High Proportion of Indeterminate QuantiFERON-TB Gold In-Tube Results in an Inpatient Population Is Related to Host Factors and Preanalytical Steps

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Background. QuantiFERON-TB Gold In-Tube test (QFT-GIT) can be used as an alternative to tuberculin skin testing (TST) for the targeted testing of latent tuberculosis. Due to many shortcomings with TST, QFT-GIT usage is increasing. QFT-GIT implementation in the inpatient setting remains unclear.

Methods. We retrospectively identified patients admitted to a tertiary care academic center who received either a TST or a QFT-GIT in the 18 months prior to and after QFT-GIT implementation in March 2012. Risk factors associated with indeterminate results were evaluated.

Results. The proportion of inpatients receiving a test for tuberculosis infection doubled following QFT-GIT implementation (1.4% vs 2.9%). After QFT-GIT became available, 75% of tested people received a QFT-GIT and 25% received a TST. We found indeterminate test results in 19.8%. Independent predictors of indeterminate results were female sex (adjusted odds ratio [AOR], 1.64), lymphopenia (AOR, 2.21), hypoalbuminemia (AOR, 6.81) and sample collection by nonphlebotomists (AOR, 3.0, vs phlebotomists). Of patients who had indeterminate results, 42% had a subsequent indeterminate result on repeat testing. All indeterminate results were due to a low mitogen response.

Conclusions. QFT-GIT testing in the inpatient setting is associated with a high proportion of indeterminate results that is associated with host factors and preanalytical errors. Careful selection of patients to be tested and training on sample processing for QFT-GIT testing should be considered to decrease indeterminate results.

Keywords. IGRA; TB screening; TB diagnostics.

QuantiFERON-TB Gold In-Tube test (QFT-GIT) is an interferon gamma (IFN-γ) release assay (IGRA) that uses an enzyme-linked immunosorbent assay to measure the amount of IFN-γ produced in response to in vitro stimulation of whole blood with specific *Mycobacterium tuberculosis* (MTB) antigens [1]. IGRA and tuberculin skin tests (TSTs) are often utilized in inpatients either for evaluating for latent tuberculosis (TB) infection (LTBI) among high-risk groups, or as an adjunctive test in addition to mycobacterial smears/cultures for diagnosis of active TB. IGRA offer several advantages over TST. The logistical advantage of a single visit is particularly important for the inpatient setting where patients are often discharged from the hospital or transferred off the floor before a TST can be read. Objective output and potential higher specificity in BCG-vaccinated individuals are additional benefits of IGRA [2, 3]. Challenges associated with IGRA include poor reproducibility, variable sensitivity [1], and high rates of indeterminate results in certain groups [4]. Indeterminate results can be due to failure of the positive control tube, with low IFN-γ production in response to phytohemagglutinin or due to failure of the negative control tube, with detection of high IFN-γ levels in the absence of TB antigens [5]. The first scenario has been related to host immunosuppression [4, 6, 7].

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preanalytical steps such as delayed incubation or inadequate shaking [8, 9], and manufacturing defects. Elucidating whether indeterminate results in the inpatient setting result from inadequate processing or from host factors, is important for optimizing implementation of QFT-GIT in this setting. Therefore, the purpose of this study was to (1) examine the proportion of indeterminate results among hospitalized patients, (2) determine factors associated with indeterminate results, and (3) evaluate changes in MTB infection testing before and after QFT-GIT implementation.

MATERIALS AND METHODS

Study Population
At the Johns Hopkins Hospital (JHH), QFT-GIT was made available for use in the inpatient setting in March 2012. We retrospectively collected available data from electronic medical records. We included all patients aged ≥18 years admitted to the hospital during the 18 months preceding QFT-GIT implementation (pre-QFT period, September 1, 2010–February 29, 2012) and 18 months following QFT-GIT implementation (post-QFT period, March 1, 2012–August 31, 2013). Outpatient QFT-GIT testing was excluded. Demographics and hospital ward were collected for all patients. For patients receiving QFT-GIT testing, the following additional clinical information was collected: laboratory data (chemistry panel, lymphocyte count, inflammatory panel and human immunodeficiency virus [HIV] serologies, and HIV RNA), person collecting blood samples for QFT-GIT testing, and time elapsed between sample collection for QFT-GIT testing and sample incubation. Primary outcome was the proportion of patients with an indeterminate test result (patients with multiple QFT-GIT results were classified as indeterminate for primary analysis, if at least 1 result was indeterminate. Secondary outcomes were factors associated with indeterminate results, proportion of patients receiving TST and QFT-GIT before and after QFT-GIT implementation, and proportion of patients undergoing repeat QFT-GIT testing. The study was approved by the JHH Institutional Review Board with a waiver of informed consent.

QFT-GIT Testing Procedures
Upon receiving clinician orders for QFT-GIT testing, either a phlebotomist or a nurse/resident draws blood according to manufacturer instructions into QFT-GIT specimen collection tubes. Usually, phlebotomists collect blood samples for testing at set times whereas nonphlebotomists (resident/nurse practitioner/bedside nurse) collect samples between phlebotomy times. Blood samples are then transported to the laboratory, where they are incubated and then sent to Quest laboratories for further processing. Current phlebotomy, transport, and laboratory procedures aim to begin incubation within 16 hours of sample collection, per manufacturer recommendations. Samples are processed twice daily. Incubation time is 22 hours at 36°C–38°C. During the study period, there was a recall of collection tubes by the manufacturer of the QFT-GIT test (Qiagen) for which 501 patients from 1291 patients meeting criteria were excluded from analysis of QFT-GIT test results. These patients were included in the analysis to estimate proportion of patients receiving TB testing. According to the manufacturer’s guidelines, an indeterminate result due to failure of the positive control tube is considered if mitogen-Nil <0.5 IU/mL.

Statistical Analysis
Statistical analyses were performed using Stata software (version 13.0; StataCorp).

Statistical significance was assumed at P < .05 for all tests. Categorical variables were compared by \( \chi^2 \) test and means of continuous variables by Student t test. Univariate and multivariate logistic regression were performed to estimate the nonadjusted odds ratio (OR) and adjusted OR (AOR) and corresponding 95% confidence interval (CI) of risk factors associated with

| Characteristic | Pre-QFT period | Post-QFT period | P Value |
|---------------|----------------|----------------|---------|
| Inpatients tested, No. | 817 | 1709 | n.s. |
| Age, y, median (IQR) | 51 (39–61) | 52 (40–62) | n.s. |
| Age category, y, No. (%) | | | |
| 18–24 | 69 (8.4) | 103 (6.0) | |
| 25–64 | 592 (72.6) | 1263 (73.9) | |
| ≥65 | 156 (19.0) | 343 (20.1) | |
| Sex, No. (%) | | | |
| Female | 355 (43.4) | 727 (42.6) | n.s. |
| Male | 462 (56.5) | 978 (57.4) | |
| Race, No. (%) | | | |
| Black | 424 (51.9) | 750 (44.4)* | < .01* |
| White | 306 (37.5) | 765 (45.3)* | |
| Hispanic | 71 (8.7) | 56 (3.3)* | |
| Asian | 14 (1.7) | 35 (2.1) | |
| Other/unknown | 2 (0.2) | 83* (4.9)* | |
| Location, No. (%) | | | |
| HIV unit | 162 (19.9) | 157 (9.2)* | < .01* |
| Medicine | 464 (57.0) | 1075 (62.9)* | |
| Surgery | 121 (14.8) | 232 (13.5) | |
| SOT | 5 (0.6) | 71 (4.1)* | |
| Oncology | 31 (3.8) | 116 (6.8)* | |
| Obstetrics | 8 (0.9) | 7 (0.4) | |
| Psychiatry | 24 (2.9) | 34 (1.9) | |
| Pediatrics* | 1 (0.1) | 16 (0.9)* | |

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; n.s., not significant; QFT, QuantiFERON; SOT, solid organ transplant.

* Sixty-nine percent were “other” and 31% were “unknown.”

* P < .01 for individual comparisons of proportions of inpatients tested with tuberculin skin test or QFT–Gold In-Tube between study periods. Oncology includes cancer and bone marrow transplant patients.
indeterminate QFT-GITs. Covariates for multivariate analysis were selected based on clinical importance and statistical significance on univariate analyses.

RESULTS

Study Population
A total of 2526 inpatients were tested for TB during the 36-month period; a third of these individuals (n = 817) were screened during the pre-QFT period with a TST whereas the remaining two-thirds (n = 1709) were screened during the post-QFT period with either a TST or a QFT-GIT. Demographics of tested patients are presented in Table 1. There was no difference in sex or age among tested individuals comparing the 2 study groups. Of all patients tested, more than half were patients admitted to medicine services in both study periods and approximately 15% to surgical services. In the post-QFT period, there was a lower proportion of African Americans and Hispanics and a larger proportion of whites among tested people. The overall number of patients admitted to the hospital between study periods was similar with similar age, sex, and racial characteristics (Supplementary Table 1).

Inpatient TB Testing Before and After QFT-GIT Implementation
In the 18 months preceding QFT-GIT implementation, 1.4% (817/57 077) of hospitalized patients received a TST compared with only 0.7% (433/58 800; \(P < .01\)) during the post-QFT period (Figure 1A). Despite this significant drop in TST use, the overall proportion of patients screened for TB after QFT-GIT became available increased to 2.9% due to additional QFT-GIT testing (433 TST plus 1291 QFT-GIT/58 800). Compared with the pre-QFT period, TB screening in the post-QFT period

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Tuberculosis (TB) testing before and after QuantiFERON-TB Gold In-Tube (QFT-GIT) implementation, for all inpatients (A), and inpatients grouped by sex (B), race (C), and inpatient service (D). n.s. indicates not significant. *Denotes \(P < .05\) for the difference between the proportion of patients receiving QFT-GIT vs tuberculin skin test (TST) in the post-QFT period.
increased for both women and men (Figure 1B) and across all racial groups except for Hispanics (Figure 1C). QFT-GIT out-numbered TST as the TB testing method in all racial groups except for Hispanics (Figure 1C). When examined by inpatient service, TB testing in the post-QFT period increased in the medicine, surgery, oncology, solid organ transplant (SOT), and pediatric wards and remained similar in the psychiatry, obstetrics, and HIV units (Figure 1D). QFT-GIT was preferred as the TB testing method by most units except for pediatrics, psychiatry, and obstetrics where patients were preferentially screened with TST (Figure 1D). Only 20% of patients undergoing QFT-GIT testing had some kind of tissue/specimen sent for mycobacteria culture as part of an evaluation for active TB.

QFT-GIT Results
Among patients with an interpretable result, 6.9% had a positive QFT-GIT whereas 93.1% had a negative QFT-GIT test. Twenty percent of patients had an indeterminate result (Figure 2). All indeterminate cases were associated with optimal negative control tubes but failure of the positive control tube (low mitogen response). Most of blood samples collected for QFT-GIT (69.7%) were obtained by nonphlebotomists. The proportion of indeterminate results was significantly larger among non-phlebotomists (23.9% vs 10% for phlebotomists; \(P < .01\)). Immunocompromised patients (HIV, lymphopenia, malignancy, and SOT or bone marrow transplant recipients) had 25.7% (69/268) indeterminate results compared to 16.6% in non-immunocomprised individuals (87/522; \(P < .01\)). Among nonimmunocomprised individuals, the proportion of indeterminate results by phlebotomist was 6.1% vs 21.4% by nonphlebotomists (\(P < .01\)). A similar trend was observed among immunocompromised patients (18.4% for phlebotomists vs 28.6% for nonphlebotomists; \(P = .08\)). Time elapsed between blood collection and sample incubation was available and analyzed in 26% of patients (205/790). Fifty-nine percent of patients had their samples incubated within 6 hours of blood collection, 36% between 6 and 16 hours, and approximately 5% >16 hours after collection. There was no difference between phlebotomist and nonphlebotomists and delay to incubation (\(P = .63\)). We further analyzed factors associated with an indeterminate QFT-GIT result in multivariate regression and found that hypoalbuminemia (AOR, 6.8 [95% CI, 3.86–12.01]; \(P < .01\)), lymphopenia (AOR, 2.21 [95% CI, 1.05–4.62]; \(P = .03\)), female sex (AOR, 1.64 [95% CI, 1.05–2.55]; \(P = .02\)), and sample collection by staff other than phlebotomist (AOR, 3.0 [95% CI, 1.7–5.3]; \(P < .01\)) were associated with an indeterminate result (Table 2) after adjusting for age, sex, race, albumin level, lymphocyte count, person collecting blood sample, delay to incubation, and hospital unit.

QFT-GIT Repeat Testing
Seventy-six patients (9.6%) had >1 QFT-GIT test performed during the study period, of which 50% had at least 1 indeterminate test result. Among patients with >1 QFT-GIT and an indeterminate result (n = 38), 58% had discordant results (indeterminate/negative), whereas 42% had concordant results (indeterminate/indeterminate) (Figure 2). Among patients with persistent indeterminate results (n = 16), 62% were women, 75% had samples collected by nonphlebotomists, and all of them had lymphopenia. For patients with >1 QFT-GIT and nonindeterminate tests, 92% had concordant results (positive/positive or negative/negative), whereas 3 patients had discordant results (negative/positive). An indeterminate result was the only risk factor associated with repeat QFT-GIT testing (AOR, 5.06 [95% CI, 3.06–8.78]; \(P < .01\)) after adjusting for age, race, sex, hospital ward, and person collecting blood sample (Supplementary Table 2).

DISCUSSION
This is the largest retrospective study assessing QFT-GIT implementation in the inpatient setting of a tertiary care academic center in the United States. We found a high proportion of indeterminate results after QFT-GIT implementation, even in relation to reports from immunocompromised patients [10, 11]. Host factors including hypoalbuminemia and lymphopenia, as well as sample collection for QFT-GIT testing by nonphlebotomists, were associated with indeterminate results. A significant proportion of patients with an indeterminate QFT-GIT had a similar result on repeat testing.

The Centers for Disease Control and Prevention recommends IGRAs for testing persons who are unlikely to return
for TST reading, and for BCG-vaccinated individuals (due to higher diagnostic specificity) for the purpose of detection of MTB infection [2]. LTBI screening most commonly occurs in the outpatient setting, but the hospital could provide additional opportunities to screen high-risk individuals, particularly those without regular access to primary care. At our hospital, 1.4% of adult inpatients were tested for MTB infection with a TST in the 18 months preceding QFT-GIT implementation. The number of tested patients in the 18 months immediately after QFT-GIT was made available more than doubled. Most patients (75%) were tested with QFT-GIT rather than TST. The reasons for the increased testing are unclear given that we did not find a change in patient factors warranting LTBI screening. We found that only a minority of these patients had additional specimens sent for acid-fast bacilli smear or mycobacterial culture as part of an evaluation for active TB; these data may suggest overuse or inappropriate usage of the test.

To date, there is little published literature on QFT-GIT implementation in inpatient settings. A recent pediatric study compared the proportion of indeterminate QFT-GIT’s between 71 outpatients and 112 inpatients and showed that QFT-GIT performed during a hospitalization was more likely to yield an indeterminate result than in the outpatient setting, with a trend toward higher risk for indeterminate results when samples were collected by nurses compared with phlebotomists [12]. By contrast, outpatient public health TB clinics have reported 0.2%–2% indeterminates when implementing QFT-GIT [13, 14]. Preanalytical test steps, such as suboptimal shaking of tubes or delayed incubation can cause suboptimal T-cell response and lead to indeterminate QFT-GIT results [8, 9]. In our cohort, there was a trend toward higher risk of indeterminate results among samples with longer times to incubation, but the association did not reach statistical significance (AOR, 1.74 [95% CI, 0.94–3.24]). However, we found that sample collection by phlebotomists reduced the risk of an indeterminate result by 3-fold compared to collection by nonphlebotomists, even after adjusting for delays in incubation and host factors. One explanation for this finding could be the postcollection steps required with QFT-GIT, including the need for shaking of the tubes. At our institution, phlebotomists undergo periodic training on sample collection for QFT-GIT testing, whereas other staff involved in

| Variable | Indeterminate QFT-GIT, No. (%) | Interpretable QFT-GIT, No. (%) | OR   | 95% CI     | AOR   | 95% CI     | P Value |
|----------|-------------------------------|-------------------------------|------|------------|-------|------------|---------|
| Age <65 y | 123 (19.7)                    | 501 (80.2)                    | Ref. |            |       |            |         |
| Age ≥65 y | 33 (19.8)                     | 133 (80.1)                    | 1.01 | 0.65–1.55  | 0.9   | 0.53–1.73  | .72     |
| Female sex | 76 (23.3)                     | 250 (76.6)                    | 1.46 | 1.03–2.09  | 1.64  | 1.05–2.55  | .02     |
| Race     |                               |                               |      |            |       |            |         |
| White    | 75 (20.6)                     | 289 (79.4)                    | Ref. |            | Ref.  |            |         |
| Black    | 63 (18.3)                     | 281 (81.6)                    | 0.86 | 0.59–1.25  | 0.88  | 0.55–1.41  | .6      |
| Asian    | 4 (26.6)                      | 11 (73.3)                     | 1.4  | 0.43–4.52  | 2.79  | 0.60–12.94 | .19     |
| Hispanic | 3 (30.0)                      | 7 (70.0)                      | 1.65 | 0.41–6.53  | 2.64  | 0.49–14.06 | .25     |
| Phlebotomist | 24 (10.0)                  | 215 (89.9)                    | Ref. |            | Ref.  |            |         |
| Nonphlebotomist | 132 (23.9)   | 419 (76.0)                    | 2.82 | 1.77–4.49  | 3.00  | 1.70–5.30  | <.01    |
| Delay to incubation |            |                               |      |            |       |            |         |
| ≤6 h     | 18 (14.8)                     | 103 (85.1)                    | Ref. |            |       |            |         |
| >6 h     | 20 (23.8)                     | 64 (76.1)                     | 1.78 | 0.87–3.63  | 1.74  | 0.94–3.24  | .07     |
| HIV negative | 4 (30.7)                    | 9 (69.2)                      | Ref. |            |       |            |         |
| HIV positive | 10 (27.7)                   | 26 (72.2)                     | 0.86 | 0.21–3.45  | 0.23  | 0.04–1.38  | .11     |
| Albumin ≥3.5 g/dL | 25 (6.7)                   | 348 (93.3)                    | Ref. |            |       |            |         |
| Albumin <3.5 g/dL | 131 (31.4)                  | 286 (68.6)                    | 6.37 | 4.04–10.05 | 6.81  | 3.86–12.01 | <.01    |
| Inflammationa | 49 (35)                      | 91 (65)                       | 3.30 | 1.38–7.90  | 1.79  | 0.65–4.91  | .25     |
| Lymphocytes 1.1–4.8 K/mm³ | 24 (18.9)                 | 103 (81.1)                    | Ref. |            |       |            |         |
| Lymphocytes <1.1 K/mm³ | 36 (34.3)                 | 69 (65.7)                     | 2.23 | 1.29–4.07  | 2.21  | 1.05–4.62  | .03     |
| Immunocompromised unitb | 37 (22.5)                 | 127 (77.4)                    | 1.14 | 0.68–1.91  | 0.85  | 0.43–1.66  | .64     |

No. indicates number of patients; P values are for multivariate analysis. Bold values represent factors with a statistically significant association with indeterminate results.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; QIT-GIT, QuantIFERON-TB Gold In-Tube; Ref., reference.

a Inflammation includes C-reactive protein (CRP) and ferritin. Reference values for CRP and ferritin are ≤0.5 mg/dL and ≤400 ng/mL, respectively.

b HIV, solid organ transplant, and oncology (hematologic and nonhematologic malignancies including bone marrow transplant recipients).
collecting blood do not receive the same degree of consistent training.

As with prior studies, we found that host factors contribute to indeterminate QFT-GIT results. Consistent with published literature, we found that lymphopenia and hypoalbuminemia were associated with indeterminate results [15, 16]. The association between hypoalbuminemia and indeterminate QFT-GIT is thought to be secondary to abnormal immune responses associated with malnutrition rather than a direct effect of low protein on assay performance [16]. We also found that female sex was associated with indeterminate results; this finding has been reported previously and may be related to intrinsic sex differences in immune response [13, 17–19].

Repeat QFT-GIT testing may be considered when an initial indeterminate result occurs [5]. In our cohort, 25% of patients with an indeterminate result underwent repeat testing. Of those who did, 42% had another indeterminate result. These findings are not surprising given that host factors or hospital test processing errors that may account for indeterminate results among inpatients are not immediately modifiable.

Our study had several limitations attributable to retrospective analyses. Reasons for QFT-GIT testing were not available, and further study is warranted. Nonetheless, we found that increased TB testing occurred immediately after QFT-GIT implementation in the absence of significant changes in patient characteristics between study periods. Between late 2012 and early 2013, there was a national TST shortage that may have contributed to this increased preference for IGRA testing. Nonetheless, our results suggest that the increased IGRA utilization preceded the TST shortage, and persisted despite availability of TST in our inpatient setting. We utilized an existing clinical database, and data on specimen processing steps were not available for all samples. We also could not capture the reasons for phlebotomy test collection vs collection by nonphlebotomists. We cannot exclude the possibility of unmeasured factors including severity of disease that may have impacted the choice of staff for sample collection and influenced test results. Nonetheless, we analyzed data on a large sample of patients and provide unique insights into possible host and health-system factors associated with indeterminate results.

CONCLUSIONS

We found a high proportion of indeterminate results among inpatients. Host factors and preanalytical steps were associated with indeterminate results. QFT-GIT testing requires a significant number of postphlebotomy processing steps that are prone to technical errors. Broader personnel training of individuals tasked with drawing QFT-GIT tests or restricting sample procurement for QFT-GIT to those with consistent training could reduce the high frequency of indeterminate results. Patients with immunosuppression and malnutrition may not be appropriate for QFT-GIT testing in the inpatient setting. Despite the potential advantages of QFT-GIT compared to TST, clinicians and institutions should consider the challenges associated with inpatient QFT-GIT implementation. Future studies are needed to identify best strategies to address modifiable risk factors associated with indeterminate QFT-GITs and cost implication of QFT-GIT use and repeat testing.

Supplementary Material

Supplementary material is available online at Open Forum Infectious Diseases (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

Notes

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Potential conflicts of interests. All authors: No reported conflicts.

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