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In Focus

Innovations in Tuberculosis Diagnostics: Progress and Translational Challenges

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Despite the long and hard battle against tuberculosis (TB), WHO estimated that 9 million people developed the disease in 2013, and nearly 1.5 million people died of TB (World Health Organization, 2014). To make matters worse, drug-resistance is a growing threat, and 3 out of 9 million TB cases are either not diagnosed, or not notified to TB control programs.

But there is some good news from the perspective of new tool introduction. Slowly but surely, the landscape of TB technologies is changing (Pai and Schito, 2015). We now have a variety of new TB diagnostics, including rapid molecular tests (e.g. Xpert MTB/RIF, Cepheid Inc., USA) for detection as well as drug susceptibility testing (DST) (UNITAID, 2014). We also have new TB drugs (e.g. bedaquiline and delamanid) on the market, and new TB drug regimens are expected within the next 2–3 years. These are major, exciting developments in the fight against a very ancient scourge.

This article reviews the current best diagnostic tools available for TB diagnosis and monitoring, and describes the most important gaps, and translational challenges for developing innovative products that can meet the needs (Table 1).

As shown in the Table, there are critical unmet needs that range from a simple, triage test for use in the community, to DST tools that can detect a range of mutations for several important drugs that will make up future drug regimens (Denkinger et al., 2015a,b). For the next-generation DST tools, a big translational challenge is the paucity of good data on the correlation of mutations with phenotypic DST results and clinical outcomes and the association with cross-resistance (Solomon et al., 2015). This is particularly important to make sure that we have companion diagnostics for emerging TB drug regimens (Denkinger et al., 2015b). The translational challenges associated with DST are reviewed elsewhere (Solomon et al., 2015).

For the development of rapid triage tests, non-sputum based tests for active TB, highly predictive LTBI tests, and an accurate test for cure, we need validated biomarkers. Although considerable efforts are being made to identify biomarkers that can meet some of these needs, progress has been slow, and the translational challenges have been reviewed elsewhere (Wallis et al., 2010).

Increased investments are necessary to support biomarker discovery, validation, and translation into clinical tools. Unfortunately, a recent analysis of the TB R&D funding landscape by Treatment Action Group showed a big gap between investment needed and actual expenditure on R&D. Donors, governments, and members of the Stop TB Partnership will need to device creative strategies to plug this gap.

While the TB diagnostics R&D space has managed to attract over 50 companies and product developers, they will require technical and funding support to overcome the translational challenges shown in Table 1. Organizations such as Foundation for Innovative New Diagnostics (FIND), Geneva, Bill and Melinda Gates Foundation, World Health Organization, UNITAID, Global Laboratory Initiative, Stop TB Partnership's New Diagnostics Working Group, Critical Path Institute, PATH, McGill International TB Centre, and several academic partners have worked together to produce several reports that are of great relevance, including a technology and market landscape report, a needs assessment study, a consensus report on target product profiles of highest priority, a series of market analyses, and a series of articles which outline the characteristics of the next-generation assays, and translational challenges for product development. All of these are available on a website (www.tbfaqs.org) created to provide answers to the most frequently asked questions by TB product developers. Hopefully, these collective efforts will result in a more robust pipeline of tools that can overcome the translational challenges, and push the agenda towards the goal of TB elimination.

Disclosures

The author has no financial or industry conflicts to disclose. He serves as a consultant to the Bill and Melinda Gates Foundation, and on the scientific advisory committee of the Foundation for Innovative New Diagnostics (FIND), Geneva.

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Table 1
Unmet needs in TB diagnosis and monitoring.

Indication for testing	Currently used tools	Limitations of existing tools	Desirable new tools (key references)	Translational challenges for new tool development (key references)
Triage test to identify individuals with presumed TB who need confirmatory testing	1. TB symptoms (e.g. 2 weeks of cough) 2. Chest x-rays	1. Symptoms lack sensitivity and specificity, especially in HIV-infected populations and children 2. Chest x-rays are sensitive, but not specific for TB	A simple, low cost triage test for use by first-contact care healthcare providers as a rule-out test, ideally suitable for use by community health workers (Denkinger et al., 2015a)	Lack of validated biomarkers (Foundation for Innovative New Diagnostics, 2014).
Diagnosis of active pulmonary TB	1. Sputum smear microscopy 2. Nucleic acid amplification tests (NAAT) 3. Cultures	1. Smear microscopy lacks sensitivity and cannot detect drug resistance. 2. NAAT are expensive and not easily deployable at the peripheral level. 3. Cultures are expensive and require BSL3 labs, and results take time.	A sputum-based replacement test for smear-microscopy; A non-sputum-based biomarker test for all forms of TB, ideally suitable for use at levels below microscopy centers (Denkinger et al., 2015a)	While several NAATs are being developed for microscopy centers, they will need to be evaluated in field conditions for policy. For the non-sputum TB test, the biggest challenge is the lack of validated biomarkers (UNITAID, 2014; Denkinger et al., 2015a; Foundation for Innovative New Diagnostics, 2014).
Diagnosis of extrapulmonary (EPTB) and childhood TB	1. Smear microscopy 2. Nucleic acid amplification tests 3. Cultures	1. Children and patients with EPTB often do not produce sputum. Invasive samples are usually necessary. Smear microscopy lacks sensitivity and cannot detect drug resistance. 2. NAAT are expensive and not easily deployable at the peripheral level. Sensitivity in EPTB samples is lower than sputum. 3. Cultures are expensive and require BSL3 labs, and results take time.	A non-sputum-based biomarker test for all forms of TB, ideally suitable for use at levels below microscopy centers (Denkinger et al., 2015a)	For the non-sputum TB test, the biggest challenge is the lack of validated biomarkers (Foundation for Innovative New Diagnostics, 2014).
Drug susceptibility testing	1. Nucleic acid amplification tests 2. Cultures	1. Current NAATs cannot reliably detect all mutations and sensitivity for drugs other than rifampicin is poor. 2. Cultures are expensive and require BSL3 labs, and results take time.	A new molecular DST for use at a microscopy center level, which can evaluate for resistance to rifampin, fluoroquinolones, isoniazid and pyrazinamide and enable the selection of the best drug regimen (Denkinger et al., 2015b).	Lack of good data on the correlation of mutations with phenotypic results and clinical outcomes and the association with cross-resistance (Denkinger et al., 2015b; Solomon et al., 2015). There is also a need to align emerging TB drug regimens with companion diagnostics (Denkinger et al., 2015b).
Diagnosis of latent TB infection (LTBI)	1. Tuberculin skin test (TST) 2. Interferon-gamma release assays (IGRA)	Neither TST nor IGRA can separate latent infection from active disease. Neither test can accurately identify those at highest risk of progression to active disease.	A test that can resolve the spectrum of TB, and identify the subset of latently infected individuals who are at highest risk of progressing to active disease, and will benefit from preventive therapy (Pai et al., 2014; Barry et al., 2009).	Lack of validated biomarkers (Pai et al., 2014; Barry et al., 2009).
Test of cure (treatment monitoring)	1. Serial smear microscopy 2. Serial cultures	1. Smears lack sensitivity, and cannot distinguish between live and dead bacilli. 2. Serial cultures are expensive and time-consuming.	An accurate test for cure that can be used to make changes in management (e.g. changes in regimens, or DST) (Wallis et al., 2010).	Lack of validated biomarkers (Wallis et al., 2010).

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