Can we predict progression from latent to active TB?

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RESEARCH ARTICLE

The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling

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1.7 billion individuals were latently infected with MTB globally in 2014, ~25% of the global population

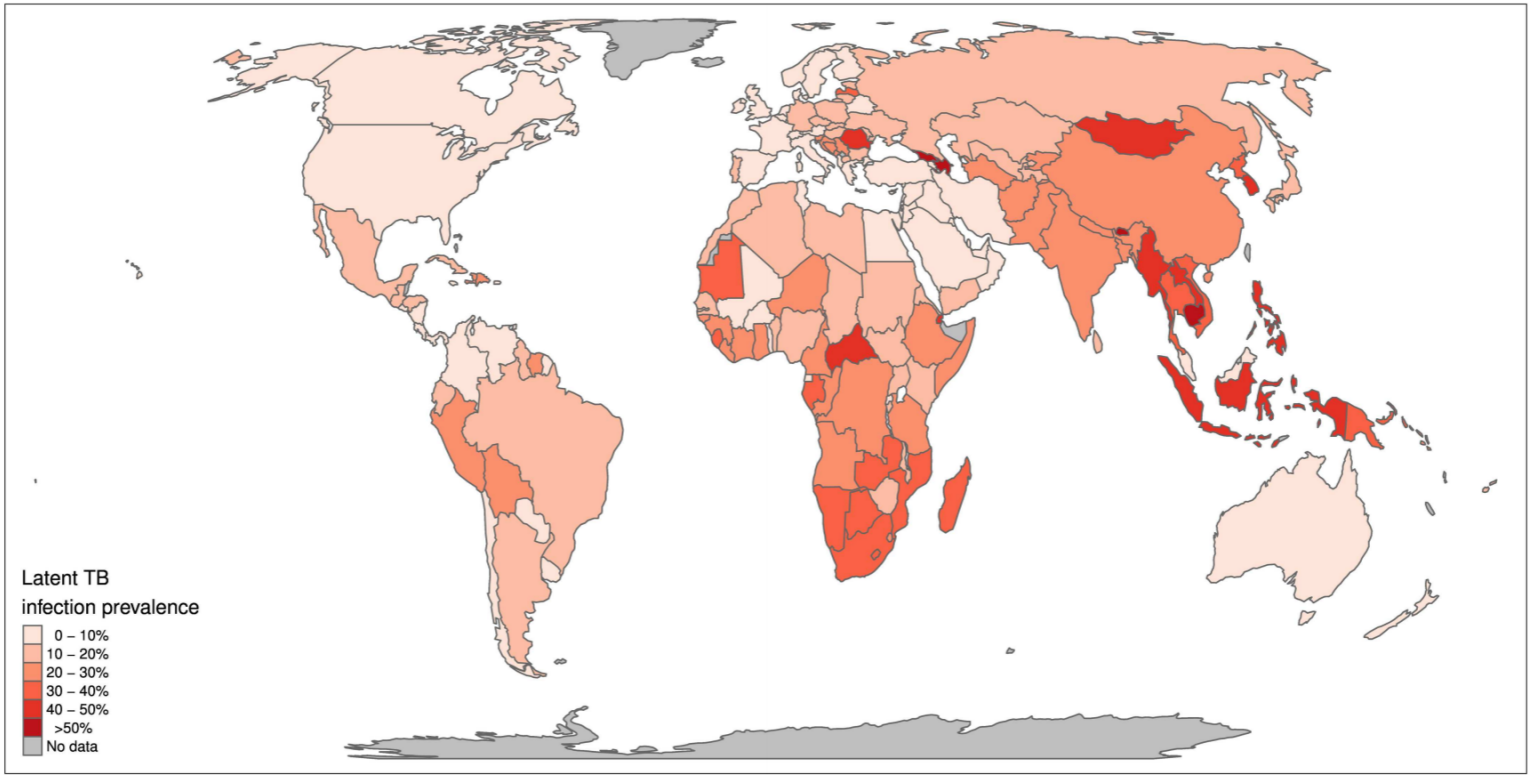


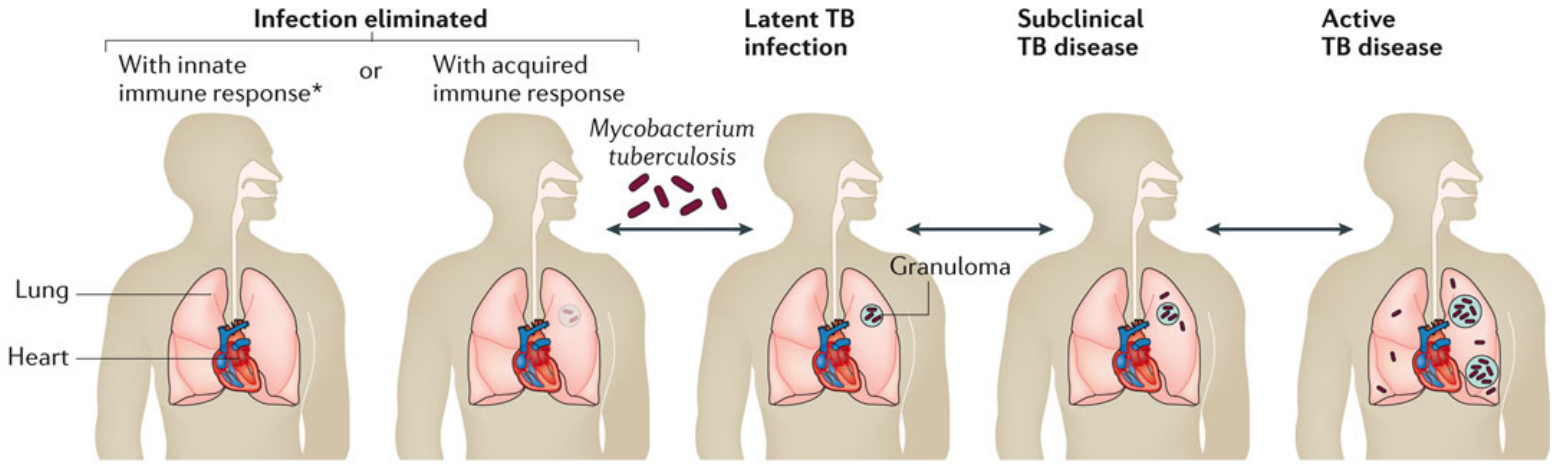
Fig 2. Global map of prevalence of latent TB infection. Median estimated population prevalence of latent *Mycobacterium tuberculosis* infection by country, 2014.

doi:10.1371/journal.pmed.1002152.g002

So, who should we treat for LTBI?

Those who really need it!

The spectrum of TB



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Nature Reviews | Disease Primers

Pai, M. *et al.* (2016) Tuberculosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.76

Existing LTBI dx cannot resolve the spectrum

TABLE 1 A comparison of available diagnostics for latent TB infection[a]

Characteristic	PPD-based tuberculin skin tests	Newer, specific skin tests (under development or validation)	Interferon-gamma release assays
Examples of products in the category	Tubersol, Aplisol, PPD RT23	C-Tb, Diaskintest	QuantiFERON-TB Gold In-Tube; T-SPOT.TB
Testing format	Intradermal skin test (*in vivo*)	Intradermal skin test (*in vivo*)	*Ex vivo* assay (ELISA or ELISPOT)
Antigens used	Purified protein derivative	ESAT-6 and CFP-10	ESAT-6 and CFP-10
Intended use	Screening for LTBI	Screening for LTBI	Screening for LTBI
Sensitivity	High	Modest	Modest
Sensitivity in immunocompromised populations	Reduced	Reduced	Reduced
Specificity	Modest	High	High
Impact of BCG on specificity	High (when BCG is given after infancy or multiple times)	None	None
Ability to distinguish latent from active TB	Low	Low	Low
Ability to predict progression to active TB disease	Modest	Unknown (but likely to be modest based on indirect evidence from IGRAs)	Modest
Ability to resolve the various stages within the spectrum of *M. tuberculosis* infection	Low	Low	Low
Reagent costs	Low	Unknown (but likely to be low based on indirect evidence from PPD-based TST)	High
Requirement for laboratories	No	No	Yes

[a]Data from reference 31. BCG, bacillus Calmette-Guérin; CFP-10, culture filtrate protein; ELISA, enzyme-linked immunosorbent assay; ESAT-6, early secreted antigen target; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; PPD, purified protein derivative.

Adapted from Pai M, Sotgiu G. Eur Resp J 2016

Meta-analysis of predictive value
15 cohort studies

published in 2012

Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis

Lancet Infect Dis 2012; 12: 45–55

Molebogeng X Rangaka, Katalin A Wilkinson, Judith R Glynn, Daphne Ling, Dick Menzies, Judith Mwansa-Kambafwile, Katherine Fielding, Robert J Wilkinson, Madhukar Pai

"Neither IGRAs nor the TST have high accuracy for the prediction of active TB…"

Predictive utility of the TST and IGRA among individuals who are not prescribed TB preventive therapy

Commissioned by WHO

Sandra Kik,
Molebogeng Rangaka
et al.

McGill

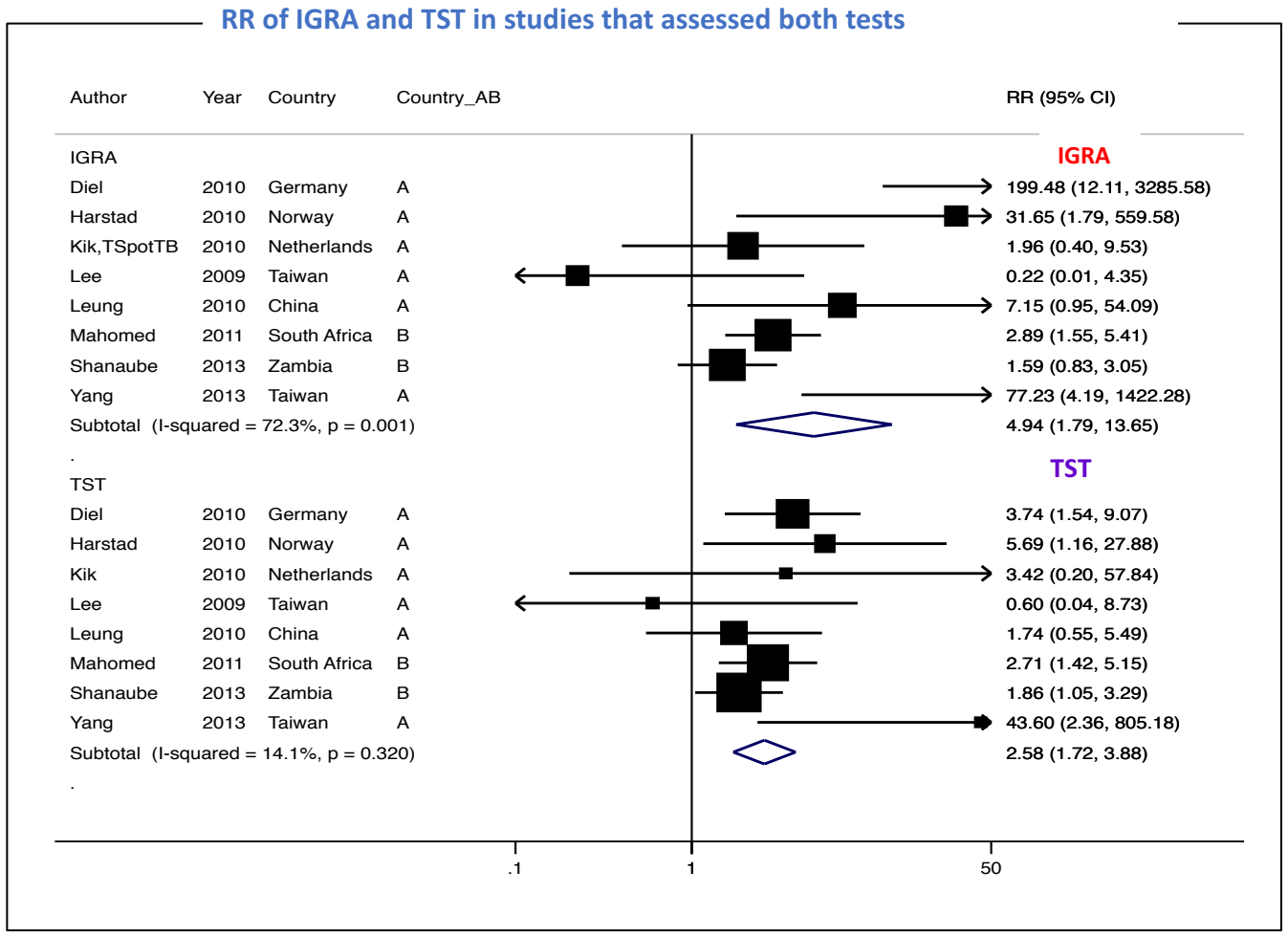
Centre international de TB McGill

McGill International TB Centre

University of Cape Town · Universiteit van Kaapstad · Yunivesithi yaseKapa

UCL

Increased Risk Ratio for TB after a positive TST or IGRA: 2.5-5 fold

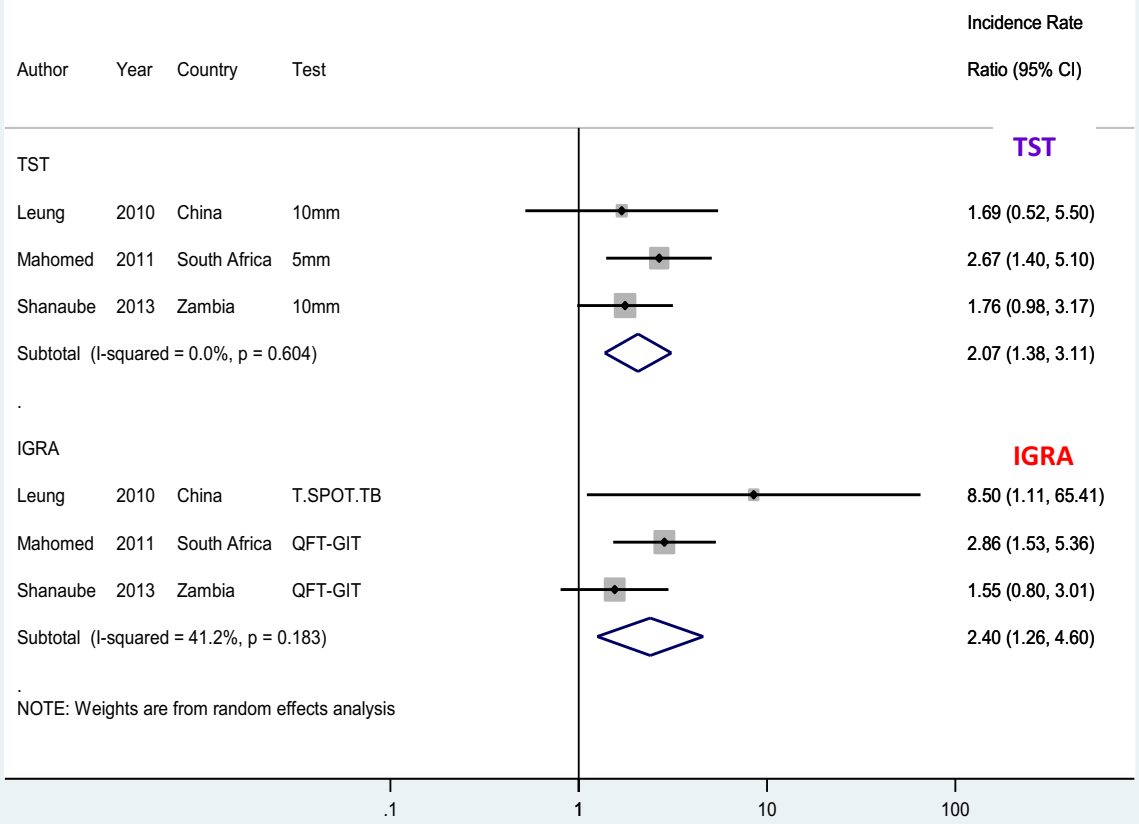


	RR, head to head	
	TST	IGRA
Overall (n=8)	**2.58 (1.72-3.88) I2=14%**	**4.94 (1.79-13.65) I2=72%**

Sandra Kik, MX Rangaka, Pai M. Unpublished data, confidential

Incidence Rate Ratio of TST and IGRA: 2-2.5 fold

IRR of IGRA and TST in head to head studies



	IRR, head to head	
	TST	IGRA
Overall (n=3)	2.07 (1.38-3.11) I2=0%	2.40 (1.26-4.60) I2=41%

Sandra Kik, MX Rangaka, Pai M. Unpublished data, confidential

Some inferences from the updated review

- Incidence rates of TB, even in IGRA positive individuals, are low, suggesting that a vast majority (>95%) of IGRA+ individuals do not progress to TB disease. This is similar to the TST.

- IGRAs have similar predictive value as the TST in head-to-head studies (perhaps slightly higher, but statistically not significant).

- All existing LTBI tests (TST and IGRAs) have only modest predictive value and may not help identify those who are at highest risk of progression to disease.

Sandra Kik, MX Rangaka, Pai M. Unpublished data, confidential

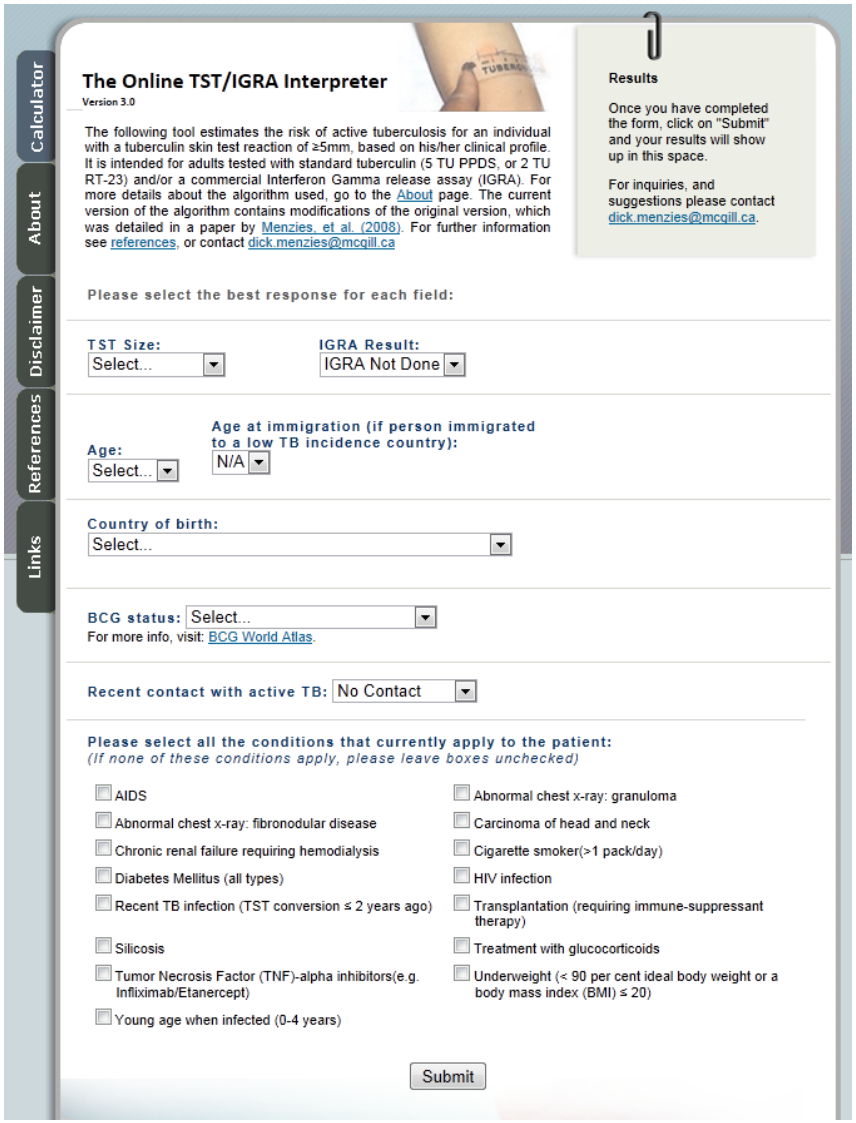
How can we squeeze predictive value out of LTBI tests?

1. Only test those who are at high risk
2. Incorporate biomarkers with other known risk factors (age, recent conversion, HIV etc.) into a composite scoring system to generate multivariable risk prediction models
3. Identify new biomarkers that are more predictive
4. Use serial testing to resolve underlying phenotypes (e.g. stable conversions)

Use composite risk prediction models: test + risk factors

http://www.tstin3d.com

Composite risk prediction models that incorporate biomarker and risk factors

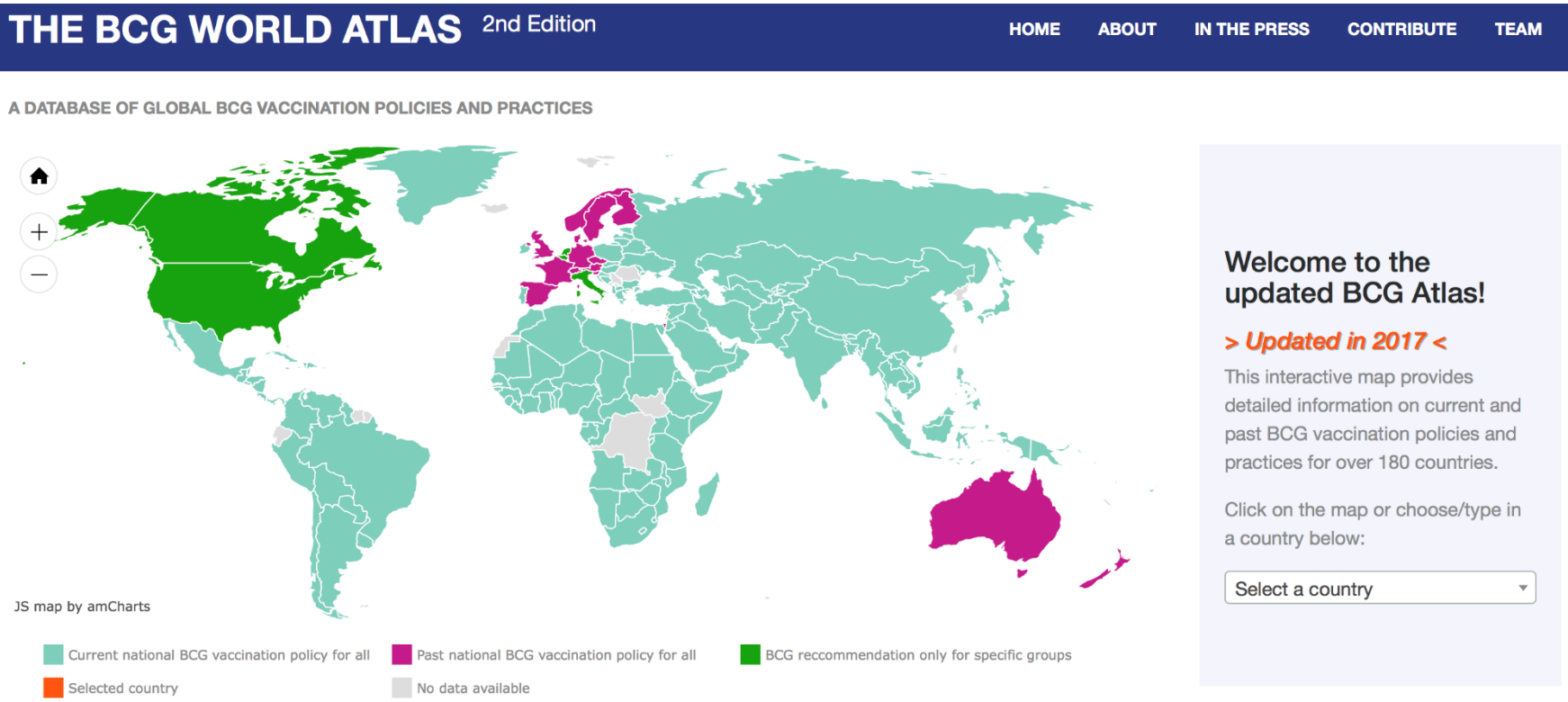


Age

Recent infection

HIV

www.bcgatlas.org

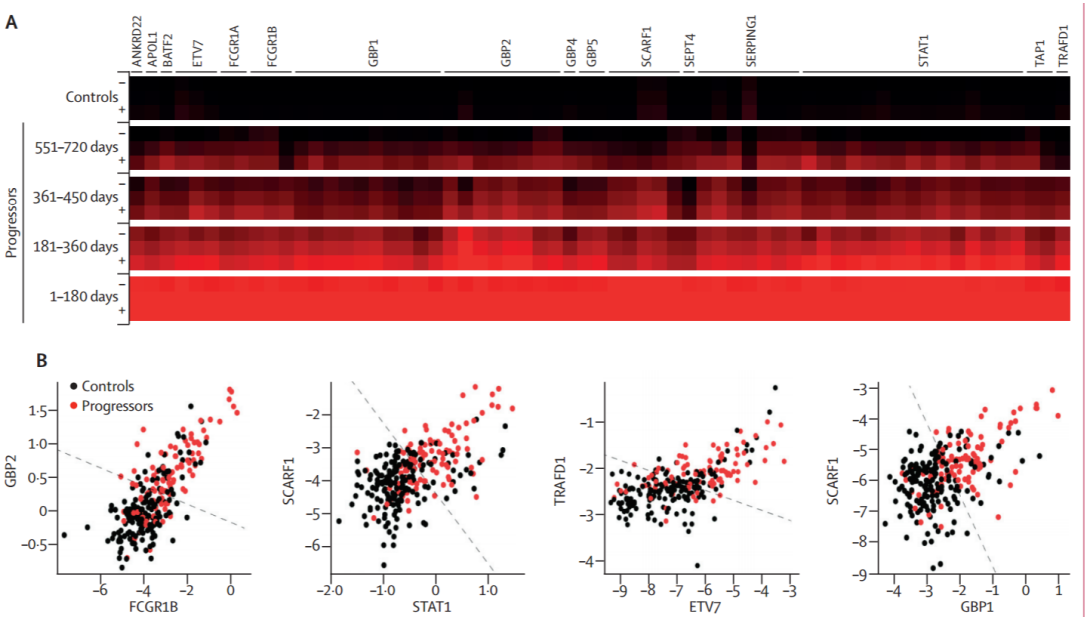


New, more predictive biosignatures

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡*

Used unbiased high-throughput screening of host blood RNA profiles to identify new signatures of risk for TB.



Zak D et al. Lancet 2016

A single IGRA or TST = limited predictive value

Can we use serial testing to resolve the phenotypes and estimate incidence of new TB infections?

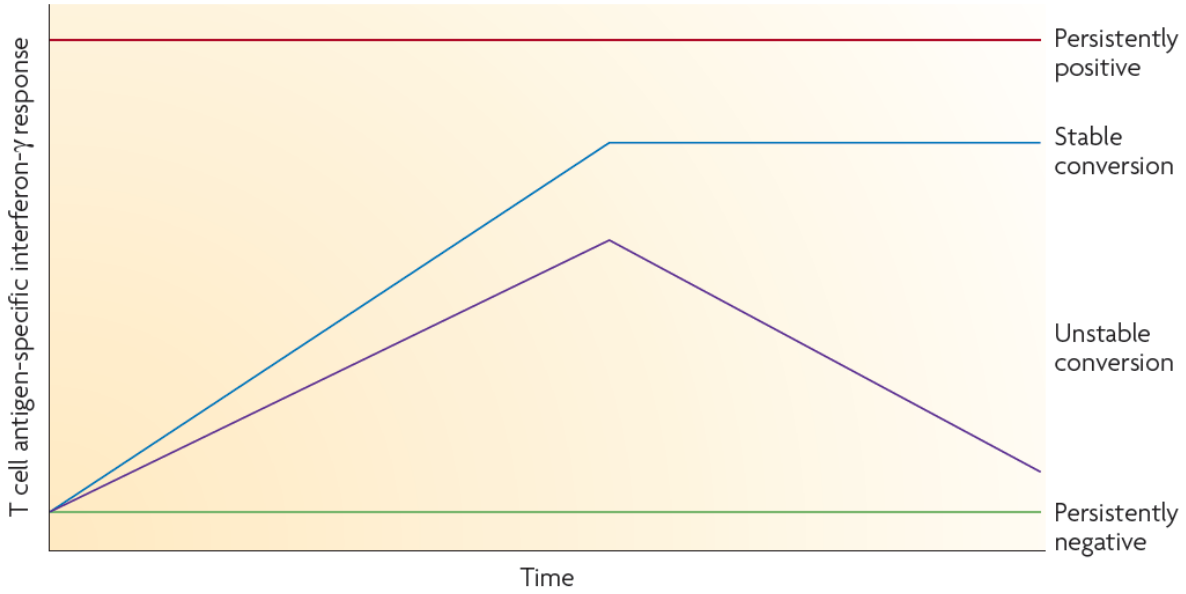


Figure 1 | **Serial testing with antigen-specific T cell interferon-γ release assays reveals underlying phenotypes that are unlikely to have the same prognosis.** The persistently positive pattern is seen in individuals who are repeatedly interferon-γ release assay (IGRA)-positive for a long time. Unstable conversion refers to individuals who convert their IGRA result from negative to positive and then revert again to negativity. Stable conversion refers to individuals who convert their IGRA result and stay converted, at least in the short term. Persistently negative refers to individuals who stay repeatedly IGRA-negative for a long time.

Pai. Nat Rev Microbiol 2010

Conversions (RR=8) are more predictive than a single test result (RR=2.5)

Predictive Value of Recent QuantiFERON Conversion for Tuberculosis Disease in Adolescents

Shingai Machingaidze[1,2,3], Suzanne Verver[4], Humphrey Mulenga[1,2], Deborah-Ann Abrahams[1,2], Mark Hatherill[1,2], Willem Hanekom[1,2], Gregory D. Hussey[1,2,3], and Hassan Mahomed[1,2]

[1]South African Tuberculosis Vaccine Initiative, Institute of Infectious Diseases and Molecular Medicine; [2]School of Child & Adolescent Health; [3]Vaccines for Africa Initiative, Division of Medical Microbiology, University of Cape Town, Cape Town, South Africa; and [4]KNCV Tuberculosis Foundation, The Hague and CINIMA, Academic Medical Centre, Amsterdam, The Netherlands

QFT conversion indicated an approximately eight-fold higher risk of progression to TB disease within 2 years when compared with non-converters.

TABLE 2. OVERALL TUBERCULOSIS INCIDENCE AND CUMULATIVE INCIDENCE BY QUANTIFERON GROUP

Study Group	n	TB Incident Cases	Observation Time (*person-yr*)	Incidence Rate per 100 person-yr (95% CI)	Cumulative Incidence (%) (95% CI)
All TB cases					
QFT converters	534	15	1,026	1.46 (0.82–2.39)	2.8 (1.58–4.59)
QFT nonconverters	629	2	1,169	0.17 (0.02–0.62)	0.32 (0.03–1.14)
Protocol-defined TB cases					
QFT converters	534	8	1,026	0.78 (0.34–1.53)	1.4 (0.65–2.93)
QFT nonconverters	629	1	1,169	0.08 (0.002–0.48)	0.16 (0.004–0.88)

Definition of abbreviations: CI = confidence interval; QFT = QuantiFERON; TB = tuberculosis.

But, even among QFT converters, the incidence rate was only 1.5 per 100 py!

AJRCCM 2012

Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study

Jason R Andrews, Elisa Nemes, Michele Tameris, Bernard S Landry, Hassan Mahomed, J Bruce McClain, Helen A Fletcher, Willem A Hanekom, Robin Wood, Helen McShane, Thomas J Scriba, Mark Hatherill

	N	Cases	Incidence (95% CI)	IRR (95% CI)	p value
Revised case definition 1					
<0·35 IU/mL	2232	16	0·7 (0·4–1·1)	Ref	Ref
0·35–4·00 IU/mL	79	2	2·5 (0·4–9·4)	3·7 (0·4–15·8)	0·23
>4·00 IU/mL	63	10	28·0 (14·9–45·7)	42·5* (17·2–99·7)	<0·0001
Culture or Xpert positive					
<0·35 IU/mL	2232	11	0·5 (0·2–0·8)	Ref	Ref
0·35–4·00 IU/mL	79	2	2·5 (0·4–9·4)	5·4 (0·6–24·8)	0·13
>4·00 IU/mL	63	7	19·6 (8·9–36·8)	43·3† (14·2–122·3)	<0·0001

Incidence reported in cases per 100 person-years. IRR=incidence rate ratio. Ref=reference. *IRR of higher than 4·00 *vs* 0·35–4·00 for revised case definition 1: 11·4 (95% CI 2·4–107·2), p<0·000047. †IRR of higher than 4·00 *vs* 0·35–4·00 for culture or Xpert positive: 8·0 (95% CI 1·5–78·8); p=0·0094.

Table 1: **Incidence of tuberculosis (cases per 100 person-years) according to day 336 QuantiFERON interferon-γ value by case definition**

"QFT conversion at very high interferon-γ values (>4.00 IU/mL) warrants intensified diagnostic and preventive intervention because of the extremely high risk of TB disease in these young children."

The uncertain science of predicting tuberculosis

Lancet Respir Med 2017
Published Online
February 15, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30059-0
See Online/Articles
http://dx.doi.org/10.1016/S2213-2600(17)30060-7
For the **Online TST/IGRA Interpreter** see http://www.tstin3d.com/

Around a quarter of the world's population is infected with *Mycobacterium tuberculosis*.[1] Unfortunately, currently available immunodiagnostic methods are unable to discriminate the stages within the spectrum of tuberculosis infection.[2,3] Neither the tuberculin skin test (TST) nor interferon-gamma release assays (IGRAs) meet the need for a highly predictive test that can identify latently infected people who are at increased risk of developing tuberculosis disease and would therefore benefit most from preventive therapy.[4] This, as well as the high prevalence of latent tuberculosis infection, makes it daunting for high-burden countries to address latent tuberculosis in their control programmes.[5]

While the search for new predictive biomarkers and biosignatures is starting to show promise,[6] are there ways to squeeze more predictive value out of existing tests? One way to do this is to make sure that people at low risk for tuberculosis infection are not screened. While this recommendation is already a part of guidelines,[7] many low-risk people still get screened in practice. A good example is the widespread annual screening of low-risk health-care workers in north America, a practice that is already posing challenges.[8]

Another approach to enhance predictive value is to use multivariable risk prediction models that incorporate clinical and epidemiological risk factors—eg, age, history of contact, HIV infection, immunosuppressive medications—with test results.[9] Online risk calculators (eg, the Online TST/IGRA Interpreter) have made this feasible.

A third approach is to use serial (repeated) testing rather than cross-sectional testing.[9] It is well known that people with recent TST conversions are at high risk of progression. Using the same logic, individuals with IGRA conversions should be at a higher risk of developing tuberculosis disease. Although limited, there is some evidence to support this hypothesis.[10]

In *The Lancet Respiratory Medicine*, Jason R Andrews and colleagues[11] analysed longitudinal data from a cohort of 2512 Bacille Calmette-Guerin-vaccinated, Quantiferon-TB Gold In-Tube (QFT)-negative and HIV-uninfected South African infants recruited into a tuberculosis vaccine trial. They investigated the association between IGRA conversion (ie, increase in interferon-γ values determined by serial QFT testing) and the risk of subsequent development of active tuberculosis disease. The results showed that QFT converters at interferon-γ values higher than 4·00 IU/mL had a significantly higher disease incidence compared with both non-converters (incidence rate ratio [IRR] 42·5; p<0·0001), and converters at interferon-γ values between 0·35 IU/mL and 4·00 IU/mL (IRR 11·4; p<0·00047).

So, the results suggest that a big spike in interferon-γ levels is strongly associated with risk of tuberculosis. But does the spike predict future risk of tuberculosis disease, or is it a consequence of subclinical or incipient disease? While ten of 63 children with QFT conversion (threshold of interferon-γ >4·00 IU/mL) were diagnosed with tuberculosis disease (28·0 cases per 100 person-years), the median time to diagnosis among these QFT converters from the time of QFT testing was merely 44 days. Thus, one can make a case that the interferon-γ levels spiked as these children were developing active tuberculosis. Therefore, an increase in interferon-γ levels is not really predictive of future risk progression to active tuberculosis, but could be due to imminent development of subclinical or incipient tuberculosis disease.

Another recent study suggested that a 16-transcript whole-blood RNA signature might prospectively identify adolescents at risk of developing tuberculosis disease.[6]

iStockphoto/JanWillemKunnen

Togun T & Pai M
Lancet RM 2017

From latent to patent: rethinking prediction of tuberculosis

Tuberculosis remains a major global health problem. It is estimated that more than 2 billion people around the world are latently infected with *Mycobacterium tuberculosis*, with a lifetime risk of progression to tuberculosis disease of 5–15%.[1] The WHO End Tuberculosis strategy, which aims to end tuberculosis as a major health problem by 2035, calls for reducing this huge reservoir for transmission by scaling up preventive therapy of individuals with latent tuberculosis infection. Preventive therapy with daily isoniazid offers 60–90% protection and combination therapies (daily isoniazid-rifampicin, weekly controlled) is an oversimplification.[5,6] Recent research postulates the existence of a spectrum from spontaneous clearance to quiescent infection and disease. Patient's position on this spectrum will be defined by their capacity to control bacillary replication.[6] The tuberculin skin test does not distinguish between these states (appendix [1A]).[5]

Several factors are known to increase the risk of progression to tuberculosis disease, including young age, low body-mass index, diabetes, tobacco smoking, HIV infection and treatment with tumour necrosis factor-α antagonists.[7] However, with the exception of the latter

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December 21, 2016
http://dx.doi.org/10.1016/
S2213-2600(16)30419-2

Tests to predict tuberculosis disease: persistent infection tests (PIT) versus incipient tuberculosis tests (ITT)

PITs have the characteristics of rule-out tests: whereas a positive result might not be very informative, a negative result provides confidence that the individual is unlikely to develop tuberculosis disease in the near future.

ITTs should be considered rule-in tests: a negative result provides limited information but a positive result indicates that tuberculosis disease will probably develop.

Cobelens F et al. Lancet Resp Med 2017

Questions for the panel

- IGRAs are an incremental advance; not transformational: any disagreements on this?
- Serial testing with IGRAs may be more predictive, but might be picking up incipient TB?
- What about the predictive biosignature? Also ITT?
- TPP for a predictive LTBI test: is it for an ITT?
- ITTs: can we really use IPT?
- What work is ongoing to develop a good CoR assay?