TARGET PRODUCT PROFILE FOR NEXT-GENERATION DRUG-SUSCEPTIBILITY TESTING AT PERIPHERAL CENTRES

Stop TB Partnership
New Diagnostics Working Group

World Health Organization

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Contents

Abbreviations and acronyms

AMK	amikacin
BDQ	bedaquiline
BPaL	bedaquiline-, pretomanid- and linezolid-based regimen
CFZ	clofazimine
DLM	delamanid
DCS	D-cycloserine
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
EMB	ethambutol
FQ	fluoroquinolones
GDF	Global Drug Facility
HIV	human immunodeficiency virus
Hr-TB	isoniazid-resistant TB
INH	isoniazid
KAN	kanamycin
LFX	levofloxacin
LMIC	low- and middle-income countries
LPA	line probe assay
LZD	linezolid
MDR/RR-TB	multidrug-resistant or rifampicin-resistant tuberculosis
MDR-TB	multidrug-resistant tuberculosis
MXF	moxifloxacin
NDWG	New Diagnostics Working Group
NGS	next-generation sequencing
Pa	pretomanid
PPV	positive predictive value
pre-XDR TB	pre-extensively drug-resistant tuberculosis
PZA	pyrazinamide
RIF	rifampicin
RR-TB	rifampicin-resistant tuberculosis
R&D	research and development
TB	tuberculosis
TPP	target product profile
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Definitions

Drug-susceptibility testing (DST)[1] refers to in vitro testing using either phenotypic methods to determine susceptibility, or molecular techniques to detect resistance-conferring mutations to a particular medicine.

Rifampicin-susceptible, isoniazid-resistant tuberculosis (Hr-TB)[2] refers to *Mycobacterium tuberculosis* strains with resistance to isoniazid (INH) and susceptibility to rifampicin (RIF) confirmed in vitro.

Rifampicin-resistant tuberculosis (RR-TB)[2] is caused by *M. tuberculosis* strains that are resistant to RIF. These strains may be susceptible or resistant to INH (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines. In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB and are eligible for treatment with MDR-TB regimens.

Multidrug-resistant tuberculosis (MDR-TB)[2] is caused by *M. tuberculosis* strains that are resistant to at least RIF and INH.

Pre-extensively drug-resistant tuberculosis (pre-XDR-TB)[3] is caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone (FQ).

Extensively drug-resistant tuberculosis (XDR-TB)[3] is caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any FQ and at least one additional Group A drug.

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1 Implementing tuberculosis diagnostics: policy framework. (WHO/HTM/TB/2015.11). Geneva: World Health Organization. 2015 (https://apps.who.int/iris/bitstream/handle/10665/162712/9789241508612_eng.pdf?sequence=1&isAllowed=y).

2 WHO consolidated guidelines on drug-resistant tuberculosis: Module 4: treatment: drug-resistant tuberculosis treatment. Geneva: World Health Organization. 2020 (https://www.who.int/publications/i/item/9789240007048).

3 Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27–29 October 2020. Geneva: World Health Organization. 2021 (https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis).

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Executive summary

Drug-resistant tuberculosis (DR-TB) is a significant driver of antimicrobial resistance worldwide. The lack of comprehensive, fast and accessible diagnostic tools threatens the progress made in the global TB response over the past two decades. Although the TB diagnostic pipeline has significantly improved in recent years, challenges remain for TB testing and diagnosis; for example, some current tools have limited diagnostic utility for some patient populations, and others present logistic and operational hurdles that hamper their uptake.

In an effort to inform research and development (R&D) priorities for TB diagnostics, the World Health Organization (WHO) released its first high-priority target product profiles (TPPs) for new TB diagnostics in April 2014.[4] TPPs provide detailed technical specifications that are important to end-users (e.g. a test's required performance) and operational characteristics to inform product developers. Four TPPs were developed in 2014, including targets on next-generation drug-susceptibility testing (DST) at the peripheral level. These TPPs were primarily identified through a priority-setting exercise and Delphi consultations,[5] and were finalized through consensus after consultation with key stakeholders.

As the term initially set for the 2014 TPPs reached the 5-year mark, the pressing need to guide the development of new technologies further led the World Health Organization (WHO) Global TB Programme to embark on an update process. That process started with the revision of the TPP on DST at the peripheral level, with support from the New Diagnostics Working Group's (NDWG) Task Force on next-generation DST. This update responds to the global community's need to accelerate progress towards universal health coverage and focus on tools that could be accessible at lower levels of care, especially DST. Improved access to DST is an essential component to tackle inequities in TB services coverage, particularly in settings where DST is mainly available at the tertiary or referral level. Treatment of rifampicin-resistant TB (RR-TB) has changed dramatically over recent years, with shorter regimens using fluoroquinolones with new and repurposed anti-TB agents (e.g. bedaquiline, linezolid and clofazamine). These are now the core drugs in the new regimens to treat DR-TB, and they have led to improved patient outcomes and reduced treatment duration. However, the emergence of drug resistance threatens these successes, necessitating accurate and early detection of resistance beyond rifampicin resistance. Additionally, the landscape has changed owing to advances in the treatment of drug-susceptible TB with shorter regimens, and increasing recognition of the need to identify isoniazid-resistant TB (which remains largely under-detected). Both regimens use fluoroquinolones, which are currently second-line drugs; thus, there is an urgent need to prioritize R&D for the TPP for DST, to address new and existing gaps.

[4] High-priority target product profiles for new TB diagnostics: report of a consensus meeting, 28–29 April 2014, Geneva, Switzerland (WHO/HTM/TB/2014.18). Geneva: World Health Organization. 2014 (https://apps.who.int/iris/handle/10665/135617).

[5] The Delphi process involves surveying a panel of experts, to reach a group opinion or decision. After each of several rounds of surveys, responses are aggregated and shared with the panel.

New technologies such as next-generation sequencing (NGS) have moved from the research domain to clinical evaluations. NGS can provide rapid and comprehensive DST with nucleotide-level specificity, and therefore needs to be considered in future planning. Thus, the update of this TPP sought to:

- provide revised TPPs, adjusted to the current context and patient and population needs, and aligned with WHO's overall strategic priorities in its thirteenth General Programme of Work (2019–2023), including the triple billion targets, and the End TB Strategy (2016–2035); and
- inform TB diagnostic developers and product development partnerships of which target products have been revised and prioritized, the required performance of new diagnostic tools to help reach the milestones of the End TB Strategy, and the operational characteristics of such tools.

Although technical or performance improvements to DST platforms are important, a crucial element of this TPP is the expectation that next-generation DST technologies will be closer to the patient and suitable for implementation at the peripheral level, and will thus improve and expedite access to care.

Efforts in updating the TPP on next-generation DST brought together multidisciplinary experts and stakeholders who contributed to this work through participation in Delphi processes, surveys, public engagement and, in March 2021, a stakeholder consultation with almost 70 experts from 25 countries.

Multiple levels of engagement with stakeholders to revise and finalize this TPP resulted in the following changes:

- the priority for testing of anti-TB agents now includes resistance testing of fluoroquinolones and other group A agents such as bedaquiline;
- the target population is more inclusive, covering individuals of all ages who require drug resistance assessment;
- sample types have been revised to include other clinically relevant specimens for TB; and
- there are new considerations for time-to-result linked to treatment decisions.

In relation to the price of individual tests, there were multiple views and perceptions about to how much these tests could cost. The common ground was to support a pricing scheme that is evidence-based and allows wide access in low- and middle-income settings; the balance of potential trade-offs (with no compromise of test performance) was also considered.

There were revisions to and clarifications in the description and targets of the level of the health care system, performance characteristics (e.g. limit of detection, analytical specificity for TB detection, indeterminate results during DST and interfering substances) and specific operational characteristics.

WHO expects that these revisions will help to inform and guide stakeholders involved in developing and implementing DST, including TB diagnostics developers, product development partnerships, academics and other stakeholders.

1 Introduction

About 10 million individuals develop tuberculosis (TB) each year. Although the number of bacteriologically confirmed TB cases has increased, the diagnostic gap remains, with many cases being missed. For example, in 2019 alone, only 57% of pulmonary TB cases had bacteriological confirmation, and 61% of these underwent further testing to determine rifampicin (RIF) resistance *(1)*. Although progress is being made, there is still a long way to go to ensure that access to rapid molecular testing methods and drug susceptibility testing (DST) is a reality for all presumed TB cases.

Almost half a million people developed rifampicin-resistant TB (RR-TB) in 2019, and 78% of those cases were estimated to have developed multidrug-resistant TB (MDR-TB). To compound the problem, there are considerable gaps between the number of individuals tested for DR-TB, and those who are enrolled in treatment. In 2019, for example, only 38% of those estimated to have MDR-TB or RR-TB (MDR/RR-TB) were enrolled for treatment. Closing these gaps in the cascade of care requires a multifaceted approach that includes improving TB care and testing for drug resistance with increased accuracy and a faster turnaround time. Meeting the 2030 targets set in the United Nations Sustainable Development Goals and End TB strategy requires intensified research and innovation in the field of diagnostics and care, to rapidly identify those affected, detect drug resistance and provide appropriate treatment. DST is, therefore, crucial to ensure that TB patients receive appropriate anti-TB therapy. Doing so will help to decrease TB-related morbidity and mortality, and help to slow the spread and development of further drug resistance. There is an urgent need for new technologies and strategies to close diagnostic gaps, including for DR-TB.

1.1 Background

The incidence of TB globally is steadily declining year on year, but is still below the targets set in the End TB Strategy *(1)*. DR-TB continues to be an additional threat owing to delays in diagnosis and treatment that fuel onward transmission. The latest global TB report from the World Health Organization (WHO) indicates that samples from 61% of the 3.6 million bacteriologically confirmed pulmonary TB cases notified globally were tested for RIF resistance, up from 7% in 2012 *(1)*. This improvement illustrates remarkable progress, but also highlights substantial challenges and gaps in resistance detection, particularly for isoniazid (INH) resistance, which is largely undetected. An estimated 13% of all new TB cases are INH resistant whereas only 3% have RIF resistance. Innovations to produce novel diagnostic tools are needed to address current and emerging gaps.

WHO's TPPs are strategic reference documents that are intended to facilitate and expedite the development of products addressing the greatest and most urgent public health need. In the context of public health, a TPP emphasizes access, equity and affordability as integral parts of the innovation process. In an effort to inform research and development (R&D) priorities for TB diagnostics, WHO released its first high-priority TPPs for new TB diagnostics in April 2014 *(2)*.

The time frame of development for tests envisioned in the initial TPP was 5 years *(2)*. Hence, this updated TPP supersedes the earlier key assumptions and targets for DST for *Mycobacterium tuberculosis (2)* and is aimed at guiding the next 5 years and moving the field forward. As described below, the present update takes into account:

- the most recent developments on new drugs and regimens *(3)*;
- recommendations on the use of novel regimens;
- new technologies entering the TB diagnostic landscape *(4)*; and
- updated definitions for pre-extensively drug-resistant TB (pre-XDR) and XDR-TB *(5)*.

For drug-susceptible TB treatment, WHO has evaluated an alternative to the 6-month regimen using RIF, INH, pyrazinamide (PZA) and ethambutol (EMB); the alternative is a 4-month combination regimen that includes a fluoroquinolone (FQ) *(6)*.

RIF-susceptible, INH-resistant TB (Hr-TB), which is more common than MDR/RR-TB, is associated with poorer treatment outcomes *(7)*; however, Hr-TB goes largely undetected because of the lack of upfront detection of INH resistance. In addition, Hr-TB requires treatment with a FQ and there is thus an increasing need for upfront testing of resistance to RIF, INH and FQ *(8)*.

Treatment regimens for DR-TB have undergone substantial changes over the past 5 years, with the emergence of new medicines such as bedaquiline (BDQ) and pretonamid (Pa) and repurposed medicines such as linezolid (LZD) and clofazimine (CFZ) *(8)*. New regimens for DR-TB regimens use a standardized shorter approach or an individualized longer one. The common factor is a need for a test that detects both TB and resistance to relevant anti-TB agents, and that is used at the peripheral level of the health care system so that it can guide treatment decisions at that level based on DST profiles.

Two shorter standardized regimens for DR-TB are recommended by WHO:

- a regimen for MDR/RR-TB where the injectable agent has been replaced by BDQ (used for 6 months), in combination with levofloxacin (LFX)/moxifloxacin (MXF), ethionamide (ETO), EMB, high-dose INH, PZA and CFZ for 4 months in the intensive phase; and
- a 6-month regimen for pre-XDR-TB that includes the new anti-TB agent, Pa, which was also recommended by WHO in 2020 for use under operational research conditions, in combination with BDQ and LZD (BPaL regimen) *(8, 9)*.

Next-generation DST at the peripheral level will need to aid regimen selection; hence, this TPP was updated to guide R&D and address relevant emerging needs. Novel diagnostic tests to be used at peripheral sites should ideally test for resistance to RIF, INH, FQ (MFX & LFX) and BDQ, to enable selection of the most appropriate treatment regimen. The prioritization of testing for these drugs is based on an assessment of the importance of each anti-TB agent in currently recommended regimens.

Changes in the treatment domain have been paralleled by rapid new developments on the diagnostics technology front. The first molecular tests that WHO has recommended for the rapid detection of drug resistance were based on reverse hybridization technologies; they provided accurate DST but required specialized infrastructure and skills. Since then, real-time molecular tests have been developed that can detect resistance to RIF and now to other drugs (e.g. INH and FQs). These tests can produce results in a matter of hours, and

because they are largely automated they can provide testing capacity outside of centralized laboratory structures.

Molecular drug resistance determination ultimately depends on a knowledge base of the mutations associated with drug resistance and their relative frequency in populations. To address this, WHO has developed a catalogue of mutations and their association with resistance, by collating a large collection of isolate data with phenotypic DST and whole-genome sequencing results. The catalogue is aimed at developers and researchers, to allow new tests to be developed and ensure consistent and robust interpretation of mutations for sequencing technologies *(10)*.

Next-generation sequencing (NGS) methods are emerging that could provide comprehensive DST profiles covering multiple gene targets with nucleotide-level resistance information and be rapid enough to affect clinical decision-making. Several targeted NGS products are coming to market that can detect resistance to the new and repurposed drugs, filling a major gap. NGS technologies are of varying complexity and size, with some small enough to be handheld.

As these treatment and diagnostic changes have evolved, WHO has revised the definition for XDR-TB and introduced a new definition for pre-XDR-TB *(5)*. The revision was also driven by a change in the positioning of the second-line injectable agents, which are no longer considered core drugs for the treatment of DR-TB. Amikacin was relegated to a Group C drug, whereas kanamycin and capreomycin are no longer recommended for use following an evidence review. The new definition was also updated to prioritize the Group A drugs that are now recommended as core drugs. The revised definitions are:

- Pre-extensively drug-resistant TB (pre-XDR-TB) is caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any FQ.
- Extensively drug-resistant (XDR-TB) is caused by *M. tuberculosis* strains that fulfil the definition of MDR/RR-TB and are also resistant to any FQ and at least one additional Group A drug.

These changes further support the need for an update of the TPP, because of the strong requirement for rapid and accurate testing for Group A medicines and the relegation in priority of the injectable agents.

The prevalence of drug resistance in a population can vary owing to factors such as prior exposure, treatment practices in different regions and the frequency of primary or acquired drug resistance. A study in five countries showed that the population-based point prevalence of FQ resistance was 4.4% or lower in four countries but 11.1% in the fifth country *(11)*. In contrast, among people with RR-TB, the point prevalence of FQ resistance was even higher, at 12.3–30.7%. Prior treatment history is also an important factor; it is well recognized that the prevalence of resistance to RIF and INH is higher among previously treated individuals than among those without a prior treatment history. In addition, heteroresistance, which is uncommon for most drugs, is well described for FQs, and is therefore an important consideration for drug and diagnostic developers. Cross-resistance has also been observed; such resistance allows a single gene target to inform treatment modifying decisions to more than one drug. Thus, for instance, mutations in the *inhA* promoter region are associated with resistance to ETO and INH, whereas mutations in the *Rv0678* gene can lead to resistance to both BDQ and CFZ *(12, 13)*.

Another important consideration is the pre-existence of drug resistance to one or more drugs, because this can alter the likelihood of resistance to other drugs and affect test performance, depending on the population selected for testing. RIF, for example, is an indicator drug – if resistance to RIF is present, resistance against other anti-TB agents is more likely to be present. In a multicountry surveillance study, the point prevalence among cases with RR-TB was above 40% for PZA and above 65% for INH, but below 30% for FQs *(14).*

Several factors make it essential to adopt appropriate and specific implementation strategies for any given new assay developed. These factors are the diversity of resources and needs in different countries; the geographical variation in the epidemiology of TB and related comorbidities, and in DR-TB; and the specialized nature of the different technical procedures. Providing guidance for implementation strategies is beyond the scope of this document; however, the characteristics defined in the TPP should be regarded from the perspective of an implementation framework *(15).*

This document outlines current needs and provides direction for the development of a rapid DST that can be used at the peripheral level of the health care system (the rapid DST test). As with other TPPs, the updated targets for next-generation DST consider characteristics pertinent to the performance of a diagnostic tool and to the sustainability of envisioned technologies (e.g. feasibility, cost and cost–effectiveness).

1.2 Objective and target audience

The overall objective of this TPP is to align developers' performance and operational targets for a next-generation DST assay for use at peripheral level with the needs of users. The target audience comprises test developers and manufacturers interested in entering the TB diagnostic market, regulatory agencies, academia, research institutions, product development partnerships, nongovernmental organizations (NGOs), civil society organizations and donors.

1.3 Development of TPPs

Diagnostic manufacturers require TPPs at an early stage of the development process so that they can be informed of the targets, technical specifications and diagnostic performance of the products. These parameters are set by a series of processes among and consensus of stakeholders, keeping in mind the objective of the TPP and its feasibility and utility for the end-user. Each TPP has specific characteristics that refer to the measurable requirement or specification (e.g. diagnostic specificity, biosafety aspects, data interpretability and storage).

This document also provides both the "minimal" and the "optimal" outputs for each characteristic in the TPP (Table 1). The minimal requirements are the lowest acceptable output for that characteristic, and the optimal are the ideal, realistically achievable output for that characteristic. Products should meet all of the minimal characteristics and as many of the optimal characteristics as possible.

Table 1. TPP terminology

Terms[a]	Definitions
Characteristic	A specific requirement or specification that is measurable.
Minimal	For a specific characteristic, "minimal" refers to the lowest acceptable output for that characteristic. To be acceptable, solutions *must* meet the minimal characteristic. However, a test may still be acceptable if shortcomings pertain to soft targets and if specific hard targets (marked with an asterisk) are missed only marginally.
Optimal	For a specific characteristic, "optimal" provides the ideal output that is believed to be realistically achievable. Meeting the optimal characteristics will provide the greatest impact for the end-users, clinicians and patients. Developers would ideally design and develop their solutions to meet the optimal requirements for all characteristics.

TPP: target product profile.

[a] The optimal and minimal requirements and characteristics define a range.

2 Methodology

This update process has built on earlier activities conducted during the development of the first high-priority TPPs for new TB diagnostics *(2)* and further engagement with key stakeholders. In addition, the methodology used in this update allowed engagement with relevant audiences, including the product development audience, at different stages of the process, in line with WHO requirements for TPP development.

2.1 Delphi process

A draft TPP document was prepared to promote discussion between the different groups of stakeholders. The draft document and a Delphi-like survey (in April–May 2019) were shared with a wide range of stakeholders: technical agencies and researchers, funding organizations, reference TB laboratories, national TB programmes, implementers and clinicians, representatives from industry, and advocates for patients. They were also shared with a broader audience through general dissemination channels such as the website of the New Diagnostics Working Group (NDWG) and the Global Tuberculosis Network. Additional working groups invited to participate in the Delphi consultation included the Global Laboratory Initiative and the European Laboratory Initiative. Participants were ask to reply to 47 specific questions, expressing their level of agreement on the proposed characteristics according to a predefined Likert scale ranging from 1 to 5 (1 – disagree, 2 – mostly disagree, 3 – don't agree or disagree, 4 – mostly agree and 5 – fully agree). Individuals were asked to provide comments when they did not agree with a statement about a characteristic (i.e. scored it at 1, 2 or 3). The Delphi process used is detailed in a report from the NDWG *(16)*.

Overall, the outcomes of the stakeholder process showed a high level of agreement for 89% of the TPP components explored *(16)*. No agreement on either the minimal or optimal requirements was reached for the following characteristics: priority of anti-TB agents for testing, price of the individual test, capital costs for the instrument, limit of detection of minor variants and indeterminate results during detection.

2.2 Public comment

A proposed revised version of the 2014 TPP on next-generation DST *(2)*, which followed changes made after the Delphi consultation, was shared online for public comment on any of the characteristics in the TPP document. The intended audience included TB programme managers, laboratory specialists, clinical practitioners, implementers, researchers, civil society organizations, industry and patient advocates. Comments were analysed quantitatively and grouped into themes when possible. Results of this public comment process are provided in Annex *2*.

2.3 Stakeholder consultation

Feedback from the public comment process was presented at a stakeholder consultation, which was conducted remotely over four sessions during March 2021. Almost 70 stakeholders from 25 countries attended the sessions, and they included participants from technical agencies and funding agencies, as well as researchers, implementers and policy-makers (see Annex 1). During the consultation, the stakeholders discussed each characteristic included in the TPP, and incorporated the feedback from the public comment to promote information sharing, exchange of views or clarification.

Changes and suggestions made during the stakeholder consultation were incorporated into the final TPP presented in Section 3, below.

3 TPP: next-generation DST at peripheral centres

Table 3.1. TPP for next-generation DST at peripheral centres

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Scope				
Key assumptions	The development **time is <5 years**; this approach would use **1 solution** for TB detection and DST; this TPP has taken the developers' perspective by assuming that new TB medicines and regimens will be implemented and available in parallel with current standard-of-care regimens, at least initially			
Rationale	To provide support for timely and **effective anti-TB therapy** in the context of the roll-out of new TB medicines and regimens; and to provide the characteristics and qualities of a test that would have a sufficiently rapid turnaround time for TB detection and would provide data about DST that can be used to inform treatment decisions			
Goal	Diagnosis of TB disease and detection of drug resistance to provide rapid triage of patients and identification of adequate treatment regimen (first-line treatment versus second-line treatment)	Diagnosis of TB disease and detection of drug resistance to inform decision-making about the optimal (individualized) regimen	The market for a test that includes TB detection and DST is all people with presumptive TB, which is approximately 10 times the number of detected cases, or about 60–70 million patients. If DST were performed in a second step, the market would be all patients in whom bacteriologically confirmed TB had been detected (about 7 million). The market for a test to detect BDQ resistance is different because the current achievable performance characteristics of a molecular test for BDQ resistance are still uncertain. Furthermore, BDQ is currently recommended for use in MDR/RR-TB patients only; therefore, a test for BDQ resistance could be used as a follow-on test only if RIF resistance has been confirmed (because a higher prevalence of resistance leads to a higher PPV for the detection of resistance to a particular anti-TB agent). This means that the market for testing for BDQ resistance is as large as the number of patients confirmed to have MDR/RR-TB, which was about 206 000, although the estimated number is much larger, corresponding to an estimated 465 000 MDR/RR-TB incident cases in 2019.	

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Priority of anti-TB agents for testing[a]	RIF + INH+ FQ + BDQ (see information on BDQ in the explanatory notes) (FQ always includes LFX and MFX)	In order of decreasing importance: Minimal + 1. PZA + LZD + Pa/DLM + CFZ 2. AMK + DCS 3. Any additional drug listed in the WHO treatment guidelines	Drug prioritization considers universal access to DST (END TB Strategy) and that effective administration of anti-TB drugs can be achieved only by knowing susceptibility testing results. This is a general principle that is becoming crucial, especially for the treatment of DR-TB. The proposed prioritization for minimal requirements considered: (i) Impacts of undetected RIF and INH resistance on patient outcomes. (ii) FQs are relevant for both first-line and second-line treatment regimens and resistance to these drugs is central to the updated pre-XDR and XDR definitions. (iii) BDQ is now one of the medicines that define XDR-TB, a Group A medicine that is included in all DR-TB regimens including the current shorter MDR/RR-TB regimen. New tests should inform decision-making for shorter and novel MDR regimens. The differentiation of resistance among FQs is more a function of interpreting mutations (i.e. evaluating the hierarchical structure of mutations) than of detecting different mutations. **BDQ** is a high priority drug, but it is recognized that relevant mutations associated with resistance are currently not fully elucidated. This is expected to change in the coming years. Furthermore, the feasibility of conducting DST for this medicine at the peripheral level may require alternative technological approaches compared with those used for other drugs (e.g. RIF). The optimal requirements are aimed to be aligned with the new WHO guidelines and to consider cross-resistance of certain drugs (e.g. BDQ and CFZ). **Sequence of TB detection and drug resistance testing:** The proportion of patients diagnosed with TB who experienced pretreatment loss to follow-up is in the range of 4% to 38%. This scenario might vary substantially among countries. Initially, testing for TB and DST might come at the expense of the sensitivity for TB detection, depending on the platform used and cost of the test. However, a delay in DST might result in patients receiving	*(5,6,8)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
			inappropriate treatment until they return. In the interim, disease transmission may have occurred. The acceptability of a longer wait time might vary among countries, and informing the patient of results on the same day if the result is not available during the first visit might be associated with substantial costs.	
Assay design	The assay should be designed in such a manner that the addition or removal of analytes does not require extensive analytical and clinical reverification and revalidation of the assay		The assay should be designed to be capable of being modified or upgraded as needed, with minimal redevelopment required. For sequencing-based assays, this should include the possibility to adjust sequence interpretation for new drugs. This is not a regulatory requirement; rather, it refers to the adaptability of the assay for updating and adding newer analytes.	
Target population	People of all ages in need of evaluation for TB and those requiring drug resistance assessment		Children aged <11 years have limited ability to produce sputum for testing; therefore, initial validation studies should focus on adults and adolescents.	
Target user of test[a]	Health care workers with minimal or moderate training	Health care workers with minimal training necessary	Minimal training: users are health care workers with limited or no competency in general laboratory practice (beginner users). Moderate training: users are health care workers with minimal or moderate competency in general laboratory practice (competent or proficient users). *Competency guidelines for public health laboratory professionals* was used to provide a term of reference *(17)*	*(1,18)*
Setting (level of the health care system)	Peripheral level of the health care system	Point-of-care	Implementation at the peripheral level should be feasible using the specifications outlined. This would embed the test in an infrastructure that is based around smear microscopy. However, the test could be implemented at higher levels of care as well. Testing for resistance to the anti-TB agents included in second-line therapy could be incorporated into separate reactions, but ideally it would be feasible to test the same specimen. For optimal requirements, it is suggested that the test be at point-of-care, with immediate accessibility for patients (e.g. bedside availability for any patient).	*(18–21)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Pricing				
Price of individual test, applicable to all public programmes, NGOs, international organizations in LMIC **(Includes the cost of reagents and consumables only, after scale-up, ex-works; excludes shipping and price subsidies. Ceiling price)**[a]	RIF + INH + FQ: US$ 10–15 Adding BDQ (price not defined, see Explanatory notes)	a) RIF + INH + FQ: maximum US$ 5 b) PZA + LZD + Pa/DLM + CFZ (price not defined, see Explanatory note) c) AMK + DCS: (price not defined, see Explanatory note)	The right to health contains entitlements that embrace access to basic health services; in turn, this includes early access to TB diagnostic tools and detection of drug resistance. The price of a test affects access and requires due consideration. Cost–effectiveness analyses should ideally be performed because these results provide a framework to compare the costs and benefits of a product against relevant comparators, including current practice. Ultimately, cost–effectiveness analysis considers whether a product demonstrates value for money; thus, it is more meaningful than a price point alone. However, a cost-effective product may be unaffordable, especially in high-burden, low- and middle-income settings, so providing an indicative price is helpful. A price range is provided for the minimal requirement with DST for RIF, INH and FQ, but these ranges are indicative not absolute. Ideally, the price of tests should be based on evidence of the actual cost of goods and estimated volumes, and a reasonable profit margin. Currently, the price of a single Xpert XDR-TB assay (for INH, FQ, second-line injectables and ethionamide) is about US$ 20. This test was originally aimed at MDR/RR-TB patients, but expanding this to all TB patients or all presumptive TB cases would substantially increase the market. A price that is higher than available technologies would be justified only if it is evidence-based and the new test brings substantial added value in terms of greatly improved performance, greater suitability for decentralization, clinical utility (i.e. affects decision-making) and the number of anti-TB agents for which resistance can be detected. The **addition of BDQ-resistance detection** to the test would require special consideration because new types of technologies may be needed and the molecular basis of resistance has not been fully elucidated; thus, an indicative price could not be determined at this time. Furthermore, a price range for tests covering the "optimal" list of prioritized drugs could also not be provided because: • the price might vary depending on the number of drugs considered; and • there are no data for predicting what the cost of assays testing for new drugs such as DLM, LZD and CFZ would be.	*(22–28)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
			The cost of phenotypic DST for first-line and second-line drugs is estimated to be in the range of US$ 50–100 (±30%). A new test should ideally be priced lower based on evidence of the cost of goods and estimated volumes, and a reasonable profit; a price within the same range or higher would need to be evidence-based and could be justified through a cost-effectiveness analysis. Ensuring access to tests while maintaining business interests can be achieved through fair pricing, which requires transparency of the cost of goods and estimated volumes, with a reasonable profit margin.	
Capital costs for the instrument (Ceiling prices)	Less than US$ 20 000 (including warranties, service contracts and technical support – at least for 3 years)	Less than US$ 5000 (including warranties, service contracts and technical support – at least for 3 years)	The lower the capital costs of the instrument are, the lower the initial cost would be, and thus the barrier to implementation would also be lower, particularly since the volume of instruments that would be distributed to peripheral centres is sizeable. The cost of the instrument should be evidence-based and should also include warranties, service contracts and technical support. Cost–effectiveness should be then evaluated during implementation according to the number of drugs and targets that a given technology can cover, the assay multiplexing and the multipurpose options offered. Additionally, test developers and manufacturers could consider offering different acquisition models, such as a reagent rental or a cost-per-result model. The reagent rental agreement would allow for countries or end-users to purchase the test at a set cost per test, including the machine, service, maintenance and technical support (with price depending on volume of tests, including tests for different indications on multiplexing instruments); whereas the cost-per-result model includes the above plus any tests that do not provide an actionable result (e.g. invalid tests).	

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Performance				
Diagnostic sensitivity for TB detection[a]	Sensitivity should be >80% for a single test when compared with 2 liquid cultures; for smear-negative TB it should be >60% and for smear-positive TB it should be 99%	Sensitivity for detecting TB should be >95% for a single test when compared with 2 liquid cultures; for smear-negative TB it should be >68% and for smear-positive TB it should be 99%	The sensitivity specified considers the currently available technologies as baseline.	*(29)*
Diagnostic specificity for TB detection[a]	Specificity should be >98% for a single test when compared with culture	Specificity should be >98% for a single test when compared with culture		*(30–32)*
Limit of detection –for DST	≤10^4 CFU/mL of sputum (or clinically relevant specimens)	≤10^2 CFU/mL of sputum (or clinically relevant specimens)	As a point of reference for CFU/mL, the corresponding smear status for the minimal requirement is a 1+ smear-positive specimen and for the optimal requirement is a smear-negative but TB-positive specimen (paucibacillary specimens). Limit of detection testing should be performed, as outlined in the US FDA's guidance document. For RIF, INH and FQ, smear-negative samples should also be detected as a minimum because current tests already achieve this.	*(33,34)*
Analytical sensitivity for DST compared with genetic sequencing as the reference standard[a]	Sensitivity should be >98% for detecting targeted SNPs for resistance when compared with genetic sequencing		For NGS technology-based assays: currently, there are no clear guidelines on the reference standard for an NGS-based diagnostic assay. In general, validating NGS results using different platforms plus different analysis pipelines is considered appropriate.	*(30–32)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Diagnostic sensitivity for DST compared with phenotypic DST as a reference standard[a]	RIF: >95% sensitivity for detection of phenotypic resistance; INH, FQ: >90% sensitivity for detection of phenotypic resistance; BDQ, LZD, CFZ, DLM, pretomanid, AMK, PZA: ≥80% sensitivity for detection of phenotypic resistance	RIF, INH, FQ, BDQ, LZD, CFZ, DLM, pretomanid, AMK, PZA: >95% sensitivity for detection of phenotypic resistance	Modelling data suggest that for rapid DST to be more cost-effective than culture, on a currently available platform it must attain an aggregated sensitivity of 88% for all clinically relevant mutations. A lower sensitivity could be tolerated for a test with high specificity, particularly if the prevalence, and thus the pretest probability, is high. The sensitivity achieved against a phenotypic internationally recognized reference standard (e.g. WHO, Clinical Laboratory Improvement Amendment) will be only as good as the mutations that are targeted (i.e. even if all known mutations conferring INH resistance are detected with 100% sensitivity when compared with a sequencing reference standard, 100% sensitivity cannot be achieved against a phenotypic reference standard because the knowledge of all molecular targets that confer resistance is incomplete). Frequency of mutations at different drug-resistant loci may vary depending on various factors (e.g. geographical region, local epidemiology and outbreaks); thus, implementation of molecular assays should carefully consider the local epidemiology in order to achieve the required sensitivity.	*(30–32)*
Analytical specificity for DST compared with genetic sequencing as the reference standard[a]	Specificity should be ≥98% for any anti-TB agent for which the test is able to identify resistance when compared with genetic sequencing as the reference standard		If alternative regimens are available, effective, safe and not too cumbersome, then a lower PPV might be tolerated. Because the pretest probability is low when individuals presenting without any additional risk factors are tested in settings with a low prevalence of resistance, the specificity must be very high. For example, if the prevalence of resistance is about 3% according to surveillance data, then a specificity of 99% results in a PPV of only 74%. A very high specificity (e.g. ≥99.7%) is thus necessary to reach a PPV of >90%. If the prevalence of resistance is ≥20% (e.g. when resistance to RIF is used as an indicator or when testing is only done in high-risk patients), a specificity of >97% is sufficient to achieve a PPV of 90%. Some mutations conferring resistance are systematically missed by current phenotypic reference standard methods, and some mutations are not associated with phenotypic resistance *(35)*.	*(36,37)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Diagnostic specificity for DST compared with phenotypic DST as a reference standard[a]	Specificity for mutations included for any anti-TB agent for which the test can identify resistance should be ≥98% when compared with the phenotypic reference standard recommended for each anti-TB agent		The estimates of specificity for molecular tests in comparison with phenotypic testing as a reference standard might be falsely low because the reference standard has limited sensitivity. Therefore, it is important to use the optimized quality-assured phenotypic reference standard for a drug in comparison. Some mutations conferring resistance are systematically missed by current phenotypic reference standard methods, and some mutations are not associated with phenotypic resistance *(35)*.	*(30–32)*
Limit of detection of minor variants	≤20% (i.e. 20 resistant bacteria out of 100)	≤3% (i.e. fewer than 3 resistant bacteria out of 100)	This parameter is highly dependent on the bacillary load. Clinical relevance of minor variants is not fully understood yet.	
Analytical specificity for TB detection	No cross-reactivity with other organisms including nontuberculous mycobacteria.			
Indeterminate results during DST[a]	<10%	<3%	Indeterminate: inconclusive results that are valid – that is, where an adequate test result has been obtained, but the result is not clearly positive or negative. Invalid: inconclusive results that are invalid – that is, the key diagnostic feature cannot be interpreted or the actual result is missing.	
Reproducibility for DST	Inter-assay coefficient of variance should be ≤10% at the high and low extremes of the assay for DST		This applies if the quantitative outcomes of a test are measurable (e.g. limit of detection and cycle threshold values).	
Interfering substances	No interference should be caused by those substances known to occur in the human respiratory and pulmonary tracts, including blood that could potentially inhibit an assay (e.g. a PCR reaction), and substances used to treat or alleviate respiratory disease or symptoms	No interference should be caused by different material for collecting swab-based and alternative paediatric specimens (e.g. stool)		

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Treatment monitoring capability	Not required	Preferable	A test that can replace smear microscopy for treatment monitoring (e.g. by detecting viable bacteria) is more likely to be adopted and to completely replace smear microscopy; thus, it would also have a larger market.	
Multiuse platform	Yes (achievable)	Yes (demonstrated)	Any technology entering this market should be able to diagnose relevant diseases other than TB. The diseases to be targeted should be those among the WHO list of poverty-related diseases; for example, communicable diseases such as SARS-CoV2, HIV, malaria, hepatitis C virus infection and antimicrobial resistance activities (i.e. priority pathogens). Of course, proper implementation strategies should be in place to select which additional diseases should be targeted along with TB in any given setting. Quality-assurance procedures would need to be performed for each disease included in the platform; thus, multiplex testing or the ability to use a platform to perform different tests will probably increase the acceptability of the new assay.	
Operational characteristics				
Sample type	Sputum and other clinically relevant specimens for TB, including (but not limited to) gastric aspirate, induced sputum, nasopharyngeal aspirate, and stool.	Unprocessed sputum and additional clinically relevant specimens for TB or other targeted diseases (see "Multiuse platform")	Additional clinically relevant specimens for TB could be alternative sample types that can easily be collected (especially for categories of patients where sputum is difficult to obtain), and specimens for extrapulmonary TB. There should be minimal specimen processing involved, if required.	
Sample volume processed by the test	0.5–2 mL	0.1–10 mL	The lowest volume possible for all types of samples ideally would be 0.1 mL, especially since HIV-positive patients and paediatric populations may have difficulty providing a sample. Similarly, if a higher volume is available, the test should be able to use that higher volume if doing so would increase sensitivity. This is especially relevant for extrapulmonary samples, which may need an additional	

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
			concentration step before testing. **However, in both high and low volume specimens, performance should not come at the expense of decreased sensitivity.** At a minimum, the test should be able to meet performance requirements with clinically relevant specimens with volumes of 0.5–2 mL, as used by current tests. The test should need only 1 sample. Any follow-on steps or reactions should not require additional samples.	
Manual preparation of samples (steps needed after obtaining sample)[a]	≤5 steps	≤1 step	There should be no need for precise volume control and precise timing. Only tests that require basic and simple laboratory skills are suited to peripheral level centres; no specific analytical procedures based on additional instruments should be required (e.g. DNA quantification, gel electrophoresis and serial dilutions). The procedure should take advantage of automation as much as possible.	*(18,21)*
Reagent integration	No specific indications, but refer to reagent kit storage and stability for restrictions	All reagents should be contained in a single device		
Time to result[a]	<6 hours for detection and DST; achieve next-day treatment decisions	<30 minutes for detection and DST (<2 hours acceptable); achieve same-day treatment decisions	The need for rapid turnaround is affected by throughput capacity and duration of testing. Rapid turnaround time is critical to reducing pretreatment loss to follow-up. A similar outcome can be achieved in different ways; for example, through matching of multiple samples for the same tests, multiple samples for different tests or using random access for testing. The time-to-result (defined as time for sample processing through test completion, excluding storing time for batching) is probably the most important parameter because extending the wait time for too long may result in patient loss to follow-up. The minimal criterion has been increased, considering newer technologies such as NGS that are currently unable to meet the previous criterion of <2 hours but would provide DST to multiple drugs simultaneously. In coming years, all technologies should be able to produce test results in <6 hours, which is critical because peripheral settings usually keep 6–8 hour work days. Finally, as patients are unlikely to wait longer than 30 minutes for a test result, any wait longer than that will typically necessitate results being delivered the following day.	*(38,39)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Daily throughput	≥10 tests	≥25tests	The daily throughput needed in most peripheral centres is <10 tests per day. Daily throughput requirements must be considered with time-to-result and sample capacity in mind, because these characteristics are all highly interrelated.	
Sample capacity and throughput	Batching should be possible	Multiple samples should be able to be tested at the same time; random access should be possible	Ideally, 1 sample should not occupy the instrument without that instrument still being able to process other samples (i.e. random access or parallel analyses should be possible). If the platform is multiplexed, then running different assays at the same time should be feasible.	
Walk-away operation	No more than 1 step of operator intervention should be needed once the sample has been placed into or on the system	There should not be a need for operator intervention once the sample has been placed into or on the instrument	Once the sample has been loaded into an instrument, then further operator intervention should not be required until detection has occurred. This characteristic is related to the characteristics for sample preparation and assay processing (i.e. the steps needing to be completed after a sample has been obtained).	
Biosafety	Requirements are similar to those for smear microscopy (low-risk TB laboratories)		To be feasible to implement at the peripheral level, minimal infrastructure for biosafety should be required. Biosafety cabinets are unlikely to be available. The technology must pose a low safety risk (comparable to that of microscopy) to health workers and others within the facility. Consult the minimum biosafety requirements as described in WHO's *Tuberculosis laboratory biosafety manual (40)*.	*(41,42)*
Waste disposal – solid	Should require no more than current WHO-endorsed TB assays at the peripheral level	Should require no more than current rapid molecular tests for TB Reusable, recyclable, or non-plastic alternatives to disposable materials	Further information is provided in WHO's *Tuberculosis laboratory biosafety manual (40)*. Increasing the amount of waste generated in comparison to that produced by smear microscopy should ideally be avoided. Environmentally friendly, sustainable packaging minimizing the environmental impact of packaging should be considered for the product's entire lifecycle.	*(40)*
Waste disposal – infectious	Similar to those for smear microscopy (low-risk TB laboratories)		Low-risk TB laboratories as described in WHO's *Tuberculosis laboratory biosafety manual (40)*. The baseline biosafety risk for managing infectious waste at the peripheral level should not be increased.	*(40)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Instrument	For instrument-based tests, build on a modular concept allowing tailoring to meet needs and upgrade additional functionalities at any time	For instrument-based tests, this ideally would be a single integrated system that is modular to allow throughput to be increased if necessary	This characteristic only applies to instrument-based tests. It is *not* a recommendation that a test be instrument-based. Ideally, a single device is preferred but modular solutions would be acceptable (e.g. for separate sample processing and detection).	
Power requirements[a]	Capable of running on standard electricity plus an ad hoc certified UPS unit delivered with the system to enable a cycle to be completed in case of a power outage; a circuit protector must be integrated within the system; the UPS should be integrated within the system where possible; and the system should be compatible for switching to a battery-operated device with the ability to run for at least 1 day on the battery and to be recharged	Capable of running on standard electricity plus an ad hoc certified UPS unit delivered with the system to enable a cycle to be completed in case of a power outage; the UPS and circuit protector must be integrated within the system; and the system should be compatible for switching to a battery-operated device with the ability to run for 1 day on the battery and to be recharged (e.g. solar-powered)	Continuous power is not always available at the level of a peripheral centre, and current experience with the use of electrical devices in settings where power supply can be intermittent showed challenges in finding appropriate UPS solutions suitable for a given instrument. UPS should come together with the instrument, and manufacturers must provide UPS capable of meeting the goal of ensuring enough power for a cycle to be completed. Also, in the optimal situation, it should be possible to switch the system into a battery-operated device that can be recharged, possibly using solar power (or another renewable source of energy where applicable).	*(18,21)*
Maintenance and calibration[a]	Preventive maintenance should not be needed more than once a year Users should be able to monitor the machine status independently from manufacturers' intervention by using appropriate internal	Preventive maintenance should not be needed more than once every 2 years Users should be able to monitor the machine status independently from manufacturers' intervention by using appropriate internal or external controls; results	Maintenance and calibration represent two challenging points for any device to be placed at the peripheral level. A maintenance alert is necessary to ensure proper functioning in settings where it is unlikely that the same person will always handle the device and that records will be kept about the duration of use. It is essential that only simple tools and minimal expertise are necessary to perform maintenance, given the number of devices that are likely to be used; additionally, service visits are unlikely to be	

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
	or external controls; results for such controls can be shared with manufacturers or appropriate control bodies to schedule appropriate on-demand intervention (maintenance or calibration); an alert should be included to indicate when maintenance is needed according to manufacturer's indications; software updates should be provided remotely	for such controls can be shared with manufacturers or appropriate control bodies to schedule appropriate on-demand intervention (maintenance or calibration); an alert should be included to indicate when maintenance is needed according to manufacturer's indications; software updates should be provided remotely	feasible outside of urban settings. The cost of maintenance should be low and service agreements should be included in the cost.	
Data analysis	Exported data should be analysable on a separate or networked PC	Data analysis should be integrated into the device; a PC should not be required; exported data should be capable of being analysed on a separate or networked PC		
Result documentation, data display	An integrated results screen and the ability to save results should be included; the device should have a have a commonly-used interface port (e.g USB or USB-c port)	An integrated results screen and the ability to save and print results should be included; the device should have a commonly-used port (e.g USB or USB-c port)	Results should be simple to interpret (e.g. positive versus negative for TB detection, or present versus absent for drug resistance). Information that would allow a more detailed interpretation of results should be available (e.g. information on the mutations detected) for surveillance purposes or more differentiated clinical decision-making; however, it should be possible to hide this information if necessary.	

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Regulatory requirements	Manufacturing of the assay and system should comply with ISO13485 as well as ISO 14971 or higher standards or regulations, and comply with ISO IEC 62304 (Medical Device Data Systems); the manufacturing facility should be assessed at a high-risk classification and certified for use by one of the regulatory authorities of the founding members of the International Medical Device Regulators Forum (formerly known as Global Harmonization Task Force); the assay must be registered for in vitro diagnostic use			*(43,44)*
Data export (connectivity and inter-operability)	Integrated ability for all data to be securely exported from the device in a user-friendly format (including data on use of the device, error rates or rates of invalid tests, and non-personalized results) over a USB port; Bluetooth connectivity should also be available, and it should be possible to import data (e.g. software for updating interpretation rules or databases)	All data should be able to be securely exported (including data on the use of the device, error rates and rates of invalid tests, and personalized, protected results) over a USB port and network; network connectivity should be available through an ethernet, wi-fi and GSM/UMTS mobile broadband modem, or a combination of these; results should be encoded using a documented standard (e.g. HL7) and be formatted as JSON text; JSON data	Mobile phone capacity is frequently available even at the level of peripheral centres. This could be leveraged for data export, quality control, supply-chain management and surveillance. As the systems will be implemented in peripheral centres, data connectivity should be adapted to the actual situation (data transfer cannot rely on high-speed Internet connectivity, and the format of the data should be adapted accordingly). Data export must include raw data and interpreted results, allowing further re-analysis in case of updated interpretation guidelines. Connectivity solutions associated with instruments should be nonproprietary, so that external solutions can be incorporated; where cloud-based storage solutions (or third-party hosting) are included, they should be compliant with country regulations and must be able to be turned off without affecting instrument functionality.	*(41,45,46)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
		should be transmitted through HTTP(S) to a local or remote server as results are generated; results should be stored locally and queued during network interruptions to be sent as a batch when connectivity is restored; Bluetooth connectivity should also be available; and it should be possible to import data (e.g. software for updating interpretation rules databases)		
Electronics and software	Should be integrated into the instrument		If an external device (e.g. a separate PC, tablet or mobile) is needed, it will probably limit the ability to update software, because not all peripheral centres have staff with the skills needed to operate a PC. Furthermore, theft or misplacement can be an issue, and separate PCs should have a mechanism for secure placement.	
Operating environment, temperature and humidity level	Between +5 °C and +40 °C with up to 70% humidity. It is important to adequately protect optics from dust in these settings	Between +5 °C and +50 °C with up to 90% humidity	High environmental temperatures and high humidity are often present in countries where TB is endemic. Tropicalized instruments or devices should be available for implementation in such settings.	*(41,47)*
Reagent kit – transport	No cold chain required; should be able to tolerate stress during transport for at least 72 hours at –15 °C to +40 °C	No cold chain should be required; should be able to tolerate stress during transport for at least 72 hours at –15 °C to +50 °C	Refrigerated transport is costly and often cannot be guaranteed for the entire transportation process. Frequent delays in transport are commonplace.	*(18,21,48)*

Characteristic	Minimal requirements	Optimal requirements	Explanatory notes	References
Reagent kit – storage and stability	12 months at +5 °C to +35 °C with up to 70% humidity; should be able to tolerate stress during transport for at least 72 hours at +40 °C; no cold chain should be required	2 years at +5 °C to +40 °C with up to 90% humidity; should be able to tolerate stress during transport for at least 72 hours at +50 °C; no cold chain should be required	High environmental temperatures and high humidity are often present in countries where TB is endemic; they are especially problematic during the transport of reagents and systems. For new products, 12 months is acceptable, because evidence to support a longer shelf life will be unavailable initially.	*(41,47)*
Additional supplies (not included in kit)	None	None		
Internal quality control	Full controls for sample processing, amplification and detection of TB and any target for detection of resistance should be included; internal controls for analysis and reporting (e.g. software version) should be included; a monitor (remote) system for checking results on the controls should be also considered		The system should be compliant with external controls.	*(47,49)*
Training and education	3 days (or 24 work hours) for staff at the level of a laboratory technician	6 work hours for staff at the level of a microscopy technician	Training should be developed according to continuing education and training models and individualized training programmes, to ensure that only properly trained, accredited people can perform the assay. Online and remote support systems should be available for retraining, monitoring or evaluating, and updating ("refresher") training. All the phases of the training should be properly documented. All training and instructions for use must be fully available at least in English, and ideally in multiple other languages as well.	

AMK: amikacin; BDQ: bedaquiline; CFU: colony forming unit; CFZ: clofazimine; DCS: D-cycloserine; DLM: delamanid; DNA: deoxyribonucleic acid; DR-TB: drug-resistant TB; DST: drug susceptibility testing; FDA: Food and Drug Administration; FQ: fluoroquinolones; GSM: Global System for Mobile Communications; HIV: human immunodeficiency virus; http: hypertext transfer protocol; INH: isoniazid; JSON: JavaScript Object Notation; LFX: levofloxacin; LMIC: low- and middle-income countries; LZD: linezolid; MDR/RR-TB: multidrug-resistant or rifampicin-resistant TB; MFX: moxifloxacin; NGO: nongovernmental organization; NGS: next-generation sequencing; PC: personal computer; Pa: pretomanid; PCR: polymerase chain reaction; PPV: positive predictive value; PZA: pyrazinamide; RIF: rifampicin; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; SNP: single nucleotide polymorphism; TB: tuberculosis; TPP: target product profile; UMTS: Universal Mobile Telecommunication System; UPS: uninterrupted power supply; US: United States; WHO: World Health Organization; XDR-TB: extensively drug-resistant TB.

[a] These characteristics were considered to be the most important.

4 Conclusion

In recent years, there have been advances in the TB diagnostic pipeline and DST for *M. tuberculosis*. However, important gaps remain, requiring improvements to existing technologies or development of new technologies that can be used closer to the level of patient care, are priced affordably for LMICs and can provide an accurate, rapid and comprehensive DST solution. Furthermore, as new anti-TB medicines and regimens are developed, DST is playing a critical role in guiding the allocation of patients into specific regimens, and is thus improving treatment outcomes and preventing the amplification of drug-resistance patterns.

In an ideal scenario, tests for detecting drug resistance would meet all the defined needs; however, achieving such a level of alignment across multiple stakeholders and end-users is unrealistic. The update of this TPP is intended to guide test developers in identifying important test features and characteristics, and aligning these with patient and programmatic needs at the country level. Although it is expected that next-generation DST would meet all of the required minimum criteria, and as many of the optimal requirements as possible, potential trade-offs may be required; thus, the criteria are indicative rather than absolute.

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Annexes

Annex 1: List of participants to the stakeholder consultation

Stakeholder consultation on target product profile for next-generation drug-susceptibility testing at peripheral centres

10–12 & 30 March 2021

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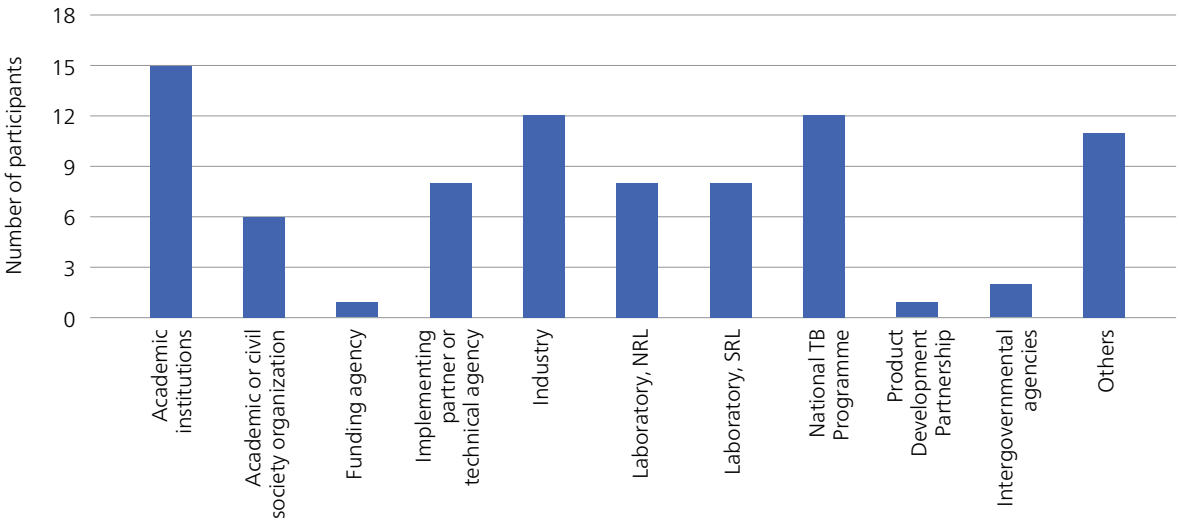
Annex 2: Overview of results of the WHO public comment process

To finalize the revised target product profile (TPP) document, in January 2021, the World Health Organization (WHO) launched an online public comment process to obtain feedback from a large array of stakeholders. The process aimed to ensure that proposed changes were objective and balanced, in terms of the needs and values of patients and other end-users, and of industry.

Through this process, stakeholders were invited to comment and share their views on the scope, target users or use setting, pricing, test performance and operational characteristics. Stakeholders were also invited to provide additional comments and questions on the proposed, updated TPP. A total of 128 individuals accessed the call for public comment and 82 agreed to participate. Fig. A1 provides an overview of the sectors represented by participants.

Fig. A1 Distribution of responses by sector (*n*=82)



NRL: national reference laboratory; SRL: supranational reference laboratory; TB: tuberculosis.

Summary of comments

Overall, the survey comments did not differ widely from the proposed TPP, and most were relatively minor. For a few specific areas in the TPP, divergent views were expressed by multiple respondents; these areas were as follows:

- giving higher priority to new drugs, particularly pyrazinamide (PZA), because the TPP is meant to provide guidance for the coming 5 years;
- expanding the target population to include children, using paediatric-friendly samples such as stool if needed; and
- lowering pricing criteria to levels that are more realistic for low-income countries (LICs).

Finally, there were some specific comments on diagnostic performance that also require attention.

Major comments

Priority of anti-TB agents for testing (Scope)

Five respondents stated that PZA must be assigned higher importance, given its role in many regimens, including for people living with HIV (PLHIV). One respondent stated that the "optimal requirements" (optimal) first level should also include bedaquiline (BDQ), linezolid (LZD), clofazimine (CFZ) and PZA. Two respondents stated that pretomanid (Pa) should replace CFZ on the optimal second level, whereas three respondents said it should be added. One respondent suggested including delamanid (DLM) with BDQ, LZD and CFZ on the optimal second level, given its role in shortened paediatric regimens; another suggested adding D-cycloserine to the optimal third level. For the "minimal requirements" (minimal), one respondent stated that first level should include fluoroquinolones (FQ), four respondents stated that BDQ ± LZD should replace amikacin (AMK) on the third level, and one stated that BDQ, CFZ ± LZD must be included.

Target population and sample type (scope)

Four respondents stated that the target population must be expanded to include children, noting that stool works well as a sample. Five respondents suggested that stool and other WHO-recommended extrapulmonary samples be included and mentioned in explanatory notes.

Pricing and costs for individual tests and instrument (pricing)

Individual test pricing was thought to be too high for low- and middle-income countries (LMIC) by six respondents from India, Japan, Netherlands and the United States of America (USA), representing academia, advocacy, implementing partners and industry. Pricing should be based on cost of goods sold and volume, not on ability to pay or value (two respondents from academia and advocacy). Suggested minimal prices for rifampicin (RIF) and isoniazid (INH) were less than US$ 10–15 (one respondent, advocacy) and US$ 18–25 (one respondent, industry). Suggested optimal prices for RIF/INH were less than US$ 5 (two respondents, advocacy and industry) and less than US$ 5 (one respondent, industry). Optimal pricing suggestions for RIF/INH/FQ/AMK were less than US$ 10 (two respondents, advocacy and industry) and US$ 15–20 (one respondent, industry).

One industry respondent disagreed with the approach of setting minimum prices, because this may stifle innovation. An advocacy respondent stated that basing non-culture drug susceptibility testing (DST) pricing on culture is unreasonable; instead, pricing should be based on existing molecular testing costs.

Considering LICs' limited ability to pay, four respondents (from academia, government, industry and implementing partners) stated that instrument costs must decrease, and three stressed that generic or universal instruments that will only require limited updating must be prioritized. New service and delivery models could be considered; for example, reagent rental models that include instrument and maintenance spread over a large volume of tests. One industry respondent noted that costs are both unrealistically low and high when considering equipment, maintenance and warranties.

Cost with respect to daily throughput (pricing and operational characteristics)

Five respondents (from academia, implementing partners and professional medical societies) raised concerns about the possibility of high costs if daily throughput is low, and suggested that distinct options for low and high incidence settings should be specified. The definition of optimal should decrease to fewer than 10 tests, and for minimal should be changed to 11–25. Three implementing partner respondents did not want batching considered, citing concerns about waiting to test.

Limits of detection, diagnostic accuracy, indeterminate results (performance)

Three respondents suggested changing the optimal limit of detection to 10 colony forming units (CFU)/mL to align with Xpert Ultra, while one noted that a limit of detection of 10^4 is too high for many PLHIV.

Regarding TB detection sensitivity, stated criteria were generally seen as too low. Separately, respondents stated that sensitivity must be equal to Xpert Ultra, higher than existing tests, and much higher in smear-negative cases. However, one respondent suggested that the criteria for minimal smear-positive should be at least 95%. DST sensitivity compared with a sequencing reference standard will differ for each drug, so a uniform requirement may be unrealistic. Compared with a phenotypic reference standard, DST sensitivity of more than 95% for all drugs is probably not feasible; instead, it would be acceptable to update targets as genetic information is elucidated (two respondents). Exceptionally, RIF sensitivity should be more than 98% and PZA minimal sensitivity should be more than 90%.

Regarding DST specificity, performance criteria is needed for the case of composite reference standards (phenotypic and sequencing combined). For analytical specificity, respondents were both appreciative and ambivalent that nontuberculous mycobacteria were mentioned.

The optimal limit of detection for minor variants should decrease to 1%, aligning with the mycobacterial growth indicator tube (MGIT), and decrease to less than 5% for minimal, because this is critical for understanding treatment success (three respondents).

Concerning indeterminant DST results, one respondent stated that the optimal value must decrease to less than 1%, while another believed that these stringent values would stifle test development. One respondent suggested including distinct values for smear-positive and smear-negative cases. Three respondents stated that reproducibility criteria should decrease to less than 5%.

Minor comments

The minimal target user was considered both underqualified and overqualified with respect to interpretation of results and clinical decision-making. Two respondents stated that treatment monitoring capability was unnecessary. Separately, respondents asked that distinct performance specifications be made for asymptomatic and symptomatic patients, and that the list of interfering substances be expanded to include other respiratory pathogens and flora, transport media and stool. One respondent suggested adding guidelines regarding product longevity. Another suggested that the instrument should run in non-air-conditioned temperatures, while another stated that it must be able to withstand high levels of ambient dust. One respondent stipulated that minimal battery power should be 24 hours.

Turnaround time should be decreased, and a rapid test format that could be performed at the point of care or bedside should be the goal. Five respondents considered the minimal time to results as being too long, with 4–6 hours (one respondent) and less than 2 hours (three respondents) suggested; also, optimal timing should decrease to less than 30 minutes.

Respondents separately noted that maintenance should be inexpensive, achievable by local staff and included in the cost of equipment; also, that manufacturers should have at least one support person available per WHO region. Another thought these criteria were not feasible. Regarding training, three respondents suggested reducing the minimal time to 2 days or less, and one mentioned the need for training for maintenance and software updates.

Four respondents mentioned a desire for reusable, recyclable or non-plastic alternatives to disposables. One respondent suggested changing biosafety and all waste disposal requirements to those of rapid molecular tests instead of microscopy. Another suggested referencing basic laboratory supplies (e.g. pipettes and a timer), which may be unavailable at peripheral settings. One respondent suggested adding a data export criterion for reporting results to client, while two respondents suggested adding requirements for virus or malware protection and data security.

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