

TB OR NOT TB?

Now the **right test** — Now the **right result**

Testing has evolved

QuantiFERON® provides a convenient replacement technology for tuberculosis (TB) infection evaluations.

LabCorp

Selecting the Replacement Standard

- QuantiFERON® (QFT®) is a convenient interferon-γ release assay (IGRA) that aids in the evaluation of tuberculosis (TB) infections (latent or active).[1] **This single blood specimen collection is recommended by the CDC for use in certain situations in which a tuberculin skin test (TST) is appropriate.** QFT is a modern alternative to the more than 100-year-old TST. QFT offers improved performance, quicker results, and is **preferred in individuals** who have received Bacille Calmette-Guérin (BCG) vaccination or who may not be in compliance for return visits to have a TST read.[2]
  - QFT has been shown to be more accurate than the TST in identifying people who may have latent TB (tuberculosis) infection.[3]
  - **QFT has been shown to be more reliable than the TST in identifying those who may progress to active TB.[4] QFT is >99% specific,**[1,5] nearly eliminating false-positive readings; and false positive rates for TST have been published as low as 3% in non–BCG-vaccinated populations[6] and as high as 65% when using a 10-mm induration as the cutoff in BCG-vaccinated populations.[7]
  - **A metaanalysis calculated a pooled sensitivity for TST at 70%,**[5] (23 of 25 studies in developed countries) and a pooled **sensitivity for QFT at 84%** (13 studies in developed countries).[5]

Improving Upon Technology Limitations

False-positive TST results may burden the system

- QFT's increased accuracy may yield better outcomes for patients, allowing for more confidence in correctly identifying TB infection, with significant cost savings through fewer false-positive results. Studies show that switching to QFT provides significant program cost advantages.[8]
- One study reported up to 32% reduction in cost compared to the TST. When deciding whether to perform a follow-up chest X ray, the study suggests that using QFT instead of TST may reduce the need. If a positive QFT result is the discrete referral decision driver vs a positive TST (using the data in the study), a QFT positive result might have reduced the chest x-ray referral by 37.5% in the group with no BCG vaccination, who also had a prior TST inoculation history. A QFT positive result might also have reduced the referrals within all study participants by 60% (includes sum of no BCG/no TST history; BCG; and TST/no BCG history participants).[8]
- QFT contains TB mycobacterial proteins (ESAT-6, CFP-10, and TB 7.7),[1] which are not found in the BCG vaccine or PPD (tuberculin purified protein derivative) TST injection.[2,9] Because of this highly specific composition, **QFT overcomes many of the shortcomings of the TST, and it is not affected by previous BCG vaccinations or exposure to non-tuberculosis *Mycobacteria*,** both with the added benefit of providing a laboratory-based, objective result.
- The tables below illustrate the reactivity of antigens from QFT and the tuberculin skin test (TST) to various species of *Mycobacteria*.[1,2,10,11]

Tuberculosis Complex	QFT TB Specific Antigens			TST Antigens
	ESAT–6	CFP–10	TB 7.7	PPD
M tuberculosis	+	+	+	+
M africanum	+	+	+	+
M bovis	+	+	+	+

BCG Substrain	QFT TB Specific Antigens			TST Antigens
	ESAT–6	CFP–10	TB 7.7	PPD
gothenburg	–	–	–	+
moreau	–	–	–	+
tice	–	–	–	+
tokyo	–	–	–	+
danish	–	–	–	+
glaxo	–	–	–	+
montréal	–	–	–	+
pasteur	–	–	–	+

Environmental strains	QFT TB Specific Antigens			TST Antigens
	ESAT–6	CFP–10	TB 7.7	PPD
M abscessus	–	–	–	+
M avium	–	–	–	+
M branderi	–	–	–	+
M celatum	–	–	–	+
M chelonae	–	–	–	+
M fortuitum	–	–	–	+
M genavense	–	–	–	+
M gordonii	–	–	–	+
M intracellulare	–	–	–	+
M kansasii	+	+	–	+
M malmoense	–	–	–	+
M marinum	+	+	–	+
M scrofulaceum	–	–	–	+
M smegmatis	–	–	–	+
M szulgai	+	+	–	+
M terra	–	–	–	+
M vaccae	–	–	–	+
M xenopi	–	–	–	+

Advantages of QFT

TST Challenges	QFT Offers Improvements
Requires multiple office visits to inject and read the TST reaction.[11]	**One office visit** for single blood draw
Higher false-positive rate (than QFT) with more follow-up required	**>99% specific, nearly eliminating false positives.**[1,5] Fewer false positives mean less follow-up.[2] False-positive results may also confound prescribing immunosuppressive therapy or workplace decisions.[8,9]
Subjective result	**Produces an objective result**
May be affected by previous BCG vaccinations	**Unaffected by previous BCG vaccinations**[2]
May boost subsequent TST test results	**Does not boost subsequent QFT test results** and less affected by prior TST[10]
TST approved for use to aid in the evaluation of TB.	**QFT is an approved alternative for use where TST is appropriate. QFT is also preferred** in individuals who have received BCG vaccination or who may not be in compliance for return visits to have a TST read. Less caution might be warranted when using QFT in children ≥5 years old than in children <5 years old.[2]

AT RISK

The CDC states that individuals at increased risk for *M tuberculosis* infection include[2]:

- Those with close contact with persons known or suspected to have active tuberculosis
- Foreign-born persons from areas with a high incidence of active tuberculosis
- Visitors to areas with a high prevalence of active tuberculosis
- Residents and employees of congregate settings whose clients are at increased risk for active tuberculosis (correctional facilities, long-term care facilities, and homeless shelters)
- Health care workers who serve clients at increased risk for active tuberculosis
- Populations defined locally with increased risk of *M tuberculosis* infection

QuantiFERON® (QFT®) may be more accurate than the TST in identifying people who may have latent TB (tuberculosis) infection.[3]



At low risk — with a low positive value

In healthy persons who have a low likelihood both of *M tuberculosis* infection and of progression to active tuberculosis 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 (using a newly collected specimen), 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.[2]

Send your patients to a LabCorp patient service center (PSC), and we will perform the specimen preparation; or you may collect and carefully follow the essential collection and incubation requirements.

Step 1
Remove tubes from box



Step 2
Collect 1 mL of blood



Step 3
Shake tube to coat



Step 4
Replace labeled tubes in box



Other Requirements

- Requires incubation within 16 hours of phlebotomy (check top of box if incubated)
- Prior to incubation, maintain tubes at room temperature (22°C ± 5°C)
- Incubate for 16-24 hours at 37°C ± 1°C
- Following 37°C ± 1°C incubation period, blood collection tubes may be held between 4°C and 27°C for 3 days prior to centrifugation at the laboratory
- Incubated specimen must be tested within 72 hours of completing incubation

References
1. QuantiFERON®-TB Gold (QFT®) ELISA [package insert]. Germantown, MD; QIAGEN Group. 2016.
2. Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection – United States, 2010. *MMWR* 2010;59(NoRR-55).
3. Diel R, Loddenkemper R, Meywald-Walter K, Niermann S, Niehaus A. Predictive value of a whole blood IFN-γ assay for the development of active tuberculosis disease after recent infection with mycobacterium tuberculosis. *Am J Respir Crit Care Med*. 2008;177:1164-1170.
4. Diel R, Loddenkemper R, Niermann S, Meywald-Walter K, Nienhaus A. Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis. *Am J Respir Crit Care Med*. 2011;183:88-95.
5. Deil R, Loddenkemper R, Nienhaus A. Evidence-based comparison of commercial interferon-γ release assays for detecting active TB: a metaanalysis. *Chest*. 2010;137:952-968.
6. 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(3):177-184.
7. Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection. *Am J Respir Crit Care Med*. 2004;170:59-64.
8. Nienhaus A, Schablon A, Le Bâcle CL, Siano B, Diel R. Evaluation of the interferon-γ release assay in healthcare workers. *Int Arch Occup Environ Health*. 2007.
9. Beglinger C, Dudler J, Mottet, et al. Screening for tuberculosis infection before initiation of anti-TNF-α therapy. *Swiss Med Wkly*. 2007;137:621-622.
10. Centers for Disease Control and Prevention: Guidelines for using the QuantiFERON®-TB Gold Test for detecting Mycobacterium tuberculosis Infection, United States. 2005;54(NoRR-15).
11. Andersen P, Munk ME, Pollock J M, Doherty TM. Specific immune-based diagnosis of tuberculosis. *Lancet*. 2000;356:1099-1104.

LabCorp

www.LabCorp.com

QuantiFERON® and QFT® are trademarks of the QIAGEN Group.
©2017 Laboratory Corporation of America® Holdings All rights reserved. L11775-0717-3

QuantiFERON®-TB Gold..... 182873

CPT 86480
Specimen Whole blood
Volume 1 mL x three tubes (see Container)
Minimum Volume 0.8 mL x three tubes
Container The QuantiFERON® collection kit contains instructions for the draw of three special QuantiFERON® collection tubes (one each): (1) gray-top (with white ring), uncoated (nil); (2) red-top (with white ring), TB antigen-coated; (3) purple-top (with white ring), mitogen-coated. A high altitude kit is also available for locations between 3350 and 6150 feet. The tubes are differentiated by a cap with a yellow ring.
Special Instructions This test is time-sensitive and specimens must be received in the laboratory within 14 hours of collection. Specimen collection times will vary depending on logistics from the blood draw location to a LabCorp lab. This test requires a special collection kit that may not be available at all PSCs.
Collection Refer to collection instructions included with draw kit. Special specimen collection kit contains three gel-barrier tubes: gray-top/white ring (nil), red-top/white ring (TB antigens), and purple-top/white ring (mitogen). All three tubes are required for a single test result. Each tube is designed to draw only 1 mL and fill time may be longer than other blood collection tubes. Because of the limited vacuum in these tubes, use a needle and holder (not a butterfly) to collect QuantiFERON® specimens. If a butterfly is required, first collect other required tubes or use another Vacutainer® tube to purge the butterfly line of air and then proceed with drawing the QuantiFERON® tubes. Fill tubes to the black fill line on the tube. If tubes are underfilled or overfilled (see kit insert), immediately redraw a replacement tube.

Following proper fill, label the tubes appropriately and shake tubes 10 times just firmly enough to ensure the entire surface of the tube is coated with blood cells to solubilize the antigen on the tube walls. After shaking, the volume may fall below the fill line. Do not centrifuge or refrigerate specimens.

Return each of the three properly filled, labeled, and shaken tubes to the box labeled "QFT® kit." Seal the top by removing tape from adhesive. Tubes should be incubated upright at 16-24 hours at 37°C ± 1°C in the box/kit within 16 hours of collection. To preserve cellular viability, specimens should be collected and sent same day, at room temperature, so as to arrive at the lab as soon as possible and within 14 hours of draw. Please indicate date and time of venipuncture on the tubes and on the test request form. If the specimen has been incubated for 16-24 hours at 37°C ± 1°C, please mark the top of the specimen box where indicated.
Storage Instructions Maintain specimen at room temperature (17°C to 27°C). Do not centrifuge, refrigerate, or ship tubes on ice.
Limitations Spontaneous interferon-γ production (independent of TB stimulation) or lack of a response to mitogen (due to anergy or immune suppression) may render the results indeterminate. A negative result should not be used alone to exclude *M tuberculosis* infection in persons with symptoms or signs suggestive of TB disease. Those who have a negative result but who are likely to have latent TB infection (LTBI) and who are at greater risk for severe illness or poor outcome if TB disease occurs, might need treatment or closer monitoring for disease.[1]

In healthy persons who have a low likelihood both of *M tuberculosis* infection and of progression to active tuberculosis 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 (using a newly collected specimen), 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.[2]

The QuantiFERON® TB test has been shown to be accurate in HIV-positive individuals with moderately advanced disease, but in the severely immunocompromised the test may be impaired by T-cell anergy.[3,4]

Active TB disease may result in a negative test as reduction of in vitro IFN-γ release has been described and may be due to suppressive cytokines associated with TB disease.[5] Patients with mycobacterial infections, other than tuberculosis, might also be responsive to ESAT-6, CFP-10, and TB7.7, as the genes encoding these proteins are present in *M kansasii*, *M szulgai*, and *M marinum*.[6]
Methodology *Mycobacterium tuberculosis* antigen-stimulated interferon-γ production with detection by enzyme-linked immunosorbent assay (ELISA). Test includes PHA (positive) and nil (negative) controls. This is also known as an interferon-γ release assay (IGRA). QuantiFERON® and QFT® are trademarks of the QIAGEN Group.
Footnotes
1. Centers for Disease Control and Prevention. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, American Thoracic Society, *MMWR Recomm Rep*. 2000; 49(RR-6):1-51.
2. Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection – United States, 2010. *MMWR* 2010;59(NoRR-55).
3. Brock I, Ruhwald M, Lundgren B, et al. Latent tuberculosis in HIV positive, diagnosed by M tuberculosis-specific interferon gamma test. *Respir Res*. 2006; 7:56.
4. 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(5):514-520.
5. Hirsch CS, Toossi Z, Othieno C, et al. Depressed T-cell interferon-gamma responses in pulmonary tuberculosis: Analysis of underlying mechanisms and modulation with therapy. *J Infect Dis*. 1999; 180(6):2069-2073.
6. Andersen P, Munk ME, Pollock JM, et al. Specific immune-based diagnosis of tuberculosis. *Lancet*. 2000; 356(9235):1099-1104.

For more information, including client-incubated test information, ask your LabCorp representative, or visit **www.labcorp.com/testmenu.**