

You can't always get what you want, but if you try sometimes (with two tests—TST and IGRA—for tuberculosis) you get what you need

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There is little disagreement that screening for latent tuberculosis (TB) infection (LTBI) prior to biologic therapy is necessary. Unfortunately, there is much less agreement with regard to how best to accomplish this task. A decade ago, we had just one screening tool, the tuberculin skin test (TST), and screening algorithms for such patients were presumably straightforward. With the recent introduction and fairly widespread adoption of interferon γ release assays (IGRAs), clinicians have a new tool that theoretically improves their ability to screen. However, since the introduction of IGRAs, the studies conducted within the biologic therapy setting that compare IGRAs and TST have been fraught with a lack of statistical power and heterogeneity (eg, differing underlying inflammatory disease states, variable immunosuppressive therapies or underlying BCG status),^{1,2} and firm conclusions regarding the relative sensitivity of these two screening tests (Quantiferon-Gold TB In-tube (QFT-IT) or the T-SPOT.TB assay) is only now becoming more clear. Kleinert *et al* and Mariette *et al* have published two studies to overcome some of these limitations,^{3,4} and along with other data, we believe the time has arrived to offer a screening algorithm that is practical in its approach. While we believe IGRAs have become the preferred screening tool in this setting, unfortunately these recent data argue that an IGRA alone is insufficient to identify all patients at risk.

TB is rumoured to infect nearly a third of the world's population. The risk of LTBI progression to active TB is clearly heightened by antitumour necrosis factor α (anti-TNF) therapy, and the absolute risk of this complication is driven by the background prevalence of LTBI in a particular region and the probability of infection in an individual. Within low prevalence countries, rates of anti-TNF-associated TB are typically 5–10-fold higher than background general populations, with greater relative risks reported from countries of higher TB prevalence.^{5–8} Screening for LTBI with the TST prior to anti-TNF start has been associated with decreasing anti-TNF-associated TB incidence, and in the past several years, data suggest that algorithms using IGRAs can assist in identifying infected patients prior to initiation of therapy.^{9–12} These tests incorporate antigens with high specificity for TB that most importantly do not cross react with *Mycobacterium bovis* strains used in BCG vaccine, and they do no cross react with most clinically relevant non-tuberculous mycobacteria (although with several notable exceptions such as *Mycobacterium marinum*, *Mycobacterium kansasii* and *Mycobacterium szulgai*). Accordingly, these tests are of greater specificity for TB, and in populations where BCG has been used, they categorise more accurately which patients are infected.¹³ Ideally, any optimal screening strategy maximises the number of truly infected persons identified and minimises the number of patients falsely diagnosed with LTBI. However, in immunosuppressive or other high risk settings, we have traditionally (and understandably) favoured sensitivity in screening for LTBI.

To date, understanding the relative merits of TST and IGRAs in the biologic setting has been difficult, primarily due to the heterogeneity of studies and the lack of controlled trials comparing the two.^{1,2} Most studies have been retrospective and

reported results for TST and one or both IGRAs in small numbers of individuals generally without controlling for differences in underlying inflammatory conditions, concomitant non-biologic disease modifying drugs (DMARDs) and steroid regimens, or BCG use, all conditions which potentially and differentially affect the performance of these tests. These studies suggest, similar to other settings where the IGRAs have been evaluated, that IGRAs offer an improvement in specificity for identifying those exposed to TB. Clearly, TST positivity is associated with BCG use, and in populations with high prevalence of BCG vaccination, the IGRA offers a clear-cut advantage.¹⁴ The question of relative sensitivity, however, has been more difficult to ascertain given the lack of a gold standard for LTBI. In most, but not all, studies conducted in immunosuppressed patients lacking BCG use, the percentage of patients with positive IGRA results is slightly higher than those with positive TST results suggesting an edge in sensitivity for the IGRAs.^{1,11,15} It is clear, however, that anergy occurs with both IGRAs and TST. Prednisone likely decreases the sensitivity of both the TST^{4,16–18} and IGRAs^{16,17,19} although some results suggest IGRAs are less suppressed in this way.^{18,20} Other studies suggest current use of anti-TNF therapy can diminish the sensitivity of the IGRAs^{21–23} and likely also the TST.¹⁶ Accordingly, screening algorithms among immunosuppressed individuals that rely upon just one test have an obvious drawback: the potential for false negative results. In fact, when studies have evaluated screening results and subsequent development of TB after anti-TNF start, it is evident that the patients who developed TB after biologic start are frequently those that screened negative at baseline.^{6,15,24} While some of these cases could represent recent infection with *Mycobacterium tuberculosis*, in regions where TB transmission is rare, it is more likely that these cases represent false negative results at baseline.

While we believe the data collected to date suggest IGRAs to be the preferred screening tool in this setting, the data published within this edition of the *Annals* highlight the need for algorithms that do not rely upon a single test. A striking feature of these, and other important recent studies, is that when TST and IGRAs are applied simultaneously within the immune-mediated inflammatory disease setting (IMID), there is little overlap in patients who test positive to either methodology, even among patients who lack a history of BCG.^{3,15} Further, the

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overlap between those that screen positive with the QFT-IT and those with T-SPOT. *TB* is surprisingly low.⁴

Mariette *et al*⁴ reported their experience across France in a population in which prior BCG exposure was frequent. The study was somewhat limited in evaluating the relative merits of TST and IGRAs directly due to a small number of IMID patients from mixed inflammatory disease populations (n=392).⁴ However, the study was unique in that a systematic approach was taken using a dual IGRA screening strategy in which results of the TST were evaluated but ignored in making decisions regarding LTBI therapy. Patients were screened with three tests, TST, T-SPOT.*TB* and QFT-IT, prior to biologic therapy, and only those testing positive with at least one IGRA were offered a rifampin/isoniazid (INH) prophylactic regimen. There are two notable aspects to this study worth further consideration. First, there were a large number of patients with positive TST results (n=50 at a 10 mm cut-point or n=97 using a 5 mm cut-point) who had negative results for both IGRAs, who then underwent TNF blockade without TB prophylaxis, and none of these patients developed TB at least up to 1 year of follow-up. Second, the dual IGRA approach taken by these investigators produced a reasonable proportion of patients with discordant IGRA results. A full third of those testing positive to either assay failed to test positive by both. Had the investigators relied upon just one assay, up to 33 patients would not have been identified for prophylaxis. While it is possible that these patients with discordant IGRA results are those with false positive results, given the high stakes of TNF blockade, we believe the improved sensitivity provided by this approach was likely important in preventing subsequent TB, particularly as TST results were ignored.

Kleinert *et al*³ performed a similar retrospective study of a national cohort in Germany, only this experience involved much larger numbers of patients (n=1529), the majority of who lacked prior BCG exposure.³ Further, unlike the French experience which ignored TST results, these investigators used a dual TST and IGRA strategy that incorporated results of both when making prophylaxis decisions. All patients received a TST and one of the IGRAs, either T-SPOT.*TB* or QFT-Gold (note: the prior generation of the QFT-IT, or 'QFT-Gold', was used, the sensitivity of which is likely less than the current QFT-IT). Disturbingly, they identified a large number (n=27) of patients with TST >15 mm who lacked BCG and

who were IGRA negative. In our minds, it is difficult to ignore such a large TST induration in the presence, or even worse, the absence of a BCG history, and a testing algorithm relying solely upon the IGRA in this instance would have missed such individuals.

Another large study published this year further illustrates the potential pitfalls in relying on a single screening test. Hsia *et al* evaluated QFT-IT and TST within the context of a large clinical development programme for golimumab involving 2282 patients with RA (n=1542), psoriatic arthritis (n=405) or ankylosing spondylitis (n=356) in which approximately 40% of patients were enrolled from regions with medium or high TB prevalence.¹³ Patients received TST and QFT-IT on the same day, and patients testing positive to either TST or QFT-IT (n=317) started INH therapy prior to golimumab treatment. Similar to the studies highlighted above, the TST and QFT-IT identified almost entirely different individuals at risk, even in the absence of the confounding factor of BCG. Among individuals lacking prior BCG vaccination, only 24 (18%) of those testing positive with either TST or QFT-IT tested positive to both tests. In using their dual testing algorithm, none of the 316 patients testing positive on either TST or QFT-IT who started prophylaxis before anti-TNF initiation developed TB during 1 year of follow-up. All five patients who developed TB after starting golimumab in this trial had screened negative at baseline and came from regions of high TB prevalence in Asia or Eastern Europe. (It should be noted that two of these five patients had what we would regard as a positive TST result at 5 and 15 mm, but according to local guidelines that take into account prior BCG use, these results were considered negative and the patients were not treated for latent TB.) These patients who developed TB likely represented a mix of false negative baseline screenings and newly acquired infection after biologic start. The latter situation raises the idea that repeat screening in areas of TB transmission might be worthwhile, and there are some limited data to suggest IGRAs could be used in such fashion,²⁵ although the frequency with which to repeat such screening is far from clear. Last, because of the sizable cohorts and the prospective study design, Hsia *et al* were able to evaluate the influence of underlying inflammatory disease type, low-dose steroid use, BCG use and other factors upon differential TST or QFT-IT results.¹³ Like many of the smaller studies that have come before it within various IMID groups, and like many of the

studies conducted within other immunosuppressive settings, their data suggest superior specificity of the IGRA, and a sensitivity similar to or greater than the TST.^{1 26-28}

While definitive and prospective trials have yet to be done that firmly establish whether the TST or IGRA is 'better' within this setting, any debate is perhaps of little functional consequence. The picture painted from the data collected to date says use them both, particularly when it matters. In regions of moderate or high TB prevalence, or in patients with TB risk factors, we believe a dual testing strategy of TST and IGRA (or even a dual IGRA strategy in regions of BCG use as reported by Mariette *et al*⁴) improves sensitivity and should be pursued. In immunocompetent patients who lack risk factors for TB and live in low incidence regions, we propose using an IGRA alone given its higher specificity and similar or greater sensitivity in detecting LTBI. The theoretical penalty for using only one test to screen patients without risk factors is low, in that very few patients will have underlying LTBI. However, in patients who are immunosuppressed at baseline in whom false negative tests are more likely, it is not unreasonable to still use two tests. This situation is akin to the population-based studies in the low incidence areas of France and Germany discussed above. In some respects, our proposed schema (figure 1) represents a 'one-size' fits all screening approach to the extent that it alleviates the rheumatologist from having to consider a BCG history, which can sometimes be difficult to ascertain. It rightly incorporates the most important issues of a priori probability (ie, background TB risk), and maximises both negative and positive predictive values of a TST or IGRA based screening algorithm. While it is clear that no single strategy will prevent all cases of TB in this setting, we believe the proposed algorithm presents a simple and likely cost-effective approach to TB prevention in this setting. The cost of the IGRAs is variable, generally between \$60 and \$150 depending on region and laboratory, and their increase in cost over TST is limited by the consideration of the healthcare worker time needed to administer and read the TST. Applying a dual testing algorithm sequentially, in that the second test is conducted only if the first test yields negative results, would help mitigate the costs of a dual testing strategy. Our proposed algorithm should be prospectively assessed with the idea that alternative algorithms could be superior for certain individuals or certain populations depending upon their risk and

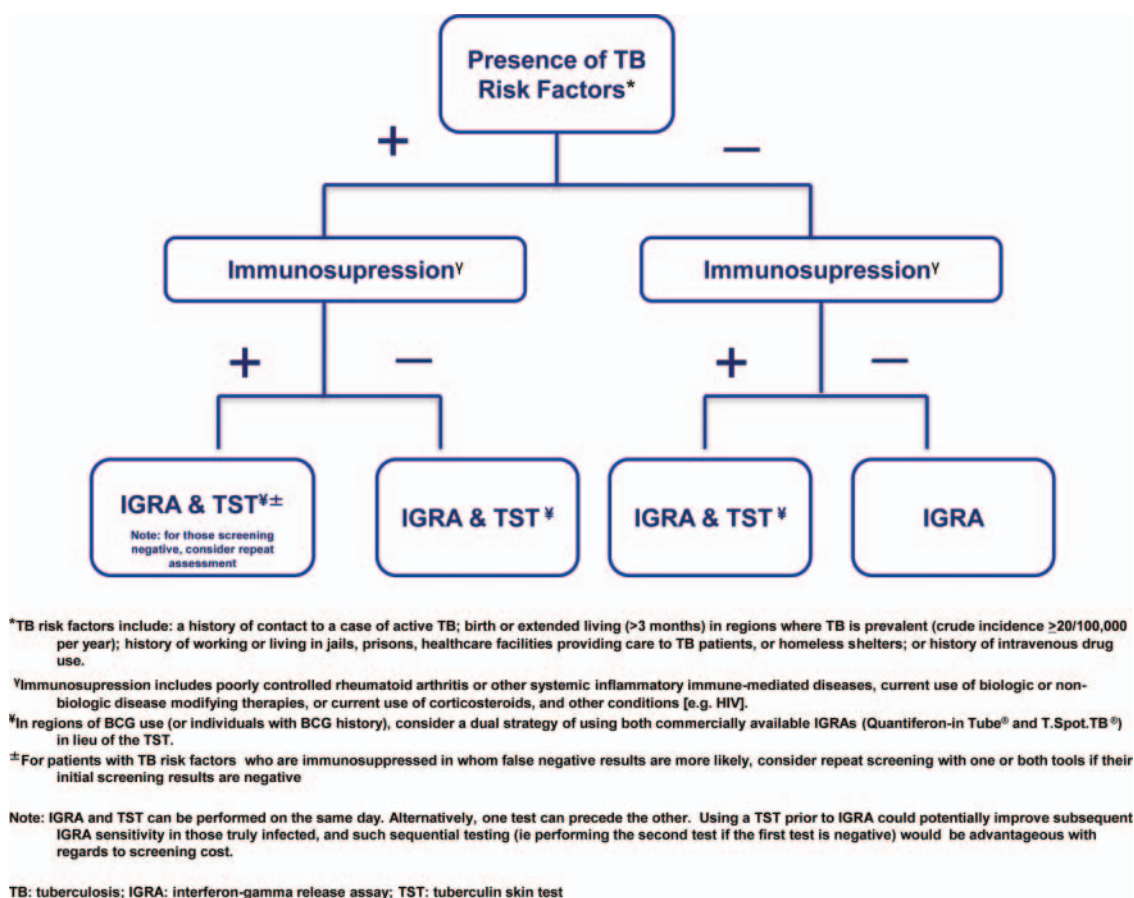


Figure 1

characteristics (eg, dual IGRA strategy in populations with BCG use). While IGRAs have undoubtedly provided benefits to rheumatology patients, we are ultimately in need of new TB diagnostics that can more reliably document persistent infection.

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