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**Tuberculosis Diagnostic  
Technology and Market Landscape**

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This report was prepared by Madhukar Pai (McGill University, Montreal) and David Boyle (PATH, Seattle), with support from UNITAID. Additional assistance was provided by Carole Jefferson. All reasonable precautions have been taken by the author to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall UNITAID or the World Health Organization be liable for damages arising from its use.



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## Abbreviations

<b>AIDS</b>	acquired immune deficiency syndrome
<b>CHAI</b>	Clinton Health Access Initiative
<b>DNA</b>	deoxyribonucleic acid
<b>HIV</b>	human immunodeficiency virus
<b>IPAQT</b>	Initiative for Promoting Affordable, Quality TB tests
<b>MDR</b>	multidrug resistant
<b>MTB</b>	mycobacterium tuberculosis
<b>MTBC</b>	mycobacterium tuberculosis complex
<b>NAAT</b>	nucleic acid amplification test
<b>PATH</b>	Program for Appropriate Technology in Health
<b>POC</b>	point-of-care
<b>RIF</b>	rifampicin
<b>TB</b>	tuberculosis
<b>US</b>	United States
<b>WHO</b>	World Health Organization

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## Foreword

Despite progress in the fight against tuberculosis (TB), an estimated 8.6 million people developed TB in 2012, and 1.3 million died from the disease (1). Many of these deaths could have been avoided through timely diagnosis and initiation of treatment – but roughly one third of people with TB do not have access to appropriate TB diagnostics. Indeed, the Global Tuberculosis Report 2013, published in October by the World Health Organization (WHO), emphasized two major challenges impeding further progress:

- the “missing three million”, or the estimated number of cases of TB not currently diagnosed or not notified to health systems;
- the crisis of multidrug-resistant (MDR) TB, where three out of four cases of MDR-TB are still not being diagnosed as such, and the huge gap persisting between cases diagnosed and treatment services for drug-resistant TB (1).

New tools are critical for transformational progress in TB control, and 2013 saw some key advances in this area. In diagnostics, much attention has focused on the continued global rollout of the Xpert® MTB/RIF assay (Cepheid Inc, CA). As of September 2013, over 4.2 million cartridges had been used in 95 of the 145 countries eligible for concessional pricing (2).

The context for use of new tools – including the evolving policy environment, market needs and the pipeline of technologies in development – is important for determining their optimal use and potential impact. For this reason, continuous monitoring of the TB diagnostics landscape is undertaken to inform potential market-based approaches to improve market function.

### 1. Overview

The UNITAID Tuberculosis Diagnostic Technology and Market Landscape is published annually and is prepared as part of a broad and ongoing effort to understand the technology and market landscape for tuberculosis (TB) diagnostics. The first edition of the landscape report was published in July 2012, with a semi-annual update published in December 2012. A second edition was published in July 2013. These documents are available at <http://www.unitaid.eu/en/resources/publications/technical-reports>.

This document is a semi-annual update to the second edition report. The purpose of this document is to highlight developments that have occurred since July 2013 – namely, in the areas of policy development, implementation and scale-up of the Xpert® MTB/RIF assay and efforts to define the characteristics of next-generation molecular tests that could replace smear microscopy. An updated technology pipeline is included for reference; however, a detailed report on newer technologies, including technologies other than nucleic acid amplification tests (NAATs), will be published in 2014 (third edition).

### 2. Methods

The UNITAID Tuberculosis Diagnostic Technology and Market Landscape: Semi-Annual Update 2013 was compiled by Madhukar Pai (McGill University, Montreal) and David Boyle (PATH, Seattle) with support from Carole Jefferson (independent consultant) and UNITAID. The material in this landscape report was gathered by the authors from publicly available information, published and unpublished reports and articles, and interviews with test developers and manufacturers. All images have been reproduced with permission from the respective companies or agencies. In particular, materials from the following published articles by the authors were adapted, with permission from the authors and copyright holders:

- Denkinger CM, Kik SV, Pai M. Robust, reliable and resilient: designing molecular tuberculosis tests for microscopy centers in developing countries. *Expert Rev Mol Diagn.* 2013 November;13(8):763–7.
- Denkinger CM, Nicolau I, Ramsay A, Chedore P, Pai M. Are peripheral microscopy centres ready for next-generation molecular tuberculosis diagnostics? *Eur Respir J.* 2013 August;42(2):544–7.

### 3. Acknowledgements and conflicts of interest

Madhukar Pai has no commercial/financial conflicts. He has received grant funding for TB diagnostics market research from the Bill & Melinda Gates Foundation. He previously served as co-chair of the Stop TB Partnership New Diagnostics Working Group and as a consultant for the Foundation for Innovative New Diagnostics. He is currently serving as a consultant for the Bill & Melinda Gates Foundation. The Bill & Melinda Gates Foundation had no involvement in the production of this report.

David Boyle currently holds a grant from the Foundation for Innovative New Diagnostics to assess the performance of the Loopamp mycobacterium tuberculosis complex (MTBC) assay in a field setting and a grant (Bill & Melinda Gates Foundation OPP 1044825) unrelated to TB in which Ustar Biotechnologies (China) is a collaborator. He has no other commercial/financial conflicts pertaining to information described in this document.

## 4. Policy updates

The World Health Organization (WHO) endorsed the Xpert® MTB/RIF assay in 2010, and published an accompanying policy to guide use in 2011. In October 2013, WHO issued updated recommendations on the use of the Xpert® MTB/RIF assay. The update was based on the recommendations of an Expert Group Meeting held in May 2013, which were subsequently endorsed by the WHO Strategic and Technical Advisory Group for Tuberculosis in June 2013 (3).

This new policy guidance expands the recommended use of the Xpert® MTB/RIF assay, including for the diagnosis of childhood TB and extrapulmonary TB, and includes an additional recommendation on the use of the Xpert® MTB/RIF assay as the initial diagnostic test in all individuals presumed to have pulmonary TB (3).

The revised WHO recommendations on the use of the Xpert® MTB/RIF assay for the diagnosis of pulmonary TB and rifampicin (RIF) resistance in adults and children are as follows:

- Xpert® MTB/RIF should be used rather than conventional microscopy, culture and drug-susceptibility testing as the initial diagnostic test in adults presumed to have MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).
- Xpert® MTB/RIF should be used rather than conventional microscopy, culture and drug-susceptibility testing as the initial diagnostic test in children presumed to have MDR-TB or HIV-associated TB (strong recommendation, very low-quality evidence).
- Xpert® MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults presumed to have TB (conditional recommendation acknowledging resource implications, high-quality evidence).
- Xpert® MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all children presumed to have TB (conditional recommendation acknowledging resource implications, very low-quality evidence).
- Xpert® MTB/RIF may be used as a follow-on test to microscopy in adults presumed to have TB but not at risk of MDR-TB or HIV associated TB, especially in further testing of smear-negative specimens (conditional recommendation acknowledging resource implications, high-quality evidence).

The revised recommendations on the use of the Xpert® MTB/RIF assay for the diagnosis of extrapulmonary TB are as follows:

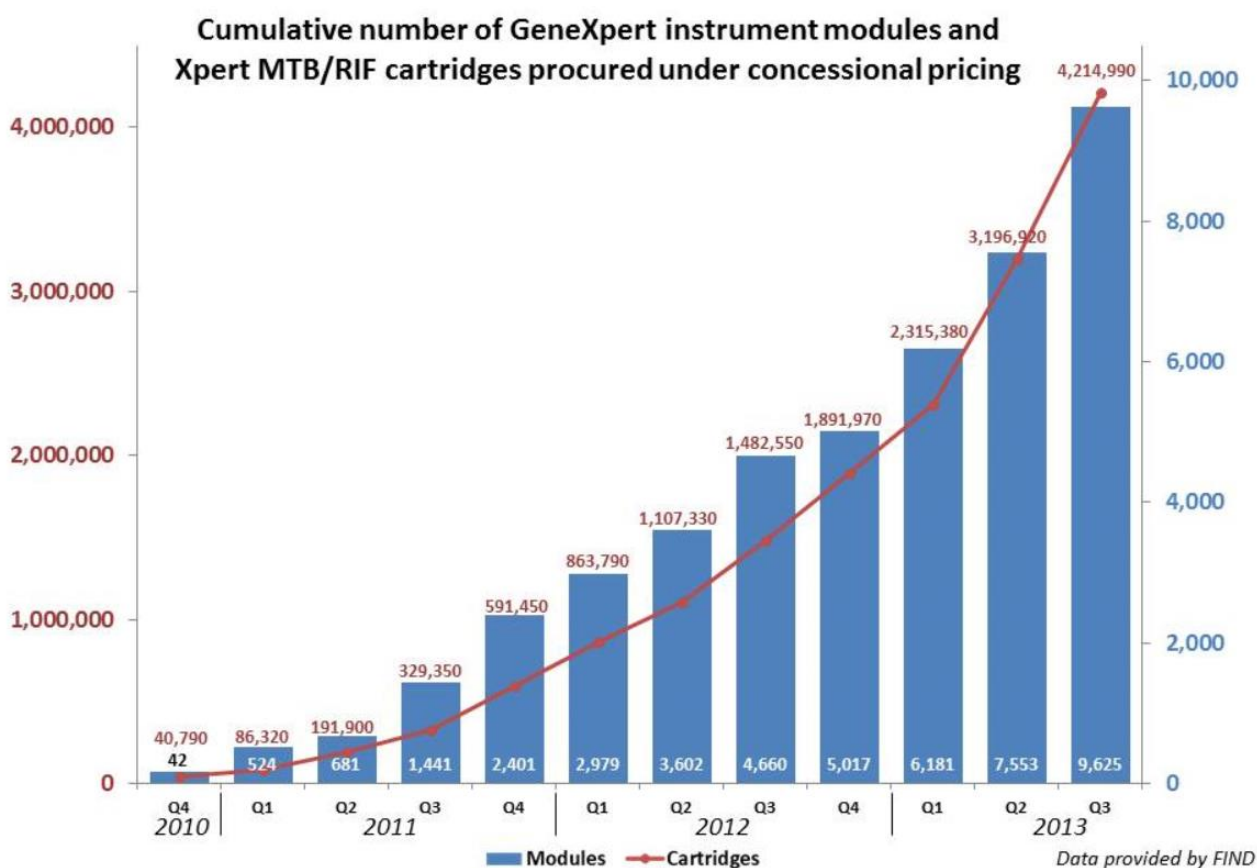
- Xpert® MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis (strong recommendation given the urgency of rapid diagnosis, very low quality of evidence).
- Xpert® MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from patients presumed to have extrapulmonary TB (conditional recommendation, very low quality of evidence).

Evidence from systematic reviews that informed the revised recommendations is included in the report of the Expert Group Meeting and the policy itself (3). These revised recommendations also are incorporated into the third edition of the International Standards for TB Care ([www.istcweb.org](http://www.istcweb.org)) that will be released on World TB Day: 24 March 2014.

## 5. Implementation of existing technologies

According to WHO, as of 30 September 2013, a total of 1843 GeneXpert® instruments and 4 214 990 Xpert® MTB/RIF cartridges have been procured worldwide in the public sector in 95 of the 145 countries eligible for concessional pricing (Figure 1) (2). Updated quarterly sales figures are publicly available via the WHO website for monitoring the rollout of the Xpert® MTB/RIF assay (2).

**Figure 1: Data from WHO on global sales of the Xpert® MTB/RIF assay**



Q: quarter

Source: Foundation for innovative new diagnostics (FIND). <http://www.who.int/tb/laboratory/mtbrifrollout/en/index.html>

In June 2012, UNITAID, the Bill & Melinda Gates Foundation, the United States Agency for International Development and the United States President's Emergency Plan for AIDS Relief announced an agreement with Cepheid Inc to reduce the cost of the test to US\$ 9.98 per cartridge (from US\$ 16.86). This purchase price is applicable to over 145 purchasers in low- and middle-income countries. In 2013, UNITAID and WHO initiated widespread scale-up of the Xpert® MTB/RIF assay. UNITAID has invested US\$ 25.9 million to purchase over 220 GeneXpert® instruments and 1.4 million test cartridges for 21 countries in Africa, Asia and Eastern Europe. Coordinated by WHO and the Stop TB Partnership, this TBxPert project is estimated to save 62 000 lives.

TB REACH, an initiative by the Stop TB Partnership supported by the Government of Canada, promotes new ways of detecting and treating TB cases. In its first wave of grants, TB REACH supported a project using the Xpert® MTB/RIF assay on a mobile van in Tanzania prior to WHO endorsement of the technology. In Wave 2, 30 of 44 projects in 18 countries used the Xpert® MTB/RIF assay as part of case-finding activities. In total, these projects planned to use over 250 000 test cartridges in 152 instruments. The projects employed a wide variety of testing algorithms and, in all projects, the test was used to test people with suspected TB rather than to determine drug susceptibility of confirmed TB patients. The projects sought



to bring the test as close to the patient as possible: many were placed on mobile units and in lower-level facilities, employing local solutions such as truck batteries, generators and solar panels to address power issues. As of 30 September 2013, over 200 000 tests had been conducted, identifying more than 28 000 individuals with TB. In Wave 3, TB REACH is supporting another 9 projects in 9 countries, using 53 244 cartridges in 18 instruments. In addition, TB REACH has partnered with UNITAID to provide support to a number of partners using the Xpert® MTB/RIF assay in its most recent funding wave. Under the UNITAID TBXpert Project, TB REACH is supporting an additional 20 projects in 12 countries. The projects plan to use 539 542 test cartridges and 133 instruments and testing commenced in the second half of 2013. Wave 4 grants are expected to be disbursed in early 2014. Early experiences from these TB REACH projects show that a number of operational issues need to be addressed to optimize implementation of the Xpert® MTB/RIF assay, including import of equipment and tests, erratic electric power supply, transportation of specimens, diagnostic algorithms, interpretation of results and case notification.

In addition to these global developments, efforts are under way to enhance uptake of the Xpert® MTB/RIF assay in the private sector in high-burden countries such as Bangladesh, India, Indonesia and Pakistan. Currently, these purchasers are excluded from accessing the negotiated price of US\$ 9.98 per test cartridge. In India, the Initiative for Promoting Affordable, Quality TB tests (IPAQT) initiative ([www.ipaqt.org](http://www.ipaqt.org)), coordinated by the Clinton Health Access Initiative (CHAI), brought together a group of private laboratories into a partnership for promoting use of WHO-approved TB tests in the highly fragmented private sector (4–6). CHAI facilitated an agreement between the participating laboratories and negotiated with suppliers/distributors of WHO-approved tests (the Xpert® MTB/RIF assay, line probe assay and liquid cultures). The laboratories that are part of the initiative sign a charter, enabling them to access lower negotiated prices for these tests in exchange for meeting certain guiding principles outlined in the charter, including case notification, affordable and agreed-upon ceiling pricing to patients and non-use of banned serological tests. The initiative, thereby, creates a sustainable “win-win-win” situation from which patients, the health-care system, laboratories and manufacturers benefit. In its first six months, the initiative has grown to include 50 member laboratories, including 5 of 6 national laboratory chains, 13 hospital labs and over 20 regional laboratory chains. In the IPAQT first quarter (April–July 2013), over 20 000 Xpert® MTB/RIF tests were used in the private sector, up from fewer than 2000 in all of 2012.

While many studies have confirmed the high accuracy of the Xpert® MTB/RIF assay (7), there are limited data on how the test impacts patient outcomes. The first randomized controlled trial of the Xpert® MTB/RIF assay was published in October 2013 and raised intriguing questions about the potential clinical impact of this tool in routine practice (8). In this pragmatic, multicentre trial, people with suspected TB were randomly assigned to nurse-performed Xpert® MTB/RIF in primary care clinics or same-day sputum smear microscopy. While the Xpert® MTB/RIF assay was found to be more accurate than smear microscopy, reduced time to treatment and resulted in more patients starting same-day treatment, these short-term benefits did not translate into lower TB-related morbidity in the longer term, partly because of high levels of empirical treatment at the clinics involved. Current cluster-randomized trials in Brazil and South Africa should provide additional insights on implementation of the Xpert® MTB/RIF assay to maximize clinical and public health benefits.

While mathematical modelling studies suggest that the Xpert® MTB/RIF assay (and similar new diagnostics) can potentially save lives and help reduce transmission (9,10), the technology’s impact may depend heavily on whether:

- national TB programmes choose to implement the Xpert® MTB/RIF assay only as a drug-susceptibility test or as a diagnostic tool among all patients with suspected TB;
- national TB programmes implement the Xpert® MTB/RIF assay in centralized and reference laboratories, rather than decentralized subdistrict-level settings;
- the Xpert® MTB/RIF assay is deployed in the best performing laboratories/areas versus in underperforming areas where even routine diagnostic capacity is limited;
- the Xpert® MTB/RIF assay can reach the level of most microscopy centres where the majority of TB testing is currently happening;

- the Xpert® MTB/RIF assay is used in point-of-care (POC) testing programmes to make rapid treatment decisions during the same visit (or day);
- the Xpert® MTB/RIF assay is accessible or affordable to first contact providers (informal/private) who often see patients first and could shorten diagnostic delays.

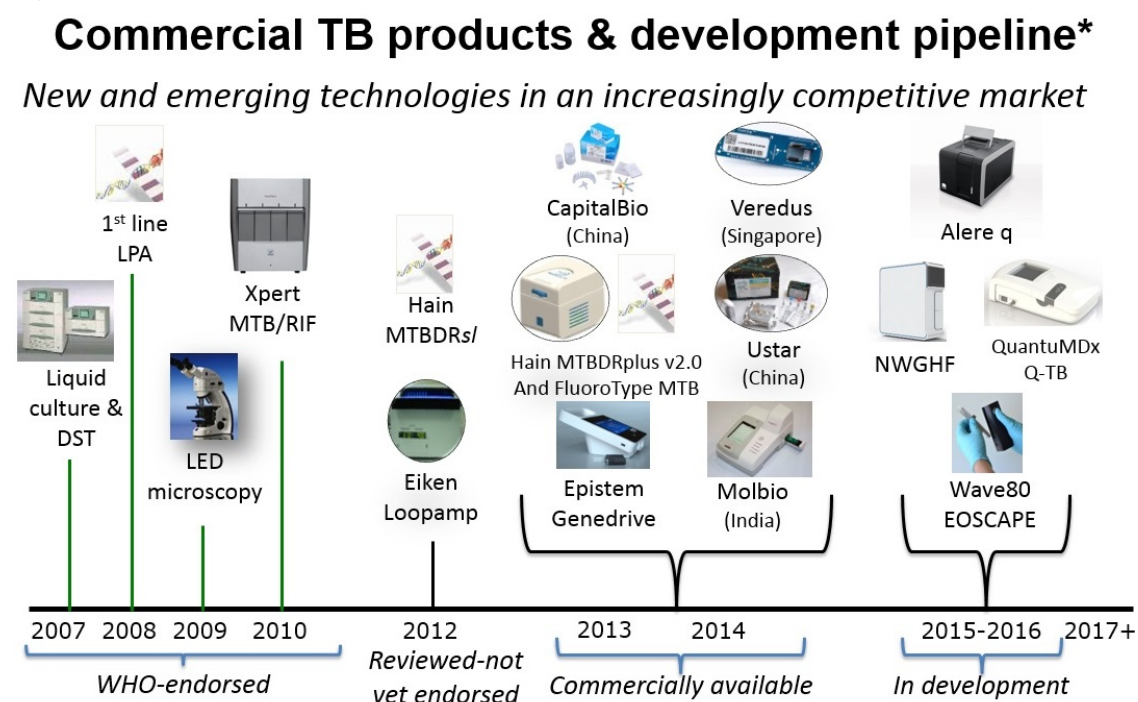
There is currently limited information on exactly where and how national TB programmes and countries are actually implementing the Xpert® MTB/RIF assay, and what fraction of those who are eligible have access to the technology.

## 6. Technology pipeline

As reviewed in the previous editions of the UNITAID Tuberculosis Diagnostic Technology and Market Landscape, there is now considerable industry interest in TB diagnostics development, with over 50 companies working in this space (11,12). While no new test has received WHO endorsement since the Xpert® MTB/RIF assay, there are several new molecular TB tests that are now on the market and approved for use in at least one country or region. Figure 2 shows the pipeline of new and emerging NAATs. While not comprehensive, this graphic is indicative of the level of research and development of molecular technologies for TB diagnosis.

There are limited published data on all of these new molecular tests. Most do not appear to be ready for WHO policy review in the immediate (two to three-year) time frame—with the exception of the Eiken Loopamp™ MTBC assay, scheduled for further WHO policy review in 2014.

Figure 2: Pipeline of commercial TB tests



DST: drug susceptibility testing; NWGHF: Northwestern Global Health Foundation

Notes: NAATs are shown; other technologies and non-commercial tests are not included. Future dates are estimated; order may change.

Source: Manufacturer outreach as part of UNITAID landscape development.

In the medium term (three to five-year time frame), several NAATs are expected to be available for use in POC testing programmes at the level of peripheral microscopy centres. These include technologies such as the Alere q and QuantuMDx Q-TB; in addition, other companies are now reporting product development in this area. In parallel, several sophisticated technologies (e.g. microarrays, sequencing) are emerging with the ability to detect resistance to several TB drugs. These technologies are not included in the pipeline graphic shown in Figure 2.

Other new and emerging (non-molecular) technologies include automated smear microscopy readers (e.g. TBDx™ by Applied Visual Sciences and Fluorobot by ConsultAsk Ltd), breath tests (e.g. BreathLink™ by Menssana Research Inc) and digital x-rays with computer-aided detection (e.g. CAD4TB by Delft Imaging Systems). There also are several products being marketed for simplified, rapid culture methods, including microscopically observed drug susceptibility (MODS™, Hardy Diagnostics), thin layer agar (NanoLogix Inc) and solid agar slants utilizing novel colorimetric indicators to discriminate mycobacteria from contaminants and no growth (e.g. TK Media® by Salubris Inc). Significant investments also are being made in biomarker research to support the development of a non-sputum-based rapid test. For example, the Bill & Melinda Gates Foundation has invested US\$ 12 million, via the **Biomarkers for the Diagnosis of Tuberculosis** programme, to validate biomarkers for use in developing a low-cost, simple-to-use test to quickly and accurately diagnose TB in low-resource settings. A comprehensive review of these non-NAAT technologies will be included in the 2014 (third edition) of the landscape report.

## 7. Unmet market needs

Although the Xpert® MTB/RIF assay is a potentially game-changing technology, it has its limitations. First, as pointed out earlier, implementation at the district level or in centralized labs still limits access for many patients who access care at more peripheral levels of the health-care system. Even those with access may encounter several weeks or months of diagnostic delay, during which TB transmission may occur. Furthermore, since the most important goal of POC testing is to make a treatment decision during the same clinical encounter or visit (13), centralized use of the Xpert® MTB/RIF assay may be less helpful for decentralized POC testing programmes at lower levels of the health-care system (e.g. primary care) where patients with TB symptoms initially seek care. Another important concern with the implementation of the Xpert® MTB/RIF assay is its high overall cost for national TB programmes in low-income countries, especially for decentralized deployment of the test (14).

A more affordable molecular POC test at the primary care level will greatly help reduce diagnostic delays and help curb TB transmission. As noted previously in the Technology Pipeline section, many new NAAT products are emerging, with claims to be “POC NAATs” (i.e. intended for more decentralized settings than the Xpert® MTB/RIF assay) (15,16). If they are designed for POC use, then, at a minimum, they should be deployable in peripheral microscopy centres where most initial TB testing currently occurs, using sputum smear microscopy. These centres are usually primary health centres with small, attached laboratories (Figure 3) with technicians trained in microscopy, and often staffed by physicians or nurses who can initiate TB treatment. Thus, these health centres are at a higher level of the health-care system than health posts or outpatient clinics that have no attached laboratories and are unlikely to be staffed by physicians.

National TB programmes in high-burden countries are heavily reliant on smear microscopy centres, with thousands of such centres established for TB testing. India alone has over 13 000 designated microscopy centres in the public sector, where over 15 million sputum smears are stained and read every year by trained microscopy technicians. These microscopy centres are linked to decentralized treatment units where first-line TB drugs are available so that TB treatment can be initiated and monitored by community-based providers of directly observed therapy.

**Figure 3: Peripheral microscopy centres in high-burden countries**



Source: Denkinger CM et al. 2013 (17) [reproduced with permission].

Because microscopy centres are usually embedded in or attached to primary health centres, they are closer to patients than district or subdistrict-level hospitals and laboratories. This, in turn, suggests that TB can be diagnosed earlier at the microscopy centre level. Therefore, these centres should be the ideal place for the implementation of a novel molecular assay that is more sensitive than smear microscopy and with a faster turnaround time to support more rapid initiation of TB therapy in an already established infrastructure.

The issues then are: Can the so-called POC NAATs for TB be deployed in peripheral microscopy centres? Are they designed for such settings? For example, can they survive the high temperature and frequent power outages that are likely in such settings? Will manual sample processing and DNA extraction prove to be a too big hurdle for basic laboratories? Can they be manufactured at an acceptable cost and produced in volumes to meet the market need?

To summarize the current state of peripheral microscopy centres, Denkinger and colleagues recently published a survey of microscopy centres in 22 countries with the highest burden of TB (18). They surveyed multiple respondents from each country and asked them to complete a simple questionnaire on a typical, peripheral microscopy centre. The results of the survey are summarized in a “heat map” (Figure 4). This graphic highlights scarcity of infrastructure (e.g. temperature control, uninterrupted power), lack of basic



equipment (e.g. biosafety hood, centrifuge) and limited skills at the level of peripheral microscopy centres in all high-burden countries, although Brazil, Russia, India, China and South Africa (the so-called “BRICS” countries) appear to have a more robust infrastructure than others surveyed.

**Figure 4: Heat map showing characteristics of peripheral microscopy centres in 22 high-TB-burden countries**

Country	Environment		Infrastructure		Available equipment							Skills			Communication			Current testing		
	Temperature	Humidity	Power	Water	N95	Pipettes	Refrigerator	Incubator	Centrifuge	Water bath	Hood	Pipetting	PCR tests	Computer	Landline	Mobile	Internet	QA Established	ZN	FM
<b>Non-BRICS</b> Congo	Yellow	Yellow	Red	Green	Yellow	Red	Yellow	Red	Yellow	Red	Red	Red	Red	Red	Red	Green	Red	Green	Green	Yellow
Zimbabwe	Yellow	Green	Red	Green	Yellow	Green	Yellow	Red	Yellow	Red	Green	Green	Red	Green	Green	Green	Yellow	Green	Green	Red
Mozambique	Red	Red	Red	Green	Yellow	Red	Yellow	Red	Yellow	Red	Red	Red	Red	Red	Yellow	Yellow	Yellow	Green	Green	Red
Ethiopia	Yellow	Red	Red	Green	Yellow	Red	Yellow	Red	Green	Red	Red	Red	Red	Red	Red	Green	Yellow	Yellow	Green	Red
Afghanistan	Red	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Red	Red	Red	Red	Red	Red	Red	Red	Green	Yellow	Green	Green	Red
Myanmar	Yellow	Green	Yellow	Green	Yellow	Red	Yellow	Red	Red	Red	Red	Yellow	Red	Yellow	Yellow	Yellow	Grey	Green	Green	Grey
Uganda	Yellow	Red	Red	Red	Red	Green	Yellow	Red	Red	Red	Red	Red	Red	Red	Yellow	Green	Red	Green	Green	Yellow
Tanzania	Red	Yellow	Red	Red	Red	Red	Yellow	Red	Red	Red	Red	Red	Red	Red	Red	Green	Red	Green	Green	Yellow
Kenya	Yellow	Red	Red	Red	Red	Red	Yellow	Red	Red	Red	Red	Red	Red	Red	Yellow	Yellow	Yellow	Green	Green	Yellow
Bangladesh	Red	Red	Yellow	Green	Red	Red	Green	Red	Red	Red	Red	Red	Red	Red	Green	Yellow	Yellow	Green	Green	Green
Cambodia	Yellow	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Yellow	Red	Green	Green	Yellow
Nigeria	Red	Yellow	Red	Yellow	Red	Red	Yellow	Red	Red	Red	Red	Red	Red	Red	Red	Green	Red	Green	Green	Red
Pakistan	Red	Yellow	Red	Red	Red	Yellow	Yellow	Red	Red	Red	Red	Red	Red	Red	Yellow	Green	Red	Green	Green	Yellow
Vietnam	Red	Red	Red	Yellow	Red	Red	Yellow	Red	Red	Green	Red	Red	Red	Red	Yellow	Green	Red	Green	Green	Yellow
Philippines	Red	Red	Red	Red	Red	Red	Yellow	Red	Red	Red	Red	Red	Red	Red	Yellow	Green	Red	Green	Green	Grey
Indonesia	Green	Red	Red	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Green	Green	Red	Green	Green	Red
Thailand	Green	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Green	Yellow	Green	Green	Green	Green	Yellow	Green	Green	Yellow
<b>BRICS</b> India	Red	Red	Yellow	Green	Red	Red	Red	Red	Red	Red	Red	Red	Red	Red	Green	Green	Yellow	Green	Green	Red
China	Green	Yellow	Green	Green	Yellow	Yellow	Green	Yellow	Yellow	Yellow	Yellow	Red	Green	Green	Green	Green	Green	Green	Green	Yellow
South Africa	Green	Yellow	Yellow	Green	Yellow	Green	Green	Green	Green	Green	Green	Yellow	Yellow	Green	Green	Green	Green	Green	Red	Grey
Brazil	Red	Red	Red	Red	Red	Yellow	Yellow	Red	Red	Red	Red	Red	Red	Red	Red	Green	Green	Green	Green	Grey
Russia	Green	Green	Green	Green	Yellow	Green	Green	Green	Green	Yellow	Red	Yellow	Red	Yellow	Green	Green	Green	Green	Green	Yellow

■ Yes/present   
■ Maybe   
■ No/not present   
■ Unsure/question not answered

Notes: Questions related to environmental conditions (Is temperature or humidity not a concern?), infrastructure (Is stable power supply, clean water supply present?), presence of equipment (Are N95 respirator, micropipettes, refrigerator, incubator, centrifuge, hot water bath or biosafety hood present?) and skills (Are staff able to operate a micropipette or computer or perform polymerase chain reaction?) and the presence of means of communication (Is landline, mobile network or internet present?). Additional questions asked about whether quality assurance (QA) measures were established and which smear methods were currently used. Countries are sorted by increasing purchasing power parity. BRICS countries are Brazil, Russia, India, China and South Africa.

Source: Adapted from Denkinger CM et al. 2013 (17) and Denkinger CM et al. 2013 (18) [with permission].

On the positive side, this survey showed that all high-burden countries have successfully established direct Ziehl-Neelsen microscopy with external quality assurance. Also, mobile phones seem to be widely available, opening the possibility of mobile health interventions to recall patients with positive results, notify cases to TB control programmes and be of use for supply-chain management and quality assurance (19).

While the Xpert® MTB/RIF assay was clearly not designed for the kind of laboratories shown in Figures 3 and 4, it is not yet clear whether other emerging NAATs can be implemented in such settings. For example, all NAATs currently on the market still require manual sample processing and DNA extraction, and the heat map suggests that this is likely to be challenging in most peripheral microscopy centres.

Based on this survey and the operational realities of microscopy centres in high-burden countries, Denkinger et al. have suggested a list of criteria (Box 1) that are important to ensuring successful implementation of sputum-based NAATs in POC testing programmes at the level of microscopy centres, and to ensure same-day initiation of anti-TB therapy (17).

**Box 1. Critical requirements for any sputum-based NAAT product intended for POC TB testing use at the level of peripheral microscopy centres in high-burden countries**

**Accuracy:**

- ◆ The assay should be more sensitive than sputum smear microscopy and ideally at least as sensitive as the Xpert® MTB/RIF assay for detection of pulmonary TB.
- ◆ It should be at least as specific as smear microscopy and Xpert® MTB/RIF for detection of pulmonary TB.
- ◆ Added ability to detect drug resistance is desirable and can be an add-on (reflex) test, if it is not integrated into the initial detection cartridge.
- ◆ Turn-around time should allow for same-day treatment initiation (<1 hour is preferable).

**Operational aspects:**

- ◆ It should not be more complex than smear microscopy.
- ◆ Basic laboratory technicians with minimal training should be able to run the NAAT.
- ◆ Manual, precision steps (especially for sample processing) should be kept to a minimum (i.e. similar to the Xpert® MTB/RIF assay).
- ◆ It should not require expensive or sensitive equipment.
- ◆ It should not rely on cold chain or additional equipment (e.g. centrifuge, refrigerator, biosafety hood).
- ◆ It should be possible to perform with reasonable throughput (minimally 15 tests per day; 30–40 tests per day may be ideal).
- ◆ It should be able to handle multiple samples, preferably asynchronous and allow for walk-away operation.

**Cost:**

- ◆ It may be more expensive than smear microscopy, but should be cheaper than Xpert® MTB/RIF.

**Environment:**

- ◆ It should be able to function at high temperatures (e.g. 40° C) and high humidity (e.g. 75%).
- ◆ It should not require continuous power and be able to run on battery backup.
- ◆ It should be implementable in a setting without separate clean rooms.

**Biosafety:**

- ◆ Since biosafety hoods are unlikely to be present, it should incorporate a mechanism to rapidly decontaminate sputum, allowing for subsequent work on the bench.

**Quality assurance:**

- ◆ It should have an internal process controls and it should be easy to set up an external quality assurance system (e.g. testing of blinded panels).
- ◆ Maintenance of the instrument should be inexpensive, easily doable at the field level and calibration should be feasible remotely or through swap-out of modules.

**Training requirements:**

- ◆ As with microscopy and Xpert® MTB/RIF, periodic, short duration training should be sufficient to implement the NAAT.

**Information and communication technology:**

- ◆ It should allow for data export over mobile phone network and thus allow for remote monitoring and direct notification of cases.

Projects are currently under way to develop detailed target product profiles for a smear replacement molecular test at the level of microscopy centres. Efforts are under way to quantify the total sputum smear replacement market in 22 high-burden countries and to quantify the current market for TB diagnostics used in Brazil, China, India and South Africa. Data from this analysis will be available in 2014. Currently available target product profiles, market data and resources of relevance to product developers are available at [www.tbfaqs.org](http://www.tbfaqs.org).

## 8. Conclusions

The still in progress rollout of the Xpert® MTB/RIF assay has had a positive influence on the TB diagnostics landscape. However, challenges remain. High costs of this technology, dependence on a single-source supplier, exclusion of the private sector in high-burden countries from negotiated pricing agreements and difficulties in implementing this test in lower tiers of the health-care delivery system (i.e. primary care centres and peripheral microscopy labs) are critical concerns. Also, it is unclear if programmes are implementing the Xpert® MTB/RIF assay as a POC testing programme to ensure same-day initiation of TB treatment. Implementation of this technology in centralized, reference laboratories for drug-susceptibility testing will probably have limited impact on TB incidence, especially in settings where delays in accessing care are substantial. If national TB programmes restrict the use of the Xpert® MTB/RIF assay to a narrow group of indications (e.g. only those with treatment failure), then this also may attenuate the potential impact of the technology.

Beyond the Xpert® MTB/RIF assay, there is a need for improved and more affordable NAATs to replace sputum microscopy in decentralized microscopy centres. While next-generation molecular tests have emerged since the Xpert® MTB/RIF assay, none of them (with the possible exception of the Eiken Loo-pamp™ assay) is likely to be WHO-endorsed within the next two to three years due to lack of evidence in intended settings.

The need for a biomarker-based, low-cost, non-sputum-based test remains a key priority. Such a test could potentially be implemented at points of first-contact in the community—not only to diagnose TB, but also potentially help triage people who require confirmatory testing. Although biomarker discovery is an active area of research and development, no test is likely to be on the market within the next five years. There is also a renewed need for new technologies to rapidly detect drug resistance, with the emergence of new TB medicines (e.g. 2012 approval of bedaquiline by the United States Food and Drug Administration; 2013 positive recommendation of delamanid by the Committee for Medicinal Products for Human Use of the European Medicines Agency) and the likely introduction of new regimens within the next few years (20).

Initiatives still in progress such as updated market analyses and development of target product profiles should facilitate greater engagement of test developers in meeting priority market needs. Continued efforts to monitor the TB diagnostics landscape will highlight market shortcomings and potential opportunities for market-based approaches to improve access to essential TB diagnostic tools.

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