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Economic challenges associated with tuberculosis diagnostic development

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Abstract

Tuberculosis remains a global health crisis in part due to underdiagnosis. Technological innovations are needed to improve diagnostic test accuracy and reduce the reliance on expensive laboratory infrastructure. However, there are significant economic challenges impeding the development and implementation of new diagnostics. The aim of this piece is to examine the current state of TB diagnostics, outline the unmet needs for new tests, and detail the economic challenges associated with development of new tests from the perspective of developers, policy makers and implementers.

Keywords

diagnostic development; diagnostics; economic evaluation; tuberculosis; tuberculosis control policy

Tuberculosis (TB) remains a global health crisis, with 8.6 million new cases globally in 2012 and 1.3 million TB deaths [1]. The burden of TB disease is not distributed equally worldwide but instead is found disproportionately in several key regions. Nearly one-fourth of all cases occur in the African region which is home to the highest TB mortality and TB incidence (255 cases/100,000 individuals). Together, the Southeast Asia and Western Pacific regions account for 58% of the world's TB cases, though incidence rates are lower than in sub-Saharan Africa [1]. HIV represents a major driver of the TB epidemic, with 20% of TB cases worldwide occurring in HIV-infected individuals and 40% of cases in the African region among HIV-infected individuals [1]. There is also disparity in the distribution of TB by country wealth. Among the 22 'high TB burden' countries identified by the WHO [1], 16 are classified as low or lower middle income by the World Bank [2]. Gross domestic product per capita and TB incidence have been shown to have a log-linear relationship, with

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each doubling of gross domestic product resulting in a nearly 40% decrease in TB incidence [3].

In order to reduce TB incidence, improvements must be made in our ability to detect TB. TB is vastly underdiagnosed – only an estimated two-thirds of those who develop TB each year are currently detected, and only 57% of these have a bacteriologically confirmed diagnosis [1]. This gap in case detection and diagnosis is the result of the poor sensitivity and specificity of current TB diagnostic tools, as well as a lack of access to diagnostic testing due to insufficient laboratory capacity. Technological innovations are now needed to improve diagnostic test accuracy and reduce the reliance on expensive laboratory infrastructure.

Although the need for new TB diagnostics is urgent, there are significant economic challenges to diagnostic test development. TB disease remains heterogeneous and complex, and test developers are likely to require strong partnerships with clinicians and researchers to provide insights about the types of tests most likely to improve case detection and reduce mortality. The size of the diagnostic market, both in high-burden/low-income countries and in low-burden/high-income countries, is often unclear [4]. The majority of TB diagnostic testing is performed outside of established market economies [5]. Uptake of new technologies in these settings is likely to be costly, and there is uncertainty about the political and financial commitment from governments and TB programs to adopt new innovations. To improve market potential globally, developers are likely to seek WHO endorsement to increase uptake; investors must thus plan for large and costly clinical trials across multiple settings to secure such approvals.

The aim of this work is to first review the current state of TB diagnostics and then examine the economic challenges associated with TB diagnostic test development from the perspectives of developers, policy-makers and implementers.

State of current TB diagnostics gaps, costs & needs

Pulmonary TB

Pulmonary TB is the most common manifestation of TB worldwide and is the target of most TB diagnostic efforts [1]. Sputum smear microscopy to identify acid-fast bacilli (AFB), a technique developed in the 1880s in which mycobacteria are directly visualized with a light or fluorescent microscope, remains the most widely utilized diagnostic for pulmonary TB worldwide [1]. Smear microscopy is appealing because it is fast and cheap with a price of US\$1–6 per sample across a range of settings [6–9]. However, reliance on smear microscopy is a major reason for the low case detection rates globally. The sensitivity of smear microscopy ranges from 20 to 80% and is particularly reduced in patients with HIV infection as well as in pediatric TB cases in whom there is less cavitory lung disease [10]. This low sensitivity is due in part to the high threshold of detection of 10,000 bacilli/ml of sputum. AFB smear microscopy is also not specific to *Mycobacterium tuberculosis*; all mycobacteria, including environmental mycobacteria that can be contaminants or colonizers in sputa, will appear positive using AFB smear microscopy.

Culture of *M. tuberculosis* from sputum remains the reference standard for diagnosis of pulmonary TB and has a limit of detection of 10–100 bacilli. The sensitivity is accordingly high, ranging from 80 to 93% [11], provided that an adequate specimen can be obtained. Mycobacterial culture is also utilized for performing standard phenotypic drug sensitivity testing and is thus necessary for identifying drug-resistant TB. Despite its advantages, mycobacterial culture has significant limitations. Culture requires 3–8 weeks for results due to the slow growth of mycobacteria, contributing to diagnostic delays. Culture techniques also require significant laboratory infrastructure, as well as skilled personnel, and are prohibitively costly for most low-income settings. Costs range from US\$12 to 35 per test in addition to capital costs associated with laboratory construction [12,13]. Consequently, culture is largely unavailable globally [11,12] – among the high burden TB countries, the majority have two or fewer laboratories in the entire country [1]. While efforts are being made to identify faster culture methods, the inherently slow mycobacterial replication time and need for strong laboratory infrastructure preclude this strategy from being economically appealing for most test developers.

The TB diagnostics pipeline, so long dormant, has recently become rich with an array of molecular diagnostic tests from early to late stages of development seeking to overcome the limitations of smear microscopy and culture [14–16]. Detection of mycobacterial nucleic acid represents a technological innovation that is not restricted by the slow mycobacterial growth characteristics and can be performed rapidly. An example of such technology that has significantly impacted the TB diagnostic market is the Xpert MTB/RIF (Xpert, Cepheid Inc., Sunnyvale, CA, USA). Xpert is a cartridge-based, fully automated, nucleic acid amplification test (NAAT) for TB and drug-resistant TB that has recently received WHO endorsement [17]. The test requires minimal technical expertise, is fully automated and self-contained and provides detection of *M. tuberculosis* as well as rifampicin resistance in approximately 2 h [18]. While offering improvements in speed, the assay has been demonstrated to have a detection limit of 100 bacilli, which is not yet as sensitive as culture [19]. When used as a replacement for smear microscopy, Xpert has demonstrated good accuracy (88% sensitivity; 98% specificity) but is not yet a replacement for culture [20]. The sensitivity appears optimized in individuals with higher bacillary burden in their lungs (98% among smear-positive, culture-positive samples) compared with those with less bacilli (68% among smear-negative, culture-positive samples) [20]. Early studies indicate that Xpert may also have utility with extrapulmonary specimens [21–24].

Despite its advantages, Xpert implementation in many high-burden settings is challenging. Xpert has significant infrastructure requirements, including a constant electricity supply, moderated temperature and humidity, as well as periodic calibration [18,25]. As it only detects rifampin resistance, culture facilities remain necessary for further drug sensitivity testing. While several studies suggest its usage is cost-effective, net costs may yet preclude affordability in many settings [13,26]. A concessional pricing structure negotiated by the Foundation for Innovative New Diagnostics (FIND) is available for many low-income/high TB burden countries and prices the cartridges at US\$9.98 and the 4-module instrument at US\$17,500; these low prices were agreed upon by the manufacturer in return for support in

conduct of clinical trials [27]. Per test costs have been estimated at US\$21–38 in FIND pricing eligible countries [6,13,28] and US\$98 in the USA [7].

Introduction of Xpert into the marketplace has significant implications for economic investment in the development of new TB diagnostic technologies. If Xpert were used for all individuals with signs and symptoms of TB, then it is estimated that the total laboratory costs would be more than double compared with using conventional reference standard tests in both high- and low-burden settings [26]. Estimates suggest that such scale-up would cost global TB programs approximately US \$400 million annually and represent a widely varying percentage of national TB budgets depending on the setting. Nonetheless, Xpert has been enthusiastically received by the global TB control community, and the worldwide rollout of the test has expanded exponentially with placement most commonly in central or peripheral laboratories [29]. Some countries including South Africa have made major investments in scale-up of Xpert technology – the total capital costs for South African national rollout of Xpert are estimated at US\$20 million [30]. These developments are welcomed by TB programs and patients, but may have unforeseen consequences for diagnostic R&D. While Xpert introduction demonstrates the presence of a large economic market for TB diagnostics, its dominant presence may create a barrier for the development and introduction of alternative technologies. New diagnostics are likely to have to compete with the Xpert price point which has dropped to less than US\$10 per cartridge in developing settings. Moreover, it is unclear if governments and TB programs will be enthusiastic about adopting newer technologies after having made significant investments in Xpert instruments, which cannot be readily transferred to alternative technologies.

HIV-associated TB, extrapulmonary & disseminated TB

TB remains the most common coinfection among those infected with HIV and is responsible for one-quarter of all HIV deaths worldwide [31,32]. HIV coinfection poses several difficulties for the diagnosis of TB. HIV-infected individuals are more likely to present with paucibacillary pulmonary disease [33,34], leading to a reduced sensitivity of smear microscopy, sputum Xpert and sputum culture testing in this population [20,35,36]. Extrapulmonary TB (EPTB) is more common among those infected with HIV, especially at lower CD4 cell counts [37]. As a result of these challenges, diagnosis of TB in HIV-infected persons is often delayed, resulting in poor treatment outcomes, particularly among those with smear-negative TB [38,39]. In sub-Saharan Africa, many HIV-infected individuals die with undiagnosed disseminated TB disease [40,41].

EPTB is also not uncommon in immunocompetent patients. In the USA, nearly 20% of reported TB cases are extrapulmonary TB, and EPTB appears to be increasing as a percentage of all TB cases [42]. The diagnosis of disseminated or extrapulmonary forms of TB is difficult. In such patients, examination of sputa (the default site of diagnostic testing) by any available method, including Xpert or mycobacterial culture, is often inadequate since the bacilli are not present in large quantities in the lungs. Diagnostic challenges arise from the difficulty of obtaining a sample from infected tissue and the paucibacillary nature of EPTB [43]. Specimen collection usually involves invasive tests (e.g., lumbar punctures, thoracentesis or paracentesis or lymph node biopsies) and is therefore expensive and

requires access to significant health care resources. Where available, a combination of smear microscopy, culture and histology of infected tissue is used for diagnosis of EPTB, though overall yield and sensitivity of culture are low depending on the site of infection [43,44]. The costs of EPTB diagnosis have not been adequately studied, but are likely to be expensive due to the reliance on mycobacterial culture and invasive sampling. There is a pressing need for the development of a 'global' test that can identify individuals with disseminated TB or EPTB without the need for mycobacterial culture or invasive procedures.

One emerging candidate for such a diagnostic test is the urine Determine TB-lipoarabinomannan (TB-LAM) Ag test (Alere Inc, Waltham, MA, USA). This simple test identifies a mycobacterial antigen (LAM) in a point-of-care lateral flow format. The test is performed on unprocessed urine, takes 20 min to obtain a result and requires no equipment or training. It represents the first true rapid, point-of-care TB diagnostic test. The test performs best in HIV-infected patients with advanced immunosuppression, the group most likely to have disseminated TB disease and presence of antigen in urine [45,46]. The sensitivity in HIV-infected individuals ranges between 30 and 70%, and the test appears to be complementary to sputum testing by conventional diagnostics [12,47]. Perhaps, more importantly for the TB diagnostic landscape is the proof of principle that disseminated forms of TB may be detectable through antigen detection in a cheap, affordable test format that is easily scalable. The test currently costs US\$3.50, on par with smear microscopy, and has been shown to be highly cost-effective for TB diagnosis in HIV-infected individuals despite suboptimal sensitivity [48].

Pediatric TB

Childhood TB contributes an estimated 10–15% of the global burden of TB, with the majority of cases occurring in the 22 high TB burden countries [1]. Pediatric TB diagnosis represents a large and untapped market for diagnostic test developers as current tools are woefully inadequate. Diagnosis of pediatric TB is complicated as children have paucibacillary TB disease [49]. Sputum culture is estimated to identify only 30–40% of pediatric TB overall [50], and the yield is particularly low given that children often are unable to produce sputa or present to primary care settings with nonspecific symptoms [49,51]. Globally, diagnosis of TB in younger children most often relies on a cluster of epidemiological, clinical and radiological findings, which leads to missed diagnoses and misdiagnoses [52]. Pediatric TB thus represents a significant opportunity for test developers. A product with improved diagnostic accuracy that could be performed on more easily obtained samples, such as blood, stool or urine, would have a significant first-mover advantage with substantial economic potential.

Needs, challenges & opportunities for new TB diagnostics

As discussed above, the current tools for diagnosis of the full spectrum of TB disease are inadequate. In 2009, the New Diagnostics Working Group of the Stop TB partnership [53] produced a comprehensive report laying out a pathway to the development of new TB diagnostics [54]. As part of this report, the group proposed a list of test criteria that represent the ideal characteristics of a new diagnostic for detection of active TB disease and provide a

framework from which to understand the challenges to TB test development. Table 1 summarizes these needs, detailing the status of current TB diagnostics in each regard, and outlines challenges and considerations for the development of tests to meet each need.

Economic challenges to diagnostic development from the test developer perspective

Need for well-defined target product profiles

A target product profile (TPP) is broadly defined as a list of product characteristics which differentiate the test under development from other available diagnostics and which outline the future usage of the test [55]. A well-defined TPP is used by developers to prioritize test characteristics. The Stop TB Partnership's roadmap of TB diagnostic test needs (summarized in Table 1) offer a starting point, but are likely not detailed enough to construct the nuanced TPPs needed to guide developers. TPPs developed by UNITAID [15] detail ideal characteristics for point-of-care tests for both adult and pediatric TB, as well as cartridge-based NAAT tests, and are in current use by developers. As highlighted in this review, TB disease is not a single homogenous entity. Infection with *M. tuberculosis* can be thought of not only as a spectrum, moving from latent (asymptomatic) to active disease [56], but also as distinct clinical entities with a plethora of disease manifestations with only partially overlapping characteristics. Given this landscape, it is highly unlikely that one single TPP or one single test will be suitable.

Additional test attributes that need clarification for test developers include: the target costs; needed test throughput; level of automation or integration with multiplexed platforms; result reporting requirements; placement within a diagnostic algorithm (e.g., screening of asymptomatic patients vs diagnosis of symptomatic patients); placement within health systems (point of care vs peripheral or centralized laboratory); target populations (HIV-infected, inpatients vs outpatients, children vs adults); target conditions (e.g., disseminated TB, EPTB [meningitis vs lymphatic vs pleural, etc.], latent TB, paucibacillary TB, pulmonary TB); and drug resistance profiles (which drugs should be evaluated in a changing treatment landscape) [57]. From this laundry list of test attributes, developers need to know which features should be prioritized in order to appropriately guide development and direct resources; these priorities may differ significantly based on setting and epidemiology. Developers need guidance on market size for different target products across settings.

'One size fits all' versus condition-specific approach

The ideal TB diagnostic test would detect and discriminate all forms of TB disease, as well as provide drug susceptibility results for first- and second-line drugs. The obstacle impeding the development of such a single 'one size fits all' TB test is the lack of a validated global biomarker that identifies active TB disease in patients. Current tests depend on direct detection of the bacilli (culture, smear microscopy, Xpert and other NAAT tests) in specified tissues or biological samples. Unlike other infectious diseases, such as HIV, the microbe is not always present in easily obtained specimens such as blood. Given that *M. tuberculosis* is not evenly distributed in all body sites, sampling one tissue type (e.g., sputum) may easily miss disease in a different site (e.g., TB meningitis). Immunological tests are often

employed in these types of conditions as a surrogate for disease. However, serological tests detecting antibody responses to *M. tuberculosis* have proven inconsistent and imprecise measures of LTBI and TB disease; given their inaccuracy, WHO has warned against the usage of such tests and some countries including India have banned their usage altogether [58–60].

To aid development of a ‘one size fits all’ test, investments are needed into basic research into TB disease pathogenesis. Current funding levels for this type of research, however, remain inadequate. In 2012, funding for basic science TB research was estimated to be less than 1/3 of the Stop TB Partnership Global Plan targets [61]. Consequently, the bulk of current tests under development are focused on direct molecular detection of TB (chiefly NAAT-based technology) [14,15]. While such tests are an important advancement in TB diagnostics, they are unlikely to meet all of the needs related to TB case detection. Many of these molecular tests do, however, offer simultaneous detection of at least rifampicin resistance, a marker for multi-drug resistant tuberculosis (MDR)-TB, which offers an important advantage in terms of prompt management of drug-resistant disease.

An alternative approach for developers is to pursue condition-specific tests, or tests that fulfill a specific niche market. An example is the Determine TB-LAM Ag test. In some ways, this assay is closest to the model of a ‘global’ test for TB disease (compared with site-specific disease) currently on the market; it detects TB disease in patients based on urinary excretion of TB antigens. However, this test has a narrow target population in whom it is useful – individuals with HIV infection and/or advanced immunosuppression with disseminated disease [45,46]. Another such example is the Hain Genotype MTBDRsl (Hain Lifesciences Inc, Germany) which offers rapid and accurate drug susceptibility testing for second-line drugs [16]. This test occupies a potential niche market for patients with MDR-TB but is limited by its need for significant laboratory infrastructure as well as skilled personnel. Such condition-specific tests have direct economic implications for developers. Despite the need for tests that play specific roles in TB diagnostic algorithms, economic viability may be compromised if the market size is narrow or restricted. In the absence of durable market examples, developers may be hesitant to pursue costly development portfolios for tests which may face important functional or implementation limitations and thus cannot provide a suitable profit margin. To promote continued development of such tests will likely require partnerships between industry, researchers and other public sector stake holders to aid with cost sharing or cost subsidization or to offer reassurance or guarantees about market uptake.

Costly development considerations

Total development costs to take a diagnostic test from research and development through commercialization in the USA have been estimated by an expert panel to be in the range of US\$12–20 million for a follow-on product with an existing platform and US\$55–106 million for new assays representing novel technology or platforms [62]. Though these ranges are wide and are not specific to TB, they represent a ballpark range of developer costs to bring a new assay to market in a high-income country. Aside from traditional costs

associated with research and development, regulatory/legal approvals and clinical studies and marketing, several TB-specific cost areas are worth highlighting.

Need for well-categorized specimens—To pursue research and development of new assays, developers require access to libraries of clinically relevant TB strains and also to well-categorized biological samples from patients. Such samples are not always readily or cheaply available. Depending on assay requirements, heavily passaged laboratory strains of *M. tuberculosis* such as H37Rv may only be of use during early stages of research, after which these strains may not accurately reflect strains currently in circulation globally. Acquisition of clinically relevant strains and clinical samples is a challenge for developers as there are limited strain banks globally. The Stop TB Partnership's collection of geographically diverse clinical TB isolates with multiple phenotypic resistance profiles is one such potential resource [63]. Biological samples from well-categorized patients are ultimately needed to assess test characteristics and validate assays. Such samples can be challenging to obtain without engagement of academic or clinical partners, which smaller or emerging test developers may not have access to. FIND maintains such a repository of limited types of clinical specimens that are available to commercial developers, with priority given to low-cost applications that are feasible in developing country settings [64].

Complex clinical study requirements—Clinical trials represent a significant cost in the development pathway of a new diagnostic test. Diagnostic accuracy studies may require significant sample sizes, across multiple settings, in order to assess sensitivity and specificity with reasonable precision in multiple target populations and subgroups. In order to conduct trials in a reasonable time frame, multiple sites are required and usually occur in high-burden countries. The landmark trial of Xpert enrolled nearly 1900 participants across five sites in four countries (Peru, South Africa, India and Azerbaijan) [65] and a follow-up implementation study enrolled 6600 participants in six countries [66]. Conducting trials in high-burden developing country settings may require establishing sufficient laboratory infrastructure to support the study in order to perform current reference standard tests (i.e., mycobacterial culture). A further challenge complicating TB diagnostic accuracy studies is the lack of adequate reference standards, particularly for assessment of diagnostic specificity. Studies targeting pediatric TB, EPTB or HIV-associated TB are particularly challenging as even culture may be an insufficient reference standard [52], making pursuit of test development for these sub-population of TB patients undesirable for most developers [67]. In order to provide easily interpretable study findings, test developers and academic partners conducting diagnostic accuracy studies should adhere to the Standards for Reporting of Diagnostic Accuracy [68].

Increasingly, for endorsement by international and national agencies, such as WHO, diagnostic test developers must also show impact of their product/interventions on patient outcomes. Such a standard is problematic for TB test developers. At a basic level, the role of TB diagnostic tests is to identify or exclude TB disease in patients. To show impact on clinical TB outcomes can be challenging, owing to the complexity and length of TB treatment which requires a well-functioning health system. A 'perfect' TB test with 100% linkage to treatment may yet fail to show clinical impact if the health system into which the

test is implemented is unable to ensure adequate medication availability (including antiretroviral therapy for HIV patients), treatment monitoring (for side effects, drug interactions) and facilitate adherence and treatment completion (e.g., with in-person daily directly observed therapy).

Regulatory requirements for diagnostic tests also vary widely by country. Some countries may require that a trial site is located in country in order to allow the test to market. These additional requirements all add to developer costs and pose an economic hurdle for test development.

Economic disparity in the market

Despite the large global burden of TB and the vast potential market size, TB remains a disease that is strongly associated with poverty and is concentrated chiefly in low- and low–middle-income countries. Global funders, nongovernmental organizations (e.g., FIND, CHAI), patient advocacy groups (Treatment Action Group) and national governments may exert downward pressure both implicitly and explicitly on test pricing, which can impact profitability. FIND has negotiated a concessional pricing structure for Xpert in exchange for supporting development, evaluation and manufacturing of the assay [27]. Despite this price structure, the global rollout of Xpert has chiefly been led by South Africa, a middle-income country, rather than other high-burden low-income countries, which still may not be able to afford to invest in Xpert. Faced with high development costs and a fixed price structure in the largest market share, developers may be reluctant to pursue a portfolio of research and development in TB diagnostics if these prices cannot be offset by sufficient market opportunity in high-income countries. It is also unclear if future developers will be afforded the same advantages that Cepheid received with evaluation of Xpert by global funders and NGOs with regard to support for clinical trials and validations studies.

Policy challenges: interpreting the evidence to make decisions

Overview of economic evaluation

The aim of economic evaluations of interventions such as diagnostic tests is to assist policymakers in allocating resources between competing programs. A policymaker may wonder, for example, whether it is preferential to implement a new TB diagnostic (such as Xpert) as a replacement for smear microscopy, given finite funding resources and the increased cost of Xpert over smear. Cost–effectiveness analysis aims to produce an estimate of effect per dollar spent, such that two alternatives can be compared equally. The preferred effect measure is typically a utility such as the quality-adjusted life-year or the disability-adjusted life-year (DALY). Quality-adjusted life-years and DALYs are both summary measures that combine reduced morbidity and mortality from disease into a single measure [69]. The incremental cost–effectiveness ratio quantifies the cost to avert one DALY, but still requires interpretation by the policy-maker through a willingness-to-pay (WTP) threshold. WTP thresholds vary not only by disease state but also by country setting, and there is no accepted standard though a commonly used rule of thumb is a threshold of three times a country's gross domestic product [70].

Challenges in performing & interpreting economic evaluation of TB diagnostics

Several issues particular to TB diagnostics make performing and interpreting economic evaluations challenging for policy-makers. First, most diagnostic studies aim to estimate test accuracy relative to a reference standard. However, in order to produce estimates of effect for economic evaluation (e.g., DALYs averted), studies must also measure clinical outcomes in patients tested with the alternative diagnostic test strategies. Assessing patient outcomes requires longitudinal follow-up of patients, which increases the study duration and cost, and are infrequently measured as part of diagnostic test accuracy studies. The impact of misdiagnosis and missed diagnoses resulting from poor diagnostic accuracy is difficult to estimate and could lead to an underestimate of the impact of new improved tests.

Second, implementation studies seeking to examine clinical outcomes must take place within the context of existing health systems, which may have insufficient or flawed infrastructure. As outlined earlier, even a highly accurate and rapid test meeting a desired TPP may fail to show improved clinical outcomes if the TB treatment program suffers from frequent drug stock outs or high rates of loss to follow-up [71]. Assigning DALYs averted directly to a diagnostic test is thus challenging as the potential effect of any new TB diagnostic may be ablated by external factors. A helpful additional metric to ‘cost per DALY averted’ could be ‘cost per additional TB diagnosis’, and though this may appear more immediately interpretable to policymakers, there are no established WTP thresholds for such endpoints.

Third, new TB diagnostics are likely to be incorporated into diagnostic algorithms in conjunction with existing TB diagnostics. As such, most cost–effectiveness analyses of new TB diagnostics compare different permutations of testing algorithms utilizing a decision analytic approach. However, most new TB diagnostic tests are evaluated in isolation (i.e., as ‘stand-alone’ tests) rather than in combination with existing algorithms or tests; the incremental diagnostic yield conferred by a new diagnostic tool over existing approaches is thus often unknown. As a result, modeling the economic impact of a new test or algorithm is often limited by a lack of needed data. Decision analytic approaches also are largely unable to account for additional downstream effects that may occur due to averted transmissions and thus potentially underestimate the impact of new TB diagnostics.

Determining the net costs for economic evaluations of TB diagnostics and diagnostic algorithms is also challenging, particularly when incorporating subsequent clinical outcomes. Downstream costs (e.g., treatment) dwarf the costs for these diagnostic tests even when considering expensive components such as equipment (e.g., the four-unit Xpert instrument). In a study of the cost–effectiveness of algorithms for TB diagnosis among HIV-infected adults in Uganda, diagnostic costs made up only about a quarter to a third of all patient costs, which included TB and HIV treatment [12]. As a result of a test’s increased ability to diagnose TB cases, more individuals incur the costs associated with treatment and costs associated with improved survival. TB diagnostic costs are often ‘once-offs’, whereas treatment costs are expensive and lengthy. Such distinctions are particularly relevant in settings of high HIV prevalence. Lifelong antiretroviral therapy costs far outweigh costs of a one-time TB diagnostic test; if programs are willing to pay for lifelong antiretroviral therapy for a TB survivor, they should always be willing to pay for the TB diagnostic testing [72].

Increased TB treatment costs resulting from improved case detection should be weighed against the potential decrease in disease transmission, which could ultimately yield increasingly fewer cases for both detection and treatment.

The findings of cost-effectiveness analyses are also highly context dependent, but often are not treated as such. As it is not feasible to wait for economic evaluations tailored to every TB landscape, policymakers are often in the position of extrapolating existing cost-effectiveness findings to their own setting, which may meet with mixed results. Finally, despite a test being 'highly' cost-effective based on country-specific WTP thresholds, it still may not translate into affordability. Budgetary limitations and competing health care priorities may render new TB tests off-limits. Decision makers may ultimately consider alternate strategies for rollout of tests, which may diminish the potential clinical and market impact and make new test development less attractive. This scenario is not restricted to low-income settings. For example, despite being found to be cost-effective for usage in all patients with suspected TB disease in the USA, some states have restricted the usage of Xpert only to those with smear-positive disease [7,73].

Programmatic challenges: which tests, when & how?

Although the pipeline of new TB diagnostics currently under development is increasingly rich, this fact also presents challenges for TB control programs deciding *which tests* to implement and *when to implement* – an 'embarrassment of riches' with significant economic implications. As an example, prior to the release of the landmark Xpert studies, South Africa committed to a rollout of the Hain Genotype MTBDR*plus* (Line probe assay [LPA]) for rapid diagnosis of MDR-TB. LPA is a technically difficult test requiring significant laboratory infrastructure but has good accuracy for detection of drug-resistant TB and dramatically shortens the time to drug susceptibility results [71,74]. After WHO endorsed LPA in 2008 [75], South Africa began test rollout in referral laboratories, representing a major health care expenditure. However, in 2010, LPA was supplanted by Xpert, a test that offered similar rapid detection of TB and drug-resistant TB in a simpler platform. South Africa has since undertaken an impressive national Xpert roll-out [76], with LPA relegated to reference laboratories and used primarily to confirm resistance results in patients identified as rifampicin resistant by Xpert. Thus, a test with an initial large economic market has been reduced to a niche test for the estimated 5–7% [71] of new TB cases with MDR-TB. Whether South Africa, a middle-income country, would be willing to similarly abandon Xpert in favor of other newer technologies is unclear, given the financial and political commitment that has been made.

As multiple technologies emerge, the pathway for implementation thus becomes cloudier. Technologies that are first to market have significant advantage over the 'fast followers'. Newer technologies may better meet TPPs desired by TB practitioners and may even be cheaper. Yet, it is unclear if TB programs will be willing or able to afford recurrent investments in new technologies as they come to market. The threshold of incremental increase in test performance needed to stimulate programmatic changes is currently unknown. Lessons from other technology-dependent industries outside of health care could be informative in supplying a decision-making framework for TB control programs.

Just as TB is treated with a multidrug regimen, we suspect that the future approach to diagnosis will involve various multitest algorithms that are setting and patient subpopulation specific. This scenario is challenging for programs as the bulk of the evidence base for new tests comes from studies where the assay was evaluated in isolation. For example, Cobelens *et al.* point out that the WHO has currently endorsed six different diagnostic technologies for TB drug susceptibility testing, each with somewhat overlapping advantages and disadvantages [77]. Such a scenario can be difficult for policymakers, program managers and donors to sort out which test or tests to include within their local or regional TB diagnostic algorithms.

Ultimately, in many circumstances, program implementation and scale-up require policy recommendations or endorsements that are typically made by WHO or National TB programs. Such policy guidance typically require multiple studies examining test performance and utility in different settings and among key subpopulations (e.g., HIV infected) to establish a sufficient evidence base for endorsement. Waiting for an adequate number of high-quality studies to be completed, including clinical impact studies, can delay policy and thus uptake the test globally with financial consequences for test developers. Moreover, while policy guidelines or endorsements may stimulate initial programmatic implementation, they do not necessarily offer information on how best to scale-up a new diagnostic tool at a national level. Diagnostic accuracy studies or demonstration studies upon which guidance is often issued, while useful, may not provide sufficient data for several crucial programmatic considerations such as required infrastructure, staffing, training and quality control and assurance. Such logistical considerations can significantly impact market uptake, clinician and patient acceptance, and widescale implementation of a new diagnostic tool.

To overcome some of these barriers to implementation, following the Xpert policy recommendations, WHO released an implementation 'How To' guidance [78]. This document offers information on positioning of the test within the health system, site selection criteria, selection of patient populations for testing, installation and running costs and a guide to pilot testing. This innovative policy support is crucial to programs that may lack expertise or resources to synthesize all available evidence and help developers who are unlikely to be able to offer comprehensive support for implementation of their product at this scale. Whether this precedent will be followed for future TB diagnostics is unclear, but speaks to the need for developers to engage with regulatory bodies for the full potential and impact of new diagnostic tools to be reached.

Conclusion

Global TB case detection remains below international targets in part due to the limitations of current TB diagnostic tools. Despite the need for new TB diagnostics, there are economic challenges to test development (Table 2). TB disease is heterogeneous and complex, and development of new diagnostic tools will require significant economic investment in basic research to yield new disease insights and to drive technological innovations. New TB diagnostics will need to be rapid, accurate and simple. As new products enter the market, they will have to compete with existing technologies such as Xpert; given tradeoffs in

diagnostic test profiles and performance, future diagnostic strategies may utilize combinations of tests to optimize TB case detection. Ultimately, there is significant economic potential for new TB diagnostics. However, the TB diagnostic market is heavily concentrated in low- and middle-income settings where there may be additional uncertainties and obstacles to scale-up new technologies. These challenges will require strong partnerships between developers, researchers and implementers.

Expert commentary

There is a clear and demonstrable need for improved TB diagnostics. Despite this fact, current expenditures for TB diagnostics research were less than US\$50 million in 2012, far short of Global Plan recommendations [4,61]. We have attempted to outline the many economic challenges that currently exist facing both test development and implementation. Technological innovations and biological insights are both urgently needed to provide better diagnostic targets and methods for simply, accurately and rapidly detecting both latent and active TB. The wide spectrum of disease phenotypes caused by *M. tuberculosis* means that there may not be a single universal TB detection strategy in the near future, an important economic consideration for developers assessing market size for future products. HIV-associated TB and pediatric TB are examples of conditions that may require targeted diagnostic products and directed economic investment. Even as new TB diagnostics meeting desired TPPs emerge, economic challenges and obstacles remain which hinder broad implementation. The impact of diagnostic tests on patient outcomes is inherently dependent on background health systems and treatment programs that may be inadequate in many settings, compromising the potential value of emerging diagnostic technologies in the eyes of policymakers. Similarly, assessment of cost-effectiveness is often a prerequisite for endorsement by national and international policymakers. These economic evaluations are methodologically difficult and depend upon availability of data that are often lacking from current TB diagnostic accuracy studies. Finally, the successful implementation and broad scale-up of new technologies require political will and financial commitment to alter the economic marketplace for TB diagnostics. South Africa is an example of a setting where new technologies have been enthusiastically embraced, but few other high-burden settings have followed suit. Stimulating TB diagnostic development and adoption will thus require improved funding and stronger partnerships between industry, public/private sector donors and governing bodies.

Five-year view

Improved measures to hasten the decline of TB incidence are needed. Only two-thirds of all cases are detected each year, resulting in a large pool of undetected infectious individuals, which fuels ongoing transmission. As such, there is a potentially large market for new TB diagnostic test development. The current pipeline for new TB diagnostics is flush with NAAT-based tests, but may require centralized laboratory placement [16], which may limit their potential to revolutionize TB case detection. Several 'fast-followers' to Xpert are poised for release into the global marketplace, but will need to be priced competitively to take a share of the market away from Xpert. Extensive diagnostic accuracy and implementation studies will be required before these tests will be embraced for rollout by

national TB control programs. Additionally, we anticipate that some emerging TB diagnostics will find important but ultimately narrow roles within TB diagnostic algorithms, limiting their economic potential – examples include the Hain GenoType MTBDRsl for second-line drug sensitivity testing and the Determine TB-LAM Ag for detection of HIV-associated TB. We anticipate that the model for development used by Xpert, where a private company partners with a nongovernmental organization, academic and governmental institutions, will be required for future successful diagnostic tests in order to ensure sufficient support for lengthy clinical studies as well as a defined market share upon introduction. Finally, we anticipate that implementers and clinicians will soon be faced with an array of diagnostic tests and strategies in order to provide a confident diagnosis of TB disease – determining optimal combinations of diagnostic tests will likely require significant investment and collaboration between developers, researchers and policymakers.

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• of interest

•• of considerable interest

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Key issues

- Tuberculosis (TB) remains a global health crisis. Only two-thirds of those who develop TB each year are currently detected.
- Current TB diagnostic tools have suboptimal sensitivity and specificity. The reference standard test, mycobacterial culture, is costly, slow and unavailable in many settings due to limited laboratory capacity. Technological innovations are now needed to improve diagnostic test accuracy and reduce the reliance on expensive laboratory infrastructure.
- New TB diagnostic tests should provide rapid test results in an easy to use format, have good diagnostic accuracy, have easy and simple specimen collection and represent a low biosafety risk during operation.
- TB disease is heterogeneous and complex, posing challenges for diagnostic test development.
- Emerging tests may have ‘niche’ markets targeting specific TB disease manifestations or target populations.
- Challenges from the test developer’s perspective include: the need for well-defined target product profiles; the push–pull between ‘one size fits all’ and a condition specific test; costly development considerations including extensive clinical trials and the concentration of disease within low-income countries.
- Challenges from the policy perspective include: difficulty in assessing patient impact of new diagnostic tools; lack of data on performance and impact of test implementation within existing diagnostic algorithms; cost–effectiveness studies may be highly context dependent and may not translate into an ‘affordable’ test.
- Challenges from the programmatic perspective include: multiple technologies emerging within a short space of time; technologies that are first to market have significant advantage over ‘fast followers’ but may not have superior target product profiles; policy while an adequate number of high-quality studies are completed; guidance for diagnostic studies often lacks crucial practical programmatic implementation considerations.

Table 1

Needs, challenges and opportunities for new TB diagnostics.

Need	State of current diagnostics	Challenges and opportunities
Rapid test results	<ul style="list-style-type: none"> • Culture takes weeks to months • Smear microscopy requires 2–3 days • Xpert has potential for 2 h at POC • Determine TB-LAM Ag is rapid (20 min) 	<ul style="list-style-type: none"> • Ideal test is point of care, maximum of 3 h to results [15] • Centralized placement of even rapid tests (e.g., Xpert) can erode turnaround times (e.g., specimen transport and reporting delays) • Test results ideally available within length of a clinic visit • Rapid tests often lack sufficient sensitivity to diagnosis full spectrum of TB disease
Easy to use test	<ul style="list-style-type: none"> • Culture requires skilled personnel and lab infrastructure • Smear microscopy requires technical training • Xpert is technically simple; requires Xpert instrument • Molecular tests such as LPA require significant lab infrastructure and skilled personnel • Determine TB-LAM Ag meets ease of use qualities 	<ul style="list-style-type: none"> • Ideal test would not be reliant on electricity • Ideal test would not require temperature or humidity control • Ideal test could be performed without technical training and have three steps maximum [15]
Good diagnostic accuracy	<ul style="list-style-type: none"> • Smear sensitivity 20–80% [10] • Culture sensitivity 80–93% [11] • Xpert sensitivity 88% [20] • Determine TB-LAM Ag sensitivity 30–70% in HIV infected [79] 	<ul style="list-style-type: none"> • Diagnostic accuracy depends on the role within diagnostic algorithm • 'Rule in' tests require sensitivity of >75% and specificity >98% [54] • 'Rule out' tests require sensitivity of >95% and specificity of >75% [15,54] • Improved sensitivity requires lower thresholds for detection – essential for detecting paucibacillary disease • High specificity needed to rule out nontuberculous mycobacteria and latent TB infections • Sensitivity of 90% for culture negative/probable TB in children [15] • Good sensitivity for detection of first- and second-line drug resistance combined with <i>M. tuberculosis</i> detection would be ideal

Need	State of current diagnostics	Challenges and opportunities
Easy and simple specimen collection	<ul style="list-style-type: none"> • Most current tests focus on sputum collection • Determine LAM TB Ag uses urine 	<ul style="list-style-type: none"> • Sputum is easy to collect in some patients but: <ul style="list-style-type: none"> – only targets pulmonary TB and misses EPTB – Difficult to collect in children or patients without a cough – Infection. Control risks with specimen collection • TB pathogenesis research needed to inform diagnostic test targets from other easily collected body specimens (i.e., blood, urine) • Ideal specimen would include urine, oral, breath or capillary blood [15]
Low biosafety risk	<ul style="list-style-type: none"> • Sputum-based platforms may require biosafety considerations • Culture requires additional biosafety infrastructure • Determine TB LAM uses a sample (urine) with minimal infection control risks 	<ul style="list-style-type: none"> • Manipulation of samples containing live bacilli can generate aerosols that can infect health care workers, laboratory staff and possibly other patients • Self-contained systems (or those operable at biosafety level 1 [15]) that eliminate biosafety concerns will be welcomed by TB programs and are likely to be prioritized, representing market potential

TB diagnostic test needs taken from New Diagnostics Working Group of the Stop TB Partnership [80].

LAM: Lipid-based assay; LPA: Line probe assay; TB: Tuberculosis; Xpert: Genotype Xpert MTB/RIF.

Table 2

Summary of economic challenges to diagnostic test development for developers, policymakers and programs.

Perspective	Challenges
Developer	<ul style="list-style-type: none"> • Need for well-defined TPP <ul style="list-style-type: none"> – TB has heterogeneous clinical manifestations (e.g., pediatric TB, EPTB, HIV-associated TB) – TPP must encompass a multitude of test attributes ranging from target costs to needed throughput, level of automation and target populations – Guidance needed on attribute prioritization and potential market sizes across settings • One size fits all vs condition-specific approach <ul style="list-style-type: none"> – No current global biomarker to identify all TB disease in all patients to aid new test development – Condition-specific niche tests may not be economically viable for developers • Costly development considerations. <ul style="list-style-type: none"> – Well-characterized specimens and biological samples are needed for test development – Diagnostic accuracy studies require large sample sizes, multiple sites, with target populations in high-burden settings without sufficient research or clinical infrastructure – Studies demonstrating improved patient outcomes with test implementation are sought by policymakers and clinicians, but challenging to conduct – TB concentrated in low- and low-middle-income countries, leading to downward pricing pressure without guaranteed market share in high-income countries
Policy	<ul style="list-style-type: none"> • Assessing patient impact (e.g., DALYs) of new diagnostic tools is affected by the existing health system • Lack of accepted WTP thresholds for alternate measures of cost-effectiveness such as 'cost per additional TB diagnosis' • Performance and impact of implementing new tests within existing diagnostic algorithms are hampered by lack of data • Overall costs of implementing new diagnostics are largely dominated by costs downstream from the diagnostic test as successful diagnosis leads to increased costs associated with treatment and improved survival • Cost-effectiveness findings may be highly context dependent • A highly cost-effective testing strategy may not translate into affordability
Programmatic	<ul style="list-style-type: none"> • As multiple technologies emerge from the diagnostic pipeline, it is unclear if TB programs will be willing or able to afford recurrent investments in new technologies as they come to market • Technologies that are first to market have significant advantages over 'fast followers' • Waiting for an adequate number of high-quality studies to be completed, including clinical impact studies, can delay policy and thus uptake of the test globally with financial consequences for test developers • Diagnostic accuracy studies or demonstration studies upon which guidance are often issued, may not provide sufficient data for several crucial programmatic considerations such as required infrastructure, staffing, training and quality control and assurance

DALY: Disability-adjusted life-years; EPTB: Extrapulmonary TB; TB: Tuberculosis; TPP: Target product profiles; WTP: Willingness-to-pay thresholds.