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New tools and emerging technologies for the diagnosis of tuberculosis: Part I. Latent tuberculosis

Madhukar Pai†, Shriprakash Kalantri and Keertan Dheda

Nearly a third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. This enormous pool of latently infected individuals poses a major hurdle for global tuberculosis (TB) control. Currently, diagnosis of latent TB infection (LTBI) relies on the tuberculin skin test (TST), a century-old test with known limitations. In this review, the first of a two-part series on new tools for TB diagnosis, recent advances in the diagnosis of LTBI are described. The biggest advance in recent years has been the development of *in vitro* T-cell-based interferon-γ release assays (IGRAs) that use antigens more specific to *M. tuberculosis* than the purified protein derivative used in the TST. Available research evidence on IGRAs suggests they have higher specificity than TST, better correlation with surrogate markers of exposure to *M. tuberculosis* in low-incidence settings, and less cross-reactivity due to BCG vaccination than the TST. IGRAs also appear to be at least as sensitive as the purified protein derivative-based TST for active TB. In the absence of a gold standard for LTBI, sensitivity and specificity for LTBI are not well defined. Besides high specificity, other potential advantages of IGRAs include logistical convenience, avoidance of poorly reproducible measurements, such as skin induration, need for fewer patient visits and the ability to perform serial testing without inducing the boosting phenomenon. Overall, due to its high specificity, IGRAs may be useful in low-endemic, high-income settings where cross-reactivity due to BCG might adversely impact the utility of TST. However, despite the growing evidence supporting the use of IGRAs, several unresolved and unexplained issues remain. The review concludes by highlighting areas where evidence is lacking, and provides an agenda for future research. Active TB and drug resistance are discussed in Part II; 423–432 of this issue.

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CONTENTS

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The WHO has estimated that approximately one-third of the world's population is infected with *Mycobacterium tuberculosis* [1,2]. This enormous pool of latently infected individuals poses a major hurdle for global tuberculosis (TB) control. Between 8 and 9 million people develop TB disease each year, and approximately 2 million die from TB every year [1,2]. Despite this tremendous global burden, case detection rates continue to be low [2]. Conventional TB diagnostic approaches utilize tests such as sputum microscopy, culture, chest radiography and tuberculin skin testing. These tools have been in use for decades. Due to the limitations of these tests, particularly in areas affected by the HIV epidemic and its associated high mortality among smear-negative cases, there is a widely felt need for more rapid, accurate and convenient tests [3–5].

Active engagement of agencies such as the Stop TB Working Group on New Diagnostics [101], the Foundation for Innovative New Diagnostics [102] and the TB Diagnostics Initiative of the Special Programme for Research and Training in Tropical Diseases (TDR), WHO [103], have led to renewed interest in the development of new tools for TB diagnosis. Similar efforts are ongoing to develop new TB

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vaccines [104] and drugs [105]. Indeed, the development of new tools figures prominently in the Global Plan to Stop TB, 2006–2015 [6].

Some excellent recent reviews are built upon in this two-part review [4,7–10], which describes advances and emerging technologies in the diagnosis of latent infection (Part 1), and active disease and detection of drug resistance (Part 2). Since the authors' focus is on new and emerging tools, refinements in existing techniques, such as microscopy and cultures, are not reviewed.

Diagnostics for latent tuberculosis

Infection with *M. tuberculosis*, in most individuals, is contained by the host immune defenses, and the infection remains latent. Due to the risk of progression from latent infection to active disease, targeted testing and treatment for latent TB infection (LTBI) is a key component of TB control in many low-incidence, high-income countries [11]. In contrast, LTBI testing and treatment is not routinely performed in high-incidence, resource-limited countries. Until recently, the only tool available to detect LTBI was the tuberculin skin test (TST). Although the TST has proved to be useful in clinical practice, it has known limitations, including variable specificity, cross-reactivity with BCG and nontuberculous mycobacterial (NTM) infection, and problems with reproducibility [12,13].

Interferon-γ release assays: rationale & evolution

Due to advances in molecular biology and genomics, an alternative has emerged for the first time in the form of a new class of *in vitro* assays that measure interferon (IFN)-γ released by sensitized T cells after stimulation by *M. tuberculosis* antigens [14–18]. Early versions of IFN-γ release assays (IGRAs) used purified protein derivative (PPD) as the stimulating antigen, but these tests have been replaced by newer versions that use antigens that are more specific to *M. tuberculosis* than PPD. These antigens include early secreted antigenic target (ESAT)-6, culture filtrate protein (CFP)-10, and TB7.7 (Rv2654). ESAT-6 and CFP-10 are encoded by genes located within the region of difference (RD)1 segment of the *M. tuberculosis* genome. They are more specific than PPD because they are not shared with any of the BCG vaccine strains or certain species of NTM (e.g., *Mycobacterium avium*) [19,20]. Thus, the use of such specific antigens in an *ex vivo* assay format is a distinguishing feature of IGRAs.

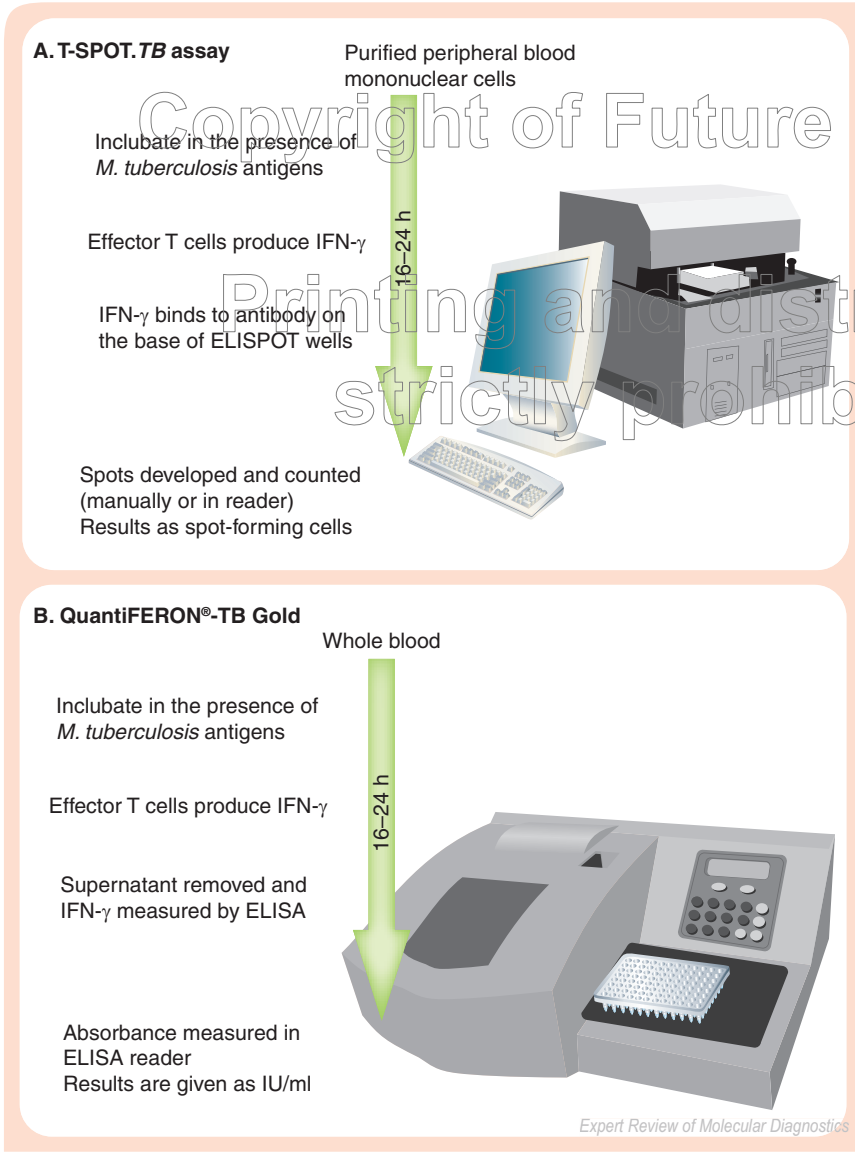

Figure 1. Commercially available region of difference 1–based IFN-γ assays for the detection of TB infection. Reproduced with permission from [15] © 2005, Lippincott Williams & Wilkins (MD, USA).
ELISA: Enzyme-linked immunosorbent assay; ELISPOT: Enzyme-linked immunospot assay; IFN: Interferon; IU: International units; TB: Tuberculosis.

Commercial interferon-γ release assay formats

Two IGRAs are now available as commercial kits (FIGURE 1): the T-SPOT.*TB*® test (Oxford Immunotec Ltd, Oxford, UK [106]) and the QuantiFERON®-TB GOLD (QFT-G; Cellestis Ltd, Carnegie, Australia [107]) assay. The QFT-G assay is available in two formats, a 24-well culture plate format (approved by the US FDA [21]), and a newer, simplified in-tube format (not currently FDA approved, but available in countries other than the USA [18]). The T-SPOT.*TB* test is currently CE marked for use in Europe, and is likely to receive FDA approval in the future. In Canada, the T-SPOT.*TB* was licensed in 2005, and the QFT-G is likely to be licensed in early 2006.

Summary of research evidence on test performance

The available research evidence on IGRAs (FIGURE 2, TABLE 1), reviewed extensively elsewhere [7,14–18,21,22], suggests that assays that use RD1 antigens have higher specificity than TST, better correlation with surrogate measures of exposure to *M. tuberculosis* in low-incidence settings, and less cross-reactivity due to BCG vaccination than the TST. IGRAs that use at least two RD1 antigens (e.g., ESAT-6 and CFP-10) appear to be at least as sensitive as the PPD-based TST for active TB (more sensitive in some studies). In the absence of a gold standard for LTBI, active TB is used as a surrogate for LTBI. FIGURE 2 shows forest plots of sensitivity and specificity (for active disease) from studies that used the research or commercial versions of the QFT-G and T-SPOT.*TB* assays [23–33]. Overall, the plot shows high specificity (>95% in most studies). Sensitivity, on the other hand, is lower and variable (75–97%).

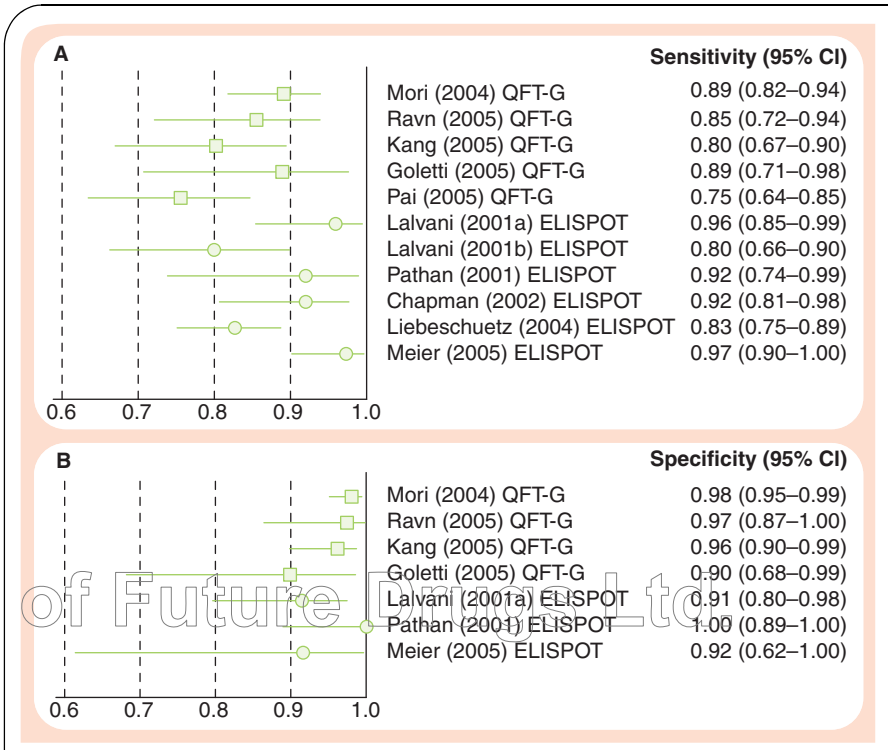

Figure 2. Forest plots of sensitivity and specificity from studies that used research or commercial versions of the QFT-G and T-SPOT.*TB* assays with region of difference 1 antigens. (A) Sensitivity in patients with active tuberculosis. **(B)** Specificity in healthy (low risk) patients without active tuberculosis (not all studies reported data on specificity). Point estimates of sensitivity and specificity from each study are shown as solid circles (ELISPOT) or solid squares (QFT-G). Error bars are 95% CIs.
CI: Confidence interval; ELISPOT: Enzyme-linked immunospot assay; QFT-G: QuantiFERON®-TB GOLD.

Given the gold standard problem, the sensitivity and specificity for LTBI cannot be directly estimated, and there is some concern that sensitivity for LTBI might be less than that of the TST, especially in vulnerable populations [21]. Besides high specificity, other potential advantages of IGRAs include logistical convenience, avoidance of poorly reproducible measurements such as skin induration, need for fewer patient visits, and the ability to perform serial testing without inducing the boosting phenomenon. Overall, due to its high specificity, IGRAs may be useful in low-endemic, high-income settings (i.e., countries that usually implement targeted LTBI screening programs), where cross-reactivity due to BCG might adversely impact the utility of TST.

Recommendations & guidelines

In December 2005, the US Centers for Disease Control and Prevention (CDC) [108] published their updated guidelines on the QFT-G assay [21]. The CDC now recommends that QFT-G may be used in all circumstances in which the TST is currently used, including contact investigations, evaluation of immigrants and serial testing of healthcare workers [21]. The guidelines suggest that QFT-G can be used in place of (and not in addition to) the TST [21]. The CDC also published its updated guidelines for preventing the transmission of TB in healthcare settings [34]. These guidelines suggest that QFT-G can be used in place of the TST for infection control surveillance, and conversion (i.e., new infection) has been defined as change from a negative to a positive result [34]. The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines were published in March 2006 [109]. This guideline recommends a two-step (hybrid) strategy for LTBI diagnosis: initial screen with TST, and those who are positive (or in whom TST may be unreliable) should then be considered for IGRA testing, if available, to confirm positive TST results.

Overall, currently available recommendations should be viewed as interim guidelines that will need revision as new evidence rapidly accumulates. For example, there are no published studies that have used the hybrid strategy recommended by NICE [109]. This approach, although reasonable, is not presently validated. Furthermore, there is limited evidence on the use of IGRAs in serial testing of healthcare workers [35]. The current recommendation on the use of the diagnostic threshold for conversion [34] does not take into account the possibility of misclassifying nonspecific IFN-γ changes as true conversions [35].

Unresolved issues & agenda for future research

The body of literature supporting the use of IGRAs is rapidly growing [14–18,21,22]. However, several unresolved and unexplained issues remain, and ongoing and new studies should help to clarify the role of these assays in various settings. TABLE 2 summarizes the major areas of uncertainty and key research questions for future work. One area of considerable confusion is discordance between TST and IGRA, and their

Table 1. Comparison of tuberculin skin test and interferon-γ release assays.

Performance and operational characteristics	Tuberculin skin test	Interferon-γ release assays
Estimated sensitivity (in patients with active tuberculosis)	75–90% (lower in immunocompromised populations)	75–95% (inadequate data in immunocompromised populations, but appears promising)
Estimated specificity (in healthy individuals with no known tuberculosis disease or exposure)	70–95% (lower in BCG-vaccinated, especially if BCG is given after infancy)	90–100% (maintained in BCG vaccinated)
Cross-reactivity with BCG	Yes	Less likely
Cross-reactivity with nontuberculous mycobacteria	Yes	Less likely, but limited evidence
Association between test positivity and subsequent risk of active tuberculosis during follow-up	Moderate-to-strong positive association	Insufficient evidence
Correlation with *Mycobacterium tuberculosis* exposure	Yes	Yes (correlated better with exposure than tuberculin skin test in some, but not all, head-to-head comparisons)
Benefits of treating test positives (based on randomized controlled trials)	Yes	No evidence
Reliability (reproducibility)	Moderate and variable	Limited evidence, but appears high; no evidence on within-subject variability during serial testing
Boosting phenomenon	Yes	No
Potential for conversions and reversions	Yes	Insufficient evidence
Adverse reactions	Rare	Rare
Material costs	Low	Moderate to high
Patient visits to complete testing	Two	One
Laboratory infrastructure required	No	Yes
Time to obtain a result	2–3 days	1–2 days, but longer if run as batches
Trained personnel required	Yes	Yes

Adapted with permission from references [10,16].

interpretation. Several studies have demonstrated discordance between TST and IGRA results; concordance estimates have ranged between 60–90% in most studies. While some discordance, especially the type where TST is positive but IGRA is negative, was probably due to prior BCG vaccination in certain studies [25,36,37], other studies found no clear explanations for discordance [38,39]. Research is needed to determine the biological basis for discordance, especially when discordance is extreme. For example, a recent study from South Africa found that, among those with large TST reactions (≥15 mm, and, therefore, high likelihood of infection), approximately one-third were negative by the QFT-G in-tube assay [39]. In a study from India, 11% of individuals with TST at least 15 mm were negative by the QFT-G in-tube assay [38]. While such discordance could be due to false-positive TST, it is plausible that IGRAs are less sensitive than TST in detecting LTBI, or IGRAs may detect only a subset of all those with LTBI (i.e., those with recent, persistent infection versus remote infection that has been cleared spontaneously or after treatment).

Discordance of the reverse type (i.e., TST negative, but IGRA positive) has also been documented, but is largely unexplained [38,40–42]. Therefore, future studies should perform thorough analyses of correlates of discordance, including a description of discordance due to variability of TST and IFN-γ values around their thresholds (cut-points). It is important to acknowledge that both TST and IGRA results are continuous measures, and, therefore, thresholds are needed to interpret them as dichotomous (positive or negative) outcomes. At least some of the observed discordance could be due to minor variations around the TST and IFN-γ thresholds.

The association between surrogate markers for TB exposure and IGRA results appears to be stronger and better defined in low TB incidence [36,37,41–44] than high-incidence settings [38,40]. The basis for this phenomenon is unclear. Variations in BCG vaccination practices might be a relevant factor. Also, in high-incidence settings, it is possible that IGRAs detect recent (effector) as well as remote (memory) T-cell responses. Furthermore, in such settings, there are several factors that might modulate

Table 2. A research agenda for future work on interferon-γ release assays .

No.	Research question
	Basic science and assay-related developments
1	To what extent does a positive IGRA result suggest previous (remote) infection (either cleared or still active) versus recent active infection? What type of T-cell responses are detected by IGRAs: effector or memory T-cell responses?
2	Can the addition of new TB-specific antigens help increase the sensitivity of IGRAs, without compromising their high specificity?
3	Can the identification of novel antigens or markers enable IGRAs to distinguish between LTBI and active disease?
4	What is the biological basis for discordance between TST and IGRA results?
5	After exposure to *Mycobacterium tuberculosis*, how long does it take for the IGRA test to become positive? How soon after TB exposure can the IGRA detect latent infection?
6	In head-to-head comparisons, what is the difference in performance characteristics of the commercial IGRAs?
7	Can IGRA technology be simplified? For example, testing with smaller quantities of blood (e.g., fingerstick) and lateral flow or strip formats.
	Test performance in high-risk and poorly studied groups
8	What is the accuracy and reliability of IGRAs in the diagnosis of active and LTBI in children?
9	What is the accuracy and reliability of IGRAs in the diagnosis of active and LTBI in individuals with HIV infection?
10	Are IGRAs more likely to produce indeterminate results in individuals with HIV infection? Is there an association between degree of immunosuppression (e.g., CD4 counts) and antigen-specific T-cell responses?
11	What is the accuracy and reliability of IGRAs in the diagnosis of active and LTBI in individuals on immunosuppressive therapies (e.g., tumor necrosis factor-α blockers)?
12	What is the accuracy and reliability of IGRAs in the diagnosis of extrapulmonary TB? Are T-cell assays likely to be less accurate in paucibacillary forms of extrapulmonary TB?
13	In close contacts of active TB, do IGRAs have a stronger correlation with surrogate markers of exposure than TST?
14	What is the impact of nontuberculous mycobacterial infections on IGRA performance?
15	What is the impact of leprosy infection on IGRA performance?
	Reproducibility and serial testing
16	What is amount of test-related variability in T-cell responses? For example, variations in IFN-γ due to variability of factors such as operators, laboratories, sample processing interval, incubation times, antigens (proteins vs peptides) and assay formats (enzyme-linked immunosorbent assay vs enzyme-linked immunospot assay)
17	What is the amount of random, biological variability of IFN-γ responses over time within the same individuals, including day–to–day, week–to–week and month–to–month variability of IFN-γ levels in the absence of TB exposure?
18	For serial testing of healthcare workers with IGRAs, which threshold for IFN-γ (cut-point) is optimal for distinguishing between true infection (i.e., conversion) and nonspecific, random variation?
19	Among healthcare workers screened with serial TST and IGRA, what is the concordance between IGRA and TST conversions?
20	How should a IGRA reversion be defined? How commonly do reversions occur? What is the clinical/epidemiological significance of reversions? What factors are associated with IGRA reversions, including treatment, baseline IFN-γ levels and variability around cut-points?
21	What is the effect of a TST on subsequent IGRA results?
22	When discordance between TST and IGRA occurs, what proportion of the overall discordance is due to variations around TST and IGRA cut-points? When discordant cases are re-tested, what proportion become concordant?

IFN: Interferon; IGRA: Interferon-γ release assay; LTBI: Latent tuberculosis infection; TB: Tuberculosis; TST: Tuberculin skin test.

Table 2. A research agenda for future work on interferon-γ release assays (cont.).

No.	Research question
	Risk prediction and modeling
23	What is the accuracy and role of IGRAs as a rule-out test for active TB? What is the negative predictive value of IGRAs for active disease?
24	What is the incidence of active disease in those with positive and negative IGRA results?
25	What is the importance and predictive value of absolute IFN-γ responses? Within IGRA-positive individuals, are individuals with stronger IFN-γ responses more or less likely to progress to active disease?
26	In the absence of a gold standard for LTBI, what is the role of mathematic modeling approaches to derive appropriate cut-points for IGRA and TST in various populations?
27	In the absence of a gold standard for LTBI, what is the role of Bayesian modeling approaches (e.g., latent class and mixture models) to determining IGRA accuracy and prevalence of LTBI?
	Issues relating to treatment
28	How do T-cell responses change during and after treatment for LTBI? What factors, including host, disease and assay characteristics, influence variability in responses after treatment?
29	How do T-cell responses change during and after treatment for active TB? What factors, including host, disease and assay characteristics, influence variability in responses after treatment?
30	Do IGRAs have a role in monitoring response to latent and active TB treatment?
31	Will treatment of IGRA-positive subjects reduce the incidence of active disease?
32	What is the ability of IGRAs to detect re-infection after treatment for both LTBI and TB disease? If IGRA results become negative after treatment, and become positive after a new exposure, does this indicate re-infection or persistence of the original infection?
	Epidemiologic applications
33	Can IGRAs be used in population surveys to estimate annual risk of TB infection and prevalence of LTBI in the community?
34	What is the accuracy and utility of screening strategies that use combinations of TST and IGRAs: for example, first screen with the TST, then confirm positive results with the more specific IGRA?
35	How does IGRA performance vary between high and low TB incidence settings?
36	In tropical, high-burden settings, what is the impact of immune-modulating factors, such as malnutrition, BCG vaccination, nontuberculous mycobacterial exposure, *Mycobacterium bovis* and *Mycobacterium leprae* exposure and helminthic infections, on T-cell-based assays?
37	In vaccine trials, can IGRAs serve as correlates of protective immunity?
38	In high-burden, developing countries, which patient or population subgroups are most likely to benefit from the use of IGRAs?
	Operational and health systems research
39	How do IGRAs and TST compare in economic and decision analyses for various screening programs (e.g., immigrant screening, contact investigations and serial testing of healthcare workers)?
40	What is the impact of switching from TST to IGRA on laboratory or clinic workload, staff workload, program costs, patient convenience and compliance with testing and follow-up?

IFN: Interferon; IGRA: Interferon-γ release assay; LTBI: Latent tuberculosis infection; TB: Tuberculosis; TST: Tuberculin skin test.

immune responses: malnutrition, BCG vaccination, NTM exposure, leprosy, helminths and tropical infections that impact the T-helper (Th)1/Th2 immune balance. These issues underscore the importance of studies from high-incidence countries [28,30,31,35,38,40,45].

There are few studies on the performance of IGRAs in vulnerable subgroups, including immunocompromised individuals (e.g., HIV/AIDS and those on immunosuppressive medications, such as tumor necrosis factor-α blockers), patients with extrapulmonary TB, contacts, children and healthcare workers. In immunocompromised individuals, IGRAs might have a higher proportion of indeterminate results (mostly due to lack of T-cell response to mitogen), and this may indicate underlying anergy [46,47]. Recent studies suggest that IGRAs may be promising in individuals with HIV infection [30,48], contacts [36,37,41–43], children [31,45] and healthcare workers [35,38], but this requires confirmation in larger studies.

For serial testing of healthcare workers, IGRAs have important theoretical advantages: they might eliminate the need for two-step testing at baseline, avoid boosting and may minimize interpretational difficulties that often hamper serial TST screening. However, there are virtually no data on the long-term reproducibility of IGRAs, particularly within-subject variability in serial testing, where conversions and reversions can occur [35]. Without data on longitudinal changes and biological variability, the results of serial IGRA testing are difficult to interpret. Preliminary data from a recent cohort study in India suggest that IGRA conversions are strongly correlated with TST conversions when stringent thresholds were used for both tests; however, it is currently unclear how much IFN-γ levels must increase in order to be considered a true conversion [35]. Therefore, longitudinal studies of serial testing will be of great interest. Such studies should perform serial TSTs concurrently, in order to provide a baseline for comparison with changes in IFN-γ responses over time.

Another area of controversy is the dynamics of T-cell responses during and after treatment for latent and active TB. As reviewed elsewhere [14,15], some studies have demonstrated declining responses after treatment, whereas others have shown unchanging, fluctuating or increasing responses during treatment. Therefore, it is not clear if these tests can be used for monitoring response to LTBI and active TB treatment. Variations in incubation periods, antigens (proteins vs peptides) and assay formats might explain some of the discrepancies [14,15].

What is the role of IGRAs in the diagnosis of active disease? The CDC guidelines recommend the use of the QFT-G assay for diagnosing infection with *M. tuberculosis*, including both LTBI and active disease [21]. According to these guidelines, persons who have positive IGRA results, regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed [21]. It is important to note that currently available IGRAs cannot distinguish between active disease and LTBI, and this may pose problems for diagnosing active disease in countries with a high-burden of LTBI. Therefore, it is important to interpret the results in a specific clinical context. In an individual being investigated for suspected TB disease, a positive result may be due to active TB or irrelevant concurrent LTBI. However, a negative IGRA result may represent a useful rule-out test, particularly in low-incidence settings [15]. However, a negative test, particularly if there is underlying immunosuppression, should not preclude further investigation or treatment if the clinical suspicion is high. The negative predictive value of IGRAs for active TB requires further evaluation.

Another important unresolved issue is whether IGRAs have the ability to identify latently infected individuals who are most likely to progress to active disease, and, therefore, most likely to benefit from preventive therapy. Although there are limited data, based on one small study of an association between IFN-γ response to ESAT-6 and subsequent progression to active TB among contacts of TB patients, the association between IGRA positivity and progression to active disease is largely unknown [49]. Long-term cohort studies are required to address this critical issue.

Lastly, a limitation of IGRAs, particularly for high-burden, resource-limited countries, is their higher material costs and the need for laboratory infrastructure and trained personnel [16]. Economic evaluations are required to better delineate the role of IGRAs in public health and routine clinical settings [22]. It is possible that the advantages of a more convenient and specific blood test might outweigh the higher costs (at least in some settings). It is also possible that hybrid strategies that combine TST and IGRA might be more cost effective [109].

Expert commentary & five-year view

Despite the enormous global burden of TB, case detection rates continue to be low, compromising TB control, particularly in areas with high HIV prevalence. Currently, TB diagnosis relies on old tools with known limitations. The long-felt need for new tools, including new diagnostics, vaccines and drugs, is currently being addressed by several global health agencies, nonprofit groups, industry, funding agencies, public–private partnerships and academic institutions [101–105].

Detection and treatment of LTBI is an important component of TB control efforts in low-incidence settings. Until recently, the TST was the only tool available to detect LTBI. The most important breakthrough in recent years has been the development of IGRAs. In less than a decade, two commercial tests (QFT-G and T-SPOT.*TB*) have been developed and licensed in many countries. Due to their high specificity and logistical convenience, IGRAs might replace the 100-year-old TST in selected low-incidence, high-income settings in the next 5–10 years. Research during the next few years will help settle unresolved issues, and define the exact role for these assays in clinical and public health settings. Further refinement (e.g., inclusion of additional antigens to increase sensitivity) and standardization of these commercial assays will also likely occur, which will enhance their utility and applicability.

At this time, the role for IGRAs in low-income, high-burden settings is rather limited. Simplification of the test format and reduction of costs might enhance applicability in such settings, particularly in selected subgroups, such as HIV-infected individuals, children and other high-risk groups. Until such time, the TST will continue to be a useful, simple, low-cost tool in developing countries where BCG vaccination is given in infancy [16], and thus has limited impact on TST results [12,13].

One important but neglected area of research is the development of an improved skin test for TB that uses specific TB antigens rather than PPD [19]. An improved skin test will be more feasible and useful in countries with limited resources to implement IGRAs. Lack of interest in improving the skin test may be due to a perceived lack of commercial viability, or due to the fact that LTBI testing and treatment is not considered a priority in high-burden countries. Although LTBI is not currently an important priority for developing countries, it will become important, at least in specific high-risk populations, because active TB case rates decrease with the rapid expansion of global directly observed treatment and short-course coverage.

Conflict of interest statement

None declared.

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Key issues

- Detection and treatment of latent tuberculosis (TB) infection (LTBI) is an important component of TB control efforts in low-incidence settings.
- Until recently, the tuberculin skin test (TST) was the only test available to detect LTBI. The TST has several known limitations.
- The biggest breakthrough for LTBI diagnosis in recent years has been the development of T-cell-based interferon-γ assays (IGRAs), which use antigens that are highly specific to *Mycobacterium tuberculosis*.
- Available research evidence on IGRAs suggests they have higher specificity than TST, better correlation with surrogate markers of exposure to *M. tuberculosis* in low-incidence settings, and less cross-reactivity due to BCG vaccination. IGRAs also appear to be at least as sensitive as the purified protein derivative-based TST for active TB.
- Sensitivity and specificity of IGRAs for LTBI are not well defined in the absence of a gold standard for LTBI.
- Besides high specificity, other potential advantages of IGRAs include logistical convenience, avoidance of poorly reproducible measurements, such as skin induration, need for fewer patient visits and the ability to perform serial testing without inducing the boosting phenomenon.
- Overall, due to its high specificity, IGRAs may be useful in low-endemic, high-income settings where cross-reactivity due to BCG might adversely impact the utility of TST. In such settings, IGRAs might replace the TST in the next 5–10 years.
- However, several unresolved and unexplained issues remain, and studies are needed to clarify the role of these assays in various settings.

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