# Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders

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**Current Opinion in Rheumatology** 2011, 23:377–384

**Purpose of review**

To provide a narrative synthesis of evidence on interferon-gamma release assays (IGRAs) for the diagnosis of latent tuberculosis infection (LTBI) in individuals with immune-mediated inflammatory disorders (IMIDs).

**Recent findings**

Only a few studies have evaluated IGRAs in IMIDs, and most were small and varied considerably with respect to the use of immunosuppressive medications and types of IMIDs. Current evidence does not clearly suggest that IGRAs are better than tuberculin skin test (TST) in identifying individuals with IMID who could benefit from LTBI treatment. To date, no studies have been done on the predictive value of IGRAs in IMID patients. Important questions remain unanswered as to the impact of immunosuppressive medications and the impact of type of IMID on IGRA performance.

**Summary**

Despite the lack of clear evidence, there is an increasing tendency for guidelines to prefer IGRA over TST in IMIDs or to recommend both TST and IGRA to enhance sensitivity. We believe the use of either test is acceptable for LTBI screening. Clinicians could consider starting with IGRAs in individuals with a history of Bacille Calmette-Guérin (BCG) vaccination after infancy or with repeated BCG vaccinations. When the index of suspicion for LTBI is high, both IGRA and TST could be performed, especially prior to initiating TNF-α inhibitor therapy. Regardless of the test used, it is important to remember that in the face of immune-suppression, both IGRA and TST can be falsely negative and are thus only diagnostic aids – they will need to be interpreted with other clinical and risk factor data.

**Keywords**

diagnostics, HIV, interferon-gamma release assays, immune-mediated inflammatory diseases, latent tuberculosis

Curr Opin Rheumatol 23:377–384

1040-8711

## Introduction

Detection and management of latent tuberculosis infection (LTBI) are key components of tuberculosis (TB) control in most high-income countries. Targeted screening of high-risk groups is the main approach used, with groups such as recent immigrants, contacts of known TB cases, and immunocompromised individuals being the most important target groups [1]. HIV infection is the most important immunocompromising condition with respect to progression from LTBI to active TB disease. However, individuals with immune-mediated inflammatory disorders (IMIDs) are also known to be at increased risk of developing active TB, particularly after initiating immunosuppressive therapies such as tumor necrosis factor-alpha (TNF-α) inhibitors [2,3•].

Screening persons for LTBI prior to initiation of TNF-α inhibitor therapy is now the standard of care [3•,4•]. However, whether individuals with IMIDs should be screened for LTBI using the tuberculin skin test (TST) or the newer interferon-gamma release assays (IGRAs) is unclear and controversial. The TST has well known limitations, including a higher risk of false-negative results in individuals with impaired cellular immunity, and a higher likelihood of false-positive results in individuals who receive the Bacille Calmette-Guérin (BCG) vaccine after infancy or receive multiple booster vaccinations [5,6]. Operational limitations include the need for repeat visits to complete testing, inter-reader and intra-reader variability in test interpretation, boosting of the immune response with serial testing, and decreased sensitivity in immunocompromised individuals. Despite

these limitations, longitudinal studies have clearly demonstrated a higher risk of active TB in TST-positive vs. TST-negative individuals, and systematic reviews of randomized trials show that LTBI treatment is highly effective in those who are TST-positive [7,8].

As an alternative to TST, in-vitro assays that measure interferon-gamma release after exposure of peripheral blood mononuclear cells to *Mycobacterium tuberculosis* (MTB)-specific antigens were developed [9]. Two such IGRAs are available as commercial tests: QuantiFERON-TB Gold In-Tube (QFT-GIT) (Cellestis Limited, Victoria, Australia) and T-SPOT.TB (TSPOT) (Oxford Immunotec, Abingdon, UK). Both tests are approved by the US Food and Drug Administration (FDA) and are also available in European and many other countries.

To better inform clinicians and policy makers, we summarize current evidence on TST and IGRAs in individuals with IMIDs. To provide the context, we begin with a brief summary of what is known about IGRAs in general, and then focus on studies comparing TST and IGRA performance in individuals with IMIDs. We conclude with a discussion on current guidelines on IGRAs in this high-risk, immunocompromised group, and some research recommendations.

## What is known about interferon-gamma release assays in general?

Like the TST, IGRAs do not directly detect infection with MTB. Instead, they quantitatively measure the magnitude of a cellular immune response to sensitization by MTB. Therefore, IGRAs and TST cannot distinguish between latent infection and active TB disease [10]. In addition, similar to the TST, a positive IGRA result may not necessarily indicate active TB and a negative IGRA result may not rule out active TB [11,12]. Thus, IGRAs and TST are not intended for active TB diagnosis in adults, but may have a supportive role in children because of limitations of other diagnostic tests.

IGRAs have excellent specificity for LTBI which is not affected by BCG vaccination [13]. In contrast, the specificity of TST varies considerably depending on when BCG is given and whether booster vaccinations are given [14]. Some countries recommend booster BCG vaccinations after infancy and into childhood, and this is known to compromise the specificity of TST. A World Atlas of BCG Policies and Practices (www.bcgatlas.org) has been recently compiled to help clinicians and public health practitioners better interpret TST results and decide on populations in which the more specific IGRAs may be more appropriate than the TST [15•].

### Key points

- Individuals with immune-mediated inflammatory disorders (IMIDs) are at increased risk of developing active tuberculosis.
- Current evidence does not clearly suggest that interferon-gamma release assays (IGRAs) are better than tuberculin skin test (TST) in identifying individuals with IMID who could benefit from LTBI treatment.
- There is an increasing tendency for guidelines to prefer IGRA over TST in IMIDs or to recommend both TST and IGRA to enhance sensitivity.
- Although either TST or IGRA is acceptable to screen for LTBI, clinicians could consider starting with IGRAs in individuals with a history of BCG vaccination after infancy or with repeated BCG vaccinations.
- When the index of suspicion for LTBI is high, both IGRA and TST could be performed, especially prior to initiating TNF-α inhibitor therapy.

Using culture-confirmed active TB as a surrogate reference standard for LTBI, the sensitivity of IGRAs may be higher than that of TST, though results vary widely in head-to-head comparisons [13]. IGRA sensitivity is lower in HIV-infected individuals as compared with individuals without HIV infection [16•], and IGRA sensitivity appears to be lower in culture-proven active TB patients in high-incidence settings as compared with low-incidence settings [17]. IGRA results seem to correlate well with risk factors and surrogate markers of TB exposure [18], but the magnitude of the association varies across populations. In most low TB incidence countries, IGRA results are not associated with BCG vaccination status.

The impact of immune suppression on IGRA performance has mostly been studied in the context of HIV infection [16•]. In a recent systematic review, Cattamanchi *et al.* [16•] identified 21 studies in which IGRA results could be compared in HIV-infected individuals with $CD4^+$ T-lymphocyte count greater than 200 cells/μl vs. less than or equal to 200 cells/μl. These data suggested that IGRAs are less affected by HIV-related immunosuppression than TST, but the differences between tests were small and results varied widely across individual studies.

IGRA-positive individuals have a higher incidence of active TB than IGRA-negative individuals, but the association (i.e. predictive value) is only modest. A majority (>90%) of those who are IGRA-positive do not seem to progress to active TB disease, even in high TB endemic settings [19–23]. In fact, current evidence suggests that all existing LTBI tests (TST and IGRAs) have only modest ability to predict progression to active TB and do not identify those at highest risk of

progression [24]. Lastly, no randomized trials have been done demonstrating the benefit of LTBI treatment in IGRA-positive vs. IGRA-negative individuals.

From an operational perspective, IGRA requires only one healthcare visit for testing and test interpretation is objective. Potential drawbacks include higher cost, requirement for blood draw, and the need for laboratory capacity. Also, IGRAs are dynamic assays with fairly high frequencies of conversions and reversions which might impact interpretation of repeat testing in high-risk patients [18,25].

In summary, IGRAs have more convenient logistics compared with TST and may be particularly useful in settings in which TST specificity is compromised by late or repeated BCG vaccinations. However, there are no data to support the efficacy of LTBI treatment in IGRA-positive but TST-negative individuals, and the safety of withholding LTBI treatment in TST-positive but IGRA-negative individuals has not been demonstrated, even in the context of BCG vaccination.

## What is the evidence on interferon-gamma release assays in immune-mediated inflammatory disorders?

Although no meta-analysis has been published, at least 14 studies [26–39] enrolling 1630 patients have compared the performance of the newest generation IGRAs and TST in individuals with various IMIDs (Table 1). To minimize the impact of BCG vaccination, we focus on 10 studies conducted in low TB incidence countries [26–28,31–33, 35,36,38,39]. In four of these studies, the percentage of BCG vaccinated patients was less than 5%. However, the study populations differed with respect to IMID type and immunosuppressive therapy. Most studies included individuals with at least four different IMIDs. Overall, the most common IMIDs evaluated were rheumatoid arthritis (RA) (611 individuals, 8 studies) [26–28,31,32,35,36,39], psoriatic arthritis (259 individuals, 9 studies) [26–28,31–33,35,36,39], inflammatory bowel diseases (IBD) (196 individuals, 4 studies) [28,36,38,39], and ankylosing spondylitis (164 individuals, 6 studies) [26,31,32,35,36,39]. Six studies included patients who were being considered for treatment with TNF-α inhibitors [28,31–33,35,39], whereas the remaining four studies included patients already taking TNF-α inhibitors [26,27,36,38].

As there is no gold standard for LTBI, all studies compared the proportion of positive results obtained with IGRAs and TST and reported the correlation between test results. Five studies also reported the association between test results and TB risk factors using multivariate analysis [26–28,31–33,35,36,38]. However, there were no longitudinal studies evaluating the risk of active TB in individuals with IMID with positive and negative IGRA results, and there

**Table 1 Summary of studies on IGRAs in IMID**

| Study | Country | Setting | *n* (eligible) | IMID conditions | Positive IGRA [*n* (%)] | Positive TST [*n* (%)] |
|---|---|---|---|---|---|---|
| QFT-Gold-In Tube | | | | | | |
| (a) Middle-income countries | | | | | | |
| Cobanoglu *et al.* [29] | Turkey | Outpatient | 68 | RA, Crohn's disease/ulcerative colitis, psoriasis, AS, other | 9 (13) | 38 (56) |
| Gogus *et al.* [30] | Turkey | Outpatient | 41 | RA, other | 9 (22) | 25 (61) |
| Ponce de Leon *et al.* [37] | Peru | NR | 106 | RA | 45 (44) | 27 (26) |
| (b) High-income countries | | | | | | |
| Bartalesi *et al.* [26] | Italy | Outpatient | 393 | RA, psoriasis, AS, other | 52 (13) | 75 (19) |
| Bocchino *et al.* [28] | Italy | Outpatient | 69 | RA, Crohn's disease/ulcerative colitis, psoriasis | 22 (32) | 18 (26) |
| Kwakernaak *et al.* [32] | The Netherlands | Outpatient | 56 | RA, psoriasis, AS, other | | |
| Matulis *et al.* [36] | Switzerland | Outpatient | 142 | RA, Crohn's disease/ulcerative colitis, psoriasis, AS, other | 17 (12) | 46 (40) |
| Schoepfer *et al.* [38] | Switzerland | Outpatient | 168 | Crohn's disease/ulcerative colitis | 14 (8) | 30 (18) |
| T-SPOT.TB | | | | | | |
| (a) Middle-income countries | | | | | | |
| Marques *et al.* [34] | Brazil | Outpatient | 48 | RA | 12 (25) | 7 (14) |
| (b) High-income countries | | | | | | |
| Behar *et al.* [27] | USA | Outpatient | 179 | RA, psoriasis, other | 9 (5) | 2 (1) |
| Bocchino *et al.* [28] | Italy | Outpatient | 69 | RA, Crohn's disease/ulcerative colitis, psoriasis | 21 (30) | 18 (26) |
| Kleinert *et al.* [31] | Germany | Outpatient | 90 | RA, psoriasis, AS, other | 7 (8) | 10 (11) |
| Laffitte *et al.* [33] | Switzerland | Outpatient | 50 | Psoriasis | 10 (20) | 20 (40) |
| Martin *et al.* [35] | Ireland | Outpatient | 150 | RA, psoriasis, AS, other | 14 (9) | 27 (18) |
| Vassilopoulos *et al.* [39] | Greece | Outpatient | 70 | RA, psoriasis, AS, Crohn's disease/ulcerative colitis, other | 16 (23) | 27 (39) |

AS, ankylosing spondylitis; IGRA, interferon-gamma release assay; IMID, immune-mediated inflammatory disease; NR, not reported; RA, rheumatoid arthritis; TB, tuberculosis.

were no randomized trials comparing the efficacy of screening with TST vs. IGRAs.

Overall, five studies evaluated TSPOT [27,31,33,35,39], four studies evaluated QFT-GIT [26,32,36,38], and one study evaluated both assays [28]. Among the studies comparing TSPOT and TST, the proportion of positive results was significantly higher for TSPOT in one study [27], significantly higher for TST in three studies [33,35,39], and did not significantly differ between tests in two studies [28,31]. TSPOT and TST results were reported to be concordant in between 72 and 93% of individuals. Three studies measured the association between TB risk factors and test results. All the three found that having one or more TB risk factors was significantly associated with having a positive TSPOT, but not TST, result. Results were similar in the five studies that compared QFT-GIT and TST. Three studies found that the proportion of positive results was significantly higher for TST [26,36,38] and two studies found no significant difference between tests [28,32]. QFT-GIT and TST results were reported to be concordant in between 64 and 89% of individuals. The two studies measuring the association between TB risk factors and test results showed conflicting results. The presence of TB risk factors was more strongly associated with having a positive TST in one study [26] and more strongly associated with having a positive QFT-GIT in the other study [36]. Indeterminate IGRA results were infrequent, occurring in less than 5% of individuals with both TSPOT and QFT-GIT.

Results were similar among the subset of studies that evaluated predominantly (i.e. >50%) RA patients [26,27,31,32,35] and among the subset of studies that included only individuals with pre-TNF-α inhibitor therapy [28,31–33,35,39].

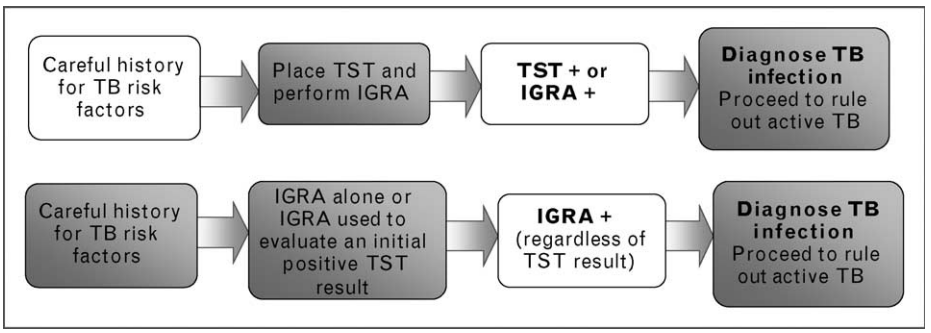
In summary, only a few studies have evaluated performance of IGRAs in IMIDs, and most were small and did not report data separately in patients in major IMID categories. In addition, study populations varied considerably with respect to use of immunosuppressive medications, particularly prednisone. As with HIV infection [16•], current evidence does not clearly suggest that IGRAs are better than TST in identifying individuals with IMID who could benefit from LTBI treatment. To date, no studies have been done on the predictive value of IGRAs in IMID patients and no meta-analysis of existing data for IGRAs in IMID patients has been published. Important questions remain unanswered as to the impact of immunosuppressive medications, both TNF-α inhibitors and others, and the impact of type of IMID on IGRA performance.

## Guidelines on the use of interferon-gamma release assays in immune-mediated inflammatory disorder

Several national and international guidelines are available to guide clinicians in screening individuals with IMID for LTBI [40–43,44•,45•,46–51]. Although all guidelines are consistent in their recommendation to screen individuals with IMID for LTBI prior to initiating TNF-α inhibitors, they differ in their recommendation of screening test [40–43,44•,45•,46–51]. Figure 1 shows the two common strategies, with their potential benefits and drawbacks [3•].

In low TB incidence countries, there is a strong tendency to discourage the use of TST, and prefer IGRAs for

**Figure 1 Two strategies for latent tuberculosis infection screening, their potential benefits and drawbacks**




Strategy one: use both screening tests and accept either positive as indication of LTBI. Benefit: this strategy maximizes sensitivity and is best suited for areas where Bacille Calmette-Guérin (BCG) is not used (e.g. United States/Canada). This strategy recognizes that the relative sensitivities of tuberculin skin test (TST) and interferon-gamma release assay (IGRA) are not well known, and that some patients with LTBI could have positive results to only one of the tests. Drawback: in areas of BCG use, some patients with discordant TST positive/IGRA negative results because of BCG exposure will be wrongly diagnosed with LTBI. This is of most concern in regions of low tuberculosis (TB) prevalence where the predictive value of positive test results for TB is lower. Strategy two: this strategy maximizes specificity and is well suited to the areas of low TB prevalence where BCG use has been prevalent (e.g. Switzerland). Benefit: patients with false-positive TST results because of BCG will be less likely diagnosed with LTBI given the tester's reliance on the IGRA as either an initial or confirmatory screening test. Drawback: like with TST, false-negative IGRAs are also possible and more likely in immunosuppressed inflammatory disease patients. Relying on IGRA alone to determine infection status will miss some truly infected patients who might have otherwise tested positive with TST. Adapted with permission [3•].

screening individuals with IMIDs. For example, German guidelines [40] recommend that IGRAs be used as the first-line test and that TST be used only if IGRA testing is negative and there is strong epidemiologic evidence of prior TB exposure; Swiss guidelines [41,42] recommend only screening with IGRAs; and Polish guidelines [43] recommend IGRA over TST for LTBI screening before TNF-α inhibitor therapy.

In contrast, guidelines or statements from the US Centers for Disease Control and Prevention (CDC) [44•] and the Canadian Tuberculosis Committee [45•] do not explicitly address the choice of LTBI screening test in individuals with IMIDs. However, recommendations for immunocompromising conditions in these guidelines could potentially be extrapolated to IMIDs. The CDC guidelines indicate that the results from both tests (IGRA and TST) may be useful in immunocompromised individuals when the initial test is negative [44•]. Similarly, the 2010 Canadian Tuberculosis Committee guideline recommends starting with TST but performing an IGRA if the TST is negative and there is a strong clinical suspicion for LTBI in immunocompromised individuals [45•]. In the absence of strong evidence, the best strategy remains unclear, and this is reflected in the diversity of recommendations in the various guidelines and position statements (Table 2) [40,42,43,44•,45•,48–52].

## Recommendations and research gaps

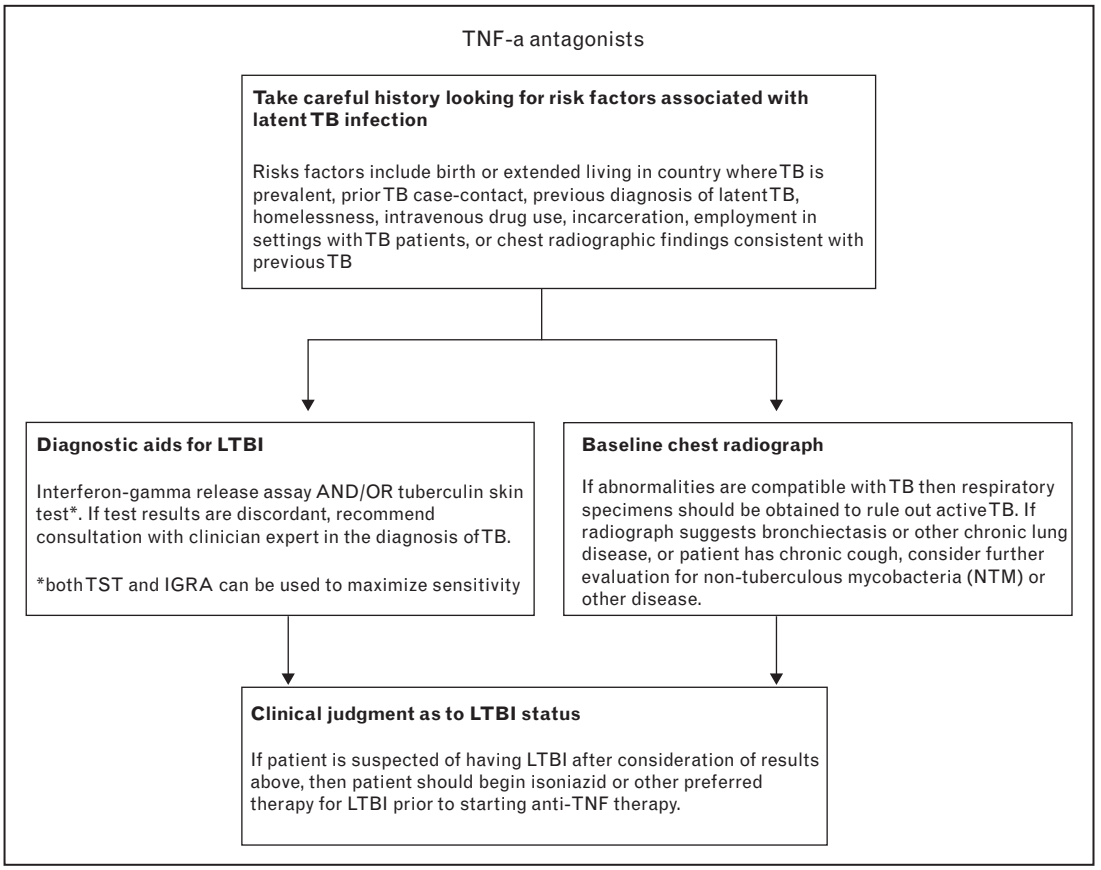
Despite the large number of published studies on IGRAs, there are still critical knowledge gaps on how these tests perform in individuals with IMIDs and the optimal screening strategy is unclear. There are no rigorous studies comparing the two major strategies shown in Fig. 1, including the assessment of cost-effectiveness of various approaches in IMID populations, and how to deal with immunosuppressed individuals who are negative by both tests (TST and IGRA). Furthermore, it is unclear if the strategies outlined in Fig. 1 should differ in high TB burden settings with high background prevalence of LTBI. Predictive value data suggest that to more accurately predict the risk of developing active TB, it may be necessary to identify additional biomarkers, or to develop composite risk prediction models incorporating biomarkers and known clinical risk factors (Fig. 2) [2,52,53].

**Table 2 Summary of major, recent country guidelines for screening in IMID**

| Country/organization | Year | Recommendation for LTBI screening |
|---|---|---|
| Centers for Disease Control (CDC), USA [44•] | 2010 | In general, an IGRA may be used in place of (but not in addition to) a TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *Mycobacterium tuberculosis* infection. Although routine testing with both a TST and an IGRA is not generally recommended, results from both tests might be useful when the initial test (TST or IGRA) is negative, when the risk for infection, the risk for progression, and the risk for a poor outcome are increased (this includes persons who are receiving immunosuppressive therapy such as TNF-α antagonists). |
| Canadian Tuberculosis Committee [45•] | 2010 | In an immunocompromised person (including patients on immunosuppressive medications), the TST should be the initial test used to detect LTBI. If the TST is positive, the person should be considered to have LTBI. However, in light of the known problem with false-negative TST results in immunocompromised populations, a clinician still concerned about the possibility of LTBI in an immunocompromised person with a negative initial TST result may perform an IGRA test. |
| Australian Rheumatology Association [48] | 2010 | Two-step tuberculin skin test (TST) OR interferon gamma release assay (IGRA) before commencing TNF-α inhibitor therapy. |
| UK Health Protection Agency [49] | 2008 | For testing for LTBI in individuals undertaking immunosuppressive therapy with TNF-α inhibitor therapy, IGRA tests may be a suitable alternative to the TST in BCG vaccinated individuals. |
| German Central Committee against Tuberculosis [40] | 2009 | IGRA is recommended before initiation of TNF-α inhibitor therapy. TST is only recommended if IGRA is negative and the patient had a high risk exposure or if IGRA is repeatedly indeterminate. |
| Polish Rheumatology Guidelines [43] | 2008 | IGRA is recommended over TST for LTBI screening before TNF-α inhibitor therapy. |
| Spanish Society of Pulmonology and Thoracic Surgery [50] | 2008 | In general, TST is recommended for LTBI screening, including for those on immunosuppressive therapy. In patients with immunocompromising conditions, an IGRA is recommended if the TST is negative. |
| Kompetenzzentrum Tuberkulos, Switzerland [42] | 2011 | IGRA is recommended prior to the administration of anti-TNF-α therapy. Use of TST is no longer recommended for screening. |
| TBNET consensus statement [51] | 2010 | IGRAs or, as an alternative in individuals without a history of BCG vaccination, tuberculin skin testing is recommended to screen all adult candidates for TNF antagonist treatment for the presence of latent TB infection. |
| Saudi Thoracic Society, Saudi Arabia [52] | 2010 | In general, TST is recommended for LTBI screening. In immunocompromised patients (including patients receiving immunosuppressive therapy), if a false-negative TST result is suspected, IGRAs may be used to rule out LTBI. |

IGRA, interferon-gamma release assay; IMID, immune-mediated inflammatory disease; LTBI, latent tuberculosis infection; TB, tuberculosis; TNF-α, tumor necrosis factor-alpha; TST, tuberculin skin test.

**Figure 2 A proposed approach to tuberculosis screening in individuals administered or scheduled to receive TNF-α antagonists**




Adapted with permission [47].

## Conclusion

Despite the lack of clear evidence, there is an increasing tendency for guidelines to prefer IGRA over TST in IMIDs or to recommend both TST and IGRA to enhance sensitivity. We believe use of either test is acceptable to screen for LTBI. Clinicians could consider starting with IGRAs in individuals with a clear history of BCG vaccination after infancy or with repeated BCG vaccinations. When the index of suspicion for LTBI is high (i.e. history of TB contact, residence or birth in high TB incidence country, or chest radiograph consistent with old TB), both IGRA and TST could be performed, especially prior to initiating TNF-α inhibitor therapy. In this high-risk context, and taking into account pretest probability and a risk–benefit analysis of treatment, if both tests are negative then it may still be reasonable to commence LTBI therapy because both TST and IGRA may be falsely negative in the face of advanced immune-suppression. Thus, regardless of the test used, it is important to remember that IGRAs and TST are only diagnostic aids – they will need to be interpreted with other clinical and risk factor data.

## Acknowledgements

K.L.W. has received research and consultant funds from Oxford Immunotec, UK. K.D. has received consultancy fees and in kind grant support for investigator-led research from both Oxford Immunotec, UK and Cellestis Limited, Australia. The other authors have no financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. A.C. receives support from the National Institutes of Health (K23HL094141). K.D. and M.P. are recipients of funding from Canadian Institutes of Health Research (CIHR), EDCTP (TBNEAT) and European Commission (TBSusgent, EUFP7). K.L.W. receives funding from the Agency for Healthcare Research and Quality (AHRQ 1K08 HS017552–01). None of these funding agencies had any involvement with this publication.

## References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 408).

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