Frequently Asked Questions on Xpert MTB/RIF assay

Contents

How does the test work?

The Xpert MTB/Rif test is a cartridge-based fully automated NAAT (nucleic acid amplification test) for TB case detection and rifampicin resistance testing, suitable for use in disease-endemic countries. It purifies, concentrates, amplifies (by rapid, real-time PCR) and identifies targeted nucleic acid sequences in the TB genome, and provides results from unprocessed sputum samples in less than 2 hours, with minimal hands-on technical time.

Although molecular amplification is already a proven technology in TB diagnosis, other existing test methods are too complex for routine and widespread use in developing countries. The need for sample processing and DNA extraction adds another level of complexity to implementation in settings where resources are limited.

GeneXpert, the test device platform, was launched by Cepheid in 2004 and simplifies molecular testing by fully integrating and automating the three processes (sample preparation, amplification and detection) required for real-time PCR-based molecular testing. The Xpert MTB/RIF test is currently the only molecular test of its kind and uses a cartridge containing all elements necessary for the reaction, including lyophilized reagents, liquid buffers and wash solutions. Target detection and characterization is performed in real time using a six-colour laser detection device.

How was the Xpert MTB/RIF test developed?

Over the past five years, the Foundation for Innovative New Diagnostics (FIND) has partnered with Cepheid, Inc. (Sunnyvale, CA) to develop Xpert MTB/RIF, an automated, cartridge-based NAAT for TB based on the GeneXpert multi-disease platform. Additional financial support came from the US NIH, and technical support from the University of Medicine and Dentistry on New Jersey (UMDNJ, Newark, NJ).

What is the public health significance?

Tuberculosis is one of the deadliest public health threats today, but there remains a lack of effective diagnostic tools. This contributes to the global TB problem, as untreated TB patients remain a source of infection for other members of the community. Untreated TB also results in considerable morbidity and mortality, especially in HIV co-infected individuals.

The most widely used method to detect TB in most disease-endemic countries is the 125 year-old sputum smear microscopy test, which has a number of drawbacks including low sensitivity (especially in HIV-positive individuals and children), inability to determine drug-susceptibility, and variable performance that depends on operator training and volition.

Conventional diagnosis of drug resistant TB relies on mycobacterial culture and drug susceptibility testing (DST), a slow and cumbersome process requiring sequential procedures for isolation of mycobacteria from clinical specimens, identification of Mycobacterium tuberculosis complex, and in vitro testing of strain susceptibility to anti-TB drugs. During this time patients may be inappropriately treated, drug-resistant strains may continue to spread, and amplification of resistance may occur.

In contrast, the Xpert MTB/Rif assay is a rapid test which identifies both the presence of M. tuberculosis and resistance to rifampicin in a single test. This can enable early and appropriate treatment initiation, as well as accelerating the implementation of MDR-TB control measures, and ultimately reducing TB case incidence. Results from large-scale studies showed that testing a single sputum sample, the Xpert MTB/RIF assay was superior in performance to conventional culture on solid media.

What does it cost?

As part of its role in the development and evaluation of diagnostic tools, FIND negotiates with manufacturing partners to obtain significant price reductions that facilitate access to these technologies. Negotiated prices are available to developing and high TB burden countries that wish to procure TB

diagnostics for use in the public and non-profit healthcare sectors, and who procure these tools with funding from the government, UNITAID, the Global Fund or other donor agencies. These discounts average 50% on diagnostic instruments, and 75% on reagents. Furthermore, FIND-negotiated agreements often contain provisions for further discounts as procurement volumes of reagents increase. FIND has negotiated preferential pricing with Cepheid for both the GeneXpert instrument and the Xpert MTB/RIF assay cartridges. The GeneXpert device comes in different sizes, offering a variable number of test modules for simultaneous sample testing. The commonly-used GX4, with 4 modules (allowing 16-20 tests per 8-hour shift) has a negotiated cost of approximately US$ 17,000 FOB (Freight on Board), prices for the test cartridges shall be published on the FIND internet site in due course, shall be valid for public sector and non-profit purchasers in all countries except high-income countries. Additional costs for delivery and installation of the systems will vary by location. Current estimates suggest that the overall running costs will be similar to those for mycobacterial culture, with much lower infrastructure and training costs.

Why choose this assay when it is more expensive than existing diagnostics?

Current liquid and solid culture diagnostic systems can take several weeks to yield detectable growth and drug-susceptibility information, and testing requires specialised laboratory facilities (including sophisticated bio-safety) and specifically trained personnel. These technologies are therefore generally focused at the national (or reference laboratory) level, are not suitable for the district level of the health system, and involve infrastructure that are very expensive to build and maintain. Furthermore, patients are lost to follow up due to the diagnostic delay which contributes to continued disease transmission and increased morbidity.

In contrast, the Xpert MTB/Rif test allows for a rapid and accurate diagnosis which helps to ensure that individuals can be commenced early on appropriate treatment. The test is specifically designed for use at the district or sub-district level of the health system.

When will this technology be rolled out in endemic countries?

WHO, GLI, FIND and other partners are currently involved in downstream activities in several countries, strengthening laboratory systems and collecting evidence on how best to implement rollout of the Xpert MTB/RIF test. WHO will provide guidance to national TB programmes on the integration of this technology into existing diagnostic algorithms and provide a robust generic protocol to guide systematic implementation during 2011.

What are the pitfalls for this new technology - are there any?

The machine requires a stable and uninterrupted electrical power supply and is linked to a computer for data analysis, which of course requires security against theft. The instrument requires at least annual calibration which presently needs to be performed by a trained technician using specialized calibration equipment. The most commonly-deployed GeneXpert device (GX4) has a limited throughput, and larger systems (or linked devices), with throughputs of up to 1000 tests/day, will carry higher capital costs.

How is WHO involved in the development of new TB diagnostics such as this one?

WHO strongly encourages the development of new diagnostics and gets involved once there is enough data available from large-scale demonstration studies in different geographical and epidemiological settings.

How soon can countries benefit from this development?

WHO policy guidance is expected before the end of 2010 and will be rapidly disseminated to Member States, technical agencies and donors.

What is the relationship between WHO, Cepheid and FIND?

WHO has a normative mandate to develop and disseminate policy guidance to Member States on new TB diagnostic tools. FIND is a non-profit Foundation and a member of the Stop TB Partnership. WHO and FIND has an independent working relationship, and WHO also reviews new tools developed outside of FIND. Cepheid co-developed the original technology with FIND and has no direct relationship with WHO.

WHO has approved several new tools over the last three years. How does this technology fit in?

The new technology will not replace the need for microscopy, conventional culture and DST or existing molecular methods such as line probe assay. It does not take away the need for central reference laboratories where DST of other anti-TB drugs needs to be done or where high volumes of specimens need to be processed. Conventional microscopy and culture are also still necessary to monitor treatment response once patients are taking anti-TB drugs. As the new technology is a relatively low-throughput technology and easy to use it may be better suited at lower levels of the health care system (e.g. at district or sub-district level). Access to appropriate treatment for cases diagnosed with the new technology is also essential, and implementation of the new technology needs to be linked to treatment services.

What training and infra structure support will be required to roll out this new technology?

Minimal training of healthcare workers is required. What will be needed are a dedicated health care worker to perform the test, a secure environment to ensure that the equipment is not damaged or stolen, and a stable electrical power supply. Proper patient or specimen referral systems will be necessary, as well as systems for rapid dissemination of results. It will also be crucial to link this new technology with the capacity of TB programmes to manage all TB cases including those associated with drug resistance.

Why has it taken so long to develop new technologies for the diagnosis of TB?

Developing new TB diagnostics is complicated and hugely expensive. A serious lack of investment into research and development for new TB tools has historically been a major challenge, compounded by a lack of recognition the importance of laboratory services in TB control.

How does this relate to the diagnosis of TB, TB/HIV, MDR-TB and XDR-TB?

The technology allows for the rapid detection of TB and resistance to rifampicin in a single test. It has a sensitivity superior to that of conventional microscopy or culture on solid media, and is therefore useful in the diagnosis of TB in HIV co-infected persons where the sensitivity of microscopy alone is low. The system simultaneously detects resistance to rifampicin, which is a good and reliable proxy for MDR-TB.

Culture and conventional drug susceptibility testing against second-line anti-TB drugs is still necessary to confirm or exclude XDR-TB and to monitor response to MDR-TB treatment.

Will WHO be advising countries to no longer test by using sputum samples and microscopy?

Microscopy will for the foreseeable future continue to play an important role in the diagnosis of TB in many settings. Microscopy will also remain an important tool for the monitoring of a patient's response to treatment, as the new technology has not been designed for this purpose.

Are there any dangers or precautions for staff?

The bio-safety precautions for performing the Xpert MTB/RIF are equivalent to the requirements for performing direct sputum smear microscopy, i.e. minimal.