

A new way to look at TB infection QuantiFERON®-TB Gold Plus

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, is preventable through proper screening and treatment.

Individuals at high-risk for TB infection and disease progression require rapid, accurate testing

Early detection of 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- $lpha$ 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 M. tuberculos

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-a 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 at-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.

>80% of

TB disease in the U.S is due to reactivation of latent TB (2)

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





QFT-Plus advantage—four tubes, one clear result

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.



 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 lithiumheparin tube.
- Easily scalable for high-throughput testing laboratories.

Figure 1. QFT-Plus Blood Collection Tubes.

Interpretation of results

QFT-Plus uses objective methods to provide qualitative results interpretation. Testing laboratory should also provide quantitative results to assist in diagnosis or exclusion of TB disease.



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).

Optimized to detect CD8 T cell responses

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-y 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 (14–16)

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



Accuracy matters in TB testing

QFT-Plus provides patients with a streamlined 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

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TST challenges	QFT-Plus solutions
Specificity as low as 59% in BCG-vaccinated patients (17)	>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 (18)	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. Single patient visit

Sensitivity

>94%

Fewer false positives than TST

Specificity **>97%**

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

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TST challenges	QFT-Plus solutions
High false positive rate causes unnecessary additional testing and costly treatment (18)	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 (19, 20)
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

Tuberculosis screening guidelines for primary care physicians

Tuberculosis (TB) screening guidelines have been updated to include the availability of modern TB infection testing methods. Interferon-gamma release assays (IGRAs), such as QuantiFERON-TB Gold Plus, were developed to aid in the diagnosis of *Mycobacterium tuberculosis* infection and to address limitations of the century-old tuberculin skin test (TST).

The USPSTF classifies LTBI screening for at-risk individuals with a Grade B recommendation – offer/provide this service (21):

- The US Preventative Services Task Force (USPSTF) encourages proactive screening for latent TB infection among at-risk individuals in the primary care setting
- At-risk includes foreign-born adults from higher prevalence countries regardless of age, duration in the U.S., or co-morbidities
- At-risk also includes individuals in congregate settings, e.g. long-term care, corrections, and homeless shelters

The Grade B USPSTF recommendation ensures that LTBI screening for at-risk adults is covered by most private health insurance, Medicaid and Medicare free of charge (22).

2010 CDC guidelines provide recommendations for test selection in the diagnosis of *M. tuberculosis* infection (4):

- IGRA may be substituted for TST in all situations as an aid in the diagnosis of M. tuberculosis infection
- IGRA is preferred over TST in patients who have received the Bacillus Calmette-Guérin (BCG) vaccination
- IGRA is preferred over TST in patient groups with historically low rates of returning to have TSTs read
- Two-step testing is not required for IGRAs, because IGRA testing does not boost subsequent test results

2018 AAP Red Book recommends IGRA testing for children (23):

- IGRA or TST can be used to detect TB infection among at-risk children age >2 years of age
- IGRAs are preferred for children who are BCGvaccinated or unlikely to return
- Children with HIV infection should receive annual TST or IGRA testing
- Risk assessment for TB should be performed at the first encounter with a health care provider, and then annually if possible

2016 American Thoracis Society (ATS)/Infectious Disease Society of America (IDSA)/CDC clinical practice guidelines preferentially recommend IGRAs for most US patients (6):

- IGRA testing is preferred for individuals ≥5 years of age with low to intermediate risk of progression, regardless of BCG status or likelihood of returning
- IGRA or TST can be used without preference in individuals ≥5 years of age with high risk of progression
- TST is preferred for children <5 years of age but IGRA is acceptable

The American Academy of Family Physicians (AAFP) endorses CDC and USPSTF guidelines, stating that (24):

- IGRA may be substituted for TST in all situations as an aid in the diagnosis of *M. tuberculosis* infection
- IGRAs avoid the subjective nature of TST and are less affected by previous BCG vaccinations
- IGRAs have favorable cost benefits in healthcare settings, correctional facilities, and homeless shelters



Choose the most tested and trusted IGRA available

QuantiFERON technology has been the subject of over 1500 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**.

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QuantiFERON-TB Gold Plus (QFT-Plus) is an in vitro diagnostic aid for detection of *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-Plus package inserts, up-to-date licensing information and product-specific disclaimers can be found at www.QuantiFERON.com. The USA format of the QFT-Plus test has not been extensively evaluated with specimens from individuals younger than age 17 years or individuals who have impaired or altered immune functions, such as those who have HIV infection or AIDS, those who have transplantation managed with immunosuppressive treatment or others who receive immunosuppressive drugs (e.g., corticosteroids, methotrexate, azathioprine, cancer chemotherapy), those who have other clinical conditions, such as diabetes, silicosis, chronic renal failure, and hematological disorders (e.g., leukemia and lymphomas), or those with other specific malignancies (e.g., carcinoma of the head or neck and lung).

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