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Transforming the diagnosis of tuberculosis: an editorial board member's opinion at the 15th year of *Expert Review of Molecular Diagnostics*

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Interview with Professor Madhukar Pai, MD, PhD by Claire Raison (Commissioning Editor)

Professor Madhukar Pai did his medical training and community medicine residency in Vellore, India. He completed his PhD in epidemiology at the University of California, Berkeley (CA, USA) and a postdoctoral fellowship at the University of California, San Francisco (CA, USA). He is currently an associate professor of epidemiology at McGill University in Montreal (Canada). He serves as the Director of Global Health Programs, and as an Associate Director of the McGill International Tuberculosis Centre. In addition, he serves as a Consultant for the Bill & Melinda Gates Foundation. He also serves on the Scientific Advisory Committee of the Foundation for Innovative New Diagnostics, Geneva, Switzerland. His research is focused on improving the diagnosis and treatment of tuberculosis, especially in high-burden countries such as India and South Africa. His research is supported by grant funding from the Gates Foundation, Grand Challenges Canada and Canadian Institutes of Health Research. He has more than 200 peer-reviewed publications. He is recipient of the Union Scientific Prize, Chanchlani Global Health Research Award and Stars in Global Health award from Grand Challenges Canada, and is a member of the Royal Society of Canada.

■ What is the current landscape of molecular tuberculosis diagnostics and what are the biggest recent advances?

In 2015, tuberculosis (TB) remains a major global health problem, with 9 million estimated cases per year and 1.5 million deaths. To make matters worse, drug-resistant TB is a growing threat. Although TB diagnosis in many countries is still reliant on old tools such as smear microscopy, new diagnostics are definitely shifting the landscape. Thanks to the success and rollout of Xpert[®] MTB/RIF (based on the GeneXpert platform by Cepheid, Inc., Sunnyvale, CA, USA), there is now considerable excitement about new diagnostics. Several companies are actively engaged in R&D, and we

now have a robust pipeline of new tools, particularly molecular diagnostics.

Two molecular tests have been endorsed by the WHO. These are the Xpert MTB/RIF test for TB and rifampicin resistance detection and the line probe assay (Genotype MTBDRplus by Hain Lifescience, Nehren, Germany) for isoniazid and rifampicin resistance detection. These tests are now used in many high-TB-burden countries, and special negotiated prices are available for the public sector in high-TB-burden countries.

Worldwide, the ongoing rollout of Xpert MTB/RIF is the most important, meaningful shift in the TB diagnostics landscape. According to the WHO, as of 31 December 2014, over 10 million

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Xpert MTB/RIF cartridges had been procured by the public sector in 116 of the 145 countries eligible for concessional pricing [1]. Thanks to Xpert MTB/RIF, many patients in developing countries are getting tested for drug resistance, and this has made us realize the value of rapid, up-front drug-susceptibility testing, and also made us aware that multidrug-resistant TB may be more prevalent than we imagined.

“the ongoing rollout of Xpert MTB/RIF is the most important, meaningful shift in the TB diagnostics landscape”

■ What are currently the biggest unmet needs in TB diagnosis?

Even today, most high-TB-burden countries are still reliant on sputum smear microscopy for TB diagnosis. In a recent study, we estimated that the 22 highest-TB-burden countries performed nearly 78 million sputum smears annually, at a value of US\$137 million in over 42,000 microscopy centers (peripheral laboratories) [2]. While sputum smear microscopy is simple, inexpensive and easy to implement in peripheral settings, it has serious drawbacks. It has limited sensitivity and cannot detect drug resistance. In particular, its performance is suboptimal in vulnerable populations such as children and those living with HIV/AIDS.

What are the most important unmet needs, and which tests are considered top priority by the TB community? To answer this, we recently conducted a study of various stakeholders [3]. Based on this analysis, the following were identified as the highest priorities:

- a point-of-care sputum-based test as a replacement for smear microscopy;
- a point-of-care, non-sputum-based test capable of detecting all forms of TB via the identification of characteristic biomarkers or biosignatures;
- a point-of-care triage test, for use by first-contact health care providers as a rule-out test;
- a rapid drug-susceptibility test at microscopy center level.

For all of the above priorities, detailed target product profiles have been developed and reviewed by an expert consensus group, convened by WHO and partners [4]. We hope that this report on target product profiles will help steer product developers in the right direction and give them sufficient guidance on product development.

■ What are the challenges for scale-up of existing molecular TB tests?

The biggest challenges for scale-up of existing molecular tests include high cost, poor state of peripheral microscopy centers where much of TB testing is currently happening and persistent under-funding of national TB programs in most developing countries. In most high-burden countries, peripheral

microscopy centers have poor infrastructure (e.g., temperature control, uninterrupted power), lack of basic equipment (e.g., biosafety hood, centrifuge) and limited skills/expertise. Thus, conventional molecular tests are not suited to this level of the health care delivery system.

A recent survey of 22 high-TB-burden countries showed that while more than 80% of these countries have a policy or algorithm that includes Xpert MTB/RIF, current implementation is mostly funded by external donors, largely dependent on testing in centralized laboratories and primarily used for patients with presumed drug resistance or HIV infection [5]. The data suggest that wide-scale implementation of Xpert is mainly happening in South Africa, while other high-burden countries continue to mainly use smear microscopy.

In 2013, our team published a paper in *Expert Review of Molecular Diagnostics*, where we advocated for a ‘robust, reliable, rapid, sputum-based molecular test that is more sensitive than smear microscopy (and, preferably, as accurate as Xpert MTB/RIF), more affordable than Xpert MTB/RIF and can be successfully deployed as a same-day test and treat program at the level of peripheral microscopy centers in high-TB-burden countries’ [6]. This statement captures the biggest challenges for existing molecular tests and includes our wish list for the next-generation assays.

“over half of all TB patients seek care in the private sector”

■ What efforts have been made to make molecular tests more affordable and accessible?

Molecular tests such as Genotype MTBDRplus and Xpert MTB/RIF have been made available at special, negotiated prices to the public sector in high-burden countries. The Foundation for Innovative New Diagnostics (FIND) based in Geneva, Switzerland, has played a key role in negotiating concessional pricing, and details of these negotiated prices are available on the FIND website [7].

In addition, for Xpert MTB/RIF, an exceptional effort was made to ‘buy-down’ the price. UNITAID, the Bill and Melinda Gates Foundation, the US Agency for International Development (USAID) and US President’s Emergency Plan for AIDS Relief (PEPFAR) made investments to reduce the cost of the test to US\$9.98 per cartridge (from the original price of US\$16.86). This buy-down price is applicable to over 145 purchasers in low- and middle-income countries.

While the above concessional prices are available to the public sector, the private sector has been excluded from such arrangements. This is unfortunate, because the private sector is an important service provider in many countries (e.g., India, Pakistan, Bangladesh, Nigeria, Philippines and Indonesia). In fact, in countries such as India, over half of all TB patients seek care in the private sector, and even poor patients seek private health care.

In India, the price of WHO-endorsed TB tests such as Xpert MTB/RIF and Genotype MTBDRplus have been reduced by

nearly 50%, via an Initiative for Promoting Affordable and Quality TB Tests (IPAQT) [8], coordinated by the Clinton Health Access Initiative, which brought together several private laboratories into a consortium for promoting use of WHO-approved TB tests in the highly fragmented private sector in India [9].

The Clinton Health Access Initiative facilitated an agreement between the participating laboratories and negotiated with suppliers/distributors of WHO-endorsed tests. Accredited laboratories that join the Initiative sign a charter and are eligible to access lower negotiated prices for these tests in exchange for meeting certain guiding principles. Member laboratories have to agree to notify all confirmed cases to the government, not exceed the agreed-upon ceiling pricing to patients and agree not to use tests that are banned or discouraged by the Indian TB program.

The underlying mechanism of the Initiative is that it creates a sustainable 'win-win-win' situation where patients, the health care system, laboratories and manufacturers benefit. Companies and laboratories benefit because of the higher volumes (even if the margins are lower), and patients benefit because good tests are now more affordable. Within 2 years of its launch, IPAQT has grown to include over 85 member laboratories across India. IPAQT is now being seen as an innovative business model to increase access to quality diagnostics in private markets. Such models could be tried out in other countries with large private health sectors.

■ What are the diagnostics in the pipeline, and when do you expect them to make an impact on the clinic? Might computational biology have a role in future TB diagnostics strategies?

The 2014 UNITAID TB Diagnostic Technology and Market report provides a good summary of the pipeline [10]. As noted in the report, in the short term (3–5 years), we expect to see a rapid expansion of the range of molecular technologies that could potentially replace smear microscopy. Examples of these molecular tests include the Alere q[®] test (Alere, Waltham, MA, USA), Genedrive[®] platform (Epistem, Manchester, UK), EasyNAT[®] (Ustar Biotechnologies, Hangzhou, China), TrueNat[®] test (Molbio Diagnostics, Goa, India), Loopamp[®] (Eiken, Tokyo, Japan) and Q-POC[®] platform (QuantuMDx, Newcastle, UK).

“we expect to see a rapid expansion of the range of molecular technologies that could potentially replace smear microscopy”

We hope that several new molecular products on the market (or in the pipeline) will compete with the Xpert technology, and at least some of them may be automated, biosafe and user-friendly enough (e.g., simple sample preparation and DNA extraction) to be deployable at the level of peripheral microscopy centers where conventional molecular tests have generally not succeeded. In addition to rapid case detection, these newer

molecular tools will have the capacity to identify drug resistance mutations and thus help countries reach the post-2015 target of universal drug-susceptibility testing for all TB patients, right at the time of initial diagnosis. This is a huge advantage of molecular diagnostics over smears.

“the market potential is huge”

In the longer term, we are waiting for the biomarker discovery field to mature and produce non-sputum-based rapid tests, as well as tests that can be used to identify those who are most likely to progress from latent infection to active TB disease. Computational biology might help identify unique biosignature patterns and thus will likely play a role in the development of such novel tests.

■ Is there a market for new TB tests? How does the economic status of the countries in which TB is most prevalent affect this?

The WHO data suggest that 9 million patients develop TB every year and, on average, 5–10 patients with TB symptoms need to be tested to identify one confirmed TB case. So, the market potential is huge, in terms of testing volumes. A recent series of studies have tried to quantify the current served available market value of TB diagnostics [2,11,12]. This includes the smear replacement market and the expenditure on TB diagnosis by countries such as Brazil and South Africa. These studies show that there is a sizeable TB diagnostic market in terms of both volume and value. Our team is also estimating the potential available market for some of the high-priority diagnostics and doing country-specific analyses for China and India.

However, the TB market is very cost-conscious. This is because TB is a disease of poverty, and the majority of TB patients in high-TB-burden countries are socioeconomically disadvantaged. In addition, national TB programs in these countries are often under-funded. So even with the buy-down of price of Xpert MTB/RIF, many high-burden countries have been unable to scale up the Xpert test to test all patients with presumed TB. Therefore, product manufacturers will need to embrace frugal innovation and develop products that can be realistically implemented at scale in low-income countries. Companies cannot develop products for developed markets and hope that such products will get taken up by high-TB-burden countries. Products need to be designed with resource-limited settings in mind, and with a cost-conscious approach.

“we will need companion diagnostics to ensure good alignment between new drug regimens and diagnostics”

■ What about new TB drugs? How can diagnostics support the introduction of new drug regimens for TB?

After nearly 5 decades, we now have new drugs for TB, including bedaquiline (Sirturo[®] by Janssen Therapeutics,

Titusville, NJ, USA), delamanid (Delyba[®] by Otsuka Pharmaceutical Co., Tokyo, Japan) and the likely introduction of a new drug regimen called PaMZ (which contains Pretomanid [previously called PA-824], Moxifloxacin [Bayer AG, Leverkusen, Germany] and Pyrazinamide) in 3 years. While this is positive news, it also means that we will need companion diagnostics to ensure good alignment between new drug regimens and diagnostics. If the PaMZ regimen is to be implemented successfully, we will need to ensure that existing molecular diagnostics are more widely used, and companies will need to develop next-generation molecular assays that can detect resistance to markers that are aligned with novel regimens such as PaMZ. For this to happen, product developers will need better data about the molecular mechanisms of resistance. Several groups such as FIND, Critical Path to TB Drug Regimens [13] and the TB Alliance [14] are working to make this happen.

■ What might other branches of medicine learn from the way in which the challenges of TB diagnostics have been tackled?

Perhaps the converse is a more relevant question: what can the TB community learn from other areas of medicine where diagnostic challenges have been successfully tackled? I think the TB

community has a lot to learn from the successes in the HIV field. The widespread use of rapid tests for HIV, the successful launch of home-based, HIV self-testing products, the successful scale-up of antiretroviral treatment programs with CD4 and viral load testing, the rich pipeline of antiretroviral drugs and the extraordinary engagement of patients and activists should inspire the TB community, so we can modernize TB control. I would be thrilled to see this happen in my lifetime.

“the TB community has a lot to learn from the successes in the HIV field”

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Expert Reviews Ltd.

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The interviewee has no financial or industry conflicts. He serves as a consultant to the Bill and Melinda Gates Foundation. He also serves on the Scientific Advisory Committee of Foundation for Innovative New Diagnostics, Geneva. No writing assistance was utilized in the production of this manuscript.

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