TB Intensive
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Interferon Gamma Release Assays (IGRA’s)
Lisa Armitige, MD, PhD
October 16, 2013

Lisa Armitige, MD, PhD has the following disclosures to make:

• No conflict of interests

• No relevant financial relationships with any commercial companies pertaining to this educational activity
Interferon-Gamma Release Assays (IGRAs)

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Overview

• Development of interferon-gamma release assays (IGRAs)
• FDA-approved IGRAs
• Current recommended use: CDC guidelines
Development of IGRAs

The Tuberculin Skin Test (TST)

- Where we started......
  100 years ago

- 0.1 ml of 5 TU PPD tuberculin injected intradermally

- Induration in millimeters read 48-72 hours after injection
TST Limitations

- Technical problems in administration and reading
- >1 visit needed
- False-negative responses
  - Anergy (compromised immunity)
  - TST reversion at old age
- Repeated TSTs boost the immune response
  - Need 2-step approach in serial testing
- False positives
  - Nontuberculous mycobacteria (NTM)
  - Bacille Calmette-Guerin vaccination (BCG)

TST vs In-vitro Assays

Underlying Principle of IGRAs

- Expose peripheral blood lymphocytes of person with suspected tuberculosis infection to antigens from *Mycobacterium tuberculosis*

- If person has been infected with *M. tuberculosis*, lymphocytes will respond by producing IFN-\( \gamma \)

- Measure total IFN-\( \gamma \) produced or number of cells that produce IFN-\( \gamma \)

IFN-\( \gamma \) release assays (IGRAs)

[Diagram showing the process of IFN-\( \gamma \) release assays]
### Original QuantiFERON-TB (QFT) versus TST

<table>
<thead>
<tr>
<th></th>
<th>QFT</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 patient visit</td>
<td>2 patient visits</td>
<td></td>
</tr>
<tr>
<td>Measurement of IFN-γ by machine (more objective)</td>
<td>Induration measured by human (more subjective)</td>
<td></td>
</tr>
<tr>
<td>Antigen: PPD</td>
<td>Antigen: PPD</td>
<td></td>
</tr>
</tbody>
</table>

### What is PPD (Purified Protein Derivative)?

- **Old tuberculin**: a sterile solution of a concentrated filtrate of *M. tuberculosis* in culture
- **PPD**: purified protein fraction precipitated from old tuberculin
- **PPD contains many antigens**
  - Some are also found in BCG and NTM
- **IGRA that uses PPD does not address issue of false-positive results related to BCG or NTM cross-reactions**
Antigens Specific to *M. tuberculosis*

Genetic Region of Difference 1 (RD-1)

- Not found in BCG or most NTM
  - NTM exceptions: *M. kansasii*, *M. szulgai*, *M. marinum*

- Codes for 9 proteins

- Two found to produce strong immunologic responses in persons infected with *M. tuberculosis*
  - 10-kDa culture filtrate protein (CFP-10)
  - 6-kDa early-secreted target antigen (ESAT-6)
Antigens for Newer Generation IGRAs

- Negative control or nil (e.g., saline, heparin)

- Positive control or mitogen: non-specific immune response stimulator (e.g., phytohemagglutinin)

- *M. tuberculosis*-specific antigens
  - Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)
  - ESAT-6, CFP-10, TB 7.7 (actually simulated using overlapping peptides)

Antigens for Gamma-Release Assays

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESAT</td>
<td>CFP</td>
</tr>
<tr>
<td>M tuberculosis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>M africanum</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>M bovis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>BCG substrain</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>gothenburg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>moreau</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>tice</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>tokyo</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>danish</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>glaxo</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>montreal</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>pasteur</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

- M abscessus
- M avium
- M branderi
- M cellatum
- M chelonae
- M fortuitum
- M gordonii
- M intracellulare
- M kansasii
- M malmoense
- M marinum
- M avenulense
- M scrofulaceum
- M smegmatis
- M szulgai
- M terrae
- M xenopi
FDA-Approved IGRAs

- **QuantiFERON®-TB (QFT)**
  - FDA approved Nov 2001, but no longer available

- **QuantiFERON®-TB Gold (QFT-G)**
  - FDA approved May 2005, but no longer available

- **QuantiFERON®-TB Gold In-Tube (QFT-GIT)**
  - FDA approved Oct 2007

- **T-Spot®. TB (T-Spot)**
  - FDA approved July 2008
QuantiFERON®-TB Gold In-Tube (QFT-GIT)

Stage 1: Whole Blood Culture in special blood collection tubes
- Collect 1mL of blood in 3 tubes
- Incubate at 37°C for 16-24 hours
- Centrifuge 5 minutes to separate plasma above gel

Stage 2: Measure [IFN-γ] & Interpret
- Collect 50 μL of plasma for ELISA
- Measure [IFN-γ] in ‘Sandwich’ ELISA
- Software calculates results and prints report

*Mtb = ESAT-6 + CFP-10 + TB 7.7

T-Spot.TB (T-Spot)

- Collect blood in CPT tube
- Recover, wash, & count PBMCs
- Aliquot 250,000 PBMCs to 4 wells with anti-IFN-γ
- Add saline, PHA, ESAT-6 or CFP-10 & incubate
- Wash away cells
- Develop & count spots where cells produced IFN-γ
What Result is Considered Positive?

- Depends on the test
- Based on calculation of IFN-γ response to TB antigens relative to IFN-γ response to nil
- Unlike TST, not risk stratified (i.e., there are not multiple cutoffs for different risk groups)
- Still somewhat complicated
  - Mitigated by software that performs calculations

### Interpretation Criteria for the QFT-GIT Test

<table>
<thead>
<tr>
<th>Nil (IU/mL)</th>
<th>TB Antigen minus Nil (IU/mL)</th>
<th>QFT-GIT (IU/mL)</th>
<th>Mitogen</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8.0</td>
<td>≤ 0.35 or &lt; 25% of Nil value</td>
<td>Negative</td>
<td>≥ 5.0</td>
<td><em>M. tuberculosis</em> infection unlikely</td>
</tr>
<tr>
<td>≤ 8.0</td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Positive</td>
<td>ANY</td>
<td><em>M. tuberculosis</em> infection likely</td>
</tr>
<tr>
<td>≥ 8.0</td>
<td>ANY</td>
<td>Indeterminate</td>
<td>ANY</td>
<td>Indeterminate</td>
</tr>
<tr>
<td>≤ 8.0</td>
<td>≤ 0.35 and or &lt; 25% of Nil value</td>
<td>Indeterminate</td>
<td>&lt; 5.0</td>
<td>Indeterminate</td>
</tr>
</tbody>
</table>
**PUBLIC HEALTH LABORATORY, EAST**

**Patient:** PATIENT.TEST QTB3  
**Acct #:** L000000000033

**Specimen:** 0903.PD000003R  
**COMP Collected:** 09/03/05-1240  
**Received:** 09/06/05-1253

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Flag</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH QUANT TB</td>
<td>0.160</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT NIL</td>
<td>0.164</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT ESAT-6</td>
<td>0.203</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT CFP-10</td>
<td>9.256</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT MIT</td>
<td>0.087</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QT ESAT-NIL</td>
<td>0.043</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QT CFP10-NIL</td>
<td>9.094</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT INTERF</td>
<td>NEGATIVE</td>
<td>L</td>
<td>NEGATIVE</td>
</tr>
</tbody>
</table>

**No ESAT-6 or CFP-10 responsiveness detected.**

**M.Tuberculosis infection unlikely, but cannot be excluded especially when:**

1. Any illness is consistent with TB disease.
2. Likelihood of progression to disease (e.g. due to immunosuppression) is increased.

---

**PUBLIC HEALTH LABORATORY, EAST**

**Patient:** PATIENT.TEST QTB1  
**Acct #:** L000000000018

**Specimen:** 0903.PL00001R  
**COMP Collected:** 09/03/05-1220  
**Received:** 09/06/05-1352

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Flag</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH QUANT TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PH QUANT NIL</td>
<td>0.122</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT ESAT-6</td>
<td>2.687</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT CFP-10</td>
<td>2.762</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT MIT</td>
<td>32.660</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QT ESAT-NIL</td>
<td>2.565</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QT CFP10-NIL</td>
<td>2.640</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QT MIT-NIL</td>
<td>32.539</td>
<td></td>
<td>IU/ML</td>
</tr>
<tr>
<td>PH QUANT INTERF</td>
<td>POSITIVE</td>
<td>H</td>
<td>NEGATIVE</td>
</tr>
</tbody>
</table>

**ESAT-6 and/or CFP-10 responsiveness detected.**

**M.Tuberculosis infection likely.**

**Note:** Quantiferon TB Gold is an indirect test for
## QuantiFERON-TB Gold

**TABLE 2. TEST SENSITIVITY AND SPECIFICITY FOR CFP-10 AND ESAT-6 AT VARIOUS CUTOFFS IN WHOLE-BLOOD IFN-γ ASSAY**

<table>
<thead>
<tr>
<th>Cutoff, IFN-γ (IU/ml)</th>
<th>CFP-10 Sensitivity (%)</th>
<th>CFP-10 Specificity (%)</th>
<th>ESAT-6 Sensitivity (%)</th>
<th>ESAT-6 Specificity (%)</th>
<th>CFP-10 and/or ESAT-6 Sensitivity (%)</th>
<th>CFP-10 and/or ESAT-6 Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>92.5</td>
<td>81.4</td>
<td>94.8</td>
<td>94.9</td>
<td>89.4</td>
<td>97.5</td>
</tr>
<tr>
<td>0.10</td>
<td>94.4</td>
<td>77.1</td>
<td>96.2</td>
<td>90.7</td>
<td>92.0</td>
<td>95.8</td>
</tr>
<tr>
<td>0.15</td>
<td>95.8</td>
<td>72.9</td>
<td>97.6</td>
<td>88.1</td>
<td>93.9</td>
<td>93.2</td>
</tr>
<tr>
<td>0.20</td>
<td>96.7</td>
<td>71.2</td>
<td>99.1</td>
<td>86.4</td>
<td>96.2</td>
<td>91.5</td>
</tr>
<tr>
<td>0.25</td>
<td>97.2</td>
<td>67.8</td>
<td>99.1</td>
<td>84.7</td>
<td>96.7</td>
<td>91.5</td>
</tr>
<tr>
<td>0.30</td>
<td>97.7</td>
<td>66.8</td>
<td>99.1</td>
<td>83.1</td>
<td>97.2</td>
<td>89.8</td>
</tr>
<tr>
<td>0.35</td>
<td>98.6</td>
<td>65.3</td>
<td>99.5</td>
<td>83.4</td>
<td>98.1</td>
<td>89.0</td>
</tr>
<tr>
<td>0.40</td>
<td>98.6</td>
<td>61.9</td>
<td>99.5</td>
<td>79.7</td>
<td>98.1</td>
<td>88.1</td>
</tr>
<tr>
<td>0.45</td>
<td>98.6</td>
<td>60.2</td>
<td>100.0</td>
<td>78.8</td>
<td>98.6</td>
<td>86.4</td>
</tr>
<tr>
<td>0.50</td>
<td>99.1</td>
<td>60.2</td>
<td>100.0</td>
<td>75.4</td>
<td>99.1</td>
<td>83.9</td>
</tr>
</tbody>
</table>

Sensitivity was determined on the basis of data from 118 patients with culture-positive tuberculosis, and specificity was determined on the basis of data from 213 low-risk subjects. The chosen cutoff (0.35) is in boldface.

---

**Interpretation Criteria for the T-Spot.TB**

<table>
<thead>
<tr>
<th>Result</th>
<th>Nil*</th>
<th>TB Response</th>
<th>Mitogen++</th>
<th>Interpretation+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>≤ 10 spots</td>
<td>≥ 8 spots</td>
<td>Any</td>
<td>M. tuberculosis infection likely</td>
</tr>
<tr>
<td>Borderline</td>
<td>≤ 10 spots</td>
<td>5, 6, or 7 spots</td>
<td>Any</td>
<td>Uncertain likelihood of M. tuberculosis infection</td>
</tr>
<tr>
<td>Negative</td>
<td>≤ 10 spots</td>
<td>≤ 4 spots</td>
<td>Any</td>
<td>M. tuberculosis infection unlikely</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&gt; 10 ≤ 10 spots</td>
<td>Any</td>
<td>Any</td>
<td>Uncertain likelihood of M. tuberculosis infection</td>
</tr>
</tbody>
</table>
T-Spot. TB

Nil Control
ESAT-6
Panel A
CFP 10
Panel B
Positive Control

Negative Result
Positive Result

Thank you to Marilyn Richardson
Indeterminate and Borderline Results

- **Indeterminate**
  - Negative control result is too high
    - High background production of IFN-γ
  - Positive control result is too low
    - Immunocompromised patients may not respond to mitogen

- **Borderline (T-Spot only)**
  - Falls within borderline zone close to negative/positive cut point

CDC Guidelines
Previous U.S. Guidelines for FDA-Approved IGRAs

2003

Guidelines for Using the QuantiFERON®-TB Test for Diagnosing Latent Mycobacterium tuberculosis Infection

Prepared by
Gerald H. Marais, M.D.
Margaret E. Vitaliano, M.D.
Division of Tuberculosis Elimination
National Center for HIV, STD, and TB Prevention

2005

Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States

Prepared by
Gerald H. Marais, MD, John Jacobs, MD, Phillip Loeb, MD, Michael F. Lukac, MD, Beverly Marshack, PhD, Andrew Vermaas, MD
Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention

Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection — United States, 2010

Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr
Data Reviewed

- Over 150 published articles
- Supplemented by unpublished data presented at August 2008 consultation
- Only published articles used and cited as evidence basis in guidelines

Summary of Data Review and Interpretation
Sensitivity

- No gold standard for latent TB infection
- TB disease used as a surrogate
  - Problematic
- Overall, tests are comparable
  - Trend for increased sensitivity with T-Spot, but limited head-to-head comparison

### Sensitivity Data

<table>
<thead>
<tr>
<th>Pooled data</th>
<th>TST</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT-GIT</td>
<td>NA</td>
<td>82%</td>
<td>NA</td>
</tr>
<tr>
<td>T-Spot</td>
<td>NA</td>
<td>NA</td>
<td>93%</td>
</tr>
<tr>
<td>TST vs QFT-GIT</td>
<td>89%</td>
<td>83%</td>
<td>NA</td>
</tr>
<tr>
<td>TST vs T-Spot</td>
<td>91%</td>
<td>NA</td>
<td>91%</td>
</tr>
<tr>
<td>All 3</td>
<td>95%</td>
<td>84%</td>
<td>91%</td>
</tr>
</tbody>
</table>
Specificity

- No gold standard
- Measured in persons with low or no identifiable risk for *M. tuberculosis* infection
- Variation in population from study to study
- Trend toward increased specificity with QFT-GIT, but head-to-head comparison data lacking
- Limited published specificity data on T.Spot in general

### Specificity Data

<table>
<thead>
<tr>
<th>Pooled data</th>
<th>TST</th>
<th>QFT-GIT</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST vs QFT-GIT</td>
<td>84%</td>
<td>99%</td>
<td>NA</td>
</tr>
<tr>
<td>TST vs T-Spot</td>
<td>86%</td>
<td>NA</td>
<td>88%</td>
</tr>
</tbody>
</table>
Special Situations and Populations

Contact Investigations

- In contacts tested, exposure characteristics associated with increased risk of infection correlate better with IGRAs than TST
  - e.g., duration of exposure to infectious patient, infectiousness of patient

- Particularly true in BCG-vaccinated contacts
Children

- Limited data, especially children < 5 y.o.
- Some studies show increased percentage of indeterminate results
- Blood drawing more difficult in very young children
- More difficult to confirm diagnosis of TB disease in children

Studies in Children

- **TST vs T-spot** (Cruz et al, Pediatrics 2011, 127: e31-38)
  - Active disease (n=31), high risk (n=74), intermediate risk (n=78), low risk (n=74)
  - Sensitivity in disease: 77% TST, 92% T-spot
  - **Conclusion:** T-Spot. TB is comparable to the TST in the diagnosis of TB disease and identification of high-risk children with tuberculosis infection and is more specific than the TST in children who have received the BCG vaccine

- **TST vs QFT-IT vs T-spot** (Detjen et al, CID 2007, 45: 322-8)
  - Children with Mtb, NTM, other infections (n=73)
  - Specificity QFT 100%, T-spot 98%, TST 58% (IGRA agreement 95.6%)
  - **Conclusions:** Both IGRAs showed high diagnostic value in bacteriologically confirmed childhood TB.
Prediction of Future Disease

- Two studies (Germany – close contacts; Austria – HIV-infected persons) suggest QFT-GIT is better than TST at predicting future TB disease
  - Very small number of TB cases (3-6 per study)
  - Confidence intervals overlap between TST and QFT-GIT

- One study from Netherlands found TST with 10 mm cutoff was better than QFT-GIT or T-Spot at predicting TB in immigrant contacts
  - Only 9 cases of TB
  - Not all differences statistically significant

- Study in Gambia showed no difference between Elispot assay (similar to T-Spot) and TST in predicting future TB

Updated Data on Prediction of Disease (Published After Guidelines)

- Contacts study (Germany) update published
  - 1414 contacts, 19 developed TB
  - QFT detected 19/19, 12.9% of QFT+ developed TB
  - TST detected 17/19, 3.1% of TST+ developed TB (5 mm cutoff)

- Study in persons with silicosis using T-Spot (Hong Kong)
  - Percentage who developed TB (N=331)
  - T-Spot+: 7.4%, TST+ (10 mm): 6.4%
  - T-Spot-: 1.9%, TST-: 3.9%
Immunocompromised Patients

- Do not appear to be significant differences in the number of positive QFT-GIT and TST results in HIV infected
- Nevertheless, discordance between QFT-GIT and TST is often high in immunocompromised
- Indeterminate results for QFT-GIT associated with low CD4 count
- Tend to be more positive test results with T-Spot across various immunocompromised populations
- More inconsistency in study results among immunocompromised populations

Interferon-Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection in HIV-Infected Individuals: A Systematic Review and Meta-Analysis

- 37 studies that included 5736 HIV-infected patients
- In 3 longitudinal studies risk of TB was higher in IGRA positive than IGRA negative patients
- In HIV-infected patients with active TB
  - T-SPOT 72% sensitivity (62-81%)
  - QFT-GIT 61% sensitivity (47-75%)
- Neither IGRA was more sensitive than TST in head-to-head competition
- T-SPOT seemed less affected by immunosuppression than QFT-GIT and TST but differences were small
Interferon-c Release Assays for the Diagnosis of Tuberculosis and Tuberculosis Infection in HIV-Infected Adults: A Systematic Review and Meta-Analysis
Miguel Santin, Laura Munoz, David Rigau

- The sensitivity and specificity of either IGRA is suboptimal to use alone for diagnosis of TB
- Risk of TB in HIV-infected individuals with a negative IGRA is low short term
- Low CD4 counts negatively affected performance of QFT-GIT more than T-SPOT
- Sensitivity for T-SPOT 70%, QFT-GIT 65%
- At best, IGRAs will miss 1 in 3 active cases of TB

Periodic Screening (e.g., Healthcare Workers)

- Some studies have shown considerable variation in IFN-\(\gamma\) response with serial testing over time
- Uncertainty about magnitude of change in result that is likely caused by new infection versus expected test variation
- Questionable significance of conversions and reversions when initial test result is near cut point
- Frequency of false-positive conversions may be higher with IGRAs because of less stringent criteria for conversion compared to TST
Cost

- U.S.-based cost effectiveness data are lacking
- Some non-U.S. studies have suggested limiting IGRA testing to persons who are TST + is most cost-effective strategy
  - Analysis highly dependent on prevalence of TB in population
- Cost of IGRA materials is greater than TST materials, but may be offset by labor costs and fewer positive test results with IGRA

Recommendations
CDC Recommendations

- TST or IGRAs should be used as aids in diagnosing infection with *M. tuberculosis*
  - Both the standard qualitative test interpretation and the quantitative assay measurements should be reported

- As with the TST, IGRAs generally should not be used for testing persons who have a low risk of infection and a low risk of disease due to *M. tuberculosis*

CDC Recommendations

- Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and cost effectiveness of testing

- IGRAs may be used in place of (and not in addition to) TST in all situations in which CDC recommends tuberculin skin testing as an aid in diagnosing *M. tuberculosis* infection, with preferences and special considerations as follow

- Despite the indication of a preference, use of the alternative test (IGRA or TST) is considered acceptable medical and public health practice
CDC Recommendations

• Populations/situations in which **IGRAs are preferred**
  – testing persons from groups that historically have poor rates of return for TST reading
  – testing persons who have received BCG (as a vaccine or for cancer therapy)

CDC Recommendations

• Populations/situations in which **TST is preferred**
  – testing children younger than 5 years old
CDC Recommendations

- Populations/situations in which there is no preference between IGRAs and TST
  - testing recent contacts of persons with infectious tuberculosis
  - periodic screening that addresses occupational exposure to TB (e.g., surveillance programs for healthcare workers)

Additional Considerations for Serial Testing

- IGRA advantages include obtaining results in a single visit and no need for two-step testing (IGRAs don’t boost subsequent test results)

- Disadvantages include a potential greater risk of false test conversion
  - IGRA conversion is defined as a change from negative to positive without any consideration of magnitude
  - Using lenient criterion to define conversion might produce more conversions than are observed with the more stringent criteria applied to TSTs
  - Recent published studies appear to validate this concern
U.S. Healthcare Worker Study
(Published After Guidelines)

- 6,530 HCWs screened with QFT-GIT at Univ. of Illinois
- 287 positive by QFT-GIT: 123 prior positive TST, 164 prior negative TST
- 135 of 164 retested within 4 weeks with QFT-GIT and TST
- Only 2 were positive by TST and 66 reverted to negative by QFT-GIT

Gandra et al. Infect Control Hosp Epidemiol 2010; 31(12)

Movement Toward a Change in IGRA Criteria for ‘Positive’


CDC Recommendations

• Routine testing with both TST and an IGRA is not recommended

• Results from both tests may be useful when the initial test is negative if increased sensitivity is desired (considered infected if either test is positive)
  – risk of infection, the risk of progression, and the risk of a poor outcome are increased
  – clinical suspicion of active tuberculosis and confirmation of *M. tuberculosis* infection is desired

CDC Recommendations

• Results from both tests may be useful when the initial test is positive if increased specificity is desired (considered infected only if both tests are positive)
  – additional evidence of infection is required to encourage compliance (such as in foreign-born healthcare workers who believe their positive TST is due to BCG)
  – in healthy persons who have a low risk of both infection and progression
CDC Recommendations

• Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate, borderline, or invalid, and a reason for testing persists

CDC Recommendations

• Each institution and TB control program should evaluate the availability, overall cost effectiveness, and benefits of IGRAs in prioritizing IGRA use in their setting
CDC Recommendations

• A diagnosis of *M. tuberculosis* infection, and the decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results
  – Decisions should not be based on IGRA or TST results alone

• Particularly relevant for managing discordant test results (e.g., TST+/QFT-)

Questions?