Tuberculin Skin Test (TST) and Interferon-gamma Release Assays (IGRA)

April 2018
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Director, Denver Metro TB Program
No Disclosures
Objectives

be able to describe:

1. Who should get tested for TB infection

2. How the TST and IGRAs are done and how to interpret the results

3. What are the pros and cons of using a TST vs. IGRA in different clinical situations
Who should get tested?

1.7 billion infected world-wide

6 -13 million infected in the U.S.
Foreign-born: 9.3%-20.5%
US-born: 0.6%-2.8%
Who should get tested?

Latent Tuberculosis Infection: Screening
Release Date: September 2016

Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade (What's This?)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic adults at increased risk for infection</td>
<td>The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations at increased risk.</td>
<td>B</td>
</tr>
</tbody>
</table>

To read the recommendation statement in JAMA, click here. To read the evidence summary in JAMA, click here.
Who should get tested?

1. **Close contact to infectious (pulmonary) TB**
   - at any time

2. **Lived (born or travelled > 1 month) to a country where TB is common**
   - Anywhere but United States, Canada, Australia, New Zealand, or Western and North Europe

3. **Current or planned immunosuppression**
   - HIV, TNF-alpha blocker, transplant
   - 1 or 2 plus diabetes, chronic renal failure, gastric bypass, head and neck cancer

Adapted from CA risk assessment  https://www.cdph.ca.gov
The Online TST/QFT Interpreter

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of 6 mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPD, or 2 TU RT-23). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Mendes, et al. (2006). For further information see References, or contact dick.mendes@ucalg.ca

Please select the best response for each field:

TST Size: 10-14 mm
QFT Result: Positive

Age: 20
Age at immigration (if person immigrated to a low TB incidence country): 20

Country of birth: India
State/Territory: National Capital Territory of Delhi

BCG status: Vaccinated age < 2 years

Results
Printable version

The likelihood that this is a true positive test (PPV) is: 100%
The annual risk of development of active tuberculosis disease is estimated to be 8.1%.
The cumulative risk of active tuberculosis disease, up to age of 80, is: 6%
Tuberculosis Screening Flowchart

At-risk person

Tuberculin test/IGRA + symptom review

Negative

LTBI treatment not indicated

Positive

Chest x-ray

Normal

Potential candidate for LTBI treatment

Concerning symptoms?

Abnormal

Evaluate for active TB
Audience Response Question

Who first developed the tuberculin skin test for diagnosing TB?

A. Robert Koch  
B. Clemens von Pirquet  
C. Florence Seibert  
D. Stefan Gryzybowski
Tuberculin Skin Test - Important Historical Points

1. 1890 - Robert Koch ("old tuberculin")
2. 1907 - Clemens von Pirquet
3. 1939 - Florence Seibert
4. 1969 - Gryzybowski and Holden
5. 1972 - Division of Biologic Standards
6. 1976 - FDA appointed a Panel on Skin Test Antigens
   - Tubersol (Sanofi Pasteur Limited)
   - Aplisol (JHP Pharmaceuticals LLC)
Purified Protein Derivative (PPD)

1. Mixture of denatured, but soluble proteins and peptides generated through autoclaving in vitro grown *M. tuberculosis* at 100° C for two hours

2. Chemical composition:
   - 93% proteins
   - 1% nucleic acid
   - 6% carbohydrate
   - Proteomic analysis has shown significant overlap between *M. avium* and *M. tuberculosis* PPD
Sensitivity and Specificity of TST in Active TB

Pooled sensitivity: 65%
Range: 31-92%

Pooled specificity: 75%
Range: 48-93%

Sester M, et al. ERJ 2011
## Specificities of Three PPD Preparations

N = 1555 persons at low risk of LTBI in 6 US cities

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive Defined as &gt;10 mm</th>
<th>Positive Defined as ≥15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Positive</td>
<td>Specificity</td>
</tr>
<tr>
<td>PPD-S1</td>
<td>17</td>
<td>98.9</td>
</tr>
<tr>
<td>Aplisol</td>
<td>28</td>
<td>98.2*</td>
</tr>
<tr>
<td>Tubersol</td>
<td>13</td>
<td>99.2*</td>
</tr>
</tbody>
</table>

* P = 0.02

Mean ± SD: Aplisol 3.4 mm ± 4.2 mm vs Tubersol 2.1 ± 3.2 mm

Tuberculin Skin Testing
Mantoux Method

5 TU of PPD

48 to 72 hours

Interpretation depends on person’s risk factors
# Criteria for a Positive TST Reaction

<table>
<thead>
<tr>
<th></th>
<th>≥ 5mm</th>
<th>≥ 10mm</th>
<th>≥ 15mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td></td>
<td>Recent immigrants</td>
<td></td>
</tr>
<tr>
<td>Close Contacts</td>
<td></td>
<td>Children</td>
<td>No risk</td>
</tr>
<tr>
<td>Fibrotic CXR</td>
<td>Residents or employees in congregate settings</td>
<td>Injection drug use</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: TST conversion = an increase of ≥10 mm within a 2-year period
Stability of Reactions and Inter-reader Variability

1. Biologic variation from test to test in the same patient is very small, approximately 1mm.
   - Chaparas et al. ARRD 1985;132:175.

2. Same reader - Standard deviations of 1.3-1.9 mm

3. Different readers - Standard deviations of 2.3-2.5 mm
   - Furcolow et al. ARRD 1967;96:1009.
Interval From Primary Infection to TST Conversion

N = 172

Number with Conversion

Interval in Weeks

0 1 2 3 4 5 6 7 8 9

Menzies D. AJRCCM 1999;159:15
TST Boosting

- Induration (mm)
  - 0
  - 5
  - 10
  - 15
  - 20
  - 25
  - 30
  - 35

- Years
  - 0
  - 5
  - 10
  - 15
  - 20
  - 30
  - 31

- TST
  - Infection
  - TST
  - TST

- Sizes:
  - 14 mm
  - 11 mm
  - 12 mm
Tuberculin Skin Test

1. False negative tests
   - Quality and stability of reagents
   - Poor technique
   - Anergy (common with HIV infection)

2. False positive tests
   - Reader error
   - Presence of cross-reacting antigens
     - Nontuberculous mycobacteria
     - Recent BCG vaccination
Audience Response Question

- 43 y/o female
- Born in Mexico, BCG-vaccinated
- Rheumatoid arthritis on prednisone and methotrexate
- Asymptomatic; 23 mm TST (by report), negative QFT, normal CXR

What would you do?

A. Repeat the TST
B. Repeat the QFT
C. Do a T-SPOT
D. Treat for TB infection
Follow-up - 43y/o with RA

Repeat TST is 27mm

Risk for infection ✔
Risk for progression ✔

Recommended latent TB treatment
• Patient didn’t tolerate INH
• 2 years later, a repeat QFT (+), treated successfully with rifampin
In Vivo and In Vitro Diagnostic Tests

Presentation of mycobacterial antigens

Antigen presenting cell

Memory T-cell

IFN-\(\gamma\)

IL-8, etc.

TNF-\(\alpha\)

IFN-\(\gamma\)

IL-8, etc.

## Species Specificity of ESAT-6 and CFP-10

<table>
<thead>
<tr>
<th>Tuberculosis complex</th>
<th>Antigens</th>
<th>Environmental strains</th>
<th>ESAT</th>
<th>CFP</th>
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<tr>
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<td><strong>ESAT</strong></td>
<td><strong>CFP</strong></td>
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<tr>
<td><strong>M tuberculosis</strong></td>
<td>+</td>
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<tr>
<td><strong>M africanum</strong></td>
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<td><strong>M bovis</strong></td>
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<td>BCG substrain</td>
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<td><strong>ESAT</strong></td>
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<td>M intracellulare</td>
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<td><strong>M kansasii</strong></td>
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<td>M smegmatis</td>
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<td><strong>M szulgai</strong></td>
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<td>+</td>
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<tr>
<td>M terrae</td>
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</tr>
<tr>
<td>M vaccae</td>
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<tr>
<td>M xenopi</td>
<td>-</td>
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</tbody>
</table>
T-SPOT.TB

8 hours

Collect peripheral venous blood → Centrifuge → Plasma, PBMCs, Red cells → Remove PBMCs, wash and count → Add PBMCs and antigens to 4 wells → Pre-coated wells → Incubate overnight → Wash, develop and dry plate → Count the coloured spots in each well

First 24 hours

T-Cell Xtend – 32 hours
QuantiFERON-Gold In Tube

1. Collect 1mL of blood into Nil, Antigen and Mitogen tubes. Shake well. Incubate tubes at 37°C for 16-24 hrs.

2. Centrifuge tubes for 15 minutes.

3. Add conjugate, plasma samples and standards to ELISA. Incubate for 120 minutes at room temperature.

4. Wash and add substrate. Read absorbance after 30 minutes.

5. Software calculates results and prints reports.

3 days

8 weeks at 2 - 8 °C
QuantiFERON-Gold Plus

Step 1. Blood Collection
Step 2. Mixing of tubes
Step 3. Incubation
Step 4. ELISA
Step 5. Calculation of results

APC

MHC I

MHC II

TB-specific antigens
- Long TB peptides
- Short TB peptides

CD8+

CD4+

Patient T cells in whole blood

IFN-γ release for laboratory quantification
QFT-TB Gold Plus

- Goal - Improved Sensitivity
- CD4 and CD8 tubes

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>QFT-Plus result</th>
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<tr>
<td></td>
<td>Indeterminate</td>
<td>Negative</td>
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<tr>
<td>Low-risk controls</td>
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<td>Active TB</td>
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<td>3</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Male</td>
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<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>2</td>
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<tr>
<td>Smear</td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>65</td>
<td>1</td>
</tr>
<tr>
<td>Positive</td>
<td>54</td>
<td>2</td>
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<tr>
<td>Localisation</td>
<td></td>
<td></td>
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<tr>
<td>PTB</td>
<td>79</td>
<td>3</td>
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<tr>
<td>EPTB</td>
<td>40</td>
<td>0</td>
</tr>
</tbody>
</table>

Barcellini, Eur Resp J Feb 11, 2016
QFT-plus for Active TB

1. Italy
   - 88% (Eur Resp J 2016)

2. Japan
   - 91% (Sci Rep. 2016 Jul 29)
   - 98.9% (J Infect Chemother. 2017 Nov 3)

3. Zambia
   - 83% (Int J Tuberc Lung Dis. 2017 Jun 1)
IGRAs – Basic similarities

- Single blood draw
- Incubate blood cells with antigens from the region of difference 1 (RD1)
  - not contained in BCG but present in *M. bovis*
  - Antigens present in *M. marinum, kansasii, szulgai, and flavescens*
- Results available in 1 day
QFT and T-SPOT Results

### QFT
- Positive (≥ 0.35 IU/mL)
- Negative (< 0.35 IU/mL)
- Indeterminate
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation

### T-SPOT
- Positive (≥ 8 spots)
- Negative (≤ 4 spots)
- Borderline (5-7 spots)
- Invalid
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation
Indeterminate QFT

- Retrospective review; public chest clinics in NYC
- 28,864 tested → 522 (2%) indeterminate
  - 264 low mitogen (assoc. with age < 10, females, Asian, U.S. born)
  - 258 high nil (assoc. with foreign-born and Hispanic)

- Repeat test with a valid result (pos/neg) in 68%

Banach, IJTLD 2011; 15(12): 1623
BCG-vaccine and IGRAs

- Numerous studies and meta-analyses of the performance of QFT-GIT and T-SPOT
- (+) TSTs associated with prior BCG vaccination regardless of TB exposure
- No association with BCG and (+) IGRA
Audience Response Question

20 y/o college student from India

- 11 mm TST, normal CXR
  “It’s due to my BCG”

- QFT positive (TB-nil = 1.15)
  “It’s boosting from the TST”

What would you do?
1. Repeat the QFT
2. Do a T-SPOT
3. Treat for LTBI
TST and boosting IGRAs (1)

- 26 healthy volunteers from South Africa

van Zyl-Smit, AJRCCM 2009; 180:49
TST and boosting IGRAs (2)

- Boosting occurred
- Most pronounced in those with a (+) test at baseline
- 3 patients changed from (-) to (+) and all were TST (+)

van Zyl-Smit, AJRCCM 2009; 180:49
TST and boosting IGRAs (3)

A. TST negative

B. TST positive

- 102 HCWs in Italy

Sauzullo, Tuberculosis 2011; 91 322
Follow-up - 20 y/o student from India

- 11 mm TST, normal CXR
  "It’s due to my BCG"

- QFT positive (TB-nil = 1.15)
  "It’s boosting from the TST"

- Repeat QFT negative (TB-nil = 0.34)
  "Finally we agree"
2 Simple Rules When Ordering Tests

1. Don’t get a test if the result isn’t going to change your management

2. Have a plan for all possible results when you order a test
Audience Response Question

Family from Nepal
- Father, mother and 3 children (2, 4, and 7)
- All BCG vaccinated at birth

How would you test for TB infection?
1. TST for all
2. IGRA for all
3. IGRA for adults and TST for children
4. IGRA for adults and older child, TST for the young children
TST vs IGRA in Children

Figure. LTBI single test prevalence by TST, QFT, TSPOT1, and TSPOT2 for 2,842 persons with age information

Ghosh, TBESC poster, NAR/NTCA 2016
Audience Response Question

35 y/o from Denver
• HIV-infected, CD4 350 on treatment
• No identified risk for TB exposure
• QFT positive (0.85)

What would you do?
A. Treat for LTBI if the CXR is normal
B. Repeat the QFT
C. Do a TST for confirmation
D. Do a T-SPOT for confirmation
High Risk Populations - HIV-infected

- Cross-sectional study
- Enrollment: Sept ’05 to July ’06
- Patient population: 336 HIV-infected patients at 2 clinics in Atlanta
- Test: TST, T-SPOT and QFT-GIT
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (+) Test</td>
<td>27</td>
<td>8.0%</td>
</tr>
<tr>
<td>All 3 (+)</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>TST (+)</td>
<td>7</td>
<td>2.5%</td>
</tr>
<tr>
<td>QFT-GIT (+)</td>
<td>9</td>
<td>2.7%</td>
</tr>
<tr>
<td>T-SPOT (+)</td>
<td>14</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Conclusion: Poor concordance among tests
High Risk Populations - HIV-infected

Background

- Less than 50% of HIV patients completed a TST
- QFT-GIT replaced the TST in 2009
- LTBI testing improved to > 90%
- Higher than expected rate of (+) tests among U.S.-born with no risk for TB exposure
- Instituted a policy of repeating all (+) QFTs in patients with no TB exposure risk
High Risk Populations - HIV-infected (6)

Methods:
- retrospective review of QFT-GIT at 2 HIV clinics in Denver, July 2009-June 2010

Results:

<table>
<thead>
<tr>
<th></th>
<th>Overall N= 1364</th>
<th>Repeat Test – No TB Risk N = 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>94 (7%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1243 (91%)</td>
<td>33 (80%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>27 (2%)</td>
<td>2 (5%)</td>
</tr>
</tbody>
</table>

Gray CID 2012; 54: e20
Follow-up – 35 y/o male from Denver

- HIV-infected, CD4 350 on HAART
- No identified risk for TB exposure
- QFT positive (0.85)
- Repeat QFT-GIT negative (0.05)
High Risk Populations – Other Immunosuppression

1. Rheumatoid Arthritis
   - QFT-G (+) similar in patients and healthy controls
     Inanc J Rheum 2009; 36:12

1. Hemodialysis
   - TST correlated with BCG vaccination
   - QFT-GIT and T-SPOT correlated with exposure risk
     Chung Clin Micro Infect 2009
IGRAs and Pregnancy

140 pregnant patients
- Mean age 18.5
- 9 (6.4%) indeterminate
- 28 (20%) TST (+)
- 15 (11%) QFT (+)

No difference by trimester correlated with:
- Increase exposure risk
- Size of TST

Table 2: Assay Response in Pregnant Patients With Different Likelihoods and Risks of Mycobacterium tuberculosis Exposure

<table>
<thead>
<tr>
<th>Exposure Risk</th>
<th>% Interferon-Gamma Release Assay–Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal*</td>
<td></td>
</tr>
<tr>
<td>No known risk, tuberculin skin test-negative</td>
<td>12</td>
</tr>
<tr>
<td>No known risk, tuberculin skin test-positive</td>
<td>0</td>
</tr>
<tr>
<td>Low to moderate†</td>
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<tr>
<td>Positive risk factors, tuberculin skin test-negative</td>
<td>91</td>
</tr>
<tr>
<td>Positive risk factors, tuberculin skin test-positive</td>
<td>26</td>
</tr>
<tr>
<td>High‡</td>
<td></td>
</tr>
<tr>
<td>Known direct contact with TB index case, tuberculin skin test-negative</td>
<td>2</td>
</tr>
</tbody>
</table>

Lighter-Fisher, Ob & Gyn 2012; 119 (6): 1088
TST and IGRAs in Healthcare Workers (1)

- CDC-funded, longitudinal study
- 4 sites: Denver, Houston, Baltimore, NYC
- Population:
  - 2,418 adult HCWs undergoing routine LTBI testing
- Intervention: TST, QFT and T-SPOT at baseline, 6, 12 and 18 months
### Results

<table>
<thead>
<tr>
<th></th>
<th>TST n(%)</th>
<th>QFT n(%)</th>
<th>T-SPOT n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (+)</td>
<td>126 (5.2)</td>
<td>118 (4.9)</td>
<td>144 (6.0)</td>
</tr>
<tr>
<td>Conversion</td>
<td>21 (0.9 )</td>
<td>138 (6.1)</td>
<td>177 (8.3)</td>
</tr>
<tr>
<td>Reversion*</td>
<td>11/12 (92)</td>
<td>81/106 (76)</td>
<td>91/118 (77)</td>
</tr>
</tbody>
</table>

*Not all converters had a repeat test*

- 11 TST-positive HCWs treated for LTBI
- No cases of active TB
Predictability for Future TB (1)

1. Meta-analysis
   - commercial and in-house assays
   - Median follow-up 4 years (IQR 2-6)

2. Results
   - Incidence in IGRA (+) was 4-48/1,000 person-yrs
   - Incidence Rate Ratio for test (+) vs test (-)
     - IGRAs 2.11 [95% CI 1.29-3.46]
     - TST 1.60 [0.94-2.72]
1. **Meta-analysis**
   - commercial and in-house assays

2. **Results** – limited to commercial IGRAs, % (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>PPV –All</th>
<th>PPV - High Risk</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGRA</td>
<td>2.7 (2.3-3.2)</td>
<td>6.8 (5.6-8.3)</td>
<td>99.7 (99.5-99.8)</td>
</tr>
<tr>
<td>TST</td>
<td>1.5 (1.2-1.7)</td>
<td>2.4 (1.9-2.9)</td>
<td>99.4 (99.2-99.5)</td>
</tr>
</tbody>
</table>
High Risk Populations – Contacts to Active TB

December 2011
- Local high school student with pulmonary TB

Contact Investigation
- QFT-GIT for close contacts
- > 2 classes = 10/19 (53%)
- 1 class = 50/140 (36%)

Expanded to > 1200 at school
High Risk Populations – Contacts to Active TB

Operational challenges using IGRAs

- Need to pre-register patients to generate labels for the lab reporting purposes
- Blood draws require more time than TST
- Vasovagal syncope a greater risk than with TST
- Time constraints for delivering specimens to the lab
- Max laboratory capacity per week
- Increased cost for testing the “worried well”
High Risk Populations – Contacts to Active TB

Contact Investigation – 1200 school contacts

- QFT-GIT for foreign-born or BCG vaccinated
- TST for everyone else

- Majority of testing completed in less than a month
Estimated Cost of IGRAs vs TST

1. Methods
   - Markov model to estimate the cost of screening using TST vs IGRAs in risk groups targeted for LTBI testing in the guidelines

2. Results
   - IGRAs are more cost effective than TST when LTBI testing is prioritized toward close contacts, HIV-infected, and foreign-born (regardless of time in the U.S.)
Estimated Cost of IGRAs vs TST

Important considerations for cost

• Who is paying and what are they paying for?
  - laboratory costs vs. person time (patients and HCWs)
  - real current costs vs. potential future costs

• Cost avoidance
  - Unnecessary CXRs and LTBI treatment (including toxicity)
My Recommendations:

- **Test people at risk for infection**
  - 1\text{st} people born or lived in a high-burden country
  - Prioritize those with risk for exposure \textbf{AND} progression (HIV, DM, ESRD etc.) if you have to

- **Prefer IGRAs if available**
  - Better in BCG-vaccinated people
  - Results are easily retrieved

- **Repeat all (+) IGRAs in lower risk people**
  - U.S. born homeless and healthcare workers
  - Consider for those with risk of progression (HIV, DM etc.) but no risk for exposure