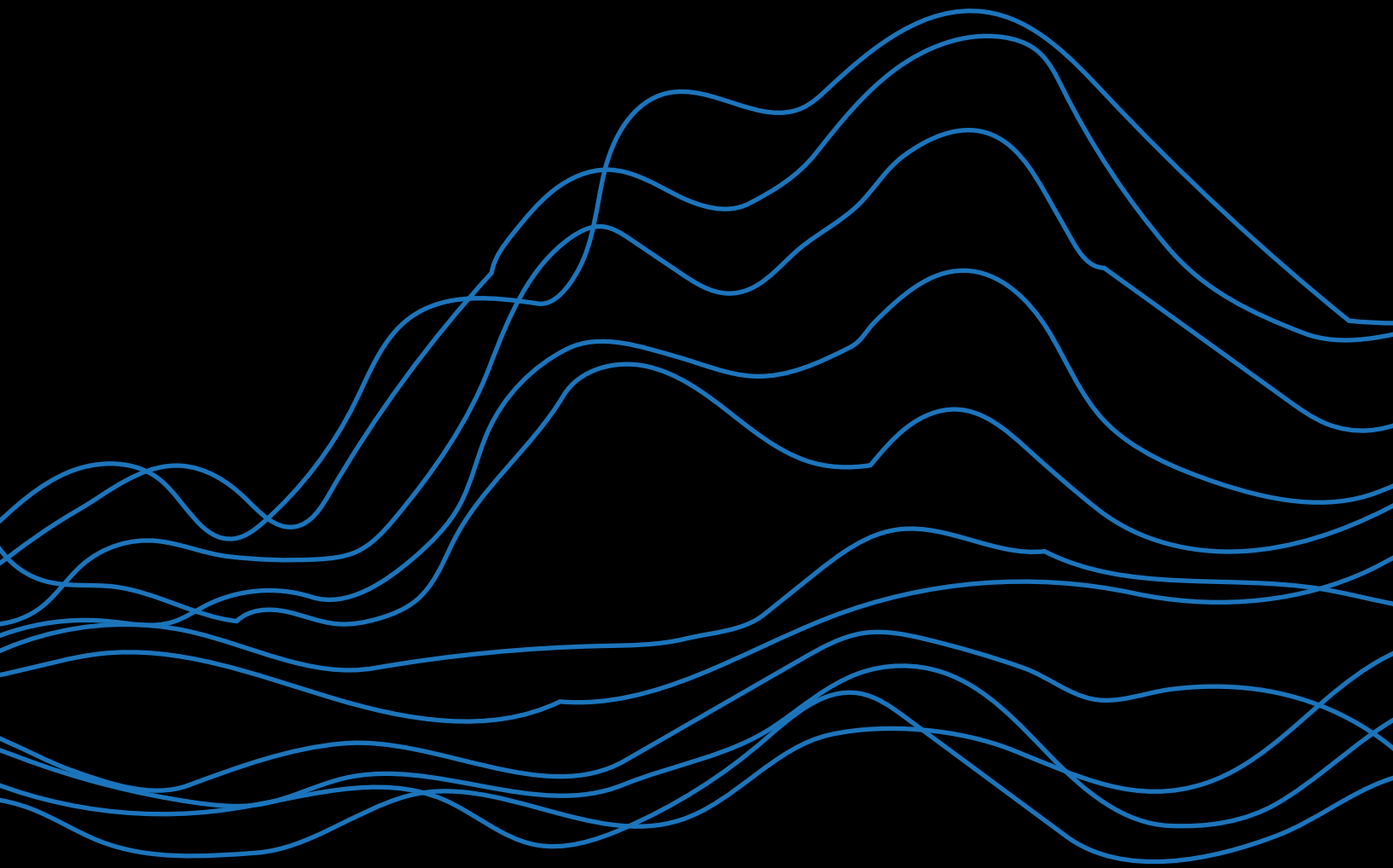
Pipeline Report » 2023

Tuberculosis Diagnostics



TAG
Treatment Action Group

Tuberculosis Diagnostics

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Introduction

Finding and diagnosing tuberculosis (TB), the world's deadliest infectious disease, continues to be the most challenging aspect of the TB **cascade of care**, hindering a more effective global response to TB. In 2022, up to 30% of people with TB remained undiagnosed and therefore untreated.[1] This undeniable crisis points to the urgent need to rethink approaches to TB **screening** and **diagnosis** to dramatically improve access in communities and across populations.[2]

The 2023 TB diagnostics pipeline is rich with innovation and is the healthiest it has ever been. The latest technologies — many from companies originally focused on COVID-19 — are beginning to respond to the call from TB-affected communities and other TB stakeholders for fast, accurate, affordable testing using samples that all people can easily provide. Research to evaluate use of **nonsputum samples** and rapid point-of-care **molecular diagnostics**, in particular, have made significant leaps forward in the past year (see Table 3).

The 2023 TB Diagnostics Pipeline Report organizes updates on the pipeline into four categories based on **use-case**: screening, diagnosis, **treatment monitoring** and **disease progression**, and testing for **TB infection**. Each section juxtaposes what the World Health Organization (WHO) currently recommends with what's in the pipeline.

Screening

In 2021, the WHO issued guidance on the use of new screening tools including chest X-ray with **computer-aided detection (CAD)** and, for people living with HIV, rapid molecular tests and **C-reactive protein**, noting that each of these technologies is more accurate than **symptom screening**, the most common TB screening method, and result in higher diagnostic yield when used in combination.[3] The higher accuracy of these tools has a lot to do with the fact that about half of all people with **active TB** are asymptomatic and only develop symptoms when TB disease continues to progress and cause tissue damage.[4,5] This is when many people first seek care for TB — after symptoms develop — often unknowingly transmitting the disease to others in the meantime. Waiting for people to present to care before screening them for TB is therefore not a sufficient strategy because it cannot detect **sub-clinical TB** and does not interrupt disease transmission before

Cascade of care: the entire pathway of TB care, including diagnosis, treatment, and cure

Screening: testing to determine whether a person is likely to have active TB and should receive TB diagnostic testing

Diagnosis: confirmation that a person has active TB based on test results and/or clinical decision-making

Nonsputum samples: easily available alternative sample types to sputum (a mixture of saliva and mucus that is coughed up from the lungs that many people are unable to spontaneously produce)

Molecular diagnostics: diagnostics that detect genetic material indicating the presence of a pathogen or disease

Use-case: specific scenarios for which TB testing interventions are needed

Treatment monitoring: testing to assess or predict the effectiveness of TB treatment

Disease progression: progression from TB infection to active TB disease

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

Computer-aided detection (CAD): artificial intelligence-based software that interprets chest X-rays with high accuracy comparable to skilled human readers

C-reactive protein (CRP): a test for nonspecific inflammation in the body that indicates the presence of disease

Symptom screening: clinical evaluation for common TB symptoms, including current cough, night sweats, weight loss, fever, and coughing up blood

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

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

the onset of symptoms;[6,7] rather, it must be complemented by active case-finding among people at high risk of TB, including people living with HIV, contacts of people diagnosed with TB, and people living in communities with high prevalence of TB.[8] Studies show that **active case-finding**, while resource intensive,[9] effectively reduces TB transmission and the burden of TB in communities over time.[10]

Active case-finding: systematic screening among people at high risk of TB and in communities with high prevalence of TB to identify who should receive further diagnostic evaluation for TB

The 2023 pipeline covers several classes of screening tools that are key to actively expanding TB screening efforts in communities (Table 1). Top on the list are tools from classes that are already recommended by the WHO: ultraportable chest X-ray devices that can be paired with artificial intelligence (AI) based CAD software to assist in detecting **presumptive TB** from chest X-rays (see ai4hlth.org for detailed information on available CAD software). Current WHO recommendations for the use of CAD, however, are only for people over 15 years of age. Efforts to validate CAD software for children and adolescents under 15 must therefore be prioritized.[11] Several pilot studies of active case-finding using ultraportable chest X-ray and CAD demonstrated the feasibility and impact of detecting early TB in communities before the onset of symptoms.[12] This is an essential strategy that has not yet been widely scaled up in high burden countries, in part due to the upfront capital cost of ultraportable X-ray devices but also because of the lack of sufficient guidance on threshold selection to define positive and negative results for CAD software and radiation protection suitable for ultraportable chest X-ray devices.[13] Improving access to chest X-rays is a high priority for TB screening as well as for diagnosing **nonsevere TB** in children to determine eligibility for the shorter four-month treatment regimen for **drug-sensitive TB (DS-TB)**.[14]

Presumptive TB: likely TB that is not yet confirmed

Nonsevere TB: TB with low bacterial load that is limited to the lymph nodes or confined to one lobe of the lungs without cavitation

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

Next on the list are entirely new classes of tests. These include AI-based **point-of-care ultrasound (POCUS)** devices that connect with smartphones and can be used to detect early tissue damage from **pulmonary** and **extrapulmonary TB**, especially among pregnant people and children.[15] This simple, portable, and relatively inexpensive screening tool, exemplified by the Butterfly iQ POCUS device, exhibits very early data with **sensitivity** and **specificity** of 91% and 61% and an AUC (area under the **ROC curve**) of 86%,[16] which is comparable to that of chest X-ray and CAD. More data is needed on the use of POCUS, especially among children. This is followed by the imPulse Una digital stethoscope by Level 42 AI that detects inaudible vibrations and audible sounds and uses AI to map these against those of healthy lungs and other tissues to detect, with relatively high accuracy, early damage associated with TB. Other digital stethoscopes and **cough apps** that detect audible lung and cough sounds indicating the early development of symptoms associated with TB also exhibit significant potential for community-based screening and even self-testing to promote early TB detection.[17] Lastly, the blood-based Cepheid MTB-HR molecular host-response test (see Table 6) has been evaluated for TB **triage** showing sensitivity of 90.3% and specificity of 62.6%.[18] However, due to the relatively high costs of GeneXpert tests and instruments, as well as service and maintenance, the test is unlikely to meet WHO Target Product Profile criteria for screening tools.[19,20]

Point-of-care ultrasound (POCUS): portable, radiation-free imaging device that detects tissue damage associated with TB

Pulmonary TB: TB in the lungs

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

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

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

ROC (receiver operating characteristic) curve: graph showing the accuracy of a diagnostic

Cough apps: mobile phone applications that apply artificial intelligence to monitor cough over time and/or detect cough patterns suggestive of TB

Triage test: test used to identify people with high likelihood of active TB

Table 1: Screening Tools

Tool* (Developer)	Type	Accuracy**	Time to Result	Price	Status
Delft Ultra (Delft Imaging, Netherlands)	Ultraportable chest X-ray	Paired with CAD software to interpret images	Within seconds 100 exposures per battery charge[21]	Not available	Commercially available
FDR Xair (Fujifilm, Japan)	Ultraportable chest X-ray	Paired with CAD software to interpret images	1 second 100 exposures per battery charge	US$49,000 Extended warranty $5,000 per year; local support available[22]	Commercially available
Europa (Aspen Imaging, USA)	Ultraportable chest X-ray	Paired with CAD software to interpret images	Within seconds 100 exposures per battery charge[23]	Not available	Commercially available
MINE ALNU (OTOM, South Korea)	Ultraportable chest X-ray	Paired with CAD software to interpret images	1 second 100 exposures per battery charge	$48,000 Extended warranty available[24]	Commercially available
Butterfly iQ (Butterfly Network, USA)	AI-based point-of-care ultrasound	Ultrasound: SE: 91% SP: 61% AUC: 86%[25]	Immediate 2+ hours scan time per battery charge	$2,699 Global access pricing available	Undergoing evaluation for TB
imPulse Una (Level 42 AI, USA)	AI-based digital stethoscope	Vibrations and audible sounds: SE: ≥ 70% SP: ≥ 85%[26]	≤ 3 minutes	≤ $100	Undergoing evaluation for TB
StethoMe (StethoMe, Poland)	AI-based digital stethoscope Self-screening	Lung sounds: Not available	Immediate	$230 per annual subscription Includes warranty[27]	Undergoing evaluation for TB
Stethee Pro (M3DICINE, Australia)	AI-based digital stethoscope	Lung sounds: Not available	Immediate	$499 Includes limited-time subscription[28]	Undergoing evaluation for TB

Tool* (Developer)	Type	Accuracy**	Time to Result	Price	Status
TimBre (Docturnal, India)	AI-based cough app	Cough sounds: SE: 85.0% SP: 82.0% AUC: 0.92[29]	< 15 minutes	$1.20 per test including consumables	Undergoing evaluation for TB
ResApp (ResApp Health, Australia)	AI-based cough app	Cough sounds: Not available	Within minutes[30]	Not available	Undergoing evaluation for TB
Swaasa (Salcit Technologies, India)	AI-based cough app	Cough sounds: SE: 90% SP: 85%[31]	10 seconds	≤ $1 per test for high-volume testing $5 per test for low-volume testing[32]	Undergoing evaluation for TB
ichroma CRP (Boditech, Korea)	Fluorescence-based immunoassay Lateral flow assay with digital reader	Blood: SE: 89% SP: 72%[33]	3 minutes[34]	Not available	Commercially available WHO-recommended for people living with HIV
LumiraDx CRP (LumiraDx, UK)	Fluorescence-based immunoassay	Blood: Close correlation with lab-based methods[35]	< 5 minutes	Test: $2 Instrument: $3,300 with 2-year warranty[36]	Commercially available WHO-recommended for people living with HIV
SeroSelectTB (SeroSelectTB Consortium)	Antibody detection	Blood: Not available	Rapid[37]	Not available	Undergoing evaluation

** Note: this table does not include computer-aided detection (CAD) software; an extensive list of CAD software can be found on the ai4hlth.org website.*

*** Accuracy according to a culture-based microbiological reference standard unless otherwise noted.*

Abbreviations:

CAD: computer-aided detection **CRP:** C-reactive protein

Box 1: Publicly Funded TB Diagnostics Research Networks

For the first time ever, in 2023, several major TB diagnostics research networks evaluating the latest point-of-care diagnostics and other novel technologies are collaborating to coordinate research and develop shared **protocols** across trial sites globally.[38] These include NIH-funded FEND-TB and R2D2 TB Network, Unitaid-funded DriveDx4TB, and USAID-funded SMART4TB. Together, these publicly funded networks comprise over 20 trial sites in 13 countries and significantly expand opportunities to rapidly evaluate and generate extensive data on emerging new TB diagnostics among adults and children to inform WHO review and policy recommendations. A key accomplishment of the collaboration is the development of consensus protocols for oral swab-based testing using Xpert MTB/RIF Ultra and Truenat MTB Plus that will be applied across research networks and sites to optimize and standardize testing and promote effective pooling of data. Many of the point-of-care diagnostic tests included in this report are currently or will soon be undergoing evaluation by these TB diagnostics research networks.

Protocols: evidence-based standardized methods or procedures

An estimated 70% of TB research is funded by the public sector, with an additional 14% from philanthropic organizations, 10% from the pharmaceutical and diagnostics industry, and 6% from multilateral organizations.[39] Yet many publicly funded TB innovations, such as GeneXpert, are commercialized by private companies without any binding obligations to ensure access.[40] The result is that companies can charge high prices irrespective of the cost of production and profit excessively, drawing from insufficient national TB program budgets and global donor funding and restricting access to lifesaving TB innovations. Therefore, it is essential for all public funding of TB R&D to include access conditions, from the earliest stages of R&D — when the potential market value of the innovations is still being assessed — through late development and commercialization, to ensure public return on public investment.

Diagnosis

In 2011, the WHO recommended the first rapid molecular test for TB, Cepheid's Xpert MTB/RIF. This test revolutionized the diagnostic accuracy, speed, and ease of testing for TB compared to the standard of care, **sputum smear microscopy**, and was the first rapid test for resistance to rifampicin. However, the limited accessibility of this technology has resulted in its failure to significantly close diagnostic gaps.[41] In 2022, just 47% of people diagnosed with TB received a rapid molecular test as the initial TB test in accordance with WHO recommendations, meaning that the majority of people diagnosed with TB were tested with smear microscopy.[42] Despite efforts to replace smear microscopy, an inaccurate diagnostic that misses half of all people with TB, the test has persisted in large part because it is simple and inexpensive, although this does not take into account the cost of missed diagnoses and subsequent suffering and death from TB. Efforts to develop better diagnostic tests that can be implemented in communities and at the point of care, thankfully, are beginning to take shape.

Sputum smear microscopy: the method of using a microscope to visually detect TB bacteria in sputum

The 2023 pipeline includes an array of next-generation urine **lipoarabinomannan (LAM) lateral flow assays** intended for all people irrespective of HIV status (Table 2) and portable point-of-care rapid molecular tests optimized for oral swab samples (Table 3). New tests within each of these classes are expected to be less expensive than what is currently available and, for those with testing instruments, service and maintenance requirements are expected to be minimal. However, the sensitivities of next-generation urine LAM and swab-based molecular tests are expected to be lower compared to sputum-based molecular testing. Currently available data for next-generation LAM tests point to sensitivities ranging around 65% and specificities around 93% in HIV-negative people.[43] Meanwhile, swab-based molecular tests exhibit similar sensitivity as next-generation LAM tests but with higher specificity.[44] Because these tests use samples that anyone can easily provide, they enable a much larger number of people to be tested in communities and at the point of care. The resulting higher diagnostic yield and improved population coverage may be reason enough to accept lower sensitivity (see Box 2). Several nonsputum **CRISPR-based TB molecular tests** are also in the pipeline at an earlier stage of development. This technology is highly sensitive and specific and is expected to also be relatively inexpensive with the possibility of instrument-free testing. To generate the necessary evidence to inform policy recommendations for nonsputum-based tests, diagnostic yield should be evaluated in dedicated pragmatic studies or **randomized controlled trials** across a range of study populations and settings using nonsputum-based reference standards to reduce the risk of bias against nonsputum-based tests. Additionally, self-sampling and self-testing for TB using simple point-of-care tests should be further explored to generate data on feasibility and potential impact.

Lipoarabinomannan (LAM): a component of the outer cell wall of TB bacteria that is discarded in the body and that is detectable in urine

Lateral flow assay: simple, paper-based tests that detect the presence of a pathogen in a liquid sample without the need for specialized or costly equipment

CRISPR-based TB molecular tests: molecular tests that detect genetic material of pathogens in samples with very high specificity, indiscriminately cutting DNA in the sample to indicate a positive test result

Randomized controlled trials: a study design that randomly assigns participants into an experimental group (receiving the intervention that is being tested) or a control group (receiving an alternative intervention, no intervention, or the standard of care)

Host-response tests: tests that detect specific changes in the body in response to the presence of a pathogen, such as *Mycobacterium tuberculosis*

Cepheid's Xpert MTB-HR, a **host-response** test that uses fingerstick blood samples and is run on a standard GeneXpert instrument, has been in development for several years and is currently undergoing evaluation for treatment monitoring and progression of disease (see Table 6). However, given available data on accuracy and cost-effectiveness, the test may be best suited as a nonsputum diagnostic test among people unable to produce sputum, including children and people living with HIV. In diagnostic accuracy studies, the test exhibits sensitivity of 87% and specificity of 94% for detection of TB among people living with HIV.[45] An assortment of other decentralized molecular tests for TB and drug resistance, similar to GeneXpert and Truenat, are also in the pipeline (Table 4). These tests generally require some laboratory infrastructure, including electricity, temperature control, and dust-free environments, so are likely to be placed at the district lab level. Most of these tests use sputum as the primary sample, but some developers have plans to also evaluate the tests using alternative sample types, including oral swabs and stool for children. The most notable tests nearing the end of the pipeline are SD Biosensor's STANDARD M10 MDR-TB, which tests for TB and resistance to rifampicin and isoniazid, and Bioneer's IRON-qPCR RFIA Kit, which tests for TB and resistance to rifampicin, isoniazid, and the fluoroquinolones (moxifloxacin and levofloxacin). Both of these tests will introduce competition with GeneXpert and Truenat, and Bioneer's test finally offers an alternative to

Cepheid's Xpert MTB/XDR, which is priced excessively at $14.90. It's essential for country programs to scale up decentralized access to rapid **drug-susceptibility testing (DST)** to improve drug resistance detection immediately following initial TB diagnosis and quickly identify the optimal treatment regimen and whether additional DST is needed.[46]

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

In 2023, **targeted next-generation sequencing (tNGS)** technology has finally been reviewed and recommended by WHO for comprehensive TB DST, bringing the TB field closer to having the technologies needed to realize **universal DST**.[47] Current tNGS products are capable of testing for drug resistance to up to 15 drugs in a single test, which takes one to two days to perform. Performing tNGS requires a set of complex instruments and highly skilled laboratory technicians, so the technology will initially be placed in central labs, with the possibility of further decentralization as the technology advances. The evidence showed very high accuracy for commonly used TB drugs for which there is sufficient knowledge of **resistance-conferring mutations** such as isoniazid and rifampicin, but lower sensitivity (although high specificity) for new and repurposed drugs, including bedaquiline, linezolid, and delamanid, for which knowledge of resistance mutations is still limited.[48] While positive results for resistance to new and repurposed drugs can be considered accurate, negative results do not rule out resistance, so **mycobacterial culture** is still required. Laboratory capacity for culture-based testing must therefore continue to be developed and strengthened in high-TB-burden countries. The next edition of the WHO catalog of ***Mycobacterium tuberculosis*** mutations — expected in late 2023 — is anticipated to inform updates that will further improve diagnostic performance of the **assays** for resistance detection, with increased mutations coverage for the new and repurposed drugs. For tNGS to be initially cost effective, it will likely require batching, which could delay turnaround time to results for up to two weeks. Speed can be improved through smaller size batching and use of lower-throughput sequencers — such as the iSeq from Illumina or MinION from Oxford Nanopore Technologies — for lower-volume settings. Experience implementing tNGS for programmatic management of **drug-resistant TB (DR-TB)** in high-income country settings has shown that larger volumes can also potentially drive down costs and improve access.[49,50]

Targeted next-generation sequencing (tNGS): 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

Universal DST: availability of drug-susceptibility testing for all people diagnosed with TB

Resistance-conferring mutations: *Mycobacterium tuberculosis* genetic mutations that are associated with resistance to specific TB drugs

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

Mycobacterium tuberculosis: the species of pathogenic bacteria that causes TB

Assay: an investigative analytic procedure or test

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

Box 2: Diagnostic Yield, Another Measure of Diagnostic Performance

Last year's Pipeline Report cautioned against the singular focus on diagnostic test accuracy as the measure of a test's clinical value, citing the case of Abbott's Determine TB LAM, a low-sensitivity test that is proven to reduce mortality by 15% among people with advanced HIV disease.[51,52] In addition to accuracy, ease of sampling, accessibility, and **diagnostic yield** must also be prioritized. Even if a test has lower sensitivity, if accessibility and sample availability result in more tests being completed, more people with TB might be diagnosed. Provided the test has high specificity, positive results can be considered accurate.[53]

This year, as **oral swab**-based molecular tests are progressing toward clinical trials, the importance of including diagnostic yield as another critical measure of a test's value is even more relevant. Early data shows that oral swab-based testing using Xpert MTB/RIF Ultra has a sensitivity of 72.4% and specificity of 100%, compared to a **reference standard** of sputum-based testing using Xpert MTB/RIF Ultra and mycobacterial culture.[54] When one considers that everyone in need of testing can easily provide an oral swab sample, while in household settings less than half of people can spontaneously provide a sputum sample (even less among children and people living with HIV), it becomes clear that a lower sensitivity oral swab-based test may ultimately result in more people with TB being diagnosed.[55] Recent modeling by FIND to inform the development of new WHO **Target Product Profiles** (TPPs) for TB diagnostics illustrates that a hypothetical test with 70% sensitivity and 98% specificity that is able to reach 75% of the population in need of testing results in more than double the number of people diagnosed, when compared to a hypothetical test with 90% sensitivity and 99% specificity that is only able to reach 25% of the population.[56]

Realizing this higher diagnostic yield in national TB programs, however, will require the roll-out of next-generation urine LAM tests (Table 2) and portable oral swab-based molecular tests (Table 3) at the point of care and in communities. As these tests progress through clinical trials and move closer to the market, it's essential that diagnostic yield is considered alongside accuracy and that effective population coverage is prioritized when making policy recommendations on the use of the tests. Improving access to diagnosis and closing the diagnostic gap might just depend on it.

Diagnostic yield: the proportion of people in a given population who are able to provide a sample and receive a diagnosis

Oral swab-based: using a swab to collect a sample from the back of the tongue or other part of the oral cavity

Reference standard: the most accurate test or combination of tests against which the accuracy of other tests can be measured and compared

Target Product Profiles (TPPs): a set of optimal and minimal test specifications for different use cases to inform new test development

Table 2: Next-Generation LAM Tests

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
SILVAMP TB LAM (Fujifilm, Japan)	Lateral flow assay	Urine: People living with HIV SE: 70.7% SP: 90.9%[57] HIV-negative people SE: 53.2% SP: 98.9%[58]	1 hour	US$6.60[59]	Undergoing evaluation Issue with manufacturing lot variability
Flow-TB (Salus Discovery, USA)	Lateral flow assay Urine/LAM concentration; visual readout; option of digital reader	Urine: Limit of detection <10 pg/mL[60] 40-200X increase in detectable LAM due to urine concentration	Not available	$1–2	Undergoing evaluation
High-sensitivity TB LAM (Abbott, USA)	Lateral flow assay Urine/LAM concentration; visual readout	Urine: Not available	< 45 minutes[61]	Not available	Undergoing evaluation
ichroma LAM Ag (Boditech, South Korea)	Lateral flow assay Fluorescence-based; requires digital reader	Urine: SE: 93% SP: 78%[62]	< 20 minutes Instrument: ichroma II	Not available	Undergoing evaluation
STANDARD F TB LAM Ag FIA (SD Biosensor, South Korea)	Lateral flow assay Fluorescence-based; requires digital reader	Urine: SE: 68.3% SP: 98%[63]	30 minutes Instrument: STANDARD F10	Not available	Undergoing evaluation
TB LAM urine LFA (Biopromic, Sweden)	Lateral flow assay	Urine: People living with HIV SE: 78% SP: 89% HIV-negative people SE: 65% SP: 93%[64]	50 minutes	$4	Undergoing evaluation
OsmoProcessor (Truly Technologies, USA)	Urine concentration device	N/A	Not available	Not available	Not yet paired with diagnostic assay[65]

** Accuracy according to a culture-based microbiological reference standard unless otherwise noted.*

Abbreviations:

LAM: lipoarabinomannan

Table 3: Portable Molecular Tests

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
TB POC (LumiraDx, UK)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	20 minutes	Test: Not Available Instrument: US$3,300 with 2-year warranty[66]	Undergoing evaluation
Logix Smart MTB (Co-Dx, USA)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	< 30 minutes Instrument: Co-Dx PCR Home[67]	Not available	Undergoing evaluation
3STEP (Salus Discovery, USA)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	< 30 minutes	Test: ~$3 Instrument: < $1,000[68]	Undergoing evaluation
TB Assay (Biomeme, USA)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	< 1 hour Instrument: Franklin[69]	Not available	Undergoing evaluation
PortNAT MTC (USTAR, China)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	40 minutes Instrument: PortNAT[70]	Not available	Undergoing evaluation
IsoAmplar MTB Kit (Boditech, South Korea)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	40 minutes[71] Instrument: IsoAmplar	Not available	Undergoing evaluation
TB Assay (Nuclein, USA)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	15 minutes Instrument: DASH[72]	Not available	Undergoing evaluation
TB Assay (FRIZ Biochem, Germany)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	30 minutes Instrument: CYCLE Dx	Test: $30[73]	Undergoing evaluation
TB Assay (Pluslife, China)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	35 min Instrument: Pluslife Mini Dock	Test: < $10 Instrument: < $200[74]	Undergoing evaluation
NABIT (Conservation X Labs, USA)	Nucleic acid amplification test Detection: MTB	Tongue swab: Not available	Not available Instrument: NABIT[75]	Not available	Undergoing evaluation
TB Assay (Sherlock Biosciences, USA)	Nucleic acid amplification test: CRISPR[76] Detection: MTB	Tongue swab: Not available	Not available	Not available	Undergoing evaluation

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
NuRapid (Jiangsu MicroDiag, China)	Nucleic acid amplification test: CRISPR Detection: MTB	Tongue swab: Not available	40 minutes Instrument: Mac-S POCT[77]	Not available	Undergoing evaluation
CHALET (Intelligenome, USA)	Nucleic acid amplification test: CRISPR Detection: MTB	Blood: Adults SE: 96% SP: 94% Children SE: 83% SP: 95%[78]	1 hour	Not available	Undergoing evaluation
PathCrisp TB Assay (CrisprBits, India)	Nucleic acid amplification test: CRISPR Detection: MTB	Saliva and nasal swabs: Not available	1 hour (post-nucleic acid extraction)[79]	Not available	Undergoing evaluation
AveloCollect (Avelo, Switzerland)	Sample collection Breath aerosol blow tube[80]	N/A	Not available	Not available	Undergoing evaluation

** Accuracy according to a culture-based microbiological reference standard unless otherwise noted.*

Abbreviations:

MTB: *Mycobacterium tuberculosis* **CRISPR:** clustered regularly interspaced short palindromic repeats

Table 4: Decentralized Molecular Tests

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
Truenat Ultima (Molbio, India)	Nucleic acid amplification test Detection: MTB	Tongue swab, other pulmonary & extrapulmonary specimens: Not available	1 hour Instruments: Trueprep Truelab	Test: US$12 Instruments: $10,000–18,000[81]	Undergoing evaluation
Truenat MTB-INH (Molbio, India)	Nucleic acid amplification test Detection: INH	MTB-positive pulmonary & extrapulmonary specimens: Not available	1 hour Instruments: Trueprep Truelab	Test: $7.90 Instruments: $10,000–18,000[82]	Undergoing evaluation Under review by Global Fund ERPD
Truenat MTB-FQ (Molbio, India)	Nucleic acid amplification test Detection: FQ	MTB-positive pulmonary & extrapulmonary specimens: Not available	1 hour Instruments: Trueprep Truelab	Test: $12 Instruments: $10,000–18,000[83]	Undergoing evaluation
Truenat MTB-BDQ (Molbio, India)	Nucleic acid amplification test Detection: BDQ	MTB-positive pulmonary & extrapulmonary specimens: Not available	1 hour Instruments: Trueprep Truelab	Test: $12 Instruments: $10,000–18,000[84]	Undergoing evaluation
Truenat MTB/ COVID-19 (Molbio, India)	Nucleic acid amplification test Detection: MTB, COVID-19	Sputum, nasopharyngeal swab: Not available	1 hour Instruments: Trueprep Truelab	Test: $16 Instruments: $10,000–18,000[85]	Undergoing evaluation
Xpert MTB/RIF Ultra (Cepheid, USA)	Nucleic acid amplification test Detection: MTB, RIF	Tongue swab: SE: 72.4% SP: 100%[86]	< 90 minutes Instrument: GeneXpert	Test: $7.97 Instrument: $9,420–19,500[87]	Commercially available Undergoing evaluation using tongue swabs
IRON-qPCR RFIA Kit (Bioneer, South Korea)	Nucleic acid amplification test Detection: MTB, RIF, INH, FQ, AMK	Sputum: Not available	40 minutes Instrument: IRON qPCR	Test: Not available Instrument: $20,869	Clinical trials started 2022; submission to WHO & ERPD review 2024–2025[88]
STANDARD M10 MDR-TB (SD Biosensor, South Korea)	Nucleic acid amplification test Detection: MTB, RIF, INH	Sputum: Not available	80 min Instrument: STANDARD M10	Not available	Undergoing evaluation Clinical trials start 2023[89]
ExAmplar MTB Kit (Boditech, South Korea)	Nucleic acid amplification test Detection: MTB	Sputum: Not available	30–55 minutes Instruments: NuActor ExAmplar RT-PCR	Not available	Undergoing evaluation

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
Tb*dtect* (Genes2Me, India)	Nucleic acid amplification test Detection: MTB	Pulmonary specimens: Not available	1 hour Instruments: RAPi-X16 RAPi-Q[90]	Not available	Undergoing evaluation
Tb*find* (Genes2Me, India)	Nucleic acid amplification test Detection: RIF, INH	Pulmonary specimens: Not available	1 hour Instruments: RAPi-X16 RAPi-Q[91]	Not available	Undergoing evaluation
Pathodetect-MTB and Rifampicin and Isoniazid Detection Kit (MyLAB, India)	Nucleic acid amplification test Detection: MTB, RIF, INH	Sputum: Not available	< 2 hours Instrument: CompactDx[92]	Not available	Undergoing evaluation
MTB/MDR Kit (Prodiag, the Netherlands)	Nucleic acid amplification test Detection: MTB, RIF, INH	Sputum: MTB SE, SP: > 94.5% RIF SE: 95.8% SP: 96.4% INH SE: 88% SP: 97.2%	3 hours Instrument: Sanity 2.0	Test: $9 Instrument: $14,000 Volume-based price reductions available[93]	Undergoing evaluation
RAPID TB (Nanjing Difei Med, China)	Nucleic acid amplification test Detection: MTB, RIF, INH	Tongue swabs, sputum: Not available	30 minutes[94]	Not available	Undergoing evaluation
Smart Sure MTB Screening Kit (Genetix, India)	Nucleic acid amplification test Detection: MTB	Pulmonary & extrapulmonary specimens: Not available	70 minutes Instruments: Mini Purifier P4 GeneNAT 300 or GeneNAT340	Test: $3.65 Instruments: $8,000–19,800[95]	Undergoing evaluation
Smart Sure MDR-TB Screening Kit (Genetix, India)	Nucleic acid amplification test Detection: RIF, INH	Pulmonary & extrapulmonary specimens: Not available	70 minutes Instruments: Mini Purifier P4 GeneNAT 300 or GeneNAT340	Test: $9.65 Instruments: $8,000–19,800[96]	Undergoing evaluation
EasyNAT MTC (USTAR, China)	Nucleic acid amplification test Detection: MTB	Respiratory specimens: Not available	25 min Instrument: EasyNAT[97]	Not available	Undergoing evaluation Commercially available in China

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
MultiNAT MTC/ MDR (USTAR, China)	Nucleic acid amplification test Detection: MTB, TB, RIF	Respiratory specimens: Not available	45–65 minutes Instrument: MultiNAT (high throughput)[98]	Not available	Undergoing evaluation Commercially available in China
TB & RIF Resistance Kit (Sansure, China)	Nucleic acid amplification test Detection: MTB, RIF	Tongue swab, sputum: Not available	1 hour Instrument: iPonatic III[99]	Not available	Undergoing evaluation
FlashDetect LyocartE MTB Assay (Coyote Bioscience, China)	Nucleic acid amplification test Detection: MTB	Respiratory specimens: Not available	< 25 minutes Instrument: FlashDetect Flash10, FlashDetect Nano[100]	Not available	Undergoing evaluation

** Accuracy according to a culture-based microbiological reference standard unless otherwise noted.*

Abbreviations:

MTB: *Mycobacterium tuberculosis* **RIF:** rifampicin **INH:** isoniazid

FQ: fluoroquinolones **BDQ:** bedaquiline **AMK:** amikacin

ERPD: Expert Review Panel for Diagnostics

Table 5: Centralized Drug-Susceptibility Tests

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
Genoscholar FQ+KM-TB II (Nipro, Japan)	Line probe assay: FQ, KM**	Sputum: FQ SE: 93.0% SP: 100%[101]	6 hours Instrument: MULTIBLOT NS-4800	Test: US$30[102]	Undergoing evaluation
LiquidArray MTB-XDR (Hain Lifescience GmbH, Germany)	High-throughput molecular: FQ, LZD, AMK, EMB	Sputum: MTB SE: 85.4% SP: 99.4% FQ: SE: 94.3% SP: 99.3% LZD: SE: Not available SP: 100%[103]	2.5–5 hours Instrument: FluoroCycler XT	Not available	Undergoing evaluation; pending WHO review in 2024

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
Sensititre (Thermo Fisher/ Mesabiotech)	Broth microdilution culture: up to 12 drugs	Sputum: Not available	10-21 days[104]	Not available	Undergoing evaluation
Phenotech (Resistell, Switzerland)	Nanomotion optical detection: RIF, INH	≥ 100 bacteria in specimen: SE: 97.4% SP: 100%	21 hours Instrument: Resistell AST	Test: $4.50 Sensor (single use): $67 Instrument: $83,438[105]	Undergoing evaluation
Deeplex Myc-TB (GenoScreen, France)	tNGS: up to 15 drugs including BDQ & LZD	Sputum: SE: 93.1–98.5% SP: 95.3–98.5%[106] (WGS reference standard)	1-2 days	Test: $50[107]	WHO recommended in 2023[108]
DeepChek Assay 13-Plex KB DST (ABL Diagnostics, France)	tNGS: up to 13 drugs including BDQ	Sputum: Not available	29 hours[109]	Not available	Undergoing evaluation
NanoTB (Oxford Nanopore Technologies, UK)	tNGS: RIF, INH, FQ, AMK, LZD, STM	Sputum: RIF, INH, FQ SE: > 94% SP: > 99%[110]	< 24 hours	Not available	WHO-recommended in 2023
TBSeq (ShengTing Biotech, China)	tNGS: up to 16 drugs	Sputum: SE: 94.8% SP: 97.9%[111]	1-2 days	Not available	WHO-recommended in 2023
CleanPlex (Paragon Genomics, USA)	tNGS: Not available	Sputum: Not available	1-2 days	Not available	Undergoing evaluation
Tuberculini (Clemedi Deutschland GmbH, Germany)	tNGS: up to 12 drugs	Sputum: SE: 84% SP: 95%[112]	< 24 hours	Not available	Undergoing evaluation

** Accuracy according to a culture-based microbiological reference standard unless otherwise noted.*

*** Kanamycin no longer recommended by WHO.*

Abbreviations:

tNGS: targeted next-generation sequencing
NH: isoniazid
BDQ: bedaquiline
KM: kanamycin
WGS: whole genome sequencing
FQ: fluoroquinolones (moxifloxacin, levofloxacin)
AMK: amikacin
RIF: rifampicin
LZD: linezolid
STM: streptomycin

Box 3: Prioritizing the Inclusion of Children and Adolescents in TB Diagnostics R&D

Diagnosing TB in children is challenging, in large part because children usually have **paucibacillary TB**, which is difficult to detect using currently available tests, and invasive procedures are often required to obtain sputum and other samples for testing.[113] Noninvasive pediatric samples such as stool are beginning to be evaluated using a standardized sample processing procedure on existing tests but so far exhibit lower sensitivity compared to sputum.[114,115] Another key challenge is that there is very limited data on the diagnostic accuracy of currently available tests among children due to the historical trend of deprioritizing children in the development and evaluation of TB diagnostics. Without this evidence, policy recommendations on the use of diagnostics among children are generally based on extrapolated data from adults with low or very low certainty of evidence. In the absence of conclusive diagnostic test results, clinicians can use WHO-recommended algorithms to clinically diagnose children based on signs and symptoms and assessed risk.[116]

Paucibacillary TB: active TB that is caused by small amounts of TB bacteria; a common form of TB among people living with HIV and children

To address this major gap in evidence and available diagnostic tests suitable for pediatric TB, a group of TB researchers led a consensus process with a range of TB stakeholders culminating in 2023 with consensus guidance on the inclusion of children and adolescents in the development and evaluation of TB diagnostics. Consensus was reached across the large majority of statements related to the timing of inclusion of children and adolescents, analytical accuracy considerations, and diagnostic test design.[117] According to the guidance, children and adolescents should be included as early as possible in the development of **pathogen-based tests** to minimize risks and should be included alongside adults for host-response test development; tests should have sufficient accuracy to detect paucibacillary TB across a range of pediatric samples; and children, adolescents, and caregivers should be consulted regarding their needs and preferences to inform the design of new diagnostics. The published consensus guidance is forthcoming.

Pathogen-based tests: tests that detect genetic material or other components of pathogens in samples

Treatment Monitoring and Testing for Progression to Active TB

Treatment monitoring tests enable clinicians to adjust individual treatment regimens — including both their duration and composition — to improve the likelihood of a positive treatment outcome, prevent excess suffering and death, and reduce the risk of developing further drug resistance. Currently available molecular diagnostics, such as GeneXpert and Truenat, detect genetic material from TB bacteria in samples but cannot differentiate between live and dead TB bacteria so cannot be used to accurately monitor the effectiveness of TB treatment. Instead, the only WHO-recommended tests for treatment monitoring are smear microscopy, which has low sensitivity, and culture, which takes two to six weeks for results. Clearly, better tests are needed.

In 2023, the WHO revised its TPP on tests for treatment monitoring, highlighting three essential use cases: to identify people who require a more intensive TB regimen at treatment initiation, to identify people at risk of a poor outcome

during treatment, and to identify people at risk of a poor outcome at the end of TB treatment.[118] Several classes of new tests in development for treatment monitoring include: pathogen-based molecular and antigen tests that detect markers of live bacteria and quantify the **bacterial load** in a sample, host-response molecular tests that detect **RNA signatures** indicative of the presence of live TB bacteria, and host-response **immunoassays** that detect specific changes to the immune response indicative of the presence of live TB bacteria. It's important to note that addressing each of these treatment monitoring use cases might not rely on a single test but instead might require a combination of tests, information, and markers, using diagnostic algorithms tailored for specific populations and use-cases. The development of treatment monitoring tests that meet the relevant WHO TPP criteria is especially important for supporting the evaluation and implementation of new TB drugs and regimens, particularly those aiming to significantly shorten treatment duration.

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

RNA signatures: specific genetic markers that can be detected and measured to indicate the presence or severity of disease

Immunoassays: tests for immune response to indicate the presence of a pathogen

Pathogen-based tests in the pipeline for treatment monitoring include TB-MBLA (Molecular Bacterial Load Assay), a test in development for several years that quantifies live bacteria in a sample and performs within four hours what mycobacterial culture takes weeks to perform. TB-MBLA pretreatment diagnostic accuracy is comparable to Xpert MTB/RIF Ultra, and the rate of conversion to negative results throughout treatment closely correlates with **time-to-culture-positivity**.[119,120,121] PATHFAST TB LAM Ag, a higher-complexity quantitative bacterial load assay from LSI Medience, detects and quantifies the TB antigen LAM in sputum samples. The accuracy of PATHFAST TB LAM Ag results also correlates well with time-to-culture-positivity, with time-to-results of less than one hour.[122]

Time-to-culture-positivity: the time it takes for mycobacterial culture to become positive, which serves as a proxy for disease severity and treatment response

Of note, the host-response tests in the pipeline are being evaluated for treatment monitoring as well as for detecting progression from TB infection to active disease, a use-case that is important to help target TB preventive treatment (TPT). For treatment monitoring, host-response tests such as Cepheid's Xpert MTB-HR show promise for early identification of treatment effectiveness as well as test of cure.[123] For progression to active disease, host-response tests have so far shown moderate accuracy to detect progression up to one year prior to the onset of active disease[124,125] but not the WHO TPP target of two years prior to the onset of active disease.[126] According to early data, the RISK 6 signature host-response test — currently under exploration by QuantuMDx — showed sensitivity of 75% and specificity of 50.3% for prediction of progression from TB infection to active disease up to one year prior to TB diagnosis.[127] The ERASE-TB trial (Early Risk Assessment in Household Contacts [≥10 Years] of TB Patients by New Diagnostic Tests in Three African Countries) is evaluating several of the tests listed in Table 6 for progression from TB infection to active disease. The trial is set to complete by the end of 2023, so new data on the accuracy of these tests for this use-case are forthcoming.[128] In addition, more research is required to better understand the spectrum of TB between TB infection and active disease and whether multiple, more nuanced and distinct disease states can be categorized and diagnosed as such, which is a prerequisite for designing and evaluating more tailored treatment regimens.[129]

Table 6: Tests for Treatment Monitoring and Progression to Active TB

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
Xpert MTB-HR (Cepheid, USA)	Molecular host-response: Sweeny 3 RNA signature	Blood: Results correlate with treatment response[130]	45 min[131] Instrument: GeneXpert	Not available	Undergoing evaluation
RISK6 signature assay (QuantuMDx, UK)	Molecular host-response: RISK6 RNA signature	Blood: Progression to active TB ≤ 1 year SE: 75% SP: 50.3%[132]	30 min Instrument: Q-POC	Not available	Undergoing evaluation
ISIT-TB (bioMérieux, France)	Molecular host-response: 30-Marker mRNA signature	Blood: Not available[133]	120 min Instrument: BioFire FilmArray	Not available	Undergoing evaluation
TAM-TB (Beckman Coulter, USA)	Host-response fluorescence-based immunoassay	Blood: Progression to active TB ≤ 6 months SE: 63% ≤ 1 year SE: 23%[134]	10 hours Instrument: Flow cytometer	Not available	Undergoing evaluation
TB-MBLA (University of St. Andrews/LifeArc, UK)	Quantitative test for bacterial load: detects 16S rRNA	Sputum: SE: 99% SP: 91%[135] Stool: SE: 77% SP: 87%[136]	4 hours Instruments: Multiple	Test: < US$15[137]	Undergoing evaluation
Capilia TB-Neo (TAUNS, Japan)	Quantitative test for bacterial load: detects MPT64	Cultured isolate: Treatment monitoring Day 14: SE: 54.8% SP: 89.5% Day 28: SE: 81% SP: 72.4%[138]	1–3 weeks for liquid culture 15 min to results[139]	Not available	Commercially available Undergoing evaluation
PATHFAST TB LAM Ag (LSI Medience, Japan)	Quantitative test for bacterial load: immunoassay	Sputum: SE: 88.8% SP: 100%[140]	≤ 1 hour Instrument: PATHFAST	Test: $32–54	Undergoing evaluation
Actiphage TB BLOOD TEST (PBD Biotech, UK)	Quantitative test for bacterial load: phage-based	Blood: Qualitative diagnostic accuracy SE: 73.3% SP: 94.2%[141]	3.5 hours Instrument: PCR thermocycler	Test: $35–50[142]	Undergoing evaluation

Tool (Developer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
TMKmt (Makerere University, Uganda)	Quantitative test for bacterial load: detects TMKmt	Blood: 100% specific to TB among people living with HIV Sputum: Detectable at low bacillary loads[143]	Not available Instruments: Multiple	Not available	Undergoing evaluation

** Accuracy according to a culture-based microbiological reference standard unless otherwise noted.*

Abbreviations:

RNA: ribonucleic acid **mRNA**: messenger ribonucleic acid **rRNA:** ribosomal ribonucleic acid

Box 4: WHO Prequalification for TB Diagnostics

Following clinical trials, evidence on the performance, feasibility, acceptability, and cost-effectiveness of new TB diagnostics is submitted to WHO for review. The WHO Global TB Program reviews the evidence, develops policy recommendations on new classes of tests, and approves new tests that fit within already existing classes. All approved tests must then undergo quality assessment by **WHO Prequalification for In-Vitro Diagnostics** within two years.[144] This quality assessment is critically important for determining the consistency of test performance and manufacturing across batches, which is necessary to ensure that approved tests meet minimum acceptable quality standards.

The majority of the TB diagnostic tests listed in this report will progress toward WHO Prequalification over the course of the next several years. After a backlog of over a year awaiting the submission of dossiers from manufacturers and available capacity to review them, WHO Prequalification finally began quality assessments of all the **nucleic-acid amplification tests (NAATs)** recommended by the WHO Global TB Program,[145] the first of several classes of WHO-recommended TB tests. This raises the concern of whether WHO Prequalification will have the capacity to rapidly review the dozens of new TB diagnostics soon-to-emerge from the pipeline or whether the backlog at WHO Prequalification could delay quality assessments and possibly jeopardize availability of these innovations to TB-affected communities.[146] It's essential that WHO Prequalification prepares with human and other resources for the influx of new TB diagnostics emerging from the pipeline.

Nucleic-acid amplification tests (NAATs): molecular tests that amplify and detect specific genetic material indicating the presence of disease

Testing for TB Infection

As high-TB-burden countries move to scale up access to **short-course TB preventive treatment (TPT)** to a broader list of key populations, access to TB infection testing must also increase. Current tests for TB infection, however, cannot differentiate between infection and active disease, so diagnostic testing is also needed to rule out active TB. Better tests for TB infection that can distinguish between TB infection and active disease are therefore needed to further improve the clinical utility of TB infection tests in supporting the scale-up of TPT. While testing for TB infection is not required before initiating TPT for people living with HIV and TB contacts under five years, it could prove beneficial for HIV-negative TB contacts over five years by providing a test result to inform decisions of whether to initiate TPT and reducing the probability of unnecessary treatment and related side effects. Unlike many of the other diagnostics listed in this report, tests for TB infection do not have a reliable reference standard.[147] Sensitivity is determined by the number of people with confirmed TB who also have a positive TB infection test result, and specificity is determined by presumed false positive results in very low-TB-burden settings.

Short-course TB preventive treatment (TPT): one month of daily isoniazid and rifapentine (1HP) or three months of once-weekly isoniazid and rifapentine (3HP)

The current pipeline of TB infection tests is composed of two classes, point-of-care **interferon-gamma release assays (IGRAs)** and **TB-specific skin tests (TBST)** (Table 7). The ichroma IGRA-TB test represents a new class of blood-based IGRAs that condense a series of laboratory-based procedures into a lateral flow assay, simplifying the test so it can be implemented in nonlaboratory settings, such as community health centers. ichroma IGRA-TB uses a digital reader to determine tests results, and while this process takes place in a matter of minutes, the samples must first be incubated for up to 24 hours before being added to the lateral flow assay. This time-to-result therefore requires a second health care visit or digital communication of results, offering limited advantage over laboratory-based IGRA tests.

Interferon-gamma release assays (IGRAs): tests that detect interferon-gamma, a biomarker of the body's immune response to TB, in blood samples

TB-specific skin tests (TBST): in-vivo tests used to detect the immune response to the introduction of TB-specific antigens in the body

TB-specific skin tests, recommended by WHO in 2022, were found to have comparable accuracy to IGRAs and are more specific than conventional **tuberculin skin tests (TST)**, which have high rates of false positive results among people vaccinated with the **Bacille Calmette-Guérin (BCG) vaccine**.[148] TB-specific skin tests are in-vivo, rather than in-vitro tests, meaning that the test takes place within the human body. TB-specific **antigen** is injected just under the skin, and after two to three days, the site of the injection is assessed to determine the result, also requiring a second health care visit or digital communication of results. More than a year after these tests were recommended, WHO Prequalification has not yet begun quality assessments, in part because WHO Prequalification does not yet have a diagnostics assessment category for in-vivo tests. While these tests are not yet on the global market and prices are still not set, TBST are expected to be significantly less expensive compared to point-of-care IGRAs, which are priced up to $12 per test.

Tuberculin skin tests (TST): in-vivo tests used to detect the immune response to the introduction of the tuberculin antigen in the body, with high rates of false positive results among people previously vaccinated with BCG

Bacille Calmette-Guérin (BCG) vaccine: the only available TB vaccine, developed over a century ago, that protects infants and young children from the most severe forms of TB

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

Table 7: Tests for TB Infection

Tool (Manufacturer)	Type	Accuracy*	Time to Result/ Instrument	Price	Status
ichroma IGRA-TB (Boditech, South Korea)	IGRA: fluorescence immunoassay Lateral flow, digital reader	Blood: 95.2% concordance with QFT-Plus[149]	Incubation: 16-24 hours Test: < 15 minutes[150] Instrument: ichroma II	Not available	Commercially available
STANDARD F TB Ag FIA (SD Biosensor, Korea)	IGRA: fluorescence immunoassay Lateral flow, digital reader	Blood: SE: 100% SP: 91.5%[151]	Incubation: 16-24 hours Test: < 15 minutes Instrument: STANDARD F F200	Test: US$4	Global Fund ERPD approved Undergoing evaluation
QIAreach QFT (Qiagen, Germany)	IGRA: fluorescence immunoassay Lateral flow, digital reader	Blood: 98.8% concordance with QFT-Plus[152]	Incubation: 16-24 hours Test: < 20 minutes Instrument: QIAreach eHub[153]	Test: $12 Instrument: $1,200[154]	Commercialization paused; future uncertain
Cy-TB (Serum Institute of India, India)	TBST: in-vivo skin test	SE: 76.0% SP: 98.0% (Pooled accuracy for TBST class)[155]	48–72 hours	Not available	Recommended by WHO in 2022; pending WHO Prequalification and EMA review
Diaskintest (Generium)	TBST: in-vivo skin test	SE: 76.0% SP: 98.0% (Pooled accuracy for TBST class)[156]	72 hours	Not available	Recommended by WHO in 2022; pending WHO Prequalification review
C-TST (Anhui Zhifei Longcom Biopharmaceutical, China)	TBST: in-vivo skin test	SE: 76.0% SP: 98.0% (Pooled accuracy for TBST class)[157]	48–72 hours	Not available	Recommended by WHO in 2022; pending WHO Prequalification review

** There is currently no reliable reference standard for tests for TB infection.*

Abbreviations:

IGRA: interferon-gamma release assay

TBST: TB-specific skin test

ERPD: Expert Review Panel for Diagnostics

EMA: European Medicines Agency

Conclusion

The 2023 TB diagnostics pipeline is the largest and most diverse it has ever been. This is a testament to the efforts, investments, and advocacy of the global TB community over the past decade — including to pivot COVID-19 diagnostics manufacturers, along with their install base of instruments, toward TB. But more must be done to expand evaluation of current tests in the pipeline across populations and geographies and increase development of new diagnostic tools that are accurate and affordable and that address the numerous use-cases required to end TB. If the status quo of high-priced tests and limited access continues, it will be no surprise if the global TB response continues to dramatically miss targets for TB diagnosis and care. New approaches, investments, innovation, fair and equitable pricing, and rapid scale-up of new tools are urgently needed.

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