Diagnostics for tuberculosis: what test developers want to know

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"For the first time, there is a lot of industry interest in tuberculosis diagnostics and enthusiasm among product developers … Capitalizing on this, it is important to sustain momentum and support test developers in developing better and more affordable tools for tuberculosis."

In 2013, tuberculosis (TB) continues to be a huge public health problem, with nearly 9 million TB cases every year [101]. Early case detection and rapid treatment remains the most important TB control strategy, and acceleration of the adoption of new TB diagnostic technologies is critical for ensuring early diagnosis and reduced TB transmission. After many decades of stagnation and reliance on antiquated tests, the TB diagnostics pipeline has greatly expanded in the past few years. In the past 5 years, several new or improved technologies have been endorsed by the WHO [1].

The Xpert® MTB/RIF technology (Cepheid Inc., CA, USA) is the biggest recent advance for rapid molecular detection of TB disease and rifampicin resistance. This WHO-endorsed test has high accuracy [2] and is currently being rolled out in many countries, supported by a buy-down of its price to under US$10 and investments by donors such as UNITAID [1].

For the first time, there is a lot of industry interest in TB diagnostics and enthusiasm among product developers [3]. Four new 'fast-follower' TB molecular tests are now on the market [4], and more than 50 diagnostic companies and test developers are actively engaged in developing TB technologies [102].

In December 2012, the US FDA approved bedaquiline, the first new TB drug in more than 40 years. Other new TB drug regimens are expected to reach the market within the next 2–3 years. Consequently, there is growing interest in developing drug susceptibility testing (DST) methods for new TB drugs.

Given the historical lack of industry investments in TB, these trends are quite remarkable. Capitalizing on this, it is important to sustain momentum and support test developers in developing better and more affordable tools for TB. After all, technologies such as Xpert MTB/RIF are still expensive and difficult to scale-up in primary care settings in high TB burden countries. Furthermore, there are many other unmet needs in TB diagnosis. For example, we need improved tests for extrapulmonary and childhood TB, and a simple test that can be used in the community to rapidly triage those who require confirmatory testing [5]. Since existing tests for latent TB infection have limited prognostic ability, we also need more predictive tests [6].

Do test developers have all the information they need to guide their decisions? Which questions matter to them? What are their critical requirements to translate ideas to products on the market? We surveyed over 25 test developers and identified ten critical questions for which credible answers are required [3]. As shown in **Box 1**, the questions range from estimates of TB burden and market size, to market potential for new tests, and cover issues such as target product profiles (TPPs), product

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Box 1. Based on input from more than 25 companies and test developers, these are the ten most critical questions of relevance to test developers and companies wanting to develop tuberculosis diagnostic technologies.

TB burden and treatment landscape

- What is the global burden of TB (including latent TB, TB/HIV and MDR/XDR-TB) and what is the current and future TB treatment landscape?

Current diagnostics landscape and pipeline

- What is the current testing landscape for TB (including latent TB and DST), and what diagnostics are in the pipeline? What is the level of access to current TB diagnostics?

Market size, potential and dynamics

- What is the market size and potential for new TB diagnostics, and what are the market dynamics around TB diagnostics?

Target product profiles

- What are the unmet diagnostic needs and TPPs of greatest relevance?

Product development support

- Where and how can test developers and companies get funding, technical assistance and secure necessary specimens/strains for test development and quality control?

Product validation support

- What kind of validation is required for a new TB diagnostic in order to enter the market and where can companies get support for such validation?

Regulation

- What are the regulatory requirements for TB diagnostics, both nationally and globally?

Policy

- Are global policy endorsements required? If so, what kind of evidence is necessary for global policy endorsements and scale-up?

Procurement and market access

- How do countries procure TB diagnostics? How autonomous is their decision making? How much is it influenced/guided by WHO and/or donors?

Scale-up

- Once a product has been validated, registered and put on the market, and once policy endorsements are obtained, what are the challenges for uptake and scale-up in high burden countries?

DST: Drug susceptibility testing; MDR: Multidrug resistant; TB: Tuberculosis; TPP: Target product profile; XDR: Extensively drug-resistant.

validation support, regulatory barriers, policy, procurement and scale-up challenges.

Beyond the high-level questions shown in Box 1, test developers asked many nuanced questions. For example, what is the likely trajectory of the TB epidemic and future patient demographics over the next 5–10 years? Is the treatment landscape likely to be dramatically different in 5 years and will universal DST be required for all TB patients at the time of initial diagnosis? What is the market potential and what are the barriers for new tests, if Xpert MTB/RIF is scaled-up to reach its saturation? What needs do technologies like Xpert MTB/RIF meet and how much market penetration can we expect for this test? What fraction of the TB testing market will remain? Are countries prepared to replace sputum smear microscopy with molecular tests? And how much are purchasers (e.g., national TB programs) willing to pay for new TB tests? Is US$10 now the price benchmark for all new TB tests?

Some of these questions have been addressed in previous market analyses and needs assessments [103–105]. However, given the rapid evolution of the TB diagnostics landscape, it is clear that updated analyses are necessary to support product development. Such analyses can convince investors and industries about the need and market potential for new tools, help develop TPPs that can guide product development and scale-up and guide investments of donors.

A previous analysis of the global TB diagnostics market estimated that more than US$1 billion were spent worldwide on TB diagnostics annually [103]. A third (US$ 326 million) of this money was spent outside of the established market economies, where 73% of TB diagnostic testing took place. In established market economies (where two-thirds of US$ 1 billion was spent), latent TB testing (i.e., tuberculin skin tests) dominated, while in nonestablished market economies, active TB testing (sputum smears and chest x-rays) dominated [103]. This analysis was conducted nearly a decade ago, and since then big shifts have occurred. For example, more expensive IFN-γ release assays are either replacing or supplementing the tuberculin skin test in many developed countries. In addition, technologies such as liquid culture, line probe assay and Xpert MTB/RIF are being actively scaled-up in developing countries. Furthermore, emerging economies are showing a substantially increased interest in new technologies for TB. India, China and South Africa account for more than 40% of the global TB burden, and are therefore the major markets for TB testing. With rapid economic growth, these countries are also making major investments in TB control. South Africa has already made impressive investments in their nationwide roll-out of the Xpert

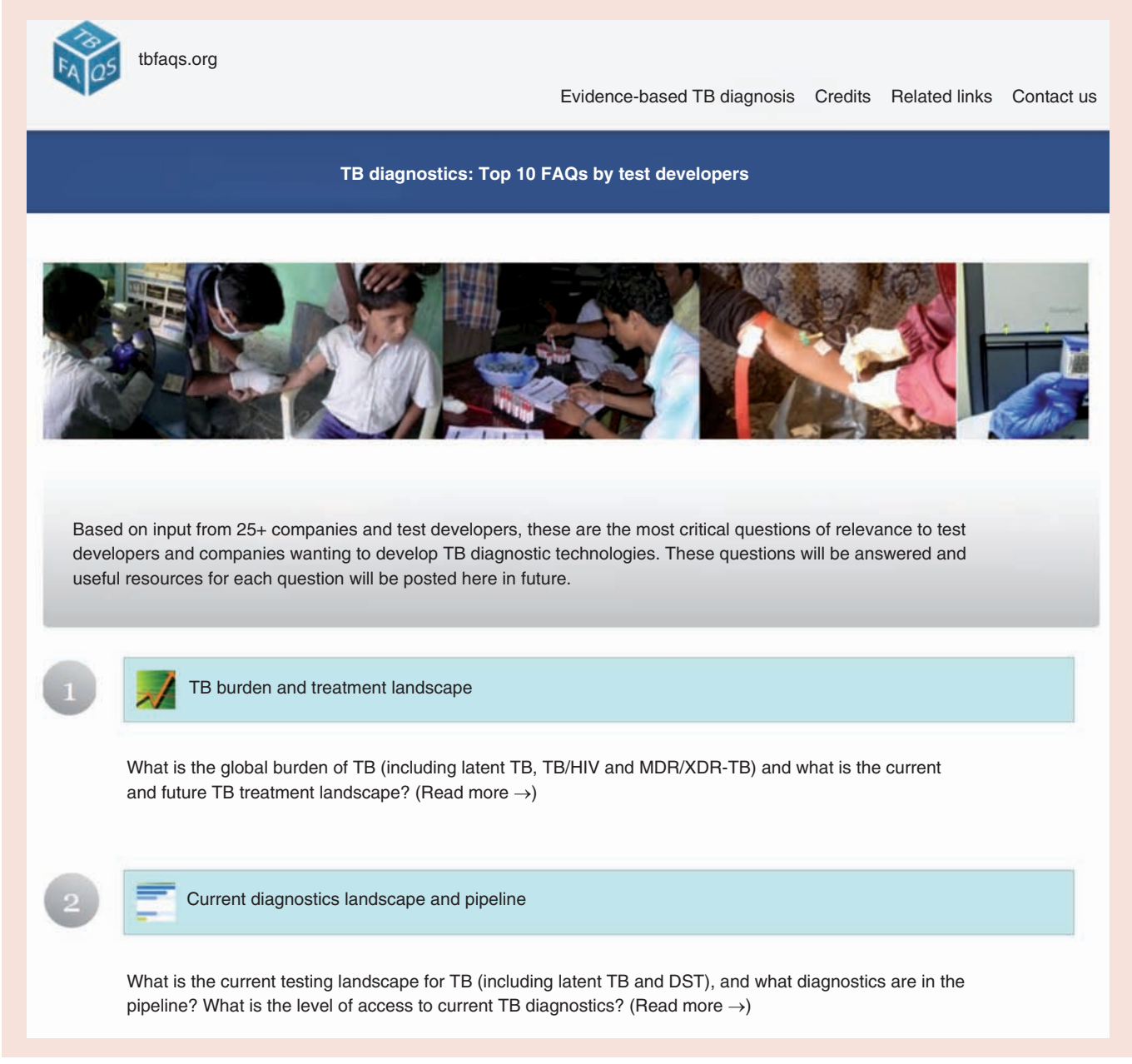

Figure 1. Website resource on top frequently asked questions by tuberculosis test developers.
DST: Drug susceptibility testing; FAQ: Frequently asked question; MDR: Multidrug resistant; TB: Tuberculosis; XDR: Extensively drug-resistant. Reproduced from [107].

MTB/RIF technology, and Brazil and India are likely to follow suit this year. To capture these recent developments, efforts are ongoing to estimate the served available market for TB diagnostics in four emerging economies (India, Brazil, China and South Africa).

Our survey showed that test developers are particularly keen to learn about market size and potential for new technologies. Test developers also need guidance on the most important TPPs, and which TPP attributes really matter. What are the top four to five features that are needed in a TB diagnostic test for developing countries? TPP attributes include: target cost (what are countries or purchasers willing to pay?); desirable sensitivity and specificity targets; infrastructure requirements; time to result; throughput; sputum versus other samples; manual versus automated; requirements for reporting of test results; point-of-care (POC) versus centralized laboratory testing; integrated or reflex drug-resistance test; which drugs to include in DST; TB-only test versus multiplexed platform and instrument/test connectivity requirements.

Although there is widespread agreement that a simple test that can be implemented as a POC testing (POCT) program is urgently needed [5,104], there is no consensus on which TPP attributes will have the biggest impact on reducing the incidence

of TB in disease-endemic countries. There is also awareness that POCT is a spectrum – a single TPP may not be able to fulfill the needs of patients, care providers and laboratory workers across a diversity of settings (e.g., home, community, clinic and laboratory) and testing goals (triage, diagnosis, monitoring and DST) [7]. There is also awareness that technology as such does not define a POCT program. Rather, it is the successful use at the POC to rapidly make treatment decisions on the basis of test results that defines a diagnostic process as POCT [7]. Thus, the focus must be on POCT programs, rather than POC technologies [7]. A project to develop TPPs for POCT programs is currently ongoing and existing TPPs have been compiled elsewhere [106].

We have created a new website resource to outline and answer the major frequently asked questions, including the more nuanced questions within each major category (Figure 1) [107]. It is now important that we answer these questions and make them available in one place, and create an active community of users who can share answers and resources. While some questions can be answered easily (e.g., current TB burden), others require completion of ongoing work (e.g., current market size and TPPs of greatest relevance). Hopefully, by 2014, key questions will be answered, and will prove to be valuable for engaging more test developers in developing better and affordable TB diagnostics.

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