technique, uses a liquid medium enhanced with growth enhancers and oxygen-sensitive fluorescent markers. This method preserves great sensitivity while drastically cutting the turnaround time to about 7–14 days. Widespread adoption in environments with limited resources is difficult, though, because contamination rates in liquid culture are higher than in solid culture and because advanced laboratory equipment, skilled workers, and biosafety precautions are needed.Both liquid and solid culture techniques are time-consuming, labor-intensive, and require strict biosafety standards, which limits their usefulness for quick TB diagnosis in high-burden situations despite their great sensitivity. Additionally, these techniques are frequently not available at outlying medical facilities, requiring centralized testing, which may cause results to be delayed even more. The **Table 1** provides Comparison of Conventional and Advanced TB Diagnostic Methods.[15]

2.3. Tuberculin skin test (TST) and interferon-gamma release assays (IGRAs)

Immunological assays that evaluate a person's immune response to M are used to diagnose latent TB infection (LTBI). bacteria-related antigens. For LTBI screening, the Mantoux test, also called the tuberculin skin test (TST), has long been employed. Purified protein derivative (PPD) is injected intradermally as part of the test, and the induration diameter is measured 48–72 hours later. Prior exposure to M is indicated by a positive result. tuberculosis, but fails to differentiate between active TB illness and LTBI. Additionally, false-positive reactions are sometimes caused by cross-reactivity between non-tuberculous mycobacteria (NTM) and Bacillus Calmette-Guérin (BCG) vaccine, which lowers the specificity of the test.[16]

Table 1: Comparison of conventional and advanced TB diagnostic methods[11,12,13,14,15,16,17,18]

Diagnostic Method	Principle	Advantages	Limitations	Turnaround Time
Smear Microscopy	Staining and microscopic detection of M. tuberculosis	Simple, low-cost, widely available	Low sensitivity, especially in paucibacillary TB	~ 1 day
Mycobacterial Culture	Growth of M. tuberculosis on solid/liquid media	Gold standard, high specificity	Slow, requiring weeks for results	2–8 weeks
Tuberculin Skin Test (TST)	Delayed-type hypersensitivity response measurement	Simple, widely used	Cannot differentiate active from latent TB	48–72 hours

Interferon-Gamma Release Assay (IGRA)	Measures immune response to TB-specific antigens	No cross-reactivity with BCG vaccine	Expensive, requires laboratory infrastructure	1–2 days
GeneXpert MTB/RIF	NAAT-based detection and rifampicin resistance	Rapid, high sensitivity and specificity	Costly, requires stable electricity and reagents	~ 2 hours
Truenat MTB	Chip-based real-time PCR for TB detection	Portable, faster than GeneXpert	Limited availability in high-burden settings	~ 1 hour
Next-Generation Sequencing (NGS)	Whole-genome sequencing for strain and resistance typing	High-resolution, comprehensive resistance profiling	Expensive, requires specialized expertise	~ 1–2 days
AI-Based Chest Radiography	Deep learning analysis of TB-related lung abnormalities	Automated, useful for mass screening	Requires large, well-annotated datasets	~ Minutes

QuantiFERON-TB Gold Plus and T-SPOT.TB are two examples of interferon-gamma release assays (IGRAs), which have become alternative immunodiagnostic methods with higher specificity than TST. These tests quantify the amount of interferon-gamma (IFN-γ) that T cells produce in reaction to M. antigens unique to tuberculosis, including culture filtrate protein-10 (CFP-10) and early secretory antigenic target-6 (ESAT-6). In BCG-vaccinated populations, IGRAs are more trustworthy than TST because they are unaffected by prior BCG vaccination. However, the diagnostic usefulness of TST and IGRAs in clinical practice is limited since they cannot distinguish between LTBI and active TB. Additionally, IGRAs are more expensive than TST and necessitate well-equipped labs and skilled staff, which makes routine adoption difficult in areas with low resources and high load.[17,18]

3. Molecular Innovations in TB Diagnostics

Mycobacterium tuberculosis (Mtb) and drug resistance mutations may now be quickly, sensitively, and specifically identified thanks to the development of molecular diagnostics, which has completely changed the detection of tuberculosis (TB). By directly identifying Mtb genetic material, these technologies get beyond the drawbacks of traditional culture-based techniques and drastically shorten the turnaround time for diagnostics. Nucleic acid amplification tests (NAATs), whole genome sequencing (WGS) and next-generation sequencing (NGS), and CRISPR-based diagnostic tools are some of the most significant molecular advancements. Particularly when it comes to multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), these methods improve surveillance, increase diagnostic accuracy, and enable individualized treatment plans for TB.[19,20]

3.1. Nucleic acid amplification tests (NAATs)

Because of their great sensitivity and capacity to identify Mtb DNA in clinical samples in a matter of hours, NAATs have become the mainstay of contemporary TB diagnostics. Cepheid created the GeneXpert MTB/RIF assay, an automated, cartridge-based real-time PCR method that can identify mutations in the rpoB gene linked to rifampicin (RIF) resistance and Mtb DNA in as little as two hours. By adding a larger DNA reaction chamber and improved probe chemistry, its successor, GeneXpert Ultra, offers increased sensitivity, making it possible to detect cases of extrapulmonary TB and paucibacillary TB. But even with their better performance, GeneXpert-based assays can't be used in environments with limited resources because they need infrastructure, skilled staff, and a constant power source. Molbio Diagnostics created the Truenat TB test, a portable, chip-based real-time PCR assay that facilitates decentralized point-of-care (POC) TB detection. It can concurrently detect rifampicin resistance and quickly identify Mtb in less than an hour, which makes it a good substitute for GeneXpert in low-resource environments. Truenat is more accessible in remote locations because it runs on a battery-powered platform, in contrast to conventional NAATs.A promising NAAT-based substitute is loop-mediated isothermal amplification (LAMP), which uses a strand-displacing DNA polymerase to amplify Mtb DNA at a steady temperature without the need for heat cycling. Field-based TB diagnostics can benefit from the high sensitivity and specificity of LAMP assays, including TB-LAMP, which require less equipment. However, for broad clinical use, additional improvement is required due to restrictions such possible cross-contamination and subjective result interpretation.[21,22]

3.2. Whole genome sequencing (WGS) and Next-generation Sequencing (NGS)

By providing thorough genotypic characterisation of Mtb strains, accurate drug resistance profiling, and improved epidemiological surveillance, WGS and NGS technologies have revolutionized TB diagnoses. Single nucleotide polymorphisms (SNPs) and structural differences linked to drug resistance can be found thanks to WGS, which offers high-resolution insights into Mtb genetic diversity. WGS makes it possible to anticipate resistance to first-line and second-line anti-TB medications quickly, in contrast to standard phenotypic drug susceptibility testing (DST), which takes weeks for culture-based results. By enabling targeted

deep sequencing of resistance-associated loci like katG (isoniazid resistance), rpoB (rifampicin resistance), gyrA/gyrB (fluoroquinolone resistance), and rrs (aminoglycoside resistance), NGS platforms, such as Illumina and Oxford Nanopore technologies, further improve TB diagnostics. By offering a thorough resistance profile, these methods enable physicians to customize treatment plans for individuals with MDR-TB and XDR-TB.Beyond clinical uses, WGS and NGS are essential for TB surveillance and epidemiology. Researchers can determine evolutionary relationships between Mtb strains, trace transmission dynamics, and locate outbreak clusters by examining genomic data. This skill is essential for directing public health initiatives, especially in high-burden environments where TB persistence is exacerbated by undiagnosed transmission. However, the widespread use of sequencing technology in routine TB diagnosis is still limited by obstacles such high costs, infrastructure needs, and the complexity of data interpretation.[23,24]

3.3. CRISPR-based TB diagnostics

As next-generation molecular tools for TB detection, CRISPR-based diagnostic assays have become popular due to their exceptional specificity and quick turnaround times. The DETECTR (DNA Endonuclease Targeted CRISPR Trans Reporter) and SHERLOCK (Specific High Sensitivity Enzymatic Reporter UnLOCKing) technologies use CRISPR-Cas enzymes, namely Cas12 and Cas13, to very sensitively identify Mtb-specific nucleic acid sequences. These methods use collateral cleavage activity, which allows for visual or instrument-based readout in a matter of minutes. Target recognition causes indiscriminate cleavage of a fluorescent or colorimetric reporter. For the detection of Mtb RNA in sputum and other clinical samples, the SHERLOCK test, which is based on Cas13a-mediated RNA detection, is very successful since it allows single-molecule sensitivity. Similar benefits are offered by DETECTR, which uses Cas12a for DNA detection and has been investigated for quick Mtb detection in environments with limited resources. Because of their extremely specific guide RNA-targeting mechanism, these CRISPR-based assays provide a number of advantages over traditional NAATs, including as compatibility with isothermal amplification, low equipment needs, and lower false-positive rates.Notwithstanding its promise, CRISPR-based TB diagnostics have issues with scalability, sample preparation difficulty, and clinical validation. More refining is needed to integrate these platforms into POC settings, especially with regard to assay robustness, multiplexing capability, and cost-effectiveness. However, there is hope for their future use in TB control programs due to the continuous improvements in CRISPR technology and the creation of portable microfluidic-based diagnostic tools.[25,26]

4. Artificial Intelligence (AI) and Machine Learning in TB Diagnosis

Disease detection, risk assessment, and clinical decision-making have all been transformed by the use of artificial intelligence (AI) and machine learning (ML) into tuberculosis (TB) diagnostics. AI-driven methods improve the precision, speed, and accessibility of TB diagnosis by utilizing deep learning algorithms, convolutional neural networks (CNNs), and data-driven predictive modeling. These developments are especially helpful in environments with low resources, where traditional diagnostics are limited by a lack of infrastructure and skilled workers. AI-driven clinical decision support systems (CDSS), digital microscopy-based bacilli identification, and automated interpretation of chest radiographs are just a few of the fields in which AI is being used in TB diagnosis. In addition to facilitating early disease detection, artificial intelligence (AI) can also enable tailored treatment approaches and improved TB control measures by enhancing conventional diagnostic modalities with AI.[27]

4.1. AI-Powered chest radiography interpretation

One of the most popular diagnostic methods for TB screening is still chest radiography, especially in high-burden environments. However, manual X-ray interpretation is frequently arbitrary, vulnerable to inter-reader variation, and constrained by the number of qualified radiologists available. A game-changing method for automating TB detection in chest X-rays is AI-based radiography analysis powered by deep learning algorithms. CNN-based image processing is used by systems like CAD4TB (Computer-Aided Detection for Tuberculosis) and qXR to identify TB-related anomalies with excellent sensitivity and specificity. These AI-powered technologies can discriminate between pathological and normal lung patterns with exceptional accuracy since they are trained on vast datasets that include both TB-positive and TB-negative radiographs.Delft Imaging's CAD4TB has undergone a great deal of field validation and has proven to be a reliable tool for TB screening programs, particularly in LMICs. Similar to this, Qure.ai's qXR is intended to help clinicians make quick decisions by categorizing lung anomalies associated with tuberculosis and evaluating the severity of the illness. These AI-based technologies have been effectively implemented in rural medical facilities with a shortage of radiologists, jails, refugee camps, and mobile screening units. Resource-constrained settings can improve TB surveillance, decrease diagnostic delays, and detect cases early by incorporating AI-powered chest radiography interpretation into national TB programs. To guarantee the broad use of AI-driven radiography screening tools, however, issues like algorithm generalizability, possible biases in training datasets, and regulatory approval barriers need to be resolved.[28,29,30]

4.2. AI in sputum microscopy analysis

Particularly in endemic areas where molecular diagnostics are not easily accessible, sputum smear microscopy is still a vital TB diagnostic technique. But traditional microscopy is time-consuming, prone to human error, and frequently has less-than-ideal sensitivity, especially when it comes to paucibacillary situations. The efficiency and accuracy of bacilli detection have been greatly increased by AI-driven automation of sputum microscopy analysis, which has also decreased diagnostic subjectivity and laboratory staff effort. To identify and categorize acid-fast bacilli (AFB) in sputum smears, automated microscopy systems use deep learning models that have been trained on annotated datasets of TB bacilli pictures. To improve bacilli visualization and quantification, AI-based solutions like Deep TB and Augmented Smear Microscopy (ASM) combine CNN topologies, object detection frameworks, and image processing approaches. These devices are capable of quickly scanning whole microscope slides, accurately identifying TB-positive samples, and producing diagnostic readouts in real time. Additionally, by facilitating remote analysis via cloud-based platforms, the combination of digital microscopy and AI-based bacilli identification improves the scalability of TB diagnostic services. The flexibility of AI-assisted sputum microscopy to be used in task-shifting programs, where non-specialist healthcare personnel can do TB screening with no training, is one of its key benefits. AI ensures diagnostic consistency while reducing dependency on skilled microbiologists by automating microscopy analysis. For a smooth adoption, however, issues with uniformity, variation in smear preparation, and connection with current laboratory operations must be resolved. Additionally, more study is needed to improve AI models for automated microscopic feature recognition in the detection of drug-resistant TB strains.[31,32]

4.3. AI-Driven clinical decision support systems

Clinical decision support systems (CDSS), which help medical professionals with risk assessment, disease prediction, and individualized treatment planning, are another example of how AI is being used in TB diagnosis beyond image analysis. AI-driven CDSS create predictive models for TB risk stratification by utilizing patient demographics, electronic health records (EHRs), and extensive epidemiological datasets. Based on unique patient profiles, these systems use machine learning algorithms to predict treatment outcomes, identify high-risk people, and distinguish between latent TB infections (LTBI) and current disease.[33] In order to provide a comprehensive approach to TB diagnosis, advanced CDSS platforms incorporate AI-driven natural language processing (NLP) to evaluate clinical notes, lab data, and radiographic findings. Precision medicine approaches to TB management are also made possible by ML models trained on genomic and transcriptome data, which make it easier to identify host immunological signals predictive of TB progression. In TB epidemic surveillance, AI-based predictive analytics are especially essential because they allow health authorities to track disease patterns, allocate resources optimally, and carry out focused intervention plans.[34]

By tailoring treatment plans according to each patient's unique response and drug susceptibility patterns, AI-enhanced CDSS provide customized medicine. Pharmacokinetic and pharmacodynamic (PK/PD) data can be analyzed by AI algorithms to customize medication dosages, reduce side effects, and enhance treatment compliance. AI-powered mobile applications combined with CDSS enable real-time patient engagement through treatment reminders, symptom monitoring, and adherence tracking in LMICs, where TB treatment adherence is a significant concern. Not with standing these developments, data privacy, ethical issues, and compatibility with current healthcare systems remain obstacles for AI-driven CDSS. Regulatory approvals, clinician education, and interdisciplinary cooperation between public health policymakers, epidemiologists, and AI researchers are necessary for the incorporation of AI in TB clinical procedures. However, as AI technologies advance, there is enormous potential for AI-powered CDSS to support global TB eradication targets, improve patient outcomes, and strengthen TB control efforts.[35,36]

5. Biosensors, Nanotechnology, and Emerging Diagnostic Tools

The combination of biosensors, nanotechnology, and non-invasive detection techniques has greatly impacted the development of tuberculosis (TB) diagnoses. By providing quick, highly sensitive, and reasonably priced solutions appropriate for point-of-care (POC) applications, these cutting-edge technologies seek to solve the drawbacks of traditional TB diagnostic instruments. The sensitivity and specificity of molecular tests are improved by nanotechnology-driven strategies, such as gold nanoparticle (AuNP) and quantum dot-based platforms, whereas biosensor-based assays use biochemical interactions to detect Mycobacterium tuberculosis (Mtb) in real time. Additionally, a promising non-invasive option for early illness identification is offered by breath-based TB detection devices that use volatile organic compound (VOC) analysis. These state-of-the-art developments aid in the creation of quick, easily accessible, and high-throughput diagnostic solutions that may be successfully implemented in environments with limited resources and high workloads.[37,38]

5.1. Biosensor-based TB detection

By combining biological recognition components with transducers to identify TB-specific biomarkers, biosensor technologies have become extremely effective instruments for TB diagnosis. Using impedance, amperometric, and

voltammetric methods, electrochemical biosensors allow for the highly sensitive measurement of TB-specific proteins, antigens, and nucleic acids. Graphene, carbon nanotubes, and metal nanoparticles are examples of nanostructured materials that have been used in electrochemical biosensors to further enhance signal amplification and enable ultra-low detection limits. Surface plasmon resonance (SPR), fluorescence, and colorimetric assays are the foundation of optical biosensors, which offer label-free, real-time, and highly specific TB detection. Rapid identification of Mtb DNA and antigens is made possible by these platforms, which allow direct contact between analytes and immobilized biomolecular probes. For proof-of-concept (POC) applications in areas with limited resources, paper-based biosensors, like lateral flow immunoassays (LFAs), provide a straightforward, affordable, and portable substitute. Notwithstanding its benefits, stability, reproducibility, and large-scale application are issues with biosensor-based TB diagnostics that call for additional developments in biosensor manufacture and validation.[39]

5.2. Nanotechnology-based approaches

By improving the sensitivity of molecular detection, facilitating quick signal transduction, and reducing assay complexity, nanotechnology has completely changed TB diagnosis. Gold nanoparticle (AuNP)-based assays use surface-enhanced Raman spectroscopy (SERS), fluorescence quenching, and aggregation-induced colorimetric changes to identify TB-specific biomarkers by taking use of the special optical and plasmonic characteristics of AuNPs. These tests are potential options for early-stage TB diagnosis because of their remarkable sensitivity in identifying Mtb DNA, RNA, and proteins at femtomolar quantities. Semiconductor nanocrystals with adjustable optical characteristics are used in quantum dot (QD)-based fluorescence detection to enhance multiplexed detection capabilities and signal contrast. For the fluorescence-based detection of Mtb antigens, QD-based immunoassays and hybrid nanomaterial platforms have been effectively used, allowing for high-specificity real-time quantification. Although techniques based on nanotechnology provide previously unheard-of advantages in tuberculosis diagnosis, issues including cost, stability, and possible cytotoxicity of nanomaterials must be resolved before they can be widely used in clinical settings.[40,41]

5.3. Breath-based TB detection technologies

An developing field in tuberculosis diagnosis is breath-based diagnostics, which provide a quick and non-invasive substitute for conventional sputum-based tests. Given its potential for early illness identification, the detection of volatile organic compounds (VOCs) specific to tuberculosis (TB) in exhaled breath has attracted a lot of attention. Certain volatile organic compounds (VOCs), such as methyl nicotinate, carbonyl compounds, and terpenes, are released as a result of Mtb infection and can be identified using gas chromatography-mass spectrometry (GC-MS), selected ion flow tube-mass spectrometry (SIFT-MS), and electronic nose (e-nose) technologies. The sensitivity and specificity of breath-based TB detection have been improved by recent developments in sensor downsizing and AI-driven pattern recognition algorithms, making it a promising tool for widespread screening. However, before clinical deployment, there are still important issues that need to be resolved, such as environmental variability, the requirement for validation across a variety of populations, and the standardization of VOC biomarker panels. The combination of breath-based diagnostics, nanotechnology, and biosensors has enormous potential to revolutionize TB diagnostics by providing quick, precise, and easily accessible treatments. In order to enable broad implementation in areas with a high TB prevalence, future studies should concentrate on enhancing assay repeatability, cost-effectiveness, and regulatory approvals.[42,43]

6. Multi-omics approaches in TB diagnosis

New developments in multi-omics technology have revolutionized our understanding of the pathophysiology of tuberculosis (TB), host-pathogen interactions, and the identification of biomarkers. Researchers have created new diagnostic techniques with enhanced sensitivity, specificity, and predictive power by utilizing metabolomics, proteomics, transcriptomics, and their combined applications. With the help of these methods, TB can be understood at the systems level, allowing for the discovery of disease-specific indicators that can improve early detection, distinguish between latent TB infections (LTBI) and active TB, and reveal how well a therapy is working. Personalized TB diagnoses are made possible by the combination of multi-omics, artificial intelligence (AI), and machine learning (ML), which further improves diagnostic accuracy.[44]

6.1. Metabolomics and proteomics: Identification of TB-specific biomarkers

Proteomics and metabolomics have become effective methods for locating TB-specific biomarkers in host biofluids, such as sputum, urine, and blood. Profiling small-molecule metabolites that represent metabolic changes linked to disease is the main goal of metabolomics. Research has shown unique metabolic markers in tuberculosis patients, such as changes in energy homeostasis, amino acid metabolism, and lipid metabolism (such as dysregulation of phosphatidylcholines and sphingolipids). Certain metabolites, like mycobacterial glycolipids and lipoarabinomannan (LAM), have been investigated as biomarkers for the diagnosis of tuberculosis (TB), especially in point-of-care (POC) assays for quick detection. Conversely, proteomics makes it possible to identify proteins that are differently expressed and suggest TB infection. Acute-phase proteins (such serum amyloid A and C-reactive protein) and host immune response mediators (like interferon-induced proteins) have been found to be

upregulated in active TB patients, according to quantitative proteomic analysis. Furthermore, Mycobacterium tuberculosis (M.tb)-specific antigens have been found in clinical samples thanks to mass spectrometry-based proteomic techniques, which have served as a foundation for innovative immunodiagnostic tests. Notwithstanding these developments, host response heterogeneity, technological difficulties, and the requirement for strong validation across a range of populations make it difficult to translate metabolomic and proteomic biomarkers into therapeutic practice.[45]

6.2. Transcriptomics for TB Detection: Host gene expression profiling

By discovering host-derived molecular fingerprints, transcriptomics—which studies gene expression patterns in response to TB infection—has transformed TB diagnosis. In order to differentiate active TB from LTBI and other respiratory illnesses, host gene expression analysis has proven especially helpful. TB-specific gene expression patterns involving interferon-stimulated genes (ISGs), inflammatory cytokines, and immunological checkpoint regulators have been found by RNA sequencing (RNA-seq) and microarray analysis. The significance of type I and type II interferon signaling pathways in TB pathogenesis has been prominently highlighted by transcriptome research; some gene panels, such the 16-gene, 3-gene, and 4-gene TB signatures, have demonstrated high diagnostic accuracy.To enable quick, non-invasive TB detection, blood-based transcriptomic tests are being developed, such as Xpert MTB Host Response (Xpert-MTB-HR). These assays use differential gene expression profiles to accurately classify the various stages of tuberculosis illness. The impact of co-infections (such HIV), inter-individual variability, and the requirement for scalable, affordable platforms for deployment in endemic areas are some of the challenges that transcriptomic-based diagnostics must overcome.[46,47]

6.3. Integration of multi-omics for personalized TB diagnosis

A promising path toward individualized TB diagnosis is provided by the integration of transcriptomics, proteomics, and metabolomics into a single multi-omics framework. Researchers can create thorough disease models that account for individual variations in TB pathogenesis by integrating multi-dimensional biological data. Finding composite biomarker panels that improve predictive value and diagnostic accuracy is made easier by multi-omics techniques. Furthermore, the development of precision diagnostics is made possible by AI-driven analytics, such as network biology techniques and machine learning-based pattern recognition, which can extract clinically significant characteristics from complicated datasets.TB detection techniques are further improved by combining multi-omics with host immunological profile and microbiome studies. For example, integrating transcriptome patterns with metabolic and proteomic markers can enhance the ability to distinguish between LTBI and active TB while forecasting the results of treatment. It may also be possible to identify those who are more likely to reactivate TB using multi-omics-guided risk stratification models, which would help with focused preventive measures. Notwithstanding these developments, there are still many obstacles to overcome, such as harmonizing data, standardizing procedures, and converting multi-omics research into affordable, field-deployable diagnostic tools. Future studies should concentrate on improving multi-omics-based TB diagnostics for use worldwide, especially in high-burden environments where accurate and timely diagnosis is essential for disease management.[48,49]

7. Challenges and Future Directions in TB Diagnostics

Continuous improvements in TB tests have greatly increased the detection methods' accessibility, speed, and accuracy. The widespread use and scalability of sophisticated TB diagnostic methods are, however, hampered by a number of issues, especially in low- and middle-income countries (LMICs), where the prevalence of TB is still disproportionately high. A multifaceted strategy including worker training, infrastructure development, cost-effective solutions, and the smooth integration of digital health advances is needed to address these issues. Additionally, strategic planning is required to optimize the impact of artificial intelligence (AI) and molecular technologies while guaranteeing equal access when integrating them into TB control efforts. In addition to discussing future prospects in AI-driven and molecular TB diagnostics, this part critically analyzes the obstacles to implementing advanced diagnostics and investigates the role of digital health and AI in TB control programs.[50]

Table 2: Future directions and challenges in TB diagnostics[50,51,52,53]

Future Innovations	Potential Benefits	Key Challenges
AI-Powered TB Screening Tools	Faster, automated diagnosis in low-resource settings	Need for large, diverse training datasets
Wearable Biosensors for TB Detection	Non-invasive, real-time disease monitoring	Sensitivity and specificity optimization

Smartphone-Integrated TB Diagnosis	Portable, remote access to diagnostic tools	Data security and regulatory compliance
Multiplexed Diagnostic Platforms	Simultaneous detection of TB and co-infections	Cost and complexity of implementation
CRISPR-Based TB Detection	Ultra-sensitive, rapid point-of-care testing	Requires further clinical validation
Affordable and Decentralized NAATs	Increases accessibility in high-burden regions	Cost reduction and sustainable supply chain

7.1. Barriers to implementing advanced diagnostics

The cost and affordability of new technology is one of the main obstacles to the widespread use of sophisticated TB diagnostics. Even while molecular diagnostics like GeneXpert MTB/RIF and Truenat have improved diagnosis accuracy, there are still substantial financial obstacles due to their expensive prices, which include maintenance, machine acquisition, and cartridge costs. The long-term sustainability of these technologies is unknown because many high-burden nations depend on donor-funded programs to maintain them. Additionally, the high expenses of CRISPR-based diagnostic systems and next-generation sequencing (NGS) further restrict their widespread use in environments with limited resources.[50] Infrastructure and training needs continue to be major obstacles in addition to budgetary limitations. In isolated or impoverished areas, advanced TB detection technologies may not be easily accessible due to the need for complex laboratory equipment, a steady electrical supply, and strict biosafety regulations. Furthermore, a trained workforce that can manage and maintain sophisticated diagnostic systems is essential to the effective deployment of molecular and AI-based diagnostics. The effective implementation of state-of-the-art TB testing technologies is hampered by the lack of trained workers in many endemic areas. To ensure the long-term viability of sophisticated TB diagnostics, these infrastructure and human resource issues must be addressed with focused expenditures in workforce training, laboratory capacity-building, and sustainable finance methods.[51]

7.2. Integration of digital health and AI in TB control programs

One promising strategy to improve TB detection, patient management, and treatment adherence is the combination of telemedicine and mobile health (mHealth) applications. Digital adherence monitoring (DAM), remote consultations, and real-time patient tracking are made possible by mHealth applications. These features are especially helpful for TB patients who live in distant areas. Video-observed therapy (VOT) and electronic medication monitors are two examples of digital adherence technologies that have shown notable increases in TB treatment compliance and decreased the likelihood of drug resistance development. Additionally, by evaluating clinical data, forecasting disease development, and providing decision-support tools for individualized TB management, AI-powered mobile applications can help healthcare providers.[52]

Real-time surveillance and disease mapping enabled by AI and digital health tools can enhance TB control efforts at the population level while also enhancing patient care. To forecast TB epidemics and direct resource allocation, AI-driven epidemiological models can examine enormous information including geospatial mapping, electronic health records, and demographic trends. To find high-risk groups and improve screening initiatives, machine learning (ML) systems can analyze data from automated microscopy, digital chest X-rays, and genomic sequencing. Health officials can enhance early detection tactics and customize therapies to particular area epidemiological trends by combining AI-driven monitoring systems with national TB control initiatives. This will ultimately lower the rates of TB transmission. The provides Future Directions and Challenges in TB Diagnostics.

Table 2 [50,51,52,53,54]

7.3. Future prospects in AI and molecular TB diagnosis

The creation of portable, extremely quick diagnostic tools that can provide accurate results at the point of care is essential to the future of tuberculosis diagnosis. The next generation of rapid diagnostic tools that require less infrastructure and sample preparation are being driven by advancements in biosensors, lab-on-a-chip technologies, and microfluidics. For decentralized TB screening programs, portable CRISPR-based assays and loop-mediated isothermal amplification (LAMP) technologies provide highly sensitive and specific TB detection with shorter turnaround times. AI-assisted diagnostic tools that use deep learning algorithms and automated picture analysis are also anticipated to improve diagnosis accuracy and efficiency in environments with limited resources.[55,56]

Increasing access to AI-driven diagnostics in locations with limited resources, where digital infrastructure and processing power are sometimes insufficient, is a major problem when using AI for TB diagnosis. This problem might be lessened by cloud-based AI models that can process TB diagnostic data remotely. This would enable medical professionals in remote locations to obtain AI-powered diagnostic insights without requiring computational resources on-site. Additionally, the creation of affordable,

smartphone-compatible AI diagnostic tools can help close the gap between technological advancement and practical application, guaranteeing that the most marginalized groups can benefit from AI-driven solutions. In order to increase the robustness, interpretability, and reduction of bias of AI-powered TB diagnostic tools in a variety of clinical and epidemiological contexts, future research should concentrate on improving AI algorithms.[57] Even though TB diagnostics have advanced significantly, widespread adoption requires overcoming manpower, infrastructure, and financial obstacles. There are revolutionary prospects to improve TB detection, treatment monitoring, and disease control initiatives through the integration of AI, telemedicine, and digital surveillance. In the future, creating affordable, portable, and AI-powered diagnostic tools will be essential to closing the gap between accessibility and innovation and eventually advancing the global TB eradication goal.[58]

8. Conclusion

With the introduction of molecular advancements and artificial intelligence (AI)-driven approaches, the field of tuberculosis (TB) diagnostics has experienced a radical change, greatly increasing diagnostic accessibility, speed, and accuracy. Although they have long been the mainstays of diagnosis, traditional techniques like smear microscopy, mycobacterial culture, and immunological assays have several drawbacks, such as low sensitivity, long turnaround times, and the inability to differentiate between latent TB infection (LTBI) and active disease. Many of these issues have been resolved by the development of nucleic acid amplification tests (NAATs), such as GeneXpert MTB/RIF, Truenat, and loop-mediated isothermal amplification (LAMP), which offer quick, highly sensitive identification of drug resistance indicators and Mycobacterium tuberculosis. Additionally, CRISPR-based biosensors and next-generation sequencing (NGS) have created new opportunities for accurate genotypic resistance profiling and real-time tuberculosis detection. Deep learning algorithms for automated radiography interpretation and machine learning (ML)-based predictive modeling are two examples of AI-powered technologies that have shown promise in improving diagnostic operations, especially in environments with limited resources. Notwithstanding these developments, obstacles like exorbitant expenses, infrastructure needs, and the requirement for qualified staff prevent these technologies from being widely used, highlighting the need for ongoing research, innovation, and calculated policy changes to close diagnostic gaps in high-burden areas. The World Health Organization's (WHO) End TB Strategy, which aims to reduce TB incidence by 90% and TB-related mortality by 95% by 2035, depends on the integration of molecular and AI-driven diagnostics. The creation of affordable point-of-care (POC) technologies that integrate thorough resistance profiling with quick detection will be crucial to the future of TB diagnostics since it will allow for early intervention and treatment optimization. Multiplexed diagnostic platforms that can simultaneously identify TB and co-infections like HIV, as well as newly emerging drug-resistant strains, should be given priority in research. Furthermore, wearable biosensors, decentralized AI-assisted screening technologies, and smartphone-integrated diagnostic apps have the potential to completely transform patient care and TB surveillance. In order to translate these technology developments into widespread adoption, cooperation between governments, academics, the commercial sector, and global health organizations will be crucial. The worldwide endeavor to eradicate tuberculosis can be greatly hastened by utilizing the synergistic potential of artificial intelligence, big data analytics, and precision molecular diagnostics. This will ultimately improve patient outcomes and lower the global TB burden.

9. Source of Funding

None.

10. Conflict of Interest

None.

References

1. Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. Major infectious diseases. 3rd ed. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017. [cited 2025 Jan 15]. Chapter 11. Available from: https://www.ncbi.nlm.nih.gov/books/NBK525174/ doi: 10.1596/978-1-4648-0524-0_ch11
2. Mehnath, S, Jeyaraj M. Approaches toward designing nanocarriers for tuberculosis drug delivery. In Elsevier eBooks; 2021:59–89. [cited 2025 Jan 15]. https://doi.org/10.1016/b978-0-12-819985-5.00012-7.
3. Zaporojan N, Negrean RA, Hodișan R, Zaporojan C, Csep A, Zaha DC. Evolution of Laboratory Diagnosis of Tuberculosis. *Clin Pract*. 2024;14(2):388–416.
4. Trajman A, Steffen RE, Menzies D. Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. *Pulm Med*. 2013;2013:601737.
5. Wang S, Inci F, De Libero G, Singhal A, Demirci U. Point-of-care assays for tuberculosis: role of nanotechnology/microfluidics. *Biotechnol Adv*. 2013;31(4):438-–49. doi:10.1016/j.biotechadv.2013.01.006
6. Heidt B, Siqueira WF, Eersels K, Hanne D, Grinsven B, Fujiwara RT et al. Point of Care Diagnostics in Resource-Limited Settings: A Review of the Present and Future of PoC in Its Most Needed Environment. *Biosensors (Basel)*. 2020;10(10):133. doi:10.3390/bios10100133
7. Yadav S, Rawal G, Jeyaraman M, Jeyaraman N. Advancements in Tuberculosis Diagnostics: A Comprehensive Review of the Critical Role and Future Prospects of Xpert MTB/RIF Ultra Technology. *Cureus*. 2024;16(3):e57311. doi:10.7759/cureus.57311
8. MacLean E, Kohli M, Weber SF, et al. Advances in Molecular Diagnosis of Tuberculosis. *J Clin Microbiol*. 2020;58(10):e01582-19. doi:10.1128/JCM.01582-19
9. Yerlikaya S, Broger T, Isaacs C, Bell D, Holtgrewe L, Gupta-Wright A et al. Blazing the trail for innovative tuberculosis diagnostics. *Infection* 2024:52(1):29–42

10. https://www.who.int/publications/i/item/WHO-HTM-TB-2015.19
11. Yayan J, Franke KJ, Berger M, Windisch W, Rasche K. Early detection of tuberculosis: a systematic review. *Pneumonia (Nathan)*. 2024;16(1):11.
12. Vilchèze C, Kremer L. Acid-Fast Positive and Acid-Fast Negative Mycobacterium tuberculosis: The Koch Paradox. MicrobiolSpectr. 2017;5(2):10.1128/microbiolspec.tbtb2-0003-2015. doi:10.1128/microbiolspec.TBTB2-0003-2015
13. Aslan G. Old Enemy in the Diagnosis of Tuberculosis:Traditional and New Methods. *J Clin Pract Res* 2024; 46(5):431–43.
14. MacGregor-Fairlie M, Wilkinson S, Besra GS, Goldberg Oppenheimer P. Tuberculosis diagnostics: overcoming ancient challenges with modern solutions. *Emerg Top Life Sci*. 2020;4(4):423-36. doi:10.1042/ETLS20200335
15. McIvor A, Gordhan BG, Waja Z, Otwombe K, Martinson NA, Kana BD. Supplementation of sputum cultures with culture filtrate to detect tuberculosis in a cross-sectional study of HIV-infected individuals. *Tuberculosis* 2021;129:102103. https://doi.org/10.1016/j.tube.2021.102103.
16. Zellweger JP, Sotgiu G, Corradi M, Durando P. The diagnosis of latent tuberculosis infection (LTBI): currently available tests, future developments, and perspectives to eliminate tuberculosis (TB). *Med Lav*. 2020;111(3):170-83. doi:10.23749/mdl.v111i3.9983
17. Sultan B, Benn P, Mahungu T, Young M, Mercey D, Morris-Jones S et al. Comparison of two interferon-gamma release assays (QuantiFERON-TB Gold In-Tube and T-SPOT.TB) in testing for latent tuberculosis infection among HIV-infected adults. *Int J STD AIDS*. 2013;24(10):775-9.
18. Theel ES, Hilgart H, Breen-Lyles M, McCoy K, Flury R, Breeher LE et al. Comparison of the QuantiFERON-TB Gold Plus and QuantiFERON-TB Gold In-Tube Interferon Gamma Release Assays in Patients at Risk for Tuberculosis and in Health Care Workers. *J Clin Microbiol*. 2018;56(7):e00614-18.
19. Mousavi-Sagharchi SMA, Afrazeh E, Seyyedian-Nikjeh SF, Meskini M, Doroud D, Siadat SD. New insight in molecular detection of Mycobacterium tuberculosis. *AMB Express*. 2024;14(1):74. doi:10.1186/s13568-024-01730-3
20. Dookie N, Rambaran S, Padayatchi N, Mahomed S, Naidoo K. Evolution of drug resistance in Mycobacterium tuberculosis: a review on the molecular determinants of resistance and implications for personalized care. *J Antimicrob Chemother.* 2018;73(5):1138-51. doi:10.1093/jac/dkx506
21. Ioannidis P, Papaventsis D, Karabela S, et al. Cepheid GeneXpert MTB/RIF assay for Mycobacterium tuberculosis detection and rifampin resistance identification in patients with substantial clinical indications of tuberculosis and smear-negative microscopy results. *J Clin Microbiol*. 2011;49(8):3068-70. doi:10.1128/JCM.00718-11
22. Zeka AN, Tasbakan S, Cavusoglu C. Evaluation of the GeneXpert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampin resistance in pulmonary and extrapulmonary specimens. *J Clin Microbiol*. 2011;49(12):4138-41. doi:10.1128/JCM.05434-11
23. Zade A, Shah S, Hirani N, Kondabagil K, Joshi A, Chatterjee A. Whole-genome sequencing of presumptive MDR-TB isolates from a tertiary healthcare setting in Mumbai. *J Glob Antimicrob Resist*. 2022:256–62. https://doi.org/10.1016/j.jgar.2022.10.004.
24. Shea J, Halse TA, Lapierre P, Shudt M, Kohlerschmidt D, Roey PV et al. Comprehensive Whole-Genome Sequencing and Reporting of Drug Resistance Profiles on Clinical Cases of Mycobacterium tuberculosis in New York State. *J Clin Microbiol*. 2017;55(6):1871-82. doi:10.1128/JCM.00298-17
25. Hassan YM, Mohamed AS, Hassan YM, El-Sayed WM. Recent developments and future directions in point-of-care next-generation CRISPR-based rapid diagnosis. *Clin Exp Med*. 2025;25(1):33. doi:10.1007/s10238-024-01540-8
26. Mustafa MI, Makhawi AM. SHERLOCK and DETECTR: CRISPR-Cas Systems as Potential Rapid Diagnostic Tools for Emerging Infectious Diseases. *J Clin Microbiol*. 2024;62(1):e0152123.
27. McClean M, Panciu TC, Lange C, Duarte R, Theis F. Artificial intelligence in tuberculosis: a new ally in disease control. *Breathe (Sheff)*. 2024;20(3):240056. doi:10.1183/20734735.0056-2024
28. Barrett R, Creswell J, Sahu S, Qin ZZ. User perspectives on the use of X-rays and computer-aided detection for TB. Int J Tuberc Lung *Dis*. 2022;26(11):1083–5. doi:10.5588/ijtld.22.0232
29. Cao XF, Li Y, Xin HN, Zhang HR, Pai M, Gao L. Application of artificial intelligence in digital chest radiography reading for pulmonary tuberculosis screening. *Chronic Dis Transl Med*. 2021;7(1):35-40.. doi:10.1016/j.cdtm.2021.02.001
30. Liang S, Ma J, Wang G, et al. The Application of Artificial Intelligence in the Diagnosis and Drug Resistance Prediction of Pulmonary Tuberculosis. *Front Med (Lausanne)*. 2022;9:935080. doi:10.3389/fmed.2022.935080
31. Harries AD, Kumar AMV. Challenges and Progress with Diagnosing Pulmonary Tuberculosis in Low- and Middle-Income Countries. *Diagnostics (Basel)*. 2018;8(4):78. doi:10.3390/diagnostics8040078
32. Desikan P. Sputum smear microscopy in tuberculosis: is it still relevant?. *Indian J Med Res*. 2013;137(3):442-4.
33. Elhaddad M, Hamam S. AI-Driven Clinical Decision Support Systems: An Ongoing Pursuit of Potential. *Cureus*. 2024;16(4):e57728. doi:10.7759/cureus.57728
34. Chen Z, Liang N, Zhang H, Huizhen L, Yijiu Y, Xingyu Z et al. Harnessing the power of clinical decision support systems: challenges and opportunities. *Open Heart*. 2023;10(2):e002432. doi:10.1136/openhrt-2023-002432
35. Marques L, Costa B, Pereira M, et al. Advancing Precision Medicine: A Review of Innovative In Silico Approaches for Drug Development, Clinical Pharmacology and Personalized Healthcare. *Pharmaceutics*. 2024;16(3):332. Published 2024 doi:10.3390/pharmaceutics16030332
36. Mennella C, Maniscalco U, De Pietro G, Esposito M. Ethical and regulatory challenges of AI technologies in healthcare: A narrative review. *Heliyon*. 2024;10(4):e26297. doi:10.1016/j.heliyon.2024.e26297
37. Mobed A, Darvishi M, Kohansal F, Dehfooli FM, Alipourfard I, Tahavvori A et al. Biosensors; nanomaterial-based methods in diagnosing of Mycobacterium tuberculosis. *J Clin Tuberc Other Mycobact Dis*. 2023;34:100412. doi:10.1016/j.jctube.2023.100412
38. Benjamin SR, de Lima F, Nascimento VAd, de Andrade GM, Oriá RB. Advancement in Paper-Based Electrochemical Biosensing and Emerging Diagnostic Methods. *Biosensors* 2023;13(7):689. https://doi.org/10.3390/bios13070689
39. Zhou L, He X, He D, Wang K, Qin D. Biosensing technologies for Mycobacterium tuberculosis detection: status and new developments. *Clin Dev Immunol*. 2011;2011:193963. doi:10.1155/2011/193963
40. Draz MS, Shafiee H. Applications of gold nanoparticles in virus detection. *Theranostics*. 2018;8(7):1985-2017.. doi:10.7150/thno.23856
41. Zhou W, Gao X, Liu D, Chen X. Gold Nanoparticles for In Vitro Diagnostics. *Chem Rev*. 2015;115(19):10575-636. doi:10.1021/acs.chemrev.5b00100
42. Badola M, Agrawal A, Roy D, Sinha R, Goyal A, Jeet N. Volatile Organic Compound Identification-Based Tuberculosis Screening among TB Suspects: A Diagnostic Accuracy Study. *Adv Respir Med*. 2023;91(4):301–9. doi:10.3390/arm91040024
43. Lim SH, Martino R, Anikst V, Zeyu X, Samantha M, Robert B et al. Rapid Diagnosis of Tuberculosis from Analysis of Urine Volatile Organic Compounds. *ACS Sens*. 2016;1(7):852-6. doi:10.1021/acssensors.6b00309
44. Borah K, Xu Y, McFadden J. Dissecting Host-Pathogen Interactions in TB Using Systems-Based Omic Approaches. *Front Immunol.* 2021;12:762315. doi:10.3389/fimmu.2021.762315
45. Yu Y, Jiang XX, Li JC. Biomarker discovery for tuberculosis using metabolomics. *Front MolBiosci*. 2023;10:1099654.. doi:10.3389/fmolb.2023.1099654
46. Singhania A, Wilkinson RJ, Rodrigue M, Haldar P, O'Garra A. The value of transcriptomics in advancing knowledge of the immune response and diagnosis in tuberculosis. *Nat Immunol*. 2018;19(11):1159-68. doi:10.1038/s41590-018-0225-9

47. Li LS, Yang L, Zhuang L, Ye ZY, Zhao WG, Gong WP. From immunology to artificial intelligence: revolutionizing latent tuberculosis infection diagnosis with machine learning. *Mil Med Res*. 2023;10(1):58. doi:10.1186/s40779-023-00490-8
48. Vitorino R. Transforming Clinical Research: The Power of High-Throughput Omics Integration. *Proteomes*. 2024;12(3):25. doi:10.3390/proteomes12030025
49. Chen C, Wang J, Pan D, Xinyu W, Yuping X, Junjie Y et al. Applications of multi-omics analysis in human diseases. *MedComm*. 2023;4(4):e315.. doi:10.1002/mco2.315
50. Yerlikaya S, Broger T, Isaacs C, Xinyu W, Yuping X, Junjie Y et al. Blazing the trail for innovative tuberculosis diagnostics. *Infection*. 2024;52(1):29-42. doi:10.1007/s15010-023-02135-3
51. Abdulgader SM, Chiwaya AM, Reeve BWP, Zaida P, Hridesh M, Desiree LM et al. Diagnostic accuracy of Truenat MTB Plus, Truenat MTB Ultima and Xpert MTB/RIF Ultra for the diagnosis of pulmonary TB in an HIV-endemic setting. *Preprint. Res Sq*. 2024;rs.3.rs-5055991. doi:10.21203/rs.3.rs-5055991/v1
52. Zhu Y, Zhao, Y, Wu Y. Effectiveness of mobile health applications on clinical outcomes and health behaviors in patients with coronary heart disease: A systematic review and meta-analysis. *Int J Nurs Sci*. 2024;11(2):258–75. https://doi.org/10.1016/j.ijnss.2024.03.012
53. Doshi R, Falzon D, Thomas BV, et al. Tuberculosis control, and the where and why of artificial intelligence. *ERJ Open Res*. 2017;3(2):00056-2017. doi:10.1183/23120541.00056-2017
54. Olawade DB, Wada OJ, David-Olawade AC, Kunonga E, Abaire O, Ling J. Using artificial intelligence to improve public health: a narrative review. *Front Public Health*. 2023;11:1196397. doi:10.3389/fpubh.2023.1196397
55. Aborode AT, Adesola RO, Scott GY, Arthur-Hayford E, Otorkpa OJ, Kwaku SD et al. Bringing Lab to the field: Exploring innovations in Point-of-Care diagnostics for the rapid detection and management of tropical diseases in Resource-Limited settings. *Adv Biomark Sci Technol*. 2025;7(1). DOI: 10.1016/j.abst.2025.01.001
56. Khuspe PR, Kokate K, Mandhare T. (2017). Cystic Fibrosis: a review. International Journal of Pharma Research and Health Sciences, 2017;5(5):1831–7. https://doi.org/10.21276/ijprhs.2017.05.02
57. Hwang EJ, Jeong WG, David PM, Arentz M, Ruhwald M, Yoon SH. AI for Detection of Tuberculosis: Implications for Global Health. *Radiol Artif Intell*. 2024;6(2):e230327. doi:10.1148/ryai.230327
58. Yadav S, Rawal G, Jeyaraman M, Jeyaraman N. Advancements in Tuberculosis Diagnostics: A Comprehensive Review of the Critical Role and Future Prospects of Xpert MTB/RIF Ultra Technology. *Cureus*. 2024;16(3):e57311. doi:10.7759/cureus.57311

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