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Validating novel diagnostic assays for tuberculosis in the context of existing tools

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Simon Mendelsohn and colleagues (June, 2021)[1] evaluated the diagnostic and prognostic accuracy of a blood transcriptomic signature (RISK11) for prevalent active tuberculosis and incipient tuberculosis among people living with HIV in five South African communities. The development and validation of novel triage tests, such as RISK11, represents a crucial step towards closing gaps in tuberculosis diagnosis and prevention.

Although assays utilising transcriptomic signatures hold exciting promise, we must not lose sight of simpler diagnostic approaches, including presenting history and readily available biomarkers, such as C-reactive protein (CRP), which is available in a lateral flow, point-of-care format. For example, against a reference standard of a single positive sputum culture for the identification of prevalent tuberculosis, RISK11's accuracy among people with HIV (area under the receiver operating characteristic curve [AUC] 80·3%, 95% CI 71·4–88·2)[1] was similar to that of CRP concentrations (AUC 82%)[2] and a simple clinical risk score assessing six patient characteristics (AUC 75%, 95% CI 69–80)[3] in the general population. Although these simpler diagnostic approaches have not been validated in the prediction of incident tuberculosis, their prognostic performance might also compare to that of RISK11 (as people with prevalent and incident tuberculosis share many characteristics).

We do not wish to discount the tremendous potential of transcriptomic signatures, but rather wish to highlight the importance of rigorously evaluating simpler diagnostic approaches—

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independently, compared against, and in combination with more advanced tools such as RISK11. Future studies could evaluate novel candidate tuberculosis triage tests alongside clinical characteristics (eg, simple risk scores) and biomarkers (eg, CRP concentrations), thereby facilitating comparisons against the actual data likely to be available to treating clinicians, and not against a hypothetical threshold based on target product profiles. Furthermore, investigators could consider the explicit synthesis—through stratification, multivariable analyses, or both—of clinical data and existing biomarkers with emerging tools, because the combined diagnostic and prognostic performance (eg, of RISK11, CD4 cell count, and clinical characteristics) might be substantially greater. The utility of such diagnostic combination approaches is well described.[2,4,5] Such analyses might require larger sample sizes and thus collaborative efforts across cohorts. However, using existing (ie, clinical, biomarker, and transcriptomic) data in combination might be simpler, more cost-effective, and more accurate than developing additional tools.

In conclusion, we are excited by the increased attention being paid to the tuberculosis diagnostic pipeline. However, it is also important to evaluate emerging diagnostic tools for tuberculosis against clinical characteristics and available biomarkers, and to identify opportunities for synergy between clinical characteristics, available biomarkers, and emerging tools to optimise tuberculosis risk prediction.

References

1. Mendelsohn SC, Fiore-Gartland A, Penn-Nicholson A, et al. Validation of a host blood transcriptomic biomarker for pulmonary tuberculosis in people living with HIV: a prospective diagnostic and prognostic accuracy study. Lancet Glob Health 2021; 9: e841–53. [PubMed: 33862012]
2. Dhana A, Hamada Y, Kengne A, et al. Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis. Lancet Infect Dis (in press).
3. Baik Y, Rickman HM, Hanrahan CF, et al. A clinical score for identifying active tuberculosis while awaiting microbiological results: development and validation of a multivariable prediction model in sub-Saharan Africa. PLoS Med 2020; 17: e1003420. [PubMed: 33170838]
4. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. BMC Med 2013; 11: 231. [PubMed: 24168211]
5. D'Acremont V, Kilowoko M, Kyungu E, et al. Beyond malaria—causes of fever in outpatient Tanzanian children. N Engl J Med 2014; 370: 809–17. [PubMed: 24571753]