

POINT-COUNTERPOINT

Should Interferon Gamma Release Assays Become the Standard Method for Screening Patients for *Mycobacterium tuberculosis* Infections in the United States?[∇]

The Centers for Disease Control and Prevention recently published updated guidelines for the use of interferon gamma release assays (IGRAs) to detect *Mycobacterium tuberculosis*. This document gives a balanced analysis of the strengths and weaknesses of IGRAs. To date, these assays have not been widely adopted in the United States by clinical laboratories. We have asked two experts, Thomas Alexander of Summa Health Care, who has adopted an IGRA for *M. tuberculosis* detection in his laboratory, and Melissa Miller of UNC Hospitals, who has evaluated one but has not chosen to adopt it, to explain how each reached this decision based on their experience with the test and the data that have been published concerning IGRA.

POINT

Virtually all individuals in the United States and many other countries of the world have undergone a tuberculin skin test (TST). While the test has undergone some changes during the past 50 years, the basic principle of the assay has not changed since the advent of the test. We have come a long way since using cool alcohol flames in an attempt to sterilize the needle in between injections (T. Alexander, personal observation), and the current purified protein derivative (PPD) extract used in the TST is a better performer than the “old tuberculin” preparation used during the middle of the last century. The TST does provide a short time to results, at least compared to *Mycobacterium tuberculosis* culture; however, the test is fraught with problems. Patients must return 48 h after the test is given to have it read. The measurement of induration, particularly in the presence of erythema, may be difficult for inexperienced technologists or nurses. Many institutions follow the CDC recommendations to give a “two-step” TST, requiring 4 separate visits for a final result. Although the test is commonly called a “TB” (tuberculosis) test, in reality, it may be positive in individuals exposed to more than 30 different mycobacteria, including *M. bovis* and the *Mycobacterium avium* complex (MAC) (6). Clearly it is time for a new approach to identifying individuals exposed to TB.

The TST is an *in vivo* measurement of cell-mediated immunity (CMI), sometimes referred to as delayed-type, or “type IV,” hypersensitivity (DTH). A difficulty in clinical laboratory immunology has been the absence of *in vitro* assays to measure antigen-specific cell-mediated

immunity or DTH. The phenomenon of major histocompatibility complex (MHC) restriction has rendered simple assay systems that could be used for many individuals difficult to develop. Historically, the few *in vitro* CMI assays that were available required a 48-h antigen stimulation step, followed by tritiated thymidine uptake. The sterile culturing techniques and the use of a radioactive reagent rendered these assays difficult for clinical laboratories to perform. Thus, most clinical measurements of DTH have been performed using *in vivo* skin tests, such as the TST. During the past decade, however, *in vitro* CMI assays have been developed that use sensitive enzyme-linked immunosorbent assay (ELISA) or fluorescent measurements of T cell products, such as gamma interferon or ATP. Currently, two *in vitro* CMI assays have been approved by the U.S. Food and Drug Administration (FDA) for diagnostic use in identifying individuals who have been exposed to *M. tuberculosis*. These assays are the QuantiFERON Gold In-Tube procedure (QFT-GIT) (Cellestis, Inc., Valencia, CA) and the T-Spot test. (Oxford Immunotec, Malborough, MA). Both assays measure gamma interferon production following either whole-blood (QFT-GIT) or mononuclear cell (T-Spot) incubation with antigens derived from *M. tuberculosis*. These procedures have been given the common name of interferon gamma release assays (IGRAs).

The IGRAs have advantages over the TST for the patient, the physician, and the laboratory. The patient only needs to be seen once (a two-step TST requires four patient visits), and that is to have the blood drawn. The QFT-GIT requires that 3 manufacturer-provided tubes are collected. Each tube has a draw capacity of only 1 ml. The T spot requires that a single

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7-ml heparinized Vacutainer tube be collected. The IGRAs' advantages for the physician and the laboratory include the tests' specificity and a more objective evaluation compared to the TST. The QFT-GIT test is read completely objectively; the T-Spot requires a combined objective and subjective reading. Both assays stimulate whole blood with the *M. tuberculosis* antigen culture filtrate product 10 (CFP10) and early secretory antigen target 6 (ESAT-6). The QFT-GIT assay also includes a third TB antigen, TB7.7, in its stimulating cocktail. These three antigens are found in only 4 *Mycobacterium* species: *M. tuberculosis*, *M. szulgai*, *M. kansasii*, and *M. marinum*. Thus, the IGRAs should be negative for patients who have received *M. bovis* bacillus Calmette-Guérin (BCG) or who have been exposed to MAC, unlike the TST, which may be positive for those patients (6).

The IGRAs are not without disadvantages to the laboratory, however. The reagents are more expensive than a single- or even two-step TST. The blood for the QFT-GIT must be appropriately incubated within 16 h of collection. Mononuclear cells must be separated from whole blood for the T-Spot assay within 8 h of collection. These requirements eliminate the possibility of referring the tests to a distant facility. Supernatants from the QFT-GIT assay may be stored and analyzed in bulk in an interferon ELISA at a convenient time. The T-Spot has more front-end hands-on time in the laboratory because mononuclear cells must be isolated from the peripheral blood prior to the incubation with antigen. The T-Spot test does not have the more complex ELISA on the back end but does require that technologists count the number of "spots" on a plate, with each spot corresponding to a positive cell. A magnifier which can be attached to a computer makes this process relatively simple.

Thus, there are *in vitro* alternatives to the TST. The most important question, however, is how the IGRAs perform in clinical situations. A PubMed (online) search for "QuantiFERON" in October 2010 found 416 articles published from 2008 to 2010; thus, there is no dearth of data. A recent meta-analysis surveyed 844 studies and included data from 27. Sensitivities for active TB were 80% for the QuantiFERON test and 81% for the T-Spot (8). Specificities averaged 79% and 82% for blood testing by QuantiFERON and T-Spot (8). Komiya et al. published data supporting T-Spot's claim of better sensitivity for patients with low lymphocyte counts: 81% for T-Spot versus 39% for QuantiFERON (5). Sester et al. conclude that although both assays are more sensitive than the TST, neither assay is sufficiently sensitive to be used to rule out active disease (8). In a study of 560 subjects at high risk for latent TB, the QuantiFERON identified 51% of the subjects as positive, compared to the TST detecting 39.4% (3). Altet-Gomez. et al. (2)

found that the IGRA tests were negative for pediatric patients with reactive TST but documented *M. avium* infection, supporting the increased specificity of the *in vitro* assays. Abdhalhamid et al., using the QuantiFERON Gold test (QFT-G; an earlier version of the QFT-GIT), found that the increased specificity of the IGRA test compared to the TST resulted in a 48.8% decrease in the overall cost to a health care system (1). This overall decrease in cost, even though the IGRA was more expensive than the TST, was due to BCG-vaccinated individuals testing negative in the IGRA. Thus, these health care workers did not require prophylactic treatment, resulting in a lower overall cost to the health system. Similar results using a simulated population of 15,000 individuals exposed to TB were reported by Deuffic-Burban et al. (4). Their study looked at cost per year of life gained by using the TST, the TST and the IGRA, or just the IGRA test. They found that although the QuantiFERON test was more expensive to perform than the TST, the cost savings per patient were over 400 Euros when the IGRA was performed (4).

Our laboratory has been performing the QuantiFERON assay (initially the QuantiFERON Gold, currently the QFT-GIT) for close to 4 years. We initially used it as an adjunct to TST testing of employees. We no longer perform the TST for employee screening; all testing is done with the QFT-GIT. The test is also used in patient evaluations, often along with a TST. Anecdotally, our initial evaluation of the QFT-G version proved instructive. One individual whom we included in our evaluation was an orthopedic surgeon who had converted to a positive TST a few years previously and had been treated with isoniazid (INH). He remained TST positive but was negative on the QuantiFERON test. Further research of history could not document a specific TB exposure but did uncover two surgeries on an AIDS patient who had MAC within the year prior to his TST conversion. Another physician included in our evaluation had received the BCG vaccine as a child and was TST positive. This individual was positive in the QFT-G assay. Further questioning showed that this individual had worked in a TB clinic during training. Thus, the histories supported the QFT-G result.

We currently perform more than 3,000 QFT-GIT tests per year. Our employee health and infection control personnel are satisfied with the test's performance and have no desire to go back to the TST. However, there are two issues that we are continuing to address. One is the collection process, and the second is interpretation of low-level-positive specimens.

As mentioned previously, the QFT-GIT requires that three manufacturer-provided tubes be collected. The interior of one tube is coated with the TB antigens, one tube is coated with phytohemagglutinin as a positive control, and one tube is uncoated as a negative control. Each tube has a draw volume of 1.0 ml. The tubes must

be vigorously shaken after collection to ensure exposure of the lymphocytes to the antigen or mitogen present in the coated tubes. This is in contrast to most phlebotomies, where vigorous shaking of the tubes is to be avoided. We do see occasional low responses to the mitogen control, invalidating the test. While this might be due to an immune deficiency in the patient, we have found this is often an occurrence when a new person is collecting the specimen. Repeat collections with proper technique yield an appropriate control value.

The second issue relates to low-positive specimens. The QFT-GIT assay has been reported to have poor reproducibility at low-positive interferon levels (7). We also have observed this. We are currently evaluating our data to determine if we should define and report a low-positive range.

In conclusion, the advantages of IGRAs is that they offer increased convenience, sensitivity, and specificity compared to the TST. While the test is more expensive than the TST, the use of an IGRA in appropriate clinical situations can reduce the overall cost to the health care system and lower the potential morbidity associated with treating many patients with positive TST due to exposure to nontuberculous mycobacteria.

REFERENCES

1. Abdalhamid, B., et al. 2010. Utilization of the QuantiFERON-TB Gold test in a two step process with the tuberculin skin test to evaluate health care workers for latent tuberculosis. *J. Clin. Microbiol.* **48**:2955–2956.
2. Altet-Gomez, N., et al. 20 August 2010. Diagnosing TB infection in children: analysis of discordances using in vitro tests and tuberculin skin test. *Eur. Respir. J.* [Epub ahead of print.] doi:10.1183/09031936.00022710.
3. Baoolal, S., D. Ramoutar, and P. E. Alpaka. 2010. Comparison of QuantiFERON-TB gold assay and tuberculin skin test to detect latent tuberculosis infection among target groups in Trinidad and Tobago. *Rev. Panam. Salud Publica* **28**:36–42.
4. Deuffic-Burban, S., et al. 2010. Cost-effectiveness of QuantiFERON-TB test vs. tuberculin skin test in the diagnosis of latent tuberculosis infection. *Int. J. Tuberc. Lung Dis.* **14**:471–481.
5. Komiya, K., et al. 2010. Impact of peripheral blood lymphocyte count on the sensitivity of 2 IFN-gamma release assays, QFT-G and ELISPOT, in patients with pulmonary tuberculosis. *Intern. Med.* **49**:1849–1855.
6. Mazurek, M., et al. 2010. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Recomm. Rep.* **55**(RR-5):1–25.
7. Perry, S., et al. 2008. Reproducibility of QuantiFERON-TB Gold In-Tube assay. *Clin. Vaccine Immunol.* **15**:425–432.
8. Sester, M., et al. 2011. Interferon-gamma release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur. Respir. J.* **37**:100–111.

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COUNTERPOINT

At our institution, the tuberculin skin test (TST) remains the primary method used to screen for latent tuberculosis infection (LTBI). In 2005, we participated

in a Centers for Disease Control and Prevention (CDC)-sponsored study applying two generations of the Celtestis QuantiFERON assay (Carnegie, Australia) to LTBI screening of patients entering an alcohol and drug treatment center in North Carolina ($n = 429$; estimated prevalence, 6.2%) (14). Subjects who had a prior positive TST, history of TB, or current symptoms of TB were excluded. Our results showed a lack of correlation of the two different QuantiFERON assays (different test antigens) with each other and with the TST. Of the positive subjects, only 37.5% of them were positive by both interferon gamma release assays (IGRAs). Indeterminate results were completely discordant between the two IGRAs. The QuantiFERON-TB Gold In-Tube assay (QFT-GIT) (now FDA approved) had 1.7% indeterminate samples, and these subjects were more likely to have had five or more previous TSTs or to have been HIV positive. Although the relatively low prevalence in this study did not provide the statistical power needed to analyze the IGRA results in depth, the results raised questions about IGRA usefulness and interpretation in low-prevalence settings, especially where there are frequently repeated TSTs. The logistical difficulties in getting the specimens to the laboratory from off site and the required laboratory investment detracted somewhat from the potential benefits of the IGRAs. Based on our initial experience with the QuantiFERON assay, we elected not to replace the TST with an IGRA for routine LTBI screening. We reserve IGRA testing (which is sent to a reference laboratory) for patients or health care workers (HCWs) that have received the BCG vaccine or are at risk for not returning for the TST reading. Only 1.2% of our workforce has been BCG vaccinated.

The main advantages touted for IGRAs, such as the QFT-GIT and the T-Spot.TB (Oxford Immunotec, Oxford, United Kingdom), are a decrease in false positives due to BCG vaccination, an increase in sensitivity for the detection of LTBI/TB, and the elimination of follow-up testing, such as TST reading and the two-step baseline TST. Without a doubt, testing of individuals that have received the BCG vaccine by an IGRA is sound clinical practice. However, the reality is that IGRAs are being used by physicians for a variety of applications beyond screening immunocompetent patients at high risk for LTBI or active TB.

Screening for LTBI and active TB. It is without question that TST reliability is dependent on the technique and experience of both the person placing the TST and the reader. However, if reading is standardized with the ballpoint pen technique, the results are reasonably reliable, with intra- and interobserver κ values of 0.70 to 0.95 (13). The comparison of performance characteristics between the TST and IGRAs is complicated by the fact that there is no gold standard for the detection of LTBI. When TST and IGRA sensitivities have been

evaluated, active TB is used as the pseudo-gold standard while specificity is generally determined using low-risk populations as a surrogate gold standard. Neither standard is appropriate for determining the performance characteristics of the TST and IGRAs for LTBI.

Nonetheless, meta-analyses have shown the pooled sensitivity of the TST to be 70 to 77% (69% in high-incidence settings and 83% in low-incidence settings) and the sensitivity of QFT-GIT to be 70 to 84% (3, 4, 11, 12). Interestingly, the T-Spot.*TB* cumulative sensitivity was reported to be 88 to 90% (4, 12). Additional data have suggested that perhaps T-Spot is the most sensitive IGRA, but this test uses peripheral blood mononuclear cell (PBMC) fractionation and quantification followed by the enzyme-linked immunospot (ELISPOT) method to measure gamma interferon-producing T cells by counting spots in microwell plates. Because of this complexity, T-Spot is not conducive to the workflow in most nonreference clinical laboratories. In the meta-analyses above, the specificities of QFT-GIT were 96% for BCG-vaccinated individuals and 99% for non-BCG-vaccinated individuals, and the T-Spot pooled specificity was 86 to 93% from studies containing mostly BCG-vaccinated subjects. The specificity of the TST improved from 59% to 97% when BCG-vaccinated individuals were removed from the analysis (12). Interestingly, one meta-analysis included subjects who were suspected to have tuberculosis but were subsequently determined to have an alternative diagnosis (16). Specificities of 75%, 79%, and 59% were reported for the TST, QFT-GIT, and T-Spot, respectively. This negative-control group more closely approximates the patients routinely tested by a clinical laboratory and may therefore be a more accurate reflection of test specificity.

Due to the inherent difficulties associated with comparing studies without head-to-head comparisons, without both sensitivity and specificity being calculated, and with variability in the TST positivity cutoff, Sadatsafavi et al. applied statistical methods and performed a latent-class meta-analysis for the estimation of test accuracy (15). Their analyses showed sensitivities of 71%, 64%, and 50% and specificities of 68%, 99%, and 91% for the TST, QFT, and T-SPOT, respectively. TST analysis did not take BCG vaccination into account, and only three studies were fit for inclusion in the analysis of T-Spot; therefore, there are limitations in this analysis. Nevertheless, the data are consistent with previous meta-analyses showing suboptimal sensitivity for both the TST and IGRAs and superior specificity of IGRAs over the TST when BCG vaccination is not considered. In populations with a low BCG vaccination prevalence, TST sensitivity and specificity are not statistically different from those of IGRAs.

Health care workers. A recent study highlighted the questionable effectiveness of using IGRA testing as a

screening tool in HCWs in the United States (7). In this year-long study, an increase was seen in HCWs testing positive for LTBI by QFT-GIT testing. The annual conversion rate was 2.5%, which represented a 25-fold increase. Of the newly “converted” QFT-GIT-positive HCWs, 49% reverted to QFT-GIT negative upon repeat while 51% remained positive, and only two (1.5%) had a positive TST. The mean gamma interferon response was statistically lower for those that reverted. The authors report that their direct costs were \$436,096 for screening of 6,530 HCWs by QFT-GIT, while the TST cost would have been \$78,360. There was an additional cost of \$85,794 related to following up the newly “converted” HCWs determined by QFT-GIT.

These data underscore the need to consider whether the current positivity threshold is appropriate for screening low prevalence populations. In addition, several publications have demonstrated that there is concern for the reproducibility of IGRA results with serial testing. A review of IGRA reproducibility data revealed that intra-subject variability was present in all studies ($n = 4$), ranging in magnitude from 16% to 80%, and was most often seen with borderline-positive IGRA results (19). This “wobble” phenomenon around the positive threshold makes interpretation difficult, particularly in the setting of serial testing (Fig. 1). Some investigators have proposed using a QFT-GIT gray zone, in which individuals would be retested prior to therapy (18). The conversion/reversion rates decreased from 11%/22% to 3.6%/4.4% and when applying a gray zone of 0.2 to 0.7 IU/ml to a medium TB incidence setting. However, there is currently no gray zone defined in the FDA-approved package insert for QFT-GIT.

HIV-positive patients. Since HIV-positive individuals are at increased risk of TB reactivation, it is critical to identify LTBI in this population. One of the perceptions of IGRAs is that results can be reliably obtained even for immunocompromised patients. The IGRA indeterminate rate reported for HIV-positive individuals varies greatly (1.8 to 28%) (5, 17). The rate of indeterminate results increases when CD4⁺ cells are <100/μl (10) or <200/μl (17). In HIV-positive patients with CD4⁺ cells at >50/μl, QFT-G has been reported to be 83% sensitive and 99% specific, but it was not accurate when CD4⁺ cells were at <50/μl (6). Not surprisingly, the T-Spot assay is more sensitive than the QFT assays for immunosuppressed patients, particularly those with lymphocyte counts of <500/μl (81%, T-Spot; 39%, QFT-GIT), since white blood cells are harvested and counted in the T-Spot assay (9). However, high rates of indeterminate results for T-Spot have also been reported (17). Of note, individuals with an anergic TST result do not appear to be at high risk for developing active TB (3), but this has not been demonstrated for IGRAs.

In general, the data for HIV-positive patients indicate

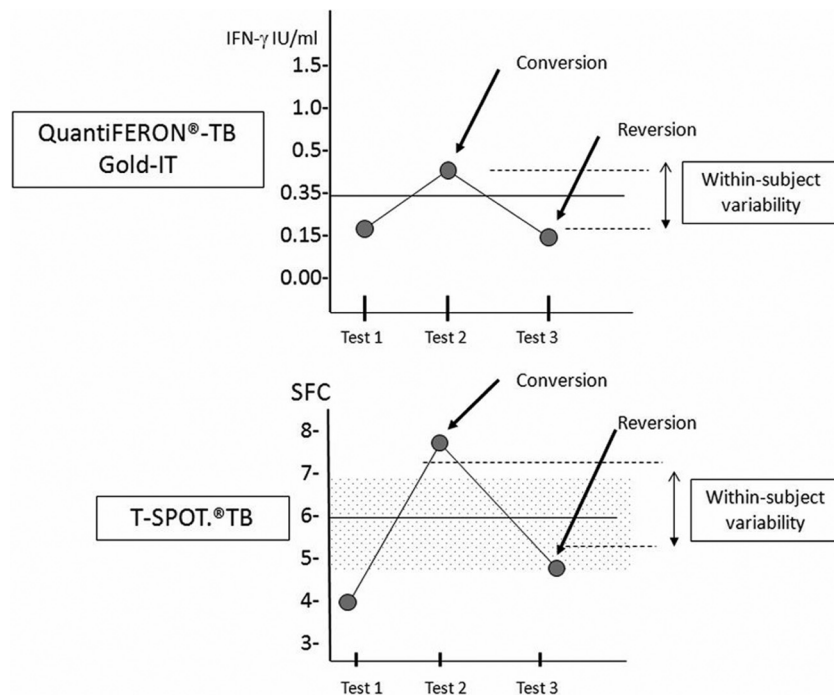


FIG. 1. Schematic of the “wobble” phenomenon seen with IGRAs. The conversion and reversion points are shown as interpreted from the manufacturers’ package inserts. The QFT-GIT assay does not have a defined gray zone, whereas the T-Spot gray zone is shown shaded (reprinted from reference 19).

very poor correlation of results between the TST, QFT-GIT, and T-Spot, making interpretation difficult. For example, one study reported that positive IGRA/TST results were discordant 72% of the time (e.g., TST⁻/IGRA⁺ or TST⁺/IGRA⁻) (10). In addition, a recent meta-analysis of the use of IGRAs with HIV-positive patients did not show an advantage in sensitivity of IGRAs over the TST (1). Prospective studies are still needed to determine if IGRA positivity is predictive of progression to active TB among HIV-positive patients and therefore confers a benefit over the TST.

Summary. Although other guidelines have been more conservative (Australia, Canada, and United Kingdom), the CDC guidelines state that an IGRA may be used in place of the TST in all situations where a TST would be employed (2). However, the data suggest that in areas of low BCG vaccination, there is no advantage to using an IGRA over the TST when there is little risk of a patient not returning. To enable our laboratory to financially support the routine implementation of QFT-GIT, we would have to include the testing volume from HCW screening. HCW compliance with TST reading is required, and the potential for a high conversion/reversion rate makes the use of IGRAs with HCWs suboptimal.

The results between IGRAs (QFT-GIT and T-Spot) can be discordant up to 20% of the time, making the clinical interpretation challenging, and IGRA results may not correlate with the TST. What is the gold stan-

dard for predicting progression to active TB? The calculation of test positive predictive value (PPV) is typically based on contact investigation data, with the extent of exposure correlated to the likelihood of a positive test. Few studies have looked at the PPV of IGRAs for development of TB, though contact tracing data provide evidence that the PPV is not significantly different for the TST and IGRAs (TST, 3.1 to 3.8%; QFT-GIT, 2.8%; T-Spot, 3.3%) (8). While the PPV of the TST has been studied extensively, prospective studies are still needed to establish the PPV of IGRAs for progression to active TB.

The conflicting and/or paucity of IGRA data on test reproducibility, the impact of serial testing, the meaning of discordant QFT-GIT/T-Spot or IGRA/TST results, and the PPV indicate the critical need for carefully designed prospective studies to inform evidence-based guidelines for the routine use of IGRAs. Data are particularly limited in high-risk populations, such as children and immunocompromised patients, who represent those most likely to benefit from preventive therapy. The clearest appropriate uses of IGRAs in routine clinical care are in populations with a high prevalence of BCG vaccination and patients at high risk for not returning for TST follow-up. However, for the routine implementation of IGRAs for detecting LTBI and active TB in our low-prevalence population with low rates of BCG vaccination and for the screening of HCWs, we will await

more compelling data to indicate that the sensitivities and/or PPV of the IGRAs are superior to those of well-performed TSTs before investing the resources needed to replace the TST with an IGRA institution-wide.

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REFERENCES

1. Cattamanchi, A., et al. 2011. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. *J. Acquir. Immune Defic. Syndr.* **56**:230–238.
2. Centers for Disease Control and Prevention. 2010. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. *MMWR Morbid. Mortal. Wkly. Rep.* **59**:1–25.
3. Dheda, K., et al. 2009. T-cell interferon-gamma release assays for the rapid immunodiagnosis of tuberculosis: clinical utility in high-burden vs. low-burden settings. *Curr. Opin. Pulm. Med.* **15**:188–200.
4. Diel, R., R. Loddenkemper, and A. Nienhaus. 2010. Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a meta-analysis. *Chest* **137**:952–968.
5. Ferrara, G., et al. 2005. Routine hospital use of a new commercial whole blood interferon-gamma assay for the diagnosis of tuberculosis infection. *Am. J. Respir. Crit. Care Med.* **172**:631–635.
6. Fujita, A., et al. 10 August 2011. Performance of a whole-blood interferon-gamma release assay with *Mycobacterium* RD1-specific antigens among HIV-infected persons. *Clin. Dev. Immunol.* [Epub ahead of print.] doi: 10.1155/2011/325295.
7. Gandra, S., et al. 2010. Questionable effectiveness of the QuantiFERON-TB Gold test (Cellestis) as a screening tool in healthcare workers. *Infect. Control Hosp. Epidemiol.* **31**:1279–1285.
8. Kik, S. V., et al. 2010. Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts. *Eur. Respir. J.* **35**:1346–1353.
9. Komiya, K., et al. 2010. Impact of peripheral lymphocyte count on the sensitivity of 2 IFN-gamma release assays, QFT-G and ELISPOT, in patients with pulmonary tuberculosis. *Intern. Med.* **49**:1849–1855.
10. Luetkemeyer, A. F., et al. 2007. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am. J. Respir. Crit. Care Med.* **175**:737–742.
11. Mori, T. 2009. Usefulness of interferon-gamma release assays for diagnosing TB infection and problems with these assays. *J. Infect. Chemother.* **15**:143–155.
12. Pai, M., A. Zwerling, and D. Menzies. 2008. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann. Intern. Med.* **149**:177–184.
13. Pouchot, J., et al. 1997. Reliability of tuberculin skin test measurement. *Ann. Intern. Med.* **126**:210–214.
14. Royce, R., et al. 2007. Estimating the tuberculosis infection prevalence in a residential alcohol and drug treatment center in central North Carolina using interferon- γ release assays and tuberculin skin test, preliminary results. *Abstr. Rethinking Epidemiol. Tuberc. Infect.: First Glob. Symp. Interferon- γ Release Assays.* Vancouver, Canada, 21 and 22 February 2007.
15. Sadatsafavi, M., et al. 2010. A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy. *J. Clin. Epidemiol.* **63**:257–269.
16. Sester, M., et al. 2011. Interferon-gamma release assays for the diagnosis of active tuberculosis: a systematic review and meta-analysis. *Eur. Respir. J.* **37**:100–111.
17. Talati, N. J., et al. 2009. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect. Dis.* **9**:15.
18. Torres Costa, J., et al. 2010. Serial testing with the interferon- γ release assay in Portuguese healthcare workers. *Int. Arch. Occup. Environ. Health* **2010**:1–9.
19. van Zyl-Smit, R. N., et al. 2009. Within-subject variability of interferon- γ assay results for tuberculosis and boosting effect of tuberculin skin testing: a systematic review. *PLoS One* **4**:e8517.

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SUMMARY

Points of agreement:

- There is no diagnostic gold standard for patients thought to have latent *M. tuberculosis* infection (LTBI) against which the performance of the TST versus IGRA can be judged. One of the major uses of IGRA would be to screen health care workers and others for LTBI. When screening populations suspected of having LTBI, the TST and IGRA have shown similar performance characteristics.
- IGRAs have very specific advantages over the TST. Because only one visit is required for IGRA versus the TST, IGRAs are of value in patients who are likely not to return for additional medical visits in a required time frame. These groups will include patients with higher risk for TB, such as the homeless, intravenous (i.v.) drug users, or individuals with other difficult social situations. Second, false-positive results are much less likely in BCG-vaccinated patients tested with IGRA.
- Both IGRAs and the TST have technical challenges in both performance and interpretation, which is probably more pronounced with the TST. Additionally, IGRAs must be performed within a fairly tight time window, making testing on nights and weekends in an Emergency Department setting problematic.
- IGRA is more expensive for the laboratory. The laboratory has no costs when the TST is used to screen patients.

Issues to be resolved:

- There are no good longitudinal studies with IGRA, so variability in test results, especially around the positivity threshold, makes interpretation of this test difficult, especially for a low-prevalence population, such as health care workers.
- Is the IGRA cost justifiable in a low-incidence population? The published data thus far appear contradictory.
- It is not known what the effect of multiple prior TST is on the accuracy of IGRAs.
- The interpretation of IGRA for HIV-infected patients with CD4 counts of less than 200/ μ l appears to be as problematic as the interpretation of the TST. Are IGRAs appropriate for HIV-infected patients with low CD4 counts? The IGRAs attempt to overcome this issue by including the phytohemagglutinin (PHA) control to

provide an indication of immune capabilities, however. The T-Spot assay also includes a mononuclear cell concentration step. The TST uses a lower induration measurement in patients with known immunodeficiency as an indicator of true positivity. Which of these parameters best overcomes the issues associated with low immune function is an unanswered question.

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