IGRAs
Clinical Interpretation and Update

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DISCLAIMER
The views expressed in this talk do not represent the views of QIAGEN, maker of QFT and other diagnostics, but rather, one from my previous profession as a US TB Controller, RTMCC TB consultant, and long-time TB Clinician

Agenda
Where we are
Calibrating Expectations – Test accuracy (factors)
Test Interpretation and management – always a doctor’s decision
Scenarios
New QFT publications on key populations
Where we are...

Continuing threats of tuberculin shortages
Massive increase use of IGRAs in the US

Déjà vu
- Providers using QFT, don’t know TB
- Providers don’t know the relationship:
  
  Test accuracy ↔ prevalence of infection or disease

Labs new to LTBI and IGRAs
- Providers want the definitive answer (not indeterminate result!) and mostly, they want a NEGATIVE!
- Unmet incorrect expectations:
  - Rule out test for active TB and all LTBI
  - Monitoring TB treatment
  - Distinguishing between active and latent TB
  - No false positives and false negatives... WHAT's that?

Where we are...

Serial testing: Most settings for mandated screening are now low risk sites for transmission.....even prisons

TEST ALL immunocompromised patients (prebiologic therapy, pre-transplant, HIV, etc):
- Mixed epidemiologic risk thereby affecting accuracy of our test
- Yet the outcome of TB is high if LTBI missed

Now that we have a choice.....

Common Provider Scenarios

1. Unexpected positive results
2. Discordant results
   - TST-positive – IGRA-negative
   - TST-negative – IGRA-positive
   - IGRA-positive – IGRA-negative
3. Indeterminate results – What to do?
2010 IGRA CDC Guidelines

- IGRA can be used in all situations where the skin test is currently being used

**IGRAs preferred:**
- BCG vaccinated persons
- Persons unlikely to return for a TST reading
- Low risk individuals
- TST preferred in children <5yrs
- No preference for serial testing
- When maximum sensitivity needed → acceptable to use both TST and IGRA

- Lab should report quantitative results

CDC/AAP Pediatric Recommendations

**2010 Updated CDC IGRA guideline**

"An IGRA is preferred for testing persons who … BCG."
- A TST is preferred for testing children aged <5 years.”

This represents a conflict for BCG vaccinated children <5 yrs

American Academy of Pediatrics Red Book

2009:
- IGRA may be useful in children who received BCG
- Cannot be recommended routinely < 5 yrs.

2012 - 2015: EVOLVING
- IGRA preferred, TST acceptable: ≥ 5 yrs with BCG or who are unlikely to return for a TST reading
- TST preferred, IGRA acceptable: ≤ 5 yrs of age
When testing for LTBI, some experts will use an IGRA in children 2 to 4 years of age, especially if they have received a BCG vaccine.

“…IGRAs consistently perform well in children 5 and older, and some data support their use for children as young as 3 years”

### Agenda
- Where we are
- Calibrating Expectations – Test accuracy (factors)
- Test interpretation and management - always a doctor’s decision

### Scenarios
- New QFT publications on key populations

## PPV and NPV (LTBI) based on current literature

<table>
<thead>
<tr>
<th>QFT-GIT (sensitivity = 81% *, specificity = 99% **)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTBI prevalence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1%</td>
<td>45%</td>
<td>99.8%</td>
</tr>
<tr>
<td>7%</td>
<td>85.9%</td>
<td>98.6%</td>
</tr>
<tr>
<td>20%</td>
<td>95%</td>
<td>95.4%</td>
</tr>
</tbody>
</table>

Limitation: No “gold standard” for LTBI, sensitivity is based on culture proven TB cases

How infection prevalence affects the accuracy of tests

- High prevalence: ↑ accuracy
- Low prevalence: ↓ accuracy (more false positives)

**Positive predictive value:** proportion with positive test results correctly diagnosed

**Negative predictive value:** proportion of subjects correctly diagnosed as negative

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**Agenda**

- Where we are
- Calibrating Expectations – Test accuracy (Factors)
- Test interpretation and management – always a doctor’s decision
- Scenarios

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**Does this remicade candidate have LTBI? (also on prednisone 20mg QD)**

55 y/o Filipino Female in US for 35 yrs

TST = negative  QFT = negative  asymptomatic

Is LTBI ruled out?
NEVER use a TST or IGRA to:

“Rule out” disease in TB suspects (symptoms, abnormal CXR or physical finding suspicious of TB)

“Rule out” LTBI in immunocompromised individuals in the setting of high exposure and high risk of disease progression (e.g., HIV, children under 5, transplant patients, those on immunosuppressive drugs)

NO TEST CAN REPLACE CLINICAL JUDGMENT!

First general rule for IGRA Interpretation from the CDC 2010 IGRA guidelines (page 12)

“Diagnoses of M. tuberculosis infection and decisions about medical or public health management should not be based on IGRA or TST results alone, but should include consideration of epidemiologic and medical history as well as other clinical information”

*CDC Updated US IGRA Guidelines, MMWR, June 2010, Vol 59, No. RR-6

Agenda

- Where we are
- Calibrating Expectations – Test accuracy (lecture)
- Test interpretation and management – always a doctor’s decision
- Scenarios, discordance, serial testing, and indeterminate results
- New QFT publications on key populations
The worried pediatrician...

2.5 y/o healthy asymptomatic Chinese-born male
• TST = 12 mm
• History of BCG at birth.

He is hyperactive and mom wants to avoid giving unnecessary medication. She successfully convinced the pediatrician to get a QFT.

QFT negative: TB Ag-nil = 0.1 IU/ml
No family history of TB or known contact

Which result should he use? TST or QFT?

IGRA Interpretation from the CDC 2010 guidelines on (page 12)

Persons with discordant test results
“require individualized judgment in assessing the quality and magnitude of each test result…the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs.”

If BCG vaccinated and not at risk of poor outcome:
• Discount TST <15mm as false negative if IGRA negative

Assessing the risk of “poor outcome”

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>110–170 times</td>
</tr>
<tr>
<td>HIV infection</td>
<td>50–110</td>
</tr>
<tr>
<td>Solid Organ Transplant</td>
<td>20–74</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30</td>
</tr>
<tr>
<td>Recent TB infection (≤2 years)</td>
<td>15</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>10–25</td>
</tr>
<tr>
<td>Carcinoma of head and neck</td>
<td>16</td>
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<tr>
<td>Abnormal chest radiograph with upper lobe fibro nodular disease typical of healed TB infection</td>
<td>6–19</td>
</tr>
<tr>
<td>TNF Alpha inhibitor therapy</td>
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</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>4.9</td>
</tr>
<tr>
<td>Children less than 4 years old</td>
<td>2.2–5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2–3</td>
</tr>
<tr>
<td>Smoker (1 pack/day)</td>
<td>2–3</td>
</tr>
<tr>
<td>Normal healthy individual</td>
<td>1</td>
</tr>
</tbody>
</table>

Source: Lobue and Menzies, Respirology 2010
San Francisco TB Control pediatric QFT experience
March 2005 - Dec 2008
First published online: December 15, 2014

N= 1092 children (0-14 y/o) tested with the QFT.
- 78% foreign-born
- 12% contacts of active TB cases
- 56 children < 2 years of age
- 236 ages 2 - 4 years
- Median 5.6 follow-up years (total 5587 person-years of follow-up)
906 QFT neg. children received no chemoprophylaxis, and none have developed active TB

N= 616 compared TST QFT
Sensitivity 85.1% 91.1%
specificity 98.1% 97.9%
Indeterminate n=823 -- 4.2%
% indeterminate not infected -- 91.4%

You are called by the Occupational Health department.....
30 y/o US born Hispanic male surgical technician has a new positive QFT on annual screen. TBAg-Nil= .65
- TST negative in 2012, 2013
- QFT negative in 2011 TBAg-Nil = 0.0
- No TB cases at the surgery center ever
- No travel out of the US within the past year
- No prior medical problems and is HIV negative
- No contact to active TB outside of facility
Risk of infection: High, medium or low?
Unexpected positive? Should you repeat his test? Did the TST boost the QFT response?
IGRA Interpretation from the CDC 2010 guidelines on (page 12)

Testing individuals with low likelihood of infection and progression:
“a single positive IGRA or TST result should not be taken as reliable evidence of M. tuberculosis infection”

1. Reassess likelihood of M.tb infection and disease progression and confirm initial test results
2. Consider repeat testing, with same initial or different test on a case-by-case basis.
3. Assume, without additional testing, that the initial result is a false positive

Serial testing: A comparison

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits required for result</td>
<td>2-4</td>
</tr>
<tr>
<td>Requirement for testing and data management</td>
<td>Trained health staff to place, read, document (manual entry)</td>
</tr>
<tr>
<td>Guidance for unexpected +result</td>
<td>None Experts would usually say &quot;no&quot; to retesting</td>
</tr>
<tr>
<td>U.S. conversion definition for low risk (Indication of &quot;new infection&quot;)</td>
<td>Quantitative increase &quot;stringent criteria&quot;</td>
</tr>
<tr>
<td></td>
<td>Qualitative - &quot;lenient criteria&quot;</td>
</tr>
<tr>
<td></td>
<td>QFT: ≥ 0.35 iu/ml (Ag-nil)</td>
</tr>
</tbody>
</table>

Tools for serial testing: A comparison

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
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</table>

"Using this lenient criterion to define IGRA conversion might produce more conversions than are observed with the more stringent criteria applied to TSTs" -page 11, bullet on "periodic screening"

Alternative definitions for classifying IGRA conversions were explored:

<table>
<thead>
<tr>
<th>QFT cut-off value</th>
<th>Conversion rate</th>
<th>P value vs. TST conversion rate of 0.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.70 IU/ml</td>
<td>53/2263 (2.3%)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>1.0 IU/ml</td>
<td>33/2263 (1.5%)</td>
<td>p=0.09</td>
</tr>
<tr>
<td>Repeat all</td>
<td>25/2263 (1.1%)</td>
<td>p=0.52</td>
</tr>
</tbody>
</table>

"As expected, raising the cut-points and/or requiring a minimum quantitative change reduced the conversion rates. However, the alternative definitions may increase the likelihood that some true infections will be missed."  

Dorman SE et al., AJRCCM 2013

Multi-center longitudinal study on serial testing of low risk HCWs comparing QFT-IT, Tspot and TST

QFT Alternative cut off value conversion rate P value vs. TST conversion rate of 0.5%

<table>
<thead>
<tr>
<th>Cut-off value</th>
<th>Conversion rate</th>
<th>P value</th>
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<tr>
<td>0.9%</td>
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Occ Health testing- Switching to QFT

Components

1. Preplacement testing: → Minimal false positives, less evaluation and treatment

2. Annual testing: → NEW +’s → true converter, variability around cut-point or false positive from low risk testing?

3. Exposure testing: → clear advantages over TST

Management solutions used by experienced Occ Health programs in US

FIRST: Rigorously assess risk!
- If no risk of exposure: RETEST!

OPTIONS:
1. Retest those with lower quantitative values: “retesting zone” (<0.35 - 1.1 IU/mL)
2. Retest all

Dichotomous cut-point not sufficient……..
Negative TST and Prediction of Reversion of QFT-GIT in US Healthcare Workers

Study on reversion among 1094 QFT+ low-risk HCWs from 7 states in the US

Key Findings:
- Reversion rate: 77% (612/1099) with initial Ag-nil <1.16 IU/mL
- If QFT value >1.16 IU/mL reversion rate by TST status as follows:
  - TST+: 6% (8/125)
  - TST-: 59% (33/56)

Significance:
- Suggests retesting of all low-risk QFT positive HCW with prior negative TST results may be advised regardless of initial quantitative result

You are called by the Occupational Health department…..

30 y/o US born Hispanic male surgical technician has a new positive QFT on annual screen, TBAg-Nil = .65
- QFT negative in 2011 TBAg-Nil = 0.0
- TST negative in 2012, 2013
- No TB cases at the surgery center where he works
- No travel out of the US within the past year
- No prior medical problems and is HIV negative
- No contact to active TB outside of facility

Risk of infection: LOW  Unexpected positive?YES
Repeat QFT, negative Which result do you believe?
Did the TST boost the QFT response? Unlikely

IGRA Interpretation from the CDC 2010 guidelines on (page 12)

Persons with discordant test results
“require individualized judgment in assessing the quality and magnitude of each test result…the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs.”

Discount positive result if:
1. Low risk for both infection and progression
2. This will increase detection specificity and decrease unnecessary treatment
Quantitative values: Where you draw the line

Despite mounting data on high rates of IGRA reversion, the clinical implications of reversion events are unclear.

<table>
<thead>
<tr>
<th>Incident TB: QFT converters</th>
<th>1.39 cases/100 person-yrs</th>
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<tbody>
<tr>
<td>Incident TB: QFT reverters</td>
<td>1.47 cases/100 person-yrs</td>
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</table>

8 folder higher than QFT neg (P = 0.011)

- TB incidence among QFT reverters no different than among those whose QFTs remained positive
- Possible Implications: Transient QFT conversion not due or variability around the QFT cut-point, or TB exposure and clearance

In high exposure setting (eg. CONTACT INVESTIGATION), conversions should be taken at face value

Andrews J et al, AJRCCM, Volume 191 Number 5 | March 1 2015, P. 584-595

You are called by the transplant doctor.....

38 y/o US born White Female accountant from Utah is awaiting liver transplant. QFT is indeterminate on pre-transplant screening

- Mitogen 0.4 IU/ml, Nil=0.1, TB Ag=0.2
- CXR- normal
- Repeat QFT: negative
- TST= 10 mm positive
- No travel ever outside of the Utah
- Cause of liver failure: Hep C from transfusion
- No contact to active TB

Should this patient be treated for LTBI?
**Persons with discordant test results**

“require individualized judgment in assessing the quality and magnitude of each test result… the probability of infection, the risk for disease if infected, and the risk for a poor outcome if disease occurs.”

*Use positive result from either if:*
1. If patient is suspected as having active TB
2. Risks for infection, progression, and a poor outcome are increased

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**Assessing the risk of “poor outcome”**

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Source: Lobue and Menzies, Respirology 2010

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**Discordant results — summary**

**Types of results:**

TST+/IGRA-    TST-/IGRA+    IGRA+/IGRA-  

**PRACTICAL APPROACH:**

- **Immunocompromised with exposure risk:** be conservative and use any positive result
- **BCG vaccinated and healthy:** Use IGRA result
- **Low risk:** assume the negative result as more valid
- **Moderate risk:**
  1) investigate exposure and medical risk
  2) Assess risk-benefit of LTBI treatment
  3) Discuss your conclusions and plan with your patient
55 y/o US-born Asian female working at the TB Clinic gets annual QFT for TB. No prior medical problems.

QFT: low mitogen indeterminate
- Nil: 0.01 IU/ml
- TB Ag: 0.00 IU/ml
- Mitogen: 0.4 IU/ml
- All prior TSTs and QFTs negative for past 20 years

REPEAT QFT?
Do CXR first?
Does she need to see her PMD for a work up for immunocompromise?

If QFT repeated, when should it be done?

---

Indeterminate QFT results – what do they mean?
- Biologic causes: inability of the individual to generate IFN-γ response
  - Transient – viral syndrome
  - Chronic (e.g., HIV with low CD4 or on high dose steroids)
- Technical issue: e.g., undershaking, overfilling, time to incubation, not incubated at proper temp,
- Physician may choose to obtain new specimen or perform other appropriate procedures

Indeterminate QFT results are not expected to change upon repeat unless there was an error with technical performance.

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55 y/o US-born Asian female working at the TB Clinic gets annual QFT for TB. No prior medical problems.

QFT: low mitogen indeterminate
- Nil: 0.01 IU/ml
- TB Ag: 0.00 IU/ml
- Mitogen: 0.4 IU/ml

REPEAT QFT: negative (assume technical error)

Do CXR first? not done
Does she need to see her PMD for a work up for immunocompromise? NO
If QFT repeated, when should it be done? Anytime if technical error suspected. Experts often advise waiting 4-6 weeks if biological reason suspected/
Agenda

Where we are

Calibrating Expectations – Test accuracy (factors)

Test interpretation and management – always a doctor’s decision

Scenarios

New QFT publications on key populations

Additional Pediatric Studies using IGRAs

Pediatric: New CDC study

Evaluation of QuantiFERON-TB Gold In-Tube and Tuberculin Skin Tests among Immigrant Children being Screened for Latent Tuberculosis Infection

Pre-entry screening of children age 2-14 from Mexico, Philippines, and Vietnam entering the US

<table>
<thead>
<tr>
<th>N=2520</th>
<th>QFT positive</th>
<th>TST 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>142 (5.6%)</td>
<td>664 (26%)</td>
</tr>
<tr>
<td>Indeterminate rate</td>
<td>13 (0.5%)</td>
<td>1.4% (age 2-5)</td>
</tr>
<tr>
<td>QFT-/TST+</td>
<td>All QFT indeterminates TST negative</td>
<td></td>
</tr>
<tr>
<td>Discordant</td>
<td>553 (83%)</td>
<td>31 (2%)</td>
</tr>
</tbody>
</table>
Key Findings:

- No active TB cases and high discordance (Vietnam 84%, PI 85%)
- Agreement between tests: poor (kappa=0.20)
- QFT+ results more strongly associated with TB exposure
  - Older age (RR TST+, 1.64 vs; RR QFT+, 3.05)
  - TB in at least one immigrating family member (RR TST+, 1.40 vs RR QFT+ 2.24)
- % children at each age who were TST-positive varied greatly by country, but much less with QFT
  (annual risk of +result: TST 1.05-5.98% vs. QFT 0.52--0.72%)

"...findings support the preferential use of QFT over TST for pre-immigration screening of foreign-born children 2 years of age and older"
**2014 Pediatric Metaanalysis on IGRAs**

*Sollai et al. BMC Infectious Diseases 2014, 14(Suppl 1):S6*  
http://www.biomedcentral.com/1471-2334/14/S1/S6

### Sensitivity (High income countries)

<table>
<thead>
<tr>
<th></th>
<th>QFT</th>
<th>T-Spot*</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL cases</td>
<td>79%</td>
<td>67%</td>
<td>78%</td>
</tr>
<tr>
<td>Microbiologically confirmed only</td>
<td>86%</td>
<td>79%</td>
<td>86%</td>
</tr>
</tbody>
</table>

### Specificity (High income countries)

<table>
<thead>
<tr>
<th></th>
<th>QFT</th>
<th>T-Spot</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>97%</td>
<td>98%</td>
<td>92%</td>
</tr>
</tbody>
</table>

*Note: T-Spot positive result based on non-US cut point of 6 spots and used blood <8 hours old.*

**IGRAs are more specific and QFT is as sensitive than TST**

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**IGRAs in predicting TB disease progression**

![Image of LTBI]

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**WHO Pooled Estimates of Predictive Utility of IGRA and TST**

Overall pooled risk ratio (RR) estimate for:

- **TST** - 2.64 (2.04-3.43) -22 studies
- **IGRA** – 8.45 (4.13-17.31) -16 studies

**Head-to-Head Studies**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pooled estimate of TST</th>
<th>I² (p-value)</th>
<th>Pooled estimate of IGRA</th>
<th>I² (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk ratio (8 studies)</td>
<td>2.58 (1.72-3.88)</td>
<td>14% (0.320)</td>
<td>4.94 (1.79-13.65)</td>
<td>72.3% (0.001)</td>
</tr>
<tr>
<td>Incidence RR (3 studies)</td>
<td>2.07 (1.38-3.11)</td>
<td>0% (0.604)</td>
<td>2.40 (1.26-4.60)</td>
<td>41% (0.183)</td>
</tr>
</tbody>
</table>

NEW: Evaluating the effectiveness of QFT-GIT in detecting LTBI and active TB during a TB outbreak in a Taiwanese university.

Li CY et al, Journal of Microbiology, Immunology and Infection (2015) 48, 263e268

Predictive rates for QFT

<table>
<thead>
<tr>
<th>Findings</th>
<th>QFT positivity</th>
<th>TB progression rate (within 1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT positivity</td>
<td>57/159</td>
<td>36%</td>
</tr>
<tr>
<td>TB progression rate (within 1 year)</td>
<td>7/57</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

"QFT-GIT test was extremely useful in accurately identifying infected and uninfected students, permitting rapid intervention and control in outbreak evaluation."

Predictive power of QFT for development of active TB

Matsumoto K et al, Kekkaku Vol 91, No.2:45-48, 2016

2644 close contacts

2268 QFT-negative or equivocal (86.8%)

2072 QFT negative (78.4%)

275 QFT-positive

Preventive treatment

3 active TB (1.1%)

2 developed TB (0.1%)

Not treated

2 developed TB (0.1%)

100 QFT-positive

Not treated

36 developed active TB (36%)

P=0.001

Mean follow: 2 years

7/57 12.3%
There is no gold standard for LTBI (no direct evidence)

LEVELS OF PROOF for test accuracy:

- Efficacy of preventive therapy
- Predictive value for active TB
- Correlation to exposure gradient
- Sensitivity/specificity for active TB
- Concordance with TST

Weakest

Stronger

Matsumoto study provides highest level of proof

QFT and BCG vaccinated populations/migrants

High Discordance Between Pre-US and Post-US Entry Tuberculosis Test Results Among Immigrant Children

- Retrospective review of the follow-up of TST+ children settling in California (2005-2013)
- Cohort age: 2-14 year
- Total: 12,544 immigrant children included: 7786 (62%) evaluated post-entry
  - 5243 (67%) were tested with TST or IGRA
  - 33% not retested

Lowenthal et al, PIDJ, Vol 35:3, P231-236, March 2016
Immigrant arrivers with pre-entry positive TST by Country of origin and date of US entry
California, October 2008–September 2013

Outcomes of domestic evaluation

Domestic follow up of TST positive children: Key findings

• Among those retested with IGRA →75% had negative results
• TST+/QFT- discordance consistent with other studies
• Nearly half had repeat CXRs post entry (almost all normal) →
  • NEEDLESS repeating of CXRs
  • IGRAs would reduce CXRs by 75%

“replacing TST with IGRA or adding IGRA as a second confirmatory test at preimmigration screening sites could reduce the number of unnecessary domestic examinations among immigrant children, diminishing the burden imposed on immigrants and US TB control programs”
Public Health: Largest IGRA study published to date

Oxford Journals June 25, 2014

Estimated prevalence of TB infection among a New York City clinic population using interferon-gamma release assays

Natalie L. Stennis, Lisa Trieu, Shama D. Ahuja, Tiffany G. Harris
New York City Department of Health and Mental Hygiene, Long Island City, New York

- N=69,273 (QFT-G and QFT-IT)
- QFT-IT test of choice for clinic and large contact investigations

Conclusion: Patient characteristics associated with a positive QFT-GIT result were consistent with known TB risk factors. Results suggest that IGRA are reliable tests for TB infection

<table>
<thead>
<tr>
<th>QFT-IT</th>
<th>TST (Historic rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>14%</td>
</tr>
<tr>
<td>negative</td>
<td>83%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>US-born</td>
<td>9%</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>19%</td>
</tr>
</tbody>
</table>

Page 7, New York City Bureau of Tuberculosis Control Annual Report 2014...

QFT... In 2014, BTBC adopted several new initiatives aimed at improving patient care and outcomes. The latest generation QuantiFERON®-TB Gold (QFT) blood-based test for TB infection was adopted by the BTBC as the standard test for TB infection in all settings.
Latent tuberculosis infection in rural China: baseline results of a population based, multicentre, prospective cohort study

- 4 sites in rural China
- Door-to-door survey with questionnaire (aged ≥ 5 years)
- TST, QFT, and digital chest radiography (≥ 15 years)
- 21,022 participants

"...prevalence of latent tuberculosis in China might be overestimated by skin tests compared with interferon-γ release assays"

<table>
<thead>
<tr>
<th>Assay type</th>
<th>(% positive) Age-and-sex-standardized</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>28 (range: 15% to 42%)</td>
</tr>
<tr>
<td>QFT</td>
<td>18 (range: 13–20%)</td>
</tr>
</tbody>
</table>

**2015 Largest prospective IGRA study in the world**

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**LTBI in rural China: baseline results of a population based prospective cohort study**

N=21,022 participants

QFT and pregnancy
**US Pregnancy Study**

**Design:** Prospective TST vs. QFT-GIT comparison study of 140 pregnant and 140 non-pregnant women receiving care at Bellevue Hospital, NYC. 90% with TB risk. 41-46% born in TB endemic country and BCG vaccinated

**RESULTS:**
- QFT was associated with a greater likelihood of TB exposure than TST
- Performance equal in both pregnant and non-pregnant state
- Agreement good between assays: 88% for pregnant patients (kappa=0.452)
- Almost two thirds of TST+ pregnant patients were negative with QFT

**CONCLUSIONS:**
- QFT performed equally well in each trimester of pregnancy compared to non-pregnant women.
- IGRAs are much more specific, at least as sensitive as TST and may be better predictor of disease.

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**Pregnancy Differentially Impacts Performance of Latent Tuberculosis Diagnostics in a High-Burden Setting**
Mathad J et al, PLOS, March 2014 | Volume 9 | Issue 3

**Design:** Cross-sectional study of 401 HIV-negative pregnant women tested with TST and QFT-GIT antepartum (154), delivery (148) and postpartum (99). 60 followed longitudinally

**RESULTS:**
- More positive by QFT: 150 (37%) QFT+ vs. 259 (14%) TST+ (p=0.005)
- Agreement (n=356):
  - Positives: 46 (13%) were concordant positive
  - 91 (25%) were discordant, 79 (22% IGRA+/TST-)
- QFT percent positivity remained stable between antepartum unlike TST
- QFT quantitative values lower at delivery
- Postpartum, both QFT and TST had significantly increased positives (QGIT 31% vs 32% vs 52%, p = 0.01; TST 17% vs 11% vs 25%, P=0.005)

**CONCLUSIONS:**
- Timing and choice of LTBI test during pregnancy impact results
- QGIT was more stable and more closely approximated the LTBI prevalence in India.
- Pregnancy stage clearly affects both tests.

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**TST-QFT comparison among HIV-infected pregnant women**

**Design:** Cross-sectional study of 252 HIV-infected pregnant women tested with TST and QFT-GIT during their 2nd/3rd trimester and at delivery. 50 studied longitudinally

**RESULTS:**
- More positive by QFT: 71 (28%) QFT+ vs. 27 (10%) TST+ (p<0.005)
- Agreement: 75% (kappa = 0.25 fair)
- 20% had IGRA+/TST- discordance during pregnancy and delivery
- Association with known TB contact: QFT > TST (OR 3.6, CI 1.2-11.1, p=0.02)

TB cases: 5/252 (2%) developed TB postpartum within one year
- All positive by QFT
- 3 had IGRA+/TST- results during pregnancy

**CONCLUSIONS:** Choice of assay affects results and IGRA+/TST- discordance may represent higher risk group for active TB postpartum
HIV: European 6-yr follow-up study

Christian Soborg, Morten Ruhwald, Peter H. Andersen and Pernille Ravn

6-year follow-up of 522 HIV-positive individuals screened for Mycobacterium tuberculosis infection in Denmark

- CD4 >200 cells/μL = 90%
- On ARV = 80%

PPV of 7% (two out of 28) and a NPV of 100% (478 out of 478) for developing active TB using the QFT-IT

Number needed to treat with INH to avoid one TB case = 14
Number needed to test to identify one QFT-IT-positive individual = 18.6

QFT-IT: safe test for ruling out risk of TB among immunocompetent HIV-positive

<table>
<thead>
<tr>
<th>QFT N=522</th>
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<tbody>
<tr>
<td>Positive</td>
<td>5% (28)</td>
</tr>
<tr>
<td>Negative</td>
<td>91% (478)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>4% (16)</td>
</tr>
<tr>
<td>Non-Caucasians</td>
<td>13.3% (14/105)</td>
</tr>
<tr>
<td>Caucasians</td>
<td>3.5% (14/401)</td>
</tr>
</tbody>
</table>

Summary

- Although better than TST, IGRA are not panaceas: Doctors must remain doctors and use their clinical assessment
- IGRA interpretation and management is as challenging as the skin test but CDC IGRA management guidance helps
- Interpretation and management of IGRA results requires assessment of
  - risk of infection and population prevalence of LTBI
  - risk of disease progression
  - risk vs. benefit of treatment
- Testing should be focused to maximize accuracy and minimize false-positive results
- New evidence continues to be favorable for QFT in all key populations with excellent NPV and correlation to risk