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Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection – United States, 2010

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Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection – United States, 2010

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Summary

In 2005, CDC published guidelines for using the QuantiFERON-TB Gold test (QFT-G) (Cellestis Limited, Carnegie, Victoria, Australia) (CDC. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR;54[No. RR-15]:49–55). Subsequently, two new interferon gamma (IFN- γ) release assays (IGRAs) were approved by the Food and Drug Administration (FDA) as aids in diagnosing *M. tuberculosis* infection, both latent infection and infection manifesting as active tuberculosis. These tests are the QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis Limited, Carnegie, Victoria, Australia) and the T-SPOT.TB test (T-Spot) (Oxford Immunotec Limited, Abingdon, United Kingdom). The antigens, methods, and interpretation criteria for these assays differ from those for IGRAs approved previously by FDA.

For assistance in developing recommendations related to IGRA use, CDC convened a group of experts to review the scientific evidence and provide opinions regarding use of IGRAs. Data submitted to FDA, published reports, and expert opinion related to IGRAs were used in preparing these guidelines. Results of studies examining sensitivity, specificity, and agreement for IGRAs and TST vary with respect to which test is better. Although data on the accuracy of IGRAs and their ability to predict subsequent active tuberculosis are limited, to date, no major deficiencies have been reported in studies involving various populations.

This report provides guidance to U.S. public health officials, health-care providers, and laboratory workers for use of FDA-approved IGRAs in the diagnosis of *M. tuberculosis* infection in adults and children. In brief, TSTs and IGRAs (QFT-G, QFT-GIT, and T-Spot) may be used as aids in diagnosing *M. tuberculosis* infection. They may be used for surveillance purposes and to identify persons likely to benefit from treatment. Multiple additional recommendations are provided that address quality control, test selection, and medical management after testing.

Although substantial progress has been made in documenting the utility of IGRAs, additional research is needed that focuses on the value and limitations of IGRAs in situations of importance to medical care or tuberculosis control. Specific areas needing additional research are listed.

Introduction

Before 2001, the tuberculin skin test (TST) was the only practical and commercially available immunologic test for *Mycobacterium tuberculosis* infection approved in the United States (1). Recognition that interferon gamma (IFN- γ) plays a critical role in regulating cell-mediated immune responses to *M. tuberculosis* infection led to development of interferon gamma release assays (IGRAs) for the detection of *M. tuberculosis* infection (2–4). IGRAs detect sensitization to *M. tuberculosis*

by measuring IFN- γ release in response to antigens representing *M. tuberculosis*. In 2001, the QuantiFERON-TB test (QFT) (Cellestis Limited, Carnegie, Victoria, Australia) became the first IGRA approved by the Food and Drug Administration (FDA) as an aid for diagnosing *M. tuberculosis* infection (5,6). In 2005, the QuantiFERON-TB Gold test (QFT-G) (Cellestis Limited, Carnegie, Victoria, Australia) became the second IGRA approved by FDA as an aid for diagnosing *M. tuberculosis* infection (7,8). CDC published guidelines for using QFT in 2003 and for using QFT-G in 2005 (6,8).

Updated IGRA guidelines are needed because since 2005, two new IGRAs have been approved by FDA, and several hundred peer-reviewed articles describing clinical studies of IGRAs have been published. This report provides updated guidance to U.S. public health officials, health-care providers, and laboratory workers for use of FDA-approved IGRAs in the diagnosis of *M. tuberculosis* infection in adults and children.

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Methods for Updating IGRA Guidelines

CDC identified relevant reports published through August 2008 by searching PubMed for articles written in English that listed “tuberculosis” as the major MeSH topic and that included either “QuantiFERON” or “T-Spot” in the title or abstract. CDC identified additional published reports by contacting test manufacturers and examining references listed in retrieved articles. These search methods identified 152 potentially relevant articles. CDC reviewed the methods used in each study to select 96 primary reports that provided data related to 1) sensitivity or specificity of QFT-GIT or T-Spot; 2) agreement of QFT-GIT and T-Spot results with each other or with TST results; 3) association of QFT-GIT or T-Spot results with risk for *M. tuberculosis* infection or subsequent active tuberculosis; or 4) evaluation of QFT-GIT or T-Spot use in contact investigations, immunocompromised persons, or children.

During August 4–5, 2008, CDC convened a meeting in Atlanta, Georgia, to consider the use of QFT-GIT and T-Spot in U.S. tuberculosis-control activities. At this meeting, tabulated study results, descriptive summaries, explanations by study authors, and commentaries from test manufacturers were presented to an Expert Committee* comprising tuberculosis-control officials, clinicians, laboratorians, and leading researchers with IGRA expertise, together with representatives of the American Academy of Pediatrics, the American Thoracic Society, the Advisory Council for the Elimination of Tuberculosis, the Association of Public Health Laboratories, CDC, FDA, the Infectious Disease Society of America, the National Tuberculosis Controllers Association, Stop TB USA, the U.S. Army, the U.S. Air Force, and the Veterans Health Administration. Data from most of the 96 primary reports used by CDC as the evidence on which these guidelines are based were available for review by the expert committee either as published articles or articles accepted for publication. CDC asked members of the Expert Committee to provide written opinions regarding how FDA-approved IGRAs should be used.

CDC used the published reports, data submitted to FDA, the product package inserts, and expert opinion related to QFT-GIT and T-Spot to prepare these guidelines. CDC coordinated development of these guidelines with the American Academy of Pediatrics, the American Thoracic Society, and the Infectious Disease Society of America.

*The names of the members of the IGRA Expert Committee and the IGRA Expert Committee presenters appear on page 25 of this report.

Background

The Epidemiology of Tuberculosis and *M. tuberculosis* Infection

Globally, nine million persons develop active disease attributable to *M. tuberculosis* infection annually, and one third of the world's population, approximately 2 billion persons, are thought to be latently infected with *M. tuberculosis* (9). Although persons with latent *M. tuberculosis* infection (LTBI) do not manifest overt symptoms of active tuberculosis and are not infectious, they are at increased risk for developing active disease and becoming infectious. Approximately two million persons die each year from active tuberculosis despite the existence of effective treatments for both latent infection and active disease.

The prevalence of active tuberculosis in the United States has declined from 6.2 cases per 100,000 persons in 1998 to 4.2 cases per 100,000 persons in 2008 (10). During 1998–2007, of the 153,555 persons in the United States who had received a diagnosis of active tuberculosis, 3,708 (2.4%) died before treatment for active tuberculosis was started, and 10,777 (7.0%) died after starting treatment but before treatment was completed (CDC, unpublished data, 2008). A TST survey in 2000 indicated that an estimated 11,213,000 U.S. residents (4.2% of the civilian, noninstitutionalized U.S. population aged >1 year) had LTBI, representing a 60% decline from 1972 (11). However, the declines were not uniform among all segments of the U.S. population, and rates of *M. tuberculosis* infection and active tuberculosis vary considerably. Categorization of the risk for infection (Box 1) and for progression to active disease (Box 2) facilitates targeted testing and selection of those persons likely to benefit from treatment for latent infection (12). Identification of persons who are at increased risk for a poor clinical outcome (e.g., meningitis, disseminated disease, or death) if active tuberculosis occurs (Box 2) is an important component of targeted testing and treatment. U.S. residents with none of the recognized risk characteristics are considered to be at low risk for both infection and disease from *M. tuberculosis*. The prevalence of *M. tuberculosis* infection among such persons is estimated to be $\leq 1\%$ (11).

Development of Interferon Gamma Release Assays (IGRAs) and Interpretation Criteria

TSTs have been used worldwide for more than a century as an aid in diagnosing both LTBI and active tuberculosis. A positive TST result is associated with an increased risk for current or future active tuberculosis (13–16). However, certain limitations

BOX 1. Risk factors for *Mycobacterium tuberculosis* infection

Persons at increased risk* for *M. tuberculosis* infection

- close contacts of persons known or suspected to have active tuberculosis;
- foreign-born persons from areas that have a high incidence of active tuberculosis (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- persons who visit areas with a high prevalence of active tuberculosis, especially if visits are frequent or prolonged;
- residents and employees of congregate settings whose clients are at increased risk for active tuberculosis (e.g., correctional facilities, long-term care facilities, and homeless shelters);
- health-care workers who serve clients who are at increased risk for active tuberculosis;
- populations defined locally as having an increased incidence of latent *M. tuberculosis* infection or active tuberculosis, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol; and
- infants, children, and adolescents exposed to adults who are at increased risk for latent *M. tuberculosis* infection or active tuberculosis.

Source: Based on CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).

* Persons with these characteristics have an increased risk for *M. tuberculosis* infection compared with persons without these characteristics.

BOX 2. Risk factors for progression of infection to active tuberculosis

Persons at increased risk* for progression of infection to active tuberculosis include

- persons with human immunodeficiency virus (HIV) infection;†
- infants and children aged <5 years;†
- persons who are receiving immunosuppressive therapy such as tumor necrosis factor- α (TNF- α) antagonists, systemic corticosteroids equivalent to ≥ 15 mg of prednisone per day, or immune suppressive drug therapy following organ transplantation;†
- persons who were recently infected with *M. tuberculosis* (within the past 2 years);
- persons with a history of untreated or inadequately treated active tuberculosis, including persons with fibrotic changes on chest radiograph consistent with prior active tuberculosis;
- persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck, or lung;
- persons who have had a gastrectomy or jejunioileal bypass;
- persons who weigh <90% of their ideal body weight;
- cigarette smokers and persons who abuse drugs or alcohol; and
- populations defined locally as having an increased incidence of active tuberculosis, possibly including medically underserved or low-income populations

Source: Based on CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR 2000;49(No. RR-6).

* Persons with these characteristics have an increased risk for progression of infection to active tuberculosis compared with persons without these characteristics.

† Indicates persons at increased risk for a poor outcome (e.g., meningitis, disseminated disease, or death) if active tuberculosis occurs.

are associated with the use of TSTs. A valid TST requires proper administration by the Mantoux method with intradermal injection of 0.1 mL of tuberculin-purified protein derivative (PPD) into the volar surface of the forearm. In addition, patients must return to a health-care provider for test reading, and inaccuracies and bias exist in reading the test. Also, false-positive TSTs can result from contact with nontuberculous mycobacteria or vaccination with Bacille Calmette-Guerin (BCG), because the TST test material (PPD) contains antigens that are also in BCG and certain nontuberculous mycobacteria (13,17,18).

In 2001, QFT became the first IGRA approved by FDA as an aid for diagnosing *M. tuberculosis* infection (5,6). This test used an enzyme-linked immunosorbent assay (ELISA) to measure the amount of IFN- γ released in response to PPD compared with controls. CDC issued guidelines on the use of QFT in 2003 (6). However, QFT specificity was less than that of TST despite the use of *M. avium* antigen as a control for nontuberculous mycobacterial sensitization and saline as

a negative control (19). QFT has not been available commercially since 2005.

To improve specificity, new IGRAs were developed. These IGRAs assess response to synthetic overlapping peptides that represent specific *M. tuberculosis* proteins, such as early secretory antigenic target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10). These proteins are present in all *M. tuberculosis* and they stimulate measurable release of IFN- γ in most infected persons, but they are absent from BCG vaccine strains and from most nontuberculous mycobacteria (20). Thus, as test antigens, these proteins offer improved test specificity com-

pared with PPD. However, ESAT-6 and CFP-10 are present in *M. kansasii*, *M. szulgai*, and *M. marinum*, and sensitization to these organisms might contribute to the release of IFN- γ in response to these antigens and cause false-positive IGRA results. Because ESAT-6 and CFP-10 are recognized by fewer T lymphocytes and stimulate less IFN- γ release compared with PPD, a more sensitive ELISA than was used for QFT is required to measure IFN- γ concentrations and responses to ESAT-6 and CFP-10.

In 2005, the QuantiFERON-TB Gold test (QFT-G) (Cellestis Limited, Carnegie, Victoria, Australia) became the second IGRA approved by FDA as an aid for diagnosing *M. tuberculosis* infection (7,8). It assesses the immunologic responsiveness of tested patients to ESAT-6 and CFP-10. For QFT-G, separate aliquots of fresh whole blood are incubated with controls and with two separate mixtures of peptides, one representing ESAT-6 and the other representing CFP-10. The amount of IFN- γ released in response to ESAT-6 or CFP-10 (i.e., the ESAT-6 Response or the CFP-10 Response) is calculated as the difference in IFN- γ concentration in plasma from blood stimulated with antigen minus the IFN- γ concentration in plasma from blood incubated with saline (i.e., Nil). For QFT-G, the TB Response is the higher of the ESAT-6 Response or the CFP-10 Response. A stipulation for FDA approval was inclusion of interpretation criteria that addressed the potential for false-positive results accompanying high Nil values (i.e., >0.7 IU/ml).

In 2005, CDC issued guidelines for using QFT-G (8), but the criteria that addressed interpretation when Nil values are high were subsequently revised (Table 1) (21). The 2005 QFT-G guidelines indicated that QFT-G may be used in all circumstances in which a TST was recommended, including contact investigations, evaluation of recent immigrants, and serial-testing surveillance programs for infection control (e.g., those for health-care workers) (8). The guidelines provided cautions for testing persons from selected populations, including persons at increased risk for progression to active disease if infected.

For IGRAs to measure IFN- γ response accurately, a fresh blood specimen that contains viable white blood cells is needed. This requirement limited the use of early IGRAs to facilities in which trained laboratorians could begin testing blood within a few hours of its collection. The QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis Limited, Carnegie, Victoria, Australia) was developed to address this limitation. In October 2007, QFT-GIT became the third IGRA approved by FDA as an aid for diagnosing *M. tuberculosis* infection (22). Control materials and antigens for QFT-GIT are contained in special tubes used to collect blood for the test, thus allowing more direct testing of fresh blood. One tube contains test antigens that consist of a single mixture of 14 peptides representing

the entire amino acid sequences of ESAT-6 and CFP-10 and part of the sequence of TB7.7. The two accompanying tubes serve as negative and positive controls: the negative-control tube contains heparin alone, and the positive-control tube contains heparin, dextrose, and phytohemagglutinin. Blood (1 ml) is collected into each of the three tubes, mixed with the reagents already in the tubes, and incubated for 16–24 hours. Plasma is separated, and the IFN- γ concentration in the plasma is determined using the same sensitive ELISA used for QFT-G. To interpret QFT-GIT as approved by the FDA (Table 2), the TB Response is calculated as the difference in IFN- γ concentration in plasma from blood stimulated with antigen (i.e., the single cocktail of peptides representing ESAT-6, CFP-10, and TB7.7) minus the IFN- γ concentration in plasma from blood incubated without antigen (i.e., Nil).

QFT-GIT was evaluated in the United States and used in other countries prior to FDA approval in 2007, and users of the test promulgated a variety of interpretation criteria. Some published reports used criteria for QFT-GIT that were similar to those being used for QFT-G. As compared with FDA-approved QFT-G interpretation criteria (Table 1), the FDA criteria approved for QFT-GIT in 2007 (Table 2) interpret tests with a Nil of 0.7–8.0 and a TB Response of 25%–50% of Nil as positive rather than as indeterminate. Also, tests with a Nil of 0.7–8.0 and a TB Response that is <25% of Nil are interpreted as negative, whereas for QFT-G they are interpreted as indeterminate.

In July 2008, T-Spot became the fourth IGRA to be approved by FDA (23). For this test, peripheral blood mononuclear cells (PBMCs) are incubated with control materials and two mixtures of peptides, one representing the entire amino acid sequence of ESAT-6 and the other representing the entire amino acid sequence of CFP-10. The test uses an enzyme-linked immunospot assay (ELISpot) to detect increases in the number of cells that secrete IFN- γ (represented as spots in each test well) after stimulation with antigen as compared to the media control (Nil). The T-Spot interpretation criteria approved by FDA for use in the United States (24) differ from those used in other countries (25). Also, the majority of published studies evaluating T-Spot have used criteria that differ from those approved by FDA. The 2008 FDA-approved interpretation criteria for T-Spot (Table 3) included a borderline interpretation for a TB Response equal to five, six, or seven spots. Use of a borderline category might address test variation and uncertainty for results near a dichotomous cut point. This might increase the assay's apparent specificity and sensitivity by minimizing false-positive and false-negative results near a dichotomous cut point. In addition, through the use of a borderline category, test conversions from negative to positive are more likely to represent a newly acquired infection.

FDA-Approved Intended Use for IGRAs

FDA has approved both QFT-GIT and T-Spot as in vitro diagnostic aids for detection of *M. tuberculosis* infection (22,23). Both tests are approved as indirect tests for *M. tuberculosis* infection (including infection resulting in active disease) when used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations. The FDA-approved indications for QFT-GIT and T-Spot are similar to indications for QFT-G and TST using either Tubersol PPD (Sanofi Pasteur Ltd., Toronto, Ontario, Canada) or Aplisol PPD (JHP Pharmaceuticals, LLC, Rochester, Michigan). Because QFT-G, QFT-GIT, T-Spot, and TST each measure different aspects of the immune response and use different antigens and interpretation criteria, test results might not be interchangeable. Different tests can yield different results.

Assessment of QFT-GIT and T-Spot Accuracy, Specificity, and Sensitivity

Limitations in Assessing Accuracy

Assessments of accuracy of tests for *M. tuberculosis* infection are hampered by the lack of confirmatory tests to diagnose LTBI and culture-negative active tuberculosis. Accuracy is a measure of the proportion of test results that are correct and encompasses assessment of specificity (the proportion of true negatives that have negative test results) and sensitivity (the proportion of true positives that have positive test results). Assessments of accuracy of tests for *M. tuberculosis* infection are difficult because there is no “gold standard” to confirm a diagnosis of LTBI or culture-negative active tuberculosis. However, approximations of accuracy, sensitivity, and specificity can be made by testing populations with known characteristics. For example, to assess the sensitivity of IGRAs, researchers can observe the proportion of positive IGRA results among persons with culture-confirmed active tuberculosis, a group for whom the IGRA should be positive (i.e., true positives). Likewise, to assess the specificity of IGRAs, researchers can observe the proportion of negative IGRA tests among persons who are very unlikely to have *M. tuberculosis* infection (i.e., assumed negatives). Researchers also can characterize factors associated with discordance between different tests or conduct follow-up studies to determine the subsequent rate of active tuberculosis for persons with positive or negative IGRA results. However, although sensitivity and specificity are inherent characteristics of the tests, with no “gold standard,” estimates of test performance might fluctuate as a result of differences in the study population and the rate of diagnostic misclassification (e.g., as a result of differences in prevalence *M. tuberculosis*

and nontuberculous mycobacterial infection, malnutrition, and immune suppression). In addition, because TSTs and IGRAs are indirect tests that measure immunologic responses and are not direct tests that detect the causative organism or components of the organism, assessments of sensitivity among persons with culture-confirmed active tuberculosis might not provide reliable estimates of sensitivity for LTBI. Immunologic differences that allow progression of infection to disease might affect immunologic test results. In addition, treatment can alter immunologic responses and might alter test results. Estimates of specificity among low-risk populations might underestimate specificity because some persons might have infection resulting from unrecognized exposure.

Assessment of test accuracy is complicated further by the use of different test methods and interpretation criteria for TST, QFT-GIT, and T-Spot in published reports. Most published reports evaluating QFT-GIT or T-Spot accuracy (26–53) (Tables 4–7) have used interpretation criteria different from those approved by FDA. Also, in published studies in which IGRA results have been compared with TST results (27,28,31–41,43–45,49,50), the TST antigens and cut points in indurations used to separate negative and positive results differed. In addition, for evaluations of QFT-GIT, some investigators used methods that did not include a positive control for QFT-GIT (28,30), in contrast to the methods approved by FDA. Inclusion of a positive control increases estimates of sensitivity by excluding indeterminate results with low Mitogen Responses, which otherwise might be interpreted as negative. For example, if blood samples are processed improperly to the point that they lose the ability to produce IFN- γ and a positive control is not used, the IGRA results for these samples will be interpreted as negative. With a positive control, they will be interpreted as indeterminate and not be included in the calculations of sensitivity (i.e., they will be removed from the denominator). This is similar to excluding persons who do not return to have their TST read from estimates of TST sensitivity.

Incorporation of a borderline category for the T-Spot as approved by FDA (Table 3) increases test accuracy by classifying results near the cut point (at which small variations might affect the interpretation) as neither positive or negative. Although not included in FDA-approved interpretation criteria for QFT-GIT (Table 2), an appropriate borderline category for QFT-GIT might increase its accuracy for the same reasons. Another tactic for improving detection sensitivity is to use any positive result from multiple tests, as is done with culture or nucleic acid amplification tests. Interpreting any positive result from multiple tests as evidence of infection typically increases detection sensitivity and decreases specificity. On the other hand, requiring positive results from two or more tests

typically has the opposite effect (i.e., decreasing sensitivity and increasing specificity).

Estimates of Sensitivity

Estimates of QFT-GIT and T-Spot sensitivity have varied widely in published studies (Tables 4 and 5), which have involved predominantly adults with culture-confirmed active tuberculosis. In general, QFT-GIT and T-Spot sensitivities are considered similar to those for TST. However, caution is required when comparing test sensitivity from these studies because 1) some cohorts were not limited to subjects with microbiologically confirmed active tuberculosis (and in reality might not have had active tuberculosis); 2) in the majority of studies, head-to-head comparisons of IGRAs were not performed in the same subjects; and 3) test methods and interpretation criteria used in reported studies often differed from those approved by FDA.

When data from published studies related to QFT-GIT sensitivity in patients with culture-confirmed active tuberculosis (26–30,32,33,35,37–39) were pooled (Table 4) and sensitivity was determined as the number of subjects with positive QFT-GIT results divided by the number with positive or negative results, pooled QFT-GIT sensitivity was 81%, compared with 70% reported by a study that estimated sensitivity on the basis of a meta-analysis (54). In studies that compared the sensitivity of QFT-GIT to that of TST in patients with culture-confirmed active tuberculosis (27,28,32,33,35,37–39), pooled QFT-GIT sensitivity was 83% and pooled TST sensitivity was 89%. In the 11 studies that compared QFT-GIT and TST in patients in whom active tuberculosis (not necessarily culture-confirmed) was diagnosed, six studies (28,32,34,37–39) demonstrated no statistically significant difference between the two tests, three studies (27,31,33) demonstrated greater sensitivity for TST, and two studies (35,36) demonstrated greater sensitivity for QFT-GIT.

When data from published studies related to T-Spot sensitivity in patients with culture-confirmed active tuberculosis (28,33,38,42,46,48,50–52) were pooled (Table 5), and sensitivity was determined as the number of subjects with positive T-Spot results divided by the number with positive or negative results, pooled T-Spot sensitivity was 91%. In studies that compared the sensitivity of T-Spot to that of TST in patients with culture-confirmed tuberculosis (28,33,38,39,50), pooled T-Spot sensitivity was 90% and TST sensitivity was 89%. In the 12 studies that compared T-Spot and TST sensitivity in patients diagnosed with active tuberculosis (not necessarily culture-confirmed), nine demonstrated no statistically significant difference in the two tests (28,31,33,38,39,43,44,49,50), and three demonstrated greater sensitivity for T-Spot (39,40,44).

In three published studies that evaluated TST, QFT-GIT, and T-Spot (28,33,39), pooled sensitivity for TST, T-Spot, and QFT-

GIT were 95%, 91%, and 84%, respectively. The largest of these studies was conducted in Singapore and involved more than 270 persons with culture-confirmed active tuberculosis (33). In that study, the estimates of sensitivity of T-Spot and of TST (using a 10-mm cutoff) were similar (94% and 95% respectively; $p=0.84$), and significantly greater than QFT-GIT (83%; $p<0.01$).

Estimates of Specificity

QFT-GIT and T-Spot are expected to be more specific than a TST because the antigens used in these tests are relatively specific to *M. tuberculosis* and should produce fewer false-positive tests (i.e., they should not produce cross-reactions after sensitization by BCG and most nontuberculous mycobacteria, such as *M. avium* complex). Estimates of QFT-GIT and T-Spot specificity in tested populations considered to be at low risk for *M. tuberculosis* infection generally are high (Tables 6 and 7). Caution is required when estimating and comparing test specificity from these studies because 1) the background risk for infection varied among studies, 2) the test methods and interpretation criteria used in the studies often differed from those approved by FDA, and 3) some persons classified as false positives might have infection resulting from unrecognized risk. Most studies comparing the specificity of QFT-GIT or T-Spot with TST have been conducted outside the United States.

In tested populations of persons unlikely to have *M. tuberculosis* infection, pooled QFT-GIT specificity was 99% (Table 6) (26,28,32,34), and pooled TST specificity from these cohorts, when available, was 85% (28,34). Pooled T-Spot specificity was 88% (Table 7) (28,40,53), and pooled TST specificity from these cohorts, when available, was 86% (28,40). Because of the small sample sizes in studies examining T-Spot specificity, additional independent studies are needed to increase the certainty of the T-Spot specificity estimate. The lower estimates of TST specificity compared with QFT-GIT and T-Spot might be attributable to false-positive TST results following BCG vaccination or exposure to nontuberculous mycobacteria. Lower estimates of TST specificity have been demonstrated for BCG-vaccinated cohorts, and in those with nontuberculous lymphadenitis (28,55,56). However, in a study in which cohorts with similar risks for infection were compared, the specificity of IGRA using ESAT-6 or CFP-10 did not differ significantly between those vaccinated with BCG and those not vaccinated (57). The effect of BCG on specificity is difficult to assess because BCG is used predominately in populations already at increased risk for *M. tuberculosis* infection.

Agreement Among Tests

Agreement among tests for *M. tuberculosis* infection varies widely in reported studies (33,58–60). Agreement in these studies has been affected by test interpretation criteria, prevalence of

infection and the proportion of infections that are confirmed microbiologically, estimates of recent and remote exposure, age, race, prior BCG vaccination, recent TST, and coexisting diseases, including nontuberculous mycobacterial infection and conditions with immunosuppression (e.g., human immunodeficiency virus [HIV] infection). Increasing age is a risk for *M. tuberculosis* infection because of longer time for potential exposure and because older persons might have been alive when tuberculosis was more prevalent. The association of older age with positive TST and IGRA results generally is attributed to *M. tuberculosis* infections that accumulate over time. The observation in some studies that increasing age is associated more strongly with TST results than with IGRA results suggests that a TST might be more sensitive than IGRAs in detecting remote infections that occurred years earlier (58,61).

Investigations examining the effect of PPD injection on subsequent IGRAs have produced conflicting results (59,62–66); outcome differences probably are attributable to differences in the study population (infected versus noninfected subjects, recent versus temporally remote infection, and risk for ongoing exposure), timing of IGRA testing after PPD injection, the IGRA format, and the definition of boosting used. PPD injection should be expected to boost anamnestic immune responses measured by IGRA originating from *M. tuberculosis* infection, but not from BCG vaccination or in nonsensitized persons. Additional studies examining the effect of PPD injection on IFN- γ responses are needed to define the frequency, magnitude, induction time, and longevity of IGRA boosting following a TST.

Uncertainty exists regarding the reproducibility of IGRA results in individual patients and the clinical significance of fluctuations in measured IFN- γ responses. Longitudinal studies have revealed considerable fluctuation in IFN- γ responses with serial testing in individual patients (59,62,63,65,67–71). These fluctuations might be attributed to limitations in the precision of IGRAs or to actual fluctuations in IFN- γ responses in the patient. Some increases in IFN- γ response might be attributed to new infection or boosting following a TST. Some decreases in IFN- γ response in individual persons might be attributed to antimycobacterial treatment. However, for the most part, fluctuations in IFN- γ responses among serially tested individual patients reported in longitudinal studies remain unexplained and nonspecific. The magnitude of these fluctuations can be of sufficient size to cause test interpretations to change from negative to positive (conversion) or from positive to negative (reversion), especially when the IFN- γ responses are near cut points separating positive and negative results. Well-controlled studies are needed to further define the causes of individual variations in IFN- γ response and to develop criteria to differentiate nonspecific variation from that associated with new or resolving infection.

Use of QFT-GIT and T-Spot in Contact Investigations

Several reports of contact investigations have included results from QFT-GIT and T-Spot (Table 8) (30,31,58,61,72–74). In two of these investigations (58,73), greater recent exposure (as measured by duration of exposure or infectiousness of the source based on a higher number of acid-fast bacilli in their sputa) was more strongly associated with positive IGRA results than with positive TST results, suggesting that IGRAs might be better than the TST at detecting recent infection. In these studies, persons with lower amounts of recent exposure were more likely to be positive by TST than IGRA, suggesting that the TST might have been better than the IGRAs at detecting remote infection that was present prior to (and therefore did not occur as a result of) the recent exposure (58). In two other investigations (72,74), neither TST nor IGRA results were associated with measures of recent exposure. In another investigation (30), the proximity of recent exposure (i.e., same room, different room, or different house) was more strongly associated with TST results than QFT-GIT results.

Value of QFT-GIT and T-Spot in Predicting Subsequent Active Tuberculosis

Of critical importance, is a test's ability to predict risk for subsequent active tuberculosis. For a person with a positive TST, the lifetime risk for active tuberculosis is estimated to be 5%–10% (16,75). However, very few longitudinal data exist on the ability of IGRAs to predict risk for subsequent active tuberculosis.

In one study in Germany involving 601 close contacts of persons with smear-positive, culture-confirmed active tuberculosis, QFT-GIT was reported to perform better than a TST using a 5 mm cut point in predicting subsequent active tuberculosis (76). Whereas five (2.3%) of 219 contacts with TST induration ≥ 5 mm developed tuberculosis, six (14.6%) of 41 contacts with positive QFT-GIT results developed the disease ($p=0.003$). However, an unusually large proportion (59%) of the contacts had TST induration that ranged from 5 mm to 9 mm. The proportion of those considered positive by TST using a 10 mm cutoff who developed active tuberculosis (five of 90 [5.6%]) was similar to the proportion positive by QFT-GIT (six of 41 [14.6%]; $p=0.1$). In addition, only two of the six contacts with positive QFT-GIT results who developed active tuberculosis had the diagnosis confirmed by culture. As noted in a published comment on the article, the sensitivity for predicting subsequent active tuberculosis did not differ significantly for the two tests (77). The QFT-GIT sensitivity was 100% (95% confidence interval [CI] = 54%–100%) and

the TST sensitivity was 83% (CI = 36%–100%) ($p=0.50$) using either a 5 mm or a 10 mm TST cut point.

Results from another study indicated that active tuberculosis developed in three of 36 (8.3%) HIV-infected persons who had positive QFT-GIT results at baseline and in none of 705 HIV-infected persons with negative QFT-GIT results at baseline during a median of 19 months of active follow up ($p<0.001$) (37). TST was performed for a subset of subjects who had positive QFT-GIT results. TST was positive for all of the tested subjects who developed active tuberculosis.

In a study of 339 immigrants to the Netherlands, TST and QFT-GIT were reported to perform similarly in predicting subsequent active tuberculosis (78). Contacts whose TST was ≥ 5 mm at 0 or 3 months after diagnosis of the index patient were followed for up to 2 years. Nine (3.1%) of 288 contacts with TST ≥ 10 mm developed active tuberculosis whereas seven (3.8%) of 184 with TST ≥ 15 mm, five (2.8%) of 178 with a positive QFT-GIT, and six (3.3%) of 181 with a positive T-Spot developed active tuberculosis. The proportions of contacts with positive results by the different tests who developed active tuberculosis were not statistically different. The sensitivity for subsequent active tuberculosis during the period of follow-up was 100% for a TST using a 10 mm cutoff, 88% for a TST using a 15 mm cutoff, 63% for QFT-GIT, and 75% for a T-Spot. While TST using a 10 mm cutoff identified the greatest number of contacts who developed active tuberculosis (nine of nine [100%]), and QFT-GIT identified the lowest number of contacts who developed active tuberculosis (five of nine [63%]), the sensitivity of the two tests were not statistically different ($p=0.08$).

In another large study, an ELISpot assay that was developed by the investigators to detect responses to ESAT-6 and CFP-10 was used to study tuberculosis household contacts in The Gambia. The ELISpot assay was positive for 11 (52%) of 21 secondary cases of active tuberculosis, compared with 14 (56%) of 25 secondary cases who were positive by TST (79). Of the 21 persons with secondary cases tested with both tests, 15 (71%) were positive by at least one of the tests. Although this proportion was not significantly greater than the proportion positive by TST alone (56%; $p=0.2$), the study indicated that positivity by either test might be the best indication for preventive treatment in this setting. Additional, larger studies are needed to estimate more accurately the performance of IGRA tests compared with TSTs.

Use of QFT-GIT and T-Spot for Testing Children

Assessment of the accuracy of IGRAs has been more difficult in children than in adults because study enrollment is more

complicated, phlebotomy is more difficult in younger children, microbiologic confirmation of infection is less frequent, and BCG might have been administered more recently. This is especially true for children aged <5 years. Few performance data exist for QFT-GIT and T-Spot testing in children (especially for those aged <5 years). For this reason, and because rates of progression from latent infection to active disease (including severe forms of the disease, such as meningitis, disseminated disease, or death as a result of *M. tuberculosis*) are higher in infants and young children, caution is warranted when using IGRAs in children aged <5 years (80).

The higher rate of active tuberculosis and severe forms of the disease in infants and children aged <5 years compared with older children suggests that the immune response to *M. tuberculosis* infection differs in these groups. Age-related immunologic differences might explain reported variations in IGRA test performance, including poorer test sensitivity, and lower production of IFN- γ in response to mycobacterial antigens and mitogen (used as a positive control) among children aged <4 years compared with children aged 4–15 years (81), an increase in response to mitogen with increasing age (82), and a higher proportion of indeterminate QFT-GIT results among children aged <5 years (43). In contrast, one large study in a tuberculosis-endemic setting found that infants and young children had robust IFN- γ responses to *M. tuberculosis* antigens, and that their responses were comparable to responses in adults and older children (83).

Older children (i.e., those aged ≥ 5 years) are less likely than children aged <5 years to develop active tuberculosis or to have severe forms of the disease; in this way, older children resemble adults. In addition, for older children, IGRA testing might be logistically easier (e.g., in the ability to draw sufficient quantities of blood). Therefore, less caution might be required when implementing IGRA testing in children aged ≥ 5 years than in children aged <5 years.

Use of IGRAs in children is subject to several limitations. First, studies evaluating IGRAs performance in children are scant. In only a few studies are separate results provided for children, and even fewer studies divide results by narrow age categories. This means that IGRA performance in children is less well understood than IGRA performance in adults. Second, indeterminate results for children are a potential limitation to implementing IGRAs into clinical practice. The frequencies of indeterminate IGRA results in children vary greatly among studies (range: 0–17%) and between different IGRA formats (31,39,43,84–89). Although the majority of indeterminate results are attributable to a low Mitogen Response, the reasons for low Mitogen Responses in young children are unclear. The mitogen might not work well in young children as a result of a lack of immunologic maturity. Differences in the mitogen

concentration used for stimulation and differences in interpretation criteria can affect the number of indeterminate results, especially when different IGRA formats are compared. Third, concerns relate to difficulties in collecting blood for these tests and the need for a relatively large volume of blood from small children (especially for infants). Finally, certain pediatricians have expressed concern that IGRAs might have lower sensitivity than TSTs in children (81,90,91).

In general, sensitivity of IGRAs in children is expected to be comparable to TST. In one study of 28 children with culture-confirmed active tuberculosis who were aged 4 months–7 years, estimates of sensitivity for TST, QFT-GIT, and T-Spot were comparable at 100%, 93%, and 93% respectively ($p=0.15$) (28). Sensitivities of these tests were also similar in another study of nine children who had active tuberculosis; six (67%) were positive by T-Spot, six (67%) were positive by QFT-GIT, and nine (100%) were positive by TST (31). In another study involving 25 children with culture-confirmed active tuberculosis, estimates of sensitivity were 88% for TST at 10 mm and 83% for TST at 15 mm, 80% for QFT-GIT, and 58% for T-Spot (39). In the same study, when children with probable active tuberculosis were included (defined on the basis of epidemiologic, clinical, and radiographic findings in the absence of a positive culture), sensitivity for TST at 10 mm fell to 71%, sensitivity for TST at 15 mm fell to 60%, and sensitivity for QFT-GIT and T-Spot fell to 64% and 50%, respectively. However, the methods used for diagnosing active tuberculosis in this study were not stated specifically and might have included use of TST results. In another study that evaluated 154 children aged 5–15 years with culture-confirmed active tuberculosis, results indicated that TST was more sensitive than QFT-GIT (90% and 76%, respectively; $p<0.01$) (27).

In general, specificity of IGRAs in children is expected to be high. For example, QFT-GIT and T-Spot demonstrated high specificity for *M. tuberculosis* infection even among children whose TST specificity was reduced to 22% because of nontuberculous mycobacterial infections (28). Additional larger studies are needed to evaluate the performance of IGRAs in children.

Use of QFT-GIT and T-Spot for Testing Immunocompromised Persons

Limited data are available regarding the use of QFT-GIT for testing immunocompromised persons (Table 9) (27,36,37,92–100). In two studies with a total of 34 HIV-infected subjects with culture-confirmed active tuberculosis, the sensitivities of QFT-GIT were 81% and 88% (27,37). In one study, the sensitivities of QFT-GIT and TST were similar (81% and 85% respectively, $p>0.99$) (27). QFT-GIT sensitivity was not

significantly different among persons with HIV infection than among those without infection (81% and 73%, respectively; $p=0.59$). In another study in Zambia involving 112 persons (59 were infected with HIV, 37 were not infected with HIV, and 16 were not tested) in whom active tuberculosis was diagnosed on the basis of sputum smear (36), QFT-GIT and TST were significantly less sensitive in persons infected with HIV than in persons not infected with HIV (76% compared with 97% for QFT-GIT; $p=0.02$ and 55% compared with 81% for TST, $p=0.04$). Among persons with HIV infection, QFT-GIT sensitivity tended to be higher than TST sensitivity (76% and 55%, respectively; $p=0.06$). However, in this study, reduced TST sensitivity might have resulted from delayed reading of TSTs, which were read 48–164 hours after PPD injection. Low CD4 counts were associated with increases in false-negative TST results and indeterminate and false-negative QFT-GIT results.

Published comparisons have not demonstrated significant differences in the proportion of positive QFT-GIT results as compared with the proportion of positive TST results among HIV-infected persons screened for *M. tuberculosis* infection (93–96). QFT-GIT results from two studies suggest that the proportion of indeterminate QFT-GIT results among HIV-infected persons (17% and 19%, respectively) is similar to the proportion among uninfected persons (14% and 0, respectively; $p=0.88$ and $p=0.18$, respectively) (27,36). However, in another study among HIV-infected persons, CD4 counts were lower in those with indeterminate QFT-GIT results as compared with those with positive or negative results ($p<0.01$) (37). Among persons with other immunosuppressive conditions, published comparisons do not show consistent agreement between results of QFT-GIT and those of TST (97–100). Without a diagnostic “gold standard” for LTBI, the accuracies of both the QFT-GIT and the TST are uncertain.

Information related to T-Spot in immunocompromised persons has been provided in relatively few published reports (Table 10) (60,96,97,101–108) with very little information related to test sensitivity in such persons (Table 5). Among persons with various immunosuppressive conditions being screened for *M. tuberculosis* infection, published comparisons of T-Spot with TST generally demonstrate either similar proportions of positive results (60,96,97,101,104,108) or that T-Spot is more often positive (103,105–107). Without a diagnostic “gold standard” for LTBI, the accuracies of both the TST and the T-Spot are suspect.

Considerations for Programs

Because of administrative and logistic difficulties associated with the TST, IGRAs are attractive diagnostic aids for detect-

ing *M. tuberculosis* infection. Unlike TSTs, IGRA results can be available within 24 hours without the need for a second visit. As laboratory-based assays, IGRAs are not subject to the biases and errors associated with TST placement and reading. However, errors in collecting, labeling, or transporting blood specimens, or while performing and interpreting these assays can decrease IGRA accuracy. Also, availability of IGRAs is limited by the need for a fresh blood sample and the potential for delays as a result of the long distances to laboratories that offer these tests.

The cost for an IGRA is substantially greater than that for a TST (109). However, this additional cost might be offset by decreases in the number of persons testing positive and the associated costs of evaluating and treating persons with positive test results (110). Use of an IGRA might increase acceptance of treatment for LTBI (111). However, cost-effectiveness studies are limited by the lack of critical data on the relative ability of these tests to predict subsequent disease.

Recommendations

General Recommendations for Use of IGRAs

- TSTs and IGRAs (QFT-G, QFT-GIT, and T-Spot) should be used as aids in diagnosing infection with *M. tuberculosis*. These tests may be used for surveillance purposes or to identify persons likely to benefit from treatment, including persons who are or will be at increased risk for *M. tuberculosis* infection (Box 1) or for progression to active tuberculosis if infected (Box 2).
- IGRAs should be performed and interpreted according to established protocols using FDA-approved test formats. They should be performed in compliance with Clinical Laboratory Improvement Amendment (CLIA) standards.
- Both the standard qualitative test interpretation and the quantitative assay measurements should be reported together with the criteria used for test interpretation. This will permit more refined assessment of results and promote understanding of the tests.
- Arrangement for IGRA testing should be made prior to blood collection to ensure that the blood specimen is collected in the proper tubes, and that testing can be performed within the required timeframe.
- Prior to implementing IGRAs, each institution and tuberculosis-control program should evaluate the availability, overall cost, and benefits of IGRAs for their own setting. In addition, programs should consider the characteristics of the population to be tested.
- As with the TST, IGRAs generally should not be used for testing persons who have a low risk for both infection and

progression to active tuberculosis if infected (except for those likely to be at increased risk in the future). Screening such persons diverts resources from higher priority activities and increases the number of false-positive results. Even with a test specificity approaching 99%, when the prevalence of *M. tuberculosis* infection is $\leq 1\%$, the majority of positive results will be false positives. If persons at low risk for both infection and progression are to be tested, selection of the test with the greatest specificity will minimize false-positive results, reduce unnecessary evaluation and treatment, and minimize the potential for adverse events from unnecessary treatment.

Test Selection

- Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection should be made on the basis of the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Results of studies examining sensitivity, specificity, and agreement for IGRAs and TST vary with respect to which test is better. Although data on the accuracy of IGRAs and their ability to predict subsequent active tuberculosis are limited, to date, no major deficiencies have been reported in studies involving various populations. As use of these tests increases, greater understanding of their value and limitations will be gained.
- An IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection, with preferences and special considerations noted below. Despite the indication of a preference in these instances, use of the alternative test (FDA-approved IGRA or TST) is acceptable medical and public health practice.

Situations in Which an IGRA Is Preferred But a TST Is Acceptable

- An IGRA is preferred for testing persons from groups that historically have low rates of returning to have TSTs read. For example, use of an IGRA might increase test completion rates for homeless persons and drug-users. The use of IGRAs for such persons can increase test completion rates, so control efforts can focus on those most likely to benefit from further evaluation and treatment.
- An IGRA is preferred for testing persons who have received BCG (as a vaccine or for cancer therapy). Use of IGRAs in this population is expected to increase diagnostic specificity and improve acceptance of treatment for LTBI.

Situations in Which a TST Is Preferred But an IGRA Is Acceptable

- A TST is preferred for testing children aged <5 years. Use of an IGRA in conjunction with TST has been advocated by some experts to increase diagnostic sensitivity in this age group. Recommendations regarding use of IGRAs in children have also been published by the American Academy of Pediatrics (112).

Situations in Which Either a TST or an IGRA May Be Used Without Preference

- An IGRA or a TST may be used without preference to test recent contacts of persons known or suspected to have active tuberculosis with special considerations for follow-up testing. IGRAs offer the possibility of detecting *M. tuberculosis* infection with greater specificity than with a TST. Also, unlike TSTs, IGRAs do not boost subsequent test results and can be completed following a single patient visit. However, data on the ability of IGRAs to predict subsequent active tuberculosis are limited. If IGRAs are to be used in contact investigations, negative results obtained prior to 8 weeks after the end of exposure typically should be confirmed by repeat testing 8–10 weeks after the end of exposure. This recommendation is similar to one used for TST, because data on the timing of IGRA conversion after a new infection are not currently available. Use of the same test format for repeat testing will minimize the number of conversions that occur as a result of test differences.
- An IGRA or a TST may be used without preference for periodic screening of persons who might have occupational exposure to *M. tuberculosis* (e.g., surveillance programs for health-care workers) with special considerations regarding conversions and reversions. For serial and periodic screening, IGRAs offer technical, logistic, and possible economic advantages compared with TSTs but also have potential disadvantages. Advantages include the ability to get results following a single visit. Two-step testing is not required for IGRAs, because IGRA testing does not boost subsequent test results. Disadvantages of IGRAs in this setting include a greater risk of test conversion due to false-positive IGRA results with follow-up testing of low-risk health-care workers who have tested negative at prior screening. CDC has published criteria for identifying conversions for TSTs and IGRAs (113). TST conversion is defined as a change from negative to positive with an increase of ≥ 10 mm in induration within 2 years. TST conversion is associated with an increased risk for active tuberculosis. An IGRA conversion is defined as a change from negative to positive within 2 years without any consideration of the magnitude of the change in TB Response. Using this lenient criterion

to define IGRA conversion might produce more conversions than are observed with the more stringent criteria applied to TSTs. Furthermore, an association between an IGRA conversion and subsequent disease risk has not been demonstrated. The criteria for interpreting changes in an IGRA that identify new infections remain uncertain. CDC encourages institutions and programs in which IGRAs are used to publish their experiences, particularly in regard to rates of conversion, reversion, and progression to active tuberculosis over time.

Situations in Which Testing with Both an IGRA and a TST May Be Considered

- Although routine testing with both a TST and an IGRA is not generally recommended, results from both tests might be useful when the initial test (TST or IGRA) is negative in the following situations: 1) when the risk for infection, the risk for progression, and the risk for a poor outcome are increased (e.g., when persons with HIV infection or children aged <5 years are at increased risk for *M. tuberculosis* infection) or 2) when clinical suspicion exists for active tuberculosis (such as in persons with symptoms, signs, and/or radiographic evidence suggestive of active tuberculosis) and confirmation of *M. tuberculosis* infection is desired. In such patients with an initial test that is negative, taking a positive result from a second test as evidence of infection increases detection sensitivity. However, multiple negative results from any combination of these tests cannot exclude *M. tuberculosis* infection.
- Using both a TST and an IGRA also might be useful when the initial test is positive in the following situations: 1) when additional evidence of infection is required to encourage compliance (e.g., in foreign-born health-care workers who believe their positive TST result is attributable to BCG) or 2) in healthy persons who have a low risk for both infection and progression. In the first situation, a positive IGRA might prompt greater acceptance of treatment for LTBI as compared with a positive TST alone. In the latter situation, requiring a positive result from the second test as evidence of infection increases the likelihood that the test result reflects infection. For the second situation, an alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results. Steps should be taken to minimize unnecessary and misleading testing of persons at low risk.
- Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists. A second test also might be useful when assay measurements from the

initial test are unusual, such as when the Nil value is higher than typical for the population being tested (e.g., IFN- γ concentration for Nil by QFT-G or QFT-GIT >0.7 IU/ml for most of the U.S. populations), the Nil value is appreciably greater than the value obtained with *M. tuberculosis* antigen stimulation (e.g. when IFN- γ concentration for Nil by QFT-G is 0.35 IU/ml greater than the concentration obtained with either ESAT-6 or CFP-10 stimulation, or when the number of spots for Nil by T-Spot is four spots greater than the number with either ESAT-6 or CFP-10 stimulation), or the Mitogen value is lower than is expected for the population being tested (e.g., the Mitogen Response by QFT-G or QFT-GIT is <0.5 IU/ml, or the number of spots in the mitogen well by T-Spot is <20). If an IGRA is to be repeated, a new blood sample should be used. In such situations, repeat testing with another blood sample usually provides interpretable results.

Medical Management After Testing

- Diagnoses of *M. tuberculosis* infection and decisions about medical or public health management should not be based on IGRA or TST results alone, but should include consideration of epidemiologic and medical history as well as other clinical information.
- Persons with a positive TST or IGRA result should be evaluated for the likelihood of *M. tuberculosis* infection, for risks for progression to active tuberculosis if infected, and for symptoms and signs of active tuberculosis. If risks, symptoms, or signs are present, additional evaluation is indicated to determine if the person has LTBI or active tuberculosis.
- A diagnosis of LTBI requires that active tuberculosis be excluded by medical evaluation, which should include taking a medical history and a physical examination to check for suggestive symptoms and signs, a chest radiograph, and, when indicated, testing of sputum or other clinical samples for the presence of *M. tuberculosis*. Neither an IGRA nor TST can distinguish LTBI from active tuberculosis.
- In persons who have symptoms, signs, or radiographic evidence of active tuberculosis or who are at increased risk for progression to active tuberculosis if infected, a positive result with either an IGRA or TST should be taken as evidence of *M. tuberculosis* infection. However, negative IGRA or TST results are not sufficient to exclude infection in these persons, especially in those at increased risk for a poor outcome if disease develops, and clinical judgment dictates when and if further diagnostic evaluation and treatment are indicated.
- In healthy persons who have a low likelihood both of *M. tuberculosis* infection and of progression to active tuber-

culosis if infected, a single positive IGRA or TST result should not be taken as reliable evidence of *M. tuberculosis* infection. Because of the low probability of infection, a false-positive result is more likely. In such situations, the likelihood of *M. tuberculosis* infection and of disease progression should be reassessed, and the initial test results should be confirmed. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis. For such persons, an alternative is to assume, without additional testing, that the initial result is a false positive.

- In persons with discordant test results (i.e., one positive and the other negative), decisions about medical or public health management require individualized judgment in assessing the quality and magnitude of each test result (e.g., size of induration and presence of blistering for a TST; and the TB Response, Nil, and Mitogen values for an IGRA), the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs.
 - Taking a positive result from either of two tests as evidence of infection is reasonable when 1) clinical suspicion exists for active tuberculosis (e.g., in persons with symptoms, signs, and/or radiographic evidence of active tuberculosis) or 2) the risks for infection, progression, and a poor outcome are increased (e.g., when persons with HIV infection or children aged <5 years are at increased risk for *M. tuberculosis* infection).
 - For healthy persons who have a low risk for both infection and progression, discounting an isolated positive result as a false positive is reasonable. This will increase detection specificity and decrease unnecessary treatment.
 - For persons who have received BCG and who are not at increased risk for a poor outcome if infected (Box 2), TST reactions of <15 mm in size may reasonably be discounted as false positives when an IGRA is clearly negative.
 - In other situations, inadequate evidence exists on which to base recommendations for dealing with discordant results. However, in the absence of convincing evidence of infection, diagnostic decisions may reasonably be deferred unless an increased risk exists for progression if infected and/or a high risk exists for a poor outcome if disease develops.

Areas for Additional Research

Although substantial progress has been made in documenting the utility of IGRAs, further studies and research are needed. Future studies should focus on determining the value

and limitations of IGRAs in situations of importance to medical care or tuberculosis control. Questions to address include the following (not listed in any order of priority):

- Are IGRAs better at predicting subsequent active tuberculosis than TST?
- Are persons with discordant TST and IGRA results at increased risk for active tuberculosis compared with persons with concordant negative results?
- Are higher IFN- γ responses associated with a greater risk for developing active tuberculosis?
- Do IGRAs perform differently in children than in adults, in those with extrapulmonary versus pulmonary tuberculosis, in those with HIV infection versus those without HIV infection, in those recently infected as compared with those infected years earlier, and in those with latent infection as compared with those with active tuberculosis?
- Why do simultaneously performed TST, QFT-GIT, QFT-G, and T-Spot results differ?
- Can sensitivity and specificity of IGRAs be improved by modification in testing methods, application of different interpretation criteria, or inclusion of additional antigens?
- What is the best approach for determining cut points for IGRA interpretation, including situations where Nil values are high or Mitogen values are low?
- To what extent does inclusion of a “borderline” interpretation improve IGRA accuracy?
- What causes variation in IGRA results and to what extent?
- What magnitude of change in IFN- γ response indicates new infection?
- After exposure, how long does it take for an IGRA to become positive?
- What is the clinical significance of IGRA reversion?
- What methods should be used to monitor IGRA quality?
- Is there an association between lymphocyte count and IFN- γ response (with or without HIV infection)?
- What effect does treatment of *M. tuberculosis* infection have on IGRA results?
- How do host and bacterial genetic factors affect IGRA results?

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TABLE 1. Interpretation criteria for the QuantiFERON-TB Gold Test (QFT-G)

Interpretation	Nil*	TB Response†	Mitogen Response§
Positive¶	Any	≥0.35 IU/ml and ≥50% of Nil	Any
Negative**	≤0.7	<0.35 IU/ml	≥0.5
Indeterminate††	≤0.7	<0.35 IU/ml	<0.5
	>0.7	<50% of Nil	Any

Source: Based on Cellestis Limited. QuantiFERON-TB Gold [Package insert]. Available at <http://www.cellestis.com/IRM/Company/ShowPage.aspx?CPID=1247>.

* The interferon gamma (IFN-γ) concentration in plasma from blood incubated with saline.

† The higher IFN-γ concentration in plasma from blood stimulated with a cocktail of peptides representing early secretory antigenic target-6 (ESAT-6) or a cocktail of peptides representing culture filtrate protein 10 (CFP-10) minus Nil.

§ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.

¶ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating that *M. tuberculosis* infection is not likely.

†† Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

TABLE 2. Interpretation criteria for the QuantiFERON-TB Gold In-Tube Test (QFT-GIT)

Interpretation	Nil*	TB Response†	Mitogen Response§
Positive¶	≤8.0	≥0.35 IU/ml and ≥25% of Nil	Any
Negative**	≤8.0	<0.35 IU/ml or <25% of Nil	≥0.5
Indeterminate††	≤8.0	<0.35 IU/ml or <25% of Nil	<0.5
	>8.0	Any	Any

Source: Based on Cellestis Limited. QuantiFERON-TB Gold In-Tube [Package insert]. Available at <http://www.cellestis.com/IRM/content/pdf/QuantiFeron%20US%20VerG-Jan2010%20NO%20TRIMS.pdf>.

* The interferon gamma (IFN-γ) concentration in plasma from blood incubated without antigen.

† The IFN-γ concentration in plasma from blood stimulated with a single cocktail of peptides representing early secretory antigenic target-6 (ESAT-6), culture filtrate protein-10 (CFP-10), and part of TB 7.7 minus Nil.

§ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.

¶ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating that *M. tuberculosis* infection is not likely.

†† Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

TABLE 3. Interpretation criteria for the T-SPOT.TB Test (T-Spot)

Interpretation	Nil*	TB Response†	Mitogen§
Positive¶	≤10 spots	≥8 spots	Any
Borderline**	≤10 spots	5, 6, or 7 spots	Any
Negative††	≤10 spots	≤4 spots	Any
Indeterminate**	>10 spots	Any	Any
	≤10 spots	<5 spots	<20 spots

Source: Based on Oxford Immunotec Limited. T-Spot.TB [Package insert]. Available at <http://www.oxfordimmunotec.com/USpageInsert>.

* The number of spots resulting from incubation of PBMCs in culture media without antigens.

† The greater number of spots resulting from stimulation of peripheral blood mononuclear cells (PBMCs) with two separate cocktails of peptides representing early secretory antigenic target-6 (ESAT-6) or culture filtrate protein-10 (CFP-10) minus Nil.

§ The number of spots resulting from stimulation of PBMCs with mitogen without adjustment for the number of spots resulting from incubation of PBMCs without antigens.

¶ Interpretation indicating that *Mycobacterium tuberculosis* infection is likely.

** Interpretation indicating an uncertain likelihood of *M. tuberculosis* infection.

†† Interpretation indicating that *M. tuberculosis* infection is not likely.

TABLE 4. QuantiFERON-TB Gold-In-Tube test (QFT-GIT) sensitivity,* by country in which study was conducted — 14 countries, 2006–2009

Country	Subjects	Confirmed TB†		QFT-GIT results						TST‡ results			% TST+ vs. QFT-GIT+ p-value††	
		No. confirmed/ No. with TB diagnosis	(%)	HIV§-positive		Inter-pretation criteria**	Positive		Indeterminate		Cutoff	Positive		
		No. +/ No. tested	(%)	No. +/ No. tested	(%)		No. +/ No. valid	(%)	No. +/ No. tested	(%)		No. +/ No. tested	(%)	
South Africa§§	Children	154/154	(100)	26/41	(63)	A	100/131	(76)	23/154	(15)	Stratified	131/146	(90)	<0.01
Germany¶¶¶	Children	28/28	(100)	NR***	NR	B	26/28	(93)	ND†††	ND	5 mm	28/28	(100)	0.49
India§§§	Adults	58/60	(97)	3/60	(5)	A	44/60	(73)	0/60	(0)	ND	ND	ND	ND
The Gambia¶¶¶¶	Adults	75/75	(100)	7/77	(9)	B	48/75	(64)	ND	ND	ND	ND	ND	ND
Spain****	Adults & children	NR/42	(NR)	NR	NR	C	33/42	(79)	0/42	(0)	5 mm	40/42	(95)	0.05
Italy††††	Mostly adults	17/17	(100)	NR	NR	C	14/17	(82)	0/17	(0)	NR	9/12	(75)	0.97
Singapore§§§§	Adults	286/286	(100)	7/238	(3)	A	224/270	(83)	10/286	(4)	10 mm	206/217	(95)	<0.01
											15 mm	158/217	(73)	ND
Japan¶¶¶¶¶	Adults	100/100	(100)	1/100	(1)	D	87/94	(93)	6/100	(6)	ND	ND	ND	ND
Denmark*****	Adults	68/80	(85)	10/56	(18)	C	65/76	(86)	4/80	(5)	10 mm	9/12	(75)	0.58
Czech	Adults	22/22	(100)	0/22	(0)	C	19/22	(86)	0/22	(0)	5	12/22	(55)	0.05
Republic†††††		0/31	(0)	0/31	(0)		24/28	(86)	3/31	(6)		22/31	(71)	ND
Zambia§§§§§	Adults	0/112	(0)	59/96	(62)	A	83/96	(86)	16/112	(14)	5 mm¶¶¶¶¶¶	62/92¶¶¶¶¶¶	(67)¶¶¶¶¶¶	<0.01
											10 mm¶¶¶¶¶¶	48/92¶¶¶¶¶¶	(52)¶¶¶¶¶¶	ND
Austria*****	HIV+ adults	10/11	(91)	11/11	(100)	D	10/11	(91)	0/11	(0)	5 mm	8/10	(80)	0.92
Multiple	Adults	121/121	(100)	3/NR	(NR)	C	99/117	(85)	4/121	(3)	10 or 15	114/136	(84)	1.0
European††††††		0/34	(0)	0/NR	(NR)		22/34	(65)	0/34	(0)		37/41	(90)	0.02
United	Children	25/25	(100)	0/35	(0)	D	20/23	(87)	2/25	(8)	10 mm	21/24	(86)	1.0
Kingdom§§§§§§		0/38	(0)				20/36	(56)	2/38	(5)		24/38	(63)	0.67

* Source: Modified from Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177–84 supplemented with additional information and compared with TST sensitivity when available.

† Tuberculosis disease was confirmed by culture and/or nucleic acid amplification test.

§ Human immunodeficiency virus.

¶ Tuberculin skin test.

** "A" = QFT-GIT was interpreted as positive if Tuberculosis (TB) Response was ≥ 0.35 IU/mL; indeterminate if TB Response was < 0.35 IU/mL and Mitogen Response was < 0.5 IU/mL; and negative if TB Response was < 0.35 IU/mL and Mitogen Response was ≥ 0.5 IU/mL. "B" = QFT-GIT was interpreted as positive if TB Response was ≥ 0.35 IU/mL; Mitogen Response was not measured. "C" = QFT-GIT interpretation criteria were not stated explicitly. "D" = QFT-GIT was interpreted as positive if TB Response was ≥ 0.35 IU/mL and Nil was ≤ 8.0 IU/mL; indeterminate if Nil ≥ 8.0 IU/mL or TB Response was < 0.35 IU/mL and Mitogen Response was < 0.5 IU/mL; and negative if TB Response was < 0.35 IU/mL, Mitogen Response was ≥ 0.5 IU/mL, and Nil was ≤ 8.0 IU/mL.

†† Fisher's exact test was used by CDC to calculate 2-tailed p-values.

§§ Source: Tsiouris SJ, Coetzee D, Toro PL, Austin J, Stein Z, el-Sadr W. Sensitivity analysis and potential uses of a novel gamma interferon release assay for diagnosis of tuberculosis. *J Clin Microbiol* 2006;44:2844–50.

¶¶ Source: Detjen AK, Keil T, Roll S, et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis* 2007;45:322–8.

*** Not reported.

††† Not done.

§§§ Source: Pai M, Joshi R, Bandyopadhyay M, et al. Sensitivity of a whole-blood interferon-gamma assay among patients with pulmonary tuberculosis and variations in T-cell responses during anti-tuberculosis treatment. *Infection* 2007;35:98–103.

¶¶¶ Source: Adetifa IM, Lugos MD, Hammond A et al. Comparison of two interferon gamma release assays in the diagnosis of *Mycobacterium tuberculosis* infection and disease in The Gambia. *BMC Infect Dis* 2007;7:122.

**** Source: Dominguez J, Ruiz-Manzano J, De Souza-Galvao M, et al. Comparison of two commercially available gamma interferon blood tests for immunodiagnosis of tuberculosis. *Clin Vaccine Immunol* 2008;15:168–171.

†††† Source: Palazzo R, Spensieri F, Massari M, et al. Use of whole-blood samples in in-house bulk and single-cell antigen-specific gamma interferon assays for surveillance of *Mycobacterium tuberculosis* infections. *Clin Vaccine Immunol* 2008;15:327–37.

§§§§ Source: Chee CB, Gan SH, KhinMar KW, et al. Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. *J Clin Microbiol* 2008;46:1935–40.

¶¶¶¶ Source: Harada N, Higuchi K, Yoshiyama T, et al. Comparison of the sensitivity and specificity of two whole blood interferon-gamma assays for *M. tuberculosis* infection. *J Infect* 2008;56:348–53.

***** Source: Ruhwald M, Bodmer T, Maier C, et al. Evaluating the potential of IP-10 and MCP-2 as biomarkers for the diagnosis of tuberculosis. *Eur Respir J* 2008; 32(6):1607-1615.

††††† Source: Bartu V, Havelkova M, Kopecka E. QuantiFERON-TB Gold in the diagnosis of active tuberculosis. *J Int Med Res* 2008;36:434–7.

§§§§§ Source: Raby E, Moyo M, Devendra A, et al. The effects of HIV on the sensitivity of a whole blood IFN-gamma release assay in Zambian adults with active tuberculosis. *PLoS ONE* 2008; 3:e2489. [E-pub]. Available at <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002489>.

¶¶¶¶¶ TST read 48–164 hours after tuberculin injection.

***** Source: Aichelburg MC, Rieger A, Breitenacker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis* 2009;48:954–62.

†††††† Source: Goletti D, Stefania C, Butera O, et al. Accuracy of immunodiagnostic tests for active tuberculosis using single and combined results: a multicenter TBNET-Study. *PLoS ONE* 2008; 3:e3417. [E-published]. Available at <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0003417>.

§§§§§§ Source: Kampmann B, Whittaker E, Williams A, et al. Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. *Eur Respir J* 2009;33:1374–82.

TABLE 5. T-SPOT.TB test (T-Spot) sensitivity,* by country in which study was conducted —12 countries, 2005–2009

Country	Subjects	Confirmed TB†				Inter-pretation criteria**	T-Spot results				TST‡ results			% TST+ vs. QFT-GIT+ p-value††
		No. confirmed/ No. with TB diagnosis	No. tested	HIV§-positive			Positive		Indeterminate		Cutoff	Positive		
				(%)	No. +/ No. tested		(%)	No. +/ No. valid	(%)	No. +/ No. tested		(%)	No. +/ No. tested	
Singapore§§	Adults	286/286	(100)	7/238	(3)	A	254/270	(94)	3/286	(1)	10 mm 15 mm	206/217 158/217	(95) (73)	0.84 ND¶¶
Spain***	Adults & children	NR/42	(NR)	NR†††	NR	B	36/39	(86)	3/42	(7)	5 mm	40/42	(95)	0.93
Germany§§§	Children aged 0–7 yrs	28/28	(100)	NR	NR	B	26/28	(93)	0/28	(0)	5 mm	28/28	(100)	0.49
South Korea¶¶¶¶	Adults	37/65	(57)	0/31	(0)	C	83/87	(95)	0/87	(0)	5 mm 10 mm	64/87 55/87	(74) (67)	<0.01 <0.01
Germany****	Adults	58/65	(89)	NR	NR	D	40/40	(100)	0/40	(0)	NR	35/40	(88)	0.05
Italy††††	Adults	23/23	(100)	0/23	(0)	E	21/23	(91)	NR	NR	ND	ND	ND	ND
Italy§§§§	Adults & children aged >15 yrs	13/24	(54)	NR	NR	F	20/24	(83)	0/24	(0)	5 mm	14/20	(54)	0.49
Germany¶¶¶¶¶	Adults	8/12	(67)	NR	NR	G	12/12	(100)	0/12	(0)	6 mm	8/10	(80)	0.39
South Korea*****	Adults & children aged >15 yrs	58/67	(87)	0/67	(0)	H	59/64	(92)	3/67	(4)	10 mm	45/66	(68)	<0.01
Switzerland†††††	Adults	89/89	(100)	0/89	(0)	I	61/61	(100)	1/62	(2)	ND	ND	ND	ND
Taiwan§§§§§	Adults & children aged 2–84 yrs	37/39	(95)	3/NR	(ND)	J	34/39	(87)	NR	NR	ND	ND	ND	ND
Switzerland¶¶¶¶¶¶	Adults & children aged >15 yrs	58/58	(100)	0/58	(0)	K	57/58	(98)	0/58	(2)	ND	ND	ND	ND
Turkey*****	Adults	NR/28	NR/28	NR	NR	B	26/28	(93)	NR	NR	10 mm	23/28	(82)	0.42
Turkey††††††	Adults & children aged >15 yrs	100/100	(100)	0/100	(0)	L	80/96	(83)	4/100	(4)	10 mm	80/99	(81)	0.79
Multiple European§§§§§§§	Adults	69/69 0/19	(100) (0)	3/NR 0/NR	(NR) (NR)	B	62/69 13/19	(90) (68)	0/69 0/19	(0) (0)	10 or 15	114/136 37/41	(84) (90)	0.06 0.09
Taiwan¶¶¶¶¶¶¶	Adults with extra-pulmonary TB	50/50 0/39	(100) (0)	2/NR	(NR)	M	40/50 31/39	(80) (79)	NR	NR	ND	ND	ND	ND
United Kingdom*****	Children	25/25 0/38	(100) (0)	0/35	(0)	F	14/24 17/34	(58) (50)	1/25 4/38	(8) (11)	10 mm	21/24 24/38	(86) (63)	0.05 0.38
Japan†††††††	Adults	49/49	(100)	NR	NR	N	47/47	(100)	2/49	(4)	ND	ND	ND	ND

See Table 5 footnotes on the following page.

TABLE 5. (Continued) T-SPOT.TB (T-Spot) sensitivity* results, by country in which study was conducted —12 countries, 2005–2009

* **Source:** Modified from Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177–84 supplemented with additional information and compared with TST specificity when available.

† Tuberculosis. Confirmed by culture and/or nucleic acid amplification test.

§ Human immunodeficiency virus.

¶ Tuberculin skin test.

** "A" = T-Spot was interpreted as positive if a test well (with either early secretory antigenic target-6 [ESAT-6] or culture filtrate protein culture filtrate protein [CFP-10]) contained 6 spots or more than the negative control well and had at least twice the spots as the negative control well, and the negative control well had ≤ 10 spots; indeterminate if not "positive" and the mitogen control well had < 20 spots or the negative control well had > 10 spots. "B" = T-Spot interpretation criteria were not explicitly stated. "C" = T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) contained 5 spots or more than the negative control well and had at least twice the spots as the negative control well and the negative control well had ≤ 10 spots and as indeterminate if the negative control well had > 10 spots. "D" = T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) contained 5 spots or more than the negative control well and had at least twice the spots as the negative control well and the mitogen control well had > 20 spots and indeterminate if the mitogen control well had ≤ 20 spots. "E" = T-Spot was interpreted as positive if the well with ESAT-6 contained at least twice the average number of spots as the negative control well or the well with CFP-10 contained at least 4 times the average number of spots as the negative control well. "F" = T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) contained 6 spots or more than the negative control well and had at least twice the spots as the negative control well and had at least twice the spots as the negative control well; wells contained 200,000 PBMCs instead of 250,000 PBMCs as recommended by the manufacturer. "G" = T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) contained 5 spots or more than the negative control well and had at least twice the spots as the negative control well; reported indeterminate results but did not explicitly state criteria; wells contained 200,000 PBMCs instead of 250,000 PBMCs as recommended by the manufacturer. "H" = T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) contained 5 spots or more than the negative control well and had at least twice the spots as the negative control well and the negative control well had ≤ 10 spots and as indeterminate if not "positive" and the mitogen control well had < 20 spots or the negative control well had > 10 spots. "I" = T-Spot was interpreted as positive if the mean number of spots in duplicate test wells (with either ESAT-6 or CFP-10) was 10 or more than the mean number of spots in duplicate negative control wells and at least twice the mean number of spots in the negative control wells; other criteria were not explicitly stated. "J" = T-Spot was interpreted as indeterminate if the mitogen control well had < 20 spots and as positive if not indeterminate and a test well (with either ESAT-6 or CFP-10) contained > 6 spots more than the negative control well. "L" = T-Spot was interpreted as indeterminate if the mitogen control well had ≤ 20 spots or the negative control well had ≥ 10 spots and as positive if not indeterminate and a test well (with either ESAT-6 or CFP-10) contained 6 spots or more than the negative control well and had at least twice the number of spots as the negative control well. "M" = T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) had ≥ 10 spots (when the negative control well had < 5 spots), or at least twice the number of spots in the negative control well (when the negative control well had ≥ 5 spots). "N" = T-Spot was interpreted as positive if the Nil well had 0–5 spots and a test well (with either ESAT-6 or CFP-10) had ≥ 6 spots more than the Nil well or if the Nil well had 6–10 spots and a test well had at least twice the number of spots as the negative control well; test is indeterminate if the number of spots in the Nil well is > 10 or the number of spots in the mitogen well is < 20 and neither test well is positive.

†† Fisher's exact test was used by CDC to calculate 2-tailed p-values.

§§ **Source:** Chee CB, Gan SH, KhinMar KW, et al. Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. *J Clin Microbiol* 2008;46:1935–40.

¶¶ Not done.

*** **Source:** Dominguez J, Ruiz-Manzano J, De Souza-Galvao M, et al. Comparison of two commercially available gamma interferon blood tests for immunodiagnosis of tuberculosis. *Clin Vaccine Immunol* 2008;15:168–71.

††† Not reported.

§§§ **Source:** Detjen AK, Keil T, Roll S et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis* 2007;45:322–8.

¶¶¶ **Source:** Lee JY, Choi HJ, Park IN, et al. Comparison of two commercial interferon-gamma assays for diagnosing *Mycobacterium tuberculosis* infection. *Eur Respir J* 2006;28:24–30.

**** **Source:** Meier T, Eulenbruch HP, Wrighton-Smith P, Enders G, Regnath T. Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice. *Eur J Clin Microbiol Infect Dis* 2005;24:529–36.

†††† **Source:** Goletti D, Carrara S, Vincenti D, et al. Accuracy of an immune diagnostic assay based on RD1 selected epitopes for active tuberculosis in a clinical setting: a pilot study. *Clin Microbiol Infect* 2006;12:544–50.

§§§§ **Source:** Ferrara G, Losi M, D'Amico R, et al. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006;367:1328–34.

¶¶¶¶ **Source:** Jafari C, Ernst M, Kalsdorf B, et al. Rapid diagnosis of smear-negative tuberculosis by bronchoalveolar lavage enzyme-linked immunospot. *Am J Respir Crit Care Med* 2006;174:1048–54.

***** **Source:** Kang YA, Lee HW, Hwang SS, et al. Usefulness of whole-blood interferon-gamma assay and interferon-gamma enzyme-linked immunospot assay in the diagnosis of active pulmonary tuberculosis. *Chest* 2007;132:959–65.

††††† **Source:** Bosshard V, Roux-Lombard P, Perneger T, et al. Do results of the T-SPOT.TB interferon-gamma release assay change after treatment of tuberculosis? *Respir Med* 2009;103:30–4.

§§§§§ **Source:** Wang JY, Chou CH, Lee LN, et al. Diagnosis of tuberculosis by an enzyme-linked immunospot assay for interferon-gamma. *Emerg Infect Dis* 2007;13:553–8.

¶¶¶¶¶ **Source:** Janssens JP, Roux-Lombard P, Perneger T, Metzger M, Vivien R, Rochat T. Quantitative scoring of an interferon-gamma assay for differentiating active from latent tuberculosis. *Eur Respir J* 2007;30:722–8.

***** **Source:** Ozekinci T, Ozbek E, Celik Y. Comparison of tuberculin skin test and a specific T-cell-based test, T-Spot.TB, for the diagnosis of latent tuberculosis infection. *J Int Med Res* 2007;35:696–703.

†††††† **SOURCE:** Soysal A, Torun T, Efe S, Gencer H, Tahaoglu K, Bakir M. Evaluation of cut-off values of interferon-gamma-based assays in the diagnosis of *M. tuberculosis* infection. *Int J Tuberc Lung Dis* 2008;12:50–6.

§§§§§§ **Source:** Goletti D, Stefania C, Butera O, et al. Accuracy of immunodiagnostic tests for active tuberculosis using single and combined results: a multicenter TBNET-Study. *PLoS ONE* 2008;3:e3417. [E-published]. Available at <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0003417>.

¶¶¶¶¶¶ **Source:** Liao CH, Chou CH, Lai CC, et al. Diagnostic performance of an enzyme-linked immunospot assay for interferon-gamma in extrapulmonary tuberculosis varies between different sites of disease. *J Infect* 2009;59:402–8.

***** **Source:** Kampmann B, Whittaker E, Williams A, et al. Interferon-gamma release assays do not identify more children with active tuberculosis than the tuberculin skin test. *Eur Respir J* 2009;33:1374–82.

††††††† **Source:** Higuchi K, Kawabe Y, Mitarai S, Yoshiyama T, Harada N, Mori T. Comparison of performance in two diagnostic methods for tuberculosis infection. *Med Microbiol Immunol* 2009;198:33–7.

TABLE 6. QuantiFERON-TB Gold In-Tube test (QFT-GIT) specificity,* by country in which study was conducted — four countries, 2007–2008

Country	Subjects	BCG [†] -vaccinated		HIV [§] -positive		Interpretation criteria**	QFT-GIT results				TST [¶] Results			% TST- vs. % QFT-GIT-p-value ^{††}
		No. vaccinated/ No. evaluated	(%)	No. +/ No. tested	(%)		Negative		Indeterminate		Cutoff	Negative		
							No. +/ No. valid	(%)	No. +/ No. tested	(%)		No. +/ No. tested	(%)	
Germany ^{§§}	Children aged 0–11 yrs w/ lymphadenitis	0/23	(0)	NR ^{¶¶}	NR	A	19/19	(100)	ND ^{***}	ND	5	2/23	(9)	<0.01
											10	5/23	(22)	<0.01
Germany ^{§§}	Children aged 0–7 yrs w/ respirator infection	0/22	(0)	NR	NR	A	21/21	(100)	ND	ND	5	22/22	(100)	1.0
											10	22/22	(100)	1.0
Japan ^{†††}	Adult students	140/168	(83)	0/168	(0)	B	158/160	(99)	6/168	(4)	ND	ND	ND	ND
Denmark ^{§§§}	High school students & staff	38/124	(31)	0/124	(0)	C	124/124	(100)	0	(0)	10	116/124	(94)	<0.01
Italy ^{¶¶¶}	Mostly adults	1/14	(7)	0/14	(0)	C	14/14	(100)	0/14	(0)	NR	8/8	(100)	ND

* **Source:** Modified from Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177–84 supplemented with additional information and compared with TST specificity when available.

[†] *Bacillus Calmette-Guerin*.

[§] Human immunodeficiency virus.

[¶] Tuberculin skin test.

** "A" indicates that QFT-GIT was interpreted as positive if Tuberculosis (TB) Response was ≥ 0.35 IU/mL; Mitogen Response was not measured. "B" indicates that QFT-GIT was interpreted as positive if TB Response was ≥ 0.35 IU/mL and Nil was ≤ 8.0 IU/mL, as indeterminate if Nil ≥ 8.0 IU/mL or the TB Response was < 0.35 IU/mL and the Mitogen Response was < 0.5 IU/mL, and as negative if the TB Response was < 0.35 IU/mL, the Mitogen Response was ≥ 0.5 IU/mL, and Nil was ≤ 8.0 IU/mL. "C" indicates that QFT-GIT interpretation criteria were not explicitly stated.

^{††} Fisher's exact test was used by CDC to calculate 2-tailed p-values.

^{§§} **Source:** Detjen AK, Keil T, Roll S, et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis* 2007;45:322–8.

^{¶¶} Not reported.

^{***} Not done.

^{†††} **Source:** Harada N, Higuchi K, Yoshiyama T, et al. Comparison of the sensitivity and specificity of two whole blood interferon-gamma assays for *M. tuberculosis* infection. *J Infect* 2008;56:348–53.

^{§§§} **Source:** Ruhwald M, Bodmer T, Maier C, et al. Evaluating the potential of IP-10 and MCP-2 as biomarkers for the diagnosis of tuberculosis. *Eur Respir J* 2008;32:1607–15.

^{¶¶¶} **Source:** Palazzo R, Spensieri F, Massari M, et al. Use of whole-blood samples in in-house bulk and single-cell antigen-specific gamma interferon assays for surveillance of *Mycobacterium tuberculosis* infections. *Clin Vaccine Immunol* 2008;15:327–37.

TABLE 7. T-SPOT.TB test (T-Spot) specificity,* by country in which study was conducted — three countries, 2006–2008

Country	Subjects	BCG [†] -vaccinated		HIV [§] status	Inter-pretation criteria**	T-Spot results				TST [¶] results			% TST-vs. % T-Spot-p-value ^{††}
		No. vaccinated/ No. evaluated	(%)			Negative		Indeterminate		Cutoff	Negative		
						No. +/ No. valid	(%)	No. +/ No. tested	(%)		No. +/ No. tested	(%)	
Germany ^{§§}	Children aged 0–11 yrs w/ lymphadenitis	0/19	(0)	NR ^{¶¶}	A	18/19	(95)	4/23	(17)	5 10	2/23 5/23	(9) (22)	<0.01 <0.01
Germany ^{***}	Children aged 0–7 yrs w/ other respiratory infection	0/21	(0)	NR	A	21/21	(100)	1/22	(5)	5 10	22/22 22/22	(100) (100)	1.0 1.0
South Korea ^{†††}	High school students	131/131	(100)	NR	B	111/ 131	(85)	0/131	(0)	10 15	103/131 125/131	(79) (95)	0.26 <0.01
United States ^{§§§}	Adults with & w/o prior MAC ^{¶¶¶¶} disease	0/18	(0)	NR	C	17/18	(94)	0/18	(0)	ND	ND	ND	ND

* **Source:** Modified from Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann Intern Med* 2008;149:177–84 supplemented with additional information and compared with TST specificity when available.

[†] *Bacillus Calmette-Guerin*.

[§] Human immunodeficiency virus.

[¶] Tuberculin skin test.

** "A" indicates that T-Spot interpretation criteria were not explicitly stated. "B" indicates that T-Spot was interpreted as positive if a test well (with either early secretory antigenic target-6 [ESAT-6] or culture filtrate protein-10 [CFP-10]) contained 5 spots or more than the negative control well and had at least twice the spots as the negative control well and the negative control well had ≤10 spots and as indeterminate if the negative control well had >10 spots. "C" indicates that T-Spot was interpreted as positive if a test well (with either ESAT-6 or CFP-10) contained 6 spots or more than the negative control well and had at least twice the spots as the negative control well and as indeterminate if not "positive" and the mitogen control well had <20 spots.

†† Fisher's exact test was used by CDC to calculate 2-tailed p-values.

^{§§} **Source:** Detjen AK, Keil T, Roll S et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis* 2007;45:322–8.

^{¶¶} Not reported.

^{***} **Source:** Detjen AK, Keil T, Roll S et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. *Clin Infect Dis* 2007;45:322–8.

^{†††} **Source:** Lee JY, Choi HJ, Park IN et al. Comparison of two commercial interferon-gamma assays for diagnosing *Mycobacterium tuberculosis* infection. *Eur Respir J* 2006;28:24–30.

^{§§§} **Source:** Adams LV, Waddell RD, von Reyn CF. T-SPOT.TB Test results in adults with *Mycobacterium avium* complex pulmonary disease. *Scand J Infect Dis* 2008;40:196–203.

^{¶¶¶¶} *Mycobacterium avium* complex.

TABLE 8. Summary of findings of published studies evaluating QuantiFERON-TB Gold-In-Tube test (QFT-GIT) and/or T-SPOT.TB test (T-Spot) in tuberculosis contacts compared with tuberculin skin test (TST) when available, by country in which study was conducted — seven countries, 2006–2008

Country	Subjects	BCG vaccinated*		TST cutoff	Findings
		No. vaccinated/No. evaluated	(%)		
South Africa†	Children aged 5–15 yrs	115/174	(66)	10 mm	QFT-GIT and TST results were associated with older age but not with recent or remote household contact.
Nigeria§	Child contacts & controls aged 1–14 yrs	187/207	(90)	10 mm	QFT-GIT and TST results were associated with acid-fast bacillus (AFB) status of source and age for children living with AFB-negative persons and controls. +TST/-QFT-GIT discordance was more common in controls and children living with AFB-negative persons. -TST/+ QFT-GIT were more common in children living with AFB-positive persons.
Denmark¶	Adult contacts w/out BCG	0/785	(0)	10 mm	TST results were associated with age but not with estimates of exposure. T-Spot results were associated with an estimate of exposure (cumulative shopping time). QFT-GIT (without mitogen) was associated with cumulative shopping time more so than T-Spot.
The Gambia**	Adult & child contacts aged ≥15 yrs	84/194	(43)	10 mm	TST more strongly associated with exposure gradient than QFT-GIT (without mitogen). For contacts sleeping in the same room as compared with those sleeping in different houses, the odds ratio for a positive TST was 4.8 (95% confidence interval [CI] = 1.3–17.1) as compared with 3.8 (CI = 1.2–12.5) for QFT-GIT.
Switzerland††	Adult & child contacts aged 16–83 yrs	238/295	(81)	10 mm	Both TST & T-Spot results were associated with age, gender, BCG, and incidence of tuberculosis in country of origin, but not to any of 5 exposure scores.
Germany§§	Adult & child contacts w/ TST >5 mm	453/812	(56)	NA	Both QFT-GIT & T-Spot results were associated with age, AFB + or coughing source, cumulative exposure time, and foreign origin. Associations with TST results were not assessed.
Spain¶¶	Adults & children	128/270	(47)	5 mm	TST results were associated with BCG. QFT-GIT & T-Spot results were not associated with BCG. Association of test results with incidence of tuberculosis in country of origin was not assessed.

* Bacillus Calmette-Guerin.

† **Source:** Tsiouris SJ, Austin J, Toro P et al. Results of a tuberculosis-specific IFN-gamma assay in children at high risk for tuberculosis infection. *Int J Tuberc Lung Dis* 2006;10:939–41.

§ **Source:** Nakaoka H, Lawson L, Squire SB, et al. Risk for tuberculosis among children. *Emerg Infect Dis* 2006;12:1383–8.

¶ **Source:** Arend SM, Thijsen SF, Leyten EM, et al. Comparison of two interferon-gamma assays and tuberculin skin test for tracing tuberculosis contacts. *Am J Respir Crit Care Med* 2007;175:618–27.

** **Source:** Adetifa IM, Lugos MD, Hammond A, et al. Comparison of two interferon gamma release assays in the diagnosis of *Mycobacterium tuberculosis* infection and disease in The Gambia. *BMC Infect Dis* 2007;7:122.

†† **Source:** Janssens J, Roux-Lombard P, Perneger T, Metzger M, Vivien R, Rochat T. Contribution of a IFN-gamma assay in contact tracing for tuberculosis in a low-incidence, high immigration area. *Swiss Med Wkly* 2008;138:585–93.

§§ **Source:** Diel R, Loddenkemper R, Meywald-Walter K, Gottschalk R, Nienhaus A. Comparative performance of tuberculin skin test, QuantiFERON-TB-Gold In Tube assay, and T-Spot.TB test in contact investigations for tuberculosis. *Chest* 2009;135:1010–8.

¶¶ **Source:** Dominguez J, Ruiz-Manzano J, De Souza-Galvao M, et al. Comparison of two commercially available gamma interferon blood tests for immunodiagnosis of tuberculosis. *Clin Vaccine Immunol* 2008;15:168–71.

TABLE 9. QuantiFERON-TB Gold In-Tube (QFT-GIT) test results in immunosuppressed persons compared with tuberculin skin test (TST) results when available — 10 countries, 2006–2008

Country	Subjects	HIV* status	QFT-GIT results				TST results			% TST+ vs. % QFT-GIT+† p-value†
			Positive		Indeterminate		Cutoff	Positive		
			No. +/ No. valid	(%)	No. +/ No. tested	(%)		No. +/ No. tested	(%)	
Denmark [§]	607 adults	607 HIV+	27/570	(4.7)	20/590	(3.4)	ND [¶]	ND	ND	ND
Chile**	116 adults	116 HIV+	17/115	(15)	0/115	(0)	5 mm	12/110	(11)	0.50
United States††	207 adults	207 HIV+	11/191	(6)	10/201	(5)	5 mm	13/201	(7)	0.94
United States ^{§§}	294 adults	294 HIV+	25/279	(9)	15/294	(5)	5 mm	19/205	(9)	0.99
Zambia ^{¶¶}	112 adults with smear + TB	59 HIV+ 37 HIV- 16 not tested	37/49 31/32 15/15	(76) (97) (100)	10/59 5/37 1/16	(17) (14) (6)	5 mm	26/47 25/31 0/14	(55) (81) (0)	0.06 0.09 <0.01
South Africa***	154 adults with Culture + TB	26 HIV+ 15 HIV- 113 not tested	17/21 11/15 72/95	(81) (73) (76)	5/26 0/15 18/113	(19) (0) (16)	10 mm 5 mm 10 mm	22/26 15/15 67/113	(85) (100) (59)	0.99 0.09 0.02
Austria†††	8 adults w/TB at baseline	8 HIV+	7/8	(88)	0/8	(0)	5 mm	8/8	(100)	ND
Austria†††	822 adults w/o TB at baseline	822 HIV+	37/775	(5)	47/822	(6)	5 mm	23/34 ^{§§§}	(74)	ND
United States ^{¶¶¶}	336 adults	336 HIV+	9/330	(3)	6/336	(2)	4 mm	7/278	(3)	0.92
Italy****	69 TNFi†††† candidates	69 HIV-	22/67	(33)	2/69	(3)	5 mm	18/69	(26)	0.49
Turkey	68 adult TNFi candidates	68 unknown	9/61	(15)	7/68	(10)	10 mm	37/61	(61)	<0.01
Switzerland ^{§§}	142 adults with autoimmune disease	142 unknown	17/134	(13)	8/142	(6)	5 mm	46/115	(40)	<0.01
Peru ^{¶¶¶¶}	106 adults with rheumatoid arthritis	106 unknown	45/104	(43)	2/106	(1)	5 mm	27/101	(27)	0.02

* Human immunodeficiency virus.

† Fisher's exact test was used by CDC to calculate 2-tailed p-values.

§ **Source:** Brock I, Ruhwald M, Lundgren B, Westh H, Mathiesen LR, Ravn P. Latent tuberculosis in HIV positive, diagnosed by the *M. tuberculosis* Specific Interferon Gamma test. *Respir Res* 2006;7:56.

¶ Not done.

** **Source:** Balcells ME, Perez CM, Chanqueo L et al. A comparative study of two different methods for the detection of latent tuberculosis in HIV-positive individuals in Chile. *Int J Infect Dis* 2008;12:645–52.

†† **Source:** Jones S, de Gijzel D, Wallach FR, Gurtman AC, Shi Q, Sacks H. Utility of QuantiFERON-TB Gold in-tube testing for latent TB infection in HIV-infected individuals. *Int J Tuberc Lung Dis* 2007;11:1190–5.

§§ **Source:** Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med* 2007;175:737–42.

¶¶ **Source:** Raby E, Moyo M, Devendra A, et al. The effects of HIV on the sensitivity of a whole blood IFN-gamma release assay in Zambian adults with active tuberculosis. *PLoS ONE* 2008;3:e2489. [E-pub]. Available at <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0002489>.

*** **Source:** Tsiouris SJ, Coetzee D, Toro PL, Austin J, Stein Z, el-Sadr W. Sensitivity analysis and potential uses of a novel gamma interferon release assay for diagnosis of tuberculosis. *J Clin Microbiol* 2006;44:2844–50.

††† **Source:** Aichelburg MC, Rieger A, Breitenacker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis* 2009;48:954–62.

§§§ Tuberculin skin testing was offered only to subjects with a positive QFT-GIT.

¶¶¶ **Source:** Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis* 2009;9:15.

**** **Source:** Bocchino M, Matarese A, Bellofiore B, et al. Performance of two commercial blood IFN-gamma release assays for the detection of *Mycobacterium tuberculosis* infection in patient candidates for anti-TNF-alpha treatment. *Eur J Clin Microbiol Infect Dis* 2008;27:907–13.

†††† Tumor necrosis factor α inhibitor.

§§§§ **Source:** Cobanoglu N, Ozcelik U, Kalyoncu U, et al. Interferon-gamma assays for the diagnosis of tuberculosis infection before using tumour necrosis factor-alpha blockers. *Int J Tuberc Lung Dis* 2007;11:1177–82.

¶¶¶¶ **Source:** Matulis G, Juni P, Villiger PM, Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a *Mycobacterium tuberculosis* antigen-specific interferon gamma assay. *Ann Rheum Dis* 2008;67:84–90.

**** **Source:** Ponce de LD, Acevedo-Vasquez E, Alvizuri S, et al. Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. *J Rheumatol* 2008;35:776–81.

TABLE 10. Published studies evaluating T-SPOT.TB test (T-Spot) among immunosuppressed persons compared with tuberculin skin test (TST) when available — eight countries, 2006–2008

Country	Subjects	HIV* Status	T-Spot results				TST results			% TST+ vs. % T-Spot+ p-value†
			Positive		Indeterminate		Cutoff	Positive		
			No. +/ No. valid	(%)	No. +/ No. tested	(%)		No. +/ No. tested	(%)	
South Africa [§]	20 HIV+ adults	20 HIV+	13/18	(72)	2/20	(10)	5 mm	10/16	(63)	0.81
	23 HIV+ children	23 HIV+	12/23	(52)	0/23	(0)		6/23	(26)	0.13
South Africa [¶]	160 adults at HIV screening clinic	74 HIV+ 86 HIV-	38/73 51/86	(52) (59)	1/74 0/86	(1) (0)	5 mm	35/67 66/77	(52) (86)	0.99 <0.01
Germany**	286 HIV+ outpatients	286 HIV+	66/267	(25)	8/275	(3)	5 mm	33/275	(12)	<0.01
United States ^{††}	336 HIV+ adults	336 HIV+	14/289	(5)	47/336	(14)	5 mm	7/278	(2.5)	0.21
Italy ^{§§}	69 HIV- TNFi ^{¶¶} candidates	69 HIV-	21/65	(32)	4/69	(6)	5 mm	18/69	(26)	0.55
Hong Kong ^{***}	134 adults w/ silicosis	134 unknown	86/128	(67)	6 ^{†††} /134	(5)	10 mm	92/134	(69)	0.90
Germany ^{§§§}	48 patients awaiting liver transplant	48 unknown	4/48	(8)	0/48	(0)	5 mm	6/47	(13)	0.71
Canada ^{¶¶¶}	203 patients on hemodialysis	203 unknown	72/189	(38)	14/203	(7)	10 mm	19/203	(9)	<0.01
Italy ^{****}	138 patients w/ hematologic disease	138 HIV-	61/129	(47)	6/135	(4)	5 mm	24/122	(20)	<0.01
United States ^{††††}	49 inmates w/ hx IVDU ^{§§§§} (of 390 total in study)	49 unknown	17/49	(35)	0/49	(0)	10 mm	6/49	(12)	0.02
Greece ^{¶¶¶¶}	70 HIV- TNFi candidates	70 HIV-	16/70	(23)	0/70	(0)	5 mm	27/70	(39)	0.07

* Human immunodeficiency virus.

† Fisher's exact test was used by CDC to calculate 2-tailed p-values.

§ **Source:** Mandalakas AM, Hesselning AC, Chegou NN, et al. High level of discordant IGRA results in HIV-infected adults and children. *Int J Tuberc Lung Dis* 2008;12:417–23.

¶ **Source:** Rangaka MX, Wilkinson KA, Seldon R, et al. Effect of HIV-1 infection on T-Cell-based and skin test detection of tuberculosis infection. *Am J Respir Crit Care Med* 2007;175:514–20.

** **Source:** Stephan C, Wolf T, Goetsch U, et al. Comparing QuantiFERON-tuberculosis gold, T-SPOT tuberculosis and tuberculin skin test in HIV-infected individuals from a low prevalence tuberculosis country. *AIDS* 2008;22:2471–9.

†† **Source:** Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis* 2009;9:15.

§§ **Source:** Bocchino M, Matarese A, Bellofiore B, et al. Performance of two commercial blood IFN-gamma release assays for the detection of Mycobacterium tuberculosis infection in patient candidates for anti-TNF-alpha treatment. *Eur J Clin Microbiol Infect Dis* 2008;27:907–13.

¶¶ Tumor necrosis factor α inhibitor.

*** **Source:** Leung CC, Yam WC, Yew WW, et al. Comparison of T-Spot.TB and tuberculin skin test among silicotic patients. *Eur Respir J* 2008;31:266–72.

††† Reclassified with second test.

§§§ **Source:** Lindemann M, Dioury Y, Beckebaum S, et al. Diagnosis of tuberculosis infection in patients awaiting liver transplantation. *Hum Immunol* 2009;70:24–8.

¶¶¶ **Source:** Passalent L, Khan K, Richardson R, Wang J, Dedier H, Gardam M. Detecting latent tuberculosis infection in hemodialysis patients: a head-to-head comparison of the T-SPOT.TB test, tuberculin skin test, and an expert physician panel. *Clin J Am Soc Nephrol* 2007;2:68–73.

**** **Source:** Piana F, Codecasa LR, Cavallerio P, et al. Use of a T-cell-based test for detection of tuberculosis infection among immunocompromised patients. *Eur Respir J* 2006;28:31–4.

†††† **Source:** Porsa E, Cheng L, Graviss EA. Comparison of an ESAT-6/CFP-10 peptide-based enzyme-linked immunospot assay to a tuberculin skin test for screening of a population at moderate risk of contracting tuberculosis. *Clin Vaccine Immunol* 2007;14:714–9.

§§§§ Intravenous- drug user.

¶¶¶¶ **Source:** Vassilopoulos D, Stamoulis N, Hadziyannis E, Archimandritis AJ. Usefulness of enzyme-linked immunospot assay (elispot) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumor necrosis factor treatment. *J Rheumatol* 2008;35:1271–6.

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