



Commentary

A 10-Gene Signature for the Diagnosis and Treatment Monitoring of Active Tuberculosis Using a Molecular Interaction Network Approach



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In 2015, there were over 10 million cases of tuberculosis, with a resulting 1.8 million deaths, making TB the biggest infectious disease killer today (World Health Organization, 2016). Early diagnosis leading to timely and appropriate treatment of TB is an essential pillar of the End TB strategy, but completion of this foundational step in the TB cascade of care is often difficult (Subbaraman et al., 2016). Smear microscopy, still the most frequently utilized diagnostic technique for TB, has low sensitivity; microbiological culture takes weeks to produce results; Xpert MTB/RIF is often inaccessible due to both cost and location (Pai and Schito, 2015). In response to these circumstances, researchers have turned to the host response to TB in an effort to identify biomarkers upon which new diagnostic techniques may be based.

Multi-gene host signatures are one such area of investigation. As reported in *EBioMedicine*, Chandra and colleagues applied a computational method that allowed them to identify a transcript signature that can diagnose active TB (Sambarey et al., 2016). In an “unbiased” approach to biomarker discovery, starting with RNA-Sequencing data from nearly 60,000 genes, the investigators constructed a molecular interaction network of genes that were involved only during active TB, ultimately selecting a 10 gene signature. By using a biological network analysis, the investigators were able to highlight the most relevant transcriptional changes occurring during active TB disease. The researchers showed that the signature discriminates between TB patients and healthy controls, individuals with latent TB infection (LTBI), people living with HIV (PLHIV), and most importantly TB and other diseases with an accuracy of 0.74. Interestingly, the signature also changes in response to anti-TB therapy, making it potentially useful for monitoring treatment

efficacy and predicting relapse. Can these early laboratory findings now be translated into a diagnostic solution with patient impact?

A sensitive point-of-care test for active TB is desperately needed, particularly in highest burden countries where availability of diagnostic services is often sparse (Huddart et al., 2016). In response to this, WHO has published a series of target product profiles (TPP) for biomarker-based diagnostic tests that can accurately detect TB and classify would-be patients (World Health Organization, 2014). It has been estimated that the market for such a technique would be over 50 million tests annually (Kik et al., 2015). A blood-based, multi-gene signature that has been tested on patients in different countries, such as that described by Sambarey et al., could be a fit for the criteria described in these TPPs, and could serve as a foundation for a future, more automated test. In the meantime, validation of these gene signatures must continue.

As its performance against a variety of control groups has been demonstrated, testing this 10-gene signature in a prospective cohort study will be an important and clinically meaningful next validation step. Within the field of TB biomarkers, and biomarkers generally (Poste, 2011), many exploratory studies are published that present promising diagnostic biomarker or biosignature candidates, but further follow-up or validation of them is relatively rare.

The 10-gene biosignature reported here is part of a growing body of research utilizing host RNA as a diagnostic biomarker for TB. Multiple research groups have published different diagnostic gene signatures for the detection of active TB in the past few years, some containing as few as three genes (Sweeney et al., 2016). Others (Zak et al., 2016) reported on a prospective cohort study to predict risk of progressing to TB disease. As well as presenting diagnostic transcript signatures for TB, these kind of studies provide cohort data so that *in silico* validation by other researchers of their own signatures is possible; Sambarey and colleagues validated their 10-gene signature against a variety of published cohorts.

While these are promising developments, it is important to mention that no signature has so far met TPP minimum requirements for sensitivity and specificity in relevant patient populations (i.e. patients with presumptive TB in the case of active TB). As well, there is currently no existing platform for near-patient testing that can run a transcript-based assay in low resource settings. These will be significant hurdles to overcome once the diagnostic performance of a transcript signature has been validated.

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The field of diagnostic TB biomarkers and biosignatures is a growing research area. Initial results are encouraging, but the path to clinical utility and patient impact is long and uncertain. For transcript signatures, refinement of diagnostic performance, assay transfer and development, clinical trials in intended settings, and regulatory approval are only some of the challenges to implementation and patient impact. Overcoming them will require integration of diverse resources, stakeholders, and decision-makers. For now, validation of promising diagnostic signatures, such as the 10-gene signature reported here, must proceed in order to continue progress in the TB biomarkers pipeline.

Disclosure

EM has no conflicting interests. TB is employed by FIND (Geneva, Switzerland), a nonprofit organization that collaborates with industry partners.

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