Pocket Guide

QuantiFERON®-TB Gold

CDC TB Testing Guidelines and Recent Literature Update

Using IGRAs for TB screening in your patients

June 2010

A full copy of the US Centers for Disease Control and Prevention (CDC) guidelines is available for viewing at www.cdc.gov/mmwr/pdf/rr/rr5905.pdf

QIAGEN®

QFT is approved by the US FDA

QFT is approved by FDA as an *in vitro* diagnostic aid for detection of *Mycobacterium tuberculosis* infection. It uses a peptide cocktail simulating ESAT-6, CFP-10 and TB7.7(p4) proteins to stimulate cells in heparinized whole blood. Detection of IFN-γ by ELISA is used to identify *in vitro* responses to these peptide antigens that are associated with *M. tuberculosis* infection.

FDA approval notes that QFT is an indirect test for *M. tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography and other medical and diagnostic evaluations.

QFT Package Inserts, available in up to 25 different languages, can be found at www.cellestis.com.

Updated CDC Guidelines

The updated CDC guidelines provide new direction for TB control in the US. Previously, QuantiFERON®-TB Gold was able to be used in any situation in which the Tuberculin Skin Test (TST) was used, **without preference**. The 2010 guidelines establish a new benchmark because they recommend IGRAs as the **preferred** TB testing method in many patients, including those who:

- are BCG vaccinated
- are unlikely to return for TST reading.

What are the limitations of the TST?

Interferon-gamma Release Assays (IGRAs) are blood tests that detect *Mycobacterium tuberculosis* infection with higher specificity than the TST[1,2].

The TST measures immune responses to tuberculin PPD, which is made up of a multitude of bacterial proteins, most of which are present in the TB vaccine, Bacille Calmette-Guérin (BCG), and shared with many environmental mycobacteria.

The TST, which has been used for TB testing for more than 100 years, has several limitations. TST results are not objective; results are subjectively read, which can lead to incorrect diagnosis. TST may also result in frequent false positives often due to cross-reactivity with BCG vaccination or responses to environmental mycobacteria. These false positives could lead to excessive retesting, radiology exams, and unneccessary precautionary treatment including antibiotics for as long as 9 months. The TST may also result in false negatives

[1] Diel *et al. Chest 2010. 137:952–68.*

[2] Pai *et al. Annals Internal Med 2008. 149:177–84.*

if the person tested is immunocompromised or otherwise unable to elicit a response to the tuberculin.

Other limitations which impair the effectiveness of the TST include the requirement that patients return for test reading; the need for proper administration to obtain a valid result; and bias in reading or interpreting the skin test reaction.

QFT—a modern alternative to the TST

The QuantiFERON-TB Gold In-Tube test (QFT®) is a US Food and Drug Administration (FDA)-approved IGRA, and preferred alternative to the TST in many national guidelines and recommendations[1].

QFT is a highly-specific (99.2% specificity[2]) controlled blood test for use as an aid to the diagnosis of infection with the bacteria responsible for TB and provides results showing an individual's T-cell response to highly specific antigens from the TB bacterium.

QFT uses enzyme-linked immunosorbent assay (ELISA) to detect interferon-gamma responses in a sample of whole blood that has been incubated with TB-specific test antigens.

[1] Pai. *IJTLD 2010. 14:S64–7.*

[2] Diel *et al. Chest 2010. 137:952–68.*

QFT is unaffected by previous BCG vaccination[3] and most other environmental mycobacteria, unlike the TST.

- QFT requires only one patient visit.
- QFT does not boost subsequent test results.
- QFT is a controlled laboratory test.
- QFT provides an objective, reproducible result that is unaffected by subjective interpretation.
- QFT results can be available within 24 hours.

[3] Pai *et al. Annals Internal Med 2008. 149:177–84.*

Use and Interpretation of QFT

The test is performed by collecting whole blood (1 mL) into each of three blood collection tubes:

- a tube containing TB-specific test antigens (ESAT-6, CFP-10 and TB7.7(p4)).
- a negative (Nil) control tube.
- a positive (Mitogen) control tube.

All three tubes are incubated at 37°C for 16 to 24 hours. The interferon-gamma concentration in the plasma is determined using a sensitive ELISA.

Interpretation Criteria for QFT

Interpretation	TB specific antigen response (IU/mL)*	Nil control (IU/mL)	Mitogen control (IU/mL)*
Positive	≥ 0.35 (and ≥ 25% of Nil)	≤ 8.0	any
Negative	< 0.35 OR ≥ 0.35 and < 25% of Nil	≤ 8.0	≥ 0.5
Indeterminate	< 0.35 OR ≥ 0.35 and < 25% of Nil	≤ 8.0	< 0.5
	any	> 8.0	any

* Corrected for Nil response

Who should be tested for TB infection?

The CDC recommend testing for individuals at increased risk of TB infection and disease, including:

- Close contacts of persons suspected to have active TB disease.
- Foreign-born persons from areas that have a high incidence of TB disease.
- Persons who visit areas with a high prevalence of TB disease.
- Residents and employees of congregate settings at risk (ie. correctional facilities, long-term care facilities, and homeless shelters).
- Healthcare workers who serve persons at increased risk of TB disease.
- Infants, children, adolescents in high-risk categories.
- Persons with HIV infection.
- Persons with a history of untreated or inadequately treated TB disease, including chest x-ray consistent with prior TB disease.

- Persons receiving immunosuppressive therapy (TNF-alpha antagonists, systemic corticosteroids) or following organ transplantation.
- Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, or cancer of the head, neck or lung.
- Specific populations at increased risk of TB disease (medically underserved, low-income, cigarette smokers or those who abuse drugs or alcohol).

IGRA is preferred for testing persons from groups that historically have poor rates of return for TST reading

CDC Specific Recommendations

- IGRAs may be used in place of (but not in addition to) a TST in all situations in which the CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection.
- IGRA is preferred for testing persons from groups that historically have poor rates of return for TST reading.
- IGRA is preferred for testing persons who have received BCG (as a vaccine or for cancer therapy).
- Either an IGRA or a TST may be used (without preference) to test recent contacts of persons with infectious tuberculosis with special considerations for follow-up testing. In contact investigations, negative results obtained prior to 8 weeks typically should be confirmed by repeat testing 8–10 weeks after the end of exposure.
- Either an IGRA or a TST may be used (without preference) for periodic screening that addresses occupational exposure to TB (eg. surveillance programs for healthcare

workers) with special considerations regarding conversions and reversions (see full guideline[1]). Two-step testing is not required since IGRA testing does not boost subsequent test results.

- TST is preferred for testing children younger than 5 years old, due to the relatively few published reports documenting the performance of IGRAs in young children. However use of an IGRA in conjunction with TST may increase diagnostic sensitivity in this age group.
- While routine testing with both TST and an IGRA is not recommended, results from both tests may be useful in the following situations when the initial test is NEGATIVE:
  - ☐ when the risk of infection, the risk of progression, and the risk of a poor outcome are increased (such as when persons with HIV infection, or children < 5 years old are at increased risk for *M. tuberculosis* infection), or
  - ☐ when there is clinical suspicion of active tuberculosis (such as in persons with

[1] www.cdc.gov/mmwr/pdf/rr/rr5905.pdf

symptoms, signs, and/or radiographic evidence suggestive of active tuberculosis) and confirmation of *M. tuberculosis* infection is desired.

- While routine testing with both TST and an IGRA is not recommended, results from both tests may be useful in the following situations when the initial test is POSITIVE:
  - additional evidence of infection is required to encourage compliance (such as in foreign-born healthcare workers who believe their positive TST is due to BCG); or
  - in healthy persons who have a low risk of both infection and progression.

IGRA is preferred for testing persons who have received BCG

- Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate and a reason for testing persists.
- Decisions should not be based on IGRA or TST results alone. A diagnosis of *M. tuberculosis* infection, and the decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results.
- Persons with a positive TST or IGRA result should be evaluated for the likelihood of *M. tuberculosis* infection, for risks of progression to tuberculosis disease if infected, and for symptoms and signs of tuberculosis disease.
- Neither an IGRA nor TST can distinguish LTBI from TB disease. A diagnosis of LTBI requires that tuberculosis disease be excluded by medical evaluation, which should include checking for suggestive symptoms and signs, a chest radiograph, and, when indicated, testing of sputum or other clinical samples for the presence of *M. tuberculosis*.

- In persons with symptoms, signs, or radiographic evidence of TB disease, and in those at increased risk of progression to tuberculosis disease if infected, a positive result with either an IGRA or TST may 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 of a poor outcome if disease develops, and clinical judgment dictates when and if further diagnostic evaluation and treatment are indicated.
- Both the standard qualitative test interpretation and the quantitative assay measurements should be reported, together with the criteria for test interpretation.
- As with the TST, IGRAs generally should not be used for testing persons who have a low risk of infection and a low risk of disease due to *M. tuberculosis*.
- IGRAs or TST should be used as aids in diagnosing infection with *M. tuberculosis*. These tests may be used for surveillance purposes or

to identify persons who are likely to benefit from treatment.

- IGRAs should be performed and interpreted according to established protocols using FDA-approved test formats. IGRAs should be performed in compliance with Clinical Laboratory Improvement Amendment (CLIA) standards.
- For BCG vaccinated persons who are not at increased risk for developing TB if infected, TST reactions <15mm may be reasonably discounted as false positives if the individual has a clearly negative IGRA result.
- If two different tests are performed, a positive result from either test should be taken as evidence of infection for those with suspected active TB or at high risk of progression.

IGRA may be used in place of TST (without preference) for periodic screening that addresses occupational exposure to TB

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