

New diagnostic technologies in development and target product profiles

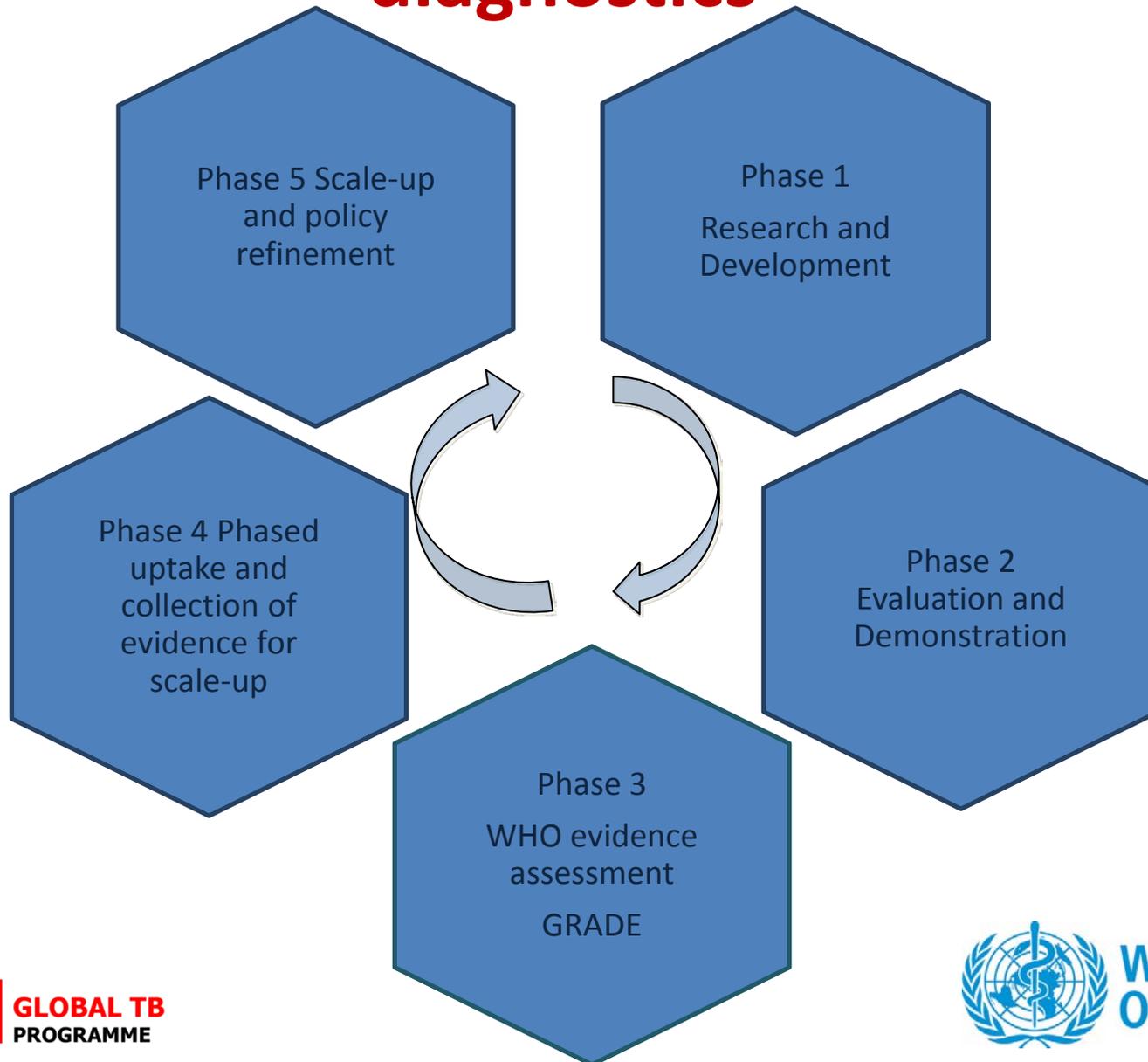
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Outline

- WHO requirements for evaluation of new TB diagnostics
- Diagnostic pipeline
- TPPs

Evidence required for WHO review of diagnostics



Phase 1: Research and Development

- Upstream research and development to define and validate a **prototype**
- Laboratory validation under international standards, **design-locked product**
- WHO interact with developers to discuss **end-user requirements**

Phase 2: Evaluation and Demonstration

- **Controlled trials** at 3-5 trial sites in high-burden TB and HIV countries
- Product **registration** with global and/or national regulatory authorities
- Specifications, performance validated in **field** trials in 5-10 sites of intended use

Phase 3: WHO evidence assessment using GRADE

- **New technologies/new indications** for use: Dossier with Phase 1 and 2 data
- **Generic technologies**: ISO13:485 standards; equivalence shown in 2-3 SRLs
- WHO is not a regulatory authority
- WHO does not recommend technologies for individual country use

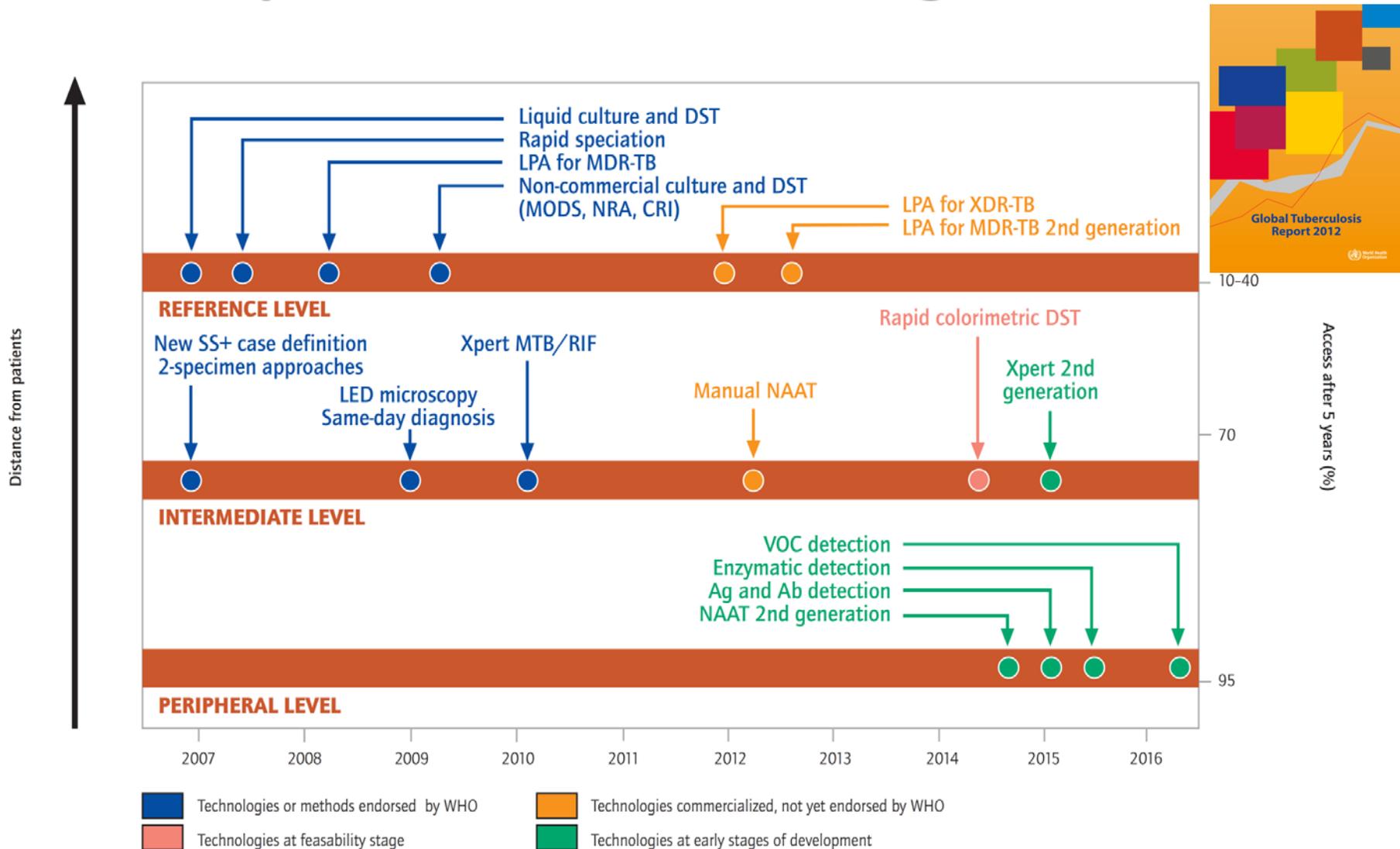
Phase 4: Phased uptake & evidence for scale-up

- Implementation in **routine TB services** in high-burden TB and HIV countries
- **Systematic evaluation**: algorithms, workload, operational issues, CE
- Lessons learnt by early implementers used for **country adaptation**

Phase 5: Scale-up & policy refinement

- **Scale-up**, with subsequent data to inform and **refine** WHO policy guidance

Pipeline for new TB diagnostics



Technologies scheduled for WHO review in 2015

- **Molecular technologies**

- TB LAMP, Eiken, Japan

- Molecular technologies for genotypic DST (including next generation sequencing technologies)

- Line probe assays

- **Non-molecular technologies**

- Alere Determine TB-LAM, Alere, USA

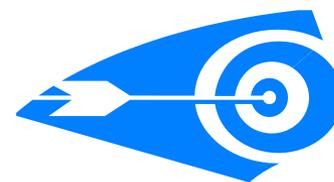
Target Product Profiles

TPPs are needed at an early stage in the diagnostic development process to inform the targets and specifications for the performance and operational characteristics of a test that will also meet the needs of end users.

- The **clinical purpose** of the test (e.g. triage, detection, DST, other)
- **Goal to be met** (e.g. start TB treatment on that day; refer for confirmatory testing)
- **Target population** (children, adults, community or HIV-clinic)
- Intended **level of implementation** in the health care system (home, community, clinic, peripheral microscopy center, hospital)

TPP attributes

- Performance characteristics
 - Sensitivity/specificity for TB detection
 - Treatment monitoring
 - DST
- Operational characteristics
 - Specimen type (sputum or other)
 - Manual steps
 - Infrastructure requirements (e.g. power, temperature control)
 - Time to result (how important is same-day results?)
 - Requirements for reporting and connectivity
 - TB only test versus multiplexed platform (e.g. + HIV, CT/NG)
 - Importance of subgroups such as HIV-infected and children
- Price targets



Draft TPPs were developed, iterated in several rounds and then put up for a Delphi survey

- Point-of-care, non-sputum based test
- Point-of-care, triage test
- Point-of-care sputum based test as a replacement for microscopy
- Point-of-care drug susceptibility testing (at microscopy center level)

Centre for Innovation in TB Care | McGill International TB Centre | Draft comments to Claudia Denkinger (claudia.denkinger@mcgill.ca) | 10/22/13

TPP for a community-based triage/referral test for identification of TB suspects

Characteristic	Optimal (ideal)	Minimal	Explanations	Ref
INTENDED USE				
Goal of Test and Potential Market	Test used at the first encounter to the health care system to identify, among patients suspected of having active TB (any site), those who do not have TB and those in need of referral for further confirmatory testing.	Test used at the first encounter to the health care system to identify, among patients suspected of having active TB (any site), those who do not have TB and those in need of referral for further confirmatory testing.	Since most individuals with suspected TB do not have TB, a triage test can help narrow down the population that needs confirmatory testing. A triage test needs to be a simple to use, low cost test for use by first-contact providers in the community (e.g., community health workers, informal providers) or persons with symptoms suggestive of TB who are seeking care (i.e. active case finding), to rule out TB (i.e. triage test negative) and direct individuals who require further evaluation (i.e. triage test positive) to a confirmatory test for TB. The triage test should have higher accuracy than the currently available sputum smears (86% and 70% sensitivity and 94% and 92% specificity for any specimen high and low HIV prevalence settings, respectively). Furthermore, triage testing could enhance rapid isolation of patients in any clinical setting and therapy and infection control. Potential market: The market size for a triage test has not been quantified but is likely to be large. Assuming nearly 9 million TB cases occur every year, and assuming that nearly 10 people with TB symptoms (suspected TB) need to be screened to identify each case, the market size is very large. The market size will also depend on the cost and characteristics of the triage test itself. A low-cost, simple to use triage test on an easy to collect sample is more likely to get scaled-up than a more expensive test that requires expertise and difficult to collect samples.	(1-4)
Drug resistance screening	None	None	DOT will be done at higher level of care (e.g. microscopy centers or district level)	
Target population	Adults and children suspected to have active TB (any site)	Adults and children suspected to have active pulmonary TB		
Target user of the test	Minimally trained community health workers and informal providers	Training at the level of an auxiliary nursing staff		
Setting (health system level)	Community/village level	Health post and primary care clinics	The level of deployment of a triage test is lower than the level of microscopy centers where TB testing and drugs are currently available; implementation at this peripheral level will considerably increase the number of patients screened for TB with the triage test and potentially shorten the diagnostic pathway.	(5)

Centre for Innovation in TB Care | McGill International TB Centre | Draft, please send comments to Sandra Via (sandra.via@mcgill.ca) | 10/22/13

TPP for a rapid, biomarker-based TB detection test for non-sputum samples (which can also detect childhood and extrapulmonary TB)

Characteristic	Optimal (ideal)	Minimal	Explanations	Ref
SCOPE				
Goal of Test and Potential Market	Rapid, biomarker-based test that can diagnose active pulmonary TB (PTB) and extrapulmonary TB (EPTB), as well as childhood TB, using non-sputum samples (e.g., urine, blood, oral mucosal transudates, saliva, exhaled air) with the purpose of initiating TB treatment within the same clinical encounter (or same day).	Rapid, biomarker-based test that can diagnose active pulmonary TB (PTB) and extrapulmonary TB (EPTB), as well as childhood TB, using non-sputum samples (e.g., urine, blood, oral mucosal transudates, saliva, exhaled air) with the purpose of initiating TB treatment within the same clinical encounter (or same day).	Simple test that uses an easily accessible sample (e.g., urine, blood, oral mucosal transudates, saliva, exhaled air) which can be performed at peripheral microscopy centers, primary care clinics and even health posts without attached laboratories to diagnose any form of active TB in adults and children. Potential market: The market for such a test has not been quantified, but is likely to be large because the product will cover multiple indications (i.e., PTB, EPTB and childhood TB), and reach lower levels of the healthcare system, and support point-of-care testing programs. As a benchmark, in the public sector alone, over 75 million sputum smears are performed for PTB each year, in 22 high burden countries (supplimented by 6k at all inclusion of EPTB and childhood TB, use of non-sputum samples, and testing at lower levels of healthcare (and inclusion of private sector) should greatly add to the potential market.	(1-4)
Drug susceptibility testing (DST)	None	None	A biomarker-based test will most likely not be able to detect drug resistance. Drug resistance testing therefore will need to be done as a reflex test by use of another (different) sample and technology and perhaps at a higher level in the healthcare delivery system where second line treatment can be offered.	
Target population	Target groups include adults and children suspected of having active TB either PTB or EPTB	Target groups include adults and children suspected of having active TB either PTB or EPTB		
Target user of test	Minimally trained technicians and primary health care workers	Trained technicians (current microscopy technicians)	When deployed at peripheral microscopy centers as well as primary care clinics and health posts, the test should be	

Centre for Innovation in TB Care | McGill International TB Centre | Draft, comments to Claudia Denkinger (claudia.denkinger@mcgill.ca) | 10/22/13

Target Product Profile- Rapid sputum-based molecular test (for microscopy centers) for TB

Characteristic	Optimal (ideal)	Minimal	Explanations/Justifications	Ref
INTENDED USE				
Goal of Test and Potential Market	Sputum-based pulmonary TB detection and detection of RIF (either sputum or reflex) to support rapid, same-day FOC initiation of therapy and early identification of MDR at the microscopy center level.	Sputum-based pulmonary TB detection to support cost initiation of therapy and increase the number of patients initiated on therapy	Optimizes TB detection that could replace smears in a decentralized setting. The IMAI should have very simple sample preparation, and be deployed at peripheral microscopy centers as replacement for sputum smears. Such a test has the potential to both increase the number of patients treated and to do so earlier in their course of disease. Potential market: <ul style="list-style-type: none"> In the public sector alone, there are over 40,000 peripheral microscopy centers performing over 75 million smears each year, in 22 high burden countries (as published by GEM 4.3). Inclusion of the private sector will further increase the smear volumes in these high burden countries. So there is a substantial potential market for a smear replacement test. 	(1-3)
Drug resistance screening	RIF	None	Possible benefits of RIF detection: <ul style="list-style-type: none"> Early rapid detection of patients who require further testing and second line therapy (thus, supporting the goal of universal DOT) Some evidence Consideration around up-front testing versus reflex testing depends on trade-off between cost, volume and turn around time (also dependent on platform technology). The target population is in line with the recommendations for sputum in the upcoming WHO guidelines.	
Target Population	Target groups are all patients suspected of having pulmonary TB and able to produce sputum, with a special focus on those at high risk of morbidity and mortality from drug resistant TB such as people living with HIV, and those at high risk of being MDR-TB.	Target groups are all patients suspected of having pulmonary TB and able to produce sputum.		
Target user of test	Healthcare workers with minimal training (e.g. microscopy technicians)	Healthcare worker with minimal training (e.g. microscopy technicians)		
Setting (health system level)	Microscopy center level (primary health centers with attached peripheral laboratories)	Microscopy center level (primary health centers with attached peripheral laboratories)	Conditions that prevail in microscopy centers in high burden countries have been described, and characteristics required for molecular tests at the level of the healthcare system have also been proposed. A test at this level would leverage already existing infrastructure based around smear microscopy and potentially reach large numbers of individuals with suspected TB.	(4, 5)

(1) Biomarker TPP - Purpose

	Optimal	Minimal
Clinical purpose	Rapid, biomarker-based test that can diagnose pulmonary TB (PTB) and ideally also extrapulmonary TB (EPTB) using non-sputum samples (e.g., urine, blood, oral mucosal transudates, saliva, exhaled air) with the purpose of initiating TB treatment within the same clinical encounter (or same day).	
Target population	Countries with medium to high TB prevalence. Target groups are adults +children (incl HIV) with suspected active TB; either PTB or EPTB	
Setting	Health posts without attached laboratories (a level lower than MCs)	Primary health clinics (with attached laboratories); Peripheral MCs
User	Health care workers with minimal training	Trained microscopy technicians

(1) Biomarker TPP - Performance

Performance characteristics	Optimal	Minimal
Diagnostic sensitivity PTB adults	<p>Sensitivity equal or better than 98% for smear-positive, culture-positive PTB, and 68% for smear-negative, culture-positive PTB in adults (i.e. like Xpert MTB/RIF)</p> <p>Overall pooled sensitivity at least 80% in adults with HIV infection.</p>	<p>Sensitivity at least better than >65% overall, but should be >98% among smear-positive, culture-positive PTB (i.e. like smear microscopy)</p> <p>Overall pooled sensitivity better than smear microscopy in adults with HIV infection.</p>
Diagnostic sensitivity EPTB adults	<p>Sensitivity equal or better than 80% ideally for all forms of microbiologically confirmed EPTB.</p>	<p>Diagnosis of EPTB is an important need and a test that is able to diagnose EPTB in addition will have significant individual patient benefits and likely achieve great acceptance in the community of care providers. No lower sensitivity defined.</p>
Diagnostic sensitivity Children	<p>Sensitivity for childhood intrathoracic TB at least equal or better than 66% (i.e. like Xpert MTB/RIF) for microbiologically confirmed TB.</p>	<p>Diagnosis of childhood TB is an important need and a test improving diagnose of TB in children in addition will have significant individual patient benefits and likely achieve great acceptance in the community of care providers. No lower sensitivity defined.</p>
Diagnostic specificity	<p>At least as specific as Xpert MTB/RIF for detection of PTB and EPTB and childhood TB (98% specificity against microbiological reference standard). Able to distinguish between active TB versus latent and past infection.</p>	

(2) Triage test - Purpose

	Optimal	Minimal
Clinical purpose	Test used at the first encounter to the health care system to identify, among patients with <u>symptoms or risk factors of active TB</u> , including HIV coinfecting patients, those who do not have TB and those in need of referral for further confirmatory testing.	Test used at the first encounter to the health care system to identify, among patients with <u>symptoms or risk factors of active pulmonary TB</u> , including HIV coinfecting patients, those who do not have TB and those in need of referral for further confirmatory testing.
Target population	Countries with medium to high TB prevalence (WHO Categories). Adults and children.	Countries with medium to high TB prevalence (WHO Categories). Adults and children.
Setting	Community/village level	Health post and primary care clinics
User	Minimally trained community health workers and informal providers	Training at the level of an auxiliary nursing staff



(2) Triage test - Performance

Performance characteristics	Optimal	Minimal
Sensitivity	>95% overall compared to confirmatory test for pulmonary TB; EPTB no lower sensitivity defined	>90% overall compared to confirmatory test for pulmonary TB
Specificity	>80% overall compared to confirmatory test	>70% overall compared to confirmatory test

(3) Sputum-based smear replacement test - Purpose

	Optimal	Minimal
Clinical purpose	Sputum-based <u>pulmonary TB</u> detection (NAAT or other) at the level of a microscopy center with the purpose of supporting initiation of TB therapy within the same clinical encounter (or same day) with a higher sensitivity of smear microscopy.	
Target population	Countries with medium to high TB prevalence (WHO Categories). Target groups are all patients suspected of having pulmonary TB and able to produce sputum.	
Setting	Microscopy center level (primary health centers with attached peripheral laboratories)	
User	Microscopy center technicians	

(3) Sputum-based smear replacement test -Performance

Performance characteristics	Optimal	Minimal
Diagnostic sensitivity	>95% single test in comparison to culture (smear negative > 68%, smear positive 99%)	>80% single test in comparison to cultures (smear negative >60%, smear positive 99%)
Diagnostic specificity	>98% specificity in comparison to culture	
Treatment monitoring possible	Yes (a test that is able to replace smear microscopy for treatment monitoring is more likely to be adopted and to completely replace smear microscopy)	No

(4) Rapid DST-Purpose

	Optimal	Minimal
Clinical purpose	Diagnosis of TB disease and detection of drug resistance to inform decision-making concerning optimal first line therapy (HRZE, REMox, vs. PaMZ), possibly presence of additional second line drug resistance and need for further testing.	
Target population	Countries with medium to high TB prevalence (WHO Categories). Target groups are all patients suspected of having TB with a special focus on those at high risk of morbidity and mortality from drug-resistant TB such as people living with HIV, and those at high risk of having MDR-TB	
Drugs	RIF > FQ (incl. Mox) > INH = PZA > AG/CAP	
Setting	Microscopy center level	

(4) Rapid DST- Performance

Performance characteristics	Optimal	Minimal
Diagnostic sensitivity compared against genetic sequencing as the reference standard ^b	Sensitivity should be >98% for detecting targeted SNPs for resistance to RIF, FQs, PZA, INH, and AGs and CAP when compared with genetic sequencing	Sensitivity should be >98% for detecting targeted SNPs for resistance to RIF, and 95% for detecting SNPs for resistance to FQs, PZA, INH, and AGs and CAP when compared with genetic sequencing
Diagnostic specificity	Specificity should be $\geq 98\%$ for any anti-TB agent for which the test is able to identify resistance when compared against genetic sequencing as the reference standard	

Meeting report will be available on WHO, GLI and NDWG websites mid-October 2014

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