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Improving TB diagnosis: difference between knowing the path and walking the path

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"As Morpheus tells Neo in the cult science fiction movie *The Matrix*: "there's a difference between knowing the path and walking the path." Development of new tools is "knowing the path" ... "Walking the path" is a longer process that involves translation of technologies and policies into impact."

The global expansion of Directly Observed Treatment, Short-course (DOTS), the Stop TB Strategy, has been an enormously successful public health intervention. Millions of TB patients have been treated and millions of lives have been saved. However, TB remains a serious public health threat. More than 9 million new cases are reported every year, and the incidence rate is falling at less than 1% per year [1].

Although many countries have met the Stop TB targets of 70% case detection and 85% cure rate by 2005, TB incidence is not falling as expected or is falling too slowly in these countries. India is a prime example and has successfully scaled-up the DOTS strategy to cover 100% of the population, and has already achieved the targets for case detection and cure. Yet, India reported over 2 million TB cases in 2009, with 280,000 deaths [1].

There may be many explanations for this inconsistency. TB is a disease of poverty with several social determinants. Merely diagnosing and treating patients with TB disease is insufficient, although clearly important [2,3]. Another important reason is that TB patients are not diagnosed and cured quickly enough, and the 70/85 targets, while helpful from a programmatic perspective, are not ambitious enough [4]. Existing diagnostic approaches do not seem to quite address this challenge, and have largely failed to interrupt TB transmission in populations with a high prevalence of HIV and drug-resistant TB. Fortunately, in 2011, we are beginning a decade with some major successes and renewed optimism, but will need to contend with some worrisome issues, if TB is to be successfully controlled.

The good

One of the best things to happen in the field of TB is the recognition that existing tools are unlikely to achieve TB elimination, followed by a resurgence of interest in new tools, backed by substantial funding and product development partnerships to develop them. This has been particularly evident in the area of diagnostics [5]. Thanks to partners such as the Foundation for Innovative New Diagnostics, the Stop TB Partnership, the WHO and the Special Programme for Research and Training in Tropical Diseases, and funding agencies such as the Bill & Melinda Gates Foundation, the Global Fund to Fight AIDS, TB and Malaria, and UNITAID, tremendous progress has been made in expanding the TB diagnostics pipeline, including a portfolio of validated technologies (Figure 1) [6]. The current pipeline is vastly better than the portfolio even 5–10 years ago when smear microscopy, a 100-year-old test, was the only option for most resource-limited settings.

Keywords: diagnosis • DOTS • new diagnostics • tuberculosis • Xpert® MTB/RIF

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In addition, thanks to rapid, evidence-based policy development by the WHO, several new TB diagnostics and approaches have been reviewed and endorsed by the WHO since 2007 (Figure 1). Furthermore, the translation of policy into delivery has also happened within a rapid timeframe with new technologies such as the line probe assays for rapid diagnosis of multidrug-resistant (MDR) TB [7].

On 8 December 2010, the WHO announced its endorsement of Xpert® MTB/RIF (Cepheid Inc., CA, USA), a cartridge-based, automated nucleic acid amplification test, which can accurately detect TB and rifampin resistance in less than 2 h [8]. Evaluations of this test have demonstrated excellent results [9]. This assay uses GeneXpert®, a fully integrated, automated platform that is easy to use with minimal training, requires little hands-on time, is not prone to cross-contamination and requires only basic biosafety facilities (Figure 2). For the first time, a molecular TB assay can be placed close to the patients, and this could lead to rapid, early point-of-care diagnosis and prompt therapy.

The WHO now recommends that Xpert MTB/RIF should be used "as the initial diagnostic test" in individuals suspected of having MDR TB or HIV-associated TB. Furthermore, Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV are of lesser concern, especially in smear-negative specimens. These recommendations have been followed by efforts to make the test affordable. Compared with the market price, a price reduction of 75% is now available to the public sector in all low- and middle-income countries [8]. However, high cost remains a major barrier for scale-up.

As suggested by models, innovative tests such as Xpert MTB/RIF have the potential to save millions of lives [10]. They also have the potential to create a positive 'virtuous cycle', whereby innovations lead to further innovations [11]. The uptake of good tests should result in better health outcomes for patients, and improved outcomes should enhance credibility of healthcare systems and enable them to attract more funding, thereby supporting the development of even better technologies and delivery methods [11]. In parallel, strong and emerging economies with high TB burdens such as India, China, Brazil and South Africa now have the capacity to develop low-cost generic or novel assays, and incorporate their scale-up to achieve impact at the country level [11].

TB control programs are finally getting more ambitious in their goals, planning beyond the 70/85 targets, and aiming for universal access; for example, India is on the verge of an ambitious Phase III of their TB control program (2012–2017) that aims to provide universal access to quality diagnosis and treatment for the entire population. As a growing economic power, India is now uniquely placed to support this ambitious TB control plan, and to make a success story that can inspire other high TB burden countries and pave the way for a more ambitious global TB control agenda.

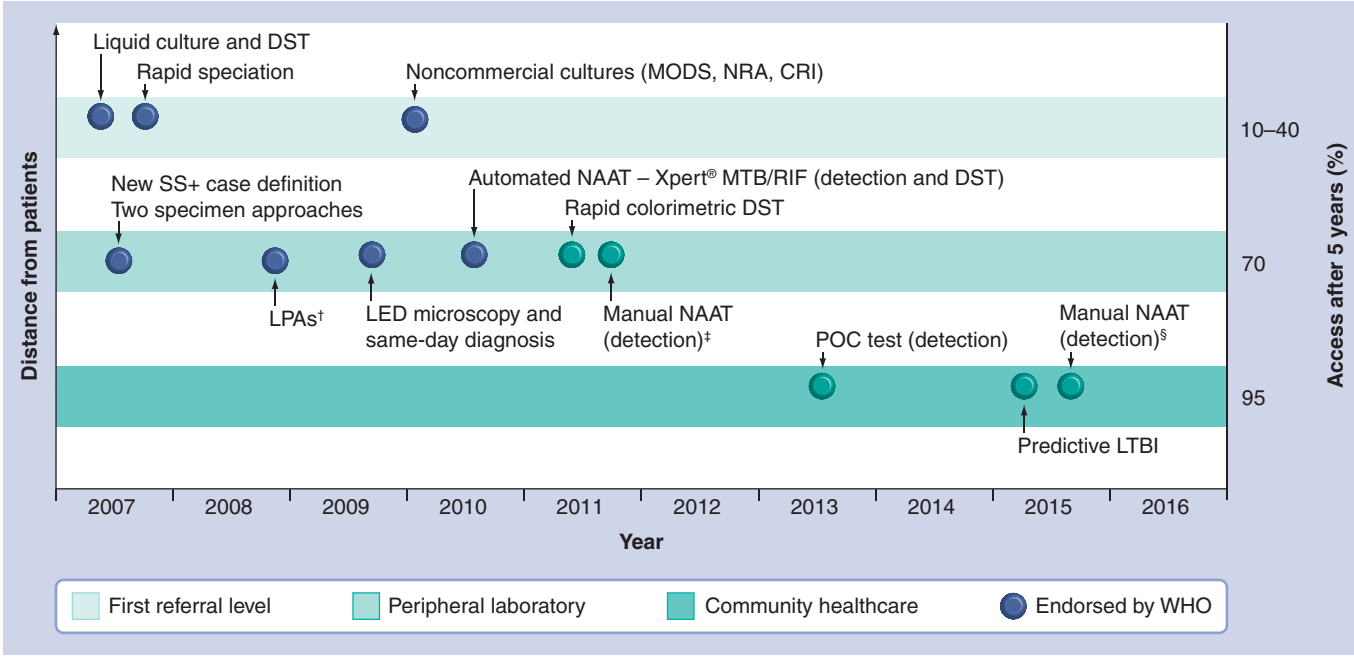

Figure 1. TB diagnostics pipeline in 2011.
†Manual NAAT: technology for MTB drug-susceptibility testing.
‡Manual NAAT: technology for MTB detection at the peripheral laboratory.
§Manual NAAT: technology for MTB detection at the community healthcare level.
CRI: Colorimetric redox indicator assay; DST: Drug-susceptibility test; LED: Light-emitting diode; LPA: Line probe assay; LTBI: Latent TB infection; MODS: Microscopic observation drug susceptibility; MTB: *Mycobacterium tuberculosis*; NAAT: Nucleic acid amplification test; NRA: Nitrate reductase assay; POC: Point of care; RIF: Resistance to rifampicin; SS+: Sputum smear-positive.
Adapted with permission from [6].

Figure 2. The Xpert® MTB/RIF test is the first molecular assay for TB that can potentially be used at the point-of-treatment.
Photo courtesy of the Foundation for Innovative New Diagnostics.

The bad & the ugly

While there are many positive trends, there are some worrisome issues that will need to be addressed if TB elimination is to become a reality. These include poor access to good diagnostic services, poor case detection rates and diagnostic delays, widespread use of inappropriate diagnostics and mismanagement of TB, lack of adequate regulation of TB diagnostics, lack of laboratory quality assurance, inadequate funding for TB control and barriers to scale-up of new technologies.

Even in 2009, the global TB case detection rate was low, with only approximately 63% of all forms of TB getting notified [1]. Diagnostic delays are common, and by the time a patient is diagnosed as having TB, they have already visited multiple care providers and infected several others in the community [12,13]. As illustrated by Michael Specter in the *New Yorker*, mismanagement of TB is a major concern, especially in the private sector in developing countries [14].

There is growing recognition of the widespread use of inaccurate and inappropriate TB diagnostics in many countries [14,15]. Published evidence clearly demonstrates that serological (antibody) tests for TB are inaccurate, inconsistent and have no clinical role in TB diagnosis [16,17]. There are no international guidelines supporting their use. If anything, the use of these tests is explicitly discouraged by the International Standards for TB Care [18]. Despite this, an estimated 1.5 million TB serological tests are carried out in India alone every year at an expenditure conservatively estimated at US$15 million per year [14,15]. This expenditure is substantial compared with the entire Indian TB control program budget, and does not account for potential harms to patients (e.g., unnecessary TB therapy because of false-positive serology results). To make matters worse, IFN-γ release assays (e.g., QuantiFERON®-TB Gold In-Tube, Cellestis Inc., Australia), while intended for latent TB diagnosis, are being misused for active TB diagnosis in high TB burden countries.

Mismanagement of TB is clearly harmful for patients. However, it is also bad for public health because every mismanaged TB patient can transmit the infection to others in the community, thus worsening the TB epidemic. Furthermore, widespread use of inappropriate tests can prevent the use of good diagnostics, and this may be a barrier for implementation of new tests. Recognizing this, the WHO recently announced its first negative policy in TB, against the use of TB serological assays [15]. However, the policy will not preclude research in this field, because of the potential for a useful, simple, point-of-care test in the future.

The regulation of diagnostics is weak in most resource-limited countries, and this allows bad diagnostics to enter the market, despite a lack of evidence or policies to support their use. In addition, there is little laboratory quality assurance in many developing countries; For example, in India a majority of the laboratories have no formal quality certification or accreditation. Thus, suboptimal tests implemented in suboptimal laboratories pose a dual threat for implementing new diagnostics.

The *New Yorker* article [14] and another recent *Lancet* World Report [15] highlighted a worrisome diagnostic and treatment ecosystem in resource-limited countries with systematic market failures throughout the value chain – private doctors receiving payments/incentives for tests ordered, over-reliance on useless tests, under-use of good diagnostics, use of a multitude of incorrect TB treatment regimens and a lack of patient support to ensure adherence to TB treatment. Thus, in countries such as India, only a proportion of patients with TB symptoms might be correctly investigated with appropriate tests, treated with the correct drug regimens, complete therapy and end up with positive outcomes (Figure 3). Indeed, this has been known for many years [19], and was inspirational in launching the public–private mix initiative to engage with the private sector for improving

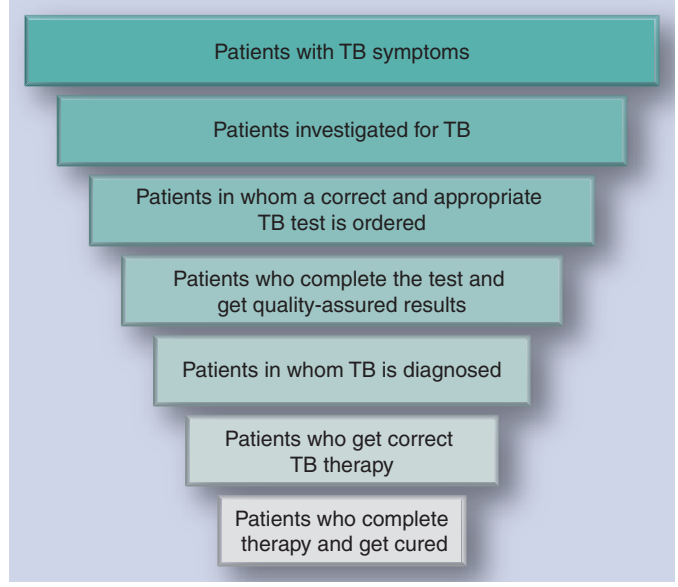

Figure 3. Misdiagnosis and mismanagement can result in only a fraction of TB patients getting correct diagnosis, appropriate therapy and positive outcomes.

TB care. Sadly, private sector engagement continues to be a low priority in many countries, despite the importance of this sector [20].

Time to walk the path

As Morpheus tells Neo in the cult science fiction movie *The Matrix*: "there's a difference between knowing the path and walking the path." Development of new tools is "knowing the path" and is merely the first step that has already been taken. "Walking the path" is a longer process that involves translation of technologies and policies into impact. Therefore, while Xpert MTB/RIF is an excellent innovation backed by a strong policy, it is unlikely to make an impact unless high-burden countries adopt this test (or develop similar lower cost alternatives), use it to replace inappropriate tests, invest funding in scaling it up, ensure that testing is followed-up with prompt treatment and engage with the private sector to address the market failures that result in mismanagement of TB. Walking this long path will require resources, commitment and persistence, but may be the only way to achieve TB elimination.

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