

# High Rates of Indeterminate TB Tests Among Hospitalized Patients: Can We Optimize Use of Interferon Gamma Release Assays in Tuberculosis?

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## ABSTRACT

In the United States, high concern for iatrogenic reactivation to tuberculosis (TB) disease secondary to prescribed immunosuppression has resulted in increased use of the QuantiFERON-TB Gold In-Tube test (QFT-GIT) to screen for *Mycobacterium tuberculosis* (Mtb) infection. The aim of our study was to determine indications for QFT-GIT testing and risk factors for indeterminate QFT-GIT results. We retrospectively identified patients with QFT-GIT testing over a six-month period in a tertiary care academic health care system and performed a record review. Inpatients were 11 times more likely to have an indeterminate QFT-GIT result than outpatients (95% CI 7.6-16.2). 61.5% inpatient QFT-GITs were ordered during workup of active TB. Providers treating exogenously or endogenously immunosuppressed patients ordered the most QFT-GITs. We highlight the significant limitations of TB screening tests in the inpatient setting and the need to test earlier in those requiring immunosuppressive therapy to avoid indeterminate results.

**KEYWORDS:** IGRA, Tuberculosis Infection, LTBI, Tuberculosis Screening, Tuberculosis Diagnostics

## INTRODUCTION

While case rates of tuberculosis disease (TB) in the United States have decreased to 2.8 per 100,000 population in 2017,<sup>1</sup> there are still an estimated 12.4 million people in the United States living with *Mycobacterium tuberculosis* (Mtb) infection.<sup>2</sup> Evidenced by a positive tuberculin skin test (TST) or interferon gamma release assays (e.g. QuantiFERON-TB Gold In-Tube test, Quiagen; QFT-GIT), 5-10% of untreated Mtb infections may develop into active TB disease.<sup>3</sup> Screening for Mtb infection is now arguably easier with laboratory-based blood tests like the QFT-GIT, which also offer increased specificity for testing Bacille Calmette-Guerin (BCG) vaccinated patients.<sup>3</sup> However, determining who and when to screen still can be confusing.

In 2016, the US Preventive Services Task Force recommended routine Mtb infection screening in people with increased risk, especially former residents of TB-endemic countries and high-risk congregate settings.<sup>3</sup> However, with

increasing use of immunosuppressive agents, such as TNF inhibitors, some healthcare systems have chosen to screen all patients for TB before initiating certain medications, regardless of exposure risk.<sup>4</sup> In immunosuppressed patients, poor immune response can result in indeterminate QFT-GIT results due to low mitogen response.<sup>5</sup> To facilitate interpretation of indeterminate qualitative results, the CDC guidelines recommend reporting both the QFT-GIT's qualitative and quantitative results.<sup>6</sup>

QFT-GIT can be difficult to interpret in clinical care, especially when the results are "indeterminate." This is more common among critically ill patients, inpatients<sup>7</sup> and patients receiving immunosuppressive medications.<sup>8</sup> Additionally, some inpatient providers still use Interferon Gamma Release Assay (IGRA) as an adjunctive test for active TB diagnosis, yet 1 in 4 patients with active TB are estimated to be IGRA negative.<sup>9</sup> The goal of our study was to explore the indications for QFT-GIT testing in our academic medical system and risk factors for indeterminate QFT-GIT results.

## METHODS

Following Lifespan's Institutional Review Board approval, we performed a retrospective review of all patients with QFT-GIT tests ordered from June to August 2015 and from November 2015 to January 2016. These dates were originally chosen for a parent quality improvement project monitoring the transition of the QFT-GIT to in-house laboratory testing, focused on potential interlaboratory and seasonal variability. The Lifespan lab serves three Brown University-affiliated hospitals, onsite outpatient clinics and Lifespan-affiliated practices in Rhode Island. Tests ordered at all sites, including those serving pediatric patients, were included in the study. QFT-GIT was performed by technicians according to the manufacturer's recommendations.<sup>5</sup> For patients with QFT-GIT testing during the study period, demographics and the ordering location were identified using the Lifespan laboratory database.

A subset analysis was then performed on adult inpatients over the age of 18 years. Clinical information of the laboratory-identified adult inpatients was abstracted from the electronic medical record (including inpatient prescription of immunomodulatory medications 14 days after or before the QFT-GIT, diagnoses associated with the hospital stay, TST

during the hospitalization, and HIV status) from Lifespan's Epic data warehouses into an Excel database. Detailed individual chart reviews were not completed for this study and outpatient prescription and pharmacy data was unavailable. ICD-9 diagnosis codes for the hospitalization were reviewed by a physician to determine if the QFT-GIT was ordered for screening or diagnosis. The determination as to whether QFT-GIT was ordered during work-up of active TB disease was made based on indicative diagnosis codes (e.g. Pneumonia, fever, cavitary disease, pericardial effusion). QFT-GIT in patients with ICD-9 diagnostic codes less suggestive of active TB disease (e.g. chest pain/shortness of breath) were not classified as being ordered for diagnosis. If the diagnosis codes for the hospitalization suggested the patient was

a transplant recipient, had a malignancy or an immune-mediated inflammatory disorder, then they were classified as having a diagnosis managed with immunosuppression.

Statistical analyses were performed using JMP Pro software (version 13.2; SAS Institute Inc). Pearson chi-squared and student t test were used to compare baseline characteristics where appropriate (Table 1) and a kappa coefficient was calculated for test concordance.

## RESULTS

A total of 1,817 QFT-GIT tests were performed during the study period. Of these, 221 (12.2%) were inpatient QFT-GIT tests and 1596 (87.8%) were performed outpatient. Among the 182 adult inpatients, 61.5% of tests ordered were on patients with ICD-9 diagnostic codes indicating they were undergoing work up for active TB disease, and 37.4% of QFT-GIT tests were on patients prescribed immunosuppressive drugs at the time of their testing (Table 1).

Comparing indeterminate to determinate test results amongst inpatients (Table 1), a greater proportion with a diagnosis managed with immunosuppression (32% vs 25%,  $p=0.34$ ) or already on immunosuppression at the time of the QFT-GIT (44% vs 34.8%,  $p=0.25$ ) had an indeterminate result, though neither reached statistical significance.

### Agreement Among Repeat Tests

We identified 30 patients with adult inpatient QFT-GITs who also had TST ordered. Of this group, 53.3% (16/30) performed prior to the requesting order for QFT-GIT. Despite concern for potential boosting phenomenon by the TST,<sup>10</sup> there was no discordance between positive QFT-GIT and TST results. However, of inpatients with negative TSTs, 63.2%, (12/19) had indeterminate QFT-GIT results.

Additionally, 11 adult patients had one repeat QFT-GIT during their inpatient stay, one patient had 3 QFT-GIT tests, and another had a repeat QFT-GIT while outpatient. Of the 12 patients with duplicate QFT-GIT tests while inpatient, only 3 had disparate results from the original test (75% concordance, kappa 0.56, SE=0.23). Two patients with negative QFT-GITs had indeterminate results on repeat testing, while one patient initially had an indeterminate result that then resulted as negative on repeat testing. For the one patient with a repeat outpatient QFT-GIT, both tests resulted as negative.

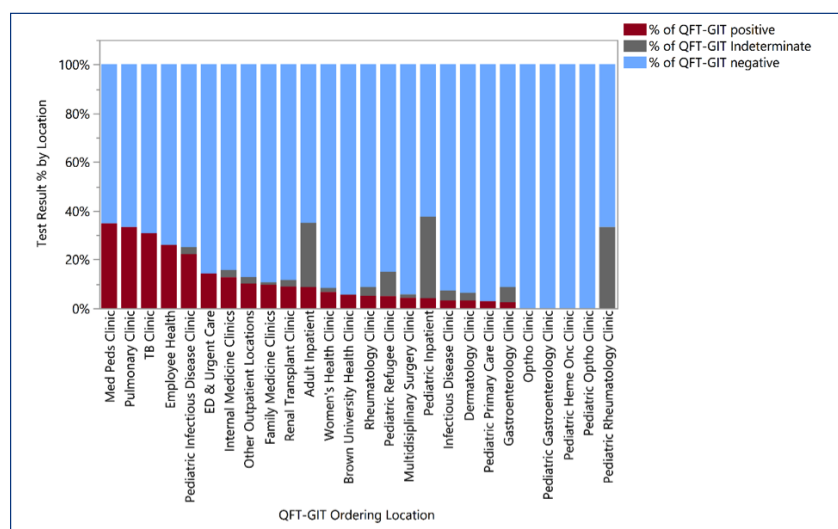
**Table 1.** A comparison of characteristics of adult inpatients who had indeterminate vs determinate QFT-GIT results (n=182).

Characteristics:	Total Inpatient n (%)	Indeterminate n (%)	Determinate n (%)	P value
Total	182	50/182 (27.5)	132/182 (72.5)	
<b>Age</b>				0.20
Over 65 years	45 (24.7)	9 (18.0)	36 (27.3)	
Under 65 years	137 (75.3)	41 (82.0)	96 (72.7)	
<b>Sex</b>				0.24
Male	93 (51.1)	22 (44.0)	71 (53.8)	
Female	89 (48.9)	28 (56.0)	61 (46.2)	
<b>HIV Positive</b>	<b>16 (8.8)</b>	<b>5 (10.0)</b>	<b>11 (8.3)</b>	<b>0.72</b>
QFT-GIT Processing Time (mean days)	3.18	3.04	3.23	0.35
<b>Active TB work up:</b>				<b>0.20</b>
Yes	112 (61.5)	27 (54.0)	85 (64.4)	
No	70 (38.5)	23 (46.0)	47 (35.6)	
<b>Dx managed with immunosuppression:</b>				<b>0.34</b>
Yes	49 (26.9)	16 (32.0)	33 (25.0)	
No	133 (73.1)	34 (68.0)	99 (75.0)	
<b>On immunosuppression prior to QFT-GIT:*</b>				<b>0.25</b>
Yes	68 (37.4)	22 (44.0)	46 (34.8)	
No	114 (62.6)	28 (56.0)	86 (65.2)	
<b>Started on immunosuppression after QFT-GIT:**</b>				<b>0.02</b>
Yes	18 (9.9)	9 (18.0)	9 (6.8)	
No	164 (90.1)	41 (82.0)	123 (93.2)	

\*The inpatient pharmacy record documented administration of immunosuppressive chemotherapy within the 2 weeks prior to QFT-GIT testing.

\*\*The inpatient pharmacy record documented administration of immunosuppressive chemotherapy in the 2 weeks following QFT-GIT testing.

Abbreviations: HIV, human immunodeficiency virus; QFT-GIT, QuantiFERON-TB Gold In-Tube test; TB, tuberculosis; Dx, diagnosis.

**Figure 1.** QuantiFERON-TB Gold in-Tube test results by ordering location

Abbreviations: QFT-GIT, QuantiFERON-TB Gold in-Tube test; Med Peds, medicine-pediatrics; TB, tuberculosis; ED, emergency department; Ophtho, ophthalmology; Heme Onc, hematology-oncology.

### Across the Academic Healthcare System

Pediatric and adult inpatients tested were more likely than outpatients to have indeterminate results (27.1% (60/221) vs 2.4% (39/1596),  $p < 0.01$ ), resulting in a relative risk of 11.11 (95% CI 7.6-16.2). Comparison of QFT-GIT tested inpatients and outpatients on the basis of age (average 48.2 vs 40.8 years old,  $p = 0.28$ ), sex (49.3% vs 44.8% male,  $p = 0.20$ ), ethnicity (18.6% vs 17.4% Hispanic or Latino,  $p = 0.65$ ), and HIV positivity (6.8% vs 6.8%,  $p = 0.98$ ) found no statistically significant differences. Examination of the locations ordering the QFT-GIT revealed that clinics caring for patients with autoimmune diseases were among those with the most frequent orders. Among the ten highest inpatient/outpatient ordering locations, rheumatology clinic accounted for 22.1% of the orders, followed by adult inpatient (15%), the TB clinic (10.7%), internal medicine (10.2%), infectious disease (9.4%), renal transplant (8.6%), family medicine (7.9%), gastroenterology (6.2%), surgery multidisciplinary (5.3%) and women's health (4.6%) clinics. The med-peds, pulmonary, TB, and employee health clinics had the highest percentage of positive QFT-GIT results, while the inpatient locations and clinics caring for immunosuppressed patients, such as infectious disease and rheumatology clinics, had a greater proportion of indeterminate results (**Figure 1**). All indeterminate results regardless of ordering location were due to poor mitogen response.

### DISCUSSION

In keeping with other studies,<sup>7,11</sup> inpatients were 11 times more likely to have an indeterminate QFT-GIT result than outpatients in our cohort. However, we also showed a high proportion of adult inpatient QFT-GITs were ordered for

evaluation of active TB (61.5%). Though limited by our reliance on ICD-9 codes, to our knowledge, this is the first study to explore the indications for QFT-GIT testing in a tertiary care academic medical system in the United States. The second pattern we observed was high provider concern for iatrogenic TB reactivation. In our cohort, this resulted in high utilization of the QFT-GIT amongst providers treating diseases managed with immunosuppression, such as rheumatology and subsequently a higher proportion of indeterminate results from locations caring for immunosuppressed patients (**Figure 1**).

Despite that one in four patients with culture-confirmed pulmonary TB will have negative IGRAs,<sup>9</sup> we observed that a majority of adult inpatient QFT-GITs in our cohort were associated with workup for active TB disease. Education regarding testing

practices for evaluation of TB disease remains necessary, even at a tertiary academic referral center. A negative TST or IGRA result cannot remove active TB from consideration and, as we have shown, almost 30% of inpatient QFT-GITs will result as indeterminate, prompting further workup and may prolong patient airborne-isolation.

Our findings suggest we are entering an era where, risk of progression from *Mtb* infection to TB disease due to immunosuppression rather than epidemiologic risk for *Mtb* infection (formerly known as targeted testing) is driving TB screening patterns. In our hospital system, pharmacy protocols, suggesting TB screening prior to initial TNF alpha antagonist therapy, contributed to 37% of inpatient QFT-GITs drawn on patients already on immunosuppressive therapy. Although differences were not statistically significant, our analysis suggests that such persons may be predisposed to having indeterminate QFT-GIT results. Similarly, a recent study reported 76% of patients receiving the equivalent of 20 mg of prednisone or greater had indeterminate QFT-GIT results, as compared to only 6% in patients receiving less than this amount of steroid ( $P < 0.001$ ).<sup>12</sup> In our study, all indeterminate results, hospital system-wide, were due to insufficient immune response. In addition, we demonstrated moderate strength agreement amongst repeat tests, suggesting that reordering the same test will likely lead to the same result in circumstance where immunosuppression continues. Our work highlights the potential opportunity to avoid indeterminate results by screening for *Mtb* infection in those at risk prior to initiation of any immunosuppression.

Due to our study's retrospective nature and the limited use of our hospital-based EMR by affiliated outpatient providers, our ability to capture all diagnoses and outpatient immunosuppressive medications was restricted. Prior studies show

low albumin,<sup>7,8,11</sup> and lymphopenia<sup>7,8</sup> to be associated with indeterminate QFT-GIT results; however, we were unable to investigate these factors and did not replicate prior associations with older age<sup>13</sup> and female sex.<sup>7,13</sup> Analytical factors contributing to QFT-GIT variability<sup>10</sup> and indeterminate results<sup>7</sup> were similarly not addressed here. As discussed above, if pharmacy protocols contributed to inpatient QFT-GIT ordering, this may reduce generalizability of our results; however, practices within our healthcare system are informed by subspecialty society recommendations<sup>4</sup> and therefore are likely in keeping with national trends.

Though inpatient contacts with healthcare may be a convenient time for Mtb infection screening, providers should be aware of high rates of indeterminate results in this setting. Screening for Mtb infection should be considered at the time of a diagnosis that might require immunosuppression rather than waiting until escalation of immunosuppressive therapy. TB disease is best investigated with tests looking for the organism, such as acid-fast smears, nucleic acid amplification tests and culture, rather than IGRAs like the QFT-GIT. With these lessons around testing, we can optimize testing practices and provide patients and providers with the information needed.

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