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Review

Current trends in tuberculosis diagnosis: Advancements and challenges

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Abstract

Tuberculosis [TB] is still a worldwide health issue, and early and accurate diagnosis of TB is essential for the management of the disease. Although conventional diagnostic methods, including sputum smear microscopy and culture methods, provide some diagnostic information, these methods have challenges in terms of sensitivity, specificity, and turnaround time. Recent TB diagnostics include molecular-based diagnostics, such as GeneXpert MTB/RIF and line-probe assays, which provide rapid and highly sensitive TB detection, including in drug-resistant cases. Next-generation sequencing and whole genome sequencing [and other "omics" technology] show potential for isolating strains of Mycobacterium tuberculosis and identifying resistance typing and epidemiological surveillance. However, there remain challenges, including high cost, availability of resources in low-resource settings, and reliance on a skilled workforce. The role of artificial intelligence [AI] is being studied, particularly with respect to TB detection in imaging, to test the accuracy of AI programs and their ability to predict TB on chest radiographic interpretation. Future directions in TB diagnostics include further development of point-of-care diagnostics, reliance on AI- and machine learning-driven algorithms in imaging and data interpretation, and advancements in access to genomic sequencing and molecular diagnostics. Increased investment in research [and studies on the cost] and supportive policy frameworks for regulatory approval pathways and reducing costs will be important to ensure further implementation and uptake of diagnostics to achieve the goal of ending TB by 2035.

Keywords: Tuberculosis diagnosis, molecular diagnostics, GeneXpert MTB/RIF, artificial intelligence, whole-genome sequencing, CRISPR diagnostics, drug-resistant TB, point-of-care tests, biosensors, microfluidics, chest X-ray interpretation, latent TB diagnosis, rapid diagnostic tests, new technologies, difficulties in diagnosis, global TB control, multidrug-resistant tuberculosis [MDR-TB], next-generation sequencing,

INTRODUCTION

Although there has been tremendous advancement in diagnostics and treatment, tuberculosis [TB] remains a significant global health issue affecting millions of people each year. Timely and accurate diagnosis is critical for effective, timely treatment and control of the disease [1]. Culture and smear microscopy have long been considered the gold standards in TB diagnosis; however, measurements of good Sensitivity and specificity and rapid results have still left much to be desired [2]. Recently, TB diagnostics have also begun to include molecular-based techniques such as GeneXpert MTB/RIF and line-probe assays, which can recognize and amplify the pathogen and detect drug resistance likely much quicker with high sensitivity than standard culture methods [3]. Next-generation sequencing [NGS] and whole-genome sequencing [WGS] are also emerging methods that potentially may reveal Mycobacterium tuberculosis strains in the future and identify and analyze patterns of resistance, thus addressing some longstanding concerns regarding epidemiological surveillance [4]. Despite the advancement efforts over these decades, the costs associated with advancing diagnostics, low availability of timesaving-tested diagnostics in low-resource settings, and reliance on a well-educated and trained labor force still present challenges [5]. Also, there is exploration into adapting artificial intelligence [AI] and digital technologies into TB diagnostics, and early signs of alleviating burdens on radiological interpretation and predictive modeling look encouraging [6].

DIAGNOSIS OF TUBERCULOSIS

The confirmation of a tuberculosis [TB] diagnosis is based on the clinical, microbiological, and molecular methods that have been used to confirm the presence of Mycobacterium tuberculosis [1]. The traditional methods for diagnosing TB are sputum smear microscopy and culture-based methods. Sputum smear microscopy is inexpensive and feasible globally but has limited sensitivity, particularly for cases of paucibacillary TB, extrapulmonary TB, and atypical manifestations of TB [7]. Mycobacterial culture is considered the gold standard for TB diagnosis, with improved sensitivity compared to sputum smear microscopy; however, it is time-consuming and can take several weeks to obtain cultures and drug resistance results, potentially delaying the start of time-critical treatment [8]. Molecular diagnostic methods have significantly shortened the time for TB diagnosis to be reported. The nucleic acid amplification tests [NAATs]—for example, the GeneXpert MTB/RIF and Xpert Ultra—are now being used to provide accurate, rapid diagnosis of TB with detection of rifampicin resistance, usually within hours [3]. The World Health Organization [WHO] recommends these tests to be the first test in those suspected of having TB [9]. Line-probe assays [LPAs] are another example of molecular diagnostic methods that provide rapid detection of multidrug-resistant TB [MDR-TB] due to the genetic mutations associated with drug resistance [10].

Research into next-generation sequencing [NGS] and whole-genome sequencing [WGS] is radically changing TB diagnosis. These technologies can support comprehensive genetic analyses and provide detailed drug resistance profiles of M. tuberculosis strains, which epidemiological surveillance may benefit control programs [11]. Direct tests of diagnostic significance, such as loop-mediated isothermal amplification [LAMP] and more lateral flow-based antigen detection testing, have improved the ability to detect TB even in limited-resource environments [12]. While these advances are important for the TB diagnostics field, there are still barriers to widespread use of systems that support these modern diagnostic methods. The development costs—and overall costs - of equipment and tests, as well as health facility-attributed costs due to deficits in laboratory infrastructure and where to find trained human resources, constrain the feasibility and utilization of molecular and genomic tests in many high-TB burden areas [5]. Addressing barriers to the use of diverse diagnostics is fundamental to global TB elimination efforts, while also addressing disparities in full accessibility to molecular and genomic diagnostics.

EMERGING TECHNOLOGIES

The rapid growth of technology ushered advancements in diagnostic procedures aimed at improving the detection, accuracy, and accessibility of tuberculosis [TB]-testing. Emerging innovations include the use of artificial intelligence [AI] to aid in TB diagnosis through deep-learning algorithms that can identify chest X-ray images with high accuracy while identifying TB in resource-poor settings that have few radiologists [6]. AI-assisted applications, such as CAD4TB, are already opening doors that demonstrate comparative sensitivity to human experts and are beginning to be incorporated as part of global TB screening programs [13]. Other innovations using next-generation sequencing [NGS] and whole-genome sequencing [WGS] are changing the TB diagnostics landscape by, in very short times, generating a comprehensive genotype profile of the Mycobacterium tuberculosis strain, rapidly informing treatment options based on drug resistance mutations. Evidence suggests that WGS could detect multidrug resistance more accurately than classical phenotypic susceptibility testing while markedly improving clinical turnaround time and time to treatment [14]. Finally, biosensors are being developed as a potential alternative to traditional TB diagnostic tests. Nanotechnology-enabled biosensor applications can selectively recognize TB-induced biomarkers such as lipoarabinomannan

[LAM] and M. tuberculosis DNA with very high sensitivity and specificity from a clinical sample [15]. Recent developments in CRISPR-based diagnostic platforms such as SHERLOCK and DETECTR have enhanced the rapid detection of TB by generating results in minutes from the presence of TB genetic material [16]. These diagnostic tools, which may one day serve at the point of care, are also likely to increase access to TB testing in the most remote settings. Microfluidics-based diagnostic systems are undergoing evaluation for their potential to automate TB testing, lower costs, and reduce sample processing time. Such lab-on-chip devices are capable of multiplex testing, detecting TB and drug resistance markers in one test [17]. Smartphone-based diagnostic tools have also developed into an exciting new intervention in which mobile devices are adapted for microscopy and AI-enabled image analysis for rapid, field-friendly TB screening [18]. Despite the advances described above, challenges such as cost, regulation, and validation studies hang over the prospects for these technologies to gain widespread application, including perhaps even in research techniques. Still, there is promise in continuing research and investment into promising emerging technologies for affordable, accessible, and accurate TB diagnostics in the near future [5].

CHALLENGES IN TB DIAGNOSIS

In spite of tremendous progress on the development of diagnostics for tuberculosis [TB], there are still numerous barriers to the early diagnosis and effective management of the disease. A primary barrier is that many of the newer diagnostic tests are unavailable or difficult to access in high-burden, low-resource environments. Molecular tests such as GeneXpert MTB/RIF have fundamentally changed TB diagnostics, but these tests are expensive and require laboratory resources and infrastructure that are difficult to implement in rural or less developed settings [1]. The need for a reliable electrical supply and controlled environments provides other barriers to TB diagnostics in many TB-endemic regions [19]. Another major challenge is the inherent difficulty of diagnosing extrapulmonary and pediatric TB. In extrapulmonary TB, sputum-based diagnostics are inadequate, as those cases will require procedures such as biopsy or analysis of cerebrospinal fluid, all of which are much more invasive than typical diagnostic methods [2]. Similarly, in pediatric TB, it is increasingly difficult to obtain quality sputum specimens from young children, resulting in underdiagnosis and missed opportunity for early treatment [20]. In addition, there are numerous tests that are not sensitive among immunocompromised individuals, such as those that are HIV positive, which further complicate TB detection [21].

The emergence of drug-resistant tuberculosis [DR-TB] raised a new challenge for diagnosis. Both multidrug-resistant TB [MDR-TB] and extensively drug-resistant TB [XDR-TB] require molecular testing, such as line-probe assays [LPAs] and whole-genome sequencing [WGS], that are often unavailable in many countries with high TB burdens [11]. Without proper diagnostic capacity to identify drug resistance, inappropriate treatment regimens are more likely, ultimately increasing the risk of treatment failure and further transmission of drug-resistant strains [22]. Another issue associated with the current state of diagnostics is the time it takes to make emerging tests available for use in TB programs. Many new tests, including CRISPR-based tests and AI-augmented diagnostics, are available as investigational test platforms but require validation with high-level regulatory approvals and incorporate the PE and overall system for general implementation [16]. Once there is general approval, however, differences in healthcare infrastructure and available funding continue to lead to inequitable access to more innovative TB diagnostics, which will continue to perpetuate the burden of disease globally [5].

Future Perspectives

The future of tuberculosis [TB] diagnosis will likely be impacted by new technologies that improve diagnostic accuracy, access, and timeliness. One area of development is in point-of-care diagnostics, aimed at bringing rapid and low-cost TB testing to low-resource settings. New tools in the areas of microfluidics and biosensing have led to the development of portable diagnostic devices to detect TB biomarkers with high sensitivity in sputum, blood, or urine samples [15]. Novel urine-based antigen detection tests for TB, such as Fujifilm SILVAMP TB-LAM, are being developed as rapid tests to diagnose TB, particularly in patients coinfected with HIV where traditional sputum-based testing may not work as well [23].

Another area of promise is the potential for artificial intelligence and machine learning to be used in diagnosing TB. AI-based algorithms are increasingly being used to analyze chest x-rays with high accuracy to assist in the early detection of TB from chest x-rays, which is particularly useful in areas where radiologists are limited [6]. AI-based software solutions, such as CAD4TB and qXR, have shown high sensitivity and specificity in screening for TB and can be expected to improve their diagnostic capabilities further in the future [13]. AI capabilities are also being integrated into molecular diagnostics to help optimize testing interpretation and promote patterns of drug resistance, opening the door towards more individualized TB treatment approaches.

Future advancements will still be the primary discussion point today regarding TB detection. WGS and NGS are expected to be more widely implemented in practice, allowing for quick identification of M. tuberculosis strains, along with mutations associated with antimicrobial resistance [25]. These provide good

insight regarding TB transmission dynamics, with antimicrobial resistance being necessary to inform any active TB control program [14]. In addition, CRISPR-based diagnostic tests, such as SHERLOCK and DETECTR, may permit high specificity and ultra-rapid TB detection in decentralized studies [16]. Future global movements and funding for TB diagnostics will therefore allow for the actual implementation of these into routine practice. Research and development funding will also be appropriate in addition to policies developing situations for regulatory approvals and cost reduction strategies to move from research laboratory into community practice [5]. Health system strengthening and affordable access will also be important for achieving the WHO target to end TB by 2035.

CONCLUSION

The advancement of TB diagnostics has momentum now with the introduction of molecular diagnostics, imaging techniques supported by artificial intelligence [AI], and genomic sequencing, accelerating speed and accuracy for TB diagnosis. There are also novel technologies yet to breach the commercial floor; CRISPR-based assays and microfluidic, point-of-care devices have the promise to increase the accessibility of TB testing even in low-resource settings. The challenges will include cost, lack of availability, and the complexities associated with testing for extrapulmonary and drug-resistant TB. All of these factors may require sustained investment in: studies, global agendas, and infrastructure. To truly facilitate the uptake of these technologies, it will be vital to coordinate more with governments, health organizations, and industry. Moving forward, there will be a need for us to be cognizant of equity in access to TB diagnostics that will hopefully incorporate innovative technology in order to achieve the World Health Organization [WHO] target of eliminating TB by 2035. If we can have an iterative process of adapting and checking new diagnosing methods, theological while a more robust and globally centered agenda occurs, it offers a glimmer of potential for TB control and the elimination of an entrenched infectious disease.

Author Contributions

Mohd Baqir, Shubham Singh & Kulbir Singh have written the draft and revised review, editing, & rewriting & Finalized the manuscript,&Tanya sharma was responsible for editing. supervision of the manuscript. All authors approved the manuscript.

Competing interests

The authors declare no conflicts of interest.

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