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Emerging technologies in tuberculosis diagnosis: A comprehensive review

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Abstract
Tuberculosis (TB) remains a global public health crisis, with an estimated 1/3rd of the global population having latent TB. The conventional approaches to diagnosis including the tuberculin skin test (TST) have inherent limitations which necessitate the urgent application of newer technologies for the diagnosis of TB. The present review will give an overall overview of the new technologies in the diagnosis of TB, their strengths and weaknesses and their potential for enhancing global control of TB. This article contain a systematic review of literature was conducted through the databases PubMed, Scopus, and Web of Science. Reports in the period from 2014 to 2024 that commented on new TB diagnostic technologies such as CBNAAT, Truenat and molecular diagnosis were included. Sensitivity, specificity, cost and access were compared. New technologies such as Interferon-Gamma Release Assay (IGRAs), Nucleic Acid Amplification Test (NAATs) and next-generation sequencing have proved to be more sensitive and specific than conventional tests. Molecular tests such as GeneXpert have facilitated the detection of TB and drug resistance promptly. Other challenges like high cost, need for infrastructure and heterogeneity of performance persist. New diagnostic technologies are transforming TB detection into a faster, more preciseand less expensive process. This article, initially discussed about the old TB diagnostic methods. Intermediately, brief about the modern technology in TB diagnostic tools. Lastly, concluded with policy attention to overcome current barriers with achieving international reach.

Keywords: Tuberculosis, TB diagnosis, CBNAAT, truenat, GeneXpert, interferon-gamma release assay

Introduction
Tuberculosis (TB) is one of the most significant health conditions in the world that is both preventable and curable. TB is brought about by the bacterium Mycobacterium tuberculosis, TB typically happens in the lungs know to pulmonary tuberculosis but can also extend to other parts of the body which leads to extra pulmonary tuberculosis [1]. The illness remains among the leading causes of mortality throughout the world, particularly in low and middle income countries whose medical infrastructure is normally substandard. The World Health Organization places the figure of 2023 at which approximately 12.6 million people were infected with TB and 1.8 million died due to the illness making it the second deadliest infectious disease after COVID-19. TB burden is inequitably spread with eight countries accounting for more than 2/3rd of the cases globally including China, India, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and the Democratic Republic of Congo. India alone accounts for nearly 27% of the global TB. It emphasizes the priority of greater diagnostic and treatment modalities in high-burden countries of greatest concern [2].

Background of Tuberculosis Diagnosis
The battle against TB is also complicated by some ongoing challenges. The most contentious issue is the emergence of drug-resistant TB (DR-TB) comprising multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). MDR-TB as resistance to one or more of the first-line drugs that specifically at least isoniazid and rifampicin, the two best most effective first-line TB drugs has become a key public health challenge. Success rates with treatment for MDR-TB are alarmingly low at about 60% because of regimen complexity with long therapy periods and serious side effects [3]. XDR-TB has further resistance to fluoroquinolones and injectable second-line agents has still poorer results with death rates more than 40% in certain contexts.

The emergence of totally drug-resistant TB (TDR-TB) poses an even greater threat as it leaves patients with virtually no effective treatment options. Another critical challenge in TB control is the high prevalence of TB-HIV co-infection [4]. HIV weakens the immune system and makes individuals more susceptible to TB infection and progression from latent to active disease. About 6% of the 10.6 million TB cases in 2022 was in individuals with HIV, and TB is the number one cause of death among people with HIV, contributing to nearly a third of AIDS mortality. The overlap of these two pandemics provides an infectious cycle where HIV speeds up the progression of TB, and TB worsens HIV-associated immune suppression. This synergy makes the diagnosis and treatment difficult as HIV-related TB tends to present with more frequent smear negative and extra pulmonary disease making the traditional diagnostic tools less efficient [5]. One of the biggest bottlenecks in the control of TB is the gigantic gap in accurate and prompt diagnosis. Early case detection is fundamental in breaking the chain of transmission, enhancing treatment success and cutting down on mortality. Yet most of the available diagnostics are beset with severe shortcomings. Sputum smear microscopy used most commonly in resource-constrained settings can detect only 50-60% of the cases i.e. miss almost half of all the cases. It does even worse in some groups e.g. children, HIV-infected individuals and those with extra pulmonary TB where the bacterial load is usually low. Culture-based methods which are more sensitive and regarded as the gold standard, are time-consuming that taking 2-8 weeks for the results and require advanced laboratory facilities that do not exist in most high-burden settings [6].

Molecular diagnosis including the GeneXpert MTB/RIF test was an enormous step up in the diagnosis of TB. GeneXpert can detect DNA of TB as well as resistance to rifampicin in two hours and is a very rapid alternative to culture. Extensive use has been undermined by its cost with the need for stable power supplies and the need for maintenance that limits its presence in distant and poorly resourced areas [7]. In addition, GeneXpert sensitivity is reduced in smear-negative and extra pulmonary TB that producing diagnostic blind spots for such challenging cases. In consideration of these limitations, there is an urgent need for new diagnostic technologies that are faster, more accurate and cost-effective in a range of healthcare settings. In the past few years, tremendous progress has been made towards designing and building new TB diagnostic tools such as next-generation sequencing (NGS) for the profiling of multi-drug resistance, AI-driven radiology for improved image reading, CRISPR-based solutions for rapid, portable, point-of-care-based detection and non-sputum biomarkers for simplified earlier diagnosis. These new technologies have the capacity to transform TB diagnosis by overcoming some of the limitations of current approaches and enabling earlier and more precise detection in pulmonary and extra pulmonary TB. This review gives an overview of the latest developments in TB diagnostics, evaluating their performance, practicability and impact on global TB control [8].

By analyzing the strengths and limitations of these new technologies, it intend to bring into perspective their promise to bridge existing gaps in diagnosis and accelerate quicker movement toward the WHO's End TB Strategy to reduce TB deaths by 95% by 2035. Their incorporation into clinical and public health practice has the potential to be a game-changer in the fight against TB and bring humanity closer to a TB-free world. Early and accurate diagnosis of TB is a cornerstone of effective disease control [9]. Diagnostic delays not only make clinical management more complicated in patients but also place them at risk of population transmission. Studies have proven in investigations that every untreated patient of TB infects about 10 to 15 individuals per year and reinitiating the cycle of infection. Besides, delay in diagnosis also causes late progression of the disease, resulting in higher mortality and healthcare costs. Delayed diagnosis in drug-resistant TB can accelerate resistance patterns, making treatment more difficult and at higher cost. Accurate diagnosis is also important to offer appropriate therapy without time wastage. False-negative tests can lead to untreated infections, while false-positive tests can subject patients to unnecessary treatment cycles and attendant side effects [10].

Therefore, improving the accuracy of diagnosis is needed to maximize treatment success rates and reduce the disease burden of TB on the health system. Delays in TB diagnosis may take place at multiple levels such as patient factors (e.g., ignorance or stigma) inefficiency of the health system (e.g., limited access to diagnostic facilities) and technical inadequacy of available tests. These delays have serious implications for individuals as well as for public health. For patients, prolongation of diagnostic delays commonly results in aggravated disease severity that can lead to serious complications such as extensive damage to the lung disseminated TB or even mortality [11]. Delayed diagnosis also predisposes to drug-resistant TB, which requires longer and more toxic therapy at greater expense. In public health terms, undiagnosed TB acts as reservoirs for ongoing transmission, particularly where the environment is high density like in households, workplaces and health facilities. This perpetuates the epidemic and undermines efforts towards the achievement of TB elimination targets [12].

Evolution of TB Diagnostics

In high-burden countries like India, delay in diagnosis accounts for the largest contribution towards the TB epidemic. Patients initially seek the private sector for treatment where diagnostic quality is unsure, leading to misdiagnosis or unconfirmed empirical treatment. Optimization of diagnostic processes and integration of new technology into healthcare systems are essential measures to mitigate delays and optimize TB control. Although widely employed, traditional TB testing methods have many disadvantages that undermine effective disease diagnosis [13]. Sputum smear microscopy, the TB test most applied, is underpowered by a low sensitivity and, especially when dealing with paucibacillary disease (e.g., in children or HIV-coinfected subjects), is inaccurate. The procedure is based on visual examination for acid-fast bacilli (AFB), not detecting as many as 50% of true active TB infections. Also, it cannot differentiate between viable and non-viable bacteria and detect drug resistance, limiting its application for clinical decision-making. Though culture is the gold standard diagnostic test for TB, its utility is limited by delayed turnaround times (2–6 weeks for solid and slightly faster for liquid cultures). It needs sophisticated laboratory facilities and bio safety practices and is therefore beyond the means of many low-resource settings. Risk of contamination

and the need for trained personnel also decrease its feasibility in decentralized health environments [14].

TST is used for identification of latent TB infection (LTBI), is low in specificity with cross-reaction with the Bacille Calmette-Guerin (BCG) vaccine and non-tuberculous mycobacteria (NTM). It also requires a return visit for reading, leading to potential loss to follow-up. These limitations highlight the need for better tests, such as interferon-gamma release assays (IGRAs), though cost remains a barrier in high-burden settings. In brief, the conventional TB diagnostics highlight the need for new, rapid, and accurate diagnostic methods. Emerging technologies, including molecular tests, biomarker-based tests, and artificial intelligence-based tests, offer the promise to revolutionize TB diagnosis. This article explores such advancements, evaluating their potential to overcome previous shortcomings and improve the management of TB worldwide [15]. The evolution of TB testing began over a century ago with sputum smear microscopy, a technique refined by Robert Koch in the late 19th century. This technique, founded on acid-fast staining of Mycobacterium tuberculosis (MTB), became the basis of TB diagnosis because it is simple and inexpensive. Microscopy, however has serious shortcomings, such as low sensitivity (particularly in HIV-coinfected individuals and children) and failure to identify drug resistance. The mid-20th century witnessed the development of culture-based methods, including Lowenstein-Jensen solid culture and subsequently automated liquid culture systems like BACTEC MGIT [16]. These tests improved diagnostic accuracy by offering greater sensitivity and the ability to perform drug susceptibility testing (DST). Culture-based diagnostics are however time-consuming, requiring weeks for bacterial growth, and need sophisticated laboratory facilities, making them inappropriate in resource-poor settings. The 21st century brought on board a molecular assay paradigm with technologies like the polymerase chain reaction (PCR), through which MTB DNA could be detected quickly by shortening the turnaround time significantly [17]. The introduction of the GeneXpert MTB/RIF assay in 2010 changed TB diagnosis because it married the automation of nucleic acid amplification testing with simultaneous rifampicin resistance testing. This innovation was a breakthrough, particularly in regions of high burden, due to its speed (two hours for results) and minimal technical sophistication required. Today, the World Health Organization (WHO) currently advises several gold-standard diagnostic tools for TB, including GeneXpert MTB/RIF, ultra-sensitive liquid culture (MGIT), and line probe assays (LPAs). GeneXpert remains a front-line diagnostic due to its rapid detection of MTB and rifampicin resistance and it is invaluable in high-TB-burden environments [18]. Here, the proper way to diagnosis of TB shown as Figure No. 01.

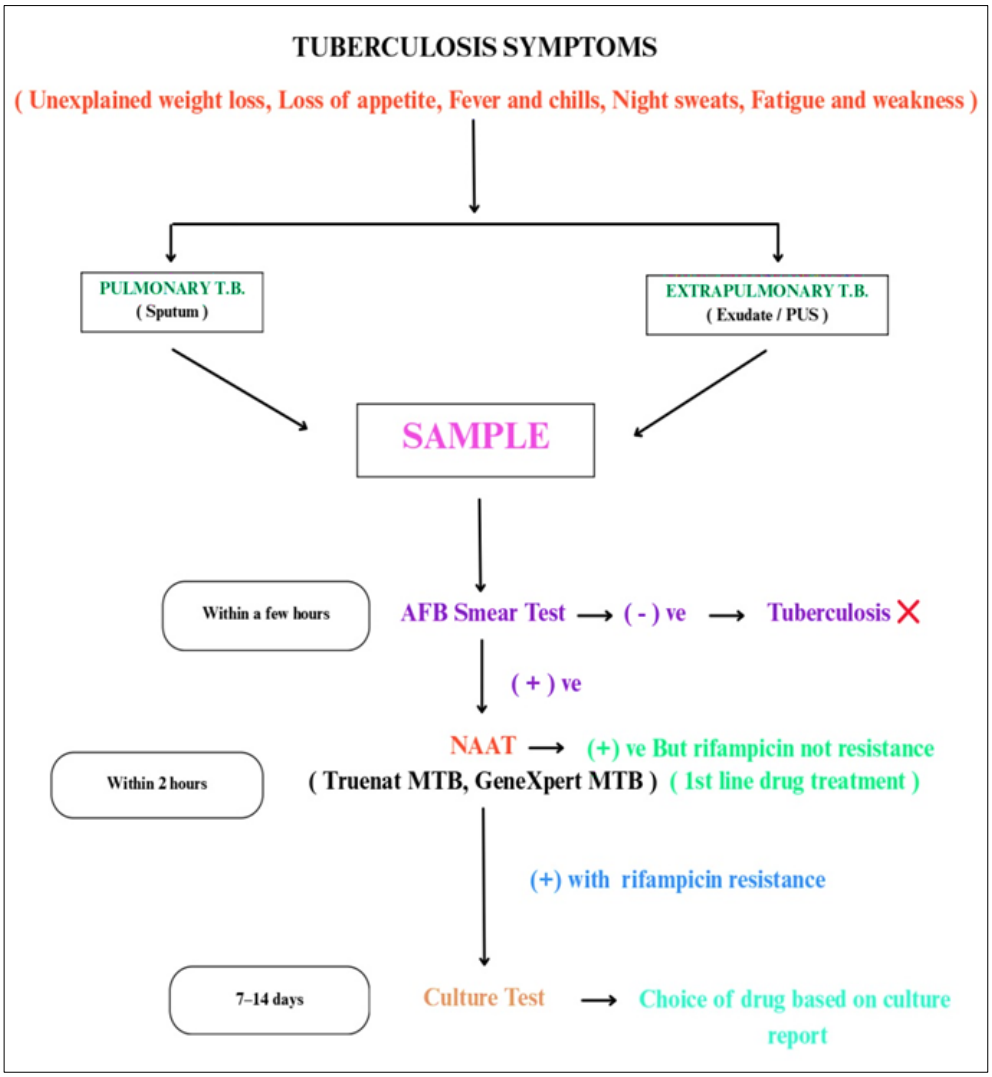

Fig 1: Systematic Flow Diagram for TB Diagnosis

Liquid culture systems are also highly sensitive and allow for complete DST, which is essential for the treatment of drug-resistant TB (DR-TB). Despite these developments, there remain gaps. GeneXpert, although extremely helpful, has the limitation of detecting only paucibacillary TB (e.g., in children or extra pulmonary TB) and is not able to detect resistance outside of rifampicin [19]. In addition, its reliance on stable electricity supply and costly cartridges restricts its large-scale use in the field. Liquid culture, although very sensitive, remains slow (up to six weeks) and requires biosafety level 3 (BSL-3) facilities, which are not available in low-resource settings. There is also the problem of unavailable point-of-care (POC) tests for rapid, decentralized diagnosis. Even with newer technology like Truenat and LF-LAM (for HIV-related TB), they are not all equally sensitive and are yet to become universally adopted. Moreover, the growing threat of extensively drug-resistant TB (XDR-TB) demands progressively improved diagnostics able to detect second-line drug resistance appropriately [20]. Overall, even with newer TB diagnostics, lots of work still needs to be done in universal, rapid, and accurate detection. The section below elaborates on new technologies, including AI-assisted diagnostics, NGS, and biomarker-based assays, which promise to overcome such deficiencies and change the face of TB control globally. That challenges in TB diagnosis continue to reiterate the need for novel technologies [21].

Classical diagnostic examinations while useful are plagued by limitations. The sputum smear microscopy, the most widely employed TB test, is of low sensitivity (50-60%), especially in HIV-coinfected individuals and children. The culture-based techniques are more precise but take several weeks, precluding early initiation of treatment. Molecular tests such as GeneXpert have high detection rates but are still expensive and require a laboratory setup, making them inaccessible in distant regions. Increasing prevalence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) necessitates quick and precise diagnostic tests to guide appropriate treatment [22]. Further, COVID-19 exacerbated healthcare infrastructure, underlining the need for decentralized, point-of-care (POC) diagnostics that can function outside of traditional laboratory settings. Emerging technologies bridge these gaps by providing quicker, more precise, and portable diagnostic testing, enabling early detection and reducing transmission. In regions with high TB burden, the lack of advanced laboratory facilities and personnel hinders efficient diagnosis [23].

Pressure mounts fast, portable and highly sensitive diagnostic assays. Early treatment is enabled by rapid diagnostics, reducing disease transmission and improving patient outcomes. Portable devices, such as handheld molecular diagnostic platforms, offer point-of-care testing in community clinics, prisons and rural locations where lab facilities are restricted. Sensitive devices play a crucial role in the diagnosis of paucibacillary TB (low bacterial load cases), extrapulmonary TB and in immuno-compromised individuals. Innovative technologies like CRISPR-based diagnostics and artificial intelligence-based imaging systems deliver almost real-time diagnoses with minimal infrastructure requirements [24]. For instance, CRISPR-Cas systems deliver very high levels of TB DNA detection accuracy, while AI-based software enhances chest X-ray interpretation accuracy for facilitating early TB detection. These innovations are transforming TB diagnosis from a laboratory-centric, centralized to a decentralized, patient-centered paradigm. New technologies are coming into prominence to address some of the present limitations inherent with traditional TB diagnosis. CRISPR-based diagnostic assays such as SHERLOCK and DETECTR use gene-editing principles to identify TB-specific DNA or RNA sequences with great specificity. Such assays are convertible into paper-strip formats for low-cost, rapid POC analysis in limited-resource settings. Artificial intelligence is revolutionizing TB screening through computerized image analysis [25].

Thousands of chest X-rays can be employed to train AI algorithms to detect TB-related abnormalities with accuracy comparable to radiologists, reducing human error and speeding up diagnosis. Mobile health apps employing AI can also offer diagnostic access to the underserved. With the aid of developing novel drug delivery architectures that allow molecular level contamination manipulation, nanotechnology has significantly more suitable the remedies field. It is far practicable to beautify treatment efficacy even as decreasing dangerous medicinal drug reactions and control frequency with the aid of utilising nanotechnology for focused treatment. ultimately, this approach results in accelerated adherence costs and higher affected person compliance. similarly to liposomes, polymeric nanoparticles, nanocrystals, nanosuspensions, nanogels, dendrimers, and niosomes, nanocarriers are important for the targeted shipping of TB medication [26]. Nanotechnology is enhancing TB detection through biosensors and nanoparticle-based assays. Gold nanoparticles, quantum dots, and magnetic nanoparticles increase test sensitivity through signal amplification in biomarker detection. The nanotechnologies at the scale of nanos allow the development of miniaturized, uncomplicated diagnostic devices suitable for application in the field. Biomarker discovery is a second important TB diagnostics frontier. Researchers are finding novel host and bacterial biomarkers in the blood, urine, and breath fluids that correlate with active TB infection. These biomarkers can be applied to non-invasive tests that can substitute for sputum-based testing, improving patient compliance and diagnostic access. In summary, the synergistic union of CRISPR, AI, nanotechnology and biomarker research is transforming TB diagnostics with quicker, more precise and accessible solutions. These technologies hold great promise to fill existing gaps in diagnosis, particularly in high-burden, low-resource settings and ultimately support global efforts towards TB elimination [27]. In time to time the tools for diagnosis of TB has been modified as given in Table No. 01.

Table 1: Timeline of Major Advances in TB Diagnostics (Graph) [25-26]

Era	Technology	Key Features
1940s	Sputum Microscopy	Low Sensitivity
2000s	IGRAs	Improved Specificity over TST
2010s	GeneXpert	Rapid MTB/RIF detection
2020s	CRISPR-based tests	High Accuracy

Technologies in TB diagnosis

Current diagnostic techniques face several challenges that confine effective TB control. The most widespread application in high-prevalence settings, sputum smear microscopy, fails to detect nearly half of active disease cases

since it is not extremely sensitive. While culture remains the standard, its utility is confounded by sluggish turnaround times of 2-8 weeks and costly laboratory infrastructure. Molecular tests like GeneXpert are more sensitive at detection but remain unaffordable in the majority of resource-poor settings due to cost and infrastructure constraints [28]. Such diagnostic lacunas are particularly concerning high-risk groups like children, HIV-infected individuals and patients with extrapulmonary TB, where traditional approaches remain inadequate.Emergence of drug-resistant strains of TB has further complicated diagnosis. Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) require specialized detection methods to guide appropriate treatment regimes. Standard phenotypic drug susceptibility testing requires weeks, with patients receiving ineffective treatment in the meantime while continuing to spread resistant organisms. This is reason enough to demand the use of rapid molecular detection that simultaneously detects Mycobacterium tuberculosis and resistance patterns within hours rather than weeks [29]. As all the test for TB diagnosis have different technology used shown in Table No.02.

Table 2: Comparative Technologies of Major TB Diagnostic Test [28-29]

Test Name	Technology	Sample Type
TST	Immune (PPD reaction)	Skin
IGRA	INF-Gama release assay	Blood
GeneXpert	NAAT (PCR)	Sputum/Exudate
LF-LAM	Lateral flow (antigen)	Urine
Truenat	Isothermal NAAT	Sputum

Recent years have witnessed groundbreaking advancements in TB diagnostic technologies that can potentially transform the detection and control of disease. Sequencing platforms of the next generation now make whole-genome analysis of TB genomes possible with rich drug resistance mutation and strain lineage information. CRISPR-based diagnostic systems offer unprecedented specificity for TB DNA sequence detection, with potential for miniaturizing to low-cost, point-of-care formats [30]. Computer programmes in artificial intelligence are revolutionizing reading of chest X-rays, boosting screening efficiency and reducing the reliance on specialty radiologists for disadvantaged populations. Technological innovations in nanotechnology are enabling novel biosensor platforms to detect TB biomarkers at high sensitivity. These include systems based on quantum dots, gold nanoparticles and other nanomaterials for signal amplification from trace levels of bacterial material [31]. Diagnostic strategies based on non-sputum approaches against volatile organic compounds in breath or selected host immune markers in blood represent another hopeful frontier, possibly making diagnosis easier and earlier. Their integration into algorithms for diagnosis would radically change work for TB control at a worldwide scale. It has been possible to apply high-level diagnostics in primary healthcare levels with the creation of molecular portable devices like the Truenat system. The digital platforms with machine learning algorithms are offering the ability to automatically analyze clinical and radiographic information, enable rapid triaging of suspected cases and enable speed, accuracy and access triple challenges of diagnosis in TB with long been issues of the field [32].

This article summarizes the current status of novel diagnostic technologies for TB, evaluating technical basis, performance in the clinic and feasibility for field implementation. Mentioned are molecular diagnostics, radiologic innovations, nanotechnology methods and AI approaches that are transforming diagnostics. Specific focus is placed on technologies well-suited for roll-out in environments of low resource, where the lion's share of the burden of TB is found. By discussing both the promise and limitations of these technologies, this review aims to enlighten policymakers, clinicians, and researchers about the new technologies that can at last help overcome one of the world's longest-standing challenges of global health. The subsequent parts will include elaborate discussions of some technological approaches, beginning with molecular diagnosis like CRISPR-based systems and next-generation sequencing platforms. Subsequent parts will explore imaging advances, nanotechnology equipment, and artificial intelligence machines, followed by presentations on challenges to implementation and the way forward for TB diagnostics. These parts put together will outline how new technologies can help the WHO achieve TB elimination by the year 2035 [33]. Sensitivity, Specificity, Time and other data of Major TB diagnostic test are shown in Table No. 03.

Table 3: Comparative Features of Major TB Diagnostic Test

Test Name	Sensitivity (%)	Specificity (%)	Time (hrs.)	Cost (INR)	Reference
TST	70	65	48-72	200-500	[34]
IGRA	80-90	95-98	24-48	3000-6000	[35]
GeneXpert	90	98	2	2000-3500	[36]
LF-LAM	50-60	90	0.5	800-1500	[37]
Truenat	85	96	1	1500-2500	[38]

Immunodiaganostics Approaches

Unlike earlier microbiological strategies, these methods have faster results and wider utility for paucibacillary and extrapulmonary TB. The tuberculin skin test (TST), the first immunodiagnostic tool, is a measure of delayed-type hypersensitivity but suffers from cross-reactivity due to BCG vaccination and NTM. Interferon-gamma release assays such as QuantiFERON-TB Gold and T-SPOT. TB offered greater specificity through detection of T-cell responses to MTB-specific antigens (ESAT-6, CFP-10) [39]. However, IGRAs cannot distinguish active from latent infection and are still costly for high-burden settings. Future advances focus on new antigens (e.g., Rv0081, Rv2389c) and multiplex assays to enhance accuracy. Lateral flow tests like the Alere Determine TB LAM Ag test provide rapid point-of-care testing, particularly for HIV-co-infected individuals, but sensitivity remains poor. Other biomarkers like IP-10, MCP-1, and IL-2 hold potential for more precise differentiation of TB states. Emerging technologies including ECLIA and multiplex bead-based assays (Luminex) permit the measurement of several cytokines simultaneously, improving diagnosis. Sputum-independent

modalities such as urine LAM and breath-based volatile organic compound (VOC) analysis are under development to allow better accessibility and detection of pediatric TB. Artificial intelligence (AI) is being harnessed to optimize biomarker interpretation, with machine learning algorithms combining multiple immune signatures to enhance diagnostic performance. Future directions include low-cost, high-sensitivity point-of-care platforms, consistent with WHO goals for global TB elimination. Challenges persist in standardization, cost, and population-specific heterogeneity. Immunodiagnostics will play a critical role to TB control, particularly in high-risk groups, as innovations continue to bridge current diagnostic gaps [40].

Interferon-Gamma Release Assays (IGRAs)

Tuberculosis diagnosis has been greatly improved by the discovery of Interferon-Gamma Release Assays (IGRAs), which are a major breakthrough in Mycobacterium tuberculosis infection detection. IGRAs are blood tests that quantify T-cells from M. tuberculosis will secrete interferon-gamma (IFN-γ) when stimulated by antigens such as ESAT-6 and CFP-10, which are not present in BCG vaccine strains and most non-tuberculous mycobacteria [41]. This particular immune response is the biological foundation of IGRA testing, with greater specificity than TST, especially in BCG-vaccinated individuals. Two commercial IGRA platforms are now available: the QuantiFERON-TB Gold Plus (QFT-Plus) and T-SPOT.TB tests. These tests also vary in methods, with QFT-Plus quantifying the concentration of IFN-γ in whole-blood supernatant using ELISA and T-SPOT.TB counting T-cells secreting IFN-γ employing ELISPOT technology. These tests have been shown to exhibit higher specificity (around 95-98%) than TST since they remain unaltered by previous BCG vaccination. Their clinical performances, however, differ based on the population in question and prevalence of TB within the setting [42].

In practice, IGRAs have been especially useful for diagnosing latent TB infection (LTBI) among high-risk groups, such as immune compromised individuals and healthcare workers. Their single-visit nature and objective readout remove the subjectivity and logistics of TST interpretation. In the diagnosis of active TB, IGRAs are moderately sensitive (70-90%) but cannot distinguish reliably between latent and active infection. This limitation necessitates their use along with other diagnostic modalities when evaluating patients with suspected active TB disease. The performance characteristics of IGRAs have been well characterized in a wide range of populations and settings. In low-incidence TB countries, the tests demonstrate excellent negative predictive value for exclusion of LTBI, and they constitute useful tools in investigations of contact [43]. Yet in countries with a high burden of TB, their value is lower owing to greater proportions of indeterminate results and diminished capacity for prediction of active disease progression. The latest technical advances in IGRA platforms, such as the incorporation of novel TB antigens and streamlined testing regimens, remain to promote greater clinical use. Although they have their benefits, IGRAs pose a number of challenges to use in everyday clinical practice. The tests need to be collected, handled and processed in the blood in strict time intervals to ensure accuracy. Cost is still a major limitation in resource-poor settings, and as with all immune-based tests, IGRAs cannot distinguish between active and latent infection. Research continues to enhance IGRA performance using new combinations of antigens and the creation of point-of-care versions that could transform TB screening programs globally [44].

Tuberculin Skin Test (TST)

The Tuberculin Skin Test (TST), also called the Mantoux test, has been a fixture of tuberculosis (TB) infection diagnosis for over a century. The test is intradermal injection of purified protein derivative (PPD), a mixture of antigens from Mycobacterium tuberculosis, which elicits a delayed-type hypersensitivity reaction in individuals previously exposed to TB. 48 to 72 hours after the test, induration at the point of injection is measured. An induration of 10 mm or greater is generally considered positive in the majority of clinical cases, though the cut-off can be different 5 mm in immune compromised individuals and 15 mm in low TB risk individuals. Despite its centuries-long tradition of use, the TST has a few obvious shortcomings, *viz*., results variability, interference by BCG vaccination, and need for follow-up visit and thus loss to follow-up upon administration in settings of limited resources. Among the biggest limitations of the TST is its inability to differentiate between latent TB infection (LTBI), tuberculosis disease, and remote BCG vaccination [45].

Since most high-TB-burden countries administer BCG vaccines routinely, false-positive results are common, reducing the test's (specificity. In addition, the sensitivity of the TST is compromised in immune compromised hosts, such as those with HIV, malnutrition or chronic illness, where anergy (inability to mount immune responses) can lead to false-negative results. The requirement for confirmatory testing or other alternative diagnoses occurs in these populations with restrictions. Despite these shortcomings, the TST continues to be used heavily because of its inexpensiveness, ease, and absence of necessity for specialized equipment in a lab. Current innovation has tried to overcome some of the TST's disadvantages. New reagents for tuberculin that possess increased specificity, such as recombinant ESAT-6 and CFP-10 antigens (that are missing from BCG strains) are currently under study [46]. Digital calipers and a smartphone application for measuring induration and minimizing inter-observer variation are also being researched as methods to standardize reading. However, the TST's reliance on a functioning cell-mediated immune response guarantees that it will never be able to function at its optimal level in highly immunocompromised patients. Relative to more recent interferon-gamma release assays (IGRAs), which are not cross-reactive with BCG and more specific, the TST remains more accessible in resource-poor environments due to it being less costly and needing minimal equipment. However, IGRAs are gaining favor in high-income countries for LTBI screening, particularly among BCG-vaccinated populations. Choice of TST vs. IGRA typically depends on local epidemiology, cost considerations, and availability of laboratory backup. In the coming years, the role of the TST in worldwide TB control may be diminished as molecular and biomarker-based diagnostics improve. But in settings where cost and infrastructure constraints persist, the TST will likely continue to be a pragmatic, if not optimal, tool for screening TB infection. Future research will need to focus on enhancing its specificity with adjunctive biomarkers or

lessened readout technologies to keep it useful in the changing world of TB diagnosis [47].

Molecular Diagnostics

Molecular testing has revolutionized the process with the capability to achieve rapid and accurate detection of Mycobacterium tuberculosis (MTB) as well as drug resistance. These advanced techniques apply nucleic acid amplification for the detection of bacterial DNA or RNA, which reduces turnaround time from weeks to hours and enhances sensitivity. GeneXpert MTB/RIF test, approved by the World Health Organization (WHO), is a game-changer in the diagnosis of TB. This automated, cartridge-based system for detecting MTB and rifampicin resistance in two hours obviates critical delays in conventional methods. Improved sensitivity (approximately 90% for pulmonary TB) in this renders it particularly valuable in high-burden settings, though challenges still persist in extra pulmonary TB and paucibacillary disease. Another innovation is the Truenat MTB assay, which is a chip-based PCR system that is portable and well-suited to decentralized settings. With equally high accuracy as GeneXpert but fewer infrastructure needs, Truenat enhances rural communities' diagnosis access. Beyond these platforms, isothermal amplification techniques like LAMP eliminate the need for complex thermal cycling and permit low-cost, rapid testing. Visual reporting and ease ensure that LAMP is suitable for peripheral clinics. Conversely, CRISPR-based assays, such as SHERLOCK and DETECTR, use gene-editing technology to detect TB DNA at high specificity and are frequently paired with lateral flow strips for simple reading. All of these imagine point-of-care testing with minimal equipment. Molecular diagnosis is also better in drug-resistant TB detection, a newly evolving public health issue. LPAs and NGS identify resistance-determining mutations beyond rifampicin, and they guide the use of individualized treatment. Technical requirements and cost, however, limit their expansion to resource-poor environments [48].

In spite of their strengths, molecular assays are hampered by obstacles such as high costs, cartridge dependency, and power requirements. Efforts towards affordable, equipment-independent alternatives continue. Incorporation of these technologies into national TB programs, combined with infrastructure development, is critical to optimize their reach. Overall, molecular diagnostics have revolutionized the detection of TB through the convergence of speed, precision, and scalability. Innovation and equitable application are central to achieving global TB control objectives [49].

Nucleic Acid Amplification Tests (NAATs)

Diagnosis of tuberculosis (TB) has been transformed by Nucleic Acid Amplification Tests (NAATs), which identify Mycobacterium tuberculosis (MTB) DNA or RNA with high specificity and sensitivity. Among them, GeneXpert MTB/RIF assay has redefined the diagnosis of TB as it was endorsed by the World Health Organization (WHO) in 2010. GeneXpert is an automated cartridge-based system that incorporates sample processing, DNA extraction, and real-time PCR amplification and provides a result in two hours. Its potential to detect MTB and rifampicin resistance in parallel has made it precious in high-burden settings. But while GeneXpert has revolutionized the diagnosis of TB, its shortcomings moderate sensitivity in smear-negative and extrapulmonary TB, high expense, and dependency on reliable electricity-have spurred the growth of next-generation NAATs [50]. Recent improvements in NAATs seek to obviate these deficiencies. GeneXpert Ultra, an updated version of the initial assay, will more than likely be more sensitive, especially in paucibacillary and HIV-related TB. A recent technology is Truenat, which is a chip-based, battery-powered PCR system with an amplicon hybridization-based detection system. Unlike GeneXpert, Truenat does not need enormous infrastructure and thus could be an even more convenient option in the field. Second, LAMP-based assays are quick and inexpensive replacements for traditional PCR, obviating the need for thermocyclers. These developments identify the trend toward quicker, lower-cost, field-deployable NAATs. In addition to regular PCR-based technology, CRISCR-Cas systems will soon become an indispensable tool in the diagnosis of TB. SHERLOCK and DETECTR assays, for instance, are CRISPR-based assays using gene-editing technology to detect MTB-specific sequences with an unparalleled level of specificity [51].

Assays can be formulated in paper-strip formats to allow point-of-care (POC) analysis in the field without the availability of advanced apparatus. Next-generation sequencing (NGS) is also gaining recognition for all-around drug resistance profiling, identifying mutations in a variety of genes in one go. Although NGS is still limited to referral labs, its potential for individualized therapy in TB is vast. All these developments aside, the amplification of NAATs continues to be an issue worldwide. Technical, training, and cost issues continue to hinder access in the resource-constrained world. Ultra-fast, inexpensive NAATs with low technical demands will be necessary for future research. Implementation of the technologies in current healthcare infrastructure will be critical to universal diagnosis and control and elimination of the disease [52].

Loop Mediated Isothermal Amplification (LAMP) for Rapid Diagnosis: Loop-mediated isothermal amplification (LAMP) has been an encouraging molecular probe of TB diagnosis superior to the traditional methods of smear microscopy and culture-based assays. LAMP is a nucleic acid amplification technique functioning at an isothermal temperature range of 60–65°C, independent of thermal cycling like in polymerase chain reaction (PCR). This aspect of LAMP makes it highly attractive to use in low-resource environments where advanced laboratory facilities are not available. The procedure is amplified target DNA with specificity and high-order sensitivity and within 60 minutes, which is much quicker than the conventional culture techniques that take weeks. Robustness and simplicity are two of the benefits of LAMP. Unlike PCR, for which accurate temperature control and costly equipment are necessary, LAMP can be conducted with inexpensive heating sources like water baths or portable battery-operated units [53]. This renders it extremely well-suited for decentralized testing in remote or underserved communities. Moreover, LAMP results are discernible to the naked eye as turbidity or color change, rendering interpretation once more independent of sophisticated equipment. A number of commercial LAMP-based TB tests, including TB-LAMP (which was developed by Eiken Chemical Co., Japan), have been approved by the World Health Organization (WHO) for implementation in peripheral health centers. The assays

have excellent diagnostic accuracy, and their sensitivity is identical to GeneXpert MTB/RIF, especially for smear-positive TB. Although superior in multiple aspects, LAMP also has some limitations that discourage its extensive usage. While it is more suitable for smear-positive cases, it is less sensitive to paucibacillary TB, including in children and HIV-co infected individuals [54].

In addition, LAMP has no detection feature of drug resistance at present, an aspect vital to the age of emerging multidrug-resistant TB (MDR-TB). There are attempts to combine LAMP with CRISPR-based detection systems to make it more suitable for resistance profiling. Another difficulty is the risk of contamination because LAMP has high amplification efficiency, and laboratory practices need to be very strict to prevent false-positive results. New technologies are directed toward improving the LAMP for point-of-care (POC) applications. Technologies such as microfluidic LAMP devices and smartphone-detectable systems are in development to improve portability and user-friendliness. Furthermore, studies are exploring the identification of new biomarkers for increasing LAMP sensitivity for extra pulmonary TB and latent TB infection. The ability of multiplex LAMP tests to detect multiple pathogens, such as TB and NTM, can further extend its diagnostic application. Overall, LAMP is a good step forward in TB diagnosis with rapid, cheap, and simple testing in resource-poor environments. While there are challenges, continued technological advancements and alignment with new technologies offer the potential for overcoming present shortcomings. As world health systems shift towards WHO's End TB Strategy objectives, LAMP-based diagnostic technologies can be poised to help drive early diagnosis as well as control TB infection globally [55].

CRISPR Based Diagnostics

CRISPR technology, first implemented as a gene editing tool, has turned out to be a new way of going about infectious disease diagnosis, e.g., TB. Specificity-based assays targeted on CRISPR-associated (Cas) proteins on MTB DNA or RNA have been found to be sensitive and specific. Compared to the traditional smear microscopy or low-sensitivity culture methods with prolonged turnaround times, CRISPR-based diagnostics offer cheap, portable, and fast alternatives. Such methods, including SHERLOCK (Specific High-sensitivity Enzymatic Reporter unlocking) and DETECTR (DNA Endonuclease Targeted CRISPR Trans Reporter), can identify TB-specific gene sequences in a matter of hours and are well-suited for use in point-of-care (POC) diagnostics in high-burden countries. One of the most significant advantages of CRISPR-based TB tests is that they are able to detect drug-resistant strains. By targeting resistance-giving mutations in rifampicin, isoniazid, and other anti-tuberculosis drugs, CRISPR tests have the potential of providing valuable information for personalized medicine [56]. For example, a CRISPR test can distinguish between drug-susceptible and multidrug-resistant TB (MDR-TB) on the basis of single-nucleotide polymorphisms (SNPs) in rpoB, katG, and inhA genes. This action is most valuable in resource-poor settings, where traditional drug susceptibility testing (DST) is not available or has a time delay. CRISPR diagnostics can even be designed to be used on lateral flow strips such that visual readouts are possible without the need for sophisticated instruments. This feature makes them better placed in decentralized healthcare setups where laboratory facilities are absent. CRISPR TB diagnostics have several issues to be addressed. Amplification and extraction of nucleic acids (for example, through the use of recombinase polymerase amplification, RPA) add to test protocol complexity but current advancements aim to integrate these procedures into one step [57].

The second is the potential off-target effect whereby CRISPR-Cas complexes can bind to non-TB DNA sequences to yield false positives. Such errors are minimized by improving specificity in guide RNAs (gRNAs) through current efforts. Cost and scalability are problems, considering the necessity to keep improving the production of CRISPR reagents and their application in low-resource settings. Nevertheless, partnerships between academic researchers, diagnostic companies, and global health organizations are propelling the translation of CRISPR diagnostics from the bench to the bedside [58]. The prospects for the future of CRISPR-based TB diagnosis are bright, with new technologies like multiplexed assays to detect multiple pathogens and resistance markers simultaneously in a single test. Use with mobile health technologies will also enhance their potential, with data sharing in real time and remote diagnosis being a reality. With the World Health Organization (WHO) expecting more speed and accuracy in TB diagnosis, CRISPR-based diagnostics have the potential to fill the diagnostic gap.With high accuracy, short turnaround time, and portability, the systems provide a revolutionary tool for TB management, particularly in high-burden, resource-limited environments. Continued investment and validation studies will be required to make them acceptable worldwide and integrate them into global TB elimination strategies [59].

Barriers in Advanced Diagnostics

Despite outstanding gains in the diagnosis of tuberculosis (TB), there are several challenges to the widespread use and adoption of new technologies, particularly in resource-limited, high-burden settings. It is quite possibly the most significant among these that advanced diagnostic machines are prohibitively expensive. GeneXpert MTB/RIF and next-generation sequencing (NGS) technology-based molecular tests are too expensive, requiring expensive machines, reagents, and maintenance, and are hence economically unfeasible for the majority of low- and middle-income countries (LMICs). Assuming that the technologies are even available, operational costs of cartridges, calibration and quality control often strain healthcare budgets, limiting their scalability [60]. Another important impediment is the lack of adequate infrastructure in remote and underserved locations. Several advanced diagnostic platforms depend on consistent electricity, temperature-regulated space, and stable internet connectivity inputs that are generally lacking in rural or conflict-affected areas. Without proper infrastructure, even the most advanced diagnostics have no use, and thus resort to more traditional methods like smear microscopy. In addition, the need for bio safety level 3 (BSL-3) laboratories for culture-based diagnostics also restricts their deployment in low-resource settings, where facilities are scarce. The second is that advanced diagnostics are complicated. With the majority of new technologies, including computer-based analysis of images and CRISPR-based diagnostics, there is a need for specialized training to properly operate and interpret these technologies [61].

Where there are deficits in highly qualified laboratory personnel in some regions, misuse of these technologies can lead to false positives, delayed intervention and incorrect diagnosis. Moreover the incorporation of new diagnosis technology into existing healthcare programs calls for holistic training programs, which are normally impracticable to enforce due to the impediment of costs and logistics. Regulatory and policy impediments further impede the rollout of new TB diagnostics. Complicated approval procedures, lack of standard guidelines, and diverse regulatory processes in nations delay the rollout of new technologies [62]. In some, inefficient supply chains and procurement distortions render diagnostic reagents and consumables not available perpetually, disordering test services. Secondly, the absence of strong public-private partnerships hinders research and development investment, impeding the evolution of affordable point-of-care products. Lastly, socio cultural and behavioral factors influence the effectiveness of advanced diagnostics. Stigma against TB, compromised health literacy, and patient reluctance to undergo testing lead to underdiagnosis. Even if advanced instruments are in place, fear of diagnosis or faith in health systems may deter patients from receiving tests, creating a window for continued transmission. Dealing with these barriers requires a multi-sectoral approach, including financial commitment, infrastructure development, training of the workforce, and community outreach to make advanced diagnostics available to those who need them most [63].

Economic and Infrastructure Challenges in Low Income Countries: Most high-burden countries lack adequate funding for their TB program, and the health systems become understaffed and ill-equipped. Even extremely effective tests such as GeneXpert need considerable investment in machines, maintenance, and trained staffthings never available in poor or rural settings. The expense of cartridges and the need for consistent power also limit their use, compelling most clinics to have to continue using outdated techniques such as smear microscopy, which detects almost half of all active TB. Without sustainable financing structures, gaps in early detection are severe enough to ensure ongoing transmission and failure in treatment outcomes. Overcome historical financial hurdles, infrastructure deficits are another core problem. The majority of low-income countries have poorly equipped laboratories with biosafety facilities for culture-based testing or molecular diagnosis. Transport infrastructure is inadequate, and sample referrals from outlying clinics to central laboratories take a long time [64]. Power failures interrupt diagnostic tests, and supply chain inefficiencies lead to stockouts of critical reagents and test kits. These logistical barriers disproportionately fall on the backs of vulnerable groups, including slum dwellers, inmates, and those living in conflict areas, where risk of TB is highest. Additionally, the lack of skilled technicians results in diagnostic mistakes and delayed reporting. Without strong laboratory networks and reliable systems of supply, even the finest diagnostic technology cannot find its way to the individuals who need it most. The financial burden of TB spills over from health systems to families and patients in the form of catastrophic costs. In poor contexts, most individuals must pay exorbitant out-of-pocket fees for diagnosis tests, transportation to healthfacilities, and loss of income when ill. They discourage individuals from seeking care promptly, leading to undetected transmission [65].

Further, the lack of integrated health information systems hinders data-driven decision-making, and it becomes difficult to monitor outbreaks or allocate resources. To bridge these gaps, a multi-sectoral approach is required, supported by more international funding, public-private partnerships, and investment in training healthcare workers. Mobile diagnostic units, solar-powered technology, and AI diagnostics can be an affordable option, but their scalability depends on local capacity development and political will. As long as the infrastructural and economic gaps are not plugged TB elimination in poor countries will be an elusive dream that still seems beyond our reach [66].

Training, Quality Control and Regulatory Hurdles

Successful adoption of cutting-edge TB diagnostics hinges not just on technological advancement but also on solid training programs, rigorous quality control procedures, and managing intricate regulatory environments. Though new technologies such as molecular tests, AI-based tools, and handheld devices have revolutionary promise, their actual utility in the field is frequently stymied by human resource deficits, variable quality assurance, and regulatory hold-ups. Overcoming these bottlenecks is essential to secure equitable access and best performance of next-generation diagnostics across heterogenous healthcare environments. One of the biggest challenges of implementing advanced diagnostics is the lack of skilled personnel who can run complex equipment and accurately interpret results. GeneXpert, CRISPR assays, and radiology supported with artificial intelligence are some of the technologies that need specific technical skills not always found in resource-poor areas [67]. For example molecular diagnostics require skills in processing samples, instrument operation, and resolving errors, whereas AI-based tools require digital data interpretation training and clinical correlation. In the absence of appropriate training, the risk of misusing them will result in inaccurate results, late diagnosis, or equipment malfunction. To fill this gap, well-organized training programs consisting of hands-on workshops, e-learning modules, and competence tests have to be embedded in national TB control programs. Collaborations among diagnostic companies, universities, and public health organizations can scale up training programs so that all levels of healthcare workers are empowered to utilize these technologies effectively. Quality control (QC) is also a decisive factor in determining the reliability of sophisticated diagnostics. Differences in test performance can occur as a result of variability in reagent storage conditions, equipment calibration, or procedural issues, especially in decentralized environments [68].

For instance, temperature variations during cartridge storage in GeneXpert can influence assay sensitivity, whereas incorrect sample collection for biomarker tests can produce false negatives. Standardized QC procedures, such as routine equipment maintenance, internal and external quality testing, and proficiency testing, are crucial to ensure diagnostic precision. Global networks such as the WHO's TB Supranational Reference Laboratories help harmonize QC standards across the world. Moreover, the incorporation of automated quality controls in diagnostic equipment, e.g., real-time error warnings in AI packages or intrinsic calibration checks in handheld machines, can reduce human-

error dependencies and increase reproducibility. Regulatory barriers also weigh down the uptake of advanced TB diagnostics. The process of new-tool authorization is highly variable across nations, tending to include long testing times for safety, efficacy and cost-efficacy [69]. In the most burdened contexts, delays in regulations can hold back the introduction of urgently required technologies, reinforcing dependency on outmoded practices. For example, although CRISPR-based diagnostics hold the potential to enable fast, low-cost TB detection, their implementation is hampered by a lack of straightforward regulatory guidelines in most nations. Simplifying regulatory channels through cooperative approaches such as the WHO Prequalification of *in Vitro* Diagnostics scheme can expedite clearances while maintaining stringent criteria. Additionally, post-market surveillance is important to track long-term performance and detect potential problems, like reagent stability in harsh climates or algorithmic bias in AI software. Conquering these hurdles necessitates a multi-sector response. Workforce training investment, universal QC systems and flexible regulatory policies will play a key role in leveraging the full potential of advanced diagnostics. By conquering these obstacles, the global health community can see to it that leading-edge technology is realized into concrete advances in TB diagnosis and treatment, most especially in those areas most in need [70].

Challenges and future directions

Despite significant progress in tuberculosis (TB) diagnosis, there are a number of hurdles to the full incorporation of new technology. Foremost among these iscost and scalability of advanced technology. Although molecular tests such as GeneXpert and Truenat enhance diagnostic performance, their limited operational cost and dependency on high-end devices restrict access in low-resource environments. Likewise, NGS and AI tool solutions are very costly and are thus not appropriate for routine use within high-burden environments. Low-cost alternatives like smartphone-compatible platforms and paper diagnostics must be brought into future strategies to offer equity of access. Another most critical challenge is validation for the high-burden, low-resource contexts. All the new diagnostics are successful in randomized clinical trials but do not work when put to practical use because of issues such as unreliable electricity, unstable temperature, and low technical proficiency. For example, CRISPR tests, while very specific, need to be stored under stable conditions that cannot be readily achieved in remote settings. Field testing to check the ruggedness, ease of use, and affordability of such technologies in varying conditions is necessary. In addition, streamlining sample collection protocols such as biomarkers aside from sputum would permit deployment in HIV-co infected patients and children, to whom there is limited access to quality sputum samples. The digital health system and tele health integration offers an opportunity for reimagining diagnostic delay. AI platforms can interpret chest X-rays and molecular test findings, facilitating real-time decision-making in primary healthcare centers. Mobile health applications can also provide remote consultation minimizing the distances patients have to travel for diagnosis [71].

Among the problems that need to be resolved in order to achieve the promise of digital solutions are gaps in internet connectivity, data privacy issues, and the need for clinician training. Emerging innovations must be founded upon interoperable systems that link diagnostic equipment with electronic health records, allowing simple data sharing for TB surveillance and program monitoring. Lastly, the role of public-private partnership in TB diagnostic innovation cannot be overemphasized. Public-private partnerships between governments, academia, and private industry are key to speeding up the development and deployment of affordable diagnostics. For instance, collaboration with drug companies can make the cost of producing rapid tests cheaper, while collaboration with technology companies can create AI diagnostics for TB. International efforts such as the Stop TB Partnership and FIND (Foundation for Innovative New Diagnostics) have already proved successful in promoting such collaborations. Ongoing investment and policy commitment are required to propel these initiatives faster so that advanced diagnostics become available to those populations most in need. In total, while emerging technologies hold great promise to transform TB diagnosis, their full value will hinge on breaking cost barriers, ensuring real-world application, leveraging digital health infrastructure, and collaborative innovation. Breaking these challenges will be the solution to responding to the WHO's vision of a TB-free world by 2035 [72].

Conclusion

The face of tuberculosis diagnosis has seen incredible change over the past few years, with new technologies presenting unparalleled possibilities for breaking through the age-old limitations of TB detection and treatment. Among the most exciting new technologies are CRISPR-based diagnostic platforms that have high sensitivity coupled with fast turnaround times, and artificial intelligence-enabled radiology software that improves the precision of TB screening in low-resource settings. Next-generation sequencing has become an effective tool for in-depth drug resistance profiling, and new biomarker-based assays hold promise for non-sputum, point-of-care diagnostics. Together, these technologies bridge key gaps in traditional diagnostic methods, especially for difficult cases of pediatric TB, HIV-associated TB, and extra pulmonary disease. The potential to transform global TB control through these new technologies is significant. Rapid molecular tests such as the portable Truenat platform have already proved to enhance rates of case detection in peripheral health facilities, whereas AI-assisted interpretation of chest X-rays is transforming mass screening programs. Innovation in non-sputum-based diagnostics such as urine LAM tests and breath-based biomarkers holds special potential for vulnerable individuals who find it difficult to cough up sputum samples. Widespread implementation of these technologies could largely eliminate diagnostic delays, allowing earlier initiation of treatment and interrupting transmission chains. For drug-resistant TB, rapid molecular testing and centralized sequencing networks could support tailored treatment regimens, enhancing results while halting further resistance. Achieving such potential, however, will take concerted effort to overcome the barriers to implementation in place today. Too many promising technologies are locked in research environments or pilot initiatives, with little presence in high-burden countries where they can do the greatest good.

The main obstacles are high prices, absence of local production capacity, inadequate training of healthcare workers, and poor laboratory infrastructure in rural settings. Immediate multi-sectoral action is required from governments, manufacturers of diagnostic tools, and global health authorities to bring about faster technology transfer and scaling up. Additional investments in implementation research are important to maximize the use of such tools across varied epidemiological contexts and their integration into national TB programs. The hour has arrived for a paradigm shift in TB diagnosis, shifting away from the use of techniques that have been around for centuries to embracing 21st-century solutions. Investments in diagnostic innovation need to be prioritized by global health actors as a pillar of TB elimination efforts. This involves the support for the creation of affordable, ruggedized forms of cutting-edge technologies that are appropriate for primary healthcare environments and enhancing health systems to provide equal access. With long term dedication and sufficient resources, these new diagnostic technologies might become a game-changer in the attainment of the WHO's End TB Strategy targets, saving eventually millions of lives and leading the world towards ending this ancient disease.

List of abbreviations

TB: Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; XDR-TB: Extensively Drug-Resistant Tuberculosis; TDR-TB: Totally Drug-Resistant Tuberculosis; HIV: Human Immunodeficiency Virus; NGS: Next-Generation Sequencing; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; TST: Tuberculin Skin Test; LTBI: Latent Tuberculosis Infection; BCG: Bacille Calmette Guerin; NTM: Non-Tuberculous Mycobacteria; IGRAs: Interferon-Gamma Release Assays; AFB: Acid-Fast Bacilli; PCR: Polymerase Chain Reaction; MGIT: Mycobacteria Growth Indicator Tube; LPAs: Line Probe Assays; NAAT: Nucleic Acid Amplification Test; PCR: Polymerase Chain; CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats; AI: Artificial Intelligence; PPD: Purified Protein Derivative; LAMP: Loop-Mediated Isothermal Amplification; TB-LAMP: Tuberculosis Loop-Mediated Isothermal Amplification; WHO: World Health Organization

Ethical Approval

Not applicable.

Consent for Publication

Not applicable.

Human and Animal Ethical Right

Not applicable.

Conflict of Interest

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