Stop TB Partnership

Implementation of ERPD-Approved Molecular Tests for Detection of TB and Resistance to Rifampicin and Isoniazid

Stop TB Information Note

In March 2020, the Global Fund's Expert Review Panel for Diagnostics (ERPD) approved the following nucleic acid amplification tests (NAATs) for detection of TB and resistance to rifampicin and isoniazid:

- Abbott RealTi*m*e MTB and MTB RIF/INH assays (Abbott Laboratories, USA), using the *m*2000 RealTi*m*e System
- BD MAX MDR-TB assay (Becton, Dickinson and Company, USA), using the BD MAX System

These molecular assays are run on high-throughput instruments that automate the DNA extraction, PCR amplification and detection steps. Both instruments have a menu of other tests available, allowing for opportunities to multiplex.

What is the Expert Review Panel for Diagnostics (ERPD)?

The ERPD is a group of independent experts who review the potential risks and benefits associated with the use of diagnostic products and make recommendations to the Global Fund (GF) and Unitaid on their use. The WHO Regulation and Prequalification Department hosts the panel.

ERPD approval allows countries to use Global Fund funding to procure products for a time-limited period, with possibility for renewal (for Abbott and BD assays, until March 2021). ERPD approval of TB diagnostics is intended as an **interim approval mechanism on the pathway to potential WHO endorsement**, either as a WHO Global TB Programme recommendation or by WHO prequalification (the WHO Prequalification Team is expected to start prequalification assessments for TB diagnostics starting in 2021).

When a GF Principal Recipient wishes to purchase ERPD-approved products, it should obtain evidence of the product's status through the "no-objection letter" process. To do this, the Principal Recipient should complete a notification form and submit it to the Fund Portfolio Manager. The form is available for download at the bottom of this page. The GF will then issue a no-objection letter for a time-limited period, allowing procurement to proceed.

WHO Global TB Programme review of the Abbott Realti*m*e and BD MAX assays

The WHO Global TB Programme has not yet convened a Guideline Development Group meeting to review the evidence on the Abbott Realti*m*e and BD MAX assays. However a Technical Expert Group (TEG) Consultation convened by WHO in July 2019 assessed available data on performance of several high-throughput NAATs, including the Abbott and BD assays. The TEG had the following product-specific findings based on available data:

- A FIND-organized comparative analytical evaluation showed that Abbott and BD assays had equal or better sensitivity for detection of TB compared to Xpert MTB/RIF. Specificity was not evaluated.
- Direct head-to-head studies using clinical specimens were limited, but available data showed that Abbott and BD assays had comparable sensitivity and specificity for detection of TB compared to Xpert MTB/RIF.
- The comparative analytical evaluation showed that Abbott and BD assays were comparable to GenoType MTBDR*plus* LPA (or slightly more sensitive) for the detection of rifampicin and isoniazid resistance.

A WHO Guideline Development Group is expected to be convened in late 2020 to review the updated evidence available on use of these tests and potentially issue recommendations.

Countries using these ERPD-approved NAATs for the clinical management of TB patients may also add to the global evidence base on their diagnostic accuracy and operational performance; FIND has developed a template that countries can use for this purpose.

Product descriptions and operational considerations

Abbott RealTi*m*e MTB and MTB RIF/INH Resistance assays, using the *m*2000 RealTi*m*e System

The Abbott *m*2000 RealTi*m*e System comprises two instruments:

- The *m*2000*sp* instrument automatically extracts DNA from the specimen and prepares the PCR plate. The dimensions of the instrument and accompanying cabinet are 145 x 79.4 x 217.5 cm, with a weight of 314.4 kg.
- The *m*2000*rt* instrument automates the PCR amplification and detection of DNA. The instrument can be placed on a benchtop and has dimensions of 34 x 49 x 45 cm, with a weight of 34.1 kg.

System testing capacity: The *m*2000 RealTi*m*e System can run up to 96 tests for *Mycobacterium tuberculosis* complex (MTBC) in a batch using the MTB assay. Purified nucleic acid from up to 22 MTB-positive patient samples can then be reflexed for detection of resistance to rifampicin and isoniazid, using the MTB RIF/INH Resistance assay. The MTB RIF/INH Resistance assay can also be used as a stand-alone test, starting from nucleic acid extraction.

Time to detection: For batches of up to 96 tests, MTBC is detected within 8.25 hours, with RIF/INH testing requiring a further 3 hours, resulting in complete results within 11.25 hours. For batches of up to 24 tests, MTBC is detected within 6 hours, with RIF/INH testing requiring a further 2.5 hours, resulting in complete results within 10.5 hours. For detection of resistance to isoniazid, the assay can discriminate and report high (*katG*) and low (*inhA*) isoniazid resistance.

Both scenarios are possible to accomplish during an 8-hour working shift, as completion of testing using the *m*2000*rt* instrument is automatic and does not require presence of a technician.

Specimen types: Inactivated sputum, bronchoalveolar lavage, NALC sediments

Multiplexing possibilities:

Many high TB burden countries are already using the *m*2000 system, including to test for HIV-1 viral load and early infant diagnosis, as well as for other diseases. Concurrent multiplexing (i.e., running tests for TB and HIV on the same instrument at the same time) is not a possibility, but a laboratory may arrange serial multiplexing of a batch of TB tests and a batch of HIV tests within laboratory working shifts.

The wide menu of available tests with GF ERPD, WHO PQ, US FDA and/or CE marking is listed below.

Assay	MTB and MTB INH/RIF Resistance	HIV-1 Qualitative	HIV-1	HBV	HCV Viral Load	HCV Geno-typing II	High Risk HPV	CT/NG	CT	CMV	EBV	SARS-CoV-2
Approval	GF ERPD, CE	WHO PQ, CE	WHO PQ, US FDA, CE	US FDA, CE	WHO PQ, US FDA, CE	US FDA, CE	WHO PQ, CE	US FDA, CE	CE	US FDA, CE	CE	WHO EUL, US FDA EUA, CE

Pricing: Global pricing is not yet available; contact the manufacturer for prices. Discussions are underway with Stop TB Partnership's Global Drug Facility (GDF) for inclusion in the GDF Catalog.

Manufacturer links: Abbott *m*2000 System, Abbott MTB assay, Abbott MTB RIF/INH Resistance assay

BD MAX MDR-TB assay, using the BD MAX System

The BD MAX system is an integrated instrument that automates the DNA extraction, PCR amplification and detection steps. The BD MAX MDR-TB assay simultaneously detects MTBC and resistance to rifampicin and isoniazid, without the need for reflexing. The only manual steps are for sample preparation and loading, and are similar to those for Xpert MTB/RIF. The instrument can be placed on a benchtop and has dimensions of 94 x 75.4 x 72.4 cm, with a weight of 113.4 kg.

System testing capacity: The BD MAX system can test up to 24 patient samples at once.

Time to detection: Test results for MTBC detection and resistance to rifampicin and isoniazid are provided within 4 hours. For detection of resistance to isoniazid, the assay can discriminate and report high (*katG*) and low (*inhA*) isoniazid resistance. Two batches, equaling up to 48 samples, can be tested within an 8-hour working shift.

Specimen types: Inactivated sputum, NALC sediments

Multiplexing possibilities:

BD MAX offers a broad syndromic menu focused on infectious disease and women's health. Due to its specific assay technology, BD MAX MDR-TB is run by itself in the instrument whereas the other BD MAX assays can be mixed in a run for concurrent multiplexing.

The wide menu of available tests with GF ERPD approval, US FDA clearance and/or CE marking is listed below. Partner assays developed by other manufacturers using Open Systems Reagents can also be run on BD MAX.

Assay	MDR-TB	Cdiff	StaphSR	MRSA XT	CPO	Enteric Bacterial	Enteric Parasite	Enteric Viral	GBS	CT/GC/TV	Vaginal Panel	SARS-CoV-2
Approval	GF ERPD, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA, CE	US FDA EUA, CE

Pricing: Global pricing is not yet available; contact the manufacturer for prices. Discussions are underway with Stop TB Partnership's Global Drug Facility (GDF) for inclusion in the GDF Catalog.

Manufacturer links: BD MAX System

Implementations considerations from the WHO Technical Expert Group (TEG) Consultation that reviewed Abbott RealTime MTB and MTB RIF/INH assays and BD MAX MDR-TB

"Implementation considerations for the centralized assay platforms should be based on where countries would place the tests in the diagnostic algorithm for TB and other diseases, as well as in-country laboratory capacity. For example, countries may consider placement of a centralized assay platform at a national reference laboratory only, which may be used for single or multiple disease testing on one platform. Alternatively, countries may have adequate infrastructure available and sufficient sample volume to consider deployment at regional referral laboratories. Consideration of the overall testing volume, for TB and other diseases for which tests are run on the platform, should be made, and the efficiencies of different run sizes determined. To ensure rapid turnaround time of samples referred to testing sites, countries should ensure that an efficient and reliable sample transportation system is available. To bring cost efficiency to testing services, consideration of integration of TB testing on existing platforms should be prioritized in locations where integrated testing is feasible. In other settings where TB diagnostic services are stand-alone and there is a high workload for TB testing, dedicated instruments may be preferred."

See also WHO Considerations for adoption and use of multidisease testing devices in integrated laboratory networks

WHO statements on the importance of testing for isoniazid resistance

From the 2018 WHO treatment guidelines for isoniazid-resistant tuberculosis:

"The overall aim of TB treatment is to achieve cure without relapse in all patients, interrupting *M. tuberculosis* transmission and preventing the acquisition (or amplification) of additional drug resistance. Globally, Hr-TB (rifampicin-susceptible, isoniazid-resistant TB) is more prevalent than MDR-TB. Efforts need to be made by all countries to move towards universal testing of both isoniazid and rifampicin at the start of TB treatment and to ensure the careful selection of patients eligible for the (H)RZE-Lfx regimen."

From the Frequently asked questions on the 2018 WHO treatment guidelines for isoniazid-resistant tuberculosis:

"How can the national TB programme expand its capacity to detect Hr-TB?

There is as yet no diagnostic platform approved for the detection of Hr-TB which matches the rapidity and convenience of Xpert MTB/RIF for rifampicin resistance. First line LPA can diagnose isoniazid resistance, complete with genotyping detail of clinical relevance, but requires substantial infrastructure typically available in a provincial or central level facility. The cost of the equipment to perform the test ranges from about USD8,000 to USD40,000, depending on local needs and if results are read automatically. Dedicated rooms in the laboratory would also be necessary. In countries eligible for preferential concessional pricing (138 eligible countries as of March 2018), the cost of a single LPA test strip is USD9.30. However, considering additional laboratory reagents and consumables required to perform the test, the total cost of performing an LPA test is approximately USD20-25. To date, more than 500 laboratories in many low and middle-income countries are known to have established LPA capacity. Typical processing time for an LPA specimen is about 2-3 days due to batching.

Liquid culture (or MGIT) could also detect Hr-TB at the level of a reference laboratory; this option has the disadvantage of an obligatory processing delay of at least 10 days. Testing on solid media is also an option but may take several months to obtain results and is therefore of limited use for baseline testing and monitoring non-response. Nonetheless, a phenotypic or molecular test result confirming Hr-TB is of equal value for clinical purposes once the method used is reliable and quality assured. Increased capacity to undertake phenotypic testing on liquid and solid media also requires substantial investment in infrastructure."