

Pipeline Report » 2019

Tuberculosis Diagnostics

A large, abstract graphic composed of numerous overlapping, flowing red lines that create a sense of movement and complexity, resembling a stylized map or a network of paths. The lines are thin and vibrant against the black background.

TAG

Treatment Action Group

The Tuberculosis Diagnostics Pipeline: New Tests, Same Barriers

By David Branigan

Introduction

Tuberculosis (TB) is the world's single most deadly infectious disease, with an estimated 10 million people developing active TB each year and approximately 1.45 million people dying from the disease—251,000 of whom have HIV coinfection.¹ TB thrives in conditions of poverty, where health systems are often inadequate and access to lifesaving health technologies limited because of high prices and lack of country scale-up of new tools. Of the estimated 10 million people who develop TB each year, only 7 million are officially diagnosed and treated. The remaining 3 million people with TB are either diagnosed but not reported, or undiagnosed and left without treatment,² putting them at risk of poor health outcomes and of spreading the disease to others. Those who are diagnosed with TB often experience delays in linkage to treatment, with long turn-around times for test results due to insufficient access to point-of-care testing and other health system failures. Upon diagnosis, people with TB often receive inadequate treatment in the absence of universal drug susceptibility testing (DST),³ which causes their health to deteriorate, furthers drug resistance, and compounds the burden of the disease.

Even under optimal health system conditions, the diagnostic tools currently in use are insufficient to close the diagnostic gap—we need new and better tools. Chest X-rays for active TB screening miss up to 13% of cases of pulmonary TB.⁴ Sputum smear microscopy—still the most widely used method of diagnosing TB—on average detects only 50% of cases.⁵ Liquid culture is the gold standard in TB diagnostic accuracy but takes two weeks or more for results. Recent developments in rapid molecular nucleic acid amplification tests (NAATs) for TB detection are close in accuracy to culture, and much faster at under two hours per test, but are not yet suitable for use in lower-level health facilities, including community health centers, where many people with TB seek care. Most of the currently available TB diagnostics use sputum as the primary sample to be tested, which is not appropriate for people with extrapulmonary TB or for those who have difficulty producing sputum, including many people living with HIV/AIDS (PLWHA), as well as children. A rapid urine-based TB detection test for seriously ill PLWHA is available, but its sensitivity is lower than ideal and its scale-up has been slow. While line probe assays and culture-based DST for first-line and some second-line TB drugs are in use in the central laboratories of high-TB-burden countries, broader uptake of DST has lagged, with only 46% of people newly diagnosed with TB being tested for resistance to the first-line drug rifampin,⁶ let alone for other first- and second-line drugs.

The World Health Organization (WHO) has developed a set of high-priority target product profiles (TPPs) to improve TB diagnostic tools. These include (1) a point-of-care non-sputum-based, biomarker-based TB diagnostic; (2) a point-of-care, first-contact triage test to evaluate for TB; (3) a point-of-care sputum-based replacement for smear microscopy; and (4) rapid TB drug susceptibility testing at the microscopy center level of the health system.⁷ These TPPs guide the research and development of new tools, and while the diagnostics currently in the pipeline are moving in the direction of these TPPs, there is still a long way to go.

Since 2017, when Treatment Action Group (TAG) last released its [TB Diagnostics Pipeline Report](#), a number of diagnostics in the pipeline have advanced in important ways, but the overall landscape of available tools has continued to present many of the same challenges with regard to affordability and access. The most significant areas of progress in the TB diagnostics pipeline build off of two groundbreaking advances of the past decade: rapid molecular tests for diagnosing TB and rifampin resistance, and rapid urine-based lipoarabinomannan (LAM) detection tests for diagnosing TB in PLWHA. Another important area of progress has been rapid DST for first- and second-line drugs, including next-generation developments in targeted and whole genome sequencing for individualizing treatment regimens. Table 1 below provides a high-level overview of what is currently in the TB diagnostics pipeline and when to expect these tools to be available, as well as some diagnostics already approved by the WHO that form an essential part of the TB diagnostics landscape. The sections that follow cover these developments and more, detailing diagnostic tests and their specifications and highlighting continued gaps in access to new diagnostic technologies.

Table 1: The TB diagnostics pipeline

Rapid molecular nucleic acid amplification tests (NAATs) for decentralized TB detection and DST				
Test	Type / Level	Manufacturer / Sponsor	Status / Market Entry	Details / Accuracy*
Xpert MTB/RIF	PCR / District / Sub-District Lab	Cepheid	WHO recommended: 2010 Market entry: 2010	Pulmonary TB - SE: 85% SP: 98% Extrapulmonary TB - SE: 31% - 97% SP: 82% - 99% RIF - SE: 96% SP: 98%
Xpert MTB/RIF Ultra	PCR / District / Sub-District Lab	Cepheid	WHO recommended: 2017 Market entry: 2017	Pulmonary TB - SE: 88% SP: 96% RIF - SE: 95% SP: 98%
Edge (platform)	PCR / Microscopy Center	Cepheid	Market entry: 2018	One test module; automated; requires environmental control; runs on external battery; ≤ 90 min per test

Omni (platform)	PCR / Community	Cepheid	Expected WHO evaluation: 2020 Expected market entry: 2020	One test module; can run on battery for 2 days; ≤ 90 min per test
Xpert XDR (INH, MXF, OFX, KAN, AMK)	PCR / District/ Sub-District Lab	Cepheid	Expected WHO evaluation: 2020** Expected market entry: 2020	INH - SE: 83.3% SP: ≥ 94.3% MXF - SE: 87.6% - 96.2% SP: ≥ 94.3% OFX - SE: 88.4% SP: ≥ 94.3% KAN - SE: 71.4% SP: ≥ 94.3% AMK - SE: 70.7% SP: ≥ 94.3%
Truenat MTB	PCR / Microscopy Center	Molbio Diagnostics	WHO evaluation: December 2019 Market entry (India): 2013	Pulmonary TB - SE: 86% SP: 99%
Truenat MTB-RIF Dx	PCR / Microscopy Center	Molbio Diagnostics	WHO evaluation: December 2019 Market entry: 2013 (India)	RIF - SE: 94% SP: 98% (LPA reference standard)
Molecular Stool Test Prep Kit	Sample preparation / District/ Sub-District Lab	FIND, Rutgers University, University of Cape Town, 42 Technology	Expected WHO evaluation: 2020** Market entry: 2021	Simplified stool processing for more easily accessible samples

Rapid biomarker-based non-sputum-based point-of-care tests for detecting TB

Test	Type / Level	Manufacturer / Sponsor	Status / Market Entry	Details / Accuracy*
Determine TB LAM	Immunoassay, Antigen-based / Community	Abbott (Alere)	WHO recommended: 2015 Market entry: 2013	CD4 count ≤ 100 - SE: 56% SP: 90% CD4 count 101-200 - SE: 26% - 49% SP: 90% - 92% CD4 count > 200 - SE: 15% SP: 96%
SILVAMP TB LAM	Immunoassay, Antigen-based / Community	Fujifilm	Expected WHO evaluation: Q4 2020** Expected market entry: Q1 2021	CD4 count ≤ 100 - SE: 84.2% SP: 85% CD4 count 101-200 - SE: 60.6% SP: 89.6% CD4 count > 200 - SE: 44% SP: 97%
TB LAM (Next-generation)	Immunoassay, Antigen-based / Community	Abbott	Early-stage development	Increased sensitivity intended for broader HIV-negative population ⁸

Centralized drug susceptibility testing				
Test	Type / Level	Manufacturer / Sponsor	Status / Market Entry	Details / Accuracy*
GenoType MTBDR Version 2.0 (RIF/INH)	PCR LPA / Reference Laboratory	Hain Lifescience	WHO recommended: 2008 (version 1.0) Market entry: 2015	RIF - SE: 98.2% SP: 97.8% INH - SE: 95.4% SP: 98.8% ⁹
GenoType MTB-DRsl Version 2.0 (FLQs, KAN, AMK, CAP)	PCR LPA / Reference Laboratory	Hain Lifescience	WHO recommended: 2016 Market entry: 2015	FLQs - SE: 100% SP: 98.9% KAN - SE: 89.2% SP: 98.5% AMK - SE: 93.8% SP: 98.5% CAP - SE: 86.2% SP: 95.9% ¹⁰
NTM+MDRTB (RIF/INH)	PCR LPA / Reference Laboratory	Nipro	WHO recommended: 2016 Market entry: 2011	RIF - SE: 96.5% SP: 97.5% INH - SE: 94.9% SP: 97.6% ¹¹
Cobas MTB-RIF/INH	PCR / Reference Laboratory	Roche	On pathway to WHO evaluation** Market entry: 2019	RIF - SE: 97.2% SP: 98.6% INH - SE: 96.9% SP: 99.4%
BD MAX MDR-TB RIF/INH	PCR / Reference Laboratory	BD	On pathway to WHO evaluation** Market entry: 2018	RIF - SE: 90% SP: 95% INH - SE: 82% SP: 100%
RealTime MTB-RIF/INH Resistance	PCR / Reference Laboratory	Abbott	WHO evaluation: 2019** Market entry: 2015	RIF - SE: 94.8% SP: 100% INH - SE: 88.3% SP: 94.3%
FluoroType MTBDR Version 2.0 (RIF, INH)	PCR / Reference Laboratory	Hain Lifescience	On pathway to WHO evaluation** Market entry: 2019	RIF - SE: 98.9% SP: 100% INH - SE: 91.7% SP: 100%
FluoroType MTBXDR (RIF, INH, AMGs, FLQs)	PCR / Reference Laboratory	Hain Lifescience	Early-stage development	
BD BACTEC MGIT system tests (BDQ, LZD, CLO, LVX, DLM)	Liquid culture / Reference Laboratory	BD	In development ¹²	

Triage or referral tests for identifying people who may have TB				
Test	Type / Level	Manufacturer / Sponsor	Status / Market Entry	Details / Accuracy*
CAD4TB	Imaging - CAD / District Lab / Hospital	Delft Imaging Systems	On pathway to WHO evaluation** Market entry: 2011	SE: 85% - 100% SP: 23% - 69%
qXR	Imaging - CAD / District Lab / Hospital	Qure.ai	On pathway to WHO evaluation** Market entry: 2018	SE: 93% - 100% SP: 92% - 99%
CAD deep learning-based algorithm	Imaging - CAD / District Lab / Hospital	Fujifilm, Lunit	On pathway to WHO evaluation**	SE: 83% - 100% SP: 80% - 100% ¹³
Aeonose for TB	Antigen-based - VOC / Community	The eNose Company	Early-stage development**	SE: 78% - 85% SP: 42% - 55%
TB Breathalyser	Antigen-based / Community	Rapid Biosensor Systems	Early-stage development**	SE, SP: > 95% (for detecting infectious pulmonary TB, according to early studies)

Tests for TB infection				
Test	Type / Level	Manufacturer / Sponsor	Status / Market Entry	Details / Accuracy*
QuantiFERON-TB Gold Plus (QFT-Plus)	IGRA blood-based / Reference Laboratory	Qiagen	WHO recommended: 2018 (earlier version) Market entry: 2018**	SE: > 94% (culture-confirmed active TB disease) SP: > 97% (false positives among people with low risk)
QuantiFERON-TB Access	IGRA blood-based / District Lab/Hospital	Qiagen	On pathway to WHO evaluation** Expected market entry: 2020	QFT-Plus accuracy with a simplified laboratory process
T-SPOT.TB	IGRA blood-based / Reference Laboratory	Oxford Immunotec	WHO recommended: 2018 Market entry: 2004	SE: 95% (culture-confirmed active TB disease) SP: 99% ¹⁴ (false positives among people with low risk)
C-Tb	Skin Test / Community	Statens Serum Institute	On pathway to WHO evaluation** Expected market entry: 2020	94% concordance with QFT-Plus

Treatment monitoring or test of cure				
Test	Type / Level	Manufacturer / Sponsor	Status / Market Entry	Details / Accuracy*
LAM-ELISA	Immunoassay – Antigen-based / Reference Laboratory	Otsuka Pharmaceutical	Early-stage development	

References are listed in the table only when not otherwise noted in the following text.

* Accuracy reported in this table is based on the culture-based microbiological reference standard unless otherwise noted.

**For more recent technologies yet to be evaluated by the WHO, the source of published evidence is mainly bench-based evaluation studies or early-stage studies (i.e., laboratory-based proof-of-concept studies), as opposed to meta-analyses of peer-reviewed studies.

Abbreviations

AMGs - aminoglycosides	KAN - kanamycin
AMK - amikacin	LAM - lipoarabinomannan
BDQ - bedaquiline	LPA - line probe assay
CAD - computer-aided detection	LVX - levofloxacin
CAP - capreomycin	LZD - linezolid
CLO - clofazimine	MGIT - mycobacteria growth indicator tube
DLM - delamanid	MTB - Mycobacterium tuberculosis
ELISA - enzyme-linked immunosorbent assay	MXF - moxifloxacin
FLQs - fluoroquinolones	OFX - ofloxacin
IGRA - interferon-gamma release assay	PCR - polymerase chain reaction
INH - isoniazid	RIF - rifampin

Sensitivity (SE): the proportion of people with a disease who are correctly identified by a diagnostic test as having the disease. Low sensitivity leads to a high number of false negative results. A sensitive test helps to rule out disease (when the result is negative).

Specificity (SP): the proportion of people without a disease who are correctly identified by a test as not having the disease. Low specificity results in a high number of false positive cases. A very specific test helps to confirm the presence of disease (when the result is positive).

Rapid Molecular Tests

Over the past decade, advances in the development of rapid, highly accurate NAATs for molecular TB detection changed the game for TB diagnostics. These tests use polymerase chain reaction (PCR), a technique to amplify trace amounts of DNA/RNA to determine with very high probability the presence of TB bacteria. Rapid molecular tests are close in accuracy to culture-based tests—the current gold standard with regard to sensitivity and specificity—but are much faster, returning results within two hours compared with a minimum of two weeks for culture. These new rapid tests are primarily designed for use on sputum specimens, but they can also be used on other samples in the case of extrapulmonary TB (i.e., cerebrospinal fluid, pleural fluid, and tissue biopsies) and are currently being evaluated for use on stool. New rapid molecular tests that will soon come out of the pipeline offer features for testing closer to the point of care along with a wider range options for rapid DST, including some second-line drugs. While Cepheid has dominated the market for rapid molecular tests since the release of its Xpert assays in 2010, Molbio's Truenat MTB and MTB-RIF Dx—currently in line to be reviewed by the WHO—offer the prospect of breaking Cepheid's monopoly and creating a more competitive market for rapid molecular tests that will hopefully lower prices to support the scale-up of these essential diagnostics.

GeneXpert assays: Two steps forward, one step back

Xpert MTB/RIF and Xpert MTB/RIF Ultra

Cepheid's GeneXpert automated molecular NAAT diagnostic platform, running its Xpert MTB/RIF cartridge assay, was the first rapid molecular test to enter the market, in 2010. That same year, the WHO recommended Xpert MTB/RIF as the initial test for TB diagnosis over the more widely available, inexpensive, but far less sensitive smear microscopy.¹⁵ Xpert MTB/RIF tests offer high accuracy for detecting pulmonary TB, with sensitivity at 85% and specificity at 98%, and for detecting rifampin resistance, with sensitivity at 96% and specificity at 98%.¹⁶ Xpert accuracy in detecting extrapulmonary TB varies depending on the specimen, with sensitivity ranging from 31% to 97% and specificity ranging from 82% to 99%.¹⁷ Xpert tests are fully automated and can be completed in just 90 minutes. GeneXpert testing, however, has infrastructure requirements, such as constant electricity and environmental control, and is relatively expensive. Thus, many countries have been slow to implement Xpert tests as the initial test for TB diagnosis as the WHO recommends.¹⁸ Because of the high cost of Xpert testing, the WHO even characterized its 2011 and 2013 policy recommendations as “conditional,” acknowledging the “major resource implications” of the recommendations, thus offering countries the option to continue to rely on smear microscopy as the initial test, despite its limitations compared to Xpert.^{19,20}

The sensitivity of Xpert testing increased with the 2017 rollout of the Xpert MTB/RIF Ultra cartridge, which detects TB bacteria at a lower threshold than the earlier Xpert MTB/RIF cartridge. This is attributable to its larger chamber for DNA amplification, which allows for more sputum, as well as the inclusion of two additional molecular

targets. Xpert Ultra can detect TB at concentrations as low as 16 bacilli per milliliter (mL) of sputum, compared with Xpert MTB/RIF's minimum detection of 131 bacilli per mL.²¹ This makes Ultra more appropriate for PLWHA and children, whose sputum tends to contain lower concentrations of TB bacteria. For the detection of TB, Xpert Ultra's sensitivity is 3% higher than Xpert MTB/RIF's (88% vs. 85%), but its specificity is 2% lower (96% vs. 98%).²² For detecting rifampin resistance, the sensitivity and specificity between Xpert MTB/RIF and Xpert Ultra are similar. In 2017, the WHO recommended Xpert Ultra to replace Xpert MTB/RIF for all people including PLWHA because of its higher sensitivity.²³ Country procurement of Xpert Ultra, however, has lagged compared with Xpert MTB/RIF, in part because of its shorter shelf life of eight months, which Cepheid confirmed has recently been extended to 16 months.²⁴

Xpert pricing: Out of step with public health needs

It is essential that the price of Xpert cartridges come down so that countries and health systems can afford to procure these tests at the high volumes needed to replace smear microscopy as the initial test for TB diagnosis. The WHO's target product profile states that the optimal price for rapid molecular tests is less than US\$4, with a maximum price of less than US\$6.²⁵

Cepheid's Xpert cartridges entered the market with the public-sector price of US\$16.86 per test for eligible high-burden developing countries (HBDCs). In 2012, Unitaid, the U.S. Agency for International Development (USAID), the (U.S.) President's Emergency Plan for AIDS Relief (PEPFAR), and the Bill & Melinda Gates Foundation negotiated with Cepheid to reduce the price of Xpert cartridges to US\$9.98 per test for the period of 2012 to 2022.²⁶ Because the negotiated agreement did not include future volume-based reductions, the price per cartridge has remained the same even though procurement volumes since the start of the agreement have far exceeded initial expectations. Greater transparency around the actual cost of goods at economies of scale will be required to calculate an appropriate volume-based price that approaches the WHO's target price.

For private-sector health providers, where patients in many countries access health care, the concessional price of US\$9.98 per Xpert cartridge is not available. Private-sector providers pay a higher price per Xpert test, which factors into higher costs for patients. According to a survey on the pricing of Xpert MTB/RIF tests in the private sector in six countries, the cost per test for patients in 2015 averaged US\$68.73 (range US\$30.26 to US\$155.44). In 2018 this increased to an average of US\$84.53 (range US\$46.70 to US\$175.00), skewed upward with the introduction of Xpert MTB/RIF in Nigeria at the high price of US\$175. This is compared with the average cost of US\$20–\$30 in national TB programs for each Xpert test.²⁷

The Initiative for Promoting Affordable and Quality TB Tests (IPAQT) in India offers one model for successfully reducing the price of TB diagnostic testing in the private sector, where 60% of people in India seek care. IPAQT established an agreement among all private-sector stakeholders, including diagnostic companies and testing laboratories, to reduce profit margins for WHO-approved TB diagnostic tests, in order to be able to offer these tests at lower prices. As part of this agreement, diagnostic companies agreed to provide concessional prices to private laboratories, which in turn agreed to pass on these savings through lower prices to patients. In India, IPAQT has successfully lowered the cost of Xpert testing in the private sector from an average of US\$67 to US\$33.²⁸ It is essential that Cepheid engage initiatives such as IPAQT, as well as other efforts to reduce prices and expand access to Xpert testing in the private sector, in order to ensure that all people seeking care for TB in all sectors of the health system have affordable access to this essential diagnostic test.

GeneXpert Omni

In 2015, Cepheid announced the much-anticipated launch of Omni, a new battery-powered platform designed to bring Xpert testing closer to the community level, but because of complications with the technology, four years later the test is still not market-ready.²⁹ Omni is undergoing further testing and is expected to be reviewed by the WHO in 2020. Omni is a portable platform with a single module that can be run on a battery for two days of operation (16 hours). It offers fully automated testing like GeneXpert, but it uses a different Xpert cartridge with a near field communication chip, and therefore standard Xpert cartridges cannot be used in the new Omni platform. Omni does not require a computer to run and is paired with a dedicated mobile device for operation.

GeneXpert Edge

Given delays with the release of Omni, as an intermediary in 2018 Cepheid released Edge, a less expensive one-module version of GeneXpert marketed to be operated closer to the point of care. Edge runs on an external battery pack and has a dust filter, making it slightly more rugged than GeneXpert. But like GeneXpert, Edge relies on air-conditioned temperatures to operate effectively, which has prevented it from being used as a point-of-care platform. Additionally, while Omni has a touted compact design, Edge has a sizable footprint that is similar to a desktop computer. Because of those factors, and its relatively high price of US\$8,945 per machine, demand for Edge has remained limited. Many countries instead prefer the higher throughput two- or four-module GeneXpert platforms because Edge does not bring testing closer to the point of care.³⁰

Xpert XDR

Cepheid has also developed a new rapid molecular DST cartridge, Xpert XDR, to test for resistance to isoniazid and second-line TB drugs moxifloxacin, ofloxacin, kanamycin, and amikacin. Xpert XDR is undergoing testing in preparation for WHO review in 2020. Similar to Omni, the cartridge was announced and anticipated years ahead of its ultimate market entry, which is expected in 2020. Xpert XDR is intended to test a sample following TB detection by Xpert MTB/RIF or Xpert Ultra, offering the most rapid DST turnaround for isoniazid and several second-line drugs to date. Sensitivities for Xpert XDR range from 70.7% for amikacin to 96.2% for moxifloxacin, and specificities are over 96%, except for moxifloxacin, which ranges from 84% to 94.3%.³¹ While the Xpert XDR cartridge will bring rapid DST for some second-line drugs closer to the point of care, DST for two of those drugs, ofloxacin and kanamycin, is no longer necessary. Due to limited evidence of effectiveness, in 2016 the WHO recommended against the inclusion of ofloxacin,³² and in 2019 recommended against the inclusion of kanamycin,³³ in drug-resistant TB treatment regimens. Similarly, amikacin is only recommended in some cases for the treatment of drug-resistant TB³⁴ and so has become less essential for DST than newer drugs such as bedaquiline, delamanid, and pretomanid, and repurposed drugs such as linezolid and clofazimine. As treatment guidelines and drug regimens continue to change, it is critical that DST development keep up with these changes and progress more rapidly so that new tools for DST do not immediately become obsolete upon release. According to Cepheid, the concessional price of Xpert XDR for HBDCs is expected to be US\$19.98 per cartridge.³⁵

Truenat: Not so fast follower

While the world anticipated fast followers to GeneXpert after its release in 2010, competitors were slow to emerge in the global market.³⁶ The India-based company Molbio Diagnostics released its Truelab PCR multidisease testing platform in India in 2013, along with its Truenat MTB and RIF chips for detecting TB and rifampin resistance. Following the recent completion of larger validation studies, Truenat MTB and MTB-RIF Dx will be reviewed by the WHO in December 2019, and if recommended, will soon enter the global market. Early studies based only on sputum specimens found Truenat MTB and MTB-RIF Dx to be 86% sensitive and 99% specific for TB detection and 94% sensitive and 98% specific for rifampin resistance,^{37,38,39} which is not far behind Xpert MTB/RIF Ultra. The anticipated entry of Molbio's Truelab platform and Truenat MTB and MTB-RIF Dx into the global TB diagnostics market in 2020 will mark the end of Cepheid's monopoly on rapid molecular TB tests.

Truenat is being marketed as the first point-of-care rapid molecular test on the market for detecting TB and rifampin resistance, because unlike GeneXpert, its Truelab testing platform is portable, is battery-powered, and does not require air-conditioned temperatures. According to Molbio, it is "infrastructure independent" and designed for low-resource settings. The company says that it can be transported in a suitcase, can run all day on a single battery charge, and just needs a table to place it on. The test takes about 60 minutes to complete: 20 minutes for the sample preparation and 35 minutes

to run the PCR. However, it is not fully automated like GeneXpert and requires micro-pipetting between stages. According to Molbio, this can be done by a trained smear microscopy technician, as there is a very low risk of sample contamination. Because of these technical requirements, Truenat will likely be positioned at the microscopy center level, close to the point of care but not at the community level of the health system. Such positioning has the potential to fill an important gap between the district laboratory where Xpert is positioned and the community where Omni is intended to be positioned.⁴⁰

Truelab comes in one-, two-, and four-module configurations, with the lattermost capable of running tests concurrently. Unlike Xpert tests, Truenat's MTB and RIF chips are separate and can only be run sequentially. Upon receiving a positive test result for TB detection, the RIF chip can then be run to test for rifampin resistance, adding another hour to the testing time. Molbio currently offers the four-module Truelab platform at US\$14,150 and the Truenat tests at the volume-based price of US\$10–\$14, with the intention to market the tests in all high-TB-burden countries.⁴¹

Stool processing kit for rapid molecular testing

The Foundation for Innovative New Diagnostics (FIND), a diagnostics product development partnership (PDP), along with Rutgers University, the University of Cape Town, and 42 Technology are developing a disposable stool processing kit that simplifies a complex laboratory process into a few easy steps to prepare stool specimens for testing on rapid molecular tests such as Xpert. The kit is intended to improve access to the use of stool samples for TB detection in babies and children, and it is hoped that it will bypass the need for sputum and reduce the need for invasive sample collection techniques in young children.⁴² A systematic review of studies on using Xpert MTB/RIF to test stool specimens (without using the stool processing kit) found its pooled sensitivity to be 67% and its pooled specificity to be 99%, with sensitivity higher among children with HIV at 79%, compared with 60% for HIV-negative children.⁴³ Validation studies on the stool processing kit are ongoing and expected to be completed and reviewed by the WHO in 2020, followed by commercial availability in 2021. The cost of the stool kit is expected to be under US\$5.⁴⁴

Phasing out smear microscopy for TB diagnosis

Although the latest rapid molecular tests offer much promise for improved TB diagnosis, the reality is that many high-TB-burden countries still rely on sputum smear microscopy as the initial TB test. Its low sensitivity of approximately 50%⁴⁵ makes it unacceptable as the initial diagnostic test at a time when highly sensitive rapid molecular tests are available and recommended by the WHO as the initial test for TB diagnosis. By detecting TB in only about half of the people with TB disease, smear microscopy leaves open a massive gap in linkage to treatment and enables the further progression and spread of the disease. For PLWHA, smear microscopy is even less sensitive at just 26%, and obtaining a sputum sample is in many cases not possible for those who are severely ill or in advanced stages of HIV.⁴⁶

Rather than scaling up procurement of rapid molecular Xpert tests, many high-TB-burden countries continue to rely on their existing networks of microscopy centers as a cost-saving measure, because of the relatively high cost of Xpert tests. In its 2011 and 2013 policy guidance, the WHO made a conditional recommendation for the use of Xpert as the initial test for TB over smear microscopy, acknowledging the “major resource implications” of the recommendation. Without clear guidance from the WHO against the use of smear microscopy for TB diagnosis, countries will continue to rely on this outdated diagnostic method, and uptake of rapid molecular tests such as Xpert will continue to reflect just a fraction of the need.

For TB treatment monitoring, however, smear microscopy continues to be needed. Xpert tests cannot be used for treatment monitoring because false positives can arise from detection of even small amounts of genetic material, including genetic material from dead TB bacilli well after cure. While smear microscopy continues to play a critical role for treatment monitoring, its use as a diagnostic test should be phased out, and rapid molecular tests such as Xpert should be prioritized as the initial test for all people who might have TB.

Rapid Lateral Flow Urine-Based LAM Tests

The rapid urine-based LAM test represents a significant milestone in TB diagnostic development, as it is the first point-of-care, non-sputum biomarker-based diagnostic test for TB that is appropriate for use at the community level. This urine-based test has become essential for PLWHA, who often have difficulty producing sputum, particularly in advanced stages of HIV. As TB LAM sensitivity is highest among people who are seriously ill with HIV, indications for the use of the test have so far been limited to this population; however, next-generation LAM tests in the pipeline offer the potential to broaden this indication.

Determine TB LAM: Use the test we've got

The second revolutionary advance in the TB diagnostics pipeline in recent years was the 2013 release of the Determine TB LAM test developed by Alere, which has since been acquired by Abbott. TB LAM is urine-based and detects the biomarker protein lipoarabinomannan (LAM) released by TB bacteria. Because of the difficulty of producing sputum for seriously ill PLWHA, along with the low concentrations of TB bacteria in disseminated, extrapulmonary TB common in PLWHA, rapid molecular tests are not always feasible as the first test for people in advanced stages of HIV. Therefore, rapid urine-based LAM tests fill a critical gap in the diagnosis of seriously ill PLWHA with high risk of TB.

Determine TB LAM is extremely simple and appropriate for use at the point of care, utilizing a lateral flow technology similar to pregnancy tests. Results are available in just 30 minutes. Its sensitivity, however, is lower than ideal, and is highest among PLWHA with low CD4 cell counts. Determine TB LAM has a sensitivity of 56% and a specificity of 90% in PLWHA with CD4 counts of 100 cells/mm³ or less, and a sensitivity

of 15% and a specificity of 96% in PLWHA with CD4 counts over 200 cells/mm³.⁴⁷ When Determine TB LAM is used in combination with a clinical exam, a chest X-ray, and Xpert, however, the proportion of PLWHA correctly diagnosed with TB increases by 35%.⁴⁸

Despite its relatively low sensitivity, Determine TB LAM offers a lifesaving option for rapidly diagnosing TB and immediately initiating treatment among seriously ill PLWHA. Because TB can progress quickly in people with advanced HIV, there is a high risk of mortality. One study found that the use of TB LAM among seriously ill PLWHA led to earlier initiation of TB treatment and decreased eight-week TB mortality by 29% among PLWHA with CD4 counts of 50 cells/mm³ or less.⁴⁹ Another study showed that mortality risk for PLWHA with a positive LAM test was 2.3 times greater than PLWHA with a negative result, emphasizing its potential as an important diagnostic tool for PLWHA, especially in high-TB-burden countries.⁵⁰ For PLWHA who show signs and symptoms of TB but receive a negative result from Determine TB LAM, further testing may be required, or depending on the degree of illness, TB treatment can be initiated empirically without a positive test result.⁵¹

At US\$3.50 per test, Determine TB LAM is the closest to WHO's target product profile cost of US\$1–\$2 for a point-of-care diagnostic test.⁵² However, scale-up of the test to reach higher volumes and lower prices has not reached its full potential. Since the test's sensitivity increases in relation to the advancement of HIV, its indication is currently limited to seriously ill PLWHA. The WHO recommended Determine TB LAM in 2015, but because of its low sensitivity, the WHO issued a limited recommendation on the use of the test to “assist in the diagnosis of TB” among seriously ill PLWHA with low CD4 counts. Within the same guidance, the WHO issued a strong recommendation against the use of Determine TB LAM for the general “diagnosis of TB,” creating confusion in the field. An additional challenge limiting the scale-up of the test is that TB and HIV programs and budgets are often siloed, so there is often a lack of clarity regarding which program is responsible for Determine TB LAM procurement.

WHO LAM guidance: Confusing recommendations limit uptake

Despite its lifesaving potential for seriously ill PLWHA at high risk of TB, the scale-up of Abbott's Determine TB LAM test in high-TB- and HIV-burden countries has left much to be desired. The 2015 WHO policy recommendations on Determine TB LAM include a conditional recommendation for the use of the test to assist in the diagnosis of PLWHA with low CD4 counts or who are seriously ill, but this positive indication is couched within a strong negative recommendation against the use of Determine TB LAM for the general “diagnosis of TB.”⁵³ This language offers no clarity for countries that are considering whether to procure and implement TB LAM tests.

Studies have shown that implementing TB LAM tests improves survival for seriously ill PLWHA, because of the rapid test result and the opportunity for immediate initiation of TB treatment.⁵⁴ Determine TB LAM, however, has not

reached its lifesaving potential because of slow uptake by country programs. A review of Determine TB LAM procurement through PEPFAR and the Global Fund showed that only 11 countries included TB LAM testing in their funding applications, indicating that countries are not implementing the test even where donor funding is available for procurement.⁵⁵

While the WHO issues recommendations based on evidence, as it should, the convoluted nature of its 2015 TB LAM recommendation did not do justice to the lifesaving potential of the test. Studies have since bolstered the diagnostic value of Determine TB LAM for PLWHA who present at health centers with signs and symptoms of TB and CD4 counts of 100-199 cells/mm³, not just the most seriously ill.⁵⁶ It does no harm to use Determine TB LAM as an initial test for anyone presenting with advanced HIV at a health center in a high-TB-burden country, so long as people who test negative and are at high risk of TB receive additional testing. It is hoped that the new WHO guidelines on TB LAM, expected to be released before the end of 2019, will take into account these types of considerations and be written more clearly.

Fujifilm SILVAMP TB LAM: Will a broader indication increase uptake?

A new TB LAM test in the pipeline is expected to offer greater sensitivity than Abbott's Determine TB LAM test and is therefore likely to extend the indication of TB LAM testing beyond seriously ill PLWHA. Fujifilm, in collaboration with FIND, is close to releasing its new SILVAMP TB LAM test, which is 30% more sensitive than Abbott's Determine TB LAM. SILVAMP TB LAM applies a technology that binds silver particles to LAM antibodies to amplify them. Unlike Determine TB LAM, which is applied directly to unprocessed urine, SILVAMP TB LAM requires the urine to undergo 40 minutes of processing before it is applied to the assay, after which several simple steps are performed to determine the result. Based on early studies, SILVAMP TB LAM was shown to have 84.2% sensitivity and 85% specificity among PLWHA with CD4 counts of 100 cells/mm³ or less and 44% sensitivity and 97% specificity⁵⁷ among PLWHA with CD4 counts over 200 cells/mm³. Because of its better sensitivity than Determine TB LAM, Fujifilm's test has the potential to be more broadly used for the diagnosis of TB in all PLWHA. This broader indication could help simplify WHO recommendations, which could in turn improve country uptake.

Clinical studies that are seeking to evaluate the sensitivity of SILVAMP TB LAM in all PLWHA are ongoing and are expected to be completed in 2020, followed by WHO review of SILVAMP TB LAM that same year, with the test expected to enter the market in 2021. If the evidence shows that SILVAMP TB LAM can be more broadly applied to all PLWHA, it could potentially lead to an indication that is not tied to CD4 counts. This would be beneficial, as many health centers in high-TB-burden countries do not have access to functioning machines to measure CD4, and waiting for CD4 testing would delay TB LAM testing in a critically narrow time span for those who are very sick.

A WHO recommendation of SILVAMP TB LAM for all PLWHA could improve country uptake, greatly increase the volumes procured, and reduce the price of the test. Compared with Abbott's TB LAM test, however, Fujifilm's TB LAM test is constructed of more expensive materials and is therefore likely to enter the market at a higher price than US\$3.50, although the company has not yet released information on the price.

Centralized Drug Susceptibility Testing

Also in the pipeline are advances in DST, the essential complementary step in the care cascade taking place after or along with TB detection. Testing the susceptibility of a particular strain of TB to certain drugs can identify drug resistance and indicate the most effective treatment regimen. With the rise of drug-resistant TB, it is imperative that all people diagnosed with TB receive DST to optimize their treatment outcomes and stop the cycle of escalating drug resistance, along with the continued spread of drug-resistant TB.

DST has conventionally been done through culture testing, which is highly accurate but takes at least two weeks for results. Line probe assays, which amplify and detect specific genetic mutations associated with resistance to certain drugs, have a much faster turnaround of one to two days but have an open-tube format that poses the risk of cross-contamination and that requires appropriate laboratory infrastructure and equipment. Next-generation molecular DST platforms currently in the pipeline, however, offer the option of high-throughput, automated PCR. These platforms can turn around results in a matter of hours, with some capable of running up to 100 tests per day. With improved linkage to point-of-care health facilities, these new DST platforms could expand access to rapid DST immediately following initial TB diagnosis, helping to make universal DST a reality. A number of these new DST platforms currently undergoing WHO review test for resistance to first-line drugs rifampin and isoniazid, but rapid DST for resistance to other new and existing second-line drugs is also critically needed. Another exciting development in DST is the use of genome sequencing, which either targets specific parts of the genome associated with resistance to certain drugs or sequences the whole genome to map the entire drug-resistance profile of a strain of TB. Genome sequencing is currently under development and is anticipated as the future of rapid centralized DST.

Next-generation rapid high-throughput molecular DST

Roche's Cobas MTB-RIF/INH, Abbott's RealTime MTB RIF/INH Resistance assay, the BD MAX MDR-TB assay, and Hain Lifescience's FluoroType MTBDR, which test for resistance to first-line TB drugs rifampin and isoniazid, are all on the pathway to WHO evaluation. According to Roche, Cobas MTB-RIF/INH, which runs on the Cobas 6800 and 8800 systems, detects resistance to rifampin at 97.2% sensitivity and 98.6% specificity and detects resistance to isoniazid at 96.9% sensitivity and 99.4% specificity.⁵⁸ Abbott's RealTime MTB RIF/INH Resistance, which runs on the m2000 RealTime System, is listed by Abbott as having clinical sensitivity of 94.8% and specificity of 100% for rifampin resistance and clinical sensitivity of 88.3% and specificity of 94.3% for isoniazid resistance.⁵⁹ A number of peer-reviewed articles from independent and Abbott-sponsored

studies confirm similar diagnostic performance.⁶⁰ The platforms for both Roche's Cobas MTB-RIF/INH and Abbott's RealTime MTB RIF/INH Resistance are already in use in the field for HIV viral load testing, offering the opportunity for testing integration across TB and HIV programs.

The BD MAX MDR-TB assay is run on the BD MAX platform, which has the capacity to test up to 24 samples at a time and up to 72 samples per eight-hour workday. The assay is designed to be used as a first-line test for MDR-TB and to be followed up with culture testing for second-line TB drugs. A recent study found BD MAX MDR-TB to have 90% sensitivity and 95% specificity for rifampin resistance and 82% sensitivity and 100% specificity for isoniazid resistance.⁶¹ Hain Lifescience's FluoroType MTBDR was designed to improve upon several flaws of its earlier WHO-recommended GenoType MTBDRplus. FluoroType MTBDR includes less hands-on time, more rapid results in just 2.5 hours, decreased risk of DNA contamination, and automatic interpretation, making it much easier to operate. According to a peer-reviewed study, FluoroType MTBDR has 98.9% sensitivity and 100% specificity for rifampin resistance and 91.7% sensitivity and 100% specificity for isoniazid resistance.⁶²

Genome sequencing

Advances in genome sequencing offer the prospect of faster, safer, and more comprehensive DST for TB. Whole genome sequencing is capable of identifying the exact and complete drug-resistance profile of a particular strain of TB, theoretically enabling clinicians to determine the best treatment regimen to combat the disease. However, more data is still needed to better correlate genetic mutations with phenotypic resistance to available TB drugs, which will be necessary to be able to definitively guide clinical care. While genome sequencing technology exists today, it requires a massive amount of data infrastructure and would be a costly upgrade for centralized DST in low- and middle-income countries. Short of sequencing the whole genome, however, another option is targeted genome sequencing, which uses more manageable amounts of data by sequencing only specific parts of the genome associated with resistance to certain drugs.

FIND, with funding from Unitaid, will be implementing a three-year project that began in October 2019 to support the introduction of targeted next-generation sequencing (NGS) for drug-resistant TB in Brazil, China, Georgia, India, and South Africa. Through the project, FIND intends to develop a model for adoption and scale-up of NGS for rapid and affordable DST, while generating clinical evidence to inform WHO guidance on the use of targeted NGS for diagnosing drug-resistant TB.⁶³ Another initiative, the CRYPTIC Project (Comprehensive Resistance Prediction for Tuberculosis: an International Consortium), aims to improve the understanding of the relationship between clinical resistance and genotype, by sequencing 100,000 whole TB genomes from diverse geographies in parallel with comprehensive DST. The results will then be stored in an open-access database to support knowledge sharing and to further efforts to ultimately identify the minority variants associated with low-level drug resistance that are selected for in treatment, and from which drug resistance emerges.⁶⁴

Triage or Referral Tests for Identifying People Who May Have TB

When people with TB do not have access to TB screening and diagnostic tests, despite often having signs and symptoms of TB, they can inadvertently pass the disease on to others and continue the cycle of TB transmission. In order to close this gap in diagnosis, it is essential to scale up inexpensive community-level tests to screen and identify people who may have TB. When results from these tests are suggestive of TB, they must then be followed by rapid, accurate confirmatory diagnostic testing. Apart from symptom screening, the most widely used triage test for pulmonary TB is the chest X-ray, which is relatively inexpensive but requires a trained radiologist to read. Expanding the use of chest X-rays as a triage tool in combination with Xpert testing is a cost-effective way to expand TB screening and to minimize the unnecessary use of Xpert tests on those with low risk of TB.

Chest X-rays have been used as a TB screening tool for a number of decades and continue to play an essential role as a triage test within the TB diagnostics algorithm, despite their shortcomings, which include insufficient sensitivity as well as the need for trained radiologists to interpret the images. In the TB diagnostics pipeline, however, technologies are being developed to address these shortcomings by utilizing artificial-intelligence-based computer-aided detection (CAD) to help interpret digital X-rays, with early studies showing high accuracy for identifying TB. In addition to X-rays, inexpensive, antigen-based breath tests are being developed to enable rapid, accurate TB screening and triage at the community level. Although these breath tests offer significant promise, they are still in the early stages of development, with more studies needed to generate sufficient evidence of their effectiveness.

Computer-aided detection

Several companies are developing CAD technologies that utilize machine-learning and artificial-intelligence algorithms to identify abnormalities in chest X-rays that are suggestive of TB with a higher degree of accuracy than trained radiologists. This technology offers real-time interpretation of chest X-rays, which can be accessed with a simple Internet connection and is particularly beneficial in remote areas with little or no access to trained radiologists. The majority of the studies on CAD technologies, however, have largely focused on development rather than clinical evaluation, so further studies will be needed.⁶⁵

One of these technologies, Delft Imaging Systems' CAD4TB, has been commercially available since 2011 and is currently undergoing studies to generate the data needed for WHO evaluation. A systematic review of studies from 2005 to 2019 using versions of CAD4TB found that for detecting chest X-ray abnormalities associated with pulmonary TB, CAD4TB sensitivity ranged from 85% to 100%, and its specificity ranged from 23% to 69%.⁶⁶ The latest CAD4TB system was trained by applying deep learning to thousands of healthy and TB-diseased X-rays from over 15 countries. The software produces an output score of 0 to 100 indicating the likelihood that

the patient has TB, which helps to quickly determine whether the X-ray should be followed by a sputum-based diagnostic test.⁶⁷ According to Delft Imaging Systems, CAD4TB is currently being used in 37 countries to screen 7,000 people each day for chest X-ray abnormalities associated with TB. CAD4TB is priced according to a pay-per-screening model and is also supplied in bundles, with the lowest volume-based price per image at US\$0.40.⁶⁸

Another company, Qure.ai, has developed qXR, an artificial-intelligence-based deep-learning system that was trained on 2.5 million chest X-rays from around the globe. Based on initial studies, qXR was found to be capable of detecting abnormalities in chest X-rays at a high rate. The studies found that qXR sensitivity ranges from 93% to 100%, with its specificity ranging from 92% to 99%.⁶⁹ All that is needed to run qXR is a laptop and an Internet connection, and when qXR finishes processing a scan, the results are immediately available on the computer interface. Using chest X-rays with qXR as a point-of-care screening tool paired with a rapid molecular test such as Xpert has the potential to reduce the time to TB diagnosis and improve linkage to treatment. qXR has been available commercially since 2018, but studies are ongoing, and the product is currently on the pathway to WHO evaluation. According to Qure.ai, the company intends to scale up the use of qXR across all high-TB-burden countries and, depending on volumes, aims to price the product in line with WHO's recommended TPP price for TB screening tests, US\$1–\$2.⁷⁰

Breath tests

New breath tests for rapid point-of-care TB screening and triage at the community level are also in the pipeline but are at an earlier stage of development. These breath tests are noninvasive and utilize technologies that detect TB antigens. Rapid Biosensor Systems is developing a device called the TB Breathalyser. The company reports that the processing time to reach the test result is just two minutes and says that early studies on Breathalyser show that the test's sensitivity and specificity for detecting infectious pulmonary TB are both above 95%.⁷¹ Another breath test, Aeonose, developed by The eNose Company, detects volatile organic compound markers in breath that are sensitive and specific for pulmonary TB. At this early stage of development, however, the company reports that the sensitivity of the test is comparable to that of chest X-rays. A recent peer-reviewed study found Aeonose sensitivity to be 78% to 85%, with specificity from 42% to 55%.⁷² With volume-based pricing, Breathalyser is expected to be priced at US\$5,⁷³ and Aeonose is expected to be priced under US\$10.⁷⁴ Although these tests show promise for the future of TB screening, they are still in the early stages of research and development with studies ongoing.

Treatment Monitoring

The basic science of biomarkers for TB is an area of ongoing research, with the aim of identifying a TB biomarker that is capable of tracking the progression of TB disease, monitoring treatment, and testing for cure. Unlike HIV treatment monitoring, which tracks the viral load of HIV as the distinct biomarker to indicate disease progression and treatment effectiveness, TB treatment lacks reliable biomarkers that can be used to monitor treatment. Currently, culture testing and smear microscopy play this role, by detecting and measuring concentrations of TB bacteria. A new technology, however, shows promise in offering the potential for biomarker-based TB treatment monitoring by measuring concentrations of LAM in sputum. While this process involves a highly complex laboratory-based test, at least one company has expressed interest in developing it into an automated cartridge-based assay.

LAM-ELISA

LAM-ELISA technology offers a new method of detecting concentrations of LAM in sputum as a potential biomarker for TB treatment monitoring. It uses an enzyme-linked immunosorbent assay (ELISA), which determines the concentration of LAM protein by measuring the antibodies directed against it. A small study found that among both LAM and culture-positive samples, there was an inverse correlation between LAM concentrations in sputum and time to detection for culture tests, with LAM concentrations declining as time to detection by culture increases. The study concluded that LAM-ELISA could be used as a biomarker to measure TB bacterial load before and during TB treatment.⁷⁵ But because of the small size of the study, additional studies will be needed to explore the predictive value of LAM concentrations as a biomarker for TB treatment effectiveness.

Otsuka Pharmaceutical is currently using LAM-ELISA for research purposes, to generate more data for further validation. Because of the complexity of the LAM-ELISA test, Otsuka does not intend to seek WHO endorsement of the current test for clinical use. However, Otsuka said they are working with a commercial partner to migrate the ELISA platform to a cartridge-based immunoassay platform to improve the user interface and transform the test into a point-of-care tool for use in the field. The new assay will use the same antibodies as in LAM-ELISA, so Otsuka expects that only a bridge study will be needed to validate the data. Once the new cartridge-based assay is developed and validated, Otsuka will then make a decision regarding WHO endorsement.⁷⁶

Tests For TB Infection

New developments in the pipeline also involve improved tests for TB infection, which include both blood- and skin-based tests. An important new blood-based test that is expected to undergo WHO evaluation in 2020 is a simplified interferon-gamma release assay (IGRA) that uses a lateral flow cartridge to replace a complex laboratory process; the intention is to bring testing for TB infection closer to the point of care. New skin

tests are also improving in sensitivity without being affected by previous bacillus Calmette-Guérin (BCG) vaccine, making them more appropriate in high-TB-burden countries where BCG vaccination is widespread. An ongoing challenge with evaluating tests for TB infection is that there is no gold standard for confirming or excluding diagnosis of TB infection. All of the existing tests measure the immunological response to TB antigens and so provide only indirect evidence for TB infection. More research is also needed to be able to determine who is most at risk for progression to active TB disease, in order to optimize the use of preventive therapy. In the meantime, testing for TB infection is not required before providing preventive therapy to those at high risk of TB, including PLWHA and children who are household contacts of people with TB.

QuantiFERON-TB Access

Qiagen is currently working on an improved test for TB infection, QuantiFERON-TB Access (QFT-Access). This builds off of the technology of the QuantiFERON-TB Gold Plus (QFT-Plus) blood-based IGRA,⁷⁷ which measures the response of both CD4 and CD8 T cells to TB antigens. According to Qiagen, QFT-Plus sensitivity is more than 94% (based on culture-confirmed active TB disease), and its specificity is more than 97% (based on false-positive rates among people with low or no known risks for TB infection).^{78,79} QFT-Access simplifies the QFT-Plus test process, making it more accessible and scalable closer to the point of care, thereby supporting the expansion of testing for TB infection in high-TB-burden countries. QFT-Access has taken a complex three-hour laboratory process with many steps requiring trained technicians and expensive machines and has simplified it into a single-use lateral flow-based cartridge. To complete the test, a single tube of blood is incubated for 16 to 24 hours, and results are determined in five to 20 minutes using the cartridge. Clinical trials for QFT-Access are ongoing, and WHO review and commercialization of the improved test are expected to take place in 2020.⁸⁰

C-Tb skin test

Important developments are also taking place to improve skin tests for TB infection, which are community-level, point-of-care tests. One of these tests, C-Tb skin test, developed by Statens Serum Institute in Denmark, shows comparable sensitivity to Qiagen's QuantiFERON-TB Gold (QFT) IGRA test and, unlike earlier skin tests, is not affected by previous BCG vaccination. C-Tb offers the possibility of expanding testing for TB infection in high-TB-burden countries, by replacing the long-standing tuberculin skin test (TST), which is compromised by previous BCG vaccination. According to early studies, C-Tb sensitivity was 94% concordant with QFT, and its sensitivity and safety profile were similar to TST's.⁸¹ C-Tb is currently on the pathway to WHO evaluation and is expected to enter the market in 2020. While a similar test, Diaskintest, has been on the market in several former Soviet republics since 2005, there has not been sufficient data on the efficacy and safety of the test to move forward with WHO review.⁸²

Conclusion and Recommendations

All of these developments in the pipeline together represent a major step forward toward improving TB diagnostic technologies. However, closing the diagnostic gap and improving linkage to TB treatment will require more than technological advancements. It will require:

- investing in studies to generate sufficient data for new diagnostic tests to undergo WHO review;
- developing clear guidelines for the placement and use of these diagnostics within complex health systems;
- integrating the latest and most effective diagnostic technologies into diagnostic algorithms in both public and private sectors;
- ensuring that there is political will and funding for TB and other health programs to scale up TB screening, including by implementing new diagnostic tools;
- holding manufacturers, product sponsors and TB diagnostics research funders accountable for ensuring transparency and pricing that promotes equitable access;
- increasing funding for expanding research and development efforts necessary to produce new and better TB diagnostic tools; and
- ensuring that our political leaders make good on their commitments to diagnose and treat all people with TB.

Many say that “TB is complicated,” but this is all the more reason to address it with the latest scientific developments and most effective technologies, along with the best that global collaboration has to offer. To close the TB diagnostics gap, we all have a role to play.

For funders:

- Increase funding for TB diagnostics research⁸³ to facilitate the development of tests that meet the WHO target product profiles for TB diagnostics, particularly those that bring TB detection and DST closer to the point of care and those based on biomarkers that do not require sputum.
- Invest in alternative mechanisms to incentivize TB diagnostics research and development that delink the costs of this investment from the price of diagnostic products, including through grants, subsidies, and cash rewards that result in open licenses, generic competition, and affordably priced diagnostic tools.
- Engage and support communities affected by TB to take a leading role in determining funding priorities and shaping future investments in TB diagnostics research, development and scale-up.

- Ensure that clinical trials of new diagnostics include all populations affected by TB, including PLWHA, children, and people with extrapulmonary TB, so that there is evidence to support the most widespread and effective use of these tools.
- Require researchers receiving funding to transparently report on the data and findings of their work, to promote trust and knowledge sharing throughout the TB diagnostics research community.

For national TB programs:

- Protect the rights of people with TB by ensuring that they have affordable access to the latest and most effective diagnostic technologies, including rapid tests for TB detection and universal DST, and that they receive rapid linkage to effective treatment and the highest quality of care.
- Procure and implement the latest and most effective TB diagnostic technologies, with particular emphasis on rapid molecular tests to replace smear microscopy, TB LAM tests for diagnosing TB in seriously ill PLWHA, and rapid molecular DST for first- and second-line TB drugs.
- Invest in strengthening health systems—including laboratories—in order to expand TB screening, to more rapidly test for TB and drug resistance closer to the point of care, and to more swiftly link those diagnosed with TB to the most effective treatment.
- Improve collaboration and coordination across TB, HIV, and other health programs and budgets to support the sufficient procurement, scale-up and availability of TB diagnostics for PLWHA, children, and other populations affected by TB.

For civil society and communities affected by TB:

- Hold funders accountable for investing in public-health-driven TB diagnostics research and development, in line with WHO target product profiles, to ensure that the pipeline results in affordable and effective new tools, as well as market competition.
- Hold countries accountable for procuring and implementing the latest and most effective TB diagnostic technologies in line with WHO guidelines, and for investing in stronger health systems—including laboratories—to expand TB screening and diagnosis, and to improve rapid linkage to effective treatment.
- Hold the WHO accountable for developing clear and evidence-based recommendations on new diagnostics to support countries to procure and implement the latest and most effective TB diagnostic technologies.
- Hold manufacturers and product sponsors accountable for investing in the research and development of new diagnostics according to WHO target product profiles, and for offering these new diagnostic products at affordable, volume-based prices that reflect the lowest possible cost of goods plus reasonable profit.

For the World Health Organization:

- Support high-TB-burden countries to integrate the latest and most effective TB diagnostics into national TB programs and other health programs where people at risk of TB present for care, and provide assistance to strengthen national TB laboratories.
- Ensure that TB diagnostic guidelines are evidence-based and composed of clear and practical recommendations that support countries to make informed procurement decisions and to uphold the highest standard of care in their TB programs.
- Improve the transparency of the TB diagnostics guideline development process, including through making the results of public consultations regarding the scope and composition of planned guideline development group meetings publicly available.
- Improve the accountability of the TB diagnostics guideline development process by inviting greater and more meaningful participation from civil society and TB-affected communities, including through helping to build technical literacy without undermining the value of the existing knowledge of these communities.

For manufacturers and product sponsors:

- End the neglect of TB by investing resources in the research and development of diagnostic technologies in line with WHO target product profiles, including rapid point-of-care diagnostics, rapid drug susceptibility tests, and non-sputum biomarker-based tests.
- Commit to offer fully transparent, volume-based pricing according to the lowest possible cost of goods plus a reasonable markup, in order to maximize country uptake and implementation of the latest and most effective TB diagnostic technologies.
- Price new TB diagnostics in a way that reflects the public and philanthropic investments in the research and development of these products and that provides a larger public return on these investments.
- Ensure that the most difficult-to-diagnose populations—PLWHA, children, and people with extrapulmonary TB—are included in diagnostics research and clinical trials that generate evidence for the most widespread use of new TB diagnostic tools.

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