SUPPLEMENT ARTICLE

Defining the Needs for Next Generation Assays for Tuberculosis

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To accelerate the fight against tuberculosis, major diagnostic challenges need to be addressed urgently. Post-2015 targets are unlikely to be met without the use of novel diagnostics that are more accurate and can be used closer to where patients first seek care in affordable diagnostic algorithms.

This article describes the efforts by the stakeholder community that led to the identification of the high-priority diagnostic needs in tuberculosis. Subsequently target product profiles for the high-priority diagnostic needs were developed and reviewed in a World Health Organization (WHO)-led consensus meeting.

The high-priority diagnostic needs included (1) a sputum-based replacement test for smear-microscopy; (2) a non-sputum-based biomarker test for all forms of tuberculosis, ideally suitable for use at levels below microscopy centers; (3) a simple, low cost triage test for use by first-contact care providers as a rule-out test, ideally suitable for use by community health workers; and (4) a rapid drug susceptibility test for use at the microscopy center level.

The developed target product profiles, along with complimentary work presented in this supplement, will help to facilitate the interaction between the tuberculosis community and the diagnostics industry with the goal to lead the way toward the post-2015 global tuberculosis targets.

Keywords. tuberculosis; diagnosis; target product profiles; prioritization; point-of-care.

In 2012, there were an estimated 9 million tuberculosis cases leading to 1.5 million deaths, the majority of which were preventable with existing treatments if diagnosed early [1]. Major gains have been made in the fight against tuberculosis over the past decades, and the world is on track to meet the targets of the 2015 UN Millennium Development Goal of reversing tuberculosis incidence. Also, all regions except for Africa and Europe are on track to achieve a reduction in the mortality rate by 50%. However, to accelerate the fight against tuberculosis and move towards post-2015 targets and finally elimination of this disease, two major challenges need to be addressed urgently: (1) Each year 3 million patients, about one third of all tuberculosis cases, are not diagnosed or notified; (2) The emergence of drug resistance against the main anti-tuberculous drugs is creating a public health crisis in many countries around the world.

Early diagnosis of tuberculosis and universal drug-susceptibility testing are the first steps necessary to identify the adequate treatment for individual patients and to prevent the spread of disease at the population level. Novel tests that reach "the missing three million patients" and curb the epidemic of drug-resistant tuberculosis are needed. These tests need to have improved performance characteristics and/or reach lower levels of the health-care system and be affordable as well as link to the needs around new drug/regimen development.

This article describes the efforts that lead to the identification of the highest priority diagnostic needs in tuberculosis and the consensus-building process that resulted in target product profiles (TPPs) for tests to address those needs.

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METHODS

Defining a List of Needs

Through interviews with representatives from national tuberculosis programs, clinical experts from industrialized, middle, and low-income countries, researchers, and clinical laboratory experts, a "wish-list" was compiled defining the most important diagnostic needs for tuberculosis [2]. In addition, the literature was searched, and recent reports and position papers were consulted. A list was then assembled of tests needed to fill important gaps in the current diagnostic landscape and whose development would be feasible in the near future [3].

Prioritization Exercise

Once a list of diagnostic needs was developed, a prioritization exercise was done in order to establish a rank order of the tests and to identify those that were perceived of highest priority [3]. Five different predefined expert groups were consulted: patient and community advocates, field practitioners and clinicians, experts from national tuberculosis programs, modelers, and market experts. All experts rated the diagnostic needs based on 10 different criteria having a 5-year time frame for deployment in mind. The criteria that were evaluated included the prioritization for their respective stakeholders group, the potential for scale up of a test addressing the respective need, and the magnitude of the effect of a test on tuberculosis incidence and mortality reduction as well as the market potential for the test.

TPP Development and Refinement

For the highest rated diagnostic needs, comprehensive TPPs were developed by McGill University, Montreal, Canada, and FIND, Geneva, Switzerland. The TPPs were assembled based on a literature search and interviews with experts and then revised in several rounds with the input provided by researchers, clinicians, policy makers, test developers, and funders. As a result of these extended and reiterative consultations, detailed and comprehensive TPPs were developed. In addition, shorter versions including only the most important characteristics were prepared and used for the consensus building process.

Consensus Building

The shortened versions of the TPPs were presented to a large stakeholder audience that included clinicians, implementers, and representatives of countries and national tuberculosis programs in a "Consensus Meeting on high-priority Target Product Profiles" convened in April 2014, by the World Health Organization (WHO) on behalf of the Global Laboratory Initiative and the New Diagnostics Working Group of the Stop TB Partnership. Leading up to the meeting, a Delphi-like process was used to facilitate consensus building. The shortened TPPs were sent to all invited meeting participants (excluding individuals working in industry in order to avoid possible bias). Individuals were asked to rate the level of agreement with each of the proposed characteristics outlined in the TPPs. It was prespecified that consensus would be achieved when at least 50% of the individuals completing the Delphi-survey would agree with the proposed characteristics. Only characteristics for which less than 75% of the responders agreed or a distinct subgroup disagreed were ultimately discussed in the consensus meeting. The final TPPs were published by WHO and partners in October 2014 [4]. This article presents the final TPPs as they were published in the meeting report.

RESULTS

In interviews and reviews of publications, the tuberculosis community identified the need for developing several tuberculosis diagnostic tests in addition to the currently available tools [2]. The list of tests (Table 1) includes triage and screening tests [5], tests for patients difficult to diagnose (ie, children, patients with human immunodeficiency virus [HIV] and patients with extrapulmonary tuberculosis) [6], a simple non-sputum-based biomarker test for diagnosis of active tuberculosis [7], a molecular smear-replacement test [8] at the microscopy center level or at even lower levels of care, drug-susceptibility tests (DST) that could be done in decentralized or centralized settings [9], a biomarker test for diagnosis of a latent tuberculosis infection that predicts progression to active tuberculosis [10] and a test for treatment monitoring [11].

Table 1. Identified Needs for Diagnostic Tests Categorized by Main Indication

TRIAGE, RULE OUT AND SYSTEMATIC SCREENING
Triage test for those seeking care[a]
An HIV/ART clinic-based test to rule out active TB
Systematic screening test for active case finding
RAPID TB DIAGNOSIS (WITH OPTIONAL DRUG SUSCEPTIBILITY TESTING)
Rapid, sputum-based, cartridge-based, molecular test for microscopy centers (with the option of add-on DST cartridge)[a]
Rapid biomarker-based instrument-free test for non-sputum samples (which can also detect childhood and extrapulmonary TB)[a]
Multiplexed test for TB and other infectious diseases
NEXT-GENERATION DRUG SUSCEPTIBILITY TEST
Centralized, high-throughput, drug susceptibility test (incorporating new drugs to support the roll out of new TB Rx regimens post 2014)
TREATMENT MONITORING TEST
Treatment monitoring test (test for cure)
PREDICTIVE TEST FOR LATENT TB INFECTION
Predictive test for latent TB infection at high risk of active TB

Abbreviations: ART, antiretroviral therapy; DST, drug-susceptibility tests; HIV, human immunodeficiency virus; TB, tuberculosis.

[a] Highlights the tests that are being addressed in this article. Target product profiles for the other identified needs are being developed independent of the effort described herein by FIND and partners.

The priority-setting exercise ultimately identified the following tests as the key priorities, which would have the most impact on incidence and morbidity reduction and potential for market entry and scale up over the coming 5years [3].

1. A rapid sputum-based test as a replacement for smear-microscopy ("smear-replacement test") with or without DST;
2. A rapid non-sputum-based test capable of detecting all forms of tuberculosis via the identification of characteristics biomarkers or biosignatures ("non-sputum based biomarker test");
3. A triage test, which should be a simple, low cost test for use by first-contact health care providers as a rule-out test ("triage test");

More details of the priority setting exercise can be found elsewhere [3]. Four TPPs were ultimately developed, dividing up the rapid sputum-based test as a replacement for smear-microscopy into one with a DST component ("rapid DST") and another one ("smear-replacement test"). The 3 TPPs that address tuberculosis detection are presented in this article. The fourth TPP that addresses the "rapid DST" is presented separately (see Denkinger CM et al in this supplement) as it discusses the very complex field of drug susceptibility testing.

TPP for a Smear-replacement Test for Tuberculosis Detection

Rationale

Smear microscopy is the most widely used tuberculosis test in high-burden countries, and its sensitivity limitations are well known [12]. The sensitivity of newer rapid tools for tuberculosis detection (eg, Xpert) still does not reach that of culture [13, 14]. More sensitive tests are needed so that patients with tuberculosis can be identified upon first presentation to the health care system and so that patients with paucibacillary disease (eg, HIV patients and children) are detected.

Xpert MTB/RIF ("Xpert," Cepheid, Inc., Sunnyvale, California) has enabled more timely and sensitive diagnosis of tuberculosis over smear microscopy and up-front DST for the key drug (rifampin) in the first-line treatment regimen [15–17]. However, the use of Xpert is limited by its cost and infrastructure requirements (eg, power, temperature controlled environment), which prohibits its placement and use in most microscopy centers [18, 19]. The rollout of Xpert has also demonstrated that new diagnostic tools do not necessarily reach additional people eligible for testing or increase the overall number of tuberculosis cases diagnosed, if they are implemented within established care settings (although Xpert does increase the number of bacteriologically confirmed cases) [20]. On the other hand, there is an increasing number of molecular tests in the pipeline that aim to be more sensitive and are specifically designed for use in resource-limited settings such as microscopy centers or peripheral health clinics [21]. Other assays for detection may conceivably be feasible as well (eg, antigen detection), but the molecular pipeline appears to be the most promising in the near future.

TPP characteristics

A more sensitive smear-replacement test would increase the number of patients diagnosed with tuberculosis and might reduce transmission and morbidity through earlier diagnosis and treatment (Table 2) [22]. Ideally a test would aim for a better sensitivity than Xpert for tuberculosis detection and be as good as liquid culture (ie, diagnostic sensitivity of >95% in comparison to culture; analytical sensitivity of less than 4.5 genome equivalents/reaction and <10e2 CFU/assay on one sample). Such a test could obviate further need for culture in drug-susceptible tuberculosis and potentially improve the trust of clinicians and patients in the diagnostic performance of tests and thereby reduce empiric treatment and overtreatment [24].

Modeling work has demonstrated that even a test with performance characteristics better than smear (50% detection of smear-negative) yet inferior to Xpert, if employed at microscopy centers and combined with good linkage to treatment, would result in a reduction in transmission over deployment of Xpert at a district level [22]. Whether up-front resistance testing such as detection of rifampin resistance in Xpert is beneficial will depend on the local epidemiology of drug-resistance and the trade-offs made by including DST (eg, in respect to time to result). A test at the level of a microscopy center would also leverage the existing treatment infrastructure for drug-susceptible tuberculosis that is already in place in these settings. Furthermore, if a smear-replacement test can also be used for treatment monitoring (eg, through detecting viable bacteria), it would be able to completely replace smear microscopy and would be more likely to be adopted by tuberculosis programs.

A sputum-smear replacement test should ideally have a fast turn-around time and allow for batching as well as random access to rapidly inform a treatment decision at the time of the first visit and link to further care [25, 26]. Due to conditions that prevail in microscopy centers in high-burden countries, a robust test with very simple sample preparation and minimal operational requirements will be necessary [8, 18]. Minimal sample handling (ie, total hands-on steps after obtaining sample) and no precision volume control and precision time steps should be required to ensure that the test is feasible with the level of expertise and training that can be expected at microscopy centers [8, 18].

Continuous power is not always available at microscopy centers in high tuberculosis burden countries; therefore, a battery operated device with charge possibility (conceivably through solar power) would be most ideal in order for a test to fit the entire breadth of settings in microscopy centers [8, 18]. High environmental temperatures and high humidity (up to 50°C and 90% humidity) are often a problem in countries where tuberculosis is endemic. Dusty environments are common and adequate protection of optics and moving parts should be considered [27]. Maintenance and calibration require special attention to ensure functionality of equipment particularly at peripheral centers. The average time to equipment/module failure should ideally be more

Table 2. TPP for a Smear-replacement Test for Tuberculosis Detection

Characteristic	Optimal Requirements	Minimal Requirements
Scope		
Goal	To develop a sputum-based test for detecting pulmonary TB at the microscopy-center level of the health-care system to support the initiation of TB therapy during the same clinical encounter or the same day	
Target population	Target groups are all patients suspected of having pulmonary TB who are able to produce sputum, in countries with a medium prevalence to a high prevalence of TB as defined by WHO[a]	
Target user of the test[b]	Health-care workers with a minimum amount of training (that is, with skills that are similar to or less demanding than those needed for performing smear microscopy)	
Setting (level of the health-care system)	Microscopy-center level (primary health-care centers with attached peripheral laboratories) or higher levels of the health-care system	
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity[b]	Sensitivity should be >95% for a single test when compared with culture (for smear-negative cases it should be >68%; for smear-positive it should be 99%)	Sensitivity should be >80% for a single test when compared with culture (for smear-negative cases it should be >60%; for smear-positive it should be 99%)
Diagnostic specificity[b]	>98% specificity when compared with culture	
Possibility of using test for treatment monitoring	Yes: a test that is able to replace smear microscopy and also be used to monitor treatment is more likely to be adopted and more likely to completely replace smear microscopy	No
OPERATIONAL CHARACTERISTICS		
Manual preparation of samples (steps needed after obtaining sample)	No steps or 1 step; precise volume control and precise timing should not be required	A maximum of 2 steps; precise volume control and precise timing should not be required
Reagent integration	All reagents should be contained in a single device	A maximum of 2 external reagents should be required; these should be part of test kit
Data export (connectivity and interoperability)	Integrated ability for all data to be exported (including data on use of the device, error rates and rates of invalid tests, and personalized, protected results) over a USB port and network	Integrated ability for all data to be exported (including data on use of the device, error rates and rates of invalid tests, and non-personalized results) over a USB port
Time to result[b]	<20 min	<2 h
Power requirements	Battery operated with recharging capability and a circuit protector	
Maintenance and calibration[b]	Preventative maintenance and calibration should not be needed until after 2 y or 5000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely or no calibration should be required	Preventative maintenance should not be needed until after 1 y or 1000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely, should calibrate itself or no calibration should be required
Operating temperature and humidity level	Between +5°C and +50°C with 90% humidity	Between + 5°C and +40°C with 70% humidity
Reagent kit – storage, stability, and stability during transport	2 years at 0°C to +50°C with 90% humidity; should be able to tolerate stress during transport (72 h at +50°C); no cold chain should be required	12 months at 0°C to +40°C with 70% humidity; should be able to tolerate stress during transport (72 h at +50°C); no cold chain should be required
Internal quality control	Full internal process controls are necessary, including controls for sample processing and amplification (for NAAT)	
PRICING		
Price of individual test[b] (costs of reagent only; after scale-up; ex-works [manufacturing costs only, excluding shipping])	<US$ 4.00 for detecting TB	<US$ 6.00 for detecting TB
Capital costs for instrument[b]	<US$ 500 per module	<US$ 1400 per module

Adapted with permission from WHO consensus meeting report on TPPs [4]

Abbreviations: NAAT, nucleic acid amplification test; TB, tuberculosis; TPPs, target product profiles; WHO, World Health Organization.

[a] High-prevalence countries are those with >40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100 000 population; and low-prevalence countries are those with <20 cases per 100 000 population [23].

[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

than 2 years, and a maintenance alert should indicate the need for preventative maintenance as it is unlikely that the same person will always handle the device and records will be kept on duration of use of a device [28]. Only simple tools and minimal expertise should be required for maintenance and repair of the equipment given the difficulty of service visits in peripheral settings [8, 18]. The scale at which a new test is adopted will depend substantially on how well it meets the specified operational characteristics.

TPP for a Non-sputum-based Biomarker Test for Tuberculosis Detection

Rationale

A highly sensitive test based on a biological sample other than sputum (such as urine, blood, saliva, or exhaled air) suitable for implementation at lower levels of care would conceivably help shorten the delay before diagnosis and enable early treatment (and thus reduce morbidity, mortality and transmission) [29, 30] (Table 3). A non-sputum based sample could also enable the diagnosis of extrapulmonary tuberculosis (EPTB) and tuberculosis in children as well as the diagnosis in patients presenting in an earlier stage of the disease (eg, patients who do not have a productive cough to provide a sputum) [25, 31].

TPP characteristics

A non-sputum based biomarker test ideally should be at least as accurate as Xpert 98% sensitive for smear-positive, culture-positive pulmonary tuberculosis (PTB), and 68% sensitive for smear-negative, culture-positive PTB in adults; however, any improvement over smear microscopy could be of value if the test has operational characteristics that make it easy to perform and uses a non-sputum-based sample [32]. For children, a test sensitivity equal or better than 66% for intrathoracic tuberculosis and equal or better than 80% for extrapulmonary tuberculosis (EPTB) in adults would be optimal, as this can currently be achieved on the appropriate samples with Xpert [1, 6, 33]. Similar to Xpert, the specificity of the test should at least be 98% compared against a microbiological reference standard. Ideally the test should be suitable for use at lower levels of the health-care system where it can reach more patients, and it should ideally not require laboratory facilities [22, 34]. Given the deployment at lower levels of the health-care system, an instrument free test would be ideal, but a small (eg, handheld) device is acceptable and would conceivably add benefits (eg, connectivity). The operational characteristics defined for a smear-replacement test at the microscopy center need to be met at a minimum.

TPP for a Community-based Triage/Referral Test for Identification of Tuberculosis Suspects

Rationale

Most individuals who present themselves to health facilities with symptoms suggestive of tuberculosis do not have tuberculosis. In order to rule out tuberculosis quickly a low-cost triage test is necessary. Only triage test positive patients will then require confirmatory testing [5, 35] (Table 4).

TPP characteristics

A triage test needs to be a simple, low-cost test with high sensitivity for use by first-contact providers in the community (eg, community health workers). Such a test can rule out tuberculosis when the result is negative. Individuals with a positive result are directed to further evaluation with a confirmatory test (eg, Xpert). Sensitivity of a triage test should ideally be as good as that of the confirmatory test (>95% of confirmatory test) as otherwise patients would be missed by the test and the strategy of testing all patients with the confirmatory test would theoretically result in a higher case notification rate. However, if a triage test is done at lower levels of care and is easier to do, conceivably more people suspected of having tuberculosis will be tested. Consequently, the test might increase the number of tuberculosis patients identified even if its sensitivity is lower than that of the confirmatory test. Therefore, the minimal sensitivity in the TPP was defined to be greater than 90% compared to the confirmatory test.

A triage test might also conceivably diagnose EPTB. For confirmatory testing, a molecular test or culture on an aspirate or biopsy would then be necessary (eg, a biopsy for lymph node tuberculosis). The specificity requirement for a triage test needs to consider the tuberculosis prevalence in the population tested, but consensus was reached that it should be optimally at least 80% and minimally at least 70%. The specificity of the test is one of the main drivers of the cost-effectiveness of an implementation strategy. The lower the specificity of the triage test, the higher the number of confirmatory tests necessary and therefore the lower the cost of a triage test needs to be to result in a cost-effective testing strategy [5].

For successful implementation at the community level, a triage test should ideally use an easily accessible sample (eg, urine, finger stick blood). The test should optimally be device-free or if a device is needed it should at least be battery-operated [8, 18]. The ideal time-to-result (including sample preparation and processing time) has not been studied; however, a rapid test is more likely to be integrated within the work flow and result in same visit decision making.

The main characteristics of these TPPs were discussed and agreed upon in the "Consensus Meeting on high-priority Target Product Profiles" convened by the World Health Organization on behalf of the Global Laboratory Initiative and the New Diagnostics Working Group of the Stop TB Partnership in April 2014 and published in October 2014 [4].

DISCUSSION

Novel tests are needed to reach "the missing three million patients" and curb the epidemic of drug-resistant tuberculosis. These tests need to have improved performance characteristics,

Table 3. TPP for a Rapid Non-sputum-based Biomarker Test for Tuberculosis Detection

Characteristic	Optimal Requirements	Minimal Requirements
SCOPE		
Goal	To develop a rapid biomarker-based test that can diagnose pulmonary TB and optimally also extrapulmonary TB using non-sputum samples (for example, urine, blood, oral mucosal transudates, saliva, exhaled air) for the purpose of initiating TB treatment during the same clinical encounter or on the same day	
Target population	Target groups are adults and children including those who are HIV-positive and suspected of having active pulmonary TB or extrapulmonary TB in countries with a medium prevalence to a high prevalence of TB as defined by WHO[a]	
Target user of the test[b]	Health-care workers with a minimum of training	Trained microscopy technicians
Setting (level of the health-care system)	Health posts without attached laboratories (that is, levels below microscopy centers) or higher levels of the health-care system	Primary health-care clinics with attached laboratories; peripheral microscopy centers or higher levels of the health-care system
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity for pulmonary TB in adults[b]	Sensitivity should be ≥98% for smear-positive culture-positive pulmonary TB, and ≥68% for smear-negative culture-positive pulmonary TB in adults (that is, sensitivity should be similar to that of the Xpert MTB/RIF assay) Overall pooled sensitivity should be ≥80% in adults with HIV infection	Overall sensitivity should be ≥65% but should be >98% among patients with smear-positive culture-positive pulmonary TB (that is, sensitivity should be similar to that of smear microscopy) Overall pooled sensitivity should be better than the sensitivity of smear microscopy in adults with HIV infection
Diagnostic sensitivity for extrapulmonary TB in adults	Ideally, sensitivity should be ≥80% for all forms of microbiologically confirmed extrapulmonary TB[c,d]	Diagnosis of extrapulmonary TB is an important need, and a test that can diagnose extrapulmonary TB in addition to pulmonary TB will have significant benefits for individual patients; additionally, it is likely to be better accepted in the community of care providers. No lower range of sensitivity was defined
Diagnostic sensitivity in children	Sensitivity for childhood intrathoracic TB should be ≥66% for microbiologically confirmed TB (that is, similar to the sensitivity of the Xpert MTB/RIF assay)[e]	Diagnosis of childhood TB is an important need, and a test that improves the diagnosis of TB in children will have significant benefits for individual patients; additionally, it is likely to be better accepted in the community of care providers. No lower range of sensitivity was defined
Diagnostic specificity[b]	At least as specific as the Xpert MTB/RIF assay for detecting pulmonary TB, extrapulmonary TB and childhood TB (that is, the test should have 98% specificity when compared against a microbiological reference standard); the test should distinguish between active TB and latent or past infection	
OPERATIONAL CHARACTERISTICS		
Sample type	Not invasive or minimally invasive, non-sputum samples (such as, urine, blood, oral transudates, saliva, exhaled air)	
Manual preparation of samples (steps needed after obtaining sample)	Sample preparation should be integrated or manual preparation should not be required	A limited number of steps only; precise measuring should not be needed for any step (such as precise measuring of volumes or time)
Time to result[b]	<20 min including time spent preparing the sample	<1 h including time spent preparing the sample
Instrument and power requirement	No instrument needed	Small, portable or hand-held instrument (weighing <1 kg) that can operate on battery or solar power in places where power supplies may be interrupted
Maintenance and calibration[b]	Disposable, no maintenance required	Preventative maintenance should not be needed until after 1 y or >1000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the instrument should be able to be calibrated remotely or no calibration should be needed
Operating temperature and humidity level	Between +5°C and +50°C with 90% humidity	Between +5°C and +40°C with 70% humidity

Table 3 continued.

Characteristic	Optimal Requirements	Minimal Requirements
Result capturing, documentation, data display	An instrument-free test with the ability to save results using a separate, attachable reader	The test menu must be simple to navigate; the instrument should have an integrated LCD screen, simple keypad or touch screen, and the ability to save results using either the instrument or a separate reader
Internal quality control	Internal controls should be included for processing the sample and detecting TB	Internal control included only for processing the sample
PRICING		
Price of individual test[b] (costs of reagents and consumables only; after scale-up; ex-works [manufacturing costs only, excluding shipping])	<US$ 4.00	<US$ 6.00

Adapted with permission from WHO consensus meeting report on TPPs [4].

Abbreviations: HIV, human immunodeficiency virus; LCD, liquid crystal display; TB, tuberculosis; TPPS, target product profiles; WHO, World Health Organization.

[a] High-prevalence countries are those with >40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100 000 population; and low-prevalence countries are those with <20 cases per 100 000 population [23].

[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

[c] The sensitivity for detecting extrapulmonary tuberculosis should also be tested against a composite reference standard that includes culture with or without a nucleic acid amplification test, histology, smear microscopy, biochemical testing, presenting signs, and response to treatment with anti-tuberculosis therapy, depending on site of infection. Xpert MTB/RIF testing has an estimated sensitivity for diagnosing tuberculosis of 84% for lymph node aspirates or other tissue samples, and 55% sensitivity for samples of cerebrospinal fluid, when compared with a composite reference standard, but Xpert MTB/RIF testing requires invasive samples [1].

[d] Xpert MTB/RIF has an estimated sensitivity for microbiologically confirmed tuberculosis of 85% for detecting tuberculosis in lymph node aspirates or other tissue samples, 80% for cerebrospinal fluid, and 44% for pleural fluid but testing requires invasive samples (from aspiration, biopsy, lumbar puncture or thoracentesis).

[e] The test's sensitivity in children should be evaluated against a composite reference standard as defined by an international panel of experts [6].

reach lower levels of the health-care system and reduce cost of diagnostic algorithms as well as link to the needs around new drug/regimen development. TPPs are important to specify end-users needs and target specifications for performance and operational characteristics that product developers should meet. While the TPPs outlined here are all based on a large number of interviews, discussions and extensive literature consultation, still many of the characteristics rely on assumptions and the consensus of expert opinion. Also, the TPPs specify the needs across a wide spectrum of settings with substantial potential differences. While modeling might be of benefit in this context, the understanding of the most essential parameters, particularly for tests that would reach a patient population that is currently not reached by tests (eg, triage test), is limited and modeling outputs are often restricted to defining the key drivers of impact and setting boundaries for those characteristics in sensitivity analyses [5, 36]. As further data become available from operational research and modeling, the outlined TPPs may require refinement. Particularly, defining the acceptable costs is difficult and transparent discussions around diagnostic pricing, cost structure and hidden costs on the one hand and affordability and cost-effectiveness on the other hand are necessary.

New tuberculosis diagnostic tests able to improve tuberculosis detection for EPTB, tuberculosis in children and other forms of paucibacillary tuberculosis could be of great benefit for individual patient management [33, 37, 38]. An outstanding question in this context concerns which reference standard should be considered to assess test accuracy for the diagnosis of these forms of the disease. Indeed microbiological culture, commonly used as the reference standard for establishing a definitive diagnosis of tuberculosis, performs poorly in children and EPTB patients [39–41]. Therefore, test accuracy for the detection of EPTB and tuberculosis in children should be evaluated against a composite reference standard including multiple diagnostic methodologies as well as clinical diagnosis criteria. A composite reference standard for the evaluation of diagnostics for childhood tuberculosis has been defined by an international expert panel and is currently being updated and revised based on latest available evidence [6, 42].

Furthermore, the development of TPPs only represents a first step to address test developers' needs. The next question that needs to be addressed is the current and potential volume and market for the new tests. This is a key issue for test developers as they consider an investment in this field [43]. To estimate the potential market, one first has to assess the currently served market. The last large-scale market assessment for tuberculosis diagnostics was performed by FIND and TDR in 2006 [44]. More recently market assessments were done for 4 BRICS countries (Brazil, South Africa, China, and India) under the lead of McGill University in collaboration with FIND, UNITAID, the New Diagnostics Working Group of the Stop TB Partnership, and multiple country level partners. The work will be documented in separate publications, with the first article published being the market assessment for Brazil [45]. An assessment of

Table 4. TPP for a Community-based Triage/Referral Test for Identification of TB Suspects

Characteristic	Optimal Requirements	Minimal Requirements
SCOPE		
Goal	To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with **any symptoms of or risk factors for active TB**, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing	To develop a test that can be used during a patient's first encounter with the health-care system to identify patients with **any symptoms of or risk factors for active pulmonary TB**, including patients coinfected with HIV, those who do not have TB and those who need referral for further confirmatory testing
Target population	Adults and children with signs and symptoms of **active TB at any site** in countries with a medium prevalence to a high prevalence of TB as defined by WHO[a]	Adults and children with signs and symptoms of **active pulmonary TB** in countries with a medium prevalence to a high prevalence of TB as defined by WHO[a]
Target user of the test[b]	Community health workers and informal providers who have had a minimum of training	Health workers trained to the level of auxiliary nurses
Setting (level of the health-care system)	Community level or village level or higher levels of the health-care system	Health posts and primary-care clinics or higher levels of the health-care system
PERFORMANCE CHARACTERISTICS		
Diagnostic sensitivity[b]	Overall sensitivity should be >95% when compared with the confirmatory test for pulmonary TB;[c] no lower range of sensitivity was defined for extrapulmonary TB[d]	Overall sensitivity should be >90% compared with the confirmatory test for pulmonary TB[c]
Diagnostic specificity[b]	Specificity should be >80% compared with the confirmatory test	Specificity should be >70% compared with the confirmatory test
OPERATIONAL CHARACTERISTICS		
Sample type	Non-sputum samples (such as urine, oral mucosal transudates, saliva, exhaled air or blood from a finger-stick)	Sputum; non-sputum samples are preferred (such as urine, oral mucosal transudates, saliva, exhaled air, or blood from a finger-stick; imaging technology
Manual preparation of samples (steps needed after obtaining sample)	Sample preparation should be integrated or manual preparation should not be required (excluding waste disposal); precise timing and measuring should not be required	2 steps (excluding waste disposal); precise timing and measuring should not be required
Time to result[b]	<5 min	<30 min
Instrument and power requirement	None	Small, portable or hand-held device (weighing <1 kg); should have an option for battery power or solar power
Maintenance and calibration[b]	Disposable, no maintenance required	Preventative maintenance should not be needed until after 1 y or 1000 samples; only simple tools and minimal expertise should be required; an alert to indicate when maintenance is needed should be included; the device should be able to be calibrated remotely, should calibrate itself, or no calibration should be required
Operating temperature and humidity level	Between +5°C and +50°C with 90% humidity	Between + 5°C and +40°C with 70% humidity
Result capturing, documentation and data display	An instrument-free test with visual readout and with the ability to save results using a separate, attachable reader	The test menu must be simple to navigate; the instrument should have an integrated LCD screen, a simple keypad or touch screen, and the ability to save results using either the instrument or a separate reader
Internal quality control	Internal controls should be included for processing the sample and detecting TB	Internal control included only for processing the sample
PRICING		
Price of individual test[b] (costs of reagents and consumables only; after scale-up; ex-works [manufacturing costs only, excluding shipping])	<US$ 1.00	<US$ 2.00

Adapted with permission from WHO consensus meeting report on TPPs [4].

Abbreviations: HIV, human immunodeficiency virus; LCD, liquid crystal display; TB, tuberculosis; TPP, target product profiles; WHO, World Health Organization.

[a] High-prevalence countries are those with >40 cases per 100 000 population; medium-prevalence countries are those with 20–40 cases per 100 000 population; and low-prevalence countries are those with <20 cases per 100 000 population [23].

[b] These characteristics were considered to be the most important, and specific consensus was asked for and reached through a Delphi survey.

[c] The performance characteristics of the triage test need to match those of the confirmatory test that will be used.

[d] The sensitivity of the triage test should be compared with the sensitivity of a composite reference standard (that includes culture with or without a nucleic acid amplification test, histology, smear microscopy, biochemical testing, presenting signs and response to treatment with anti-tuberculosis therapy, depending on site of infection) to account for the fact that the test may detect cases of early tuberculosis or extrapulmonary tuberculosis in cases in which a standard microbiological reference standard might not perform well.

the market for a potential smear-replacement test has also been published [12]. The market potential for the novel tests described in the TPPs above was assessed based on the served available market combined with country specific epidemiological data. The results of these market projections are presented in this supplement in a separate article (see Kik et al [3, 12]).

The achievable volume for a test will be part of the consideration when test developers define the test price. For countries the question will be whether the rollout of a test is possible given the available budget. This question can be answered by considering the number of patients that will be tested, the likely algorithms with which a test will be used, and the available country budget based on the current spent [46]. The results may on the one hand inform test developers as they consider the price point for a novel test and on the other hand it will inform national programs, donors, and funders. Such an exercise was undertaken considering the 4 novel TPPs and is presented here in a separate article (Pantoja et al [46]).

In summary, this article describes 3 out of 4TPPs that were identified as the highest priority by the tuberculosis community and the consensus that was reached on the most important performance and operational characteristics. Our work, together with complementary work presented in this supplement, aims to facilitate the interaction between the tuberculosis community and the diagnostics industry with the goal of leading the field toward achieving the post-2015 global targets [47].

Notes

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