Blood transcriptomic biomarkers for tuberculosis screening: time to redefine our target populations?

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The seminal observation that blood transcriptomic changes can predate diagnosis of active tuberculosis set the field on a course to evaluate their potential impact as screening tools for early detection of disease.[1] Early detection would allow prompt treatment initiation, which could permit shorter courses of therapy and reduce morbidity, mortality, and onward transmission of infection.

In the study published by *The Lancet Global Health*, Simon C Mendelsohn and colleagues[2] make an important contribution to the field by assessing the diagnostic accuracy and prognostic ability of an 11-gene transcriptomic signature (RISK11) among people living with HIV in South Africa. Mendelsohn and colleagues[2] use an observational cohort study design that overcomes the inherent risk of spectrum bias present in case-control studies, in which the inclusion of more extreme phenotypes can lead to overly optimistic assessments of diagnostic accuracy.[3] In addition, they use real-time PCR technology with predefined test thresholds amenable to development for clinical diagnostic tests. The study is well conducted, using robust outcome definitions and comprehensive statistical analyses. Nonetheless, such studies can be challenging. Despite the focus on people living with HIV, who represent an important target group for early tuberculosis detection and prevention efforts, and the inclusion of 820 individuals with valid RISK11 results, there were only eight prevalent and eight incident primary outcome tuberculosis events. The authors found that RISK11's performance approached (albeit did not meet) WHO's target product profile benchmarks for screening and prognostic tests,[4] but the low event rate led to wide CIs in the performance metrics.

So where does the field go next? Several key questions should be answered before blood transcriptomic biomarkers can be considered for programmatic implementation. First, a wide range of emerging transcriptomic, proteomic, metabolomic, and microbiological biomarkers have been proposed to facilitate early tuberculosis diagnosis.[5] The study by Mendelsohn and colleagues[2] suggests that RISK11 might perform better than alternative triage strategies (ie, WHO's symptom screen or the Alere Determine TB lipoarabinomannan [LAM] assay) and an interferon-γ release assay as a prognostic test (QuantiFERON TB Gold-Plus). However, four other candidate blood transcriptomic signatures have consistently performed well in systematic head-to-head assessments for prevalent and incident tuberculosis,[6,7] and a point-of-care assay of C-reactive protein[8] and a urine Fujifilm SILVAMP TB LAM assay[9] have shown strong potential for tuberculosis screening among people with HIV. Head-to-head assessments of these promising biomarkers will be an important extension of the study by Mendelsohn and colleagues and could identify the best performing candidates. Such comparisons should also include health economic considerations. For example, the current cost of a blood transcriptomic test is likely to far exceed the minimum WHO target of less than US$2 for a triage test;[4] cheaper assays (eg, point-of-care C-reactive protein) might have a competitive advantage in this regard. Future approaches could also consider integrating biomarker results into multivariable prediction tools to improve discrimination between disease states.[10]

Second, how individuals with a positive blood transcriptomic biomarker test should be treated remains to be determined. Thus far, clinical trials have dichotomised the management of tuberculosis into preventive treatment for latent infection (with fewer agents for shorter periods of time) and treatment of tuberculosis disease (with more agents for longer periods of time). Subclinical or incipient disease that might be detected by blood transcriptomic biomarkers falls into the gap between these two ends of the spectrum. Early data from randomised controlled trials have long been presented to show that paucibacillary (smear-negative) disease might be adequately treated with truncated antimicrobial regimens,[11,12] but 3 months of weekly rifapentine and isoniazid did not reduce the incidence of tuberculosis among HIV-uninfected, RISK11-positive people in the general population in the CORTIS trial.[13]

Finally, it remains unclear whether the diagnostic accuracy or prognostic ability achieved by RISK11 among ambulatory people living with HIV is sufficient to

translate into clinical utility, a reduction in tuberculosis incidence, or cost-effectiveness. Notably, Mendelsohn and colleagues found that the positive predictive values of RISK11 were only 2·5% for primary prevalent tuberculosis and 3·2% for primary incident tuberculosis. These values reflect a combination of low event rates and imperfect test specificity, underlined by the fact that 35% of people were RISK11-positive at baseline. Previous data have also shown that test sensitivity wanes markedly after a 3–6-month time horizon, suggesting that blood transcriptomic biomarkers reflect only short-term risk of disease.[6,13] Taken together, this evidence suggests that the optimal implementation of these biomarkers will require careful selection of target populations who are at the highest risk of disease in the short term to maximise positive predictive values and reduce the number needed to treat with tuberculosis therapy. Such target groups could include recent case contacts and, potentially, people with HIV during intensified screening for subclinical disease before antiretroviral therapy initiation.[14]

MN has a patent pending for a method for detecting active tuberculosis (WO2017/050483). RKG declares no competing interests.

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