Inflammatory bowel disease (IBD) currently represents a substantial economic burden affecting nearly 4 million people worldwide. However, since the emergence of anti-tumor necrosis factor alpha (anti-TNF-α) therapy, patient outcomes have shown improvement facilitating their establishment in IBD management. While these treatments have been shown to improve prognosis, increased utilization and earlier administration of these therapies has led to a growing concern about the risk of opportunistic infections. Of particular concern is the potential reactivation of latent tuberculosis infection (LTBI), which in this clinical scenario often presents in an aggressive and disseminated fashion. Therefore, current guidelines mandate screening of LTBI prior to commencing anti-TNF therapy as early diagnosis can facilitate effective preventative therapy.

The predominant tool for the diagnosis of LTBI has been the tuberculin skin test (TST), which utilizes purified protein derivative (PPD) to elicit a delayed-type T-cell-mediated hypersensitivity reaction. However, the TST has a number of limitations including false positivity due to the nonspecific nature of PPD leading to crossreactivity with nontuberculosis mycobacterium (NTM) and individuals vaccinated with Bacille–Calmette–Guerin (BCG); false positivity due to a boosting phenomenon; subjectivity of reaction size; and the requirement of two healthcare visits to obtain results. Of particular concern to the IBD population is an increased likelihood for false-negative results with impaired cellular immunity, such as in those under immunosuppressive therapy (IST). Recently made commercially available, interferon gamma release assays (IGRAs) have provided an alternative method to diagnose LTBI. IGRAs measure the release...
of interferon-gamma from whole blood (QuantiFERON-TB Gold [QFT-2G] and QuantiFERON-TB Gold In-Tube [QFT-3G]; Cellestis, Carnegie, Australia) or peripheral blood lymphocytes (T-SPOT.TB; Oxford Immunotec, Abingdon, UK) after stimulation by tuberculosis antigens. These tests have garnered support because their results are not prone to a boosting effect, and their antigens are more specific for Mycobacterium tuberculosis. However, IGRAs are not without their drawbacks, such as their higher cost and the need for appropriate infrastructure. Furthermore, they carry the potential for indeterminate results which can impair decision-making, specifically in the immunosuppressed population, where indeterminate results appear to be more frequent.

A number of studies have recently assessed the performance of IGRAs in IBD. However, uncertainty remains regarding the superiority of IGRAs over the TST for diagnosing LTBI in IBD as well as the appropriate timing for screening. While guidelines universally support screening prior to starting anti-TNF therapy, many patients are already receiving IST, which may impact the performance of both tests. Due to these uncertainties, we conducted a systematic review and meta-analysis to assess the utility of IGRAs in the diagnosis of LTBI in patients with IBD.

**MATERIALS AND METHODS**

**Search Methods and Study Selection**

We searched Medline (1948 to June 1st, 2011) and EMBASE (1980 to June 1st, 2011) to identify all studies evaluating IGRAs in IBD with the following strategy: (“Inflammatory bowel diseases [MeSH]” OR “Inflammatory bowel disease” OR “Crohn disease [MeSH]” OR “Ulcerative colitis [MeSH]” OR “IBD” OR “Crohn”*) AND (“Tuberculin [MeSH]” OR “Tubercul in test [MeSH]” OR “TST” OR “Interferon gamma assay” OR “Interferon gamma release assay” OR “IGRA” OR “Quantiferon” OR “Elspot” OR “TSPOT” OR “ESAT6” OR “CFP10”). The authors (N.S. and N.F.) selected these search terms based on previous well-received systematic reviews on LTBI diagnostic tests. Hand searching bibliographies of relevant reviews, guidelines, and included articles was subsequently performed to identify any further studies for inclusion.

Studies (abstracts and/or full-text articles) published in English that assessed the performance of three IGRAs (QFT-2G, QFT-3G, TSPOT.TB) in IBD were included. Studies were excluded if they: 1) were not written in English; 2) evaluated a noncommercial, in-house or older generation IGRA; 3) reported insufficient data on desired outcomes (e.g., no IGRA outcomes); 4) lacked appropriate study design (e.g., assessed TB diagnostic tests to decipher between TB and IBD); 5) had fewer than 10 IBD participants; 6) lacked IBD-specific outcomes; and 7) were review articles or commentaries. Pertinent information was requested from authors if it was felt that this would impact study eligibility. Moreover, further information was obtained from conference abstracts through online sources if available. If there was a suspicion of overlapping study populations, the larger study population was selected for inclusion. If an outcome was quantified exclusively within the smaller study, results were included for the outcome of interest.

**Data Extraction**

Two reviewers (N.S. and N.F.) independently reviewed the amassed citations from the search strategy to identify potential studies for full-text review. Subsequently, articles were independently selected for inclusion and data were extracted utilizing a standardized data extraction form. Disagreement at any stage between the two reviewers was resolved by consensus. If consensus could not be reached, a third reviewer (B.B.) was consulted for a final consensus. Data were extracted for the following variables: year of publication, country of origin, total number of IBD participants, population demographics (including percent BCG vaccinated and percent on immunosuppressive therapy), version of IGRA, timing of IGRA in relation to TST, dose of PPD, TST cutoff, TST results, IGRA results, percent agreement between IGRAs and TST, 2 × 2 table [IGRA+/TST+, IGRA+/TST−, IGRA+/TST−, IGRA−/TST+], predictive estimates of IGRA for active TB, and outcomes assessing the impact of IST on IGRA and TST results. If subanalyses for specific therapeutic regimens concerning the impact of IST on IGRA and TST results were available, these were extracted as well (e.g., double IST [two or more immunosuppressive agents], anti-TNF therapy, steroids, and thiopurines/MTX).

**Outcomes Assessment**

We utilized a hierarchy of outcomes developed for the assessment of IGRAs in human immunodeficiency virus (HIV)-infected individuals as a template to identify primary outcomes relevant for this review. All outcomes were chosen a priori. The only outcome with sufficient data for analysis was the agreement between IGRAs and TST results. We focused our analysis on percent agreement instead of kappa coefficients, as the latter are susceptible to variation due to its dependence on prevalence or the distribution of test results.

To further evaluate the utility of IGRAs in IBD, we assessed the proportion of indeterminate IGRA results and the impact of IST on TST and IGRA results. In particular, the odds ratio (OR) was used as a measure of the impact of IST on the results of the two tests. As the definition of IST varied between studies, subgroups were created for these outcomes to avoid the pooling of conflicting definitions.

**Assessment of Study Quality**

A modified version of the QUADAS quality assessment tool was used to evaluate the quality of included studies. It is a validated tool for the appraisal of diagnostic accuracy studies warranting inclusion in systematic reviews. Modification was warranted due to the lack of a sufficient gold standard in
the diagnosis of LTBI. Each QUADAS item was scored as "yes," "no," or "unclear." Three reviewers (N.S., N.F., B.B.) independently reviewed all QUADAS items for each included study with discrepancies being resolved by consensus.

**Data Synthesis and Meta-analysis**

We extracted all data pertaining to our desired outcomes where available and calculated the outcome’s estimate and 95% confidence interval (CI). If zero events were reported in any outcome, we used the treatment arm continuity correction method to calculate ORs. Forest plots were created first to visually assess heterogeneity between studies and Cochran’s Q test was done to assess heterogeneity across studies. This was followed by I² statistics to characterize the variation due to heterogeneity between studies. Pooled estimates were then obtained using a random effects model if greater than two studies were available in any group/subgroup. If only two or less were available, their outcomes were summarized. For the purpose of pooling outcomes, the QFT-2G and QFT-3G were assumed to be equal. Analyses were conducted using SAS (v. 9.2, Cary, NC) and R (v. 2.12).

**RESULTS**

**Search Results and Study Description**

Of the 301 citations identified from our electronic database search and 14 citations identified from our search of the gray literature, 56 citations were selected for full-text review (Fig. 1). Following full-text review, nine unique studies comprising 1309 IBD participants were included for analysis (Table 1). As one study assessed both QFT-3G and TSPOT.TB, there were 10 unique evaluations (three QFT-2G, five QFT-3G, and two TSPOT.TB). In eight studies TST was also performed in conjunction with IGRAs. Reasons for exclusion were: not written in English, older-generation IGRA, insufficient data, inappropriate study design, lack of IBD-specific data, less than 10 IBD participants, review/commentary, and overlapping.

**TABLE 1. Characteristics of Included Studies**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Country</th>
<th>IGRA</th>
<th># IBD Patients</th>
<th>Mean Age (y)</th>
<th>% Male</th>
<th>% BCG Vaccinated</th>
<th>% IST</th>
</tr>
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<tbody>
<tr>
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<td>QFT-3G, TSPOT.TB</td>
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<td>43</td>
<td>49</td>
<td>NR</td>
<td>85</td>
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<td>QFT-3G</td>
<td>24</td>
<td>31 IST+, 41 IST-</td>
<td>54</td>
<td>100</td>
<td>58</td>
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<tr>
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<td>100</td>
<td>72</td>
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<td>United States</td>
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<td>41</td>
<td>46</td>
<td>NR</td>
<td>40, 58a</td>
</tr>
<tr>
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<td>NR</td>
<td>NR</td>
<td>0.84</td>
<td>88b</td>
</tr>
<tr>
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<td>QFT-3G</td>
<td>93</td>
<td>34c</td>
<td>43</td>
<td>34d</td>
<td>NRc</td>
</tr>
<tr>
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<td>France</td>
<td>QFT-2G</td>
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<td>NR</td>
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<td>NRd</td>
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<tr>
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<td>TSPOT.TB</td>
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<td>34 AF+, 32 AF-c</td>
<td>48</td>
<td>86e</td>
<td>81</td>
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<td>QFT-3G</td>
<td>168</td>
<td>41</td>
<td>49</td>
<td>70</td>
<td>81</td>
</tr>
</tbody>
</table>

Ref.: reference; IGRA, interferon-gamma release assay; IBD, inflammatory bowel disease; BCG, Bacille-Calmette Guerin; IST, immunosuppressive therapy; NR, not reported; AF, Anti-TNF therapy;

a40% of patients were on IS therapy (methotrexate, azathioprine, mercaptopurine, thioguanine, mycophenolate mofetil or lenalidomide), 58% were on anti-TNF therapy;
bThis % value was calculated from Table 1 of Guidi et al’s 2010 poster available through myDDW. http://www.ddw.org/wmspage.cfm?parm1=718;
cMedian value;
d28/83 (34%) had a prior BCG-vaccination. 10 individuals were listed as unknown;
eBreakdown of treatments which patients were receiving was available, however we were unable to calculate the % of patients on IST from the provided data;
f19% of patients were on Anti-TNF therapy, however, an overall estimate of IST was not reported;
g81/94 (86%) had a prior BCG-vaccination. Six individuals were listed as unknown.
The two studies deemed to have inappropriate study design were utilizing TB diagnostic tests to facilitate diagnosis between IBD and TB. Overall, most studies satisfied the majority of QUADAS items included for quality analysis (Table 2). However, there was a high degree of uncertainty for QUADAS items #2 and #4, as many studies did not adequately describe the selection criteria for their study, as well as the timing between TST and IGRA testing.

### Agreement Between IGRA and TST

Six studies\(^35\text{-}39,41\) provided sufficient data to calculate percent agreement between IGRA and TST (6 QFT-2G/QFT-3G and 1 TSPOT.TB) (Fig. 2). Overall, the percent agreement between QFT-2G/QFT-3G and TST was 85% (95% CI 77%–90%) with significant heterogeneity between studies (\(I^2 = 74.5\%), \text{ } P = 0.0015\)). Within the single study that utilized TSPOT.TB,\(^35\) concordance was found in 72% of cases (95% CI 64%–78%). All studies reported a greater proportion of IGRA+/TST+ (range 3.85%–25.00%) results compared to IGRA+/TST− (range 1.28%–6.45%) results.

### Proportion of Indeterminate Results

The percentage of indeterminate results was reported in seven studies\(^35\text{-}38,40,41,43\) for QFT-2G/QFT-3G (Fig. 3). Five percent (95% CI 2%–9%) of all QFT-2G/QFT-3G results were found to be indeterminate. Significant heterogeneity was found between studies (\(I^2 = 83.5\%), \text{ } P < 0.0001\)). Alternatively, two studies reported the percentage of indeterminate results\(^35,42\) for TSPOT.TB with estimates ranging from 3%–5%.

### Impact of IST

Across the four outcomes (agreement, IGRA+ results, IGRA indeterminate results, TST+ results) which we assessed with regard to the effects of IST, seven studies

---

**TABLE 2. QUADAS Quality Assessment Results of Included Studies**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Item #1(^a)</th>
<th>Item #2(^b)</th>
<th>Item #4(^c)</th>
<th>Item #8(^d)</th>
<th>Item #12(^e)</th>
<th>Item #13(^f)</th>
<th>Item #14(^g)</th>
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</thead>
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<td>Yes</td>
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</tbody>
</table>

\(^a\) QUADAS Item #1 - Representative patient sample. Yes = if patients were either ambulatory or inpatients suffering from IBD;  
\(^b\) QUADAS Item #2 - Selection criteria clearly described. Yes = if relevant information provided;  
\(^c\) QUADAS Item #4 - Time between tests acceptable. Yes = if IGRA performed prior to the TST;  
\(^d\) QUADAS Item #8 - Adequate index test description. Yes for all studies unless methods of administration largely deviated from the manufacturer’s recommendations;  
\(^e\) QUADAS Item #12 - Same clinical data available as in practice. Yes for all studies as IGRA results are automated;  
\(^f\) QUADAS Item #13 - Uninterpretable/intermediate results reported. Yes = if authors reported indeterminate results;  
\(^g\) QUADAS Item #14 – Withdrawals explained. Yes = if exclusions after enrolment were explained.

---

**FIGURE 2. Agreement between IGRAs and TST.**
(six QFT-2G/QFT-3G, one TSPOT.TB) provided sufficient data. \(^{36-40,42,43}\) As studies had different definitions of IST, we grouped them accordingly: IST\(^A\) (excluding anti-TNF therapy), IST\(^B\) (including anti-TNF therapy), anti-TNF therapy, steroid therapy, thiopurines/MTX therapy, and double IST. For pooling purposes, we considered IST\(^A\) (excluding anti-TNF therapy) and IST\(^B\) (including anti-TNF therapy) comparable. Qumseya et al (IST\(^C\))\(^{38}\) utilized a definition of IST that allowed patients on anti-TNF therapy to be considered in their No IST group and therefore was not used in pooling estimates with IST\(^A\) and IST\(^B\).

Two studies\(^{36,39}\) provided sufficient data to assess the impact of IST on agreement between QFT-2G/QFT-3G and TST. The results were split. Ministro et al showed the odds of concordance was higher in IST\(^+\) individuals as compared to individuals not on IST (OR 2.44, 95% CI 0.41–14.75; IST\(^+\): Events 11, Total 14; IST\(^-\): Events 6, Total 10), whereas Guidi et al. found the odds of concordance was lower in IST\(^+\) individuals (OR 0.11, 95% CI 0.0001–195.06; IST\(^+\): Events 60, Total 67; IST\(^-\): Events 5, Total 5).

Seven studies were identified\(^{36-40,42,43}\) to assess the impact of IST on IGRA\(^+\) results (Fig. 4). However, only four studies (two IST\(^A\), two IST\(^B\)) were available to

\[
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{Study} & \text{QFT-2G/QFT-3G} & \text{TST}\(^C\) & \text{TSPOT.TB} \\
\hline
\text{QFT-2G/QFT-3G} & & & & \\
\hline
\text{Arias (2011)} & 4 & 164 & 14.4 & 0.02 (0.01, 0.06) & \\
\text{Ministro (2011)} & 0 & 24 & 5.3 & 0.00 (0.00, 0.14) & \\
\text{Papay (2011)} & 30 & 208 & 18.2 & 0.14 (0.10, 0.20) & \\
\text{Qumseya (2011)} & 9 & 340 & 16.7 & 0.03 (0.01, 0.05) & \\
\text{Belard (2011)} & 7 & 93 & 16 & 0.06 (0.03, 0.15) & \\
\text{Del Tedesco (2010)} & 4 & 93 & 14.3 & 0.04 (0.01, 0.11) & \\
\text{Scheepers (2008)} & 5 & 168 & 15.1 & 0.03 (0.01, 0.07) & \\
\text{Pooled Estimate} & 59 & 1090 & 100 & 0.05 (0.02, 0.09) & \\
\hline
\end{array}
\]

**FIGURE 4.** Proportion of IGRA indeterminate results.
calculate pooled estimates. Pooled estimates showed that IST significantly affects QFT-2G/QFT-3G+ results (pooled OR 0.37, 95% CI 0.16–0.87; $P = 0.02$). Thiopurines/MTX and double IST also negatively impacted IGRA+ results; however, their results were nonsignificant. Steroids appeared to have little impact on QFT-3G+ results. Due to the limited number of studies among IST groupings in assessing the relation between IST and IGRA indeterminate results, no pooling was undertaken. Among the four studies36–38,40 that used QFT-2G/QFT-3G, IST appears to have a positive correlation with indeterminate results, albeit in an insignificant manner (Fig. 5). Belard et al.40 who assessed the impact of steroid therapy on IGRA indeterminate results, was the only study with a significant positive correlation. Five studies were used to assess the impact of IST on TST+ results36,37,39,40,43 (Fig. 6). In pooled estimates, IST significantly impaired TST+ results (pooled OR 0.28, 95% CI 0.10–0.80; $P = 0.02$). However, significant heterogeneity

<table>
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<tr>
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<th>IST- Events</th>
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<th>Forest Plot</th>
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</tbody>
</table>

**FIGURE 5.** Impact of IST on indeterminate IGRA results. IST, immunosuppressive therapy; Anti-TNF, anti-TNF therapy; MTX, methotrexate; ISTA definition does not include anti-TNF therapy; ISTB definition does include anti-TNF therapy; ISTC study had patients on anti-TNF therapy within their No IST group, and therefore was not included in our pooled estimate.

<table>
<thead>
<tr>
<th>Study</th>
<th>IST+ Events</th>
<th>Total</th>
<th>IST- Events</th>
<th>Total</th>
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<tr>
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</tbody>
</table>

**FIGURE 6.** Impact of IST on TST+ results. IST, immunosuppressive therapy; Anti-TNF, anti-TNF therapy; MTX, methotrexate; ISTA definition does not include anti-TNF therapy; ISTB definition does include anti-TNF therapy.
was present ($I^2 = 62.6\%, \ P = 0.0457$). Similar trends were seen throughout IST specific subgroups, albeit to a more modest degree.

DISCUSSION

This is the first systematic review and meta-analysis to assess the performance of IGRAs in IBD. It highlights the inability to determine the superiority of the IGRAs or the TST. This may be due to the lack of a gold standard in the diagnosis of LTBI and a lack of important outcomes required to assess test performance. While individuals with IBD are more likely to develop active TB after initiating anti-TNF therapy, most individuals do not. Therefore, the ability of LTBI diagnostic tests to predict which cases are more inclined to progress to active TB dictates their utility. Within our included studies, there was only one case of active TB, therefore limiting our ability to assess the capacity of IGRAs to predict active TB. The lack of these cases also prevented us from measuring sensitivity as current methodology for quantifying sensitivity uses active TB as a substitute marker in the absence of a gold standard. Furthermore, there are currently no randomized trials showcasing the benefit of prophylactic therapy based on IGRA results (+ vs. −).45

Our analysis provides a number of important outcomes. It shows a modest to strong agreement between IGRAs and the TST. However, when agreement was stratified by IST, differing results were seen. This may be partly explained by the discrepancy in BCG vaccination status between the two studies. In a study with a high rate of vaccination, concordance could be dramatically affected in the IST− population. With the introduction of IST, this could suppress both tests, leading to a higher likelihood of agreement. This is in contrast to a population with a low rate of BCG vaccination, where the differing effect of IST between the TST and the IGRAs may increase discordance in the IST+ population. Higher rates of indeterminate results were found in our analysis when compared with a number of studies assessing the performance of IGRAs in more generalized populations. This is possibly due to the higher frequency of IST in our included studies. Most important, our study demonstrates that both the IGRAs and the TST appear to be impaired by IST, with the impact being greater on TST results. These findings are in agreement with a recent meta-analysis assessing the performance of IGRAs in HIV.30

The lack of evidence to clearly support either the IGRAs or the TST helps to explain the discrepancies among current recommendations. Recommendations vary from suggesting either IGRAs or TST as first-line to utilizing both tests to increase detection. The European Crohn’s and Colitis Organization (ECCO) endorses the utilization of TST alongside patient evaluation (including assessing TB risk factors, physical examination, and chest x-ray) for assessment of risk of LTBI in patients with IBD. IGRAs were suggested in BCG-vaccinated individuals. In individuals at high risk of LTBI, ECCO suggests screening prior to other forms of IST, not just anti-TNF therapy. Based on our findings, we feel that either the IGRAs or the TST can be used to screen for LTBI in IBD but one should consider performing these tests when patients are not using any IST. For patients who are BCG-vaccinated, IGRAs may be a more favorable choice, as BCG increases false TST positivity. This is further supported by a recent analysis that showed that among multiple screening strategies, utilizing QFT-2G in BCG-vaccinated individuals is the most cost-effective.

Our study supports the suggestion that individuals, particularly those who are at high risk, who are starting other forms of IST, should be considered for screening prior to initiation of therapy. Both the IGRAs and the TST were shown to be negatively affected by IST. However, because our subanalysis had a limited number of studies, and many associations were nonsignificant, it is difficult at this time to determine before which specific forms of IST should LTBI screening be undertaken.

Our study has a number of limitations. Due to the limited number of full-text studies, we included relevant abstracts. This hindered our ability to thoroughly assess study methodology. The overall limited number of included studies hindered our ability to rigorously assess the affect of specific forms of IST on both IGRAs and the TST. The results of our pooled estimates suffered from heterogeneity. Reasons for heterogeneity between studies could be variation in BCG vaccination status, the percentage of individuals with risk factors for LTBI, possible variation among TST/IGRA test cutoff parameters, and the difference in IST definitions among studies. The difference among studies with regard to IST definitions further impaired our ability to pool studies. Ultimately, this limited the strength of conclusions that could be made. Lastly, this is not a robust review to evaluate the role of the TST in IBD since our focus was on IGRAs.

While studies continue to emerge, we are currently unable to universally recommend either the IGRAs or the TST for diagnosis of LTBI in patients with IBD. The strengths and weaknesses of both the TST (relatively inexpensive, nonspecific nature of PPD, hypersensitivity reactions, subjectivity of reaction size, two healthcare visits required for interpretation) and the IGRAs (not prone to a boosting effect, specific nature of TB antigens utilized, increased cost, and increased laboratory capabilities required) should be weighed to facilitate the selection of LTBI diagnostics tests for regional/national screening programs. Our study shows that both the IGRAs and the TST are negatively affected by IST. Therefore, this should
provide further evidence for committees and policymakers when suggesting screening protocols in IBD. Moreover, this study emphasizes that for individuals on IST, clinicians should not rely solely on either the TST or IGRA for diagnosing LTBI. Further research in this area is needed to devise an effective screening strategy encompassing key factors such as TB risks, IST, and BCG vaccination. Moreover, studies focusing on the sensitivity and the predictive capacity of IGRA for active TB will aid in the decision regarding using them as first-line diagnostic tests for LTBI in IBD.

In conclusion, although we are not able to identify a superior test among current LTBI diagnostic methods, both IGRA and the TST were impaired by IST. Therefore, concerning the effective management of IBD, screening for LTBI prior to commencing patients on IST should be a consideration. Ultimately, regardless of what method is chosen to screen for LTBI, it is imperative that screening be performed in all patients prior to commencing anti-TNF therapy, which currently is not being universally achieved.

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