Clinicians Guide to QuantiFERON®-TB Gold

1) What is QuantiFERON®-TB Gold?

QuantiFERON®-TB Gold is an *in vitro* laboratory diagnostic test using a whole blood specimen. It is an indirect test for *M. tuberculosis*-complex (i.e., *M. tuberculosis, M. bovis, M. africanum, M. microti, M. canetti*) infection, whether tuberculosis disease or latent tuberculosis infection (LTBI), It cannot distinguish between tuberculosis disease and LTBI, and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

QuantiFERON®-TB Gold is a new test with a new design that replaces the first-generation version of QuantiFERON®-TB.

2) What is the scientific basis of the test?

QuantiFERON®-TB Gold is an *in vitro* diagnostic test using peptide cocktails simulating ESAT-6 and CFP-10 proteins to stimulate cells in heparinized whole blood. These proteins are absent from all BCG strains and from most non-tuberculosis mycobacteria with the exception of *M. kansasii*, *M. szulgai* and *M. marinum*. Individuals infected with *M. tuberculosis*-complex organisms usually have lymphocytes in their blood that recognize these and other mycobacterial antigens. This recognition process involves the generation and secretion of interferon-γ (IFN-γ). The detection and subsequent quantification of IFN-γ forms the basis of the QuantiFERON®-TB Gold test.

3) What is its intended use?

QuantiFERON®-TB Gold is an *in vitro* laboratory diagnostic test using a whole blood specimen. It is intended for use as a **diagnostic aide** for *M. tuberculosis*-complex infection, whether tuberculosis disease or LTBI.

4) What type of specimen is needed?

At least 4 mL of heparinized whole blood collected by venipuncture is needed for testing. An evacuated tube (5, 9, or 10 mL) with heparin should be completely filled. Anti-coagulants other than heparin are not suitable. Blood tubes should be held and transported at room temperature (22° ± 5°C) and must be transported to laboratories to allow initiation of testing within 12 hr.

4) What are its merits?

QuantiFERON®-TB Gold test results do not appear to be affected by BCG vaccination. Results can be available as soon as one day after collecting a blood specimen, and only one patient encounter is required for testing. Doing a QuantiFERON®-TB Gold test does not influence the results of future QuantiFERON®-TB Gold tests.

QuantiFERON®-TB Gold has been evaluated with specimens from patients with culture-confirmed tuberculosis disease and from apparently healthy adults with and without identified risk factors for *M. tuberculosis* infection.

5) What are its limitations?

Specimens for testing must be transported to laboratories to allow initiation of testing within 12 hr. Thus, communication with laboratories is needed to coordinate collection and transportation requirements.

The performance of the QuantiFERON®-TB Gold test has not been evaluated with specimens from the following groups of individuals:

1. Individuals who have impaired or altered immune function because of human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS); immunosuppressive drugs including those used for managing organ transplantation; clinical conditions including diabetes, silicosis, chronic renal failure, hematological disorders (e.g., myeloproliferative disorders, leukemias and lymphomas); or other specific malignancies (e.g., carcinoma of the head, neck, or lung).
2. Individuals with a high likelihood of *M. tuberculosis* infection progressing to tuberculosis disease.
3. Patients who have been treated for either LTBI or tuberculosis disease.
4. Individuals with medical conditions other than, or in addition to, LTBI or tuberculosis disease.
5. Individuals younger than age 17 years.
6. Pregnant women.

Medical treatments or conditions that impair immune functions can potentially reduce IFN-γ responses and prevent detection of a specific response to ESAT-6 and CFP-10. Some specimens may not have sufficient lymphocytes to detect specific IFN responses.

The lymphocytes from patients with infections caused by *M. kansasii*, *M. szulgai* or *M. marinum* may also have IFN-γ responses because the genes encoding both ESAT-6 and CFP-10 are present in these other mycobacteria. (QuantiFERON®-TB Gold is not intended for diagnosing infections caused by *M. kansasii*, *M. szulgai* or *M. marinum*.) Some individuals may have high background levels of IFN-γ or heterophile antibodies that interfere with detection of responses to ESAT-6 and CFP-10.

6) Who can be tested ?

QuantiFERON®-TB Gold can be used for patients who are being evaluated for possible *M. tuberculosis*-complex infection, whether tuberculosis disease or LTBI.

7) How are the results reported?

For any result, diagnosing or excluding tuberculosis disease, and assessing the probability of LTBI, requires a combination of epidemiological, historical, medical, and diagnostic findings that should be taken into account when interpreting test results. See general guidance on the diagnosis and treatment of tuberculosis disease and LTBI **(http://www.cdc.gov/nchstp/tb/)**. QuantiFERON®-TB Gold results are reported as positive, negative, or indeterminate:

QuantiFERON®-TB Gold Result	Report/Interpretation
Positive (ESAT-6 and/or CFP-10 responsiveness detected)	*M. tuberculosis* infection likely See text above
Negative (No ESAT-6 or CFP-10 responsiveness detected)	*M. tuberculosis* infection unlikely, but cannot be excluded especially when 1. any illness is consistent with tuberculosis disease 2. likelihood of progression to disease (e.g., because of immunosuppression) is increased See text above
Indeterminate	Test not interpretable See text above

8) Results of Clinical studies

The sensitivity and specificity of diagnostic tests for LTBI such as QuantiFERON®-TB Gold, cannot be reliably estimated because there is no definitive standard method for the diagnosis of latent tuberculosis infection (LTBI). In order to approximate sensitivity and specificity, QuantiFERON®-TB Gold was evaluated in three groups of patients

TABLE 1. QuantiFERON®-TB Gold results for persons with no reported risk for *M. tuberculosis* infection.

STUDY	BCG Status	Total tested	No. QFT-Gold[a] Indeterminate	No. QFT-Gold[a] Positive / No. Valid Tests	QFT-Gold[a] % Negative (95% CI)	No. TST[b] Positive / No. Tested	TST[b] % Negative (95% CI)
Japanese nursing recruits (Mori et al, 2004)	100% vaccinated	216	7	4 / 209	98.1% (95.2-99.5)	36 / 113[cd]	68.1%[cd] (58.7 –76.6)
Australian (Unpublished)	30% vaccinated	100	8	2 / 92	97.8% (92.4-99.7)	TST[b] not done	TST[b] not done
USA (Unpublished)	0% vaccinated	548	11	1 / 537	99.8% (99.0-100)	5[d]/ 548	99.1% (97.9 – 99.7)
TOTAL				**7 / 838**	**99.2%** (98.3 – 99.7)		

TABLE 2. QuantiFERON®-TB Gold results for patients with culture-confirmed tuberculosis disease.

STUDY		No. QFT-Gold[a] Indeterminate	No. QFT-Gold[a] Positive / No. Valid Tests	QFT-Gold[a] % Positive (95% CI)	No. TST[b] Positive / No. Tested (≥ 5 mm)	TST[b] % Positive (95% CI)
Japanese tuberculosis patients (Mori et al, 2004)[19]		4	102 / 114	89.5% (83.8-95.1)	50 / 77[c]	64.9%[c] (53.2-75.5)
Australian (Unpublished)	Pulmonary	0	20 / 24	83.3% (83.8-95.1)	ND	ND
	Extra-pulmonary	0	13 / 17	76.5% (50.1-93.2)	ND	ND
US tuberculosis patients (unpublished)		1	21 / 23	91.3% (72.0-98.9)	19 / 24	79.2% (57.8 – 92.9)
TOTAL			**156 / 178**	**87.6%** (82.8-92.5)		

[a]QuantiFERON®-TB Gold [b]Tuberculin skin test

[c]Used Japanese tuberculin purified protein derivative (PPD); these results are not directly comparable with those obtained with the tuberculin skin test antigens approved in the United States.

[d]Positive results defined as induration ≥ 15 mm.

with tuberculosis disease (Japan, Australia, USA) and three groups of persons at low risk of *M. tuberculosis* infection in the same countries. Specificity was approximated by the percentage of QuantiFERON®-TB Gold negative results in persons with low risk (no known risk factors) of tuberculosis infection (Table 1). Sensitivity for the detection of *M. tuberculosis* infection was approximated by the percentage of patients with culture-confirmed tuberculosis disease who had received ≤ 1 week of anti-tuberculosis treatment (Table 2) for whom QuantiFERON®-TB Gold results were positive.

In the USA study with 900 military recruits, blood was drawn for QuantiFERON®-TB Gold when a TST was placed. Demographic and risk factors were gathered in a standard survey at the time of testing. Of the recruits with a QuantiFERON®-TB Gold test, 824 recruits also had TST results, had never been treated for *M. tuberculosis* infection and had completed surveys for assessing related risk. Results were available for 276 subjects with reported risks for *M. tuberculosis* infection but who denied prior treatment for LTBI or tuberculosis disease. Risks included: 1) birth or residence for > 1 month in a country with tuberculosis rates greater than 10/100,000 per year, 2) contact with a tuberculosis case, 3) residence or employment in a jail, prison, hospital, nursing home, homeless shelter, or drug rehabilitation center, and 4) prior diagnosis of tuberculosis. For the 270 military recruits who related risks for tuberculosis infection and had a valid QuantiFERON®-TB Gold result, agreement with the TST is shown in Table 3.

TABLE 3. QuantiFERON®-TB Gold and TST results for recruits with risk factors reported for LTBI.

	TST +	TST -	TOTAL
QFT-Gold +	4	0	4
QFT-Gold -	29	237	266
TOTAL	33	237	270

Patient repeatability and effect of tuberculin skin test on subsequent QuantiFERON®-TB Gold *testing:* As part of the US military recruit study (predominantly no reported risk), a subset of the recruits were retested between 4 and 5 weeks after the original QuantiFERON®-TB Gold test and TST. QuantiFERON®-TB Gold results for 562 recruits were available at both time points. QuantiFERON®-TB Gold results agreed with earlier results 99.3% (558/562). Of the 5 initially QuantiFERON®-TB Gold positive recruits, 4 remained positive, and 3/562 changed from initially negative to positive at second test. Repeatability was 99.5% (375/377) for the Low-Risk group and 98.9% (183/185) for those with any reported risk for *M. tuberculosis* infection.

References: Mori T, et al. Specific detection of tuberculosis infection with an interferon-gamma based assay using new antigens. *Am J Respir Crit Care Med. 2004. 170: 59-64.*

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