AN ACTIVIST'S GUIDE TO
TUBERCULOSIS
DIAGNOSTIC TOOLS

TAG
Treatment Action Group

INTRODUCTION

Diagnosing tuberculosis (TB) is an essential step toward ensuring that all people with TB receive effective treatment and are ultimately cured of the deadly disease. While no TB diagnostic test is perfect, the technologies and tools used to diagnose TB continue to improve because of investments in TB research and development, making them more accurate, simple, and appropriate for use at the **point-of-care**. As TB diagnostic tools evolve, so do the recommendations and guidance from the World Health Organization (WHO) on how these tools should be optimally used in country programs. The following guide reviews current and forthcoming TB diagnostic tools and details the latest WHO guidance on the use of these tools.

All people at risk of TB have the right to TB diagnostic testing at the highest standard of care. In 2020, the United Nations Committee on Economic, Social, and Cultural Rights (CESCR) released a general comment on the right of all people to the benefits and applications of scientific progress. In the comment, the CESCR explained that an essential element of the right is "quality," which it defined as "the most advanced, up-to-date and generally accepted and verifiable science available at the time, according to the standards generally accepted by the scientific community."[1] The WHO is the primary body for determining the quality of TB diagnostic tools and for providing detailed policy recommendations and guidance on the optimal use and implementation of these tools. As part of this, the WHO keeps an essential diagnostics list (EDL) of WHO-recommended TB diagnostic tests that countries should prioritize and implement.[2] Yet, many countries have failed to fully scale up and implement TB diagnostic testing in accordance with WHO guidance and the EDL, thus failing to fulfill their human rights obligations under the **right to science** and the right to health.[3]

The TB diagnostic pathway is the entry point through which people with TB access the **TB cascade of care**. Under optimal circumstances, TB-affected communities are regularly offered TB screening and testing, followed by TB treatment or **TB preventive therapy (TPT)**[4] as appropriate (see *Figure 1: The highest standard of care for TB diagnosis*). In actuality, however, many people seek care only after developing symptoms of active TB, and they often face stigma when doing so.[5,6,7] Of those who are diagnosed, many do not receive the drug-susceptibility testing necessary to inform optimal treatment regimens. Meanwhile, low rates of TB preventive therapy (TPT) initiation persist among high-risk people, leaving them at risk of developing active TB disease.[8]

POINT-OF-CARE: the location where a person presents to care for a disease or condition

RIGHT TO SCIENCE: the right of all people to enjoy the benefits of scientific progress and its applications enshrined in Article 15 of the International Covenant on Economic, Social and Cultural Rights

TB CASCADE OF CARE: the entire pathway of TB care, including diagnosis, treatment, and cure

TB PREVENTIVE THERAPY (TPT): treatment taken by people with TB infection to prevent progression from infection to active TB disease; TPT is also sometimes given to protect people who are uninfected but at risk of TB exposure and infection

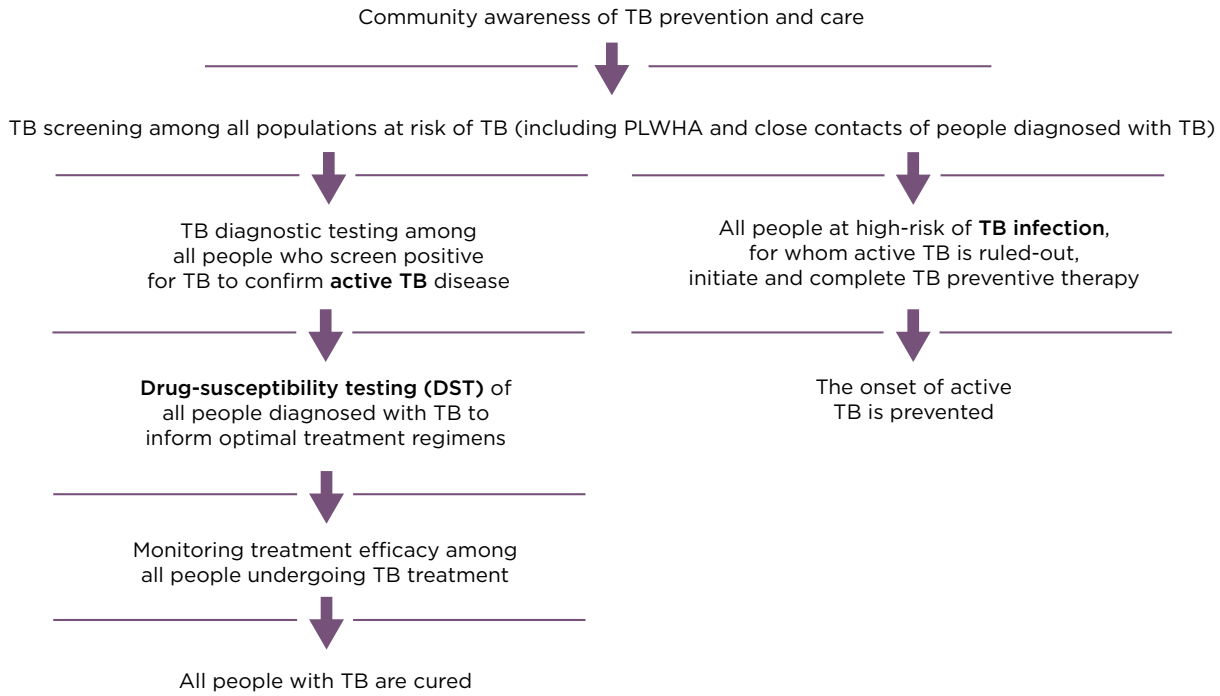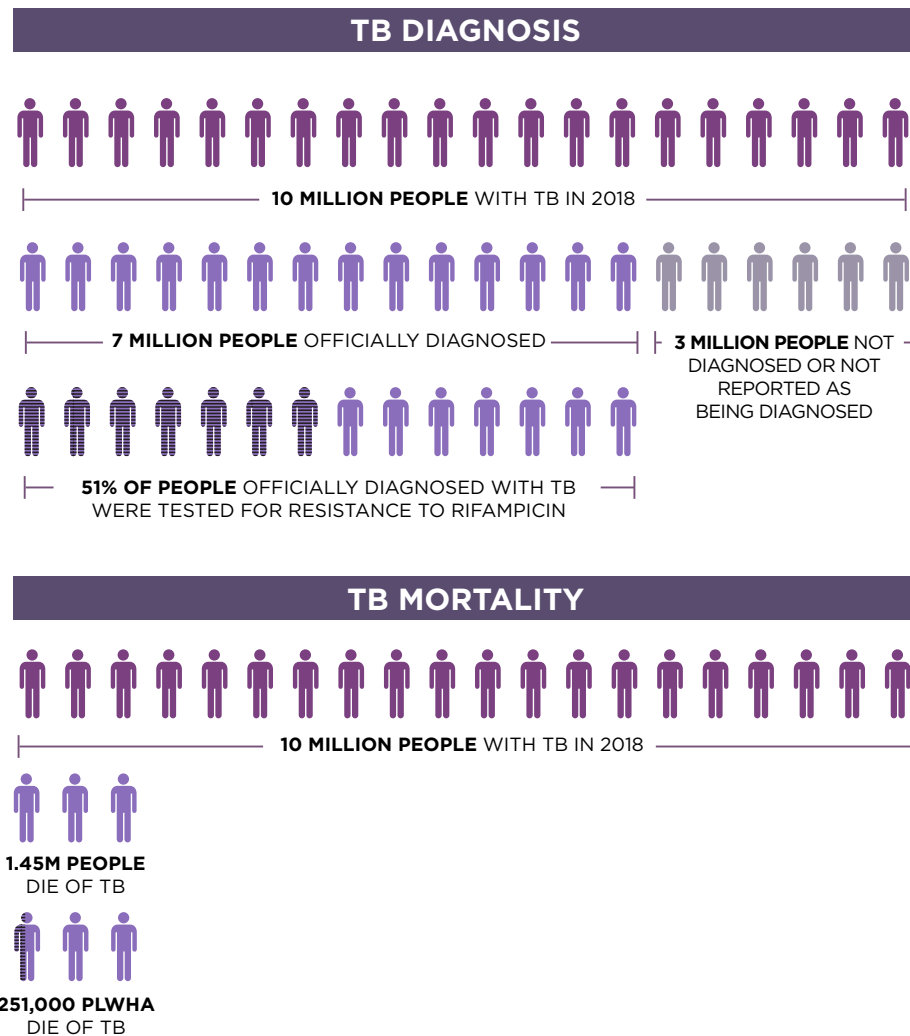*Figure 1: The highest standard of care for TB diagnosis*

Community awareness of TB prevention and care

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TB screening among all populations at risk of TB (including PLWHA and close contacts of people diagnosed with TB)

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TB diagnostic testing among all people who screen positive for TB to confirm **active TB** disease

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Drug-susceptibility testing (DST) of all people diagnosed with TB to inform optimal treatment regimens

↓

Monitoring treatment efficacy among all people undergoing TB treatment

↓

All people with TB are cured

All people at high-risk of **TB infection**, for whom active TB is ruled-out, initiate and complete TB preventive therapy

↓

The onset of active TB is prevented

Figure 2: The global state of TB in 2018[9]

TB DIAGNOSIS

10 MILLION PEOPLE WITH TB IN 2018

7 MILLION PEOPLE OFFICIALLY DIAGNOSED

3 MILLION PEOPLE NOT DIAGNOSED OR NOT REPORTED AS BEING DIAGNOSED

51% OF PEOPLE OFFICIALLY DIAGNOSED WITH TB WERE TESTED FOR RESISTANCE TO RIFAMPICIN

TB MORTALITY

10 MILLION PEOPLE WITH TB IN 2018

1.45M PEOPLE DIE OF TB

251,000 PLWHA DIE OF TB

ACTIVE TB: 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-SUSCEPTIBILITY TESTING (DST): tests used to determine resistance to TB drugs

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

These critical failures of TB screening and diagnosis contribute to overall high rates of active TB, continued transmission of TB in communities, development of increased resistance to TB drugs, and avoidable suffering and death from TB. In 2018, 10 million people developed active TB disease globally. Of these, only 7 million people were officially diagnosed, leaving a gap of 3 million people with TB—30 percent—who were either not diagnosed or not reported as being diagnosed. Only about half of those who were diagnosed with TB also received drug-susceptibility testing for resistance to the TB drug rifampicin, a powerful TB medicine that alongside isoniazid forms the backbone of first-line treatment for TB. Also in 2018, an estimated 1.45 million people—including 250,000 people with HIV/AIDS—died from TB, a disease that is preventable and curable.[10]

In order to realize the highest standard of care for the diagnosis of TB, national TB programs must implement TB diagnostic tools in accordance with WHO recommendations. Yet, major barriers stand in the way of making this standard of care a reality for all people with TB. These include high prices of many TB diagnostic tools; slow uptake of WHO-recommended TB diagnostic tools by countries; insufficient donor and domestic funding to introduce, fully scale up, and implement these TB diagnostic tools in routine use; health system inefficiencies; and diagnosis-related catastrophic costs for people with TB. These barriers must be removed if the world is to realize the highest standard of care for TB diagnostic testing and to close the TB diagnostic gap.

We wrote this guide to support activists to advocate at both country and global levels for access to TB diagnostic testing at the highest standard of care for all people at risk of TB. This guide details the latest WHO recommendations that inform this standard of care, along with the array of available TB diagnostic tools and how they should be optimally used in country programs, including among special populations such as children, people with extrapulmonary TB, and people living with HIV/AIDS (PLWHA). The organization of the guide generally follows the TB diagnostic pathway. It begins with a review of tools used for diagnosing active TB disease, which include (1) screening tools to determine whom to test for TB, (2) diagnostic tools to **microbiologically confirm** the presence of TB, (3) drug-susceptibility tests to identify resistance to TB drugs, and (4) tools for monitoring the efficacy of TB treatment. It then reviews tools for diagnosing TB infection, discusses key access considerations for realizing the right to science for TB diagnosis, and details ways that activists can take action to ensure that all people at risk of TB receive quality TB diagnostic testing.

MICROBIOLOGICAL CONFIRMATION: detecting the physical presence of TB bacteria in a given sample

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1. DIAGNOSING ACTIVE TB DISEASE

Stages for diagnosing active TB disease include first determining whom to test and then performing diagnostic testing capable of microbiologically confirming the presence of TB bacteria in samples such as **sputum** from the lungs, extrapulmonary specimens from other parts of the body, urine, or stool. The WHO recommends that people who screen positive for TB symptoms should also be screened for HIV and receive a chest X-ray as a second screening test and that those with an abnormal chest X-ray suggestive of TB should be further evaluated for TB with a TB diagnostic test. The WHO recommends **rapid molecular tests** to be used as the initial test for diagnosing TB and resistance to rifampicin. If a sample tests positive for resistance to rifampicin, health care workers should perform comprehensive drug-susceptibility testing for other first- and second-line TB drugs to inform optimal treatment regimens.

BOX 1: REFERENCE STANDARDS FOR MEASURING TB DIAGNOSTIC TEST ACCURACY

Liquid culture is the most **sensitive** and **specific** test for diagnosing active TB disease, or the "gold standard" of TB diagnostic testing. As such, liquid culture is commonly used as the **microbiological reference standard (MRS)** for most test accuracy studies, establishing the reference against which the performance of other tests can be compared. But even liquid culture is not perfectly accurate, and in some cases it is not able to detect active TB, even when TB bacteria are present. This is especially the case for many children and PLWHA, who often have small amounts of TB bacteria in the body, called **paucibacillary TB**, or TB spread throughout the body, called **disseminated TB**. Because microbiological reference standards perform worse in children and PLWHA, a **composite reference standard (CRS)**—including liquid culture, clinical evaluation of TB symptoms, and in some cases chest X-rays—can also be used to measure test accuracy in these populations.

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

RAPID MOLECULAR TESTS: diagnostic tests that rapidly detect the DNA of TB bacteria and/or TB DNA mutations associated with resistance to certain drugs

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 REFERENCE STANDARD (MRS): 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

PAUCIBACILLARY TB: active TB that is caused by small amounts of TB bacteria; a common form of TB among PLWHA and children

DISSEMINATED TB: active TB that is spread throughout the body and not just in one site; a common form of TB in PLWHA

COMPOSITE REFERENCE STANDARD (CRS): a standard of accuracy that includes the microbiological reference standard plus clinical evaluation of TB symptoms and in some cases chest X-rays, which may be used when the accuracy of the microbiological reference standard alone is likely to be inadequate (for example among PLWHA and children), and against which the accuracy of other tests may be compared

1.1 Determining whom to test: contact tracing and screening high-risk groups

Table 1: Screening tools

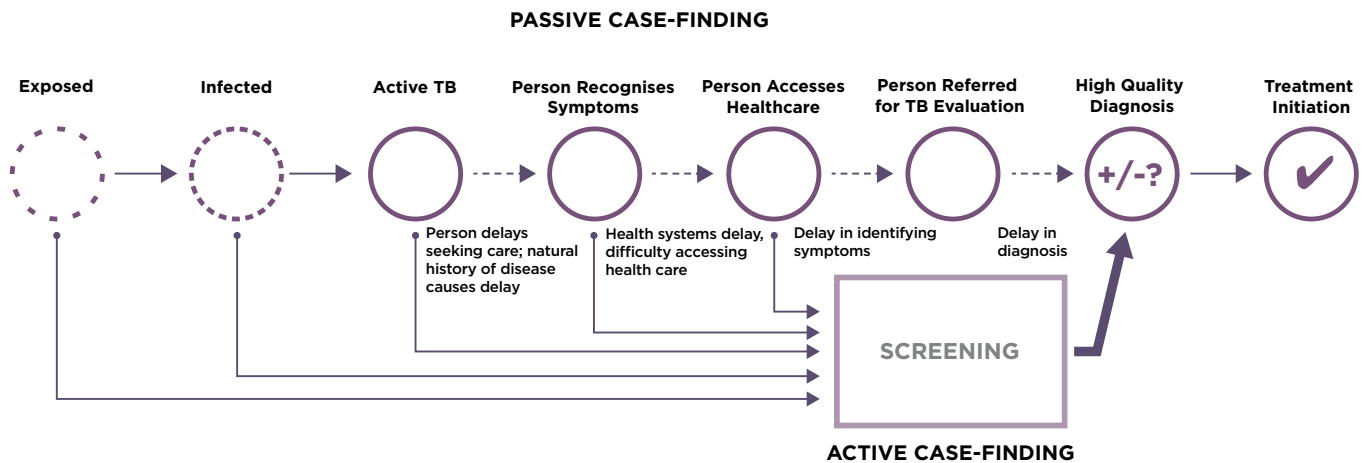| Screening tool	Sensitivity*	Specificity*	Cost (USD)	Manufacturer	WHO recommendation
Symptom screening	77% (any TB symptom)	68% (any TB symptom)	N/A	N/A	People who screen positive for TB symptoms should be screened for HIV and receive CXR as a second screening test[11]
Chest X-ray (CXR)	90% (following positive symptom screen)	56% (following positive symptom screen)	$1 (digital CXR)[12]	Multiple	People with an abnormal CXR suggestive of TB should be given a TB diagnostic test[13]
CAD4TB	85–100%	23–69%[14]	$0.45 to $0.95[15]	Delft Imaging	The WHO is expected to review computer-aided detection (CAD) software in mid to late 2020
qXR	71%	80%[16]	$0.40 (lowest volume-based price)[17]	Qure.ai	
* Microbiological reference standard (MRS)					

It is not necessary to test everyone for TB. The prevalence of TB differs by geographic location and population group. The WHO does not recommend "indiscriminate" screening of all people for signs and symptoms of TB. Rather, the WHO recommends "systematic" screening of people in countries with high prevalence or burden of TB and of specific populations at high risk of TB, including household contacts or close contacts of people with active TB disease; PLWHA; incarcerated people; people in detention centers; and people with poor access to health services, such as people living in urban slums and homeless people.[18] TB screening methods recommended by the WHO include symptom screening to evaluate people for TB symptoms and chest X-rays to identify any lung abnormalities that may be suggestive of TB. In combination, these screening methods have high sensitivity to help to rule out TB, but low specificity to rule in TB, meaning that they are appropriate for identifying at a high level of sensitivity the people who may have TB, but cannot definitively differentiate TB from other diseases or conditions. People who screen positive for TB therefore require further diagnostic testing.

Determining whom to test for TB can involve active case-finding or passive case-finding. Active case-finding systematically screens people who are in high-prevalence areas or who are at high risk for TB. The aim is to identify people with TB early in the progression of the disease so that they can rapidly initiate treatment, thereby reducing TB transmission, as well as suffering and death from TB. Active case-finding includes **contact tracing** of household contacts and other close contacts of people diagnosed with active TB disease. Passive case-finding evaluates people for TB as a part of routine health care or when people present to care with TB symptoms. Active case-finding in addition to passive case-finding is preferable to passive case-finding alone, because the multiple barriers people with TB must overcome before accessing TB diagnosis and care in many settings contribute to lengthy delays and further progression and transmission of the disease.[19]

CONTACT TRACING: identifying the household contacts and close contacts of people with TB

Figure 3: Active versus passive case-finding

PASSIVE CASE-FINDING

Adapted from WHO image *Comparison of patient-initiated and provider-initiated screening pathways for the diagnosis and treatment of tuberculosis (TB)*[20]

1.1.1 Symptom screening

Symptom screening involves an assessment of a person's symptoms followed by clinical evaluation to determine whether the symptoms may be indicative of TB. Common symptoms of **pulmonary TB** include: current coughing (for any duration), night sweats, weight loss, fever, and coughing up blood (called **hemoptysis**).[21] Common symptoms of **extrapulmonary TB** include night sweats, weight loss, and fever. Upon positive symptom screen, health professionals may recommend a chest X-ray and/or TB diagnostic testing.

1.1.2 Chest X-rays

Chest X-rays, or **radiographic imaging**, produce an image of the internal structures of the lungs that enables medical professionals to identify any lung abnormalities that may be suggestive of TB. On the chest X-ray images, air in the lungs appears as black space, and lung abnormalities—such as lesions caused by TB—appear as grey or white shadows. Because such abnormalities may also be suggestive of other diseases such as pneumonia, further testing is required. Among PLWHA, for whom lung abnormalities due to TB are less common, chest X-rays are less sensitive for detecting possible TB. X-ray imaging may be film-based or digital, with a preference for digital imaging because of the lower amount of radiation required, better control over image contrast, no need for expensive film, and compatibility with **computer-aided detection (CAD)** software. CAD, which uses artificial intelligence (AI) algorithms and deep-learning systems to assist in identifying lung abnormalities on chest X-rays, is particularly beneficial for use in low-resource settings where access to trained radiography technicians may be limited. However, technical guidance on the use of these tools will be needed—particularly in regard to setting the threshold score to differentiate between normal and abnormal chest X-ray images. The WHO is expected to review CAD technologies—including CAD4TB and qXR software—in mid to late 2020.

PULMONARY TB: TB in the lungs

HEMOPTYSIS: coughing up of blood or blood-stained mucus from the lungs, which generally occurs later in the progression of pulmonary TB

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

RADIOGRAPHIC IMAGING: an imaging technique that projects small amounts of radiation through the body to produce an image of its internal structures (e.g., X-ray)

COMPUTER-AIDED DETECTION (CAD): artificial-intelligence-based computer software that assists medical professionals to detect lung abnormalities on chest X-rays and to interpret results

Table 2: Comparison of available computer-aided detection (CAD) tools[22]

CAD tool	Company	Online & offline use*	Primary health setting use	Processing time per image	Price per image (USD)
CAD4TB	Delft Imaging	Yes	Yes	<20 seconds	$0.45 to $0.95
DxTB	DeepTek	Yes	Yes	2 seconds	Volume-based pricing
InferRead DR Chest	InferVision	Yes	Yes	<5 seconds	Flexible pricing
JF CXR-1	JF Healthcare	Yes	Yes	5 seconds	Volume-based pricing
Lunit INSIGHT CXR	Lunit	Yes	Yes	20 seconds	Volume-based pricing
qXR	Qure.ai	Yes	Yes	<1 minute	$0.40 (lowest volume-based price)[23]
XrayAME	EPCON	Yes	Yes	20 seconds	Flexible pricing

* Online use requires internet connectivity. Offline use requires purchase of a separate system, which may cost up to US$6,000, that houses the AI software and the comparative CXR data.

1.2 Microbiological confirmation of active TB disease

In order to diagnose active TB disease, tests must be sufficiently sensitive and specific—with very small percentages of **false negative** and **false positive** results—and must be capable of rapidly confirming the microbiological presence of TB bacteria in samples. There are several methods for microbiological confirmation, which follow the basic typology of "see the bugs," "grow the bugs," and "multiply the bugs."

"See the bugs": The most prominent method of diagnosing and microbiologically confirming TB throughout history has been smear microscopy, in which technicians directly see the TB bacteria in samples using a microscope. Smear microscopy is a century-old technology that is insufficiently sensitive as a TB diagnostic test—detecting TB in only 50 percent of sputum samples with TB bacteria present.[26] Because of this low sensitivity, the WHO does not recommend smear microscopy as an initial TB diagnostic test.

"Grow the bugs": Liquid culture—another method for microbiologically confirming TB—is the most sensitive and specific TB test, and as such it is the "gold standard" for TB diagnosis. To perform testing by liquid culture, technicians must grow the TB bacteria in order to detect it; confirmatory results can take about two to six weeks. Liquid culture is thus not appropriate as an initial TB diagnostic test, because while a person is waiting for results, their TB disease will continue to progress and may spread in households and communities.

"Multiply the bugs": Rapid molecular tests, on the other hand, are highly sensitive and specific for detecting and microbiologically confirming TB and are capable of producing results in less than two hours. These tests rapidly multiply DNA sequences indicative of TB bacteria, thereby amplifying them so that they can be detected in samples. Rapid molecular tests are recommended by the WHO as the initial TB diagnostic test for all people being evaluated for TB.

FALSE NEGATIVE: a test result that incorrectly indicates the absence of a disease or condition, when the disease or condition is in fact present

FALSE POSITIVE: a test result that incorrectly indicates the presence of a disease or condition, when the disease or condition is in fact absent

BOX 2: SHORTCOMINGS OF EXISTING TB DIAGNOSTIC TOOLS; CHARACTERISTICS OF THE NEW TOOLS WE NEED

Closing the TB diagnostic gap will require not only more testing, but also better tools. No TB diagnostic test available today is perfect, and many have significant shortcomings, such as: insufficient accuracy (sensitivity and specificity); long time to results (requiring multiple visits to health facilities, which contributes to **loss to follow-up** for treatment initiation); sample testing performed away from the point-of-care (requiring sample transport systems); overreliance on sputum samples (which are difficult for children and PLWHA to produce and are not appropriate for extrapulmonary TB); use of expensive **instruments** with significant infrastructure requirements (such as constant electricity and air conditioning); and high prices for tests and instruments (which limit the capacity of countries to scale up and implement these tools). We must nonetheless use the tools we have in ways that maximize their effectiveness, while pushing for greater affordability and access and advocating for investment in the research and development (R&D) necessary to produce simpler, more accurate tests that can be performed closer to the point-of-care.

The WHO, in collaboration with the Foundation for Innovative New Diagnostics (FIND), has developed a set of target product profiles (TPPs) to guide the R&D of new TB diagnostic tools, which address many of the shortcomings of existing tools. The TPPs define the ideal types of tools that are needed according to different **use cases for TB diagnosis**, along with their ideal characteristics and target price per test. The WHO TPPs for new diagnostic tools include:

1. A rapid **biomarker**-based non-sputum-based test for detecting TB (target price: < US$4)

2. Community-based **triage** or referral test for identifying people with presumptive TB (target price: < US$1)

3. Rapid sputum-based test for detecting TB at the **microscopy center** level of the health care system (target price: < US$4)

4. **Next-generation drug-susceptibility testing** at microscopy centers (target price: < US$10)[24]

5. A test for predicting progression from TB infection to active disease (target price: < US$5)[25]

LOSS TO FOLLOW-UP: when people with TB drop out of the cascade of care

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

USE CASES FOR TB DIAGNOSIS: specific scenarios for which TB diagnostic intervention is needed

BIOMARKER: a measurable indicator of the presence or severity of a disease

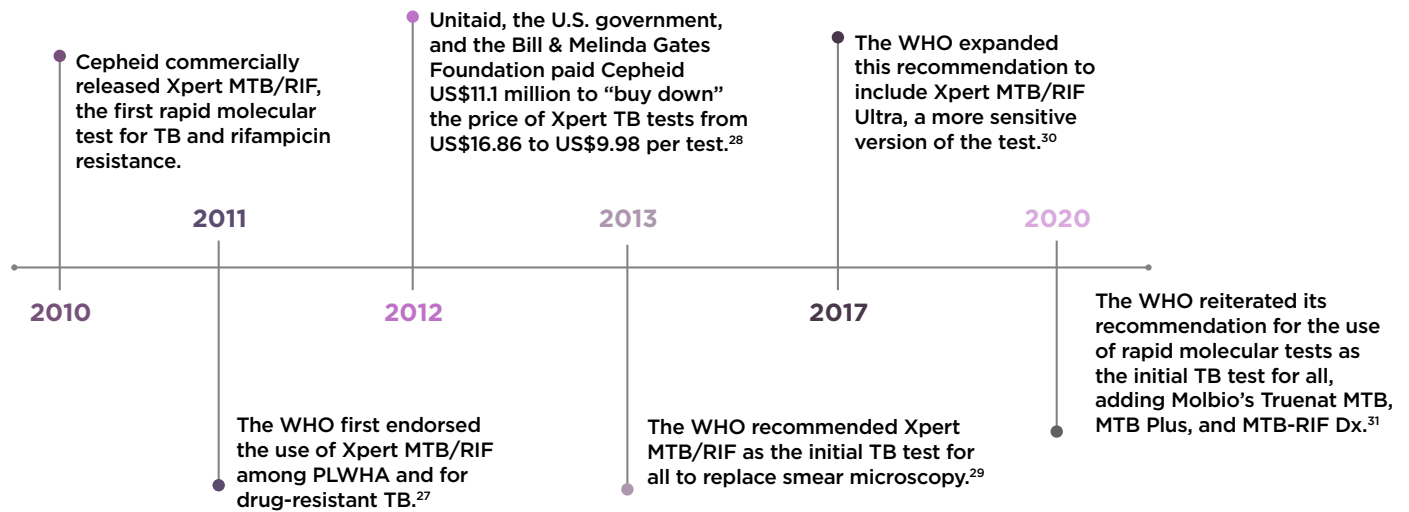**TRIAGE:** prioritization of care based on assessed need

MICROSCOPY CENTER: a facility where smear microscopy is performed, generally at the sub-district level

NEXT-GENERATION DRUG-SUSCEPTIBILITY TESTING: new technologies for drug-susceptibility testing, which include whole-genome and targeted-genome sequencing

Figure 4: Ten years of rapid molecular tests

Cepheid commercially released Xpert MTB/RIF, the first rapid molecular test for TB and rifampicin resistance.

Unitaid, the U.S. government, and the Bill & Melinda Gates Foundation paid Cepheid US$11.1 million to "buy down" the price of Xpert TB tests from US$16.86 to US$9.98 per test.[28]

The WHO expanded this recommendation to include Xpert MTB/RIF Ultra, a more sensitive version of the test.[30]

2011

2013

2020

2010

2012

2017

The WHO reiterated its recommendation for the use of rapid molecular tests as the initial TB test for all, adding Molbio's Truenat MTB, MTB Plus, and MTB-RIF Dx.[31]

The WHO first endorsed the use of Xpert MTB/RIF among PLWHA and for drug-resistant TB.[27]

The WHO recommended Xpert MTB/RIF as the initial TB test for all to replace smear microscopy.[29]

In addition to testing for TB, rapid molecular tests marketed by the companies Cepheid and Molbio also test for **resistance** to the first-line TB drug rifampicin. Resistance to rifampicin is indicative of rifampicin-resistant TB (RR-TB), but it may also be indicative of multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). Upon receiving a positive result for rifampicin resistance, drug-susceptibility testing to comprehensively test for resistance to other TB drugs must follow, but TB treatment must be initiated immediately with regimens selected in accordance with the local prevalence and forms of drug-resistant TB (DR-TB). Upon receipt of confirmatory DST results, treatment regimens may be adjusted and further optimized. Forms of DST include rapid and high-throughput molecular tests and line probe assays (LPAs) (multiply the bugs), liquid culture (grow the bugs), and next-generation sequencing.

RESISTANCE: mutations that occur in TB bacteria enabling them to survive the presence of a TB drug

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BOX 3: REPLACING SMEAR MICROSCOPY AS THE INITIAL TB DIAGNOSTIC TEST

In spite of the WHO recommendation since 2013 for the use of rapid molecular tests as the initial TB test for all, many countries failed to fully scale up rapid molecular tests and instead continue to rely on the significantly less sensitive, and less expensive, smear microscopy. According to a survey of 16 high-TB-burden countries, reasons for the slow scale-up of Xpert MTB/RIF as the initial TB test for all include "high costs," "poor sensitization of clinical staff," "insufficient service and maintenance provision," and "inadequate resources for sustainability and expansion."[32] To fully meet testing needs, countries with high burdens of TB would have to procure six times as many rapid molecular tests as they are currently procuring, not to mention the need for additional testing instruments and expanded service and maintenance plans.[33] At US$10* per Xpert test under the "buy down" agreement, and US$9–$12 per Truenat test, fully scaling up and implementing these tests is too expensive. Lower prices of rapid molecular tests combined with increased donor and domestic funding will be required to facilitate the country transition to rapid molecular testing as the initial TB diagnostic test for all (see *Box 8: Time for $5 campaign* for more information on fair pricing of Xpert tests).

* US$9.98 per Xpert TB test is the public-sector price for 145 high-burden and developing countries[34]

1.2.1 Rapid molecular tests for TB and rifampicin resistance

Table 3: Rapid molecular tests

Rapid molecular test	Sensitivity* (sputum)[35]	Specificity* (sputum)[36]	Cost (USD)	Manufacturer	WHO recommendation[37]
Xpert MTB/RIF	MTB: 85% RIF: 96%	MTB: 98% RIF: 98%	$10[38]	Cepheid	Xpert MTB/RIF and Xpert MTB/RIF Ultra are recommended as the initial tests for pulmonary and extrapulmonary TB and rifampicin resistance in adults and children.
Xpert MTB/RIF Ultra	MTB: 90% RIF: 94%	MTB: 96% RIF: 99%	$10[39]	Cepheid	
Truenat MTB**	MTB: 73%	MTB: 98%	$9[40]	Molbio	Truenat MTB, MTB Plus, and MTB-RIF Dx are recommended as the initial tests for pulmonary TB and rifampicin resistance in adults and children.
Truenat MTB Plus**	MTB: 80%	MTB: 96%	$12[41]	Molbio	
Truenat MTB-RIF Dx**	RIF: 84%	RIF: 97%	N/A (included in the price of MTB chips)	Molbio	

*Accuracy estimates for pulmonary TB using the microbiological reference standard (MRS); see Box 5 below for Xpert MTB/RIF and Xpert MTB/RIF Ultra accuracy estimates for extrapulmonary TB and children
**Truenat sensitivity and specificity based on limited data including results from the microscopy center level

Abbreviations:
MTB: *Mycobacterium tuberculosis*; RIF: rifampicin

The WHO recommends rapid molecular tests as the initial TB test for all people being evaluated for TB and rifampicin resistance. These tests include Cepheid's Xpert MTB/RIF and Xpert MTB/RIF Ultra and Molbio's Truenat MTB, MTB Plus, and MTB-RIF Dx.[42] Rapid molecular tests are **nucleic acid amplification tests (NAATs)** that use **polymerase chain reaction (PCR)** technology to multiply and detect target **DNA sequences** indicative of TB and rifampicin resistance. Rapid molecular tests are run by adding a portion of the sample to be tested to the test cartridge or chip and inserting it into the PCR instrument. Rapid molecular tests are highly sensitive diagnostic tests that produce results in less than two hours.
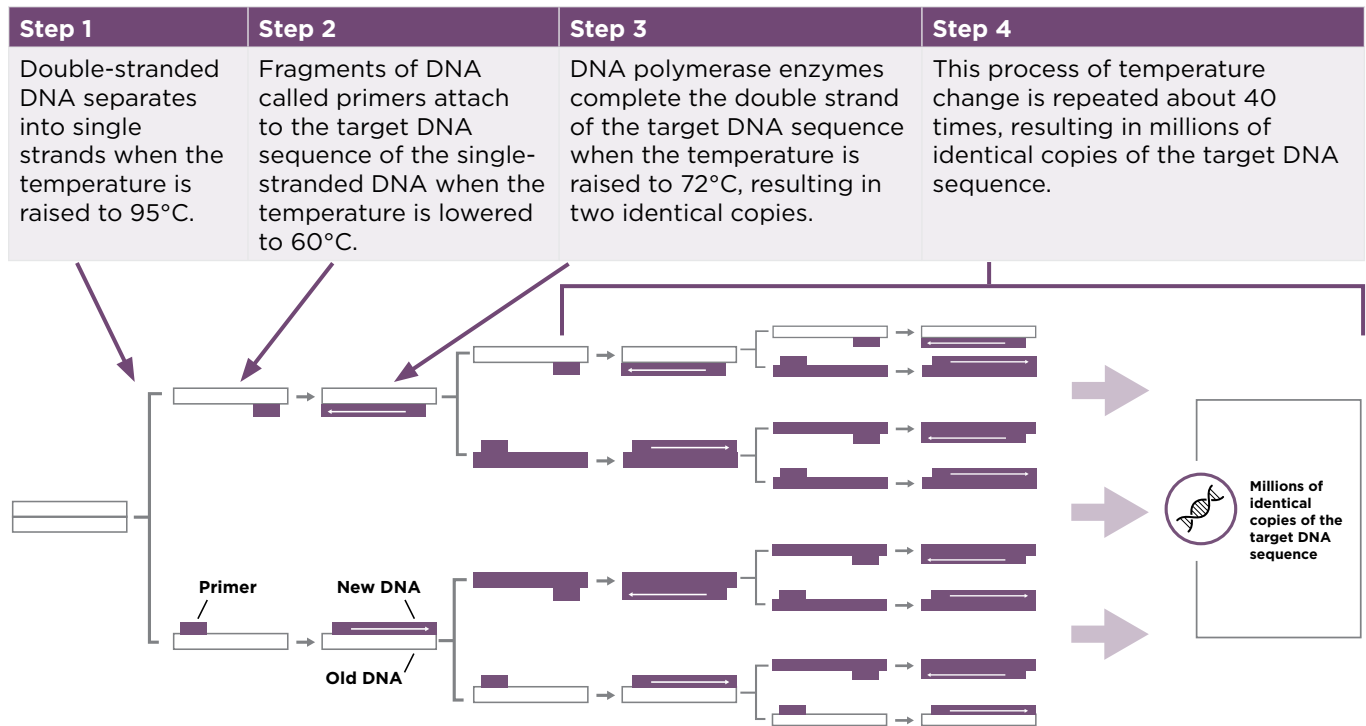
Rapid molecular tests are designed for use in decentralized settings, such as district laboratories for Xpert tests and microscopy centers for Truenat tests. Ideally, these tests could be operated even closer to the point-of-care, but they require the use of expensive instruments that at minimum require a dedicated testing space and some access to electricity. In order to test samples from community health centers and other point-of-care settings, these tests require sample transport systems to be in place. Sample transport systems are often inefficient and can delay turn-around times for results, sometimes up to two weeks.[44] Such delays are unacceptable for rapid molecular tests and contribute to loss to follow-up for treatment initiation. If sample transport systems are to be used, they must be part of efficient diagnostic networks that prioritize rapid turn-around times for results and rapid linkage to TB treatment.[45]

NUCLEIC ACID AMPLIFICATION TESTS (NAATS): tests that multiply specific DNA sequences in order to amplify and detect them

POLYMERASE CHAIN REACTION (PCR): a method used to rapidly and exponentially multiply specific DNA sequences, which quickly results in millions of copies

DNA SEQUENCES: distinct pieces of genetic code that can be used as a marker to identify specific molecules or traits

Figure 5: Polymerase chain reaction (PCR)[43]

Step 1	Step 2	Step 3	Step 4
Double-stranded DNA separates into single strands when the temperature is raised to 95°C.	Fragments of DNA called primers attach to the target DNA sequence of the single-stranded DNA when the temperature is lowered to 60°C.	DNA polymerase enzymes complete the double strand of the target DNA sequence when the temperature is raised to 72°C, resulting in two identical copies.	This process of temperature change is repeated about 40 times, resulting in millions of identical copies of the target DNA sequence.

1.2.1.a Xpert MTB/RIF and Xpert MTB/RIF Ultra

In 2020, the WHO recommended the use of Xpert MTB/RIF and Xpert MTB/RIF Ultra as an initial test for TB and rifampicin resistance for all people being evaluated for pulmonary and extrapulmonary TB, strengthening and expanding its earlier 2013 recommendation.[53] Compared to Xpert MTB/RIF, Xpert MTB/RIF Ultra is a more sensitive but less specific test, and it is priced the same at US$10. The increased sensitivity of Xpert MTB/RIF Ultra is due to additional **probes** capable of detecting very small concentrations or "traces" of TB, which makes it more appropriate for use among children and PLWHA, who often have paucibacillary or disseminated forms of TB. The lower specificity of Xpert MTB/RIF Ultra, or its higher rate of false positive results, is particularly prominent among people who had prior TB. When Xpert MTB/RIF Ultra probes detect only the "traces" of TB—and do not detect more substantial concentrations of TB bacteria—this produces what are called "**trace results**," which in many cases are inconclusive test results because of their high rate of false-positivity.[54]

PROBES: fragments of DNA that bind to and signal the presence of target DNA sequences, enabling their detection

TRACE RESULTS: the detection of only traces of TB DNA, without detection of more substantial amounts of TB DNA

Xpert tests are cartridge-based, fully automated tests that are run using the GeneXpert system. GeneXpert instruments are available in 1-, 2-, 4-, 16-, 48-, and 80-module configurations, which reflect the number of tests that can be performed at the same time.[55] These instruments have significant infrastructure requirements, including continuous electricity and air-conditioned temperatures ≤ 30°C.[56] Cepheid is also marketing the GeneXpert Edge system, a battery-powered 1-module instrument that is portable, but it also requires air-conditioned temperatures ≤ 30°C, limiting its use closer to the point-of-care. To overcome this barrier to performing Xpert tests at the point-of-care, Cepheid developed Omni, a 1-module, battery-powered instrument that does not require air-conditioned temperatures, but which is yet to be widely rolled out. Because currently available GeneXpert instruments are positioned for use at the district laboratory level, they rely heavily on sample transport systems for samples from health centers at the community and sub-district levels, which can delay the turn-around times for results—sometimes up to two weeks[57]—and contribute to loss to follow-up for treatment initiation.

BOX 4: DIAGNOSING TB IN SPECIAL POPULATIONS

Children
Children who are infected with TB are much more likely to progress to active TB disease than adults and are more likely to develop extrapulmonary forms of the disease. Because of the generally low amounts of TB bacteria in children, called paucibacillary TB, the sensitivity of TB diagnostic tests is generally lower in children compared with adults. Therefore, there are many situations when a child has TB, but even highly sensitive rapid molecular tests cannot detect it. In such situations, TB treatment may be initiated based on empirical diagnosis, according to the best judgment of clinicians. The WHO recommends the use of rapid molecular test Xpert MTB/RIF Ultra in children using sputum specimens, **gastric specimens**, **nasopharyngeal specimens**, and stool specimens, and it recommends performing two tests on any available specimens.[46] Acknowledging that children often have difficulty producing sputum, and in order to avoid invasive procedures required to obtain other samples, stool specimens may be used. FIND and the KNCV Tuberculosis Foundation are supporting the development of a simple stool processing kit for use with rapid molecular tests to improve the ease and reliability of stool testing procedures.[47,48]

People with extrapulmonary TB
People with extrapulmonary TB have TB outside of the lungs and in other parts of their bodies, such as the **lymph nodes**, the **pleural cavity** surrounding the lungs, the brain and spinal cord (called TB meningitis), the bones or joints, and the **abdominal cavity**. Because TB bacteria are not located in the lungs in these cases, sputum samples cannot be used, and other extrapulmonary samples must be obtained for testing from the area of the body that may be infected. The WHO recommends using rapid molecular tests Xpert MTB/RIF and Xpert MTB/RIF Ultra for extrapulmonary TB in samples including **cerebrospinal fluid** specimens, **lymph node aspirate**, **lymph node biopsy**, **pleural fluid**, urine, **synovial fluid**, **peritoneal fluid**, **pericardial fluid**, and blood.[49]

People living with HIV/AIDS
PLWHA are much more likely than HIV-negative people to progress from TB infection to active TB disease. TB is the number one killer of PLWHA worldwide, causing about 250,000 deaths annually.[50] PLWHA are also more likely than HIV-negative people to have disseminated TB—TB spread throughout the body—or paucibacillary TB. This results in lower concentrations of TB in a given sample and lower sensitivity of TB diagnostic tests in PLWHA. Many PLWHA with advanced HIV disease, or AIDS, often have difficulty producing sputum, so tests that rely on sputum are not optimal for this population. Urine-based tests, such as the LAM test (see Section 1.2.3), which is most sensitive in people with AIDS, can be used to support the rapid diagnosis of TB among PLWHA, in combination with rapid molecular tests such as Xpert or Truenat.[51] For PLWHA who present to care late when they have already developed AIDS, rapid point-of-care TB testing using the urine LAM test can lead to rapid TB treatment initiation and can save lives.[52]

GASTRIC SPECIMENS: samples collected from the contents of the stomach, which may contain mucus from the lungs that has been swallowed

NASOPHARYNGEAL SPECIMENS: mucus samples collected from the nasal passages using a swab

LYMPH NODES: small bean-shaped structures located in different parts of the body and connected by the lymphatic system, which filter harmful substances and contain white blood cells that help fight infection

PLEURAL CAVITY: the space between the two membranes surrounding the lungs, which is filled with fluid

ABDOMINAL CAVITY: the large space in the torso of the body that contains many organs

CEREBROSPINAL FLUID: clear fluid found in the brain and spinal cord

LYMPH NODE ASPIRATE: a sample drawn from the lymph nodes using a fine needle

LYMPH NODE BIOPSY: a piece of a lymph node that is surgically removed for testing

PLEURAL FLUID: fluid that is found between the two membranes that surround the lungs

SYNOVIAL FLUID: fluid that is found between the cartilage in joints

PERITONEAL FLUID: fluid that lubricates the walls of the tissues of the abdominal cavity and organs

PERICARDIAL FLUID: fluid that is found in the membrane surrounding the heart

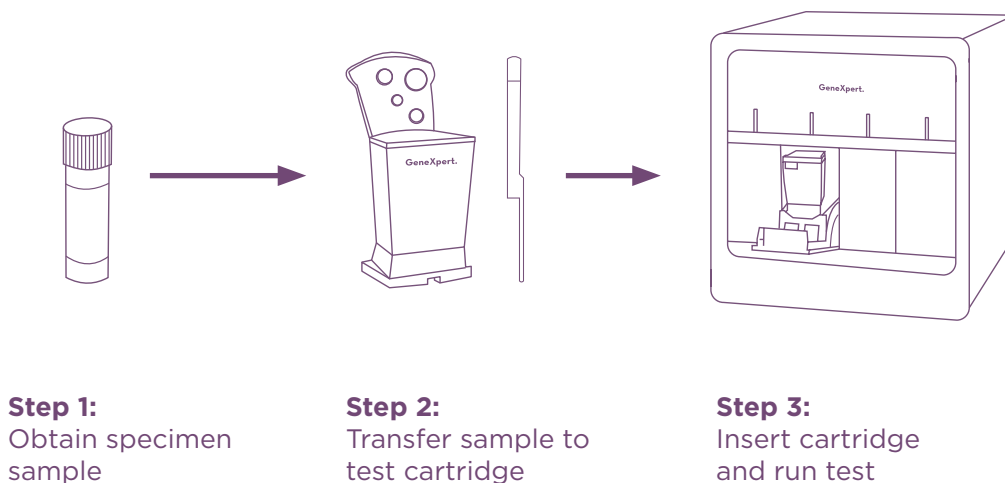**1.2.1.b Truenat MTB, MTB Plus, and MTB-RIF Dx**

In 2020, the WHO also recommended Truenat MTB, MTB Plus, and MTB-RIF Dx as an initial test for TB and rifampicin resistance for all people being evaluated for pulmonary TB.[58] The WHO approval of Truenat tests has introduced much-needed competition into the global market for rapid molecular tests, which has not existed since the release of Xpert MTB/RIF in 2010. Truenat tests are designed for use at the microscopy center level of the health system, which is closer to the point-of-care than the district laboratory level where GeneXpert instruments are generally placed. This positioning may decrease reliance on inefficient sample transport systems, thereby reducing turn-around times for results and loss to follow-up, which may improve health outcomes for people with TB.[59]

The WHO found the sensitivity and specificity of Truenat tests to be comparable to Xpert tests—acknowledging that since Truenat is still new, a more complete picture of test performance will emerge as new data become available, including its accuracy for detecting TB among children and PLWHA, as well as in extrapulmonary samples. Compared to Truenat MTB, Truenat MTB Plus includes additional probes that increase the sensitivity of the test, which—pending additional performance data—should make it an appropriate test for use in children and PLWHA with paucibacillary or disseminated TB. Unlike Xpert tests, which simultaneously test for TB and rifampicin resistance, Truenat uses separate test chips for TB and rifampicin resistance, which are tested sequentially, requiring a technician to manually micro-pipette the sample to the test chips. Upon positive results for TB, the same sample may be added to the MTB-RIF Dx chip to test for rifampicin resistance.
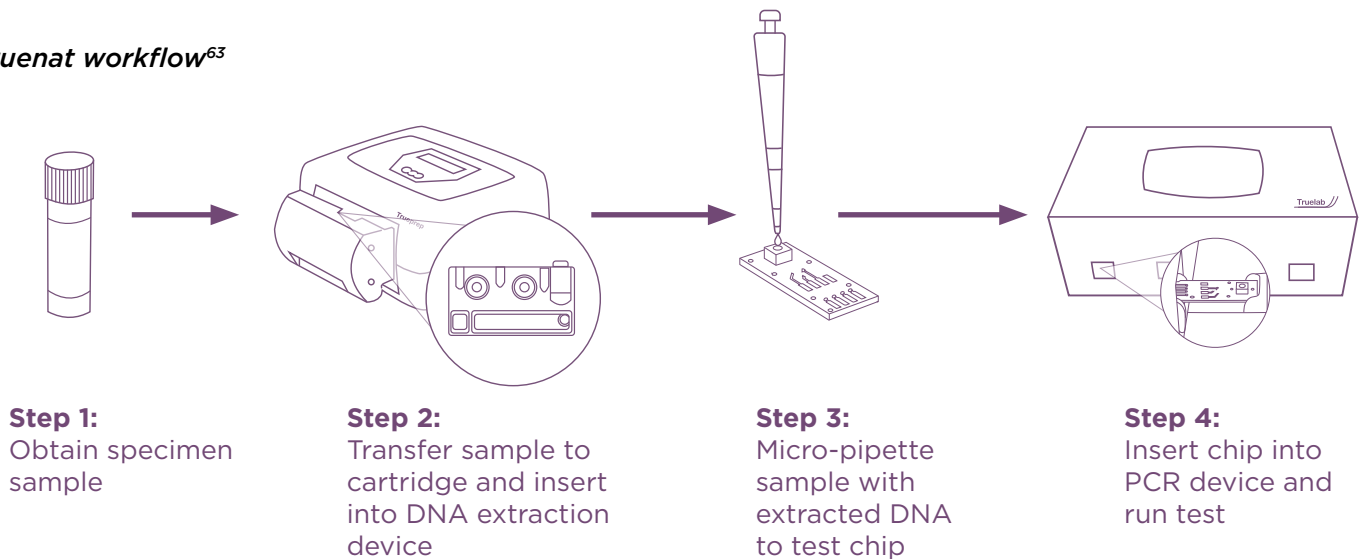
Truenat tests are semi-automated and are performed using the Trueprep sample preparation device that extracts the DNA and the Truelab PCR device that produces the result. Unlike Xpert tests that are fully automated, Truenat tests require several manual steps by trained technicians, including micro-pipetting the sample from the Trueprep device to a Truenat test chip before inserting it into the Truelab device. Trueprep and Truelab instruments are battery-powered, run a full eight-hour day on a single battery charge, and may be operated without air conditioning at temperatures ≤ 40°C,[60] enabling them to be positioned in microscopy centers. Truelab instruments are available in 1-, 2-, and 4-module options.[61]

Figure 6: GeneXpert versus Truenat workflows

GeneXpert workflow[62]

Step 1:
Obtain specimen sample

Step 2:
Transfer sample to test cartridge

Step 3:
Insert cartridge and run test

Truenat workflow[63]

Step 1:
Obtain specimen
sample

Step 2:
Transfer sample to
cartridge and insert
into DNA extraction
device

Step 3:
Micro-pipette
sample with
extracted DNA
to test chip

Step 4:
Insert chip into
PCR device and
run test

BOX 5: SENSITIVITY AND SPECIFICITY OF XPERT TESTS IN PEOPLE WITH EXTRAPULMONARY TB AND CHILDREN

Xpert MTB/RIF and Xpert MTB/RIF Ultra have varying sensitivity and specificity for extrapulmonary TB among adults. In cerebrospinal fluid specimens, lymph node aspirate, lymph node biopsy, pleural fluid, urine, synovial fluid, peritoneal fluid, pericardial fluid, and blood, Xpert MTB/RIF sensitivity ranges from 50% for pleural fluid to 97% for synovial fluid, and its specificity ranges from 79% for lymph node biopsy to 99% for pleural fluid. In cerebrospinal fluid specimens, lymph node aspirate, lymph node biopsy, pleural fluid, urine, and synovial fluid, Xpert MTB/RIF Ultra sensitivity ranges from 71% for pleural fluid to 100% for urine, and its specificity also ranges from 71% for pleural fluid to 100% for urine. For the detection of rifampicin resistance in adults using extrapulmonary specimens, the WHO found Xpert MTB/RIF to be 96% sensitive and 99% specific, and Xpert MTB/RIF Ultra to be 97% sensitive and 99% specific.

For use among children, who generally have difficult-to-diagnose paucibacillary TB, Xpert MTB/RIF and Xpert MTB/RIF Ultra are less sensitive in sputum and other specimens including gastric specimens, nasopharyngeal specimens, and stool specimens. Xpert MTB/RIF sensitivity ranges from 46% for nasopharyngeal specimens to 73% for gastric specimens, with specificity ranging from 98% to 100% for all specimen types. Xpert MTB/RIF Ultra sensitivity ranges from 46% for nasopharyngeal specimens to 73% for sputum, with specificity ranging from 97% to 98% for all specimen types. The WHO also noted the added benefit of performing two Xpert tests to help diagnose TB in children, using any two available samples, including stool. For the detection of rifampicin resistance in children using sputum, the WHO found Xpert MTB/RIF to be 90% sensitive and 98% specific.[64]

1.2.2 Loop-mediated isothermal amplification (TB LAMP)

Table 4: Loop-mediated isothermal amplification (LAMP) tests

LAMP test	Sensitivity* (sputum)	Specificity* (sputum)[65]	Cost (USD)	Manufacturer	WHO recommendation[66]
TB LAMP	78%	98%	≥$6[67]	Eiken Chemical	TB LAMP may be used as a replacement test for smear microscopy. Rapid molecular tests are the preferred initial TB test.

* Microbiological reference standard (MRS)

In 2016, the WHO also recommended loop-mediated isothermal amplification, or TB LAMP, as a replacement test for smear microscopy. TB LAMP is a test-tube-based molecular test appropriate for use at the microscopy center level of the health system. TB LAMP also targets DNA sequences indicative of TB and employs a loop-based nucleic-acid amplification technique to multiply these sequences in order to detect them and produce a result. TB LAMP is less expensive—as little as US$6 per test[68]—than rapid molecular tests, and it takes just 40 minutes to produce a result, but the test also has lower sensitivity for TB detection: 78%. TB LAMP cannot test for resistance to rifampicin, and so the WHO only recommends the use of TB LAMP as a test to replace smear microscopy in areas of low prevalence of drug-resistant TB.[69] In light of the WHO recommendation for the use of rapid molecular tests as the initial test for TB and rifampicin resistance for all people being evaluated for TB, country uptake of TB LAMP has remained limited.

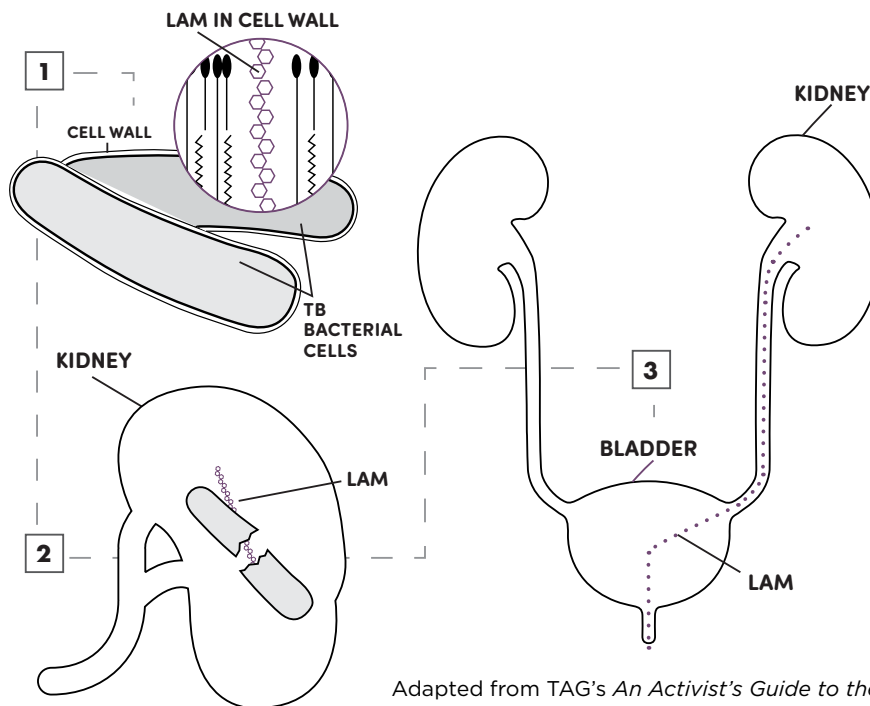### 1.2.3 Urine LAM tests to support rapid TB diagnosis among PLWHA

Table 5: LAM tests

LAM test	Sensitivity*[70] (urine)	Specificity*[71] (urine)	Cost (USD)	Manufacturer	WHO recommendation
Determine TB LAM Ag	56% 0–100 CD4 cells/mm^3 25.3% 101–200 CD4 cells/mm^3	93.6% 0–100 CD4 cells/mm^3 96.7% 101–200 CD4 cells/mm^3	$3.50	Abbott (formerly Alere)	For use in PLWHA with (1) signs and symptoms of TB, (2) serious illness, or (3) AIDS, with less than 200 CD4 cells/mm^3 for inpatients, and less than 100 CD4 cells/mm^3 for outpatients[72]
SILVAMP TB LAM	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	Not yet available	Fujifilm	The WHO is expected to review SILVAMP TB LAM in 2021

* Microbiological reference standard (MRS)

The urine **lipoarabinomannan (LAM)** test is a rapid point-of-care TB test for use among PLWHA. Urine LAM is the only true instrument-free point-of-care TB test, and it is the only TB test that has been shown to reduce deaths.[73] For PLWHA who present to care with AIDS, rapid TB testing and immediate initiation of treatment can be a matter of life or death. LAM testing uses urine as a sample, which is easily obtainable for PLWHA with advanced HIV disease, or AIDS, who often have difficulty producing sputum. Urine LAM tests detect the TB biomarker LAM, a component of the outer cell wall of TB bacteria. Many PLWHA have disseminated TB, or TB spread throughout the body. When TB bacteria in the kidneys shed LAM, the kidneys clear the LAM into the urine, which is how it can be detected (see *Figure 7: Detecting LAM in urine*).[74]

LIPOARABINOMANNAN (LAM): a component of the outer cell wall of TB bacteria that is a biomarker indicating the presence of TB bacteria

Figure 7: Detecting LAM in urine

Adapted from TAG's *An Activist's Guide to the LAM Test*[75]

1.2.3.a Determine TB LAM Ag

Abbott's Determine TB LAM Ag test is a simple, paper-based, **lateral-flow assay**—similar to a pregnancy test—that can detect the presence of LAM in urine in just 25 minutes. A small amount of urine is applied to the test strip, and results can be determined based on the gradient of the line that appears on the strip—with a darker line indicating a positive result. Abbott's LAM test is inexpensive, costing just US$3.50 per test,[76] and has been shown to be cost-effective for health systems.[77] The test is most sensitive in people living with HIV with AIDS, and test sensitivity increases as CD4 cell count decreases. Among PLWHA with signs and symptoms of TB irrespective of CD4 cell count, the test is about 52% sensitive in inpatient settings, and among people living with HIV with AIDS (CD4 count ≤200 cells/mm^3), the test is about 64% sensitive in inpatient settings.[78]

In 2015, the WHO recommended the Abbott LAM test to "assist in the diagnosis" of TB in a limited population of PLWHA with advanced HIV disease, or AIDS.[79] In 2019, the WHO expanded this indication to include PLWHA with (1) signs and symptoms of TB, (2) serious illness, or (3) AIDS, with less than 200 CD4 cells/mm^3 for inpatients, and less than 100 CD4 cells/mm^3 for outpatients. The 2019 recommendations explicitly apply to adults, adolescents, and children living with HIV/AIDS. In combination with LAM tests, the WHO recommends rapid molecular testing with Xpert MTB/RIF Ultra or Truenat MTB Plus to confirm TB diagnosis and increase the **diagnostic yield** of the tests,[80,81] and to test for resistance to rifampicin. Upon LAM-positive results, the WHO recommends immediate initiation of treatment while waiting for rapid molecular test results.[82]

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

DIAGNOSTIC YIELD: the likelihood of a test or combination of tests to provide the information needed to establish a diagnosis

Abbott's LAM test has been commercially available since 2013 and recommended by the WHO since 2015, yet uptake of this test has remained limited. Countries with high burdens of TB and HIV cite budget limitations as the primary barrier to adopting and implementing LAM testing, along with "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."[83] "Five years after the WHO recommended the use of LAM testing, fewer than 10 countries have translated policy into practice by rolling out LAM within their national programs. People living with HIV/AIDS have a right to access this life-saving test. The fact that LAM testing is still largely unavailable is a violation of their rights and a missed opportunity to save lives."[84]

1.2.3.b SILVAMP TB LAM

Fujifilm, with support from FIND, has developed SILVAMP TB LAM, a new LAM test that has been shown to be 30 percent more sensitive than the Abbott LAM test.[85] This increased sensitivity results from the use of a technology that binds silver particles to the **antibodies** that attach to LAM **antigens** in order to amplify them. SILVAMP TB LAM is constructed using more expensive materials and is also slightly more complicated; it requires a 40-minute incubation period and an intermediary step to produce a result. The Fujifilm LAM test is not yet commercially available and is expected to be reviewed by the WHO in 2021. It is essential that Fujifilm's SILVAMP TB LAM enters the market at a price comparable to Abbott's Determine TB LAM Ag, in order to enable rapid country uptake and implementation of the new test. Though it may be tempting to wait for Fujifilm and others to deliver more sensitive LAM tests, it is imperative that the currently available LAM test is scaled up and implemented to improve TB diagnosis and to prevent avoidable suffering and deaths from TB among PLWHA.

ANTIBODIES: blood proteins that are used by the immune system to neutralize pathogens such as bacteria

ANTIGENS: molecules or components of a pathogen such as bacteria that induce an immune response

For more information on the LAM test, including the benefits of LAM testing, its availability in countries with high burdens of TB and HIV, and how to take action to improve country uptake, see TAG's *An Activist's Guide to the LAM Test* and *The LAM Test Availability Dashboard*.[86,87]

1.2.4 Drug-susceptibility testing

Table 6: Drug-susceptibility tests

Drug-susceptibility test	Sensitivity* (sputum)	Specificity* (sputum)	Cost (USD)[88]	Manufacturer	WHO recommendation
GenoType MTBDRplus Version 2.0	RIF: 98.2% INH: 95.4%	RIF: 97.8% INH: 98.8%	$7.50	Hain	The WHO recommends line probe assays GenoType MTBDRplus Version 2.0, GenoType MTBDRsl Version 2.0, and Genoscholar NTM+MDRTB II as initial tests for drug-susceptibility, rather than liquid culture[89,90]
GenoType MTBDRsl Version 2.0	FLQs: 100% AMK: 93.8% CAP: 86.2%	FLQs: 98.9% AMK: 98.5% CAP: 95.9%[91]	$7.50	Hain	
Genoscholar NTM+MDRTB II	RIF: 96.5% INH: 94.9%	RIF: 97.5% INH: 97.6%	$16	Nipro	
BACTEC MGIT 960 system	BDQ: 100% DLM: 100% PMD: 100% LZD: 100% CFZ: 100%	BDQ: 100% DLM: 100% PMD: 100% LZD: 100% CFZ: 100%	Varies	BD	Liquid culture using the BACTEC MGIT 960 system is the preferred method for phenotypic DST[92]

Drug-susceptibility test	Sensitivity* (sputum)	Specificity* (sputum)	Cost (USD)	Manufacturer	WHO recommendation
Xpert MTB/XDR	INH: 83.3% MXF: 87.6–96.2% AMK: 70.7%	INH: 99.2% MXF: 94.3% AMK: 99.6%[93]	Not yet available	Cepheid	The WHO is expected to review Xpert MTB/XDR, RealTime MTB RIF/INH, BD MAX MDR-TB (RIF/INH), cobas MTB-RIF/INH, FluoroType MTBDR Version 2.0, and Genoscholar PZA TB II in late 2020
RealTime MTB RIF/INH Resistance	RIF: 94.8% INH: 88.3%	RIF: 100% INH: 94.3%[94]	Not yet available	Abbott	
BD MAX MDR-TB (RIF/INH)	RIF: 90% INH: 82%	RIF: 95% INH: 100%[95]	Not yet available	BD	
cobas MTB-RIF/INH	RIF: 97.2% INH: 96.9%	RIF: 98.6% INH: 99.4%[96]	Not yet available	Roche	
FluoroType MTBDR Version 2.0	RIF: 98.9% INH: 91.7%	RIF: 100% INH: 100%[97]	Not yet available	Hain	
Genoscholar PZA TB II	PZA: 98.9%	PZA: 91.8%[98]	Not yet available	Nipro	

* Microbiological reference standard (MRS)

Abbreviations:

AMK: amikacin	BDQ: bedaquiline
CAP: capreomycin	CFZ: clofazimine
DLM: delamanid	FLQs: fluoroquinolones
INH: isoniazid	LZD: linezolid
MXF: moxifloxacin	PMD: pretomanid
PZA: pyrazinamide	RIF: rifampicin

After many years of TB treatment using the same drugs, strains of TB bacteria have emerged that are resistant to one or more TB drugs. Drug-resistant TB (DR-TB) takes on a range of profiles, including rifampicin-resistant TB (RR-TB), isoniazid-resistant TB (HR-TB) multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB). MDR-TB exhibits resistance to both **first-line TB drugs** rifampicin and isoniazid—the most powerful TB drugs—and may include resistance to the second-line fluoroquinolones, moxifloxacin or levofloxacin. XDR-TB exhibits resistance to both rifampicin and isoniazid, resistance to the fluoroquinolones, and resistance to **second-line** injectable agents, such as amikacin. Currently recommended DR-TB treatment regimens, including for XDR-TB, are all-oral, and the WHO recommends that countries phase out the use of second-line injectables because of their adverse side effects, which may include hearing loss.[99]

See TAG's _An Activist's Guide to Treatment for Drug-Resistant Tuberculosis_ for the latest information on WHO-recommended DR-TB treatment regimens.[100]

Upon detection of rifampicin resistance after rapid molecular testing with Xpert or Truenat tests, comprehensive drug-susceptibility testing (DST) should be initiated to test for further drug resistance. DST includes molecular tests and line probe assays (LPAs) that target DNA sequences in the TB bacteria that are associated with resistance to certain drugs. It also includes liquid culture that must be used for new TB drugs such as bedaquiline, delamanid, and pretomanid, and repurposed TB drugs such as linezolid and clofazimine, which are recommended by the WHO for the treatment of MDR-TB and XDR-TB. Since these TB drugs are new or newly repurposed for TB treatment, the specific target DNA sequences associated with resistance to these drugs are yet to be identified, so **phenotypic**—rather than **genotypic**—DST is necessary.

FIRST-LINE TB DRUGS: drugs that are used to treat drug-susceptible TB (i.e., rifampicin, isoniazid, ethambutol, and pyrazinamide)

SECOND-LINE TB DRUGS: drugs that are used to treat TB that is resistant to first-line TB drugs

PHENOTYPIC: observable growth of TB bacteria

GENOTYPIC: detection of target DNA sequences that indicate the presence of TB or drug-resistant TB

1.2.4.a Rapid molecular tests

Cepheid is developing an Xpert MTB/XDR cartridge for use with the GeneXpert system. Xpert MTB/XDR is designed to be a follow-on test to Xpert MTB/RIF or Xpert MTB/RIF Ultra and to test for resistance to isoniazid, moxifloxacin, ofloxacin, kanamycin, and amikacin. Because of changes in WHO-recommended treatment regimens, however, ofloxacin and kanamycin are no longer included in any TB treatment regimens, so DST for these drugs is no longer necessary. Use of Xpert MTB/XDR will require an upgrade to a new version of the GeneXpert module that uses a 10-color system for detecting target DNA sequences; Xpert MTB/XDR will not be compatible with the older 6-color modules. The WHO is expected to review Xpert MTB/XDR in late 2020.

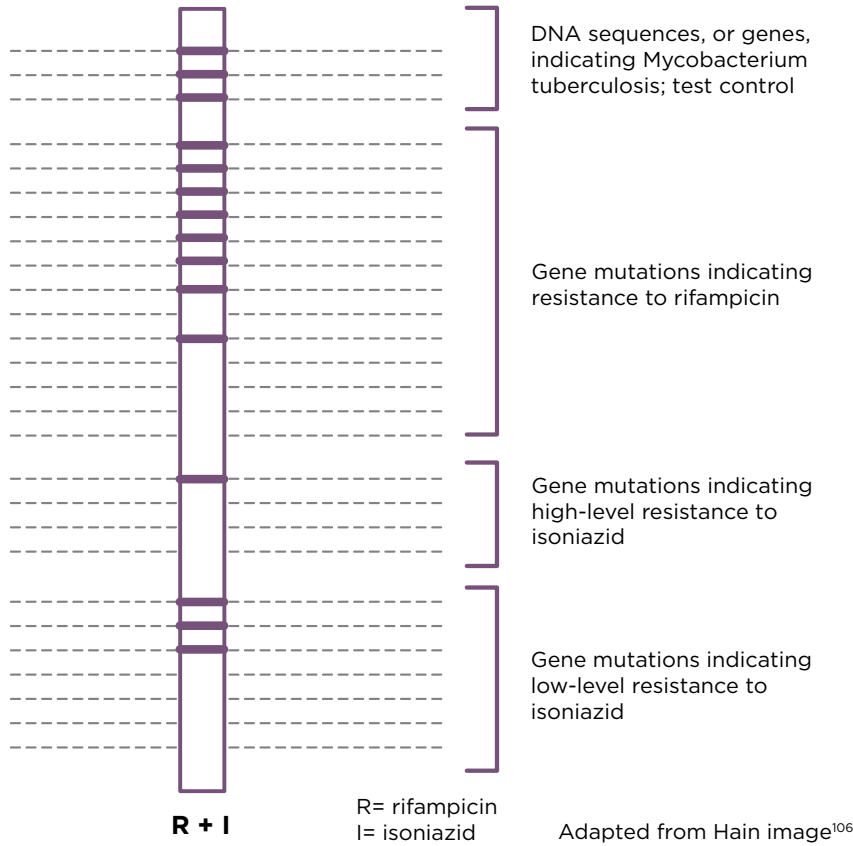### 1.2.4.b High-throughput molecular tests

High-throughput molecular tests are automated and highly sensitive and specific molecular tests that use the same polymerase chain reaction (PCR) technology as rapid molecular tests Xpert and Truenat. However, high-throughput molecular tests are run on instruments capable of performing a much larger number of tests at a time and are designed to be positioned in central laboratories. Currently available high-throughput molecular tests for resistance to rifampicin and isoniazid include Abbott's RealTime MTB RIF/INH and Roche's cobas MTB-RIF/INH, which are run on instruments capable of performing 96 tests at a time; Hain's FluoroType MTBDR Version 2.0, which is run on an instrument capable of performing up to 95 tests at a time;[101] and BD's BD MAX MDR-TB (RIF/INH), which is run on an instrument capable of performing 24 tests at a time—all producing results within several hours. While each of these tests is on the pathway to WHO evaluation, Abbott's RealTime MTB RIF/INH and BD's BD MAX MDR-TB (RIF/INH) have already been reviewed and approved by the Expert Review Panel for Diagnostics (ERPD), an interim approval mechanism of The Global Fund to Fight AIDS, Tuberculosis and Malaria.[102] In addition to drug-susceptibility testing, these same manufacturers also market high-throughput molecular tests for TB detection. The accuracy, speed, and capacity to test large numbers of samples at a time are clear advantages of high-throughput molecular tests, but their centralized placement makes them unavailable where most people present to care for TB. Additionally, the costs for these tests—as well as any subsidized pricing schemes—are yet to be made public.[103]

1.2.4.c Line probe assays

In 2016, the WHO recommended the use of line probe assays (LPAs) as the initial DST for first- and second-line TB drugs—rather than liquid culture—because LPAs are highly accurate and rapidly produce results within one day—compared with about two to six weeks for culture-based DST. LPAs detect target DNA sequences that are associated with resistance to first-line and some second-line TB drugs. LPAs recommended by the WHO include Hain's GenoType MTBDRplus Version 2.0 and Nipro's Genoscholar NTM+MDRTB II that test for resistance to first-line drugs rifampicin and isoniazid,[104] and Hain's GenoType MTBDRsl Version 2.0 that tests for resistance to the fluoroquinolones and to second-line injectable agents, such as amikacin.[105]

Figure 8: Detecting drug resistance using line probe assays (LPAs)

An example of Hain's GenoType MTBDRplus Version 2.0 LPA strip indicating a positive result for resistance to rifampicin and isoniazid

DNA sequences, or genes, indicating Mycobacterium tuberculosis; test control

Gene mutations indicating resistance to rifampicin

Gene mutations indicating high-level resistance to isoniazid

Gene mutations indicating low-level resistance to isoniazid

R + I

R= rifampicin
I= isoniazid

Adapted from Hain image[106]

LPAs are laboratory-based, open-format tests that require a number of manual steps to be performed by a laboratory technician. LPAs use PCR technology to multiply the target DNA sequences in test tubes and to amplify them so that they can be detectable. Once the DNA has gone through a sufficient number of cycles of amplification, a LPA strip is placed in the solution filled with amplified DNA. The LPA strip has several probes for specific target DNA sequences at different locations along the strip. If these target DNA sequences are present in the solution, they bind to the probes and form colored bands on the strip, indicating a positive result for resistance to specific TB drugs. LPA sensitivity is limited to a set of prominent target DNA sequences associated with resistance to certain TB drugs, so LPAs do not detect all of the DNA mutations that may contribute to resistance.[107]

1.2.4.d Liquid culture

Liquid culture—the "gold standard" of TB diagnosis—is an essential TB diagnostic tool for country laboratories. Liquid culture is a form of phenotypic DST (grow the bugs)—as opposed to genotypic DST (multiply the bugs). Culture-based DST requires the physical growing of TB bacteria in the presence of a pure drug substance. If the TB bacteria grow in the presence of the drug, then this indicates a positive result for resistance to that drug. If the TB bacteria do not grow, then this indicates TB susceptibility to that drug. Solid culture—a method of growing TB bacteria from a sample in a solid gelatin-like substance—is less expensive than liquid culture, but it takes longer for results: four to eight weeks. Liquid culture, on the other hand, generally produces DST results in about two to six weeks.

While rapid tests such as molecular tests and LPAs are recommended by the WHO as initial tests for TB susceptibility to first-line and some second-line TB drugs, liquid culture is recommended as the initial DST for new TB drugs such as bedaquiline, delamanid, and pretomanid, as well as repurposed drugs such as linezolid and clofazimine. This is because the specific target DNA sequences

associated with drug resistance to these new and repurposed drugs are yet to be identified and made available as targets for rapid testing with molecular tests or LPAs. For culture-based DST, the WHO recommends liquid culture using BD's BACTEC MGIT 960 system as the preferred method.[108] The BACTEC MGIT 960 system can hold up to 320 tubes of liquid culture at a time and is capable of automatically identifying which tubes are positive and which tubes are negative for TB bacteria growth. Pure drug substances must be procured in order to perform liquid-culture-based DST for these new and repurposed drugs.

BOX 6: NEXT-GENERATION SEQUENCING—THE FUTURE OF DST?

The purpose of drug-susceptibility testing is to identify the TB treatment regimen that best matches the drug-susceptibility profile of a given strain of TB bacteria. The currently available DST methods may be combined to achieve this end, but even under ideal circumstances, this takes significant resources and time—time that many people with DR-TB simply do not have. When a person is not responding to a TB treatment regimen because of drug resistance, their TB disease may continue to progress and may develop increased drug resistance, leading to onward TB transmission and significant suffering and increased risk of death.

Next-generation sequencing (NGS), which includes full or targeted TB genome sequencing, offers the possibility to accurately identify the complete drug-susceptibility profile of a strain of TB within a day or two. The widespread use of next-generation sequencing DST could be a game-changing tool to rapidly identify and implement optimal TB treatment regimens and to improve treatment outcomes for people with DR-TB. The uptake of NGS has been slow because of the costs involved in scaling up the technology as well as the ongoing need to extensively map TB genomes from around the world and to match specific DNA sequences with phenotypic resistance. As this TB genomic data becomes more readily available, and as NGS technologies become more affordable, next-generation sequencing will become a critically important tool for diagnosing and effectively treating DR-TB; however, significant information technology infrastructure and training will be necessary for countries to implement NGS.[109]

1.3 Treatment monitoring

Table 7: Tests for treatment monitoring

Test for treatment monitoring	Sensitivity*	Specificity*	Cost (USD)	Manufacturer	WHO recommendation
Smear microscopy	50% (sputum)	98%[110] (sputum)	$0.26 to $10.50[111]	Multiple	The WHO recommends the use of smear microscopy and culture, rather than smear microscopy alone, for monitoring TB treatment[112]
BACTEC MGIT liquid culture	100%	100%	$16.88[113]	BD	
Solid culture	100%	100%	$12.35[114]	Multiple	
* Microbiological reference standard (MRS)					

1.3.1 Smear microscopy and culture

During treatment for drug-susceptible or drug-resistant TB, it is essential that the effectiveness of the treatment regimen is closely monitored, in order to identify treatment failure as quickly as possible so that the treatment regimen can be adjusted if needed. The pivotal moment in TB treatment is the conversion of samples from TB-positive to TB-negative, which generally takes place after two to three months of treatment. The tools currently used to monitor TB treatment include smear microscopy and culture. Rapid molecular tests and other genotypic tests cannot be used for treatment monitoring because they cannot differentiate between dead and live TB bacilli. Smear microscopy produces rapid results in a matter of minutes but is less sensitive than culture for detecting the presence of TB bacteria in samples. Because of the high sensitivity of culture, the conversion of samples from culture-positive to culture-negative is the most important evidence of the efficacy of TB treatment, although it may take two to six weeks for culture to produce results. The WHO recommends using both smear microscopy and culture to monitor TB treatment.[115] Research is underway to develop new and better tests for TB treatment monitoring, but none of these tests is near to commercialization. In the meantime, smear microscopy must continue to be used as a tool for treatment monitoring and cannot yet be completely replaced (see *Box 3: Replacing smear microscopy as the initial TB diagnostic test*).

2. DIAGNOSING TB INFECTION

Table 8: Tests for TB infection

Test for TB infection	Sensitivity*	Specificity*	Cost (USD)	Manufacturer	WHO recommendation
Tuberculin skin test	70%	66%[116]	$0.08 to $5.62[117]	Multiple	Either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) may be used to test for TB infection, but this is not a requirement for initiating TPT among PLWHA or child household contacts of people with TB[118]
QuantiFERON-TB Gold Plus	85–100%	87–100%[119]	$15.90[120]	Qiagen	
T-SPOT.*TB*	88–90%	88–92%	$8.78[122]	Oxford Immunotec	

* Accuracy is estimated; there is no "gold standard" for TB infection test accuracy

About a quarter of the world's 7.8 billion people have TB infection that is not contagious and in most cases does not develop into active TB disease. People with TB infection have a 5 percent to 15 percent lifetime risk of developing active TB disease.[123] For close contacts of people with active TB disease, and for PLWHA, this risk is much higher.[124] TB preventive therapy (TPT) is recommended by the WHO to help prevent progression of TB infection to TB disease. Testing for TB infection and ruling out active TB can help identify people who should take TPT; however, diagnosing TB infection is not a precondition for initiating TB preventive therapy, which can be initiated directly among high-risk populations, such as PLWHA or children who are household contacts of people with active TB, and for whom active TB has been ruled out.[125] Research is underway to develop tools for detecting the stage in which TB progresses from TB infection to active TB disease, which is called **incipient TB**. Although some promising biomarkers for incipient TB have been identified,[126] tests to detect these biomarkers are not near to commercialization.

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

See TAG's *An Activist's Guide to Rifapentine for the Treatment of TB Infection* for more information on TB infection and TPT.[127]

Current tools for diagnosing TB infection include tuberculin skin tests (TST) that consist of an **intradermal injection** just under the skin and interferon-gamma release assays (IGRAs) that are laboratory-based and require blood samples. Both tests detect a person's immune response to the introduction of TB antigens, which indirectly points to past exposure to TB bacteria. Both tests have lower sensitivity in children and people with compromised immune systems, such as PLWHA. Neither test is capable of detecting whether TB infection will progress into active TB disease. Neither test can differentiate between TB infection and active TB disease, so they cannot be used to diagnose active TB. For those who test positive for TB infection, evaluation of symptoms and chest X-rays may be required to rule out active TB disease before initiating TPT. There is no "gold standard" of accuracy for tests for TB infection. Test sensitivity may be estimated according to the percentage of people who test positive for TB infection and go on to develop active, culture-confirmed TB; test specificity may be estimated according to the number of false positive results among populations with very low risk of TB infection. The uptake and implementation of tests for TB infection by countries with high burdens of TB remains limited, but it could be improved through price reductions of these tests and the development of better tests for TB infection that are easy to implement at the point-of-care in community health settings.[128]

2.1 Tuberculin skin tests (TST)

Tuberculin skin tests are the most common form of tests for TB infection globally. These tests are inexpensive and appropriate for low-resource settings. The test consists of an intradermal injection of tuberculin antigens just under the skin—usually in the arm—and an assessment after 48–72 hours to measure the size of the **induration**, or the amount of swelling at the site of the injection. The size of the swelling is associated with the strength of the immune response and indicates the presence of antibodies to the tuberculin antigens. Because some of the tuberculin antigens used in TST are common to those used in the Bacille Calmette-Guérin (BCG) TB vaccine, TST may indicate an immune response among people with prior BCG vaccination who do not have TB infection. Such false positive results in people with BCG vaccination contribute to lowering the specificity of TST. Other skin tests such as the C-Tb skin test, which may soon be available on the global market, use TB antigens that are not common to those used in the BCG vaccine, thereby reducing false positive results and improving the specificity of the test.[129] All skin tests for TB infection require a second follow-up visit with a health professional two to three days after receiving the injection to assess the immune response.
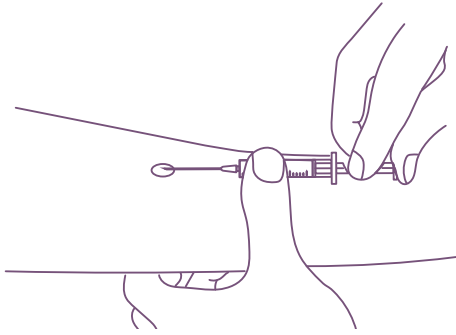
INTRADERMAL INJECTION: an injection just under the surface of the skin

INDURATION: inflammation or swelling that forms a measurable bump

Figure 9: Tuberculin skin test procedure

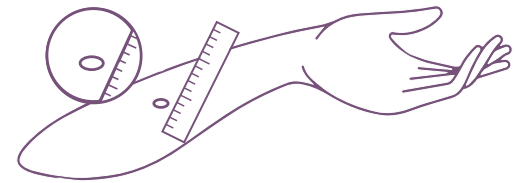**STEP 1:**
Intradermal injection of tuberculin antigens

STEP 2:
Wait 48-72 hours

STEP 3:
Measure the diameter of the induration at the site of the injection and interpret the result

2.2 Interferon-gamma release assays (IGRAs)

Interferon-gamma release assays (IGRAs) are more expensive tests for TB infection than TST and require substantial lab infrastructure. IGRAs are laboratory-based and test blood samples for an immune response to TB antigens. The TB antigens used by IGRAs are not common to those in the BCG vaccine, so specificity of IGRAs is not affected by prior BCG vaccination. IGRAs detect and measure the amount of interferon gamma proteins released from white blood cells during the immune response to TB antigens. The release of interferon gamma proteins is a relatively specific aspect of the immune response to TB antigens. IGRAs can produce results within one day and have a sensitivity and specificity for TB infection that is comparable to TST,[130] but because they require substantial lab infrastructure, IGRAs are less commonly used in low- and middle-income countries than TST. The WHO recommends two commercially available IGRAs: QuantiFERON-TB Gold Plus—which replaced the earlier version QuantiFERON-TB Gold In-Tube—manufactured by Qiagen, and T-SPOT.*TB*, manufactured by Oxford Immunotec.[131]

3. REALIZING THE RIGHT TO SCIENCE FOR TB DIAGNOSTIC TESTING

Under the right to science, all people at risk of TB have the right to quality TB diagnostic testing. Realizing this right in practice, however, requires identifying the **systemic barriers** that prevent access to quality TB diagnostic testing and developing advocacy initiatives to address and remove them. On a societal level, such systemic barriers include insufficient funding, insufficient political will, and insufficient market leverage. On an individual level, such barriers include extensive TB-related social stigma, health system inefficiencies resulting in long delays for TB diagnosis, and TB-diagnosis-related **catastrophic costs** for people with TB. These systemic barriers are closely connected, and it is essential that TB activists work together in solidarity at all levels to address these barriers. TB activists should make it clear to country governments, global donors, and diagnostics companies that we will not accept anything short of the highest standard of care for TB diagnostic testing and we will continue to advocate in more effective and transformative ways until we achieve this.

SYSTEMIC BARRIERS: barriers that are constituted within the structures and institutions of society

CATASTROPHIC COSTS: health care costs that cause tremendous financial burden on individuals and families

3.1 Fair pricing for TB diagnostic tools

TB diagnostic testing should be free for all people at risk of TB. People being evaluated for TB should not face any financial hardship when accessing quality TB diagnostic testing. In order for countries to provide free TB diagnostic testing in accordance with WHO recommendations, TB diagnostic tools must be priced fairly, so that they can be fully covered by national programs or government health insurance schemes.

Fair pricing means that these tools must be priced in relation to their **cost-of-goods-sold (COGS)**, which is the amount it costs a manufacturer to produce each diagnostic tool. Volume-based pricing must also be applied, so that as sales volumes increase—and result in manufacturing efficiencies that reduce COGS—the tool prices decrease. Additionally, pricing must reflect the public and philanthropic investments in the research and development (R&D) and roll-out of TB diagnostic tools, to ensure that the public does not pay twice for these tools. In order to ensure that pricing is fair, COGS as well as R&D costs and public and philanthropic investments must be made transparent. These data points are public health information and not "**trade secrets**." The civil-society-led Time for $5 campaign, as an example, is calling on Cepheid to reduce the price of Xpert tests to US$5, to support countries to scale up rapid molecular tests as the initial TB test for all (see *Box 8: Time for $5 campaign*).[136] Diagnostics companies have the responsibility to work with countries to achieve fair pricing structures for TB diagnostic tests, to enable countries to meet their human rights obligations under the right to science and the right to health.

COST-OF-GOODS-SOLD (COGS): the cost of manufacturing a product, which includes materials, labor, overhead, and intellectual property royalties

TRADE SECRETS: a type of intellectual property composed of confidential information that provides a business with a competitive edge

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BOX 7: TB DIAGNOSTIC TESTING IN THE CONTEXT OF COVID-19

Before the onset of the COVID-19 pandemic, TB diagnosis was the most challenging aspect of the TB cascade of care. In 2018, 3 million people—or 30 percent of people with TB—were either not diagnosed or not reported as being diagnosed with TB.[132] This is in part because many country programs have continued to rely on smear microscopy as the initial TB test, despite its low sensitivity and the WHO recommendation to use more sensitive rapid molecular tests as the initial TB test. Before COVID-19, it would take many people with TB up to eight weeks to receive a TB diagnosis, and in the context of COVID-19, this delay has been extended, resulting in people with TB progressing to more advanced stages of the disease and increasing the risk of TB transmission.[133]

In the urgent response to the COVID-19 pandemic, many TB laboratories have shifted their focus toward COVID-19 and away from TB, and many TB testing instruments such as GeneXpert are likely to be used for COVID-19 testing, which may result in reduced capacity to test for TB and other diseases. Meanwhile, diagnostics companies have repurposed manufacturing lines to produce more COVID-19 tests, thereby reducing production of tests for TB. Additionally, many funders and researchers—in their urgent response to the pandemic—have directed significant resources and efforts toward responding to COVID-19, often at the expense of ongoing investments and research to develop new and better TB tests.[134]

TB stakeholders must not abandon TB in the context of COVID-19; rather:

- governments must maintain routine TB testing services even while expanding services to meet the demand for COVID-19 testing;

- donors must not shift funding from TB to COVID-19—acknowledging that TB is already severely underfunded—and must instead expand overall resources;

- diagnostics companies must not deprioritize the production of tests for TB and other diseases of poverty for more profitable COVID-19 tests;

- researchers must not abandon TB research for COVID-19 research and must build upon progress made to ensure a robust pipeline of new TB diagnostics; and

- activists must redouble efforts to advocate for access to TB diagnostic testing and hold all stakeholders accountable for maintaining their commitments to TB.[135]

3.2 Country uptake and implementation of quality TB diagnostic tools

Under Article 15 of the International Covenant on Economic, Social, and Cultural Rights, countries are obligated to fulfill the right to science for people at risk of TB by ensuring that they have access to quality TB diagnostic testing.[143] Many country governments, however, have failed to fully scale up and ensure access to TB diagnostic tools in accordance with WHO recommendations, failing to meet their human rights obligations under the right to science. Since 2013, the WHO has recommended rapid molecular tests as the initial TB test for all people being evaluated for TB; yet today, in 2020, smear microscopy—with its lower sensitivity—continues to be used as the initial TB test by many countries. The TB standard of care requires immediate drug-susceptibility testing to comprehensively inform optimal treatment regimens, yet in 2018, only about 50 percent of people diagnosed with TB received DST for rifampicin resistance,[144] let alone DST for other first- and second-line TB drugs.

Country governments must increase domestic health funding and TB budgets in order to sufficiently invest in strengthening health systems—including laboratory infrastructure and capacity—and fully scaling up and implementing quality TB diagnostic tools. Countries must also update national TB and HIV program policies and implementation guidelines in accordance with new WHO recommendations; ensure that TB screening and diagnostic testing are deployed and integrated at all levels of the health system and included in the provision of both active and passive care; and conduct countrywide training of health workers in the implementation of new TB diagnostic tools and diagnostic algorithms. Global donors also have the responsibility to increase funding to support countries to strengthen health systems and laboratories, and to procure quality TB diagnostic tools at scale. For example, to ensure that donor funds are used to support country uptake of WHO-recommended TB diagnostic tools, over the past several years civil-society activists advocated for LAM testing for PLWHA to be included in the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) Country Operational Plans (COPs). In the wake of this advocacy, the number of countries that included LAM testing in their COPs doubled from six countries in 2018 to 12 countries in 2019, but overall uptake of LAM testing remains low.[145]

3.3 Access to new and better TB diagnostic tools

Realizing the right to science for TB diagnostic testing also requires significant investment in the research and development of new and better tools in accordance with the WHO's target product profiles, which establish the ideal use cases and characteristics of tools needed to close the TB diagnostic gap and to end TB. For example, the current TB diagnostic toolkit lacks true point-of-care TB diagnostic tests that are rapid, accurate, cheap, and instrument-free; it lacks any tests for detecting the progression of TB infection to active TB disease; and it lacks diagnostic tests that are highly accurate for PLWHA and children. Addressing and filling the gaps in the current TB diagnostic toolkit requires more investments in TB R&D by country governments, global donors, and diagnostics companies.[146] It also requires community engagement in the development of new TB diagnostic tools. Diagnostics developers and manufacturers must invite such engagement at an early stage in the development of new tools, so that communities can meaningfully inform critical design and access considerations and ensure that new TB diagnostic tools will meet the needs of TB-affected communities.

BOX 8: TIME FOR $5 CAMPAIGN

In 2011, the diagnostics company Cepheid partnered with FIND to develop its high-burden developing country concessional pricing program, pricing its Xpert MTB/RIF TB test at $16.86.[137] Acknowledging the game-changing nature of rapid molecular tests for TB, in 2012, Unitaid, the U.S. government, and the Bill & Melinda Gates Foundation paid Cepheid $11.1 million to "buy down" the price of the test to $9.98 for 10 years, through 2022. Even this price was too high for many countries, which could not afford to fully scale up Xpert MTB/RIF as the initial TB test for all as the WHO recommended (see *Box 3: Replacing smear microscopy as the initial TB diagnostic test*). Even as Cepheid's annual sales volumes increased from under 2 million tests in 2012 to nearly 12 million tests in 2018[138]—resulting in substantial manufacturing efficiencies and lower production costs—the price of Xpert TB tests was not reduced.

In 2019, the civil-society-led Time for $5 campaign was formed to demand that Cepheid lower the price of Xpert tests for TB and other diseases to US$5, inclusive of the cost of service and maintenance.[139] This target price was informed by an independent cost-of-goods-sold (COGS) analysis, which found that it costs Cepheid between US$2.95 to US$4.64 to produce each Xpert TB test.[140] It also found that the manufacturing efficiencies that Cepheid achieved through expanded TB test production also apply across Xpert tests for other diseases, such as HIV, hepatitis C, and other sexually transmitted infections (STIs). Additionally, the development of GeneXpert technology and the global roll-out of Xpert MTB/RIF tests was made possible through over US$160 million in public funding from the U.S. government,[141] not to mention the massive amounts of public and philanthropic funding used to procure and scale up GeneXpert instruments and Xpert TB tests in high-TB-burden countries over the past decade.

The Time for $5 campaign has corresponded with Cepheid through a series of open letters, in which the civil-society signatories detailed their demand for an all-inclusive US$5 price for all Xpert tests and for transparency of COGS. Cepheid responded that the company disagrees with the findings of the independent COGS analysis, but that it cannot share its actual COGS because this is "sensitive" and "competitive" business information.[142] It is unacceptable that Cepheid continues to rake in massive profits off of the sale of Xpert tests while people with TB have limited access to these publicly funded tests because of their high price. The Time for $5 campaign is continuing to escalate its demand for transparent COGS and fair pricing of Xpert tests for TB and other diseases. For more information on how to get involved with the campaign, please contact TAG's TB Project Officer David Branigan at david.branigan@treatmentactiongroup.org.

4. TAKING ACTION: DEMAND ACCOUNTABILITY AND ACTION

This Activist's Guide provides information on the optimal use of TB diagnostic tools and how these tools should be implemented in health systems to realize the highest standard of care for TB diagnosis. It also highlights critical gaps in the uptake and implementation of TB diagnostic tools and identifies barriers that limit access to quality TB diagnostic testing. Removing these barriers to access and closing the TB diagnostic gap requires accountability and action from country governments, global donors, and diagnostics companies. Activists can demand this by:

1 **Calling on country governments to:**

- increase funding for TB research and development (R&D) to meet or exceed fair share funding targets,[147] and include conditions of cost-of-goods-sold (COGS) transparency and fair pricing—reflective of COGS, volumes, and public and philanthropic investments—as part of all R&D funding agreements with TB diagnostics developers;

- increase domestic funding for health and expand TB budgets to sufficiently invest in strengthening national health systems—including laboratory infrastructure and capacity—and fully scaling-up and implementing quality TB diagnostic tools in accordance with WHO recommendations, while engaging in pooled procurement with other countries and global donors to secure TB diagnostic tools at the lowest possible prices through shared volumes; and

- update national TB and HIV program policies and implementation guidelines in accordance with new WHO recommendations, and establish clear plans for the rapid introduction, scale-up, and implementation of WHO-recommended TB diagnostic tools and algorithms, including through countrywide training of health workers and lab technicians in the use of new diagnostic tools and technologies.

2 **Calling on global donors to:**

- increase funding for the R&D of new TB diagnostic tools, and include binding access commitments requiring COGS transparency and fair pricing as a condition of R&D funding;

- increase funding support for countries to invest in the introduction, full scale-up, and implementation of quality TB diagnostic tools in accordance with WHO recommendations; and

- coordinate together and with countries to apply collective procurement power and leverage toward negotiating lower prices for TB diagnostic tools reflective of COGS, volumes, and public and philanthropic funding, and invest in building regional and country know-how and capacity—including through technology transfer—for generic diagnostics manufacturing.

3 **Calling on diagnostics companies to:**

- invest in the R&D of new TB diagnostic tools in line with the WHO target product profiles and engage communities—including community advisory boards (CABs)—to inform design and access considerations in the early stages of the development of these new tools;

- commit to transparency and fair pricing structures and work with governments, global donors, and other actors to develop prices that transparently reflect COGS, volumes, and public and philanthropic investments; and

- ensure that new TB diagnostic tools are accessible in all countries with high burdens of TB, that service and maintenance plans—if applicable—are effective and priced equitably and affordably, and that sufficient manufacturing capacity is in place to reach volumes that fully meet the supply and pricing needs of all high-TB-burden countries.

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