



Detect TB infection with confidence

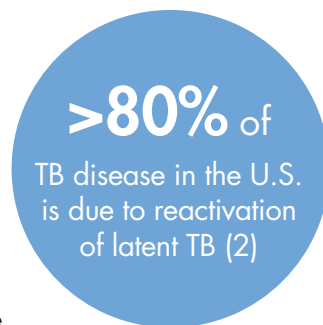
QuantiFERON®-TB Gold Plus

Advancing the science of TB testing
with innovative CD8 technology

Sample to Insight

The importance of testing for TB infection in the U.S.

In the United States, 13 million individuals are believed to silently carry latent TB infection (1). Without treatment, they are at risk for developing active TB disease. The good news is that TB disease is preventable and curable. If TB infection is recognized early, effective preventive treatment can be provided by a doctor.



Individuals at high-risk for TB infection and disease progression require rapid, accurate testing. Early detection TB infection is critical to prevent the spread of the disease (3). Approximately 10% of those infected with latent TB will develop active TB as a result of reactivation at some point in their lifetime(4). The U.S. Centers for Disease Control and Prevention (CDC) identifies specific groups at higher risk for TB exposure and for progression to active TB (4). The increased risk of developing active TB for many of these at risk groups has been quantified in an independent research meta-analysis (5).

Table 1. Individuals at increased risk of TB infection or TB progression (4)

Increased risk for TB infection	Increased risk for TB progression
Close contacts of active TB cases	Individuals living with HIV
Healthcare workers	Persons receiving TNF- α inhibitors
Foreign-born persons	Persons with diabetes mellitus
Persons in congregate settings	Persons with chronic renal failure
Persons in correctional facilities	Persons receiving corticosteroids
Persons in long-term care facilities	Organ transplant recipients
Persons who abuse drugs or alcohol	Persons recently infected with <i>M. tuberculosis</i>

Table 2. Groups at increased risk for developing active TB (5)

Risk group	Fold risk
HIV/AIDS	50–170
Transplant recipients	20–74
Hemodialysis	10–25
Recent TB infection	15
Abnormal chest X-ray	6–19
TNF- α inhibitors	2–9
Diabetes	2–5

The CDC recommends IGRAs, like QFT[®]-Plus, for the majority of the U.S. testing population

According to the CDC, Interferon-gamma Release Assays (IGRAs) are preferred for TB testing in most risk groups, including (6):

- Those likely to be infected with TB.
- Anyone with low or intermediate risk of disease progression.
- Those for whom it has been decided that testing for latent TB infection is warranted.

IGRAs are also **strongly recommended** in those who are also BCG-vaccinated, or unlikely to return to have their TST read.

QFT-Plus is the modern solution for TB infection detection

QuantiFERON-TB Gold Plus (QFT-Plus) is the next generation of the industry-leading IGRA for TB detection, QuantiFERON-TB Gold (QFT). QFT-Plus uses the same principle, test procedures, and reliable technology that you trust. QFT-Plus is now optimized with innovative tuberculosis-specific antigens that elicit both CD8 and CD4 T cell responses – enabling a more comprehensive assessment of cell-mediated immune response to TB infection (7).

QuantiFERON-TB Gold Plus provides:

- Single visit testing
- Highly accurate and reproducible results
- Convenient and objective lab-based testing
- Innovative CD8 T cell technology, providing a more comprehensive view of the immune response to TB infection
- Flexible blood collection and scalable laboratory workflows



QFT-Plus advantage—four tubes, one clear result

Optimized
to detect CD8
T cell responses

The QFT-Plus test uses a peptide cocktail simulating *M. tuberculosis* proteins to stimulate cells in heparinized whole blood. Detection of interferon- γ (IFN- γ) by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection.

Mitogen – Positive Control	Low response may indicate inability to generate IFN- γ
Nil – Negative Control	Adjusts for background IFN- γ
TB1 – Primarily detects CD4 T cell response	
TB2 – Optimized for detection of CD4 and CD8 T cell responses	

- Unique blood collection tubes enable immediate exposure of blood lymphocytes to highly specific TB antigens.
- Requires just 4 ml of whole blood – 1 ml in each of the 4 tubes.
- Option of drawing blood into a standard lithium-heparin tube.
- Fastest and easiest IGRA available, with no tedious lymphocyte isolation, subjective cell counting, diluting or culturing.
- Easily scalable for high-throughput testing laboratories.

Figure 1. QFT-Plus Blood Collection Tubes.

Interpretation of results

Results of the QFT-Plus assay are interpreted objectively using QuantiFERON-TB Gold Plus analysis software.

QFT-Plus Positive	→	<ul style="list-style-type: none"> • <i>M. tuberculosis</i> infection is likely • Nil ≤ 8.0; and • TB1 and/or TB2 minus Nil ≥ 0.35 and $\geq 25\%$ of Nil
QFT-Plus Negative	→	<ul style="list-style-type: none"> • <i>M. tuberculosis</i> infection is NOT likely • Nil ≤ 8.0, Mitogen minus Nil ≥ 0.5; and • TB1 and TB2 minus Nil < 0.35 or ≥ 0.35 and $< 25\%$ of Nil
QFT-Plus Indeterminate	→	<ul style="list-style-type: none"> • Likelihood of <i>M. tuberculosis</i> infection cannot be determined • Nil > 8.0 • Nil ≤ 8.0 and TB1 and TB2 < 0.35 or ≥ 0.35 and $< 25\%$ of Nil and Mitogen minus Nil < 0.5

Figure 2. Interpretation of results. All values are IU/ml IFN- γ . Indeterminate results may relate to the immune status of the individual being tested, or may be related to technical factors (e.g., incomplete ELISA plate washing). Important: Diagnosing or excluding tuberculosis disease, and assessing the probability of latent TB infection, requires a combination of epidemiological, historical, medical, and diagnostic findings that should be taken into account when interpreting QFT-Plus results (7).

QFT-Plus leads the industry with innovative CD8 technology

During *M. tuberculosis* infection, CD4 T cells play a critical role in immunological control through their secretion of the cytokine IFN- γ . Evidence now also supports a role for CD8 T cells in host defense against *M. tuberculosis*. CD8 T cells produce IFN- γ and other soluble factors to (8–10):

- Suppress *M. tuberculosis* growth
- Kill infected cells
- Directly lyse intracellular Mycobacteria

Moreover, TB-specific CD8 T cells that produce IFN- γ have been:

- More frequently detected in those with active TB disease vs. latent infection (11, 12)
- Associated with recent exposure to TB (13)
- Detectable in active TB subjects with HIV co-infection and young children (14, 15)

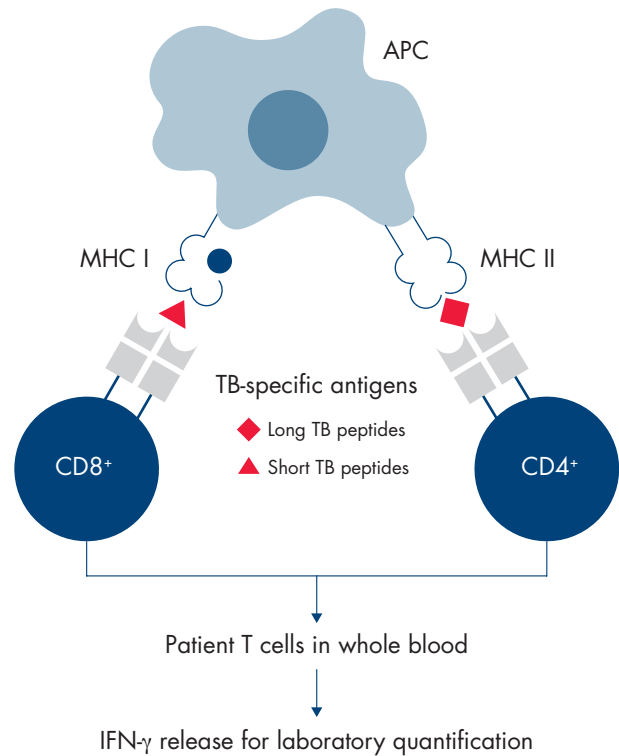


Figure 3. QFT-Plus IGRA technology. APC, antigen-presenting cell; MHC, major histocompatibility complex.



Accuracy matters in TB testing

QuantiFERON-TB Gold Plus is the patient centered, more affordable way to test for TB infection that produces more accurate results than the century-old tuberculin skin test (TST).

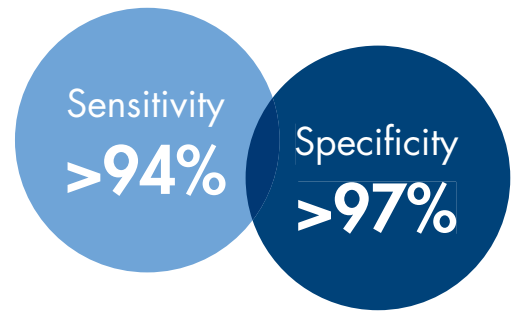


Table 3. QFT-Plus provides highly accurate detection of TB infection



TST challenges	QFT-Plus solutions
Specificity as low as 59% in BCG-vaccinated patients (16)	>97% specific, nearly eliminating false positive results and providing peace of mind for patients and physicians
Low sensitivity can cause missed true positives, putting contacts at risk (17)	Higher sensitivity (>94%) than the TST, enabling truly infected patients to be identified and to receive appropriate antibiotic therapy
False positives from cross-reaction with the BCG vaccine and other environmental mycobacteria (7)	Unaffected by the BCG vaccine and most non-TB mycobacteria, reducing unnecessary antibiotic treatments

QFT-Plus provides a patient centered, cost-effective solution for TB infection screening

You can remove the costly burden that inaccurate TB screening results place on your practice and on your patients. QFT-Plus produces fewer false positive results than the tuberculin skin test. QFT-Plus is also widely covered by Medicare, Medicaid and private insurance.

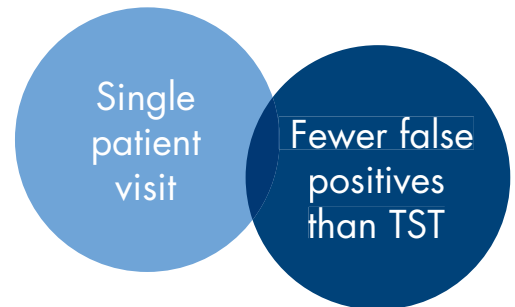


Table 4. QFT-Plus provides more single visit, cost-effective testing



TST challenges	QFT-Plus solutions
High false positive rate causes unnecessary additional testing and costly treatment (17)	Low false positive rate reduces the cost and burden of unnecessary antibiotic treatment
High program costs resulting from second visits, unnecessary x-rays and treatment	Consistently shown to be more cost-effective in screening situations (18, 19)
Requires return visit to read the TST reaction	Results can be sent directly to the physician, eliminating return visits for patients who test negative and encouraging follow-up for patients who test positive

Take control of your TB testing workflow

QFT-Plus offers industry leading flexible blood collection options

QFT-Plus employs standard phlebotomy procedures using whole blood to make sample collection easy and fast. Sample incubation can occur on-site or at the testing laboratory, providing your practice with complete flexibility and convenience.

Option 1: Direct Draw – Collect 1 ml of whole blood directly into each of four QFT-Plus blood collection tube and hold at room temperature for up to 16 hours prior to incubation.

Option 2: Single Lithium Heparin Tube – Draw at least 5 ml of blood into a single blood collection tube containing lithium heparin as the anticoagulant. Blood collected into a single lithium heparin tube may be stored at room temperature or refrigerated for up to 53 hours prior to transfer to QFT-Plus tubes and incubation.



QFT-Plus offers a streamlined and scalable laboratory workflow

QFT-Plus is the fastest and easiest IGRA available, with no tedious lymphocyte isolation, subjective cell counting, diluting or culturing. Results can be available using QFT-Plus analysis software within 24 hours, with no second patient visit required.

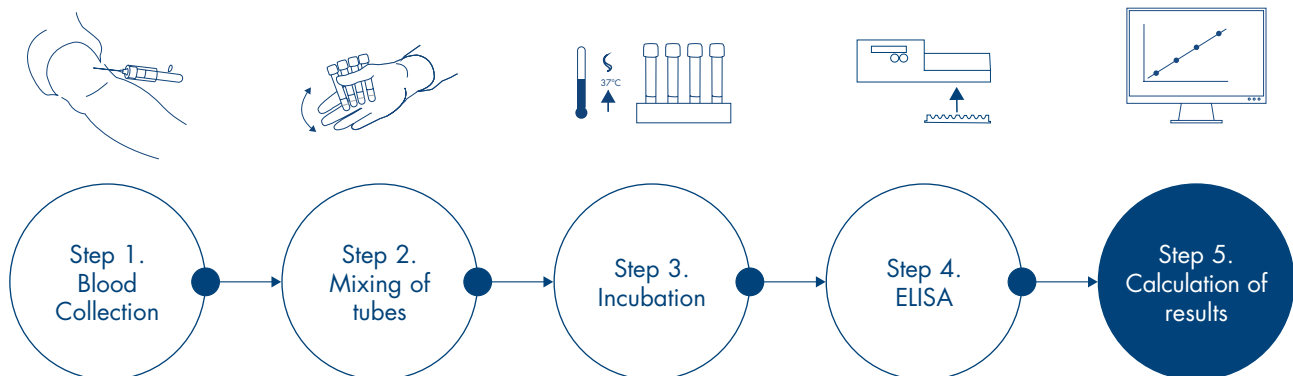


Figure 4. Streamlined QFT-Plus workflow, from patient sample to diagnostic insight.

Choose the most tested and trusted IGRA available

QuantiFERON technology has been the subject of over 1300 clinical and scientific studies. QFT-Plus provides a comprehensive view of the immune response to TB infection – and the convenience of a single patient visit. To learn more, contact your QIAGEN sales representative, or visit www.QuantiFERON.com.

Ordering Information

Product	Contents	Cat. no.
QuantiFERON-TB Gold Plus 2 Plate Kit ELISA	Microplate Strips; IFN- γ Standard, lyophilized; Green Diluent; Conjugate 100x Concentrate, lyophilized; Wash Buffer 20x Concentrate; Enzyme Substrate Solution; Enzyme Stopping Solution	622130
QFT-Plus Dispenser Pack (25 CT)	25 QFT-Plus Blood Collection Tubes packs, each including: Nil, TB1, TB2, and Mitogen tubes	622433
QFT-Plus Blood Collection Tubes (50X)	QFT-Plus Blood Collection Tubes: Nil, TB1, TB2, and Mitogen tubes (50 each)	622536

*Blood collection tubes for high altitudes are also available. For more information contact your QIAGEN sales representative or visit www.qiagen.com.

References

- Houben, R.M. and Dodd, P.J. (2016) The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med.* **13**, e1002152.
- Horsburgh, C.R. and Rubin, E.J. (2011) Clinical practice. Latent tuberculosis infection in the United States. *N. Engl. J. Med.* **364**, 1441-1448.
- Salinas, J.L., et al. (2016) Leveling of Tuberculosis Incidence – United States, 2013–2015. *MMWR* **65**, 273–278.
- Centers for Disease Control and Prevention. (2010) *MMWR* **59**(RR05), 1.
- Lobue, P. and Menzies, D. (2010) Treatment of latent tuberculosis infection: an update. *Respirology* **15**, 603–622.
- Lewinsohn, D.M. et al. (2017) Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin. Infect. Dis.* **64**, 111-115.
- QuantiFERON-TB Gold Plus (QFT-Plus) ELISA Package Insert. 1095849 Rev. 01 June 2017.
- Turner, J. et al. (1996) Stimulation of human peripheral blood mononuclear cells with live *Mycobacterium bovis* BCG activates cytolytic CD8+ T cells in vitro. *Immunology* **87**, 339.
- Brookes, R.H. et al. (2003) CD8+ T cell-mediated suppression of intracellular *Mycobacterium tuberculosis* growth in activated human macrophages. *Eur. J. Immunol.* **33**, 3293.
- Stenger, S. et al. (1998) An antimicrobial activity of cytolytic T cells mediated by granulysin. *Science* **282**, 121.
- Day, C.L. et al. (2011) Functional capacity of *Mycobacterium tuberculosis* specific T cell responses in humans is associated with mycobacterial load. *J. Immunol.* **187**, 2222.
- Rozot, V. et al. (2013) *Mycobacterium tuberculosis*-specific CD8+ T cells are functionally and phenotypically different between latent infection and active disease. *Eur. J. Immunol.* **43**, 1568.
- Nikolova, M. et al. (2013) Antigen-specific CD4- and CD8-positive signatures in different phases of *Mycobacterium tuberculosis* infection. *Diagn. Microbiol. Infect. Dis.* **75**, 277.
- Chicchio, T. et al. (2014) Polyfunctional T-cells and effector memory phenotype are associated with active TB in HIV-infected patients. *J. Infect.* **69**, 533.
- Ongaya, A. et al. (2013) *Mycobacterium tuberculosis*-specific CD8+ T cell recall in convalescing TB subjects with HIV co-infection. *Tuberculosis* **93**, S60.
- Pai, M., Zwerling, A., and Menzies, D. (2008) Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Ann. Intern. Med.* **149**, 177–184.
- Diel, R., Loddenkemper, R., and Nienhaus, A. (2010) Evidence-based comparison of commercial interferon-gamma release assays for detecting active TB: a metaanalysis. *Chest* **137**, 952.
- Kowada, A. et al. (2008) Cost effectiveness of interferon-gamma release assay for tuberculosis contact screening in Japan. *Mol. Diagn. Ther.* **12**, 235–251.
- Kowada, A. et al. (2015) Cost-effectiveness of interferon-gamma release assay for systematic tuberculosis screening of healthcare workers in low-incidence countries. *J. Hosp. Infect.* **89**, 99-108.

QFT-Plus is an in vitro diagnostic aid for detection of *Mycobacterium tuberculosis* infection. It uses a peptide cocktail simulating ESAT-6 and CFP-10 proteins to stimulate cells in heparinized whole blood. Detection of interferon- γ (IFN- γ) by ELISA is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. QFT-Plus 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 multiple languages, as well as up-to-date licensing information and product-specific disclaimers can be found at www.QuantiFERON.com.

Trademarks: QIAGEN®, Sample to Insight®, QFT®, QuantiFERON® (QIAGEN Group). Registered names, trademarks, etc., used in this document, even when not specifically marked as such, are not to be considered unprotected by law. 1107785 07/2017 PROM-11186-001 © 2017, QIAGEN, all rights reserved.

Ordering www.qiagen.com/contact | Technical Support support.qiagen.com | Website www.QuantiFERON.com