

# Two interferon gamma release assays for predicting active tuberculosis: the UK PREDICT TB prognostic test study

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**Declared competing interests of authors:** Ibrahim Abubakar is a member of the Health Technology Assessment (HTA) Commissioning Board. Ajit Lalvani is a named inventor on several patents underpinning the T-SPOT.TB test assigned by the University of Oxford to Oxford Immunotec Ltd and has royalty entitlements from the University of Oxford. He was the scientific founder of Oxford Immunotec Ltd and ceased to be a director 10 years ago. He is a member of the National Institute for Health Research (NIHR) Efficacy and Mechanism Evaluation Board. Charlotte Jackson was funded by NIHR, during the conduct of the study, and reports personal fees from Otsuka Pharmaceutical, outside the submitted work. Chris Griffiths is involved in NIHR-funded clinical trials units. Jonathan J Deeks is Chairperson of the NIHR HTA Efficient Studies Themed Board, Chairperson of the NIHR HTA Multimorbidities in Older People Themed Board, Deputy Chairperson of the NIHR HTA Commissioning Board, Chairperson of the NIHR HTA Monitoring Strategy Group, a member of the NIHR HTA Methods Group for Diagnostic, Technologies & Screening, a member of the NIHR HTA Methods Group for Elective & Emergency Specialist Care, a member of the NIHR HTA Programme Commissioning Strategy Group and a member of the NIHR HTA Strategy and Oversight Group. The other authors have no competing interests to declare.

Published October 2018

DOI: 10.3310/hta22560

## Scientific summary

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Health Technology Assessment 2018; Vol. 22: No. 56

DOI: 10.3310/hta22560

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# Scientific summary

## Background

Although there has been a decline in the incidence of tuberculosis (TB) in the UK over the past few years, rates remain higher than in most Western European countries. This study has investigated the predictive values and cost-effectiveness of different combinations of the tuberculin skin test (TST) and two interferon gamma release assays (IGRAs) in contacts (of people with TB) and new entrants to the UK.

## Objectives

1. To assess the prognostic value of the two current IGRAs compared with the standard Mantoux test for predicting active TB among untreated individuals at increased risk of latent TB infection (LTBI), among contacts of active TB cases and among new entrants to the UK from high-TB-burden countries.
2. To assess the cost-effectiveness of various screening strategies [including the two-step approach recommended by the National Institute for Health and Care Excellence (NICE)] using IGRAs and/or TST in defined patient groups (contacts and new entrants to the UK stratified by age and risk).

## Methods

A prospective cohort design was used to investigate the predictive value of the two commercial IGRAs and the tuberculin Mantoux skin test. Participants were recruited in TB clinics, general practices and community settings. Contacts of active TB cases, migrants who were born in high-TB-burden countries but had arrived in the UK within the previous 5 years or those who had travelled frequently in the previous 5 years were eligible to take part if they were aged  $\geq 16$  years. Outcomes include incidence rate ratios comparing the incidence of active TB in those with a positive test result compared with those with a negative result for each assay and combination of assays, positive and negative predictive values and cost per quality-adjusted life-year (QALY) for each screening strategy.

## Results

The study recruited 10,045 participants between May 2010 and July 2015. A total of 175 participants had active TB at baseline (diagnosed or treated  $< 21$  days after being recruited) and another 260 were treated for LTBI, leaving 9610 evaluable participants, of whom 97 (1.0%) developed active TB. For the primary analyses, data for the 6386 participants with all test data (including 77 participants who developed active TB) were used.

A positive result for TST<sup>a</sup> (a skin induration of  $\geq 5$  mm) was a significantly poorer predictor of progression to active TB than positive results for all other tests. Compared with TST<sup>b</sup> alone [positive if (1) there is a skin induration of  $\geq 6$  mm following the standard TST and the participant was not known to have had a bacillus Calmette–Guérin (BCG) vaccination or (2) there is a skin induration of  $\geq 15$  mm for those known to have had a BCG vaccination], T-SPOT<sup>®</sup>.TB (Oxford Immunotec Ltd, Oxford, UK), TST<sup>a</sup> + T-SPOT.TB, TST<sup>a</sup> + IGRA and the three combination strategies including TST<sup>b</sup> were significantly superior predictors of progression. Compared with the T-SPOT.TB test alone, TST<sup>a</sup> + T-SPOT.TB, TST<sup>b</sup> + QuantiFERON<sup>®</sup> TB Gold In-Tube (QFT-GIT; Cellestis International Pty Ltd, Chadstone, VIC, Australia) and TST<sup>b</sup> + IGRA were significantly superior predictors of progression and, compared with QFT-GIT alone, T-SPOT.TB, TST<sup>a</sup> + T-SPOT.TB, TST<sup>a</sup> + QFT-GIT, TST<sup>a</sup> + IGRA, TST<sup>b</sup> + T-SPOT.TB, TST<sup>b</sup> + QFT-GIT and TST<sup>b</sup> + IGRA were significantly superior predictors of progression.

When evaluating the negative predictive performance of tests and strategies, negative results for TST<sup>a</sup> + QFT-GIT were significantly poorer predictors of non-progression than negative results for TST<sup>a</sup>, T-SPOT.TB and TST<sup>a</sup> + IGRA. Negative results for TST<sup>b</sup> + QFT-GIT were significantly poorer predictors of non-progression than negative results for TST<sup>a</sup>, TST<sup>b</sup>, T-SPOT.TB, TST<sup>a</sup> + T-SPOT.TB, TST<sup>a</sup> + IGRA, TST<sup>b</sup> + T-SPOT.TB and TST<sup>b</sup> + IGRA, which all performed better.

The most cost-effective LTBI testing strategy is TST<sup>b</sup> + QFT-GIT. However, the estimated cost and QALY differences between the LTBI testing strategies were small, in particular QFT-GIT, TST<sup>b</sup> + T-SPOT.TB and TST<sup>b</sup> + QFT-GIT gave very similar incremental net benefit estimates.

## Conclusion

This study investigated the optimal screening strategy for LTBI, based on existing technologies. It did not find evidence that any particular test or combination of tests was superior to other approaches in identifying individuals who would go on to develop active TB. However, a two-step approach that combined TST<sup>b</sup> with an IGRA was the most cost-effective testing option.

## Implications for health care

The current recommendation by NICE for contacts is to offer the Mantoux test using a 5-mm threshold (the more cost-effective option), and consider IGRAs if TST is not available. Our results demonstrate that a two-step process using the more nuanced TST<sup>b</sup> strategy, which stratified the TST by prior BCG vaccination, followed by an IGRA, was the most cost-effective approach.

## Implications for future research

Further research to develop new markers with better predictive ability utilising transcriptomics, new antigens and cytokines, metabolomics and proteomics is ongoing. Ongoing work with the Prognostic Evaluation of Diagnostic IGRAs ConsorTium (PREDICT) biobank is likely to result in better biomarkers for progression and the development of new assays. The cost-effectiveness of these new assays, using progression data from this study, should be assessed.

The limited ability of current tests to predict who will progress to active TB limits the utility of latent TB detection and treatment. The widespread treatment of groups who may have a positive IGRA or TST result is unlikely to be cost-effective; the most cost-effective delivery of treatment is likely to be focused on the highest-risk groups. Further research should investigate the implications of these results on the NHS England/ Public Health England national TB screening programme for migrants from high-TB-burden countries.

## Study registration

This study is registered as NCT01162265.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.513

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

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## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/68/01. The contractual start date was in May 2010. The draft report began editorial review in August 2017 and was accepted for publication in January 2018. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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