

The background of the cover features several thin, flowing orange lines that curve across the black space, creating a sense of movement and depth. The lines vary in thickness and direction, some starting from the top left and curving towards the bottom right, while others are more horizontal or slightly curved.

Pipeline Report » 2021

Tuberculosis Diagnostics

Tuberculosis Diagnostics

Steady progress to bring TB diagnosis closer to the point of care

November 2021

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Introduction

Tuberculosis (TB) diagnosis remains the weakest link in the TB cascade of care. When people with TB are not diagnosed or insufficiently diagnosed (without appropriate **drug-susceptibility testing**), **morbidity** and the risk of **mortality** from TB increase. In 2020, deaths from tuberculosis increased for the first time since 2005, claiming the lives of an estimated 1.5 million people, including 214,000 people living with HIV (PLHIV).¹ Of the estimated 10 million people who developed active TB disease in 2020, only 5.8 million were officially diagnosed, a decrease of 18% compared to 2019 following the onset of COVID-19.² A recent study showed that due to COVID-19-related impacts, deaths from TB could increase by up to 20% over the next five years.³ This sobering reality underscores the need to rapidly improve access to better tools for TB screening and diagnosis.

Challenges and barriers to TB diagnosis are many, including insufficient tools, high costs of available tools, stigma and other socioeconomic factors limiting access to care, health system inefficiencies,⁴ and insufficient uptake and implementation by country programs of available tools for TB screening and diagnosis.⁵ All of these barriers must all be addressed in parallel.⁶ The TB diagnostic pathway often begins with symptoms, but once symptoms have developed, TB transmission may have already occurred.⁷ Socioeconomic and health system barriers to TB diagnosis further delay access to care and extend this risk of transmission. Bringing TB screening and diagnostic tools closer to the **point of care** in communities to identify possible TB across the spectrum from **TB infection** to **active TB disease** (including before symptoms develop) and to universally test for TB drug resistance will help to address these barriers and will be essential for closing the TB diagnostic gap and reducing transmission.

The following report shows that the TB diagnostics pipeline is indeed responding to these challenges and barriers along the TB diagnostic pathway by attempting to overcome the limitations of existing tools, which include insufficient accuracy, over-reliance on **sample transport systems** and laboratory infrastructure, and high costs. The pipeline is also indicating a diversification of tools, which

Drug-susceptibility testing: tests used to determine *Mycobacterium tuberculosis* (MTB) resistance to TB drugs

Morbidity: the condition of suffering from a disease

Mortality: death; the proportion of people with a specific disease who die from that disease

Point of care: the location where a person presents to care for a disease or condition

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

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

Sample transport systems: transporting specimens for diagnostic testing from the point of care to more centralized laboratories that have the equipment and trained technicians needed to perform the test, often resulting in a delayed turnaround time to results

could promote improved competition, better pricing, and further innovation. TB diagnostics developers are representing an increasingly broader range of stakeholders, including private diagnostics developers, philanthropic organizations making targeted and strategic research and development (R&D) investments, and public-private partnerships working to advance innovation for the public good. Regulatory pathways for new diagnostics are also improving. The WHO Global TB Program is shifting toward a diagnostic class-based approach to developing guidance and is working with the WHO Pre-qualification Program starting in 2022 to enable rapid review of tools within already recommended classes,⁸ and the Global Fund to Fight AIDS, Tuberculosis and Malaria Expert Review Panel for Diagnostics (ERPD) is playing an increasingly more prominent role in providing interim approval of new TB tools. To support uptake of diagnostic tools, WHO continues to update its Essential Diagnostics List (EDL) of WHO-recommended tools to provide guidance to countries to develop national EDLs and policies for the adoption and implementation of these tools according to country-specific priorities and needs.⁹

The overall outlook on the TB diagnostics pipeline is optimistic, though it is important to emphasize that no single tool will close the diagnostic gap and end TB. Instead, a suite of tools tailored to a range of **use cases** (purposes and settings) must be implemented in concert, and these tools must be made available at affordable prices with adequate and reliable service and maintenance of testing **instruments** to facilitate country uptake. The WHO and the Foundation for Innovative New Diagnostics (FIND) have developed a series of Target Product Profiles (TPPs) to provide guidance to diagnostics developers on the types of new tools that are needed according to different use cases. These TPPs set the optimal and minimal performance and operational criteria that these tools should meet, including accuracy, setting, time to results, and price. Since many of these TPPs were developed in 2014, the WHO has initiated a process to revise the TPPs in the coming years, starting with the new TPP for TB drug-susceptibility tests in peripheral centers, released earlier this year.¹⁰

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

Instruments: specialized equipment or machines that are used to perform complex diagnostic tests

This report is structured according to the TPPs, and includes the following sections:

1. Tests for TB screening and triage
2. Urine LAM tests
3. Tests to replace smear microscopy as the initial TB diagnostic test
4. Next-generation drug-susceptibility tests to inform TB treatment
5. Tests for detecting incipient TB and for treatment monitoring
6. Tests for TB infection

It is important to note, however, that some tools in development could have multiple applications across several TPPs, and other tools may even require the development of new TPPs that do not yet exist.

1. Tests for TB Screening and Triage

Tools for TB screening are different from tools for diagnosing TB. Tools for TB screening, such as symptom screening and chest X-ray, can identify people who may have TB and who should undergo further evaluation for TB. These tools can also be used to **triage** people presenting to care in health facilities to identify whether a person should be further evaluated for TB. TB screening tools are not sufficiently **sensitive** and **specific** to be used for TB diagnosis. TB diagnosis requires (1) **microbiological confirmation** of the presence of TB using a sensitive and specific WHO-recommended TB diagnostic test, or (2) **clinical diagnosis** of TB based on signs and symptoms and assessed risk, which is necessary among some children and PLHIV with **paucibacillary TB** (low **bacterial load** of *Mycobacterium tuberculosis* [MTB]) for whom microbiological confirmation may not be possible. Treatment for active TB can only be initiated following TB diagnosis.

In March 2021, the WHO released new guidelines on TB screening that expanded the range of tools the WHO recommends for the implementation of systematic screening among high-risk populations and in communities with high burdens of TB. The guidelines for the first time recommended computer-aided detection (CAD) tools to assist in the interpretation of chest X-rays and provided new recommendations on the use of C-reactive protein (CRP)—a test for TB-related inflammation—as well as **rapid molecular tests** such as GeneXpert and Truenat to screen for TB among PLHIV. These recommendations have the potential to change the game for TB screening efforts, greatly expanding possibilities for TB screening beyond the WHO four-symptom screen (current cough, fever, weight loss, or night sweats) and incorporating artificial intelligence (AI) algorithms to support clinical decision-making.

Chest X-ray can detect **pulmonary TB** even prior to the onset of TB symptoms, which is a stage of TB that is characterized as **sub-clinical TB**—the early onset of active TB disease when bacterial load is still relatively low. Detecting and diagnosing TB at this stage would have a huge effect on reducing TB transmission as well as morbidity and mortality from TB. Yet, due to the historically high cost and infrastructure requirements of chest X-ray and limited access to trained clinicians able to read X-ray images, scaling up access to this technology in low-resource settings was not feasible until now. Today, several ultra-portable X-ray devices are commercially available (see Table 1 below) and these can be paired with CAD tools for community-level TB screening.¹¹ Studies found that AI-based CAD technologies have comparable accuracy compared to trained human readers and can even outperform them in high burden settings.^{12,13} The FIND and Stop TB Partnership-supported website ai4hlth.org details the range of available CAD products, and a selection of these are detailed below in Table 1. Both CAD and ultra-portable X-ray devices are now available in the Global Drug Facility diagnostics catalog.¹⁴ Ultra-portable X-ray devices, however, are still very expensive, and prices will need to drop to better facilitate country uptake. That said, these ultra-portable X-ray devices are capable of producing about 200 images per day with a very fast time to result; therefore, high-volume use could potentially improve the cost-effectiveness of investments in these devices.

Triage: prioritization of care based on assessed need

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

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

Microbiological confirmation: directly detecting the physical presence of TB bacteria in a sample

Clinical diagnosis: making a diagnosis based on signs and symptoms and other risk factors, without microbiological confirmation from a sensitive and specific test

Paucibacillary TB: active TB that is caused by a smaller number of TB bacteria; a common form of TB among PLHIV and children

Bacterial load: the quantity of TB bacteria in the body or in a sample

Mycobacterium tuberculosis (MTB): the species of pathogenic bacteria that causes TB

Rapid molecular tests: diagnostic tests that can rapidly detect the genetic material of TB bacteria and TB genetic mutations associated with resistance to certain drugs

Pulmonary TB: TB in the lungs

Sub-clinical TB: active TB disease before the onset of TB symptoms

An ongoing challenge with using chest X-ray as a screening tool is its limited diagnostic accuracy among children due to variable image quality and the lack of reading skills to interpret child chest X-ray images compared to adults.¹⁵ The WHO guidance currently only recommends CAD tools among people aged 15 and over, even though a number of CAD tools have been trained on X-rays of children as young as four years.¹⁶ Efforts are currently underway to build an archive of pediatric X-ray images, similar to the FIND and Stop TB Partnership archive of adult X-rays assembled for the ongoing validation of new CAD tools, to validate these CAD tools in children and generate evidence for WHO policy.¹⁷ Additionally, there is little to no evidence of the differing accuracy of CAD tools when used among different populations including PLHIV and people with paucibacillary TB. More studies are needed to better understand these differences to inform the appropriate **threshold** settings for interpretation of CAD results among these populations.¹⁸

Threshold: the accepted minimum abnormality score of CAD technologies that indicates a person should be referred for confirmatory diagnostic testing

Other technologies being explored to enable affordable community-level screening for pulmonary TB include point-of-care ultrasound (POCUS), a technology that is cheaper, safer, and more portable than X-ray. POCUS devices are relatively easy to use by non-specialist clinicians—they can plug into a smartphone, and some are equipped with AI to interpret findings. POCUS devices can be powered by rechargeable batteries, utilize ultrasound gels made from simple ingredients such as cornstarch, water, and cassava flour, and cost as little as a couple hundred dollars, making them particularly appropriate for use in resource-limited settings where X-ray may not be available.¹⁹ While POCUS meets the TPP in terms of cost and speed, the current available data is not sufficient to determine whether POCUS is capable of meeting the minimum TPP criteria for diagnostic accuracy. More and higher-quality studies will be needed to generate sufficient evidence for WHO review.²⁰

Another technology in the pipeline showing significant promise as a tool to support TB screening and diagnosis as well as treatment monitoring is one that you can download on your smartphone—a cough app. Companies such as Hyfe have developed AI-based apps to detect and quantify cough as a biomarker for TB, with applications for very low-cost and very high-volume TB screening as well as for monitoring the effectiveness of TB treatment.²¹ The technology also has the potential capability of differentiating between cough caused by, for example, tuberculosis, pneumonia, or COVID-19.²² There is much work to be done to further develop and validate the accuracy of cough apps, but they are already available for download, for free. In fact, user data will be essential to generate the extensive amounts of cough data needed to improve the technology. Because quantifying cough will require the app to be “listening” continuously over a period of time for explosive cough sounds, this does have significant privacy implications, which developers will need to address and mitigate. Similar to CAD tools, validating cough apps will require an archive of cough sounds from a variety of settings, which will enable standardized comparison and validation of different tools. As a virtually free and globally scalable TB screening and diagnostic tool, cough apps have the potential to be deployed as a **global public good**.

Global public good: a resource that benefits all people worldwide without exclusion

Table 1: Tests for TB Screening and Triage

Target Product Profile: Community-based triage or referral test for identifying people presumed to have TB ²³									
Sensitivity*		Specificity*		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*		Lowest Level of Use	Time to Results	Price per Image/ Test/Tool		Stage of Development/ WHO Review	
Delft Light (Delft Imaging)	Ultra-portable X-ray	—		Community (200 exposures/ battery charge)	10 seconds ²⁴	US\$66,750 (full kit including portable solar panel) Warranty extension 1-year: US\$4,460 ²⁵		Commercially available in the GDF catalog	
FDR Xair (Fujifilm)	Ultra-portable X-ray	—		Community (100 exposures/ battery charge)	2–3 seconds ²⁶	US\$47,000 (full kit) Warranty extension 1-year: US\$5,000 ²⁷		Commercially available in the GDF catalog	
Impact (MinXray)	Ultra-portable X-ray	—		Community	~4 seconds ²⁸	US\$47,500 ²⁹		Commercially available Plans to list in the GDF catalog	
HandMed (JLK)	Ultra-portable X-ray	—		Community	< 3 seconds	US\$30,000 to US\$45,000 1-year warranty; From 2nd year onwards, 15% of price charged as maintenance fee ³⁰		Commercially available	
CAD4TB (Delft Imaging)	CAD	SE: 90% fixed SP: 72.9% ³¹	PLHIV: SE: 80.4% SP: 52.0% ³²	Community	< 20 seconds ³³	Software license: US\$12,750 Offline unit: US\$2,750 Support & maintenance (1-year): US\$5,100 ³⁴		Recommended by WHO in 2021 Commercially available in the GDF catalog	
InferRead DR Chest (Infervision)	CAD	SE: 90% fixed SP: 62.1% ³⁵		Community	5–10 seconds ³⁶	Software license: US\$2,700 Offline unit: US\$2,082 Support & maintenance (1-year): US\$232 ³⁷		Recommended by WHO in 2021 Commercially available in the GDF catalog	

Target Product Profile: Community-based triage or referral test for identifying people presumed to have TB ²³									
Sensitivity*		Specificity*		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*		Lowest Level of Use	Time to Results	Price per Image/ Test/Tool	Stage of Development/ WHO Review		
qXR (qure.ai)	CAD	SE: 90% fixed SP: 74.3% ³⁸ PLHIV: SE: 78.9% SP: 51.6% ³⁹		Community	< 1 min	Customized pricing proposals depending on the volumes ⁴⁰	Recommended by WHO in 2021 Plans to include in GDF catalog		
INSIGHT CXR (Lunit)	CAD	SE: 90% fixed SP: 67.2% ⁴¹ PLHIV: SE: 86.3% SP: 45.2% ⁴²		Community	5–20 seconds	First 1K exams: US\$1.40 Next 9K exams: US\$1.10 Next 90K exams: US\$0.83 Next 900K exams: US\$0.41 ⁴³	Recommended by WHO in 2021 Plans to include in GDF catalog		
JLD-02K JVIEWER-X (JLK)	CAD	SE: 90% fixed SP: 86% ⁴⁴		Community	< 10 seconds	Image: US\$0.84 to US\$1.20 Offline unit: US\$5,000 to US\$8,000 ⁴⁵	Projected year of WHO review: 2022		
Hyfe App (Hyfe)	Mobile phone cough app	Data not yet available		Community	Monitoring frequency over time	Free for users in low- and middle-income countries ⁴⁶	Early development/ pending validation		
C-reactive protein (CRP) (various manufacturers)	Finger-prick blood test	PLHIV: SE: 77.7–79.8% SP: 62.8–66.6% ⁴⁷		Community	~3 min	< US\$2 ⁴⁸	Recommended by WHO in 2021 Commercially available		

*Compared to a **microbiological reference standard**

**Company-reported data

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

Box 1: Applying COVID-19 Diagnostic Innovations to TB

The COVID-19 pandemic brought about unprecedented investments in the rapid development and rollout of new vaccines, therapeutics, and diagnostics. Investment in the R&D of COVID-19 diagnostics amounted to an estimated US\$804,047,665 in 2020,⁴⁹ nearly ten times the \$94,308,097 estimated total investments in TB diagnostics R&D in 2019.⁵⁰ In the first year of the COVID-19 pandemic, “rapid **antigen tests**” and **polymerase chain reaction** “PCR tests” made it into everyday conversations and mainstream news articles. For TB, the question now is not only “how can we increase TB diagnostics R&D investments,” it is also “how can we leverage and translate the advances made in the development of COVID-19 diagnostics for TB.”

Several COVID-19 diagnostic innovations that may be applied to TB are worth noting, especially the innovative sampling techniques used for COVID-19, which show that it may be possible to shift TB diagnosis away from reliance on **sputum**—a relatively difficult sample to obtain, especially among children and PLHIV. Tongue swabs are of particular interest as an alternative sample to sputum for detecting TB. Tongue swabs draw from the same respiratory sample as sputum that accumulates on the back of the tongue; although, there is a lower bacterial load in tongue swab samples compared to sputum. According to preliminary data, tongue swab samples appear to be about 88% sensitive compared to sputum testing using Xpert MTB/RIF Ultra.⁵¹ The trade off, which may be worth it, is that tongue swab samples may lead to a higher number of samples to test, because more people, including children and PLHIV, will be able to provide a tongue swab sample. To build a body of evidence, head-to-head comparison studies between tongue swabs and sputum will be needed.⁵²

Another COVID-19 diagnostic innovation to note is the advancement of point-of-care rapid molecular tests—including single-use self-tests that are available over the counter in some high-income country pharmacies.⁵³ Many of these rapid molecular tests for COVID-19 run on platforms capable of testing for multiple diseases. Several companies, such as QuantuMDx and LumiraDx, first launched COVID-19 tests and are now developing **assays** for TB (see Section 3 below). These companies may also develop tests for **bi-directional testing** of TB and COVID-19 (testing for both diseases simultaneously, given that they both share similar symptoms). In addition to developments in R&D, COVID-19 also spurred developments in manufacturing capacity, particularly for **lateral flow** rapid antigen tests. To leverage and transfer this manufacturing capacity to TB, FIND has begun engaging several major diagnostics manufacturers to also develop lateral flow assays for TB, drawing from a catalog of TB **biomarkers** assembled by FIND.^{54,55}

Antigen: molecules or components of a pathogen that induce an immune response

Polymerase chain reaction amplification: a process of repeatedly raising and lowering the temperature to replicate nucleic acid sequences that quickly results in millions of copies

Sputum: a mixture of saliva and mucus that is coughed up from the lungs

Assay: an investigative analytic procedure or test

Bi-directional testing: integrated testing for two different diseases or medical conditions at the same time

Lateral flow assay: a simple, paper-based test that detects the presence of a target substance in a liquid sample without the need for specialized or costly equipment

Biomarker: a measurable biological indicator of the presence or severity of a disease

2. Urine LAM Tests

Sputum coughed up from the lungs is the sample with the highest *MTB* bacterial load for pulmonary TB, so it has been used as the primary sample from the origins of TB diagnostic testing using smear microscopy to the introduction and use of rapid molecular tests over the past decade. Yet, sputum is not always the most appropriate or available sample, especially for children and some PLHIV who have difficulty producing sputum and for people with **extrapulmonary TB**. Alternate samples are therefore needed. Apart from direct detection of TB bacteria in samples, biomarkers that point to the presence of TB in the body can also be used to assist in the diagnosis of TB. The most well-studied TB biomarker is lipoarabinomannan, or LAM, a component of the outer cell wall of TB bacteria that is discarded in the body and can be detected in urine (as well as in sputum and blood).^{56,57}

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

The currently available urine LAM test, Determine TB LAM Ag from Abbott, has relatively low sensitivity but is moderately sensitive among PLHIV with advanced HIV disease or AIDS—those who are most at risk of dying from TB.⁵⁸ Determine TB LAM is a simple lateral flow assay, like a pregnancy test, that can be implemented at the point of care using unprocessed urine that produces results in just 25 minutes and costs just \$3.70 per test. For PLHIV, rapid diagnosis at the point of care and immediate linkage to TB treatment is critical, especially for people with AIDS, for whom waiting days for test results may be life-threatening (which is too often the reality).⁵⁹ Studies have shown that the use of urine LAM tests reduces the risk of mortality among PLHIV and increases the proportion of PLHIV who are started on TB treatment.⁶⁰ These benefits are gained notwithstanding the relatively low sensitivity of Determine TB LAM amounting to 42.3% among PLHIV inpatients and 27.9% among outpatients.⁶¹ In 2019, WHO strengthened and expanded its recommendations on the use of LAM testing to assist in the diagnosis of all PLHIV with signs and symptoms of TB, serious illness, or advanced HIV disease.⁶² In spite of these recommendations and the proven benefits of LAM testing, however, many countries with high burdens of TB and HIV have been slow to adopt and implement LAM testing in routine care.⁶³ In response to a 2019 survey, countries with high burdens of TB and HIV listed budget limitations, lack of country-specific data and piloting, administrative hurdles such as regulatory agency approval, lack of coordination between national TB and HIV programs, and small perceived patient population as the main barriers to adopting and scaling up urine LAM.⁶⁴ To realize the mortality benefits of this simple and inexpensive test, national TB and HIV programs must adopt WHO recommendations and institute national policies for the routine use of urine LAM testing.

A next-generation LAM test in development, SILVAMP TB LAM from Fujifilm, offers significantly higher sensitivity among PLHIV compared to Determine TB LAM (see Table 2 below). 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 it easier to visually read the test result. SILVAMP TB LAM also shows promise to support TB diagnosis among children with a high **pre-test probability** of TB, including children living with HIV and malnourished children.⁶⁵ Among HIV-negative people, SILVAMP TB LAM is about five times more sensitive for TB compared to Abbott's Determine TB LAM test.⁶⁶ 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. It also costs more, with a projected introductory price of about \$7.⁶⁷ In efforts to reduce the price of the test, Fujifilm has redesigned the assay to make it smaller by using less materials and has also shifted to automated manufacturing in Vietnam.⁶⁸ The bridging studies to generate clinical evidence needed to validate concordance between the redesigned assay and the original assay have unfortunately been delayed due to COVID-19, pushing back the projected timing of WHO review and commercial availability further into 2022.

Pre-test probability: the likelihood that a person has a disease, based on prevalence and other risk factors, before the test result is known

Recognizing the potential for making urine LAM tests more sensitive for use among HIV-negative people in addition to PLHIV, and realizing rapid, low-cost, point-of-care testing for TB in communities, several companies and philanthropic organizations have invested in the development of third-generation LAM tests. These third-generation tests apply various methods such as urine concentration or the use of digital readers to improve the performance of the test with the aim of meeting the minimal TPP criteria for biomarker-based diagnostic tests or at least for triage tests for all people being evaluated for TB. Among the organizations investing in third-generation LAM tests are the Bill & Melinda Gates Foundation, PATH, Global Health Labs, and FIND who are collaborating and working with several diagnostics developers including Salus Discovery to pool expertise and drive forward a portfolio of ultra-sensitive LAM tests. The Salus Discovery test utilizes a simple urine concentration device capable of processing a large volume of urine (20 mL) to achieve a larger concentration of LAM in the urine sample that is tested using the lateral flow assay.⁶⁹ Other diagnostic companies developing third-generation LAM tests include Abbott, Biopromic/Asahi Kasei, Mologic, Boditech, and SD Biosensor. The LAM test by SD Biosensor utilizes a battery-powered digital reader to facilitate accurate interpretation of results. While it may be more difficult to place a reader-based technology at the point of care, the added connectivity for communicating results from remote settings is an advantage.⁷⁰ Third-generation LAM tests are beginning to show promise, though they are still in an early stage of development, and the challenge of detecting very small amounts of LAM in urine remains significant. For example, the current version of the SalusGen 3 assay can detect LAM with a **limit of detection** of 25 picograms (pg)/mL, but to achieve around 90% sensitivity for all people being evaluated for TB, including PLHIV and HIV-negative people, a limit of detection down to 10 pg/mL will be needed. To reach this low limit of detection, it is possible that urine concentration combined with the use of a digital reader will be required.⁷¹

Limit of detection: the lowest concentration of a substance that can be detected by a test

Table 2: Urine LAM Tests

Target Product Profile: A rapid biomarker-based non-sputum-based test for detecting TB ⁷²									
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	< 60 min	< 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		
Determine TB LAM Ag (Abbott)	Urine LAM test/lateral flow	PLHIV: 34.9% Inpatient: 42.3% Outpatient: 27.9% HIV-: 10.8%	PLHIV: 95.3% Inpatient: 95% Outpatient: 95.4% ⁷³ HIV-: 92.3% ⁷⁴	Community	25 min ⁷⁵	US\$3.70 ⁷⁶	Commercialized since 2013 Recommended by WHO in 2015		
SILVAMP TB LAM (Fujifilm)	Next-generation urine LAM test/lateral flow	PLHIV: 70.7% Inpatient: 70.4% Outpatient: 70.6% HIV-: 53.2%	PLHIV: 90.9% Inpatient: 90.8% Outpatient: 90.4% ⁷⁷ HIV-: 98.9% ⁷⁸	Community	< 60 min	Projected price of US\$7 per test ⁷⁹	Projected year of WHO review: 2022 In the process of Global Fund ERPD review ⁸⁰		
SalusGen 3 (Salus Discovery)	Ultra-sensitive urine LAM test/lateral flow	PLHIV: 86.5% HIV-: 60% 90%–95% target sensitivity for HIV- ⁸¹	PLHIV: 89% HIV-: 97% ⁸²	Community	90 min ⁸³ (includes urine concentration)	Not yet available	Early development		
Third-generation LAM (Abbott)	Ultra-sensitive urine LAM test/lateral flow	Not yet available		Community	< 60 min ⁸⁴ (includes urine concentration)	Not yet available	Early development		
Third-generation LAM (Biopromic/Asahi Kasei)	Ultra-sensitive urine LAM test/lateral flow	Not yet available		Community	Not yet available	Not yet available	Early development ⁸⁵		

Target Product Profile: A rapid biomarker-based non-sputum-based test for detecting TB ⁷²									
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	< 60 min	< 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
Third-generation LAM (Boditech)	Ultra-sensitive urine LAM test/lateral flow	Not yet available		Community	Not yet available	Not yet available	Early development ⁸⁶
Third-generation LAM (Mologic)	Ultra-sensitive urine LAM test/lateral flow	Not yet available		Community	Not yet available	Not yet available	Early development ⁸⁷
Third-generation LAM (SD Biosensor)	Ultra-sensitive urine LAM test/lateral flow	Not yet available		Community (utilizes digital reader)	Not yet available	Not yet available	Early development Clinical trials expected in 2023 ⁸⁸

*Compared to a microbiological reference standard

3. Tests to Replace Smear Microscopy as the Initial TB Diagnostic Test

Rapid molecular tests are capable of rapidly and accurately diagnosing and microbiologically confirming the presence of TB. Rapid molecular tests have been available and WHO-recommended since 2011, yet a decade later this technology has not significantly increased the proportion of people diagnosed with TB who are microbiologically confirmed to have the disease.⁸⁹ In 2020, just 59% of people diagnosed with pulmonary TB were microbiologically confirmed either through the use of a WHO-recommended rapid molecular test or smear microscopy, a technology from the 1800s that is no longer recommended by the WHO as an initial TB test.⁹⁰ The remaining 41% of people were clinically diagnosed without microbiological confirmation. This proportion has remained about the same since 2005.⁹¹ While there is a critically important role for clinical diagnosis, especially among children for whom rapid molecular tests are less sensitive due to the paucibacillary nature of pediatric TB, this massive shortfall in microbiological confirmation and seeming lack of progress is concerning. In 2013, WHO recommended rapid molecular tests for TB and resistance to rifampicin as the initial TB diagnostic test to replace smear microscopy,⁹² strengthening this recommendation in 2020.⁹³ WHO-recommended rapid molecular tests have sensitivity for TB up to 90% (Xpert MTB/RIF Ultra) compared to smear microscopy with an average sensitivity of 50%.⁹⁴ Yet, in 2020, just 1.9 million or 33% of the 5.8 million people diagnosed with TB received a WHO-recommended rapid molecular test as the initial test. Of the 49 countries with high burdens of TB, only 21 countries (43%) reported that a WHO-recommended rapid molecular test had been used as the initial test for more than half of their TB diagnoses.⁹⁵

The commercial availability and WHO recommendation of Cepheid's GeneXpert rapid molecular tests since 2011 did not translate into access to this technology. There are several factors that contributed to this slow and insufficient scale-up, including high prices,⁹⁶ inadequate service and maintenance of instruments in peripheral settings,⁹⁷ and operational requirements of GeneXpert, such as electricity, air-conditioned temperatures of 30°C or below, and dust-free environments. Additionally, Cepheid held a decade-long monopoly on rapid molecular testing for TB from 2010 until 2020, when the WHO also recommended Truenat rapid molecular tests as initial tests for TB. In the absence of competitive pressure throughout this period, Cepheid did not reduce prices in accordance with volumes sold and did not significantly improve upon its provision of service and maintenance—prioritizing profit over improving access to TB testing. In August 2021, Cepheid continued to put profit before the needs of TB-affected communities by deciding to cancel commercialization of GeneXpert Omni, the portable point-of-care rapid molecular testing instrument that Cepheid had promised to launch since 2015, setting back progress toward realizing access to rapid molecular testing at the community level.⁹⁸ Cepheid's one-module battery-powered GeneXpert Edge is not a sufficient replacement for Omni because it requires air-conditioned temperatures similar to standard GeneXpert instruments, therefore positioning it at the district lab level. The availability of affordable point-of-care technologies is an important precondition to improve rates of TB testing, but effective systems of implementation are also needed to realize these results.⁹⁹

Competition to break Cepheid's monopoly is finally being realized. Molbio is ramping up to globally distribute Truenat TB tests, and the pipeline is producing new and better rapid molecular tests and testing instruments. Molbio reported that the company is currently distributing Truenat in over 35 countries across continents and that it has the manufacturing capacity to produce over 350,000 tests per day or over 120 million tests per year. The Stop TB Partnership and USAID are also working with national TB programs under the New Tools Project to roll out Truenat in 11 countries in Africa and Asia.¹⁰⁰ Truenat instruments—Trueprep and Truelab—can be run at temperatures as high as 40°C and can be implemented in peripheral labs closer to the point of care than GeneXpert. The Stop TB Partnership, USAID, and

the Global Laboratory Initiative recently published a Truenat Implementation Guide, which emphasizes that a country doesn't need to choose just one rapid molecular test to meet its needs, and that Truenat (and other new rapid molecular diagnostics for that matter) can be scaled up and implemented in countries alongside existing GeneXpert infrastructure.¹⁰¹

Following the introduction of Truenat, several other companies are also developing rapid molecular tests for TB, including SD Biosensor, Bioneer, and LumiraDx, with some pushing the envelope on portability, speed, and affordability. SD Biosensor is developing cartridge-based TB tests (similar to GeneXpert) that produce results in less than 60 minutes. These tests are automated and run on the company's STANDARD M10 instrument that is capable of both **isothermal** and PCR amplification. The instrument offers scalable modular configurations of up to eight modules and can be operated at temperatures up to 35°C (compared to 30°C for GeneXpert) making it somewhat more suitable for use at the peripheral level in primary care health centers.¹⁰² FIND is currently doing a feasibility evaluation of STANDARD M10 TB tests and is likely to partner with SD Biosensor on trials to generate evidence for WHO policy.¹⁰³ Another company, LumiraDx, is developing a rapid TB test with support from the Bill & Melinda Gates Foundation that is run on the portable LumiraDx instrument, a small, battery operated molecular and **immunoassay** instrument with the potential to be used for point-of-care TB testing at the community level. More than 5,000 LumiraDx platforms are already in use in African countries, primarily for COVID-19 testing.¹⁰⁴ LumiraDx utilizes an innovative qSTAR amplification technology that reduces the time required for **nucleic acid** amplification and produces results in just 20 minutes.^{105,106} This rapid time-to-results could enable higher daily throughput of tests on the same instrument as well as the possibility of a person being tested for TB and receiving confirmatory results during a single health care visit. Research is ongoing, but it is possible that the TB test may be based on the use of tongue swab samples rather than sputum. LumiraDx is expected to offer the TB test and instrument at much lower prices compared to GeneXpert, and due to the simple and compact design, LumiraDx is also expected to have much higher production capacity. The introduction of LumiraDx TB tests will clearly be a major step forward toward improving access to rapid molecular testing for TB at the point of care. In addition, FIND is in contact with a host of other manufacturers of rapid molecular tests for COVID-19 and is in the process of engaging these manufacturers to also develop assays for TB.¹⁰⁷

Other rapid molecular diagnostics to look out for are **CRISPR-based diagnostics**, which can detect target **DNA** sequences of pathogens rapidly and with very high accuracy. The important difference between CRISPR and other rapid molecular diagnostic technologies is that the CRISPR detection step can take place using a low-cost lateral flow assay. While CRISPR-based diagnostics generally still require nucleic acid extraction and amplification, research into amplification-free CRISPR diagnostics is ongoing.¹⁰⁸ Several companies have developed CRISPR tests for COVID-19 and are now developing tests for TB.¹⁰⁹ It will be important to follow these developments and prepare for the possibility of deploying rapid and potentially low-cost CRISPR-based diagnostics for TB in the coming years.

Isothermal amplification: a simple and efficient process of replicating nucleic acid sequences at constant temperature that quickly results in millions of copies

Immunoassay: a test that measures a person's immune response to indicate the presence or concentration of a pathogen

Nucleic acids: chemical compounds that carry genetic information and that make up genetic material including DNA and RNA

CRISPR-based diagnostics: molecular tests that utilize CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) nucleic acid sequences derived from DNA fragments of pathogens and associated enzymes to detect nucleic acid sequences of pathogens with very high specificity and upon detection to indiscriminately cut the DNA present in the sample indicating a positive test result

DNA: deoxyribonucleic acid, a form of nucleic acid that carries genetic information

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 ¹¹⁰									
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		< 20 min	< 2 hours	< \$US4	< US\$6
Test/Tool (Manufacturer)	Type	Sensitivity*/ Specificity*		Lowest Level of Use	Time to Results	Price per Test/Tool	Stage of Development/ WHO Review		
Xpert MTB/RIF (Cepheid)	Rapid molecular PCR/assay	MTB: SE: 85% SP: 98% RIF: SE: 96% SP: 98% ¹¹¹		District lab	< 90 min	US\$9.98 ¹¹²	Recommended by WHO in 2011		
Xpert MTB/RIF Ultra (Cepheid)	Rapid molecular PCR/assay	MTB: SE: 90% SP: 96% RIF: SE: 94% SP: 99% ¹¹³		District lab	< 90 min	US\$9.98 ¹¹⁴	Recommended by WHO in 2017		
GeneXpert (Cepheid)	Rapid molecular PCR/instrument	—		District lab (operating temperature up to 30 °C)	< 90 min	10-color w/ laptop: US\$9,920 (1-module) US\$13,030 (2-module) US\$19,500 (4-module) ¹¹⁵	Commercially available in the GDF catalog		
Truenat MTB (Molbio)	Rapid molecular PCR/assay	SE: 73% SP: 98% ¹¹⁶		Primary care clinic with lab/ Community	< 60 min	US\$9 ¹¹⁷	Recommended by WHO in 2020 Commercially available in the GDF catalog		
Truenat MTB Plus (Molbio)	Rapid molecular PCR/assay	SE: 80% SP: 96% ¹¹⁸		Primary care clinic with lab/ Community	< 60 min	US\$9 ¹¹⁹	Recommended by WHO in 2020 Commercially available in the GDF catalog		
Trueprep, Truelab (Molbio)	Rapid molecular PCR/instrument	—		Primary care clinic with lab/ Community (battery operated; operating temperature up to 40 °C)	< 2 hours (< 60 min MTB, < 60 min RIF)	US\$10,000 (1-module) US\$14,000 (2-module) US\$18,000 (4-module) ¹²⁰	Commercially available in the GDF catalog		

Target Product Profile: Rapid sputum-based test for detecting TB at the microscopy center level of the health care system¹¹⁰

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		< 20 min	< 2 hours	< \$US4	< US\$6

Test/Tool (Manufacturer)	Type	Sensitivity*/ Specificity*	Lowest Level of Use	Time to Results	Price per Test/Tool	Stage of Development/ WHO Review
STANDARD M10 TB detection assay (SD Biosensor)	Rapid molecular PCR or isothermal/ assay	Not yet available	Primary care clinic with lab	< 60 min ¹²¹	Not yet available	Undergoing feasibility evaluation ¹²²
STANDARD M10 (SD Biosensor)	Rapid molecular PCR & isothermal/ instrument	—	Primary care clinic with lab (operating temperature up to 35°C)	< 60 min ¹²³	Not yet available	Commercially available in 2021
TB detection assay (LumiraDx)	Rapid molecular qSTAR/assay	Not yet available	Primary care clinic with lab/ Community	~20 min ¹²⁴	Not yet available	Early development ¹²⁵ Projected commercial availability in 2023
LumiraDx instrument (LumiraDx)	Rapid molecular qSTAR & immunoassay/ instrument	—	Primary care clinic with lab/ Community (20 test cycles per battery charge; operating temperature up to 30°C; no maintenance required) ¹²⁶	~20 min ¹²⁷	US\$5,000 ¹²⁸	Commercially available
TB detection assay (QuantuMDx)	Rapid molecular PCR/assay	Not yet available	Primary care clinic with lab/ Community	30 min ¹²⁹	Not yet available	Early development
Q-POC (QuantuMDx)	Rapid molecular PCR/instrument	—	Primary care clinic with lab/ Community	30 min ¹³⁰	US\$15,000 (initial price) ¹³¹	Late development
AccuPower MTB&NTM Real-Time PCR Kit (Bioneer)	Rapid molecular PCR/assay	SE: 87.25% SP: 98.34% ¹³² **	District lab (for use on ExiStation instrument)	< 3.5 hours	PCR kit: US\$6.77 PCR and extraction kit: US\$10.83 ¹³³	Commercially available since 2017

Target Product Profile: Rapid sputum-based test for detecting TB at the microscopy center level of the health care system¹¹⁰

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		< 20 min	< 2 hours	< \$US4	< US\$6

Test/Tool (Manufacturer)	Type	Sensitivity*/ Specificity*	Lowest Level of Use	Time to Results	Price per Test/Tool	Stage of Development/ WHO Review
IRON qPCR (Bioneer)	Rapid molecular PCR/instrument	—	District lab (battery operated; operating temperature up to 30°C)	< 60 min ¹³⁴	Not yet available	Design-locked Commercially available in 2022
ExiStation (Bioneer)	Rapid molecular PCR/instrument	—	District lab	< 3.5 hours ¹³⁵	US\$50,000 ¹³⁶	Commercially available
TB detection assay (Blink DX)	Rapid molecular PCR/assay	Not yet available	Primary care clinic with lab	Not yet available	Not yet available	Feasibility ¹³⁷
Blink One (Blink DX)	Rapid molecular PCR/instrument (open platform without proprietary assays)	—	Primary care clinic with lab (battery operated)	Not yet available	Not yet available	Late development ¹³⁸
Simple One-Step Solution (SOS) (KNCV Tuberculosis Foundation) Optimized Sucrose Flotation (OSF) (TB Speed/University of Bordeaux) Stool Processing Kit (SPK) (FIND/Rutgers)	Rapid molecular/ stool sample processing	SE: 53% SP: 98% ¹³⁹ (pooled accuracy using Xpert MTB/RIF Ultra on processed stool)	District lab (for use with Xpert MTB/RIF Ultra)	10 min incubation (SOS) ¹⁴⁰ 45 min sedimentation/ incubation (OSF) 30 min incubation (SPK) ¹⁴¹	Not yet available	Reviewed by WHO in 2021

*Compared to a microbiological reference standard

**Company-reported data

Sample processing: the standardized preparation of samples for testing

Box 2: Time for \$5 Coalition Continues to Push for \$5 GeneXpert Tests

Since 2019, the global civil society Time for \$5 Coalition has called on Cepheid to reduce the price of GeneXpert tests to \$5, inclusive of the cost of service and maintenance, across diseases, to support countries to scale up access to testing according to WHO recommendations.¹⁴² This demand is based upon a Médecins Sans Frontières (MSF) commissioned independent analysis that found it likely costs Cepheid between \$2.95 and \$4.64 to manufacture each GeneXpert test at volumes of 10 million—volumes that were exceeded in 2017 for TB test sales in the public sector alone.¹⁴³ This demand is also based upon evidence of substantial public investment that supported the R&D of GeneXpert technology amounting to at least \$252 million along with additional public investment in the global rollout of the technology. This extensive public investment in GeneXpert R&D and rollout stands in contrast to the lack of public sector ability to secure fair and equitable prices for GeneXpert tests and adequate service and maintenance of GeneXpert instruments.¹⁴⁴

In 2021, the Time for \$5 Coalition—composed of over 150 civil society member organizations globally—has continued to push Cepheid for \$5 GeneXpert tests and has also begun to call on global health donors, country governments, and other health actors to engage in collective negotiations with Cepheid for \$5 GeneXpert tests across diseases and to scale up Truenat and other rapid molecular tests to promote competition.¹⁴⁵ Cepheid has held a decade-long monopoly on rapid molecular testing for TB, charging high prices that limited access to rapid molecular testing.¹⁴⁶ It is time that Cepheid is held accountable to ensure public return on public investment by pricing GeneXpert tests fairly and equitably, according to the cost-of-goods-sold (COGS) plus a reasonable profit margin of at most 10–20%.¹⁴⁷

After extensive public funds and resources had been invested in the R&D and trialing of Cepheid's portable point-of-care GeneXpert Omni instrument, which the company had planned to launch since 2015, Cepheid decided in August 2021 to cancel commercialization of Omni without explanation, mitigation plans, or consideration of the impact of this decision on affected communities. On October 14, 2021, the Time for \$5 Coalition sent an open letter to Cepheid calling on the company to reinstate plans to launch GeneXpert Omni to improve access to point-of-care rapid molecular testing for TB and other diseases at the community level, reiterating the demand to price GeneXpert tests at \$5, inclusive of service and maintenance, across diseases.¹⁴⁸ It is important for the public to have full transparency from Cepheid regarding the reasons for the decision to cancel the launch of GeneXpert Omni as well as Cepheid's plans to mitigate the impacts of this decision on TB-affected communities.

4. Next-Generation Drug-Susceptibility Tests to Inform TB Treatment

According to the End TB Strategy, all people diagnosed with TB should universally receive drug-susceptibility testing (DST) in line with current WHO-recommended TB treatment regimens. This will ensure that all people being treated for TB receive the most effective TB treatments that reduce morbidity and mortality from TB and slow the development of TB drug resistance worldwide.¹⁴⁹

Earlier this year, the WHO led a stakeholder consultation process to revise and update the TPP for next-generation DST at peripheral centers, incorporating the full range of DST technologies including rapid molecular tests and **next-generation sequencing (NGS)** into a single TPP. The TPP describes the ideal DST tool as one that would rapidly and accurately detect TB and the range of mutations associated with drug resistance in a single test; although, the TPP acknowledges that given current technological constraints, achieving this is likely to require at least two separate tests. One key highlight of the new TPP is that new DST tools should have the capacity to detect mutations associated with resistance to rifampicin, isoniazid, fluoroquinolones, and bedaquiline as a minimum requirement, to be in line with the updated WHO recommendations on TB treatment regimens. Information regarding resistance to these four drugs at the outset of TB diagnosis is critical to provide clinicians with the necessary information to select and initiate optimal treatment regimens for **drug-susceptible TB (DS-TB)** and **drug-resistant TB (DR-TB)**, and to determine whether to test for resistance to any other TB drugs. Initiating optimal treatment regimens immediately following TB diagnosis maximizes the likelihood of treatment success and minimizes morbidity and the risk of mortality from TB. It's important to note that the inclusion of bedaquiline in this minimal requirement is forward-thinking; this is because the mutations associated with drug resistance to bedaquiline are yet to be clearly defined, in part because they are not grouped in a specific area of the **genome**, but rather appear to be spread across multiple areas of the genome.¹⁵⁰ Another important highlight of the TPP is that the optimal price of DST tools has been set at \$5 or less—to support widespread scale-up of these tools—with the articulation that test prices should be evidence-based according to the cost of production and projected volumes.

Earlier this year, WHO issued recommendations on the use of several next-generation drug-susceptibility tests for TB, introducing a new system of categorizing tests based on level complexity (low, moderate, or high complexity) considering infrastructure and equipment requirements as well as the technical skills required by laboratory staff to perform the tests.¹⁵¹ Following the commercial availability and WHO recommendation of Cepheid's Xpert MTB/XDR assay (classified by WHO as a "low-complexity assay"), several new rapid molecular drug-susceptibility tests are currently in development by Molbio, SD Biosensor, and Bioneer, among other companies. These tests can be performed using the instruments detailed above in Table 3. Of note, Molbio is developing new tests for resistance to isoniazid and fluoroquinolones to add to its menu of test chips for TB detection and resistance to rifampicin. The upcoming availability of

Next-generation sequencing (NGS): a technology capable of sequencing the genome with very high throughput, speed, and at a much lower cost compared to conventional Sanger sequencing

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

Genome: all genetic information of an organism

Truenat MTB-INH and MTB-FQ represents further progress in the pipeline toward meeting the minimal TPP criteria for drug resistance targets (short of bedaquiline); however, these test chips are currently expected to be sold for \$9 each, which is more than the optimal TPP target price of \$5 for a single test for resistance to all of these drugs; although, Molbio has expressed willingness to negotiate on price.¹⁵² The combined price of Truenat MTB-INH and MTB-FQ is notably still lower than the \$19.80 price of Cepheid's Xpert MTB/XDR (see Table 4 below). In addition to the high price, Xpert MTB/XDR can only be run on new 10-color GeneXpert instrument modules and not the standard 6-color modules, meaning that countries will have to invest in expensive new 10-color GeneXpert instruments or module configurations to run the test. Molbio's development and introduction of Truenat MTB-INH and MTB-FQ offers an important alternative to Cepheid's Xpert MTB/XDR. Also in the pipeline is Bioneer's IRON qPCR RIFA Kit that tests for resistance to rifampicin, isoniazid, fluoroquinolones, and amikacin, which will introduce additional competition and is another important rapid molecular drug-susceptibility test to look out for. This new test will be run on Bioneer's IRON qPCR instrument, a battery-powered instrument that will likely be positioned at the district lab level. Bioneer is expected to launch the IRON qPCR RIFA Kit in 2022.¹⁵³

Several new **high-throughput** centralized tests (classified by WHO as “moderate complexity assays”) for detection of TB and resistance to rifampicin and isoniazid were recommended by the WHO in 2021, including tests from Abbott, BD, Roche, and Hain, which are all designed for use on large multi-disease testing instruments that are generally placed in central laboratories. While there has been a decisive push for point-of-care molecular testing, centralized high-throughput molecular testing can also play a critically important role in TB programs by enabling a high volume of tests for TB and drug resistance to be run each day, particularly in densely populated urban areas where sample transport or referral systems are more efficient and feasible than in rural areas. In 2021, WHO also recommended Nipro's **line probe assay** for pyrazinamide resistance (classified by WHO as a “high complexity assay”). Line probe assays involve complex laboratory procedures and are generally placed at the central lab level.¹⁵⁴

According to the TPP, the optimal number of drug resistance targets to be incorporated into a single drug-susceptibility test is basically all the drugs included in WHO-recommended treatment regimens for DS-TB and DR-TB (including **multidrug-resistant TB [MDR-TB]** and **extensively drug-resistant TB [XDR-TB]**). This is not a pipe dream but is already a reality with **targeted next-generation sequencing**, a technology that is becoming increasingly more routine in high-income countries—such as the United States, the United Kingdom, Japan, and a number of European countries—and increasingly more appropriate for use in low-resource settings.^{155,156} TB NGS assays in development are capable of providing comprehensive DST results in one to two days and can be used in place of **mycobacterial liquid culture** (which takes up to six weeks for results) to rapidly inform clinical decision-making and optimal treatment regimen selection. The use of NGS technology for COVID-19 surveillance has demonstrated that

High-throughput: the capacity of certain testing instruments to run a large number of tests at the same time

Line probe assay (LPA): a complex lab-based test that requires nucleic acid amplification and utilizes a strip-based technology to detect genetic sequences of pathogens in a sample, including genetic mutations associated with drug resistance

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, the fluoroquinolones, and second-line injectable drugs such as amikacin

Targeted next-generation sequencing: a form of genetic sequencing that focuses on specific areas of the genome for in-depth analysis, which is more rapid and cost effective compared to whole genome sequencing

Mycobacterial liquid culture: a method of growing bacteria in a liquid medium for up to six weeks to detect the presence of bacteria or determine drug resistance

this technology can in fact be implemented across low- and middle-income countries.¹⁵⁷ Due to the complex nature of NGS, it is not likely to reach the optimal TPP target price of \$5 per test any time soon, but the extraordinary benefits of these tests along with evidence of the costs involved could justify higher prices. As scientific understanding of *MTB* genomics and mechanisms of drug resistance continues to develop, NGS assays are expected to only get more accurate.

The workflow of NGS for TB is composed of several steps requiring a suite of different laboratory instruments: (1) nucleic acid extraction, (2) amplification of the targeted region of the genome using TB NGS assay reagents, (3) sequencing the amplified target DNA, and (4) interpreting the sequencing results using specialized software. There are several new NGS assays for TB in development; the two most prominent are Deeplex Myc-TB from GenoScreen and DeepChek Assay 13-Plex from ABL, both of which are similar. These assays both test for the same array of mutations associated with TB drug resistance and can be run directly from sputum samples in addition to cultured *MTB* isolates. In principle, other sample types could also be run on these assays, but more research on diagnostic accuracy will be needed. After the DNA from the samples is sequenced, clinicians can use the software paired with the assays to interpret the results, which present the entire drug resistance profile of all the strains of *MTB* present in the sample based on the latest available information on mutations associated with drug resistance. The overall time to results for these NGS assays for TB is about one to two days. In addition to assays, there are several sequencing instruments that are commercially available from Illumina, Thermo Fisher, and Oxford Nanopore that are designed to be relatively inexpensive and appropriate for use in decentralized labs. Larger, more expensive sequencers with higher throughput are also available and would be more appropriate for central labs.

The Unitaid-funded FIND-led Seq&Treat project to demonstrate the feasibility of implementing TB NGS assays in routine care has engaged developers of TB NGS assays and shepherded them through the process of assay optimization and validation. The project has also enabled the development of the first-ever standardized catalog of TB mutations associated with drug resistance, published earlier this year by the WHO, to support the ongoing development of TB NGS assays and to provide regular updates as knowledge of *MTB* drug resistance continues to grow.¹⁵⁸ NGS assays can be quickly updated to include these new mutations, similar to a software update. The Seq&Treat project is currently in the clinical evaluation phase to generate evidence for WHO review and policy development. Subsequently, the project aims to assess various implementation models for NGS in different settings, such as centralized and decentralized approaches, to be able to provide practical guidance to country programs. A key goal of the project is to facilitate the inclusion of targeted NGS end-to-end solutions in global procurement mechanisms, such as the Global Drug Facility catalog, further facilitating adoption and implementation in country programs.

Reagent: a substance or compound that causes a particular chemical reaction

End-to-end solutions: a diagnostic system that provides a complete functional solution from beginning to end, from sample to result

Table 4: Next-Generation Drug-Susceptibility Tests to Inform TB Treatment

Target Product Profile: Next-generation drug-susceptibility testing at peripheral centers ¹⁵⁹							
Sensitivity*		Specificity*	Lowest Level of Use	Time to Results		Price per Test	
Optimal	Minimal	Optimal/ Minimal	Optimal/ Minimal	Optimal	Minimal	Optimal	Minimal
> 95% (RIF, INH, FLQ, BDQ, LZD, CFZ, DLM, PTD, AMK, PZA)	> 95% (RIF) > 90% (INH, FLQ) ≥ 80% (BDQ, LZD, CFZ, DLM, PTD, AMK, PZA)	≥ 98% (any anti-TB agent)	Primary care clinic with lab	< 30 min (< 2 hours acceptable)	< 6 hours	≤ US\$5 (RIF, INH, FLQ)	US\$10–15 (RIF, INH, FLQ)

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/assay	INH: 94% FLQ: 94% AMK: 73% ETH: 54%	98–100% (INH, FLQ, AMK, ETH) ¹⁶⁰	District lab (requires 10-color GeneXpert instrument modules)	< 90 min	US\$19.80 ¹⁶¹	Recommended by WHO in 2021 Commercially available in the GDF catalog
Truenat MTB-RIF Dx (Molbio)	Rapid molecular PCR/assay	RIF: 84%	RIF: 97% ¹⁶²	Primary care clinic with lab	< 60 min	Included in the US\$9 price of Truenat MTB and MTB Plus ¹⁶³	Recommended by WHO in 2020 Commercially available in the GDF catalog
Truenat MTB-INH (Molbio)	Rapid molecular PCR/assay	Not yet available		Primary care clinic with lab	< 60 min	US\$9 ¹⁶⁴	Design-locked Undergoing validation
Truenat MTB-FQ (Molbio)	Rapid molecular PCR/assay	Not yet available		Primary care clinic with lab	< 60 min	US\$9 ¹⁶⁵	Design-locked Undergoing validation
STANDARD M10 MDR-TB (SD Biosensor)	Rapid molecular PCR/assay	Not yet available (RIF, INH)		Primary care clinic with lab	< 60 min ¹⁶⁶	Not yet available	Undergoing feasibility evaluation ¹⁶⁷
IRON qPCR RIFA Kit (Bioneer)	Rapid molecular PCR/assay	Not yet available (RIF, INH, FLQ, AMK)		District lab (for use on IRON qPCR instrument)	< 60 min ¹⁶⁸	Not yet available	Design-locked Commercially available in 2022
Accupower TB&MDR Real-Time PCR Kit (Bioneer)	Rapid molecular PCR/assay	INH: 81.2% RIF: 95.7%**	INH: 95.8% RIF: 95.7% ^{169***}	District lab (for use on ExiStation instrument)	< 3.5 hours	PCR kit: US\$12.50 PCR and extraction kit: US\$16.56 ¹⁷⁰	Commercially available since 2013 Plans to submit dossier to Global Fund ERPD in 2021
Accupower XDR-TB Real-Time PCR Kit-A (Bioneer)	Rapid molecular PCR/assay	FLQ: 84.1% AMK: 67.4%**	FLQ: 99.1% AMK: 100% ^{171***}	District lab (for use on ExiStation instrument)	< 3.5 hours	PCR kit: US\$12.50 PCR and extraction kit: US\$16.56 ¹⁷²	Commercially available since 2019

Target Product Profile: Next-generation drug-susceptibility testing at peripheral centers¹⁵⁹

Sensitivity*		Specificity*	Lowest Level of Use	Time to Results		Price per Test	
Optimal	Minimal	Optimal/ Minimal	Optimal/ Minimal	Optimal	Minimal	Optimal	Minimal
> 95% (RIF, INH, FLQ, BDQ, LZD, CFZ, DLM, PTD, AMK, PZA)	> 95% (RIF) > 90% (INH, FLQ) ≥ 80% (BDQ, LZD, CFZ, DLM, PTD, AMK, PZA)	≥ 98% (any anti-TB agent)	Primary care clinic with lab	< 30 min (< 2 hours acceptable)	< 6 hours	≤ US\$5 (RIF, INH, FLQ)	US\$10–15 (RIF, INH, FLQ)

Test/Tool (Manufacturer)	Type	Sensitivity*	Specificity*	Lowest Level of Use	Time to Results	Price per Test/ Tool	Stage of Development/ WHO Review
TB drug resistance assay (QuantuMDx)	Rapid molecular PCR/assay	Not yet available		Primary care clinic with lab/ Community	< 45 min ¹⁷³	Not yet available (volume-based pricing)	Early development
TB drug resistance assay (Blink DX)	Rapid molecular PCR/assay	Not yet available		Primary care clinic with lab	Not yet available	Not yet available	Feasibility ¹⁷⁴
Real-Time MTB-RIF/INH Resistance (Abbott)	High-throughput molecular PCR/assay	MTB: 96.1% RIF: 94% INH: 89%	MTB: 97.6% RIF: 99% INH: 98% ¹⁷⁵	Central lab (94 max samples per run)	7 hours (specimen to results) ¹⁷⁶	Not yet available (volume-based pricing) ¹⁷⁷	Recommended by WHO in 2021 Plans to include in GDF catalog
BD MAX MDR-TB (BD)	High-throughput molecular PCR/assay	MTB: 93% RIF: 99.1% INH: 90%	MTB: 95.1% RIF: 98.2% INH: 99.8% ¹⁷⁸	District lab (24 max samples per run)	4.6 hours (specimen to results) ¹⁷⁹	Not yet available	Recommended by WHO in 2021
cobas MTB-RIF/INH (Roche)	High-throughput molecular PCR/assay	MTB: 93.3% RIF: 91% INH: 80%	MTB: 96.7% RIF: 96% INH: 98% ¹⁸⁰	Central lab (94 max samples per run)	5.5 hours ¹⁸¹	Not yet available	Recommended by WHO in 2021
FluoroType MTBDR Version 2.0 (Hain)	High-throughput molecular PCR/assay	MTB: 91.7% RIF: 97% INH: 70%	MTB: 99% RIF: 100% INH: 100% ¹⁸²	Central lab (94 max samples per run)	4.5 hours ¹⁸³	Not yet available	Recommended by WHO in 2021
Genoscholar PZA TB II (Nipro)	Molecular line probe assay (LPA)/assay	PZA: 81.2%	PZA: 97.8% ¹⁸⁴	Central lab	6 hours	US\$30 per test ¹⁸⁵	Recommended by WHO in 2021 Plans to include in GDF catalog
Deeplex Myc-TB (GenoScreen)	Targeted next-generation sequencing/ assay	SE: 95.3% SP: 97.4% ¹⁸⁶ (RIF, INH, PZA, EMB, FLQ, AMK, ETH, BDQ, CLO, LZD)		District lab	24–48 hours	US\$50–US\$60 ¹⁸⁷	Design-locked Application to Global Fund ERPD ongoing On pathway to WHO review
DeepChek Assay 13-Plex TB Drug-Susceptibility Testing V1 (ABL)	Targeted next-generation sequencing/ assay	Not yet available (RIF, INH, PZA, EMB, FLQ, AMK, ETH, BDQ, CLO, LZD) ¹⁸⁸		District lab	31 hours	Not yet available Competitive pricing ¹⁸⁹	On pathway to WHO review

Target Product Profile: Next-generation drug-susceptibility testing at peripheral centers ¹⁵⁹							
Sensitivity*		Specificity*	Lowest Level of Use	Time to Results		Price per Test	
Optimal	Minimal	Optimal/Minimal	Optimal/Minimal	Optimal	Minimal	Optimal	Minimal
> 95% (RIF, INH, FLQ, BDQ, LZD, CFZ, DLM, PTD, AMK, PZA)	> 95% (RIF) > 90% (INH, FLQ) ≥ 80% (BDQ, LZD, CFZ, DLM, PTD, AMK, PZA)	≥ 98% (any anti-TB agent)	Primary care clinic with lab	< 30 min (< 2 hours acceptable)	< 6 hours	≤ US\$5 (RIF, INH, FLQ)	US\$10–15 (RIF, INH, FLQ)

Test/Tool (Manufacturer)	Type	Sensitivity*	Specificity*	Lowest Level of Use	Time to Results	Price per Test/Tool	Stage of Development/WHO Review
Tuberculosis IVD test (Clemedi)	Targeted next-generation sequencing/assay	Not yet available		District lab	< 48 hours	Not yet available	Late development ¹⁹⁰
MDR-TB assay (SML Genetree)	Targeted next-generation sequencing/assay	Not yet available		District lab	< 48 hours	Not yet available	Late development ¹⁹¹
MinION (Oxford Nanopore)	Next-generation sequencing/instrument	—		District lab	< 48 hours	Starting from US\$1,000 ¹⁹²	Commercialized
iSeq 100 (Illumina)	Next-generation sequencing/instrument	—		District lab	9.5–19 hours ≤ 1.2 Gb output ¹⁹³	US\$19,900 ¹⁹⁴	Commercialized
MiniSeq (Illumina)	Next-generation sequencing/instrument	—		District lab	≤ 5–24 hours ≤ 7.5 Gb output ¹⁹⁵	US\$49,500 ¹⁹⁶	Commercialized
Ion GeneStudio S5 System (Thermo Fisher)	Next-generation sequencing/instrument	—		District lab	19 hours ≤ 15 Gb output ¹⁹⁷	US\$65,000 ¹⁹⁸	Commercialized

*Compared to a microbiological reference standard

**Company-reported data

Abbreviations

First-line drugs:

EMB: ethambutol
INH: isoniazid
PZA: pyrazinamide
RIF: rifampicin

Second-line drugs:

AMK: amikacin
BDQ: bedaquiline
CLO: clofazimine
DLM: delamanid
ETH: ethionamide

Second-line drugs (cont'd):

FLQ: fluoroquinolones (i.e., moxifloxacin and levofloxacin)
LZD: linezolid
PTD: pretomanid

5. Tests for Detecting Incipient TB and for Treatment Monitoring

The spectrum of TB from infection through active disease cannot be defined by clear-cut stages, although attempts have been made to articulate these.¹⁹⁹ For example, TB infection is a state of persistent immune response to *MTB* bacteria, which in some cases can develop into active TB disease. TB infection that is not fully contained by the immune system, resulting in bacterial replication that leads to progression toward active TB, is called **incipient TB**. TB disease before the onset of symptoms when bacterial load is still relatively low is called sub-clinical TB. TB disease with a higher bacterial load resulting in TB symptoms is called active TB disease. As active TB disease begins to develop, symptoms may be mild for many months before a person seeks care. During this time, TB transmission could occur. It is critical to develop diagnostics capable of detecting or predicting the risk of progression from TB infection to active TB disease to identify who would benefit most from TB preventive treatment so that the onset of active disease may be prevented, along with associated morbidity and mortality from TB and onward TB transmission. The challenge is that **pathogen**-based diagnostics are not sufficiently sensitive to detect incipient TB due to the very low bacterial load in samples during this stage.

All these stages of TB, however, can be characterized by a relationship between TB bacteria and a person's or host's response to the pathogen. The presence and replication of TB bacteria in the body produces a detectable and quantifiable response, as does the killing off of TB bacteria by TB treatment. Host response diagnostics show promise not only for detecting incipient TB with low-level bacterial replication but also for monitoring the effectiveness of TB treatment.²⁰⁰ 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 regarding the composition and duration of treatment regimens and to improve and expedite the conduct of clinical trials of new TB drugs and treatment regimens.

There are two main types of host response diagnostics in the pipeline for incipient TB and treatment monitoring—blood-based **RNA** tests and blood-based immune response tests. The RNA tests, or transcriptomic assays, can detect and quantify the expression of specific **gene signatures** in the **RNA transcriptome** that are activated by the presence of TB bacteria, thus serving as biomarkers for the presence and bacterial load of TB in the body. These tests utilize the same nucleic acid extraction and amplification technologies as rapid molecular tests. A range of transcriptomic gene signatures show promise, including Sweeney3, RISK6, and RISK11, and according to early studies the performance of these gene signatures has been found to be similar.²⁰¹ Several companies including Cepheid, QuantuMDx,

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

Pathogen: a bacterium, virus, or other microorganism that can cause disease

RNA: ribonucleic acid, a form of nucleic acid that converts the genetic information of DNA into proteins and that is involved in DNA replication

Gene signatures: a single gene or combined group of genes in a cell with a particular expression associated with a biological process caused by a pathogen

RNA transcriptome: the set of all RNA transcripts in the body

and bioMérieux are developing transcriptomic biomarker-based assays for incipient TB and treatment monitoring utilizing finger-prick blood samples. The performance of these assays does not yet meet the minimal criteria set in the TPP for incipient TB and treatment monitoring, including the capability to predict progression to active TB up to two years prior to the onset of active disease; therefore, more R&D is needed to improve their performance (see Table 5 below).²⁰² Hopefully the prices for these tests will also be made affordable so they can eventually be scaled up in low-resource settings. These host response RNA tests are expected to be validated and commercially launched within the next couple of years.

Similar to host response RNA tests, immune response tests are capable of detecting and quantifying a person's immune response to viable TB bacteria, which can serve as a biomarker for the presence of TB bacteria and bacterial load. Several companies are developing host immune response tests for differentiating between TB infection and active TB and for treatment monitoring. Among these tests are the TAM-TB assay from Beckman Coulter, which characterizes the expression of TB-specific biomarkers (CD38 and CD27) by the immune system's **CD4 T cells**, and T-Track TB, an **enzyme-linked immune absorbent spot (ELISpot)** assay from MIKROGEN, which quantitatively measures the expression of the CXCL10 gene. These assays are complex lab-based assays with a turnaround time of about 24 hours; however, it is possible that the instruments used to perform these assays could be made smaller and more portable, similar to instruments for rapid molecular testing.²⁰³

In addition to host response tests, several pathogen-based assays for treatment monitoring are in development to detect and quantify biomarkers indicating the presence of viable TB bacteria and bacterial load. One assay, the Molecular Bacterial Load Assay (TB-MBLA), developed by the University of St. Andrews and LifeArc, detects and quantifies a specific gene in TB bacteria—16S rRNA—that is only expressed in viable TB bacteria. TB-MBLA utilizes sputum samples and produces results that enable clinicians to measure the bactericidal effect of TB drugs and provide a long-term assessment of treatment response for slow responders. TB-MBLA is highly accurate with results that strongly correlate with the **time to culture positivity**. Compared to mycobacterial liquid culture, TB-MBLA has a lower risk of contamination and produces results in a few hours rather than several weeks, making TB-MBLA a practical replacement of culture for TB treatment monitoring.²⁰⁴ Another assay by TAUNS Laboratories worth noting utilizes sputum samples to detect MPT64, a protein that is highly specific to viable TB bacteria. Similar to TB-MBLA, the assay can quantify MPT64 to monitor the effectiveness of TB treatment and may be used as a surrogate to mycobacterial culture.²⁰⁵

CD4 T cells: a subset of white blood cells that play an important role in a person's immune system by helping to trigger the body's response to infection

Enzyme-linked immune absorbent spot (ELISpot): a technique by which immune markers can be detected and quantified

Time to culture positivity: the time it takes mycobacterial liquid culture to positively detect the presence of bacteria, which is in direct correlation to the bacterial load in the sample

Table 5: Tests for Detecting Incipient TB and for Treatment Monitoring

Target Product Profile: A test for predicting progression from tuberculosis infection to active disease ²⁰⁶									
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*	Lowest level of use	Time to results	Price per test	Stage of development
Xpert-MTB-HR (Cepheid)	Blood-based host RNA response/ PCR Sweeney3 gene signature	Incipient TB/ Treatment monitoring	Triage: SE: 90% SP: 55.8% Diagnosis: SE: 65.7% SP: 95.3% ²⁰⁷	District lab	Not yet available	Comparable to pricing of other GeneXpert tests	Mid-stage development Expected launch in 2023 ²⁰⁸
RISK6 signature assay (QuantuMDx)	Blood-based host RNA response/ PCR RISK6 gene signature	Incipient TB/ Treatment monitoring	Incipient TB ≤ 12 months of incident TB: SE: 75% SP: 50.3% Triage: SE: > 90% SP: 56% ²⁰⁹	Primary care clinic with lab/ Community	< 45 min ²¹⁰	PCR-based test pricing	Mid-stage development Projected year of WHO review: 2022
RISK11 signature	Blood-based host RNA response/ PCR RISK11 gene signature	Incipient TB/ Treatment monitoring	Incipient TB among PLHIV: SE: 88.6% SP: 68.9% ²¹¹	Not yet available	Not yet available	Not yet available	Not yet available
FilmArray Assay (bioMérieux)	Blood-based host RNA response/ PCR TB-specific 20-gene signature	Incipient TB/ Treatment monitoring	Robust sensitivity and specificity for differentiating active TB from TB infection ²¹²	District lab	60 min ²¹³	Not yet available	Mid-stage development
TAM-TB (Beckman Coulter)	Blood-based host immune response/ flow cytometry CD38 and CD27 T-cell markers	Incipient TB/ Treatment monitoring	Diagnosis: SE: 82.2% SP: 93.4% ²¹⁴ Treatment monitoring: Clear trend of T-cell markers with treatment success at 1 month and 6 months of treatment ²¹⁵	District lab	24 hours	Not yet available	Mid-stage development

Target Product Profile: A test for predicting progression from tuberculosis infection to active disease ²⁰⁶									
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*	Lowest level of use	Time to results	Price per test	Stage of development
T-Track TB (MIKROGEN)	Blood-based host immune response/ ELISpot CXCL10 gene signature	TB infection/ Active TB rule-out test	SE: > 95%** SP: > 90%** ²¹⁶ Successful differentiation between TB infection and active TB in feasibility studies ²¹⁷	Central lab	~24 hours (incubation period plus < 6 hours assay execution)	Comparable to IGRAs	Late development Expected launch in 2021
TB-MBLA (University of St. Andrews/ LifeArc)	MTB bacillary load in sputum/PCR 16S rRNA gene signature	Incipient TB/ Treatment monitoring	SE: 85% SP: 97% (compared to Xpert MTB/RIF) ²¹⁸ Strong positive correlation in time to sputum culture conversion ²¹⁹	Primary care clinic with lab	< 6 hours	Not yet available	Design-locked Undergoing evaluation studies ²²⁰
MPT64 ELISA (TAUNS Laboratories)	MTB bacillary load in sputum/ ELISA (enzyme-linked immunosorbent assay) MPT64 protein marker	Treatment monitoring	Predicting positive culture: SE: 81% Predicting negative culture: SP: 89.5% ²²¹	Central lab	Not yet available	Not yet available	Not yet available

*Compared to a microbiological reference standard

**Company-reported data

Box 3: The Need for Evidence-Based Pricing of Diagnostics

GeneXpert tests have been available since 2010 and recommended by the WHO as the initial TB diagnostic test since 2013, yet over the past decade many countries with high burdens of TB have been unable to fully scale up rapid molecular testing due to the high prices of GeneXpert tests and instead continue to rely on less-expensive and less-accurate smear microscopy.²²² The 2012 buy-down agreement that lowered the price of GeneXpert TB tests to \$9.98 per test did not include any conditions for transparency of the cost of production or volume-based price reductions. Despite rising volumes, Cepheid has not reduced the price of GeneXpert TB tests, limiting access.²²³ This cautionary tale highlights the need for evidence-based pricing of essential and life-saving diagnostics. These diagnostics must be priced affordably based on the cost of production and volumes so that they will be scalable and may be fully adopted and implemented in national programs.

FIND has stipulated such a condition for affordable and evidence-based pricing in their Global Access Policy, requiring lowest sustainable prices based on COGS plus a reasonable profit margin as a condition of funding.²²⁴ FIND further articulated conditions for transparent and affordable COGS-based pricing in their recent request for proposals for developers of molecular diagnostic platforms for decentralized diagnosis of acute respiratory illness.²²⁵ In the recently revised TPP for drug-susceptibility testing in peripheral centers, the WHO also established norms and expectations regarding evidence-based pricing, noting that “ideally, the price of tests should be based on evidence of the actual cost of goods and estimated volumes, and a reasonable profit margin,” and that “ensuring access to tests while maintaining business interests can be achieved through fair pricing, which requires transparency of the cost of goods and estimated volumes, with a reasonable profit margin.”²²⁶ These steps taken by FIND and WHO are encouraging, but it is important for other TB diagnostics R&D funders and stakeholders to follow suit. Continued efforts to develop a standardized methodology for determining COGS and a global framework for the fair pricing of diagnostics will further facilitate and support a shift toward a more equitable system of diagnostics pricing.

6. Tests for TB Infection

About one quarter of the world’s population has TB infection, amounting to about two billion people. People with TB infection have a 5–15% lifetime risk of developing active TB disease and are at highest risk of developing active TB during the first two years after infection.²²⁷ Certain population groups are also at higher risk of developing active TB, such as PLHIV with compromised immune systems and household contacts of people with active TB. TB preventive treatment (TPT) is a critical intervention to prevent the onset of TB among people with TB infection—especially among high-risk groups—and is characterized as essential to achieving the ambitious targets of the End TB Strategy 2016–2035.²²⁸ Testing for TB infection can be an important way to help determine who may be eligible for TPT, but diagnosing TB infection is not a precondition and should not be a barrier to TPT initiation among PLHIV and child household contacts of people with active TB who are at higher risk of dying from TB.²²⁹

There is not a TPP for tests for TB infection; 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.²³⁰ Tests for TB infection, such as skin and blood tests, are immunoassays that test for the body's immune response to the introduction of TB antigens, but these tests are unable to differentiate between TB infection and active TB disease. The most used test for TB infection globally is the tuberculin skin test (TST), which is an inexpensive injection of TB antigens just under the skin that is assessed after 48–72 hours for swelling, which indicates prior exposure to TB and therefore TB infection. TST, however, 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.²³¹ Other commonly used tests, particularly in high-income countries, are interferon gamma release assays (IGRAs), which are highly accurate blood-based tests that are not affected by prior BCG vaccination but that are expensive and generally require well-equipped laboratories to be performed.

To improve the specificity of skin tests among people with prior BCG vaccination and to scale up testing for TB infection in countries with high burdens of TB, new skin tests have been developed that utilize antigens—such as the ESAT6-CFP10 antigen—that do not overlap with the antigens used in the BCG vaccine. These novel skin tests include C-Tb from Serum Institute of India, Diaskintest from Generium, and C-TST (or EC Skin Test) from Anhui Zhifei Longcom. The WHO is currently in the process of compiling the evidence on the performance, safety, and acceptability of these tests as well as another skin test—DPPD from HDT Bio and Creative Biolabs—and is expected to issue recommendations on the use of these novel skin tests in 2022. In addition to new skin tests, the diagnostics company Qiagen—one of the main producers of lab-based IGRAs globally—has developed a new form of IGRA called QIAreach QFT that can be performed at the primary care level. This test is based upon the same technology as Qiagen's QuantiFERON (QFT) Plus IGRAs, with about the same level of accuracy. Following an incubation period, samples are then transferred to a lateral flow assay that is inserted into a digital reader to interpret results. QIAreach QFT tests are expected to be commercialized at about \$10 per test, more than five times the price of skin tests, which may limit the uptake of this simpler form of IGRA. An ongoing challenge for both skin tests and IGRAs is the requirement of a second visit to a health facility to receive results, due to the turnaround time of two to three days for skin tests and one day for IGRAs.

Table 6: Tests for TB Infection

Test (Manufacturer)	Type	Sensitivity* / Specificity*	Lowest level of use	Time to results	Price per test	Stage of development/ WHO review
QIArearch QFT (Qiagen)	Immunoassay blood test/ IGRA	98.8% concordance with QFT Plus IGRA ²³² (QFT Plus SE: 91-94% SP: 95-96% ²³³)	Primary care clinic with lab	< 20 min (with prior incubation for 16-24 hours)	US\$10 (exploring lower concessional pricing based on volumes) ²³⁴	Projected year of WHO review: 2022 Submitted data for Global Fund ERPD review ²³⁵
C-Tb (Serum Institute of India)	Immunoassay skin test ESAT6-CFP10 antigen	94% concordance with QuantiFERON Gold In-Tube ²³⁶ (QuantiFERON Gold In-Tube SE: ≤ 92% SP: > 99% ²³⁷)	Community	48-72 hours	Highly cost effective and could be supplied in large volumes ²³⁸	WHO review: 2022 Commercial availability: 2022
Diaskintest (Generium)	Immunoassay skin test ESAT6-CFP10 antigen	SE: 91.18% 87.16% concordance with QuantiFERON-TB Gold In-Tube ²³⁹	Community	72 hours	US\$1.43 ²⁴⁰	WHO review: 2022
C-TST/EC Skin Test (Anhui Zhifei Longcom Biopharmaceutical Co., Ltd)	Immunoassay skin test ESAT6-CFP10 antigen	SE: 90.64% SP: 91.12%** ²⁴¹	Community	48-72 hours	Not yet available	WHO review: 2022 Commercially available
DPPD (HDT Bio) (Creative Biolabs)	Immunoassay skin test DPPD antigen	Improved sensitivity and specificity compared to PPD-based TST, including among PLHIV ²⁴²	Community	48-72 hours	Not yet available	WHO review: 2022

*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.

**Company-reported data

Conclusion

The research and development pipeline of new TB screening and diagnostic tools is clearly moving in the right direction, bringing more accurate and rapid technologies closer to the point of care; yet, the longstanding systemic challenges of insufficient TB R&D funding, weak health systems, and high prices of TB screening and diagnostic technologies must be addressed. Transferring COVID-19 technologies to TB is a key opportunity but it does not address the insufficient political will that has allowed TB, a preventable and curable disease, to continue to plague people and communities around the world, especially in low- and middle-income countries. The years of progress in the fight against TB that have been lost due to COVID-19 means that more people will get sick and die from this terrible disease. It's time for all TB stakeholders, including governments, donors, diagnostics developers, researchers, and community activists, to step up and create the innovative and equitable systems we need to be able to rapidly develop and fully roll out point-of-care TB screening and diagnostic testing for TB and DR-TB in TB-affected communities around the world. Achieving this will require more TB R&D funding and innovation; better engagement of TB-affected communities in research; more efficient pathways for WHO policy-making; full commitment by countries to adopt new tools, expedite regulatory processes, and ensure sufficient budget allocations; fair and equitable pricing of TB diagnostics that is transparent and based on evidence; and continued fierce and evidence-informed activism by communities affected by TB, who are and must be recognized as the real leaders of the transformative change necessary to end TB.

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