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New transcriptomic blood test to screen for TB disease and monitor response to TB treatment

Researchers from the South African Tuberculosis Vaccine Initiative (SATVI) at the University of Cape Town, the Center for Infectious Disease Research in Seattle, and a large consortium of collaborators have developed a new simple blood-based test that can identify healthy individuals who are at risk of developing TB disease, identify those with subclinical or clinical disease, and can inform how well a patient would respond to TB treatment.

This 6-gene RNA biomarker, known as RISK6, was validated in seven independent cohorts across two continents using quantitative real-time (qRT) polymerase chain reaction (PCR). The researchers also demonstrate that the test, which can be applied to capillary blood collected by finger prick, could be developed into a rapid, fingerprick blood-based test device for use at the point of care. This advance, published in the journal *Scientific Reports* on 25 May 2020, paves the way for point-of-care field evaluation and implementation studies of this test in community and primary care settings.

More than 1.7 billion persons are estimated to be infected with the bacterium *Mycobacterium tuberculosis* globally, of which 10 million developed TB disease and over 1.4 million died in 2018 (*WHO Global TB Report 2019*). Our current diagnostic tools rely on the detection of *Mycobacterium tuberculosis* in sputum, which is only possible in people with advanced disease and who can produce sputum samples. We currently do not have any effective tests that can detect the bacterium or the disease in people who are not symptomatic. We also do not have tests that can predict which healthy individuals who are infected with the bacterium (latent TB), will progress to TB disease. Effective tools to monitor the response to TB treatment are also lacking.

There is growing cognisance in the scientific community that if we are to reduce *Mycobacterium tuberculosis* transmission and curb the infection rate, we will need to find and treat individuals with TB disease much earlier during their disease progression, ideally before they develop symptoms. Even better, a prognostic test that can identify healthy individuals who are at high risk of progression to disease would allow a physician to prescribe a targeted course of preventive antibiotic treatment before transmission occurs, preventing individuals with TB from infecting others. In South Africa it is estimated that the average person with TB can infect up to 10 people before being diagnosed and receiving treatment. Such a prognostic test would allow more efficient use of TB preventive therapies. In South Africa, as in many developing countries, where 60-80% of sections of the population are infected with the bacterium, latent TB is not treated as part of the standard of care, because treating such vast numbers is not feasible.

In this study, the investigators show that the prognostic performance of the new RISK6 test significantly exceeded that of previous candidate tests discovered in the same South African cohort. RISK6 performance for diagnosing subclinical and clinical disease in both HIV-uninfected and HIV-infected persons met or approached the benchmarks for a new test set out in published World Health Organization target product profiles for non-sputum-based triage or screening tests. In addition, RISK6 scores correlated with degree of lung immunopathology, measured by positron emission tomography, and tracked TB treatment response, demonstrating utility as treatment response biomarker. RISK6 also allowed identification of patients with failed TB treatment prior to treatment initiation, demonstrating that a blood test may be used to guide or adjust TB treatment to achieve better efficacy. The study also showed that performance of the test in capillary blood samples collected by finger-prick was noninferior to venous blood collected in PAXgene tubes. RISK6 has the potential to fill a critical gap in tools required to achieve non-sputum screening of communities to identify those at greatest need for treatment, and to monitor treatment response.

A particular strength of this paper is the extensive validation of the RISK6 test in 7 external human study cohorts assembled by clinical collaborators from The Gambia, Ethiopia, South Africa, Peru, and Brazil. This large consortium includes collaborating researchers from Stellenbosch University, Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine at the University of Cape Town, the Centre for the AIDS Programme of Research in Africa, and the South African Medical Research Council in South Africa; the Medical Research Council of the Gambia; Max Planck Institute for Infection Biology in Germany; Harvard Medical School, Hagler Institute for Advanced Study at Texas A&M University, Vanderbilt University School of Medicine and the Catalysis Foundation for Health in the USA; and Fundação Oswaldo Cruz in Brazil.

Read the full study.

ENDS

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