Pipeline Report » 2022

Tuberculosis Diagnostics

TAG
Treatment Action Group

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Introduction

All people at risk of tuberculosis (TB) have a right to quality TB screening and diagnostic testing in accordance with the World Health Organization (WHO) recommended standard of care.[1] For the majority of people who develop **active TB** each year, however, this right is far from being realized. In 2021, only 6.4 million of the estimated 10.6 million people who developed active TB were diagnosed and notified.[2] Of these, just 2.4 million received a rapid molecular test as the initial diagnostic test for TB and resistance to the first-line drug rifampicin, as WHO recommends. Of the estimated 450,000 people who developed **multi-drug resistant TB (MDR-TB)** in 2021, only one in three were diagnosed and enrolled in TB treatment. As a result of insufficient access to quality TB testing and linkage to treatment and care in 2021, combined with COVID-19-related disruptions in accessing care, TB deaths continued to increase since 2019: 1.6 million people died from TB (a preventable and curable disease), including 187,000 people living with HIV[*] and 216,570 children.[3] It could not be any clearer — as a global community we must do better.

Investments in TB diagnostics research and development (R&D) reached an all-time high in 2020 at US$129.4 million, but this is far from the level of investment needed.[4,5] For comparison, 2020 investments in COVID-19 diagnostics R&D surpassed $804 million, more than six times the investment in TB in the same year. These investments catalyzed the rapid development and evaluation of a range of COVID-19 diagnostics, including portable point-of-care molecular tests and at-home rapid tests. A similar level of investment in TB diagnostics R&D would accelerate development timelines for critically needed new tools and expand the base of evidence required to formulate strong policy recommendations on the use of these tools. As we move forward, it is important to take stock of current gaps in available TB screening and diagnostic tools and identify where investments should be focused to accelerate TB diagnostics R&D and the equitable delivery of needed tools and interventions to close the TB diagnostic gap. The following

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

Multi-drug resistant TB (MDR-TB): TB that exhibits resistance to both first-line TB drugs, rifampicin and isoniazid

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[*] TB remains the largest killer of people living with HIV — globally, one in four people living with HIV who develop TB die from it. This is a shameful statistic that must be addressed by scaling up access to tools to prevent, detect, and treat advanced HIV disease or AIDS and TB/HIV co-infection at the primary care level of the health system.

Pipeline Report is structured to highlight these gaps and is organized according to the following top five research priorities:

1. **Pediatric TB Diagnostics**
2. **Point-of-care Urine LAM Tests**
3. **Non-sputum Point-of-care Molecular Tests for TB and DR-TB**
4. **TB Screening and Triage Tools**
5. **Algorithms for TB Screening and Diagnostic Testing**

A set of tables detailing the current pipeline of TB screening and diagnostic tools with data and information on performance and operational characteristics as well as development timelines is included in <u>Annex 1</u>.

Priority 1: Pediatric TB Diagnostics

In 2020, 1.1 million children aged 15 years and below were estimated to have developed active TB, but only 36.5 percent were diagnosed and notified. For children under five years, the TB detection gap is even larger, with only 27.5 percent diagnosed and notified in 2020.[6] Diagnosing TB in children is challenging for several reasons: (1) children with TB have smaller amounts of TB bacteria **(paucibacillary TB)** compared to adults, making it more difficult to detect; (2) children cannot easily produce **sputum** and have an increased risk of extra-pulmonary forms of TB, including **disseminated TB** (spread throughout the body), so sample collection among children can be challenging, often requiring invasive procedures to obtain a specimen for testing; and (3) TB signs and symptoms among children generally overlap with symptoms of other common childhood diseases.[7,8] Additionally, children have largely been underprioritized in TB diagnostics R&D, so currently available TB screening and diagnostic tests were either developed for adults and later adapted to children or insufficiently evaluated in pediatric populations. This has resulted in an overreliance on sample types that are less appropriate for children (sputum), insufficient diagnostic accuracy (**sensitivity** and **specificity**) of these tests among children, and extrapolation of data from adults to make conditional (or sometimes no) policy recommendations on the use of these tests among children.

There are several recent developments that represent positive steps toward improving capacity to test for TB among children. In 2020, WHO recommended stool as a noninvasive sample for diagnostic testing using Cepheid's Xpert MTB/RIF Ultra, and in 2021, several procedures were evaluated to standardize stool sample preparation for molecular testing,[9] including the Optimized Sucrose Flotation[10] and Simple One Step methods.[11,12] Use of stool samples increases the ease of sample collection and diagnostic yield among children, however, stool samples are less accurate (SE: 56.1%, SP: 98.0%) than other more invasive samples such as **gastric aspirate** (SE: 70.4%, SP: 94.1%).[13,14] For TB screening, computer-aided detection (CAD) artificial intelligence (AI) algorithms have been validated for diagnostic accuracy on adult X-ray databases but not yet on child X-ray databases.

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

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

Disseminated TB: TB that is spread throughout the body; a form of TB more commonly found among children and people living with HIV

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

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

Gastric aspirate: an invasive sample type that involves obtaining gastric fluid from the stomach by inserting a tube into the nostril, guiding it down toward the stomach, and drawing gastric fluid through the tube using a syringe

In 2021, WHO recommended the use of CAD tools with digital chest X-rays for TB screening among adults but did not include children in this recommendation due to a lack of data on diagnostic accuracy among children. Efforts are underway by FIND and Stop TB Partnership to compile a database of child X-rays to support development of CAD algorithms for children and to validate the accuracy of CAD for TB screening and diagnosis among children.

Several non-sputum diagnostics in the pipeline are also showing promise for improving pediatric TB diagnosis. These include Cepheid's Xpert MTB-HR fingerstick blood test and Beckman Coulter's TAM-TB blood test developed to detect progression from **TB infection** to active TB disease but with potential applicability as a non-sputum diagnostic **triage test** among children and people living with HIV (see Table 4).[15,16] Next-generation urine **lipoarabinomannan (LAM)** tests also show promise for use among children (see Table 2). Preliminary data on the diagnostic accuracy of the SILVAMP TB LAM next-generation LAM test among children (including children living with HIV and HIV negative children) shows sensitivity of 42–63 percent and specificity of 84–93 percent according to a **microbiological reference standard**, and sensitivity of 11–33 percent and specificity of 85–97 percent according to a **composite reference standard**.[17] Third-generation urine LAM tests in development (see Priority 2) offer the prospect of more sensitive urine-based testing among all children being evaluated for TB. Additionally, tongue swab and face mask **bioaerosol** samples for rapid molecular testing are being evaluated on existing molecular tests, such as GeneXpert and Truenat, and prioritized for the development of new molecular tests (see Priority 3), which is an encouraging area of research pointing to the possibility of moving beyond reliance on sputum to improve the ease of sampling and **diagnostic yield** of molecular diagnostics. Despite this notable progress, the paucibacillary nature of TB in children will remain a challenge until technologies with better accuracy among children are developed. While every effort to **bacteriologically confirm** TB in children should be made, **clinical diagnosis** based on signs and symptoms of TB[18] and assessed risk must still remain a necessary tool to link children to TB treatment and reduce child mortality from TB.[19] To aid clinicians, WHO recently launched a set of model **diagnostic algorithms** that incorporate clinical decision-making for pediatric TB diagnosis.[20]

Access Conditions on TB Diagnostics R&D Funding Agreements

A key consideration for the R&D of new TB screening and diagnostic tools is whether they will be sufficiently affordable and accessible for high-TB-burden low- and middle-income countries (LMICs) to scale up in accordance with WHO recommendations. Too often, public funding subsidizes and de-risks the development of new diagnostics only for private companies to commercialize diagnostic products at prices that are unaffordable. For example, the public invested more than $250 million in the R&D of Cepheid's GeneXpert technology, with additional

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

Triage test: a test used to prioritize care based on assessed need

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

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

Composite reference standard: 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 people living with HIV and children), and against which the accuracy of other tests may be compared

Bioaerosol: a form of sample collection whereby a person exhales biological material that is collected as a respiratory sample for diagnostic testing

Diagnostic yield: the likelihood of a test or combination of tests providing the information needed to establish a diagnosis

Bacteriological (or microbiological) confirmation: directly detecting the physical presence of TB bacteria in a sample

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

Diagnostic algorithm: a step-by-step method for making a diagnosis using a combination of screening and/or diagnostic tools and approaches for different populations and settings

significant investments in the roll out of GeneXpert technology in LMICs.[21] This substantial public investment in the R&D of GeneXpert technology stands in contrast to the ongoing lack of public sector ability to secure fair and equitable pricing and sufficient service and maintenance for GeneXpert tests and instruments. Including access considerations in public investment in the earliest stages of R&D is therefore an essential component of ensuring access once diagnostic technologies become available. Waiting until these technologies are available is too late.[22] Examples of access conditions for publicly funded technologies include transparency of **cost-of-goods-sold (COGS)** based on volumes; guaranteed fulfillment of orders from LMICs; price matching of comparable products that enter the market; and, where possible, terms for licensing and technology transfer that promote equitable access.[23] Investment in local production of diagnostics in LMICs is also needed to promote regional and local ownership and autonomy in regard to the R&D, manufacturing, and supply of diagnostics.[24]

Cost-of-goods-sold (COGS): the cost of manufacturing a product, which includes materials, labor, overhead, and intellectual property royalties

Priority 2: Point-of-care Urine LAM Tests

The first and only available rapid **point-of-care** TB diagnostic test is Abbott's Determine TB LAM Ag test, which is a simple, inexpensive **lateral flow** rapid TB test for people living with HIV that detects the TB **antigen** LAM in urine. Because many people living with HIV have difficulty producing sputum samples, urine LAM testing plays a critical role in the diagnosis of TB. Even though Determine TB LAM has been recommended by WHO for people living with HIV since 2015, reduces mortality among inpatients by 15 percent, increases the number of outpatients linked to TB treatment,[25] returns results in under 25 minutes, and costs just $3.70 per test, it is still not widely scaled-up and implemented in accordance with WHO recommendations in countries with high burdens of TB and HIV.[26]

Fujifilm has developed a next-generation point-of-care urine LAM test, SILVAMP TB LAM, which showed significantly improved sensitivity in early studies compared to Determine TB LAM among people living with HIV[27] and among HIV negative people[28] and returns results in about an hour (see Table 2). SILVAMP TB LAM uses a technology that binds silver particles to LAM antigens to amplify detection and make it easier to read the result. SILVAMP TB LAM is also a lateral flow **assay**, but it is comprised of more plastics and other materials. Even though Fujifilm shifted manufacturing from Japan to Vietnam to lower costs, SILVAMP TB LAM is still expected to enter the market at a higher price than Determine TB LAM. Further evaluation studies of SILVAMP TB LAM have unfortunately revealed significant variability in performance between production batches, making the test, in its current form, inappropriate for clinical management.[29,30]

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

Lateral flow test: 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

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

Assay: an investigative analytic procedure or test

Fujifilm is working to address the issue of variability by optimizing production for quality stabilization. Once optimization is complete, further clinical studies will take place to generate evidence for WHO review in late 2024 or early 2025.[31] These delays are unfortunate given the significant potential of the Fujifilm assay to offer improved diagnostic performance and outcomes among people living with HIV compared to Determine TB LAM.

Perhaps the largest gap in the available tools to diagnose TB is the lack of a rapid point-of-care TB test for all people being evaluated for TB (including HIV negative people). Several developers are working to fill this gap by developing more sensitive so-called third-generation urine LAM tests for all people being evaluated for TB, irrespective of HIV status or type of TB — **pulmonary TB** or **extrapulmonary TB (EPTB)**.[32,33] Among these companies are Abbott, Salus Discovery (supported by the Bill & Melinda Gates Foundation), Boditech, Biopromic, and SD Biosensor (see Table 2). To improve the diagnostic performance of these assays, companies are incorporating innovative approaches including urine concentration to increase the amount of LAM that is detectable in a given sample, as well as the use of various types of signal amplification including fluorescence and digital readers to improve the sensitivity and precision in interpreting the test results. Several third-generation LAM tests are advancing toward later stages of development, and clinical trials to evaluate the diagnostic performance of these assays are expected to take place in 2023 as part of the FIND-led DriveDx4TB project, funded by Unitaid.[34,35] Once available, and if the promise of increased sensitivity holds true, these tests are likely to change the game for TB diagnosis by becoming the first ever rapid point-of-care TB tests for all people, irrespective of HIV status, while also offering potential options for TB self-testing (see TB Self-testing: Considerations for Future Research).

Pulmonary TB: TB in the lungs

Extrapulmonary TB (EPTB): TB in parts of the body outside the lungs

Integrated Multi-disease Molecular Diagnostic Testing

Molecular diagnostic technology enables the use of the same diagnostic instruments to detect a range of infectious diseases and conditions, including TB, HIV, viral hepatitis (HBV, HCV), COVID-19, human papillomavirus (HPV), and other sexually transmitted infections (STIs) including chlamydia and gonorrhea. This inherent multi-disease capacity of molecular diagnostics (see Priority 3) opens up the possibility of integrated approaches to testing for multiple diseases and co-infections at the same time, even during a single healthcare visit using point-of-care molecular testing instruments. Such integration could improve efficiency of testing and maximize use of existing diagnostic infrastructure by country programs while easing the burden on people seeking care by reducing the number of health care visits required to receive comprehensive diagnosis and linkage to treatment. This integration of testing should take place at all levels of the health

system, including rapid molecular testing at the point of care as well as centralized **high-throughput** molecular testing. The multi-disease capacity of molecular diagnostics also opens up opportunities for pooling procurement of tests across diseases and leveraging overall volumes in negotiations with diagnostic companies. In June 2022, Treatment Action Group (TAG) and Médecins Sans Frontières (MSF) Access Campaign organized a Roundtable on Access to Multi-disease Molecular Diagnostics to build consensus regarding how to increase access to multi-disease molecular diagnostics, including by promoting competition; ensuring sufficient service and maintenance; advancing innovative models for procurement; and establishing the conditions for transparent, fair, and equitable pricing.[36] The key Roundtable output is a set of ten shared Principles for Access to Multi-disease Molecular Diagnostics, which should now be operationalized by country programs, donors, and other global health actors.[37]

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

Priority 3: Non-sputum Point-of-care Molecular Tests for TB and DR-TB

Since 2013, WHO recommended rapid molecular tests as the initial TB diagnostic test to replace **smear microscopy**, which relies on sputum and is only about 50 percent sensitive for detecting TB and cannot test for drug resistance.[38] Despite this WHO recommendation and the low sensitivity of smear microscopy, nearly a decade later many TB programs continue to rely on smear microscopy as the initial TB diagnostic test. In 2021, approximately two-thirds of people were diagnosed with TB using smear microscopy.[39] There are several reasons for the slow scale-up of rapid molecular TB tests by country programs. Currently available rapid molecular TB tests are expensive — Cepheid's Xpert MTB/RIF Ultra costs $10 per test and $19,000 per 4-module instrument, while Molbio's Truenat costs $9 per test and $18,000 per 4-module instrument.[40] Due to infrastructure requirements such as electricity, air-conditioned temperatures, and dust-controlled environments, GeneXpert instruments are generally placed at the district level, which is only **near-point-of-care**, therefore requiring systems for transporting samples from peripheral health centers to district labs for testing. Truenat testing, which was recommended by WHO in 2020, is suitable for peripheral levels but includes a manual step of pipetting the sample from one instrument to another, so is not fully automated, requires more hands-on time, and introduces more risk of error or contamination. Service and maintenance of GeneXpert instruments has also proven expensive and insufficient, often leading to instrument downtime. Due to Cepheid's decade-long monopoly on rapid molecular testing for TB, competitive pressure needed to drive down prices

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

Near-point-of-care: testing that requires the transportation of samples from the point of care to a more centrally located laboratory for testing

and improve provision of service and maintenance has been lacking. While Molbio's Truenat is currently being rolled out globally with support from USAID and Stop TB Partnership through the introducing New Tools Project (iNTP),[41,42] more competitors are needed in the market to realize the benefits of competition on pricing and service.

There are two key considerations for the development of new molecular diagnostics. One is the need to place diagnostic instruments in primary care settings where the majority of people seek care for TB. When molecular diagnostic instruments are placed in more central locations such as district laboratories, systems are required to transport samples from the point of care to the laboratories for testing. Such hub-and-spoke models can be highly inefficient in rural areas and can lead to diagnostic delays of more than two weeks and high rates of **loss to follow-up**.[43] It is therefore critical to strengthen sample transport systems while at the same time scaling up access to testing at the point of care. The XPEL-TB trial, a study of the impact of point-of-care molecular testing at peripheral health centers in Uganda, found that point-of-care molecular testing combined with implementation improvements led to a 56 percent increase in the number of people diagnosed with TB and linked to treatment within two weeks compared to the standard of care using a hub-and-spoke model to transport samples to district labs for testing.[44] While this is just one study, it points to the value and potential of point-of-care molecular testing combined with implementation improvements to help close the TB diagnostic gap. More studies that investigate the impact of bringing TB screening and diagnostic testing into communities and to the point of care are needed.[45]

The second consideration for the development of new molecular diagnostics is ensuring that all people will be able to produce a sample for testing. Most TB diagnostics have been developed and evaluated using sputum samples, but given that not all people — particularly children and people living with HIV — can easily produce sputum, a new approach is needed. Fortunately, researchers and diagnostic developers are learning from COVID-19 methods of swab-based sampling and are evaluating existing molecular diagnostics and developing new molecular diagnostics using tongue swabs. When tested using Xpert MTB/RIF Ultra, tongue swabs exhibit less sensitivity (SE: 77.8%)[46] compared to sputum (SE: 90%),[47] though this may be partially due to the fact that Xpert MTB/RIF Ultra was developed and optimized for use with sputum. It will therefore be important for new diagnostics to be developed and optimized for use with tongue swabs. Even if the sensitivity of tongue swab samples proves to be slightly lower compared to sputum, the overall diagnostic yield is expected to be significantly higher, given that all people in need of testing will be able to easily produce a sample. In addition to tongue swabs, face mask sampling for use on rapid molecular tests also shows significant promise for improving the ease of sampling and even offering the prospect of self-sampling at home (see TB Self-testing: Considerations for Future Research).

Loss to follow-up: when the health system loses contact with people who have TB for a variety of reasons, but largely due to delays in returning results from diagnostic testing

Fortunately, a tongue swab-based true-point-of-care molecular test for TB is in the pipeline, but at an early stage of development. LumiraDx is developing a TB assay using tongue swab samples for use on their ultraportable, battery-operated platform, which is designed to be placed in primary care settings and may also be implemented at the community level. This one-module instrument turns around results in less than 20 minutes. The LumiraDx instrument and TB test are expected to enter the market at a fraction of the price of GeneXpert and other near-point-of-care instruments (see Table 3). While this true-point-of-care molecular test is still in the early stages of development, it represents a new class of TB diagnostics that offer the prospect of fully replacing smear microscopy as the initial TB test and realizing the diagnostic benefits demonstrated by the XPEL-TB trial. However, the LumiraDx test is expected to only test for TB and not for resistance to rifampicin so will require rapid referral for follow-on drug-susceptibility testing.

SD Biosensor is working on an MDR-TB assay for detection of TB and resistance to **first-line drugs** rifampicin and isoniazid on their STANDARD M10 platform, which is similar to GeneXpert in regard to infrastructure requirements so is expected to be similarly placed at the district lab level. STANDARD M10 instruments are modular and can be configured with up to eight instrument modules connected to one digital interface. SD Biosensor is currently evaluating the MDR-TB assay on sputum and will hopefully also incorporate tongue swabs and stool into their evaluations to ensure that sufficient evidence is generated on the diagnostic accuracy of the test for non-sputum samples more appropriate for children, people living with HIV, and people with EPTB. Additionally, Bioneer is working on a Q-RFIA assay to detect TB and resistance to first-line drugs rifampicin and isoniazid for MDR-TB and to **second-line drugs** fluoroquinolones (moxifloxacin and levofloxacin) and aminoglycosides (injectable amikacin). This all-in-one TB detection and drug resistance assay will have a clear advantage over Xpert MTB-XDR (recommended by WHO in 2021), which does not test for resistance to rifampicin and requires prior testing with Xpert MTB/RIF Ultra. Bioneer's Q-RIFA assay will be run on the 2-module IRON-qPCR instrument that is battery operated but will likely also be placed at the district lab level due to its requirement of air-conditioned temperatures. Both the SD Biosensor and Bioneer assays represent positive steps forward, but they do not yet meet the updated WHO Target Product Profile (TPP) on **drug-susceptibility testing (DST)** in peripheral health centers, which states the optimal initial TB test should detect TB and resistance to rifampicin, isoniazid, fluroquinolones, and bedaquiline.[48] DST for resistance to bedaquiline is critically needed given its importance across regimens for DR-TB and increasing concerns regarding emerging resistance,[49] but rapid molecular tests are not yet capable of testing for resistance to bedaquiline due to insufficient knowledge of the specific genetic **mutations** associated with bedaquiline resistance. Rapid molecular tests can, however, test for resistance to fluoroquinolones, which is becoming increasingly important as efforts to scale up the new 4-month **Study 31** treatment regimen for drug-sensitive TB continue.[50]

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

Second-line drugs: drugs that are used to treat TB that is resistant to first-line TB drugs (e.g., the fluoroquinolones, bedaquiline, and linezolid)

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

Mutations: distinct changes to the TB genome that may be associated with resistance to certain TB drugs

Study 31: A randomized, controlled trial that demonstrated the efficacy of a 4-month, short-course rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of drug-sensitive TB

In addition to rapid molecular tests for TB, another more centralized molecular test for drug resistance is nearing the end of the pipeline. WHO is expected to review evidence on the diagnostic accuracy and use of **targeted next-generation sequencing (tNGS)** assays for comprehensive DST for TB in early 2023 and to issue policy recommendations on their use in late 2023. tNGS assays are "targeted" because they map specific sections of the TB **genome** with known mutations associated with drug resistance rather than mapping the entire genome, making efficient use of the **sequencing instruments**. The results from a single tNGS test will provide an accurate and comprehensive profile of TB drug resistance (with some assays testing for resistance to up to 15 drugs, see Table 3) to inform optimal treatment regimens for different forms of drug resistant TB, including MDR-TB, **extensively drug-resistant TB (XDR-TB)**, and **pre-XDR-TB**. tNGS assays are also relatively fast, with a turnaround time to results of one to two days, compared to liquid culture, which takes two to six weeks. tNGS assays can be run directly on clinical samples (sputum, stool, etc.) and do not require the use of **culture isolates** for testing. The introduction of tNGS DST into country program TB diagnostic networks will establish new capacity for rapid DST that has the potential to improve treatment outcomes and reduce morbidity and mortality from DR-TB.

Under the Unitaid-funded Seq&Treat grant, FIND is generating evidence on the performance of tNGS assays for TB in the form of **end-to-end solutions**, from sample prep, library prep, and sequencing to reporting. Among the manufacturers developing tNGS assays for TB are Genoscreen, ABL, and Oxford Nanopore. All of these assays are paired with **informatics software** to interpret the results of the test and assist clinicians to identify the optimal treatment regimen. This software is user friendly and can be easily updated with new drug resistance targets as these are identified and added to the WHO catalog of mutations associated with drug resistance.[51] tNGS assays are expected to be initially placed in central labs, with the future possibility of further decentralization closer to the point of care.

TB Self-testing: Considerations for Future Research

The global response to the COVID-19 pandemic brought about a number of diagnostic innovations. Most notable among these is the large-scale deployment of **rapid antigen tests**, which were made available — primarily in higher-income countries — for self-testing at home.[52] This simple innovation of empowering people to test themselves for COVID-19 to better protect their families and communities not only helped slow the spread of the pandemic but increased the agency of individuals to take an active role in the public health response. While COVID-19 is a very different disease from TB, the experience of using simple, inexpensive lateral flow tests for COVID-19 and receiving rapid results at home raises the question: Why can't we do this for TB?

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

Genome: all genetic information of an organism

Sequencing instruments: complex instruments capable of mapping the genome (or a targeted portion of the genome) from available genetic material in a sample with a high level of accuracy

Extensively drug-resistant TB (XDR-TB): TB that exhibits resistance to both rifampicin and isoniazid, the fluoroquinolones, and other group A drugs (e.g., bedaquiline or linezolid)

Pre-XDR-TB: TB that is resistant to both rifampicin and isoniazid, and the fluoroquinolones

Culture isolate: a sample type developed using mycobacterial culture to grow and isolate TB bacteria from other bacteria and microbes in a sample

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

Informatics software: a type of software developed to help clinicians manage and interpret the large amount of information resulting from tNGS testing

Rapid antigen tests: simple, inexpensive tests that detect molecules or components of a pathogen (such as a virus or bacteria) in a sample and rapidly return results

There are a number of considerations in answering this question, the most important of which is ensuring linkage to further diagnostic evaluation and care for people who test positive for TB. It's important to recognize, however, that it's in the inherent self and community interest for people who test positive to seek care. Perhaps mobile phone-based digital tools can also be deployed to assist people with the self-testing process and to provide them with information and resources for seeking care following a positive result. In actuality, this is not a distant possibility — it's already the reality for tools such as mobile phone cough apps that monitor cough and its frequency and severity over time as an objective biomarker for respiratory disease (see Priority 4). As urine LAM tests become increasingly accurate and affordable, as new sample types including tongue swabs and bioaerosol capture like blow tubes or face masks combined with point-of-care rapid molecular tests are further developed, and as **CRISPR-based TB tests** are developed, the prospect of self-sampling and even self-testing for TB comes ever closer. It's important to move beyond traditional paradigms for TB testing and recognize the potential for TB self-sampling and self-testing to empower individuals to better protect themselves, their families, and their communities from TB and to have greater agency to be part of the public health response to end TB**.**

Priority 4: TB Screening and Triage Tools

In addition to confirmatory TB diagnostics, there is a critical need for better technologies and improved efforts to screen and triage for TB, especially for **subclinical TB**, prior to the onset of symptoms. Once a person with TB develops symptoms, this is a sign that they already have some damage to their lungs or other tissues, and TB transmission has already likely occurred.[53] In 2021, WHO issued new guidance on **systematic screening** for TB, recommending new tools including AI-based CAD tools to assist clinicians to accurately interpret digital chest X-rays and rapid molecular tests and C-reactive protein (CRP) to screen for TB among people living with HIV. All of these tools are more sensitive and specific for TB compared to the WHO four-symptom screen (cough, fever, weight loss, night sweats) and are better able to detect subclinical TB.

Following the release of WHO recommendations on TB screening, a number of CAD tools entered the market and several CAD tools and ultraportable chest X-ray devices have been added to the Global Drug Facility (GDF) diagnostics catalog.[54] Deploying CAD and ultraportable X-ray devices in systematic screening efforts among high-risk populations and in high-prevalence community settings

Subclinical TB: active TB disease before the onset of TB symptoms

Systematic screening: engaging in systematic efforts to screen for TB among people at high risk of TB and in communities with high prevalence of TB to identify who should receive further diagnostic evaluation and confirmatory TB diagnostic testing

offers the prospect of identifying more people with subclinical TB, rapidly linking them to treatment, and helping to prevent onward TB transmission. Detailed information on currently available CAD tools can be found on the Stop TB Partnership and FIND-supported website ai4hlth.org, and more information on the use of CAD tools in combination with ultraportable digital X-ray devices is available in the FIND landscape analysis.[55] WHO also recommended the use of CRP, a non-specific test for inflammation that uses fingerstick blood samples, to screen for TB among people living with HIV. Because CRP tests turn around results in less than five minutes, they can be easily implemented as a triage test at the point of care to inform clinical decision-making regarding the need for further diagnostic evaluation for TB or initiation of **TB preventive treatment (TPT)**. According to initial data, CRP out-performs symptom screening, but only among people living with HIV who have not yet initiated anti-retroviral treatment (ART).[56] More data will be needed to assess the diagnostic performance of CRP among all people being evaluated for TB, including HIV negative people. Several companies including LumiraDx and Boditech developed CRP assays that are currently being evaluated for TB. The LumiraDx CRP test is expected to be priced at $2 per test and to be run using the point-of-care LumiraDx instrument, which is also capable of running confirmatory molecular diagnostic tests for TB (see Priority 3).

Several new AI-based tools are in development that detect and monitor cough and lung sounds — so-called acoustic epidemiology — with potential applications for TB screening, diagnosis, and treatment monitoring. Cough can often be challenging to qualitatively describe, let alone quantify, but new AI-based cough apps offer a potential solution by making cough a more objectively quantifiable biomarker for TB.[57] Cough apps by Hyfe, Docturnal, ResApp Health, and Salcit Technologies all offer potential solutions (see Table 1), with some apps exhibiting sensitivity for TB greater than 90 percent and specificity greater than 70 percent in early studies, meeting the WHO TPP requirements for a community-based TB triage test.[58,59] All of these cough apps are available for download on mobile phones and depend on user data to train the AI algorithms and improve the accuracy of apps, so the more these apps are used in particular settings and among particular populations, the more accurate they will become. Longitudinal monitoring is one application, whereby the cough app is constantly "listening" for cough sounds to monitor the frequency and severity of cough over time; however, this introduces significant privacy concerns that the app manufacturers are working to address. Another application is for cough apps to be used as triage tools to classify cough sounds according to disease, such as differentiating whether a cough is likely to be caused by TB or COVID-19. Since cough also reduces during effective TB treatment, cough apps may also be used as an additional tool for monitoring the effectiveness of TB treatment. Other tools in development for TB treatment monitoring to replace **mycobacterial culture** are rapid tests for TB **bacillary load** such as the Molecular Bacterial Load Assay (TB-MBLA) as well as **host-response tests** such as Xpert MTB-HR (see Table 4). In addition to being valuable new technology for TB screening and triage, cough

TB preventive treatment (TPT): a course of treatment that can prevent the development of active TB disease among people with TB infection

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

Bacillary (or bacterial) load: the quantity of TB bacteria in the body or in a sample

Host response tests: tests that detect and quantify specific expressions or changes in the body in response to the presence of TB bacteria, that can predict progression from TB infection to active TB, and that can be used to monitor the effectiveness of TB treatment

apps are also innovating in the field of self-testing and self-monitoring for TB — a potential that has yet to be fully explored and evaluated (see TB Self-testing: Considerations for Future Research).

In addition to cough apps, AI-powered digital stethoscopes are being developed with applications for TB. Companies such as Level 42 AI and M3DICINE are developing digital stethoscopes capable of detecting audible and inaudible lung sounds to identify vibracoustic biosignatures indicative of TB and other respiratory diseases such as COVID-19. Digital stethoscopes are intended to be deployed for TB screening and triage in outpatient primary care settings. While the hardware for these technologies is design-locked, their application for TB is still in an early stage of evaluation. The one limitation of cough apps and digital stethoscopes, however, is that because the tools are designed to detect respiratory symptoms such as cough, they are not useful for detecting subclinical TB or EPTB.

Host response tests in the pipeline, on the other hand, are developed specifically for early detection of subclinical TB and predicting progression from TB infection to active TB disease **(incipient TB),** with additional application for TB treatment monitoring. Host response tests detect and quantify expresions and changes in host **biomarkers** in response to the presence of TB bacteria. These biomarkers include changes in the expression of certain **RNA** genes or in the immune response to TB. Because these expressions or changes in biomarkers are also quantifiable, they can be used to monitor the effectiveness of TB treatment. The host response tests in development by Cepheid, QuantuMDx, and Beckman Coulter all show significant promise (see Table 4) but do not yet meet the optimal TPP performance criteria for diagnostic tests or tests for predicting progression from TB infection to active disease. Cepheid's Xpert MTB-HR test has sufficient diagnostic performance to be used as a triage test;[60] meanwhile, the RISK6 **gene signature** test (currently in early development by QuantuMDx) is capable of predicting progression from TB infection to active disease within one year but not yet within the TPP target of two years (although, predicting progression within one year is still useful and better than no predictive ability).[61] All of these tests require **nucleic acid amplification** or other laboratory instruments so are not expected to be implemented at the point of care, with the exception of the QuantuMDx test, which is expected to be developed for use on the ultraportable, battery powered Q-POC instrument. Beckman Coulter's TAM-TB assay, which detects changes in a host's immune response to TB, exhibits similar diagnostic performance as Xpert MTB-HR.[62] The notable additional advantage of all of these tests is that they use blood as a sample, so there is significant potential to deploy them as non-sputum triage tests among children, people living with HIV, and people with EPTB. It is therefore critical that these populations are included in clinical trials to ensure evidence necessary for policy recommendations is generated. Because all of these tests require expensive instruments to be run, they are unlikely to enter the market at the low prices required for widespread implementation as TB screening tools and are more likely be used as non-sputum TB triage tests in health facilities.

Incipient TB: a stage of TB during which TB infection progresses toward active TB disease

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

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

Gene signature: a single gene or combined group of genes that form a distinct expression in response to a particular pathogen and may be used as a biomarker for detecting the presence of that pathogen

Nucleic acid amplification: a chemical process whereby specific target sequences of the genome in a sample undergo rapid replication resulting in millions of copies, increasing the likelihood that the target sequences will be detectable by a molecular test

Community Engagement in TB Diagnostics R&D and Roll-out

Community engagement in TB diagnostics R&D and roll-out is not only the ethical and right thing to do, it is also the useful thing to do. In 1983, a group of activists living with HIV launched the Denver Principles, demanding that people living with HIV are "involved at every level of decision-making" and "included in all AIDS forums with equal credibility as other participants, to share their own experiences and knowledge."[63] The active involvement and inclusion of people living with HIV has been instrumental for the R&D of new tools for HIV treatment and prevention and how these tools are rolled out and provided in communities. Engaging communities affected by TB at the earliest stages of R&D[64] and funding civil society organizations in high burden countries to build diagnostic literacy and generate demand among communities[65] for the roll-out of new TB diagnostic tools is still an underutilized approach. This points to both the historic lack of sufficient community engagement as well as opportunities for strengthening community engagement and improving TB diagnostics R&D and roll-out in the future.[66] Community engagement helps to ensure that new TB screening and diagnostic tools are designed to meet the needs of communities affected by TB, evaluated among the right populations and with the most appropriate sample types to generate evidence for policy recommendations, and rapidly scaled up by countries in response to community demand.

Priority 5: Algorithms for TB Screening and Diagnostic Testing

There is currently no single tool that can be used to accurately diagnose all forms of TB among all affected populations in all settings. We must therefore utilize a combination of tools with different strengths that may be applied to different use cases and settings so that, when combined, these tools lead to efficient and accurate diagnosis and rapid linkage to treatment. A range of TB screening and diagnostic tools are currently available and recommended by WHO, which has issued a set of model TB screening and diagnostic algorithms for the use of these tools that may be adapted and implemented by country programs.[67,68] Many of these tools have been evaluated individually, with studies focusing primarily on the diagnostic accuracy of individual tools. More research is therefore needed to evaluate the diagnostic accuracy and diagnostic yield of combinations of tools and algorithms optimized for different settings and populations (e.g., algorithms for diagnostic testing and clinical diagnosis among children, see Priority 1). For example, TB screening and diagnostic testing will necessarily look different in a large urban center compared to a rural resource-limited area,

with different combinations of tools and different TB screening and diagnostic algorithms. Fortunately, under the Unitaid-funded START 4-ALL project, the London School of Tropical Medicine (LSTM) will be advancing research on TB screening and diagnostic algorithms and combinations of tools with the aim of generating evidence to support the expansion of TB screening and diagnostic testing in community and primary care settings.[69]

Additionally, it is important for researchers and policymakers to move beyond the singular focus on diagnostic accuracy as the sole measure of the diagnostic value of a test. A good example of how this singular focus has undermined the roll-out of a valuable diagnostic tool is that of Determine TB LAM. Since it was first recommended by WHO in 2015, the low sensitivity of Determine TB LAM among all people living with HIV has been perceived as limiting the utility and even the quality of the test, despite its sufficient sensitivity and proven mortality benefit among people with advanced HIV disease or AIDS — those who are most at risk of dying from TB. This false perception undermined the real value of the test when used in combination with accurate rapid molecular tests. TB LAM is simple to implement, uses urine samples that people living with HIV can easily produce, and returns results in under 25 minutes enabling rapid linkage to TB treatment. When Determine TB LAM is used in combination with accurate rapid molecular tests for diagnosing TB, the overall diagnostic yield is significantly increased and lives are saved.[70] In addition to research looking at how tests can be optimally combined with other tests to improve diagnostic outcomes, we must engage in more operational research to also investigate how TB screening and diagnostic tools can be better implemented to deliver improved person-centered care, including home-based testing (see TB Self-testing: Considerations for Future Research).[71]

The costs of using combinations of tools must also be considered to cost out different algorithms and determine feasibility for different settings. For example, it is important for researchers to investigate specific questions such as: What is the diagnostic yield, accuracy, and cost-effectiveness of deploying CAD and ultraportable chest X-ray devices in community-based systematic screening efforts combined with tongue swab sampling and molecular testing using point-of-care versus high-throughput instruments? Answers to such specific questions will yield valuable evidence to inform the optimal deployment of combinations of tools for different use cases and in different settings and guide efficient and effective roll-out and implementation by country programs. As new tools continue to become available, such as the anticipated introduction of tNGS assays in 2023 and third-generation urine LAM assays in 2024, the evaluation of optimal combinations of tools and algorithms will continue to be a high priority, because algorithms and approaches must continually be updated.

Conclusion

The top five TB diagnostic research priorities detailed in this Pipeline Report are all being advanced by a range of stakeholders, but more must be done. TB diagnosis remains the weakest link in the TB cascade of care, and closing the TB diagnostic gap is a prerequisite for linking people who have TB with effective treatment and care and reducing morbidity and mortality from TB. Therefore, investments in TB diagnostics R&D must be increased, and affordable and equitable access to new TB screening and diagnostic tools must be prioritized and ensured from the earliest stages of R&D. TB-affected communities should be engaged throughout all stages of TB diagnostics R&D and roll-out — not as an afterthought or a checkbox but as valued partners providing meaningful input to improve the resulting products, evidence, and demand for new tools. The United Nations High-Level Meeting on Tuberculosis in 2023 presents a new opportunity to garner more ambitious funding, targets, and political commitments to end TB. We are at a unique moment to accelerate innovation, improve our approaches, and deliver better, more affordable, and equitably accessible tools to progressively realize and fulfill the right of all people at risk of TB to quality TB screening and diagnostic testing.

Annex 1: TB Diagnostics Pipeline, 2022

Table 1: Tests for TB Screening and Triage

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Hyfe App	**Hyfe** (USA)	**Cough app:** Longitudinal cough monitoring for TB screening, treatment monitoring	**Cough sounds:** Not yet available	**Home/ Community**	Real-time results (passive collection over time)	Free for users in low- and middle-income countries[72]	Commercially available Pending validation[73]
TimBre	**Docturnal** (India)	**Cough app:** Bidirectional screening for TB and COVID-19,[74] TB triage, treatment monitoring	**Cough sounds (high-fidelity lossless WAV file):** SE: 85.0% SP: 82.0% AUC: 0.92[75]	**Community/ Primary care setting** (Online or offline use with external server)	< 15 minutes	Price per test: $1.20 (including license and consumables: surgical mask and device filter)	Commercially available Pending validation[76]
ResApp	**ResApp Health** (Australia)	**Cough app:** TB screening, triage	**Cough sounds:** Not yet available	**Home/ Community/ Primary care setting**	Not yet available	Not yet available	Commercially available Pending validation[77]
Swaasa	**Salcit Technologies** (India)	**Cough app:** TB screening, triage	**Cough sounds (10 second recording of solicited cough):** SE: 90.36% SP: 84.67%[78]	**Community/ Primary care setting**	≤ 15 seconds	Price per test: < $1	Commercially available Pending validation[79]
Stethee Pro	**M3DICINE** (Australia)	**Digital stethoscope:** TB screening, triage	**Lung/cough sounds:** Not yet available	**Community/ Primary care setting**	Not yet available	Price per test: Not yet available Hardware price: $499	Commercially available Pending validation[80]
imPulse Una	**Level 42 AI** (USA)	**Digital stethoscope:** TB screening, triage	**Vibracoustic TB biosignatures:** AUC: 0.80[81]	**Community/ Primary care setting**	< 4 minutes	Price per test: Not yet available Hardware COGS: $75–$100	Commercially available Pending validation[82]

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Reveal 35C	**KA Imaging** (Canada)	**Detector screen to enhance chest X-ray resolution (using dual-energy technology):** TB screening	**Chest X-ray:** Higher sensitivity compared to conventional X-ray imaging	**Primary care setting** (Portable, battery-powered detector screen)	Immediate imaging from chest X-ray	Hardware price: $125,000	Commercially available Pending validation[83]
ichroma CRP (ichroma immuno-analyzer)	**Boditech** (Korea)	**C-reactive protein:** TB screening	**Blood:** Not yet available	**Primary care setting**	Not yet available	Not yet available	Commercially available Pending validation[84]
LumiraDx CRP (LumiraDx)	**LumiraDx** (UK)	**C-reactive protein:** TB screening among all people at risk of TB	**Blood:** Correlation of 0.94 between LumiraDx point-of-care CRP and laboratory-based methods[85]	**Community/ Primary care setting** (Portable and battery-operated; current install base of 5,000 instruments in African region)	< 5 minutes	Price per test: $2 LumiraDx instrument price (inclusive of 2-year warranty): $3,300	Commercially available Evaluation ongoing for TB screening among PLHIV and HIV-negative people[86]
SeroSelectTB	**SeroSelectTB Consortium**	**Lateral flow:** TB triage	**Blood, saliva:** Not yet available	**Primary care setting**	Not yet available	Not yet available	Early-stage development[87]

Performance (sensitivity, specificity, AUC) listed according to a microbiological reference standard

*** All prices listed in United States Dollars (USD)*

Abbreviations:

SE: sensitivity   **SP:** specificity   **CRP:** C-reactive protein   **COGS:** cost-of-goods-sold   **AUC:** area under the receiver operating characteristic (ROC) curve

Table 2: Urine-LAM Tests for TB Diagnosis

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
SILVAMP TB LAM	Fujifilm (Japan)	Lateral flow: Diagnosis for PLHIV (Evaluation among HIV-negative people and children ongoing for expanded indication)	Urine: PLHIV SE: 70.7% SP: 90.9%[88] HIV-negative SE: 53.2% SP: 98.9%[89] Children (irrespective of HIV status) SE: 60.0% SP: 95.0%[90]	Community/ Primary care setting	1 hour	Estimated price per test: $6[91]	Late-stage development (Optimization of production for quality stabilization is ongoing) **Projected ERPD review:** late 2023/early 2024 **Projected WHO review:** late 2024/early 2025[92]
Flow-TB	Salus Discovery (USA)	Lateral flow, urine concentration: Diagnosis for all people being evaluated for TB	Urine: Target sensitivity (irrespective of HIV status): 90.0–95.0%[93]	Community/ Primary care setting	1.5 hours[94] (including urine concentration)	Not yet available	Early-stage development
High-sensitivity TB LAM	Abbott (USA)	Lateral flow: Diagnosis for all people being evaluated for TB	Urine: Not yet available	Community/ Primary care setting	< 45 minutes	Not yet available	Early-stage development **Projected ERPD and WHO review:** 2025[95]
Third-generation LAM	Boditech (Korea)	Lateral flow: Diagnosis for all people being evaluated for TB	Urine: Not yet available	Community/ Primary care setting	Not yet available	Not yet available	Early-stage development[96]
Third-generation LAM	Biopromic (Sweden)	Lateral flow: Diagnosis for all people being evaluated for TB	Urine: Not yet available	Community/ Primary care setting	Not yet available	Not yet available	Early-stage development[97]

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Third-generation LAM	**SD Biosensor** (Korea)	**Lateral flow, digital reader:** Diagnosis for all people being evaluated for TB	**Urine:** PLHIV target sensitivity: >90% HIV-negative target sensitivity: >65% Target specificity: >95%[98]	**Community/ Primary care setting**	15–30 minutes	Not yet available	Early-stage development **Projected ERPD and WHO review:** late 2023–2024[99]

Performance (sensitivity, specificity) listed according to a microbiological reference standard

** *All prices listed in United States Dollars (USD)*

Abbreviations:

SE: sensitivity   **SP:** specificity   **PLHIV:** people living with HIV   **ERPD:** Global Fund Expert Review Panel for Diagnostics

Table 3: Molecular Tests for TB and DR-TB Diagnosis

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Truenat Ultima (Trueprep/Truelab)	**Molbio** (India)	**Rapid molecular:** Diagnosis	**Tongue swab:** SE: 90.9% SP: 100%[100]	**Peripheral lab**	1 hour	Not yet available	Late-stage development[101]
Truenat MTB-INH (Trueprep/Truelab)	**Molbio** (India)	**Rapid molecular:** DST (INH) Follow-on drug-resistance test	**Sputum:** Not yet available	**Peripheral lab**	1 hour	Not yet available	Early-stage development[102]
Truenat MTB-FQ Trueprep/Truelab)	**Molbio** (India)	**Rapid molecular:** DST (FQ) Follow-on drug-resistance test	**Sputum:** Not yet available	**Peripheral lab**	1 hour	Not yet available	Early-stage development[103]
Truenat MTB-BDQ (Trueprep/Truelab)	**Molbio** (India)	**Rapid molecular:** DST (BDQ) Follow-on drug-resistance test	**Sputum:** Not yet available	**Peripheral lab**	1 hour	Not yet available	Early-stage development[104]
Avelo Breath Test	**Avelo** (Switzerland)	**Sample collection:** Diagnosis/DST using existing molecular tests	**Bioaerosol (blow tube):** Not yet available	**Community/ Primary care setting**	≤ 10 minutes (target: ≤ 5 minutes)	Not yet available	Early-stage development[105]
Mask-based Bioaerosol Test	**FIND/42T/ University of Leicester** (Switzerland/UK)	**Sample collection:** Diagnosis/DST using existing molecular tests	**Bioaerosol (face mask):** Not yet available	**Home/ Community/ Primary care setting**	Sampling time: 30 minutes	Not yet available	Late-stage development[106]
LumiraDx TB assay (LumiraDx)	**LumiraDx** (UK)	**Rapid molecular:** Diagnosis/DST using existing molecular tests	**Tongue swab:** Not yet available	**Community/ Primary care setting** (Portable and battery-operated; current install base of 5,000 instruments in African region)	< 20 minutes[107]	Price per test: Not yet available LumiraDx instrument price (inclusive of 2-year warranty): $3,300	Early-stage development[108]

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
RFIA Kit (IRON qPCR)	**Bioneer** (Korea)	**Rapid molecular:** Diagnosis/DST (RIF, FQ, INH, AMK) May be used as initial test for TB and drug resistance IRON qPCR capable of testing for up to 40 molecular targets in a single test	**Sputum:** Not yet available	**Peripheral lab/ District lab** (Battery-operated)	40–50 minutes	Not yet available	Late-stage development Evaluation ongoing[109]
STANDARD M10 MDR-TB (STANDARD M10)	**SD Biosensor** (Korea)	**Rapid molecular:** Diagnosis/DST (RIF, INH) May be used as initial test for TB and drug resistance	**Sputum:** Not yet available	**Peripheral lab/ District lab**	1.25 hours	Not yet available	Late-stage development Projected commercial availability: 2023[110]
NanoDetect-TB (Liquid chromate-graphy mass spectrometer [LC-MS])	**Nanopin** (USA)	**Antigen-based (CFP-10 and ESAT-6):** Diagnosis	**Blood:** Children SE: 85.0% SP: 100%[111]	**District lab**	3–4 hours	Not yet available	Early-stage development[112]
Actiphage (PCR analyzer)	**PBD Biotech** (UK)	**Phage-based:** Diagnosis	**Blood:** SE: 73.3% SP: 100%[113]	**District lab/ Central lab**	3–3.5 hours	Projected price per test: $35	Early-stage development[114]
Genoscholar FQ+KM-TB II (MULTIBLOT NS-4800)	**Nipro** (Japan)	**Line probe assay:** DST (FQ, KAN)	**Sputum, culture isolate:** FQ SE: 93.0% SP: 100%[115]	**Central lab**	6 hours	Price per test: $30	Evaluation ongoing[116]

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Deeplex Myc-TB (PCR analyzer, sequencer, informatics software)	GenoScreen (France)	**tNGS assay:** DST (15 first- and second-line TB drugs including: RIF, INH, PZA, EMB, FQ, AMK, KAN, CAP, STM, ETH, BDQ, CLO, LZD)	**Sputum, culture isolate, stool:** Culture isolate: SE: 95.3% SP: 97.4%[117] Sputum, stool: High concordance with mycobacterial culture DST[118,119]	**District lab/ Central lab**	1–2 days	Price per test: $50	Design-locked **Projected ERPD and WHO review:** 2023[120]
BacterioChek-TB (PCR analyzer, sequencer, informatics software)	ABL (Luxembourg)	**tNGS assay:** DST (12 first- and second-line TB drugs including: RIF, INH, PZA, EMB, FQ, AMK, KAN, CAP, STM, ETH, BDQ, CLO)	**Sputum, culture isolate:** Not yet available	**District lab/ Central lab**	1–2 days	Not yet available	Late-stage development[121]
TB assay (PCR analyzer, sequencer, informatics software)	Oxford Nanopore Technologies (UK)	**tNGS assay:** DST (first- and second-line TB drugs)	**Sputum, culture isolate:** Not yet available	**District lab**	1–2 days	Not yet available	Early-stage development[122,123] **Projected ERPD and WHO review:** 2023
Tuberculini CLX101 (PCR analyzer, sequencer, informatics software)	Clemedi (Switzerland)	**tNGS assay:** DST (12 first- and second-line TB drugs)	**Sputum, culture isolate:** Not yet available	**District lab/ Central lab**	1–2 days	Not yet available	Late-stage development Evaluation ongoing[124]

Performance (sensitivity, specificity) listed according to a microbiological reference standard

** *All prices listed in United States Dollars (USD)*

Abbreviations:

SE: sensitivity   **SP:** specificity   **RIF:** rifampicin   **INH:** isoniazid   **PZA:** pyrazinamide   **EMB:** ethambutol   **FQ:** fluoroquinolones   **BDQ:** bedaquiline

LZD: linezolid   **CLO:** clofazimine   **ETH:** ethionamide   **AMK:** amikacin   **KAN:** kanamycin   **CAP:** capreomycin   **STM:** streptomycin   **DST:** drug-susceptibility testing

PCR: polymerase chain reaction   **tNGS:** targeted next-generation sequencing   **ERPD:** Global Fund Expert Review Panel for Diagnostics

Table 4: Tests for Predicting Progression to Active TB and Treatment Monitoring

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Xpert-MTB-HR (GeneXpert)	**Cepheid** (USA)	**Host RNA response:** Triage, progression to active TB, treatment monitoring	**Blood:** Triage SE: 90.0% SP: 86.0% AUC: 0.94[125]	**District lab**	Not yet available	Not yet available	Early-stage development
RISK6 signature assay (Q-POC)	**QuantuMDx** (UK)	**Host RNA response:** Triage, progression to active TB, treatment monitoring	**Blood:** Triage SE: 90.9% SP: 87.8% AUC: 0.94[126] Progression to active TB within 12 months of incident TB SE: 75.0% SP: 50.3%[127]	**Community/ Primary care setting** (Portable and battery-operated)	30 minutes	Not yet available	Feasibility stage complete Evaluation ongoing through early 2023 prior to product development[128]
ISIT-TB (BioFire FilmArray)	**bioMérieux** (France)	**Host RNA response:** Triage, progression to active TB, treatment monitoring	**Blood:** Not yet available	**District lab**	< 1 hour	Not yet available	Early-stage development[129]
TAM-TB (Flow cytometer)	**Beckman Coulter** (USA)	**Host immune response:** Triage, progression to active TB, treatment monitoring	**Blood:** Triage SE: 82.2% SP: 93.4% AUC: 0.87[130] Progression to active TB among PLHIV (6–12 months prior to symptomatic TB) SE: 86.0% SP: 86.0%[131]	**District lab**	24 hours	Not yet available	Early-stage development

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
TB-MBLA (PCR analyzer)	**University of St. Andrews/ LifeArc** (UK)	**Quantitative test for bacillary load:** Treatment monitoring	**Sputum, stool:** Sputum: SE: 99.0% SP: 91.0%[132] Stool: SE: 77.0% SP: 87.0%[133]	**District lab**	4 hours	Projected price per test: $20	Design-locked Evaluation ongoing **Projected ERPD and WHO review:** 2024–2025[134]
MPT64 (ELISA system)	**TAUNS** (Japan)	**Quantitative test for bacillary load:** Treatment monitoring	**Sputum:** SE: 88.0% SP: 96.7% SE (day 28): 81.0% SP (day 14): 89.5%[135]	**District lab**	5 hours[136]	Not yet available	Early-stage development
PATHFAST-LAM (PATHFAST immuno-analyzer)	**LSI Medience** (Japan)	**Quantitative test for bacillary load:** Treatment monitoring	**Sputum:** Not yet available	**Peripheral lab/ District lab**	< 17 minutes[137]	Not yet available	Early-stage development[138]
Treatment response module (CAD)	**Qure.ai** (India)	**CAD:** Treatment monitoring	**Chest X-ray:** 10 chest X-ray descriptors found to significantly correlate with treatment success[139]	**Primary care setting**	< 1 minute[140]	Not yet available	Early-stage development

Performance (sensitivity, specificity, AUC) listed according to a microbiological reference standard

** *All prices listed in United States Dollars (USD)*

Abbreviations:

SE: sensitivity **SP:** specificity **RNA:** ribonucleic acid **ELISA:** enzyme-linked immunosorbent assay **AUC:** area under the receiver operating characteristic (ROC) curve

ERPD: Global Fund Expert Review Panel for Diagnostics **PCR:** polymerase chain reaction **CAD:** computer-aided detection

Table 5: Tests for TB Infection

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
QIAreach QFT (QIAreach e-Hub)	**Qiagen** (Netherlands)	**IGRA (lateral-flow using digital reader):** Diagnosis of TB infection	**Blood:** 98.8% concordance with QuantiFERON Gold Plus (QFT Plus)[141] QFT Plus SE: 91.0–94.0% SP: 95.0–96.0%[142]	**Primary care setting**	< 20 minutes (after prior incubation for 16–24 hours)	Price per test: $12 eHub digital reader price: $1,200.40[143]	Commercialization paused pending new supply information ERPD-approved; Pending WHO review[144]
ichroma IGRA-TB (ichroma immuno-analyzer)	**Boditech** (Korea)	**IGRA (lateral-flow):** Diagnosis of TB infection	**Blood:** SE: 81.6% SP: 97.5%[145] 92.0% concordance with QFT Plus[146]	**Primary care setting**	15 minutes (after prior incubation for 16–24 hours)	Not available	Commercially available Pending validation[147]
VIDAS TB-IGRA (VIDAS 3 immuno-analyzer)	**bioMérieux** (France)	**IGRA:** Diagnosis of TB infection	**Blood:** SE: 97.5% SP: 97.5%[148]	**District lab/ Central lab**	17 hours	Not available	Commercially available Pending validation[149]
TB-Feron FIA (STANDARD F analyzer)	**SD Biosensor** (Korea)	**IGRA:** Diagnosis of TB infection	**Blood:** 98.81% concordance with QFT Plus[150]	**District lab/ Central lab**	15 minutes (after prior incubation for 16–24 hours)	Price per test: $11	Commercially available Pending ERPD and WHO review[151]
TB-Feron ELISA	**SD Biosensor** (Korea)	**IGRA:** Diagnosis of TB infection	**Blood:** SE: 98.03% SP: 98.55%[152]	**District lab/ Central lab**	1.5 hours (after prior incubation for 16–24 hours)	Price per test: $9	Commercially available Pending ERPD and WHO review[153]
Cy-TB	**Serum Institute of India** (India)	**TBST skin test:** Diagnosis of TB infection	**In-vivo:** SE: 76.0% SP: 98.0% (WHO pooled accuracy for TBST class of tests)[154]	**Community/ Primary care setting**	48–72 hours	Cost-effective compared to TST	Recommended by WHO in 2022[155]

Test/Tool (Instrument)	Manufacturer (Country)	Type: Use case	Specimen type: Performance*	Intended level of use	Time to results	Price**	Stage of development
Diaskintest	**Generium** (Russia)	**TBST skin test:** Diagnosis of TB infection	**In-vivo:** SE: 76.0% SP: 98.0% (WHO pooled accuracy for TBST class of tests)[156]	**Community/ Primary care setting**	72 hours	Price per test: $1.43[157]	Recommended by WHO in 2022[158]
EC-test	**Anhui Zhifei Longcom Biopharmaceutical** (China)	**TBST skin test:** Diagnosis of TB infection	**In-vivo:** SE: 76.0% SP: 98.0% (WHO pooled accuracy for TBST class of tests)[159]	**Community/ Primary care setting**	48–72 hours	Cost-effective compared to TST	Recommended by WHO in 2022[160]

Performance (sensitivity, specificity) listed according to a microbiological reference standard

** *All prices listed in United States Dollars (USD)*

Abbreviations:

SE: sensitivity   **SP**: specificity   **IGRA:** interferon-gamma release assays   **TBST:** TB-specific skin test   **ELISA:** enzyme-linked immunosorbent assay

ERPD: Global Fund Expert Review Panel for Diagnostics

Endnotes

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