

Pipeline Report » 2020

Tuberculosis Diagnostics

TAG

Treatment Action Group

The Tuberculosis Diagnostics Pipeline Report: Advancing the Next Generation of Tools

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Introduction

Diagnosing tuberculosis (TB) is one of the most challenging aspects of the TB cascade of care. In 2019, an estimated 10 million people developed active TB, but nearly 30 percent were either not diagnosed or not reported as being diagnosed.¹ This is in part because many countries have not fully scaled up and implemented available TB diagnostic tools according to World Health Organization (WHO) recommendations.² It is also because many of the diagnostic tools that are currently available and recommended by the WHO do not sufficiently meet the needs of people at risk of TB or of health systems in terms of accuracy, time to results, affordability, and appropriateness for use at the point-of-care (for more information on currently available WHO-recommended tools, see TAG's *An Activist's Guide to Tuberculosis Diagnostic Tools*).³ Without early and accurate diagnosis and rapid linkage to care, TB continues to spread in households and communities, and people with TB are put at greater risk of morbidity and mortality from the disease. National programs can do a better job of implementing available TB diagnostic tools, but new and better tools are necessary to enable low-cost, rapid, and accurate TB screening and diagnosis closer to the point-of-care, and to ensure that all people at risk of TB receive the care they need.

The WHO and the Foundation for Innovative New Diagnostics (FIND) developed a set of target product profiles (TPPs) to guide the development of new TB diagnostic tools.⁴ The TPPs detail the types of tools that are needed according to different **use cases** and establish the criteria these tools should meet in terms of optimal and minimal performance and operational characteristics. The different use cases focus on the detection of TB at different stages of disease progression, which include **TB infection**, **incipient TB**, and **active TB disease**; for different forms of the disease, such as **drug-susceptible TB (DS-TB)** or **drug-resistant TB (DR-TB)**; and in different settings of use, such as communities, primary care clinics, and district or central laboratories. The different criteria focus on technical performance, such

Use cases: specific scenarios for which TB screening or diagnostic interventions are needed

TB infection: infection with *Mycobacterium tuberculosis* (MTB), sometimes referred to as latent TB infection (LTBI)

Incipient TB: a stage in the spectrum of TB infection indicating the progression to active TB disease

Active TB disease: TB that actively reproduces in the body, causes tissue damage that makes people sick, and is capable of being transmitted from one person to another

Drug-susceptible TB (DS-TB): TB that can be effectively treated with first-line TB drugs isoniazid and rifampicin

Drug-resistant TB (DR-TB): TB that is resistant to at least one TB drug

as **sensitivity** and **specificity**; and operational characteristics, such as level of use in the health system, time to results, and price. While a number of the WHO-recommended diagnostic tools that are currently in use meet some of the minimal and optimal TPP criteria, none meet all of the minimal TPP criteria, underscoring the urgent need for continued research, development, and innovation.

Fortunately, the current TB diagnostics pipeline includes a number of promising new and next-generation technologies that demonstrate progress is being made toward meeting the TPPs. The 2020 Tuberculosis Diagnostics Pipeline Report details the range of new TB diagnostic tools currently in the pipeline and highlights the ways in which these tools are expected to meet the TPPs, and where they might fall short. It also details some of the science and technology behind these tools and discusses considerations for implementing them in health care settings. The report is organized according to the TPPs defined by the WHO and FIND, and includes the following sections:

1. Tests for TB screening and triage
2. Point-of-care biomarker-based tests that do not require sputum
3. Tests to replace smear microscopy as the initial TB diagnostic test
4. Next-generation drug-susceptibility tests to inform TB treatment
5. Next-generation sequencing for detection of drug resistance
6. Tests for detecting incipient TB and for treatment monitoring
7. Tests for TB infection

1. Tests for TB screening and triage

TB screening and triage tests are needed to support early identification of people who may have TB. It is important for these tools to be very sensitive so that people with TB are not missed by these tests. People who screen positive for TB are then referred for confirmatory diagnostic testing with a more sensitive and specific rapid molecular test, such as Cepheid's Xpert MTB/RIF or Molbio's Truenat MTB. Because TB screening and triage tests are needed to test a large number of people—through systematic screening programs in communities or routine care in health facilities—it is very important for these tests to be simple, affordable, and able to be implemented at the point-of-care.

The most widely used TB screening and triage test that people receive for TB is the WHO four-symptom screen, which tests for current cough, fever, weight loss, and night sweats, and is about 77 percent sensitive and 68 percent specific for detecting any TB symptom.⁵ This test, by definition, is only sensitive among people who have already developed TB symptoms, which is after TB bacteria have begun

Sensitivity (SE): a test specification that represents the proportion of people with a disease that a test correctly identifies as having the disease

Specificity (SP): a test specification that represents the proportion of people without a disease that a test correctly identifies as not having the disease

to damage tissues in the lungs or other parts of the body and after TB may have spread to other people. Chest X-rays, another available screening and triage tool for **pulmonary TB** with sensitivity ranging from 87 to 98 percent and specificity around 75 percent,⁶ are capable of detecting the onset of TB disease earlier than the four-symptom screen (i.e., before symptoms appear). A review of prevalence surveys of 23 countries in Africa and Asia showed that nearly 50 percent of people with bacteriologically confirmed TB in communities screened negative for symptoms. It also showed that 90 percent of people with bacteriologically confirmed TB were detected through the use of chest X-rays, highlighting the important role chest X-rays could play for TB screening given the limited sensitivity of symptom screening.⁷ Chest X-rays, however, have historically not been feasible to implement on a large scale in systematic screening programs because X-ray machines are generally costly and bulky, and because many low- and middle-income countries do not have sufficient access to trained radiologists to read and interpret X-ray images.⁸

These barriers to implementing chest X-rays on a wider scale may soon be reduced with the development and scale-up of lightweight, portable X-ray machines for use at the community level and computer-aided detection (CAD) software to assist health workers in reading and interpreting X-rays in decentralized health settings. Computer-aided detection utilizes artificial intelligence (AI) deep learning networks to identify lung abnormalities suggestive of TB on chest X-ray images, with a number of studies showing that CAD has comparable performance to trained human readers.⁹ These new tools could help to fill a critical gap for TB screening and triage by making chest X-rays more feasible to implement on a large scale at or close to the point-of-care in low- and middle-income countries. CAD software can either be accessed online, which requires an internet connection, or offline through the use of a small computer server unit with the database of chest X-rays and the AI software. Where online cloud-based systems are established, CAD technologies can integrate with them to seamlessly and rapidly turn around results to reduce loss to follow-up and improve linkage to care.¹⁰ The increased use of chest X-rays combined with CAD as a screening and triage tool could also help to target and optimize the use of more expensive rapid molecular tests—extending the reach of diagnostic systems and health budgets. The WHO is reviewing CAD tools as a class of technologies in 2020 and will release recommendations on the use of these tools in 2021. More information and a more comprehensive list of the range of CAD tools in the pipeline are available on the Stop TB Partnership-hosted website ai4hlth.org. In addition to portable X-ray machines and CAD technologies, breath tests to detect biomarkers indicative of the presence of TB bacteria in the lungs are also in the pipeline, though these tests are still at an early stage of development.

Table 1: Tests for TB screening and triage

Target Product Profile: Community-based triage or referral test for identifying people suspected of having TB ¹¹									
Sensitivity* (pulmonary TB)		Specificity* (pulmonary TB)		Lowest level of use		Time to results		Price per test	
Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal
> 95%	> 90%	≥ 80%	≥ 70%	Community	Health post	< 5 min	< 30 min	< US\$1	< US\$2

Test/tool (Manufacturer)	Type	Sensitivity*/ Specificity*/ AUC**	Lowest level of use	Time to results	Price per image/ test/tool	Stage of development/ WHO review
Delft Light (Delft Imaging)	Portable X-ray	—	Community	10 seconds ¹²	~US\$83,000 (including portable solar panel) ¹³	Commercially available
FDR Xair (Fujifilm)	Portable X-ray	—	Community	2–3 seconds	US\$70,000 to US\$100,000 ¹⁴	Commercially available
Impact (MinXray)	Portable X-ray	—	Community	~4 seconds ¹⁵	US\$47,000 to US\$50,000 ¹⁶	Commercially available
HandMed (JLK Inspection)	Portable X-ray	—	Community	< 3 seconds ¹⁷	Varies ¹⁸	Commercially available
CAD4TB v6 (Delft Imaging)	CAD	SE: 95% SP: 80% AUC: 0.92 ¹⁹	Community	< 20 seconds ²⁰	Image: US\$0.82 to US\$1.11; Offline unit: US\$7,000 ²¹	WHO review: 2020
qXR v3 (qure.ai)	CAD	SE: 95%*** SP: 82%*** AUC: 0.94 ²²	Community	< 1 min	Image: Volume-based pricing; ²³ Offline unit: price not available	WHO review: 2020
INSIGHT CXR (Lunit)	CAD	SE: 95% SP: 76% AUC: 0.94 ²⁴	Community	20 seconds	Image: Volume-based pricing; ²⁵ Offline unit: price not available	WHO review: 2020
JLD-02K JVIEWER-X (JLK Inspection)	CAD	Not yet available	Community	< 10 seconds	Varies ²⁶	Projected year of WHO review: 2021
TB Breathalyser (Rapid Biosensor Systems)	Breath test	SE: > 95% SP: > 95% (early data from field trials) ²⁷	Community	2 min	< US\$5 per test; < US\$2,000 for the reader ²⁸	Early stage development
Aeonose (The eNose Company)	Breath test	SE: 81% SP: 60% ²⁹	Community	Rapid	< US\$10 ³⁰	Early stage development

* Microbiological reference standard: a standard of accuracy established by a highly sensitive and specific test used to microbiologically confirm the presence of TB, against which the accuracy of other tests may be compared

** Area under the ROC curve—an alternate measure of accuracy that combines sensitivity and specificity with 1 representing perfect performance (100% sensitivity and 100% specificity)

*** Sensitivity and specificity for qXR v2

2. Point-of-care biomarker-based tests that do not require sputum

The most commonly used sample for diagnosing TB is sputum coughed up from the lungs. However, many children and people living with HIV/AIDS (PLWHA) are not able to produce a sputum sample. Sputum is also not a useful sample for **extrapulmonary TB**, which usually requires invasive procedures to obtain other samples for diagnostic testing from sites outside the lungs that are affected by TB (i.e., lymph nodes, the pleural cavity surrounding the lungs, the brain and spinal cord, bones or joints, and the abdominal cavity). Developing sensitive **biomarker**-based tests that utilize easy-to-obtain samples such as urine or blood and that can be performed at the point-of-care are therefore a high priority. One example of a biomarker-based test is the LAM test, which detects lipoarabinomannan (LAM), a component of the outer cell wall of TB bacteria that is released in the body and that can be detected in urine. Abbott's Determine TB LAM Ag for PLWHA is currently the only available LAM test. It is an instrument-free, paper-based lateral flow assay that is inexpensive at US\$3.50 per test, produces results in less than 25 minutes, and is easy to perform at the point-of-care by a minimally trained health worker. While this test has been commercially available and recommended by the WHO for use among PLWHA since 2015,³¹ uptake of the test has remained very limited.³² This is in spite of the fact that the LAM test has been shown to support rapid TB diagnosis among PLWHA and to save lives of people with advanced HIV disease, or AIDS.³³ Because the sensitivity of the currently available LAM test is only sufficient for use among PLWHA with low CD4 cell counts (sensitivity: 56% among PLWHA with 0–100 CD4 cells/mm³, and 25.3% among PLWHA with 101–200 CD4 cells/mm³)³⁴, the test cannot be used among HIV-negative people. For more information on LAM testing for PLWHA, see TAG's [An Activist's Guide to the LAM Test](#).

Next-generation sensitive LAM tests are needed to improve rapid point-of-care TB diagnosis among all PLWHA and for use among children, people with extrapulmonary TB, and HIV-negative people. Several new next-generation LAM tests are in the pipeline, including Fujifilm's SILVAMP TB LAM, which is 30 percent more sensitive among PLWHA than Abbott's Determine TB LAM Ag.³⁵ SILVAMP TB LAM achieves this improved sensitivity by binding silver particles to the LAM antigen, thereby amplifying the detection of LAM in the sample and making the test easier to visually read. Fujifilm's new LAM test, however, is also more complex than the Abbott test, requiring a sample incubation period and additional steps, with a longer time to results of about an hour. FIND is currently coordinating multiple evaluation trials of SILVAMP TB LAM and the WHO is expected to review the test in 2021. Since the main hurdle for the wider use of point-of-care LAM tests is the low sensitivity of the tests, several funders have partnered with companies to develop methods to increase the sensitivity of these tests. These methods include concentrating urine to increase the amount of LAM in each sample and using a digital reader to more accurately read the results of the assay. These next-generation LAM tests are still in early stages of development, so information regarding their performance and operational characteristics is currently limited; however, these tests are expected to be developed and reviewed by the WHO within the next several years. The impending availability of inexpensive, simple, and more sensitive tests for all people at risk of TB will surely mark the beginning of a new era of widespread point-of-care TB testing.

Extrapulmonary TB: TB in parts of the body outside the lungs

Biomarker: a measurable element of the host or pathogen that indicates the presence or severity of a disease

Table 2: Point-of-care biomarker-based tests that do not require sputum

Target Product Profile: A rapid biomarker-based non-sputum-based test for detecting TB ³⁶									
Sensitivity*		Specificity*		Lowest level of use		Time to results		Price per test	
Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal
≥ 98%– ≥ 66%	> 98%– > 65%	≥ 98%	≥ 98%	Health post	Primary-care clinic with lab	< 20 min	< 1 hour	< US\$4	< US\$6
Test/tool (Manufacturer)	Type	Sensitivity*	Specificity*	Lowest level of use	Time to results	Price per test	Stage of development/ WHO review		
SILVAMP TB LAM (Fujifilm)	Urine LAM test	87.1% 0–100 CD4 cells/ mm ³ ; 62.7% 101–200 CD4 cells/ mm ³	80.5% 0–100 CD4 cells/ mm ³ ; 95% 101–200 CD4 cells/ mm ³ ³⁷	Community	< 60 min	Not yet available	WHO review: 2021		
Next- generation sensitive LAM (Abbott)	Urine LAM test	Not yet Available	Not yet available	Community	Not yet available	Not yet available	Early development ³⁸		
Next- generation sensitive LAM (Gates Foundation/ Salus Discovery)	Urine LAM test	90–95% target sensitivity ³⁹	Not yet available	Community	Not yet available	Not yet available	Early development		
Next- generation sensitive LAM (Global Good/ Biopromic)	Urine LAM test	Not yet Available	Not yet available	Community	Not yet available	Not yet available	Early development ⁴⁰		

*Microbiological reference standard

3. Tests to replace smear microscopy as the initial TB diagnostic test

In 2013, the WHO recommended rapid molecular tests to replace smear microscopy as the initial test for diagnosing TB.⁴¹ Smear microscopy—a technology from the late 1800s—is only about 50 percent sensitive for detecting TB and cannot detect drug resistance,⁴² but it is inexpensive (US\$2 per test).⁴³ Cepheid’s rapid molecular tests Xpert MTB/RIF and Xpert MTB/RIF Ultra, on the other hand, cost US\$9.98 per test for 145 low- and middle-income countries,⁴⁴ not to mention the costs of expensive GeneXpert instruments and service and maintenance plans (US\$17,500 for the four-module instrument and laptop, and nearly US\$8,000 for a three-year extended warranty).⁴⁵ In spite of the higher sensitivity of rapid molecular tests, the added benefit of testing for resistance to the first-line TB drug rifampicin, and the WHO recommendation to use rapid molecular tests as the initial TB diagnostic test, many countries have continued to use smear microscopy as the initial test,⁴⁶ citing high prices as one of the primary barriers to expanding use of rapid molecular tests.⁴⁷ In 2020, the WHO also recommended Molbio’s Truenat MTB and MTB-RIF Dx rapid molecular test to be used as an initial TB diagnostic test.⁴⁸ Compared to

GeneXpert, which requires constant electricity and air-conditioned temperatures, Molbio's Truenat testing instrument is battery powered and can be run without air conditioning. As such, Truenat can be implemented closer to the point-of-care in microscopy centers, but it also costs around US\$10 per test and relies on an expensive instrument (approximately US\$18,000 for the four-module Truelab instrument and the Trueprep device).⁴⁹

Rapid molecular tests that are accurate, inexpensive, and able to be implemented even closer to the point-of-care are urgently needed. Several companies are developing new testing systems to bring rapid molecular testing to the community level. While these platforms may help to meet the optimal TPP criteria with regard to level of use, it is currently uncertain how affordable they will be for low- and middle-income countries. The point-of-care platform that is furthest along in the pipeline is Cepheid's GeneXpert Omni, a battery-powered and portable testing instrument that runs GeneXpert test cartridges with an added near-field communication (NFC) chip to enable connectivity and communication between the cartridge and the instrument. GeneXpert Omni is currently undergoing equivalence studies and is expected to be reviewed by the WHO in 2021.⁵⁰ Earlier in the pipeline are Q-POC from QuantuMDx and NanoDetector from Ontera, which are both portable point-of-care instruments that aim to make rapid molecular testing less expensive and more accessible at the point-of-care, while also offering greater connectivity to communicate and track test results. In particular, QuantuMDx claims that the company's Q-POC will deliver rapid molecular testing at a fraction of the current price.⁵¹ Another company, Bioneer, is developing IRON-qPCR, a cartridge-based automated TB testing instrument similar to GeneXpert that is designed for use in primary care clinics and that will run Bioneer's TB, **multidrug-resistant TB (MDR-TB)**, and **extensively drug-resistant TB (XDR-TB)** tests, which are also in development.⁵²

While each of these companies are developing testing instruments to run proprietary tests, Blink DX is charting a different course with its Blink One Analyser instrument and One Cartridge that can be adapted by test developers for use with different reagents to detect molecular targets for TB and other diseases. Blink DX's new system offers the possibility of a shared development and product platform to support the rapid development and deployment of point-of-care molecular tests.⁵³ Since Blink One is still early in the pipeline, information on the system's performance is not yet available. In addition to new platforms, KNCV Tuberculosis Foundation, University of Bordeaux, and FIND/Rutgers are developing centrifuge-free stool processing kits to simplify and standardize the preparation of stool samples from children for use on Xpert MTB/RIF Ultra.^{54,55,56} These new tools are expected to reduce the need for invasive procedures to obtain sputum or other samples to be tested from children for diagnosing TB. Notwithstanding the development of these new rapid molecular testing platforms and other tools, the pipeline for new rapid molecular TB tests is relatively dry, considering that rapid molecular tests are recommended by the WHO as the initial TB diagnostic test for all people being evaluated for TB.

Multidrug-resistant TB (MDR-TB): TB that exhibits resistance to both first-line TB drugs rifampicin and isoniazid, and that may include resistance to the second-line fluoroquinolones, moxifloxacin or levofloxacin

Extensively drug-resistant TB (XDR-TB): TB that exhibits resistance to both rifampicin and isoniazid, resistance to the fluoroquinolones, and resistance to second-line injectable drugs, such as amikacin

Table 3: Tests to replace smear microscopy as the initial TB diagnostic test

Target Product Profile: Rapid sputum-based test for detecting TB at the microscopy center level of the health-care system ⁵⁷									
Sensitivity*		Specificity*		Lowest level of use		Time to results		Price per test	
Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal
> 95%	> 80%	> 98%	> 98%	Primary-care clinic with lab (microscopy center)		< 20 min	< 2 hours	< US\$4	< US\$6

Test/tool (Manufacturer)	Type	Sensitivity*/ Specificity*	Lowest level of use	Time to results	Price per test/ tool	Stage of development/ WHO review
TB Detection Assay (QuantuMDx)	Rapid molecular PCR/assay**	Not yet available	Primary care clinic/ Community	< 30 min ⁵⁸	Not yet available	Early stage development/ Projected year of WHO review: 2022 ⁵⁹
AccuPower MTB Real-Time PCR Kit for use on IRON qPCR platform (Bioneer)	Rapid molecular PCR/assay	Not yet available	Primary care clinic	< 1 hour ⁶⁰	Not yet available	On pathway to WHO review
GeneXpert Omni (Cepheid)	Rapid molecular PCR/platform**	—	Primary care clinic/ Community	< 90 min ⁶¹	Not yet available	WHO review: 2021
Q-POC (QuantuMDx)	Rapid molecular PCR/platform	—	Primary care clinic/ Community	< 30 min ⁶²	US\$15,000 (initial price)	Late development ⁶³
IRON-qPCR (Bioneer)	Rapid molecular PCR/platform	—	Primary care clinic	< 60 min ⁶⁴	Not yet available	On pathway to WHO review
NanoDetector (Ontera)	Rapid molecular PCR/platform	—	Primary care clinic/ Community	< 20 min ⁶⁵	Not yet available	Early development
Blink One (Blink DX)	Rapid molecular PCR/platform	—	Not yet available	Not yet available	Not yet available	Early development ⁶⁶
Stool processing solutions (KNCV Tuberculosis Foundation; TB Speed/ University of Bordeaux; FIND/Rutgers)	Rapid molecular PCR/sample processing**	—	District laboratory (for use with Xpert MTB/RIF Ultra)	Not yet available	Not yet available	WHO review: 2021

*Microbiological reference standard

**Assay: a test to detect the presence or severity of a disease; Platform: an instrument or device used to run a test or range of tests; Sample processing: the standardized preparation of samples for testing

4. Next-generation drug-susceptibility tests to inform TB treatment

The WHO recommends rapid molecular tests as the initial diagnostic test for TB and resistance to rifampicin—followed by universal drug-susceptibility testing (DST). DST should be undertaken according to the relevant WHO guidelines for other first-line drugs (including isoniazid and pyrazinamide), second-line drugs (including fluoroquinolones and amikacin), and new and repurposed drugs (bedaquiline, delamanid, pretomanid, linezolid, and clofazimine).⁶⁷ In 2019, only 61 percent of people diagnosed with pulmonary TB were also tested for resistance to rifampicin; of the half a million people who developed rifampicin-resistant TB in 2019, an estimated 78 percent had multidrug-resistant TB.⁶⁸ Existing tools for DST include molecular line probe assays that provide results in one day but are complex multi-step tests, and mycobacterial liquid culture that involves the growth of TB bacteria and can take between two to six weeks for results. Both of these forms of DST are generally suited for use in central laboratories. New tools are urgently needed to scale up rapid and accurate drug susceptibility testing closer to the point-of-care to inform the optimal selection of TB treatment regimens, improve treatment outcomes, and guard against propagation of drug-resistance.

A number of new molecular tests for drug-susceptibility are soon to be reviewed by the WHO in 2020. Among these are Cepheid's Xpert MTB/XDR, the first rapid, decentralized test for XDR-TB. Xpert MTB/XDR tests for resistance to isoniazid, ethionamide, fluoroquinolones, and amikacin. It also tests for resistance to the injectable drugs kanamycin and capreomycin, which are no longer recommended by the WHO in any TB treatment regimens. Xpert MTB/XDR, however, does not test for resistance to bedaquiline and linezolid, group A drugs and core components of WHO-recommended all-oral treatment regimens for drug-resistant-TB, or for resistance to other new and repurposed drugs commonly used in MDR- and XDR-TB treatment regimens. Because Xpert MTB/XDR tests for more molecular targets than earlier Xpert TB test cartridges, it cannot be run on the standard six-color GeneXpert modules, and instead requires an upgrade to Cepheid's new ten-color module,⁶⁹ which is expected to be expensive for country programs.

Several new **high-throughput** centralized tests for resistance to rifampicin and isoniazid will also be reviewed by the WHO, including tests from Abbott, BD, Roche, and Hain, which are all designed for use on already-existing multi-disease platforms in central laboratories. While there has been a decisive push for point-of-care molecular testing, centralized high-throughput molecular tests also have an important role to play in the diagnostic systems of countries. The high volume of tests that can be performed each day could help countries to scale up molecular testing for TB and drug resistance, particularly in densely populated areas of high-TB-burden countries where sample transport or referral systems are more efficient and feasible than in rural areas. Another molecular test being reviewed by the WHO in 2020 is Nipro's line probe assay for pyrazinamide resistance, for use in central

High-throughput: the capacity of certain testing instruments to run a large amount of tests at the same time and in a given day

laboratories. While these centralized drug susceptibility tests are welcome additions to the diagnostic toolkit of countries, more drug-susceptibility testing options are needed in primary-care settings. As TB resistance emerges against new and repurposed drugs, rapid tests for resistance to these drugs must be developed to ensure that DST keeps pace with WHO-recommended treatment regimens, and to minimize the further development of resistance by enabling optimized and appropriate regimen selection.

Table 4: Next-generation drug-susceptibility tests to inform TB treatment

Target Product Profile: Next-generation drug-susceptibility testing at microscopy centres ⁷⁰									
Sensitivity*		Specificity*		Lowest level of use		Time to results		Price per test	
Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal
> 95%	> 95%– > 90%	> 98%	> 98%	Primary-care clinic with lab (microscopy center)		< 30 min	< 2 hours	< US\$10	–

Test/tool (Manufacturer)	Type	Sensitivity*	Specificity*	Lowest level of use	Time to results	Price per test/tool	Stage of development/WHO review
Xpert MTB/XDR (Cepheid)	Rapid molecular PCR	INH: 91.4% FLQs: 93.1% AMK: 70.7% ETH: 64.7%	INH: 99.1% FLQs: 98.5% AMK: 99.4% ETH: 98.3% ⁷¹	District lab	< 2 hours	US\$19.80 ⁷²	WHO review: 2020
AccuPower Q-RFIA PCR kit for use on IRON qPCR platform (Bioneer)	Rapid molecular PCR	Not yet available (RIF, INH, FLQs, AMGs) ⁷³		Primary care clinic	< 1 hour ⁷⁴	Not yet available	On pathway to WHO review
TB Drug Resistance Detection (QuantuMDx)	Rapid molecular PCR	Not yet available (drug resistance targets will be based on current and anticipated WHO-recommended regimens)		Primary care clinic/Community	< 45 min	Not yet available (Volume-based pricing)	Early stage development/Projected year of WHO review: 2022 ⁷⁵
RealTime MTB RIF/INH Resistance (Abbott)	High-throughput molecular PCR	RIF: 94.8% INH: 88.3%	RIF: 100% INH: 94.3% ⁷⁶	Central lab	~ 3 hours	Not yet available (Volume-based pricing) ⁷⁷	WHO review: 2020
BD MAX MDR-TB (BD)	High-throughput molecular PCR	RIF: 90% INH: 82%	RIF: 95% INH: 100% ⁷⁸	Central lab	< 4 hours ⁷⁹	Not yet available	WHO review: 2020
cobas MTB-RIF/INH (Roche)	High-throughput molecular PCR	RIF: 97.2% INH: 96.9%	RIF: 98.6% INH: 99.4% ⁸⁰	Central lab	3 hours ⁸¹	Not yet available	WHO review: 2020
FluoroType MTBDR Version 2.0 (Hain)	High-throughput molecular PCR	RIF: 98.9% INH: 91.7%	RIF: 100% INH: 100% ⁸²	Central lab	≤ 2.5 hours ⁸³	Not yet available	WHO review: 2020

Test/tool (Manufacturer)	Type	Sensitivity*	Specificity*	Lowest level of use	Time to results	Price per test/tool	Stage of development/WHO review
AccuPower TB & MDR Real-Time PCR Kit on ExiStation platform (Bioneer)	High-throughput molecular PCR	Not yet available (RIF, INH) ⁸⁴		Central lab	< 2 hours (not including DNA extraction) ⁸⁵	Not yet available	Projected year of WHO review: 2021
AccuPower XDR-TB Real-Time PCR Kit on ExiStation platform (Bioneer)	High-throughput molecular PCR	Not yet available (FLQs, AMGs, EMB, STM) ⁸⁶		Central lab	< 2 hours (not including DNA extraction) ⁸⁷	Not yet available	Projected year of WHO review: 2021
Genoscholar PZA TB II (Nipro)	Molecular line probe assay	PZA: 98.9%	PZA: 91.8% ⁸⁸	Central lab	6 hours	US\$30 ⁸⁹	WHO review: 2020

*Microbiological reference standard

Abbreviations

<i>First-line drugs:</i>	<i>Second-line drugs:</i>
EMB: ethambutol	AMGs: aminoglycosides (i.e., amikacin, kanamycin, and capreomycin)
INH: isoniazid	AMK: amikacin
PZA: pyrazinamide	ETH: ethionamide
RIF: rifampicin	FLQs: fluoroquinolones (i.e., moxifloxacin and levofloxacin)
	STM: streptomycin

5. Next-generation sequencing for detection of drug resistance

Accurate and comprehensive drug-susceptibility testing for resistance to TB drugs is critically needed to effectively diagnose and treat drug-resistant TB. While currently available tools for drug-susceptibility testing—such as rapid and high-throughput molecular tests, line probe assays, and liquid culture—may be used in combination to individualize and optimize DR-TB treatment regimens, implementing this range of tests takes considerable time and resources. In the meantime, the improper use of TB treatment regimens may increase drug resistance and morbidity and mortality from TB. Next-generation sequencing (NGS) for TB drug resistance, however, can deliver comprehensive testing for drug-susceptibility at needed levels of accuracy in a single test, which produces results to inform individualized, optimal DR-TB treatment regimens in less than two days. NGS can also test for varying degrees of drug resistance and identify multiple strains of TB with different drug resistance profiles in a given sample. Compared to currently available molecular tests that target specific gene mutations, NGS provides the option of detecting mutations associated with resistance in a wider region of the genome, or even the whole genome. Through deep sequencing (sequencing thousands of times), an accurate picture of drug resistance-related mutations present in the sample can be observed. Several NGS technologies are currently being explored by FIND as part of the Seq&Treat project, with studies ongoing in Brazil, China, Georgia, India, and South Africa.⁹⁰ NGS technologies are expected to be reviewed by the WHO within the next several years. While NGS offers the possibility to dramatically advance country capacity to effectively test for and treat DR-TB, these technologies will likely be initially positioned at the central laboratory level.

Several new NGS TB assays are being developed and are on the pathway to WHO review. These include Deeplex Myc-TB from GenoScreen, which is one of the tools being explored as part of the FIND Seq&Treat project, and another is DEEPCHEK-TB RPOB/INHA from ABL.⁹¹ The Deeplex Myc-TB assay tests for resistance to rifampicin, isoniazid, pyrazinamide, ethambutol, fluoroquinolones, streptomycin, kanamycin, amikacin, capreomycin, ethionamide, bedaquiline, clofazimine, and linezolid, while also identifying the different strains of TB bacteria in a given sample.⁹² GenoScreen will update the assay to test for resistance to delamanid and pretomanid when the genetic mutations associated with resistance to these new drugs are identified. The assay includes access to cloud-based software that provides a user-friendly interface to interpret the sequencing results and inform clinical decisions. Deeplex Myc-TB is currently being validated for use on Illumina sequencing platforms, including the iSeq 100, which is Illumina’s most affordable offering capable of sequencing up to 13 samples in 24 hours.⁹³ Before adding the sample to the sequencer, however, the DNA must first be extracted and then amplified using a separate thermocycler polymerase chain reaction (PCR) device. Data management systems and server capacity will also be required to process the sequencing results. Another new sequencing platform is Oxford Nanopore’s MinION, which is a portable and relatively inexpensive sequencing device that can be used in combination with a laptop, offering the prospect of bringing NGS-based drug-susceptibility testing closer to the point-of-care in the near future.⁹⁴

Table 5: Next-generation sequencing for detection of drug resistance

Target Product Profile: Detection of resistance associated mutations in <i>Mycobacterium tuberculosis</i> complex utilizing Next Generation Sequencing ⁹⁵									
Sensitivity*		Specificity*		Lowest level of use		Time to results		Price per test (targeted NGS)	
Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal
> 99%– > 90%	> 95%– > 85%	> 98%	> 95%	District laboratory	Central laboratory	≤ 24 hours	≤ 72 hours	< US\$15	< US\$60

Test/tool (Manufacturer)	Type	Accuracy*	Lowest level of use	Time to results	Price per test/ tool	Stage of development/ WHO review
Deeplex Myc-TB (GenoScreen)	Targeted sequencing assay	SE: 95.3% SP: 97.4% ⁹⁶	District laboratory	24–48 hours	~US\$60 to US\$70 ⁹⁷	On pathway to WHO review
DEEPCHEK-TB RPOB/INHA (Tgen/ABL)	Targeted sequencing assay	Not yet available (RIF, INH)	District laboratory	~30 hours ⁹⁸	Not yet available	Late development
iSeq 100 (Illumina)	Sequencing platform	–	District laboratory	< 24 hours	US\$19,900 ⁹⁹	Commercialized
MinION (Oxford Nanopore)	Sequencing platform	–	District laboratory	< 48 hours	Starting from US\$1,000 ¹⁰⁰	Commercialized

*Microbiological reference standard

6. Tests for detecting incipient TB and for treatment monitoring

The lack of tests for detecting or predicting the risk of progression from TB infection to active TB disease—a stage called incipient TB—constitutes a significant gap in the currently available toolkit of WHO-recommended TB diagnostic tools. We do have tests for TB infection, but these cannot distinguish between TB infection and active TB, and the best tools that we currently have for detecting the early

onset of active TB are chest X-rays followed by confirmatory diagnostic testing with a rapid molecular test. Tests for incipient TB would enable country programs to identify people most at risk of developing active TB and to more feasibly target the scale-up of TB preventive therapy (TPT) to prevent the onset of active TB and reduce onward TB transmission. Such tests could potentially be deployed in widespread systematic screening programs among high-risk groups and in high-prevalence settings or as triage tools where people at risk of TB present to care. Ending TB will depend on this testing capability, by enabling targeted interventions such as TPT to reduce the pool of people who are at risk of progressing to active TB disease.¹⁰¹ Many tests under development for incipient TB are also of interest as tools for treatment monitoring. The best tools we currently have for treatment monitoring are liquid culture—which can take two to six weeks for results—and smear microscopy—which has insufficient sensitivity. New tools capable of more rapidly and accurately detecting a person’s response to treatment offer the potential to greatly improve clinical decision-making with regard to the composition and duration of treatment regimens, and to improve and expedite the conduct of clinical trials of new TB drugs and treatment regimens.

Many of the tools that are currently in the pipeline for detecting incipient TB are also being explored for use as treatment monitoring tools, because they are based upon some of the same biomarkers that indicate the presence or severity of active TB. Biomarkers being explored for incipient TB and/or treatment monitoring can include markers of the host’s response to a pathogen and markers of the pathogen itself. Host response biomarkers can be used to detect and quantify specific changes to a person’s RNA or immune response to TB bacteria, which can indicate different stages of TB, including non-progressing TB infection, incipient TB, active TB disease, treatment success or failure, and post-treatment cure. These specific changes include the expression of distinct gene signatures in a person’s RNA **transcriptome** that are associated with TB-related inflammation, and distinct phenotypic changes of CD4 T cell activation and maturation markers associated with the body’s immune response to TB. Several host response biomarkers are currently being evaluated to detect and predict the risk of progression from TB infection to active TB disease, and to measure the effectiveness of TB treatment and predict the duration of needed treatment.

A number of transcriptomic biomarkers are currently being evaluated, and several gene signatures show promising levels of accuracy for different use cases.¹⁰² Companies such as Cepheid, bioMérieux, and QuantuMDx are developing molecular tests to detect and measure different RNA gene signatures in blood, with potential applications as tests for incipient TB and for treatment monitoring. For example, Cepheid’s Xpert-MTB-HR tests for the **Sweeney3** RNA gene signature,¹⁰³ and QuantuMDx is developing a test for the **RISK6** RNA gene signature.^{104,105} While all of these tests are in early stages of development, the Cepheid and QuantuMDx tests are the most advanced in the pipeline. Based on early studies, transcriptomic biomarker-based tests to detect or predict progression to active TB are sufficiently sensitive in the three- to six-month period preceding the onset of active TB,¹⁰⁶ which does not meet the TPP goal of up to two years prior to the onset of active

Transcriptome: the set of all RNA transcripts responsible for DNA replication in the body

Sweeney3: a host RNA gene signature composed of three genes (GBP5, DUSP3, and KLF2) that is a biomarker for TB

RISK6: a host RNA gene signature composed of six genes (GBP2, FCGR1B, SERPING1, TUBGCP6, TRMT2A, and SDR39U1) that is a biomarker for TB

TB.¹⁰⁷ These tests are generally being developed for use on molecular PCR instruments and are expected to carry a similar price tag as other currently available rapid molecular tests, so at this stage, these tests are not likely to be feasible for use in population-level screening programs, but they may be feasible for use as triage tests where people at risk of TB present to care. The host immune response test TAM-TB, being developed by Beckman Coulter, also shows great promise to be used as a test for detecting incipient TB and for treatment monitoring. TAM-TB detects and characterizes changes in the phenotype of TB-specific CD4 T cells that are associated with the immune response to active TB, as compared to a healthy phenotype indicating non-progressing TB infection or post-treatment cure. Early studies demonstrate a clear trend between the characterization of these markers and the different stages of a successful treatment response, indicating a potentially valuable role in treatment monitoring.¹⁰⁸

Pathogen biomarkers, such as components or specific genes of TB bacteria, can also be used to evaluate the effectiveness of TB treatment by measuring the bacillary load of viable TB bacteria. The Molecular Bacterial Load Assay (MBLA) from the University of St. Andrews and LifeArc offers significant promise as a rapid and accurate test for treatment monitoring. MBLA is a molecular test that utilizes PCR to amplify a specific RNA gene (16S ribosomal RNA) from viable TB bacteria in order to quantify the number of live TB bacteria in sputum, essentially performing the same task as mycobacterial liquid culture in a matter of hours instead of weeks.¹⁰⁹ In as little as three days, 16S ribosomal RNA that is detected by MBLA is able to indicate the bactericidal effect of TB drugs and to provide a long-term assessment of treatment response for slow responders.¹¹⁰ MBLA will undergo validation studies in late 2020, and will be available as a research tool in early 2021.¹¹¹

Table 6: Tests for detecting incipient TB and for treatment monitoring

Target Product Profile: A test for predicting progression from tuberculosis infection to active disease ¹¹²									
Sensitivity*		Specificity*		Lowest level of use		Time to results		Price per test	
Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal	Optimal	Minimal
≥ 90%	≥ 75%	≥ 90%	≥ 75%	Health post	Primary-care clinic with lab	≤ 24 hours	2–5 days	< US\$5	< US\$10–100
Test/tool (Manufacturer)	Type	Potential use case	Sensitivity*/ Specificity*/ AUC**	Time to results	Price per test	Stage of development			
Xpert-MTB-HR (Cepheid)	Host blood RNA response/PCR	Incipient TB/ Treatment monitoring	Incipient TB triage (PLWHA): SE: 90% SP: 55.8% AUC: 0.89 ¹¹³	Not yet available	Comparable to pricing of other Xpert tests ¹¹⁴	Early development; Expected launch in 2023 ¹¹⁵			
RISK6 signature assay (QuantuMDx)	Host blood RNA response/PCR	TB infection/ Incipient TB	Not yet available	< 30 min ¹¹⁶	PCR-based test pricing	Early development/ Projected year of WHO review: 2022 ¹¹⁷			
FilmArray Assay (bioMérieux)	Host blood RNA response/PCR	Treatment monitoring	Not yet available	< 1 hour ¹¹⁸	PCR-based test pricing	Early development ¹¹⁹			

Test/tool (Manufacturer)	Type	Potential use case	Sensitivity*/ Specificity*/ AUC**	Time to results	Price per test	Stage of development
TAM-TB (Beckman Coulter)	Host blood immune response	Incipient TB/ Treatment monitoring	Treatment monitoring: All T cell markers reverted to healthy state by end of treatment, showing a clear trend at 1 month and 6 months of treatment ¹²⁰	Not yet available	Expensive technique requiring specialized equipment ¹²¹	Early development
RTT TB (Lophius Biosciences)	Host blood immune response/PCR	TB infection/ Active TB rule-out test	SE: > 95% SP: ~95% ¹²² Successful differentiation between TB infection and active TB in feasibility studies ¹²³	18–32 hours	Comparable to IGRAs	Early development; Expected launch in 2022 ¹²⁴
TB-MBLA (University of St. Andrews/ LifeArc)	MTB bacillary load in sputum/ PCR	Treatment monitoring	Treatment monitoring: Decrease in bacillary load closely correlates with time to culture positivity ¹²⁵	< 6 hours ¹²⁶	Not yet available	Late development

*Microbiological reference standard

**Area under the ROC curve—an alternate measure of accuracy that combines sensitivity and specificity with 1 representing perfect performance (100% sensitivity and 100% specificity)

7. Tests for TB infection

There is currently no TPP for tests for TB infection, also known as latent TB infection (LTBI); however, there is a WHO and Stop TB Partnership framework for the evaluation of tests for TB infection to guide the development of new tests.¹²⁷ Tests for TB infection remain important diagnostic tools for surveillance and may be used to identify people who are eligible for TB preventive therapy; although, TPT can be initiated directly in high-risk groups such as PLWHA and household contacts of people with TB without testing for TB infection.¹²⁸ Tests for TB infection, such as skin and blood tests, are immunoassays that test for the immune response to the introduction of TB antigens, but these tests cannot differentiate between TB infection and active TB disease. The most commonly used test for TB infection globally is the tuberculin skin test, though this test has low specificity among people previously vaccinated with the Bacille Calmette-Guérin (BCG) TB vaccine, which is commonly administered in countries with high burdens of TB.¹²⁹

Newly developed skin tests—including C-Tb from the Serum Institute of India and Diaskintest from Generium—use a different set of TB antigens that do not overlap with those used in the BCG vaccine, thereby improving the specificity of these skin tests among people with prior BCG vaccination and making them more appropriate for use in countries with high burdens of TB. Interferon gamma release assays

(IGRAs) are laboratory-based blood tests for TB infection with high sensitivity and specificity that are also not affected by prior BCG vaccination.¹³⁰ Because these tests are expensive and require laboratory infrastructure, they have not been commonly implemented in low- and middle-income countries. To address this limited access to IGRA testing, Qiagen has developed Access QFT, a lateral flow IGRA test that produces results in less than 20 minutes and can be used at the point-of-care at the community level—the same level as skin tests. Access QFT uses a digital reader to accurately read the lateral flow test results and has added connectivity for communicating and tracking results.

Table 7: Tests for TB infection

Test (Manufacturer)	Type	Sensitivity*/ Specificity*	Lowest level of use	Time to results	Price per test	Stage of development/ WHO review
C-Tb (Serum Institute of India)	Immunoassay skin test	94% concordant with QuantiFERON Gold In-Tube ¹³¹ (SE: ≤ 92% SP: > 99% ¹³²)	Community	48–72 hours	Affordable pricing compared to other skin tests ¹³³	WHO review: 2021
Diaskintest (Generium)	Immunoassay skin test	87% concordant with QuantiFERON Gold In-Tube ¹³⁴	Community	48–72 hours	~US\$1.15 ¹³⁵	WHO review: 2021
Access QFT (Qiagen)	Immunoassay blood test/IGRA	95.6% concordant with QFT Plus ¹³⁶ (SE: > 94% SP: > 97% ¹³⁷)	Community	< 20 min ¹³⁸	~US\$10 ¹³⁹	WHO review: 2021

*There is no gold standard for tests for TB infection. Sensitivity is estimated by the percentage of people who test positive for TB infection and go on to develop active TB; specificity is estimated according to the number of false positive results among populations with very low risk of TB infection.

Take Action

FIND and the WHO developed target product profiles to guide the development of new TB diagnostic tools according to a set of necessary use cases for screening and diagnosing TB and DR-TB in different settings, which include optimal and minimal criteria for performance and operational characteristics. These TPPs give diagnostics companies and research and development (R&D) funders targets and parameters to aim for and hopefully meet. A number of the new tools detailed in this report are edging closer to the TPPs, and some are meeting them, such as CAD tools that enable rapid, accurate, and inexpensive interpretation of chest X-ray results in decentralized low-resource settings. As new TB diagnostic tools approach the TPPs and advance through the pipeline, the prospect of ending TB appears increasingly more tangible. Yet, many of the same systemic barriers that have historically limited access to TB diagnostic tools remain. Addressing and overcoming these barriers—which include (1) insufficient funding for TB diagnostics R&D and for country programs, (2) slow uptake and implementation of TB diagnostic tools within country programs, (3) lack of transparency and accountability for fair pricing of TB diagnostic tools, and (4) paywalls that restrict access to TB diagnostics research—will require concerted advocacy initiatives and pressure from TB-affected communities, civil society, and other stakeholders, who should accept nothing less than the highest standard of TB care for all people at risk of TB. TB advocates can demand accountability and action by:

Calling on country governments to:

- Increase funding for TB R&D to reach and exceed fair share funding targets¹⁴⁰ and contribute toward meeting the annual global funding target of US\$135 million for the research and development of TB diagnostics;¹⁴¹
- Increase program budgets for TB and TB-HIV and raise the necessary resources to scale up and implement new TB diagnostic tools;
- Engage in pooled procurement with other countries and global donors to secure TB diagnostic tools and applicable service and maintenance plans at the lowest possible prices through shared volumes;
- Increase uptake of new tools by implementing currently available tools according to WHO recommendations and optimizing TB diagnostic networks;
- Break down silos between national TB and HIV programs and promote the optimal use of shared diagnostic technologies between programs;
- Invest in strengthening central and decentralized laboratory infrastructure and capacity to expand access to testing and accommodate new technologies; and
- Invest in manufacturing capacity for the regional production of TB diagnostic tests and test components.

Calling on TB diagnostics R&D funders to:

- Prioritize and increase funding for TB diagnostics R&D, while not diverting resources from TB to COVID-19;
- Include conditions in all public and philanthropic funding agreements requiring:
 - fair pricing of TB diagnostic tools, including transparency of the cost of production (cost-of-goods-sold [COGS]) and volume-based pricing;
 - engagement with TB-affected communities, including community advisory boards, to inform TB diagnostics R&D efforts and study protocols; and
 - open-access publishing of all results of TB diagnostics research to ensure these are freely accessible to all TB researchers globally irrespective of their ability to pay;
- Invest in the development of diagnostic platforms that run non-proprietary tests; and
- Promote non-exclusive licensing and technology transfer for the regional manufacturing of TB diagnostic technologies in all R&D funding partnerships.

Calling on diagnostics companies to:

- Prioritize the continuation and expansion of TB diagnostics R&D, while not diverting resources and capacity from TB to COVID-19;
- Direct all TB diagnostics R&D toward developing tools that meet the optimal TPP criteria and operational characteristics, including price;
- Voluntarily commit to public transparency of COGS and to volume-based price adjustments for all new TB diagnostic tools, and adopt lower profit margins to account for public and philanthropic funding invested in the R&D and roll-out of new tools;
- Publicly disclose all investments made by the company and by public and philanthropic funders in the R&D of new TB diagnostic tools; and
- Engage TB-affected communities, including community advisory boards, in all stages of TB diagnostics R&D to ensure that new TB diagnostic tools are developed with community input and reflect community needs and priorities.

Calling on the WHO and FIND to:

- Continue investing resources and technical capacity in the R&D and evaluation of new TB diagnostic tools in accordance with the TPPs;
- Articulate and generate the evidence necessary for strong recommendations and clear guidance on the use of new TB diagnostic tools;
- Actively advise and provide support to national TB programs to scale up and implement new TB diagnostic tools according to WHO recommendations; and
- Directly engage national TB programs and affected communities in the process of defining priorities for new TB diagnostic tools and of developing guidelines and recommendations on the use of these tools.

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