Clinical Review

QuantiFERON®-TB Gold | TNF-α inhibitor

Assessing the risk for latent tuberculosis infection (LTBI) in inflammatory rheumatic patients awaiting TNF-α inhibitor therapy:

Evidence base and clinical experience with QuantiFERON-TB Gold

Edited by: Professor Stephan Gadola, DM, PhD, FRCP
Chair of Immunology and Consultant Rheumatologist, Faculty of Medicine
University of Southampton, United Kingdom

This document provides healthcare professionals with an evidence-based guide on the use of QuantiFERON-TB Gold (QFT®) for the risk assessment of LTBI in patients with immune-mediated inflammatory diseases who are being treated with disease-modifying antirheumatic drugs (DMARDs) and who are being considered for biologic therapy with TNF-α inhibitors.

QIAGEN®

Knowing the LTBI risk before TNF-α inhibitor therapy is vital

TNF-α inhibitors have revolutionized the treatment of different chronic and disabling inflammatory diseases of the joints, skin, and gut. However, these drugs expose patients to a significantly increased risk of active tuberculosis (TB), particularly during the first six to 12 months of therapy.[1-4] TNF-α inhibitor therapy increases the risk for TB in Rheumatoid Arthritis patients six to 11.5-fold[2-4]

Active TB in these patients is thought to arise from "re-activation" of LTBI, which can be silent for many years.

TB during TNF-α inhibitor therapy is different – and more dangerous[1-4]

- Late diagnosis, due to suppressed symptoms of infection
- >50% of patients have extrapulmonary or disseminated disease
- High morbidity and mortality, often drug-resistant disease

It is mandatory to screen patients awaiting TNF-α inhibitor therapy for LTBI to identify those at risk of developing active TB

Screening strategies for LTBI

There is no "gold-standard" for the diagnosis of LTBI. The decision to give anti-TB chemoprophylaxis before starting TNF-α inhibitors is made by the clinician based on three different types of information: The patient's **life-history** (e.g. previous household exposure to TB), **X-ray imaging** of the lungs, and **immunological testing**.

Immunological testing aims to measure the patient's cell-mediated memory immune response to TB antigens. For >100 years clinicians only had one such test available – the **Tuberculin Skin Test (TST,** also known as the Mantoux). **QuantiFERON-TB Gold** belongs to a new class of immunological test for LTBI which is based on modern immune assay technology and recent key insights into antigenic differences between TB pathogens and other mycobacteria. This new class of tests is referred to as Interferon-gamma (IFN-γ) Release Assays, or IGRAs.

Limitations of the TST in inflammatory rheumatic patients

Assay design:

- **Lack of positive and negative controls**

  It is impossible to decide whether a negative TST result is true or false-negative. In a given population negative TST results are clearly more common in inflammatory rheumatic patients compared to healthy people, suggesting a high rate of false-negative TST results in patients. Negative TST results may therefore give false security and expose patients to a higher risk of developing active TB upon initiation of TNF-α inhibitor therapy[4]

- **Two patient visits within 72 hours required**

  Between five and 65% of TST results are not read,[5-8] and these test results are therefore unavailable. Although TST may induce boosting and elicit a false-positive immunologic response, the effect of repeated TST in these patients is not as yet known

- **Invasive test**

  In the TST, Tuberculin is injected into the skin. Tuberculin contains a mixture of mostly unspecified mycobacterial components, detergents and organic compounds

- **Subjective read-out (induration thresholds range from 5 to 15mm, depending on patient and risk profile)**

Reduced sensitivity in patients with immune-mediated diseases with or without immunosuppression:[9-13]

- In a recent study of 101 Rheumatoid Arthritis patients and 93 healthy subjects from a high TB burden country, with high BCG vaccination rate, TST was positive in 65.6% of healthy controls, but only 26.7% of Rheumatoid Arthritis patients. This indicates a much lower sensitivity and, hence, high rate of false-negative TST results in the patients[11]
- Corticosteroid therapy is strongly associated with a negative TST[10]

Insufficient antigen specificity for TB-causing pathogens:[14,15]

- Most antigens contained in Tuberculin are shared by harmless environmental pathogenic mycobacteria and also the attenuated *Mycobacterium bovis* vaccine strain, Bacille Calmette-Guerin (BCG). Not surprisingly, BCG vaccination or previous infection with non-tuberculous mycobacteria can cause false-positive TST results[16-19]

IGRAs: Modern Immune Assays for TB

IGRAs are a new class of highly TB antigen-specific immune assays that exhibit several improvements in test format over the TST:

- **One patient visit, non-invasive test format.** IGRA are performed using a one-off small volume venous blood sample. If required, repeated IGRA testing (e.g. after new exposure to a TB case) can be performed without any effect on the patient's immune reactivity to TB antigens
- **Fully controlled.** In contrast to the TST, IGRAs incorporate negative and positive control measurements that allow the clinician to more safely interpret test results. In approximately 5% of Rheumatoid Arthritis patients, including those receiving immunosuppressive DMARD therapy, the positive control of IGRA fails to elicit a proper response.[16,18] These so-called "indeterminate" results may indicate to the clinician that it may not be safe to make therapeutic decisions based on the IGRA
- **Objective results**. IGRAs measure the TB antigen-specific activation of IFN-γ producing effector memory T-lymphocytes.[20] QuantiFERON-TB Gold is based on a robust Enzyme-linked Immune Assay (ELISA) format that enables automated, objective, quantitative determination of IFN-γ cytokine secretion in whole blood in response to TB antigens
- **Pathogen specificity.** IGRAs are based on the knowledge of key genetic differences between pathogenic and non-pathogenic mycobacteria, which is why they exhibit the highest degree of TB antigen specificity. In contrast to the TST, IGRAs are not affected by BCG vaccination status or prior infection with non-tuberculous mycobacteria other than *M. kansasii, M. marinum,* and *M. szulgaii*. The QuantiFERON-TB Gold assay incorporates three TB pathogen specific proteins, ESAT-6, CFP-10 and TB7.[7]
- **Current infection vs. cured.** IGRAs are *in vitro* assays which involve an antigen/whole blood incubation period of <24 hours. This time is sufficient to activate (peripheral) effector memory T-lymphocytes that are present in people with current TB infection, but not a response by central memory cells that are present in individuals with cured, past TB infection, thus further minimizing the risk of false-positives

QuantiFERON-TB Gold is a third-generation IGRA with over 550 peer-reviewed studies assessing its use across diverse populations.

QuantiFERON-TB Gold enables superior LTBI risk assessment compared with the TST

Multiple studies have found QuantiFERON-TB Gold and other IGRAs to be more sensitive than the TST for detection of active TB.[16] Also, several studies in patients with chronic immune diseases have reported superior performance of QuantiFERON-TB Gold over the TST, and most of these studies examined the performance of these tests in Rheumatoid Arthritis patients awaiting TNF-α inhibitor therapy.[9,11,14,17,21,22]

- The pooled sensitivities of QuantiFERON-TB Gold and the TST, respectively, for detection of active TB in a recent meta-analysis were 84.5% and 71.5% in the developed world setting, where TNF-α inhibitor use is likely[16]
- None of 835 QuantiFERON-TB Gold-negative untreated close TB contacts progressed to active TB within a period of 18 months, whereas 17.2% of untreated QuantiFERON-TB Gold-positive close TB contacts developed active TB during the same period of time[23]
- In other studies, QuantiFERON-TB Gold results were more strongly associated with TB risk factors (odds ratio 23.8) than the TST (odds ratio 2.8),[17] and the sensitivity of QuantiFERON-TB Gold was less affected by disease status and DMARD therapy in Rheumatoid Arthritis than the TST[11]

QuantiFERON-TB Gold results are associated with TB risk factors

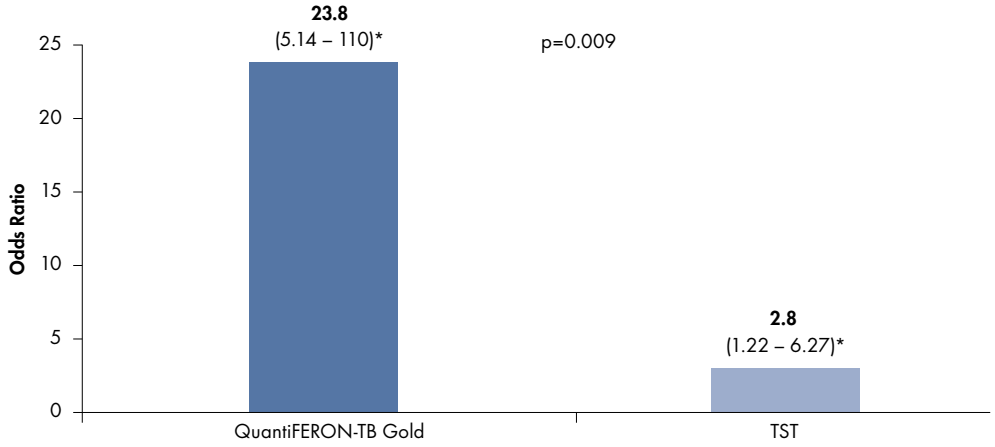


Figure adapted from Matulis G *et al.* 2008.[11] Patients with a risk factor for LTBI were 23.8-times more likely to have a positive QuantiFERON-TB Gold result (2.8-fold for TST; difference p=0.009).* 95% CI

QuantiFERON-TB Gold is more accurate than TST for identifying TB infection in immunosuppressed patients[17,24] who are thus at greater risk of developing active TB[4,25] prior to TNF-α inhibitor therapy.

QuantiFERON-TB Gold identifies TB risk more accurately than the TST

The superior specificity of QuantiFERON-TB Gold (99.2%) compared to the TST is particularly evident in BCG vaccinated populations (TST specificity: 59%), while it is also manifest in non-BCG vaccinated subjects (TST specificity: 97%).[9,16]

The **predictive value of QuantiFERON-TB Gold and the TST for progression to active TB was studied** in 601 close TB contacts who had not received chemoprophylaxis. It was found that 14.6% (6 of 41) of the QuantiFERON-TB Gold positive, untreated subjects developed active TB compared to only 2.3% (5 of 216) of TST-positive untreated subjects.[26]

Specificity of QuantiFERON-TB Gold

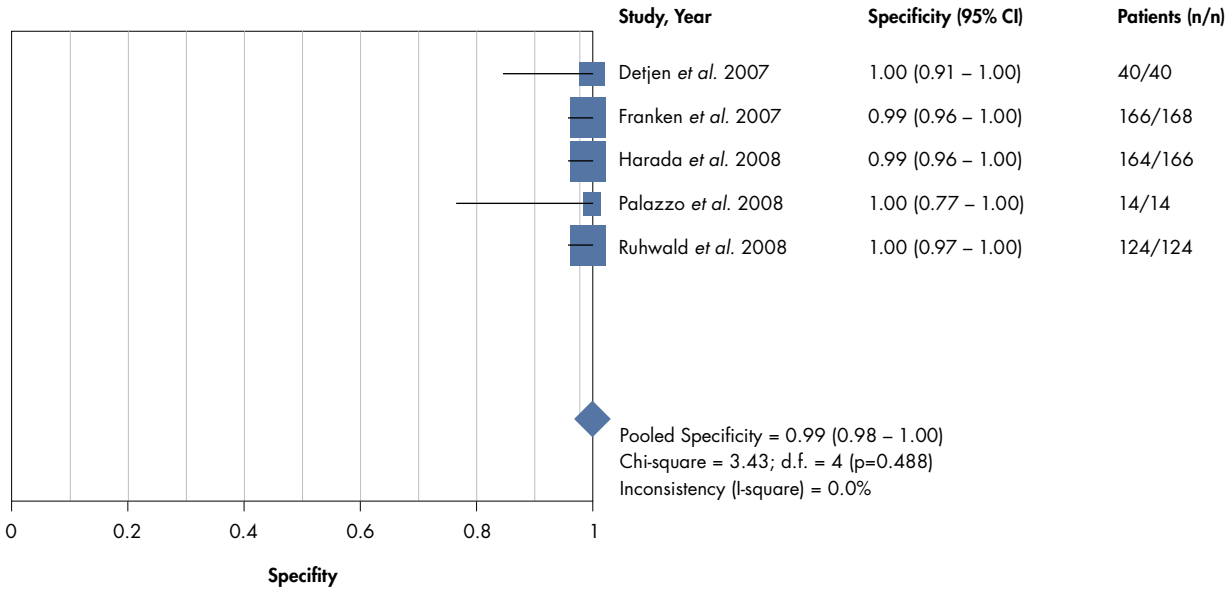


Figure adapted from Diel R *et al.* 2010.[16] Forest plot of QuantiFERON-TB Gold specificity. The pooled specificity of the QuantiFERON-TB Gold in developed and developing countries to detect active TB was evaluated from five studies targeted at evaluating QuantiFERON-TB Gold specificity, including a total of 513 patients with a low risk of *M. tuberculosis* infection. Only four of these 513 tested persons were positive in the QuantiFERON-TB Gold.

QuantiFERON-TB Gold results correlate with the presence of LTBI risk factors in arthritis patients receiving DMARD therapy

In the absence of a gold-standard for diagnosing LTBI, the sensitivity and specificity of existing tests cannot be directly determined. A study in Switzerland therefore compared the performance of the QuantiFERON-TB Gold and the TST in relation to the presence of LTBI risk factors in 142 consecutive patients with chronic inflammatory rheumatic conditions (119 with Rheumatoid Arthritis), including 126 patients on DMARD and biologic therapy (DMARDs, corticosteroids ≤ 10 mg/d and/or TNF-α inhibitors).[17] QuantiFERON-TB Gold results were more closely associated with the presence of LTBI risk factors (odds ratio, OR, of 23.8) than those of the TST (OR of 2.77), and the difference between the tests was statistically significant (p=0.009).

QuantiFERON-TB Gold is not affected by BCG

False-positive LTBI test results can lead to unnecessary TB chemoprophylaxis, with associated side effects, inconvenience for the patient, and cost. In contrast to the TST, QuantiFERON-TB Gold is unaffected by BCG vaccination status, thereby enabling clinicians to predict the presence of LTBI with a higher degree of accuracy. In a recent study from an intermediate TB burden country, none of the 16 TST-positive/QFT-negative patients with rheumatic disease developed active TB over 24.5 months of TNF-α inhibitor therapy, despite the fact that all 16 patients were given TNF-α inhibitors without prior TB chemoprophylaxis.[18]

Screening for LTBI in inflammatory rheumatic patients receiving DMARD therapy using QuantiFERON-TB Gold is not influenced by BCG vaccination status.[17]

Repeated testing with QuantiFERON-TB Gold

There are many situations in which a clinician may deem it necessary to repeat LTBI screening in immunosuppressed patients, for example, if a patient has been exposed to TB. QuantiFERON-TB Gold is carried out in test tubes and thus patients are not exposed to the TB specific antigens of the test, as would occur with the *in vivo* TST. Hence, the QuantiFERON-TB Gold can be repeated as often as needed without exerting any confounding impact on the patient's immune reactivity. In contrast, the TST alters immune reactivity to TB antigens.[27]

Suitable for use in immunosuppressed patients

Better accuracy in immunosuppressed inflammatory rheumatic patients

To improve upon the limitations of the TST, QuantiFERON-TB Gold was specifically designed as an objective, controlled assay.

- The TB Antigen tube assesses the IFN-γ response to highly-specific TB antigens
- The negative control tube adjusts for background noise
- The positive (phytohemaglutinin) control tube can be useful to indicate the general T cell-mediated immune status of a patient. Phytohemaglutinin activates T cells in an antigen-independent way

Interpretation Criteria for QuantiFERON-TB Gold:

- A **positive test** result indicates the presence of TB antigen-specific T cells in the patient's peripheral blood and a high likelihood of LTBI
- A **negative test** result indicates that the patient's T cells could be activated by phytohemaglutinin in a non-specific way (positive control), but that no TB-specific T cells were present in the blood sample. This is the most common scenario and means that LTBI is highly unlikely to be present
- An **indeterminate test** result may indicate either technical error (e.g. positive and/or negative control fail) or may be related to the immune status of the individual being tested (e.g. positive control fails, due to heavy immune suppression or T-cell anergy)

Interpretation criteria for QuantiFERON-TB Gold

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.

Low rates of indeterminate results with QuantiFERON-TB Gold

A recent meta-analysis reported the average indeterminate rate for QuantiFERON-TB Gold in immunosuppressed patients is 4.42%.[16]

Suitable for inflammatory rheumatic patients on immunosuppressive therapy

The effect of immunosuppressive therapy (oral prednisolone tablets or long-acting injectable corticosteroids) on QuantiFERON-TB Gold and on the TST in patients with inflammatory rheumatic diseases or inflammatory bowel disease prior to TNF-α inhibitor therapy has been analyzed in several studies.[10,17]

- The rate of indeterminate QuantiFERON-TB Gold results and negative TST results is higher in patients taking oral prednisolone above 10 mg/day[10]
- Methotrexate and other conventional DMARDs do not exert relevant impact on the performance of QuantiFERON-TB Gold[10,17]
- The rate of indeterminate results was not higher in 84 patients treated with TNF-α inhibitors compared to patients treated with DMARDs only. However, TNF-α inhibitors decreased the odds for a positive QuantiFERON-TB Gold result, indicating the importance of LTBI screening prior to commencement of TNF-α inhibitor therapy

Most patients awaiting TNF-α inhibitor therapy are already treated with immunosuppressive DMARD therapy which impacts on the reliability of the TST[31] but not the QuantiFERON-TB Gold.[17]

QuantiFERON-TB Gold is suitable for use in inflammatory rheumatic patients on immunosuppressive therapy.

Indeterminate QuantiFERON-TB Gold results occur in a small proportion of inflammatory rheumatic patients.

Indeterminate results are more likely in patients treated with higher oral corticosteroid doses or with TNF-α inhibitor therapy.

International recommendations for LTBI screening of patients prior to TNF-α inhibitor therapy

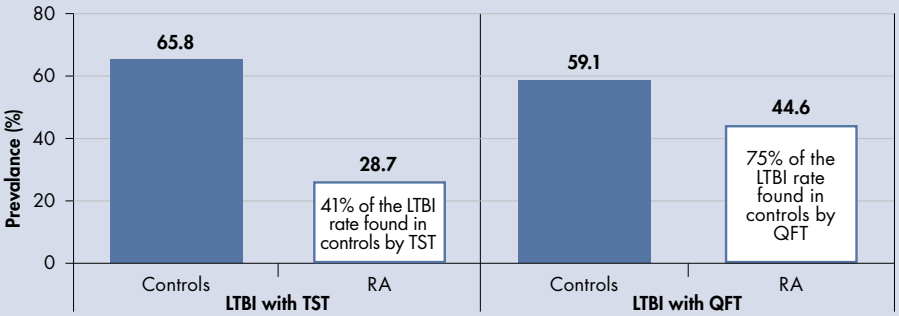
All patients should be screened for TB with a detailed medical history, chest X-ray and:

	Guideline or position statement
Use of an IGRA alone	Germany Switzerland Japan Bulgaria Poland Austria
Use either an IGRA or TST	Australia (Australian Rheumatology Association) Denmark (IGRA favoured) France (IGRA preferred) USA (US CDC)[28]* Bosnia & Herzegovina[29]
Use both an IGRA and TST	European Centre for Disease Prevention and Control (ECDC) UK (alternatively IGRA alone) USA (may be considered if either initial test negative; US CDC)[4]** Portugal Czech Rebublic Croatia Slovakia South Korea The Netherlands Ireland (TST preferred)
TST followed by an IGRA if TST negative	Canada Italy Spain Saudi Arabia
TST followed by an IGRA if TST positive	Spain Norway
TST alone	Brazil
No recommendations	Finland Australia (National TB Advisory Committee)

Table adapted from Denkinger CM *et al.* 2011.[7] IGRA: interferon-gamma release assay; TST: tuberculin skin test. Some countries are listed multiple times because recommendations vary across risk groups.

*Guidance for immune-suppressed patients; no specific guidance for TNF-α inhibitor therapy. **Situation 1, p11

Summary of published studies in immune-mediated diseases

Publication	Main Finding
Matulis G, Jüni P, Villiger PM and Gadola SD. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a *Mycobacterium tuberculosis* antigen-specific interferon γ assay *Ann Rheum Dis* 2008; 67:84-90.[17]	This study compared the performance of QuantiFERON-TB Gold and the TST in 142 consecutive patients with chronic inflammatory rheumatic conditions in a low TB incidence, high BCG vaccination rate country (Switzerland). 126 patients received immune suppressive therapies (70 on methotrexate, others on azathioprine, ciclosporin, leflunomide, cyclophosphamide, hydroxychloroquine, sulfasalazine, mycophenolate, mofetil or sirolimus, oral prednisone up to 10 mg/day), including 84 patients on TNF-α inhibitors. 83% of patients were BCG vaccinated. The rate of indeterminate results with QuantiFERON-TB Gold was 6% among 126 immunosuppressed and 16 non-immunosuppressed patients. Patients with a risk factor for LTBI were 23.8-times more likely to have a positive QuantiFERON-TB Gold result (2.8-fold for TST; difference p=0.009). Prior BCG vaccination had an effect on TST but not QuantiFERON-TB Gold results (p=0.025). Neither corticosteroids nor conventional disease-modifying antirheumatics significantly affected QuantiFERON-TB Gold results, but the odds of a positive result were decreased in patients on TNF-α inhibitors (OR 0.21; p=0.006). **QuantiFERON-TB Gold is unaffected by prior BCG vaccination, less affected by conventional disease-modifying antirheumatics and corticosteroids than the TST in patients with chronic inflammatory rheumatic conditions.**
Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S, Gutierrez C, Cucho M, Alfaro J, Perich R, Sanchez-Torres A, Pastor C, Sanchez-Schwartz C, Medina M, Gamboa R and Ugarte M. Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. *J Rheumatol* 2008; 35:776-781.[11]	This cross-sectional study assessed the performance of QuantiFERON-TB Gold in patients with RA in a highly TB-endemic area. Patients with RA (101) and controls (93) were screened from an area where the prevalence of latent TB in the general population has been estimated to be 68%. In comparing the concordance between RA and control patients, there was a statistically significant lower proportion of positive TST results recorded in the RA group (27/101, 26.7%) as compared with controls (61/93, 65.6%; p<0.001). The QuantiFERON-TB Gold test tested positive for 45/101 (44.6%) of RA patients, which was significantly lower than that for controls (55/93, 59.1%; p=0.04). All control subjects had valid QuantiFERON-TB Gold results. Overall, the rate of TST positivity in RA patients was only 41% of that for the controls — significantly lower than for the QuantiFERON-TB Gold assay, where the positivity rate for RA patients was 75% of that for the controls (p=0.008).  **Adaptation of Figure 1. Prevalence of latent tuberculosis infection (LTBI) according to tuberculin skin test (TST) and QuantiFERON-TB Gold In Tube test (QFT).** The number of patients who tested positive was more comparable between RA patients and controls with the QFT (44.6% vs 59%, respectively), whereas the TST detected significantly less LTBI among patients with RA compared to controls (65.6% vs 26.7%). **The QuantiFERON-TB Gold test was more sensitive than the TST in identifying latent TB infection in patients with RA.**

Publication	Main Finding
Inanc N, Aydin SZ, Karakurt S, Atagunduz P, Yavuz S, Direskeneli H. Agreement Between QuantiFERON-TB Gold Test and Tuberculin Skin Test in the Identification of Latent Tuberculosis Infection in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. *J Rheumatol* 2009; 36:2675-2681.[9]	This study in 140 consecutive patients, 82 with RA and 58 with Ankylosing Spondylitis (AS), were screened with QuantiFERON-TB Gold for the detection of latent TB before and after 6 months of TNF-α inhibitor therapy. As a comparison, QuantiFERON-TB Gold was also performed on 49 healthy controls. The percentages of positive QuantiFERON-TB Gold tests were comparable in RA and AS patients (37% vs. 32%). The rate of positive QuantiFERON-TB Gold tests in healthy controls (29%) was also similar to the RA and AS patients. In contrast to QuantiFERON-TB Gold results, a high rate of TST positivity was observed in AS, compared to RA (82% vs 55%; p=0.02). Rheumatoid Arthritis / Ankylosing Spondylitis TST (-) / TST (+) / Total / TST (-) / TST (+) / Total **QFT (-)** 29 / 18 / 47 / 8 / 27 / 35 **QFT (+)** 5 / 25 / 30 / 1 / 19 / 20 **Total** 34 / 43 / 77 / 9 / 46 / 55 **Kappa** 0.42 / 0.14 **Adaptation of Table 2. Agreement between QFT and TST in patients with rheumatoid arthritis and ankylosing spondylitis** **The ability of QuantiFERON-TB Gold to identify a comparable prevalence of latent TB among RA/AS and healthy controls supports the view that QuantiFERON-TB Gold is less susceptible to external factors than TST.**
Sauzullo I, Mengoni F, Scrivo R, Valesini G, Potenza C, Skroza N, Marocco R, Lichtner M, Vullo V and Mastroianni CM. Evaluation of QuantiFERON-Gold In-Tube in human immunodeficiency virus infection and in patient candidates for anti-tumor necrosis factor-alpha treatment. *Int J Tuberc Lung Dis* 2010; 14(7):834-840.[22]	This study assessed patients with immune-mediated inflammatory disease (IMID) in a country with low TB prevalence for latent TB infection. Patients (195) with immune-mediated inflammatory disease who were candidates for treatment with TNF-α blockers were screened for TB with a clinical evaluation, chest X-ray (CXR), TST and QuantiFERON-TB Gold (QFT). 56% of patients were on immune suppressive treatment (10 mg/day prednisone, 10 mg/week methotrexate + glucocorticoid or 150 mg/day cyclosporine + methotrexate + glucocorticoid). **Patients with IMID (n=195)** QuantiFERON Results **Positive (n = 35) n (%)** / **Negative (n = 137) n (%)** / **Indeterminate (n = 26) n (%)** **TST-positive** 27 (84) / 26 (19) / 5 (19) **TST-negative** 5 (16) / 111 (81) / 21 (81) **Adaptation of Table 2. Discrepancies between the TST and QuantiFERON-TB Gold test results were found in 31 patients.** In particular, 26 patients were QuantiFERON-TB Gold-negative/ TST-positive. Of these patients, 11 (42.3%) were BCG-vaccinated and four (15.3%) were farmers who were potentially exposed to environmental non-TB mycobacteria. **QuantiFERON-TB Gold provides good diagnostic accuracy and high LTBI detection level, in patients taking immunosuppressive drugs.**

Publication	Main Finding
Chang B, Park HY, Jeon K, Ahn JK, Cha HS, Koh EM, Kang ES, Koh WJ. Interferon-γ release assay in the diagnosis of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists in Korea. *Clin Rheumatol* 2011; accepted article in press; DOI 10.1007/s10067-011-1771-9.[18]	This study in 108 consecutive patients with inflammatory arthritis including RA and AS, were evaluated for latent TB before starting TNF-α inhibitor therapy during a 24-month period using the TST and QuantiFERON-TB Gold tests. No patients developed active TB during a median of 18 months. Discrepancies between test results occurred in 16 patients (15/16, 94% with AS) who had positive TST and negative QuantiFERON-TB Gold results and did not develop TB during a median of 24.5 months of TNF-α inhibitor therapy. **QuantiFERON-TB Gold can accurately identify patients who are truly infected, reducing the effects of false-positive results as seen with the TST.**
Chiu H-Y, Hsueh P-R and Tsai T-F. Clinical experience of QuantiFERON-TB Gold testing in patients with psoriasis treated with tumor necrosis factor blockers in Taiwan. *Br J Dermatol* 2011; 164:553-559.[14]	QuantiFERON-TB Gold was performed on all patients who were candidates. Overall, patients had a median of 24 weeks (range 4 to 307) exposure to TNF-α inhibitors. Twelve patients (11%) who were treated with TNF-α inhibitors and eight (15%) without TNF-α inhibitors had positive QuantiFERON-TB Gold results. Of all TNF-α inhibitor users, only one patient (0.68%) who had a negative TST but positive QuantiFERON-TB result and did not receive prophylactic treatment, developed TB. **QuantiFERON-TB Gold can be used to screen for latent TB in a tuberculosis endemic area where BCG-vaccination coverage is high.**
Kwakernaak AJ, Houtman PM, Weel JFL, Spoorenberg JPL and Jansen TLTA. A comparison of an interferon-gamma release assay and tuberculin skin test in refractory inflammatory disease patients screened for latent tuberculosis prior to the initiation of a first tumor necrosis factor α inhibitor. *Clin Rheumatol.* 2011; 30:505-510.[15]	This study assessed 56 patients with immune-mediated inflammatory diseases including RA (51.8%), AS (30.4%), psoriatic arthritis (PA; 8.9%), undifferentiated spondylarthropathy (US; 3.6%), juvenile idiopathic arthritis (JIA; 1.8%), adult-onset Still's disease (1.8%) and sarcoidosis (1.8%). Of the 56 patients, nearly half (48.2%) had received methotrexate (± corticosteroids), 5.4% had received leflunomide (± methotrexate ± corticosteroids), 1.8% had received azathioprine and corticosteroids, 5% received only corticosteroids, and 35.7% did not have any previous immunosuppressive treatment. Only 9 patients (16.1%) tested positive for latent TB with either TST or QuantiFERON-TB Gold. There were discrepancies between the test results; 1 patient had a negative TST and positive QuantiFERON-TB Gold test, and 5 patients had positive TST and negative QuantiFERON-TB Gold tests. There were no indeterminate results for QuantiFERON-TB Gold. The negative-TST/positive-QuantiFERON-TB Gold patient had a previous TB infection. The patients with positive-TST/negative- QuantiFERON-TB Gold were either BCG-vaccinated or had a medical history of prior-TB exposure. None of these patients who tested negative with QuantiFERON-TB Gold developed TB during treatment with TNF-α inhibitors in the follow-up period (1–2 years). Immune suppression did not appear to significantly lower CD4+ T lymphocyte cell counts and therefore lower indeterminate results of IGRA, despite systemic corticosteroid treatment in half of the patients. **QuantiFERON-TB Gold is useful for screening immunosuppressed patients.**

Notes

References: 1. Keane J *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor aplha-neutralizing agent. *N Engl J Med* 2001; 345:1098-1104. **2.** Bongartz T *et al.* Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies. Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006; 295(19):2275-2285. **3.** Wallis RS *et al.* Granulomatous infectious diseases associated with tumor necrosis factor antagonists. *Clin Infect Dis* 2004; 38(9):1261-1265. **4.** Gomez-Reino JJ *et al.* Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicentre active-surveillance report. *Arthritis Rheum* 2003; 48(8):2122-2127. **5.** Kariminia A *et al.* Comparison of QuantiFERON TB-G-test to TST for detecting latent tuberculosis infection in a high-incidence area containing BCG-vaccinated population. *J Eval Clin Pract* 2009; 15(1):148–151. **6.** Cheng TL *et al.* Strategies to increase adherence with tuberculosis test reading in a high-risk population. *Pediatrics* 1997; 100(2 Pt 1):210–213. **7.** Chaisson RE *et al.* Effects of an incentive and education program on return rates for PPD test reading in patients with HIV infection. *J Acquir Immune Defic Syndr Hum Retroviral* 1996; 11(5):455–459. **8.** Vinton P *et al.* Comparison of QuantiFERON-TB Gold In-Tube Test and tuberculin skin test for identification of latent Mycobacterium tuberculosis infection in healthcare staff and association between positive test results and known risk factors for infection. *Infect Control Hosp Epidemiol* 2009; 30(3):215–221. **9.** Inanc N *et al.* Agreement Between QuantiFERON-TB Gold Test and Tuberculin Skin Test in the Identification of Latent Tuberculosis Infection in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis. *J Rheumatol* 2009; 36(12):2675-2681. **10.** Belard E *et al.* Prednisolone Treatment Affects the Performance of the QuantiFERON Gold In-Tube Test and the Tuberculin Skin Test in Patients with Autoimmune Disorders Screened for Latent Tuberculosis Infection *Inflam Bowel Dis* 2011; 17(11):2340-2349. **11.** Ponce de Leon D *et al.* Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. *J Rheumatol* 2008; 35(5):776-781. **12.** Mow WS *et al.* High incidence of anergy in inflammatory bowel disease patients limits usefulness of PPD screening before infliximab therapy. *Clin Gastroenterol Hepatol* 2004; 2(4):309-313. **13.** Ponce De Leon D *et al.* Attenuated response to purified protein derivative in patients with rheumatoid arthritis: study in a population with a high prevalence of tuberculosis. *Ann Rheum Dis* 2005; 64(9):1360-1361. **14.** Chiu H-Y *et al.* Clinical experience of QuantiFERON-TB Gold testing in patients with psoriasis treated with tumour necrosis factor blockers in Taiwan. *Br J Dermatol* 2011; 164(3):553-559. **15.** Kwakernaak AJ *et al.* A comparison of an interferon-gamma release assay and tuberculin skin test in refractory inflammatory disease patients screened for latent tuberculosis prior to the initiation of a first tumor necrosis factor α inhibitor. *Clin Rheumatol.* 2011; 30(4):505-510. **16.** Diel R *et al.* Evidence-based comparison of commercial interferon-γ release assays for detecting active TB: a metaanalysis. *Chest* 2010; 137(4):952-968. **17.** Matulis G *et al.* Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon γ assay *Ann Rheum Dis* 2008; 67(1):84-90. **18.** Chang B *et al.* Interferon-γ release assay in the diagnosis of latent tuberculosis infection in arthritis patients treated with tumor necrosis factor antagonists in Korea. *Clin Rheumatol* 2011; accepted article in press; DOI 10.1007/s10067-011-1771-9. **19.** Mazurek GH *et al.* Comparison of a whole-blood interferon-gamma assay with tuberculin skin testing for detecting latent *Mycobacterium tuberculosis* infection. *JAMA* 2001; 286(14):1740-1747. **20.** Pai M *et al.* New tools and emerging technologies for the diagnosis of tuberculosis: Part I. Latent tuberculosis. *Expert Rev Mol Diagn* 2006; 6(3):413-422. **21.** Cobanoglu N *et al.* Interferon-gamma assays for the diagnosis of tuberculosis infection before using tumour necrosis factor-alpha blockers. *Int J Tuberc Lung Dis* 2007; 11(11):1177–1182. **22.** Sauzullo I *et al.* Evaluation of QuantiFERON-TB Gold In-Tube in human immunodefi ciency virus infection and in patient candidates for anti-tumour necrosis factor-alpha treatment. *Int J Tuberc Lung Dis* 2010; 14(7):834-840. **23.** Haldar P *et al.* S13 Contact Screening with single-step TIGRA testing and risk of active TB infection: The Leicester cohort analysis. Abstract of the oral presentation on the annual meeting of the BTS. *Thorax* 2009; 64:A10-A13. **24.** Garcovich S *et al.* Clinical applicability of Quantiferon-TB-Gold testing in psoriasis patients during long-term anti-TNF-alpha treatment: a prospective, observational study. *J Eur Acad Derm Venereol* 2011; article accepted in press; DOI: 10.1111/j.1468-3083.2011.04220.x. **25.** Salgado E and Gómez-Reino JJ. The risk of tuberculosis in patients treated with TNF antagonists. *Expert Rev Clin Immunol* 2011; 7(3):329-340. **26.** Diel R *et al.* Predictive Value of a Whole Blood IFN-g Assay for the Development of Active Tuberculosis Disease after Recent Infection with *Mycobacterium tuberculosis* AJRCCM 2008, 177(10): 116470. **27.** van Zyl-Smit R *et al.* Within-Subject Variability and Boosting of T-Cell Interferon-γ Responses after Tuberculin Skin Testing. *Am J Respir Crit Care Med* 2009; 180(1):49-58. **28.** Mazurek GH *et al.* Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection. MMWR 2010; 5:1-28. **29.** Žutić H *et al.* Recommendations for Treatment of Active and Latent Tuberculosis Before and During The Tumor Necrosis Factor Antagonists Therapy in Bosnia and Herzegovina. 2011 *Journal of Medical Faculty University of Sarajevo, Bosnia & Herzegovina* 2011; 46(1): 60-72. **30.** Denkinger CM *et al.* Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion? *Clin Microbiol Infect* 2011; 17(6):806-814. **31.** Ledingham J *et al.* British Thoracic Society (BTS) recommendations for assessing risk and managing tuberculosis in patients due to start anti-TNF-α treatments. *Rheumatol* 2005; 44(10):1205-1206. *Rheumatol Int* 2007; 27(12):1143-1148.

QuantiFERON®-TB Gold (QFT®) is CE marked. QFT is approved by the US FDA.

QFT is approved by the 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.

Cellestis, a QIAGEN Company

World Headquarters ▪ Cellestis International ▪ +61 3 8527 3500 ▪ info@cellestis.com
Asia/Pacific ▪ QIAGEN Singapore PTE Ltd ▪ +65 6854 8100 ▪ asiapac@cellestis.com
Australia/New Zealand ▪ Cellestis International ▪ +61 3 8527 3500 ▪ anz@cellestis.com
Europe/Middle East ▪ Cellestis GmbH ▪ +49 6151 428 590 ▪ europe@cellestis.com
Japan/Korea ▪ QIAGEN KK ▪ +81 3 6890 7300 ▪ jp.kr@cellestis.com
North America/South America ▪ Cellestis Inc ▪ +1 661775 7480 ▪ customer.service@cellestis.com