Testing for TB Infection

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March 22, 2017
Objectives:

- Explain the use of TST and IGRA testing
- Recognize the clinical presentation of tuberculosis
Strategies for Eliminating TB

- Distinctive strategies needed, based on their specific epidemiologic characteristics, for maintaining skills and resources for finding increasingly rare TB cases, containing outbreaks, and ending transmission

- Capacity for all the essential components of a TB prevention and control program must be retained
Essential Components for TB Prevention and Control

- Planning and developing policy
- Finding and managing suspected and confirmed TB cases
- Prevention: finding and managing LTBI
- Providing lab and diagnostic services
- Collecting and analyzing data
- Provide consultation, training, and education
Testing for TB Infection

• Limited by inability to identify *Mycobacterium tuberculosis* in people with latent infection
• Diagnosis is indirect and based on detecting host immune response to infection (cell-mediated immunity)
  – Tuberculin skin test (TST)
  – Interferon gamma release assays (IGRA)
• Not able to accurately predict risk of reactivation
TB Testing

- Measures cell-mediated immunity via delayed type hypersensitivity response to TB antigens
- Not able to accurately predict risk of reactivation
Tipping the Scale: Targeted Testing for TB Infection

• Identify groups at highest risk:
  – High prevalence of latent infection
  – More likely to reactivate or progress to disease once latently infected

• Reduce screening groups at low risk to lessen false positives
  – Low risk groups likely to be exposed in future (e.g., HCW) is one exception

• Decision to test = decision to treat
High Prevalence of TB Infection

- Close contacts of patients with TB disease
  - Over half lifetime risk of reactivation occurs in 1-2 years post-conversion
- Foreign-born (*recent immigrants* <5 years)
  - In one series, 43% of foreign-born cases with TB disease had no indication for testing by current guidelines, 65% had been in US > 5 years
- Injection drug users
- Homeless
- Prisoners
- Other epidemiologically defined high-risk groups, may vary based on area

Horsburgh and Rubin, NEJM, 2011; Cain and Mackenzie, CID, 2008; Walter et al., CID 2008
### Risk for Progression from TB Infection to TB Disease

<table>
<thead>
<tr>
<th>Risk Factor and Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced, untreated HIV infection</td>
<td>9.9 (8.7–11)</td>
</tr>
<tr>
<td>Moss et al.(^{10})</td>
<td></td>
</tr>
<tr>
<td>Pablos-Méndez et al.(^{16})</td>
<td>9.5 (3.6–25)</td>
</tr>
<tr>
<td>Close contact with a person with infectious tuberculosis(^\dagger)</td>
<td>6.1 (5.5–6.8)</td>
</tr>
<tr>
<td>Ferebee(^{17})</td>
<td></td>
</tr>
<tr>
<td>Radiographic evidence of old, healed tuberculosis that was not treated</td>
<td>5.2 (3.4–8.0)</td>
</tr>
<tr>
<td>Ferebee(^{17})</td>
<td></td>
</tr>
<tr>
<td>Treatment with ≥15 mg of prednisone per day(^\ddagger)</td>
<td>2.8 (1.7–4.6)</td>
</tr>
<tr>
<td>Jick et al.(^{18})</td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>2.4 (2.1–2.8)</td>
</tr>
<tr>
<td>Pablos-Méndez et al.(^{16})</td>
<td></td>
</tr>
<tr>
<td>Treatment with TNF-α inhibitor</td>
<td>2.0 (1.1–3.5)</td>
</tr>
<tr>
<td>Askling et al.(^{19})</td>
<td></td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>1.7 (1.5–2.2)</td>
</tr>
<tr>
<td>Pablos-Méndez et al.(^{16})</td>
<td></td>
</tr>
<tr>
<td>Weight ≥10% below normal</td>
<td>1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>Palmer et al.(^{20})</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>1.5 (1.1–2.2)</td>
</tr>
<tr>
<td>Bates et al.(^{21})</td>
<td></td>
</tr>
</tbody>
</table>

\(^\dagger\) Close contact with an infectious person; \(^\ddagger\) Treatment with ≥15 mg of prednisone per day; \(^\ddagger\) Treatment with TNF-α inhibitor.
Approved tests for LTBI

QuantiFERON®-TB Gold In-Tube (Cellestis) measures interferon gamma

T-SPOT®.TB test (Oxford Immunotec) measures peripheral blood mononuclear cells that produce interferon gamma
TST Administration

• Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm

• Produce a wheal 6 to 10 mm in diameter
Reading the TST

• Measure reaction in 48 to 72 hours

• Measure induration, not erythema

• Forearm: Transversely to the long axis of the forearm
  – Record in mm

• Ensure trained health care professional measures and interprets the TST
## Interpretation of TST Results

<table>
<thead>
<tr>
<th>INDURATION DIAMETER</th>
<th>INDIVIDUAL RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5 mm</td>
<td>Positive test result for:</td>
</tr>
<tr>
<td></td>
<td>- Persons with HIV infection</td>
</tr>
<tr>
<td></td>
<td>- Recent contacts of persons with active TB disease</td>
</tr>
<tr>
<td></td>
<td>- Persons with evidence of old, healed TB lesions on chest X-rays</td>
</tr>
<tr>
<td></td>
<td>- Persons with organ transplants and other immunosuppressed persons, including those receiving prolonged corticosteroid therapy (the equivalent of &gt;15 mg/d of prednisone for one month or more) and TNF-α blockers</td>
</tr>
<tr>
<td>≥10 mm</td>
<td>Positive test result for:</td>
</tr>
<tr>
<td></td>
<td>- Persons who have immigrated within the past 5 years from areas with high TB rates*</td>
</tr>
<tr>
<td></td>
<td>- Injection drug users</td>
</tr>
<tr>
<td></td>
<td>- Persons who live or work in institutional settings where exposure to TB may be likely, such as hospitals, prisons, homeless shelters, SROs, and nursing homes</td>
</tr>
<tr>
<td></td>
<td>- Mycobacteriology laboratory personnel</td>
</tr>
<tr>
<td></td>
<td>- Persons with clinical conditions associated with increased risk of progression to active TB, including: silicosis; chronic renal failure; diabetes; more than 10% below ideal weight or BMI &lt; 18.5; gastrectomy/jejunoileal bypass; some hematologic disorders (such as leukemia and lymphomas); and certain cancers (such as carcinoma of the head, neck, or lung, leukemias, and lymphomas)</td>
</tr>
<tr>
<td></td>
<td>- Children &lt; 5 years, and children or adolescents exposed to adults in high-risk categories</td>
</tr>
<tr>
<td></td>
<td>- Persons with prolonged stay in areas with high TB rates*</td>
</tr>
<tr>
<td>≥15 mm</td>
<td>Positive test result for:</td>
</tr>
<tr>
<td></td>
<td>- Persons at low risk for active TB disease for whom testing is not generally indicated</td>
</tr>
</tbody>
</table>

*nyc.gov/health*
False TST Results

• False positive
  – BCG vaccination
  – Non-tuberculous mycobacteria infection
  – Improper administration or interpretation

• False negative
  – Very young (<6 months)
  – Inability to mount an immune response (e.g., HIV or TB itself)
  – Recent infection (<10 weeks since exposure)
  – Very remote infection
  – Recent live virus vaccination
  – Improper administration or interpretation
TST Do’s and Don’ts

• Do test:
  – Prior to immunosuppression
  – 8-10 weeks after prior negative TST for a contact

• Don’t test:
  – Previous positive result (documented)
  – <6 weeks after live virus vaccine (can be done at same time as vaccine)
  – Prior severe reaction
Two Step Testing

Use two step testing for initial skin testing of adults who will be retested periodically

- If first test positive, consider the person infected
- If first test negative, give second test 1-3 weeks later
- If second test positive, consider person infected
- If second test negative, consider person uninfected
Tuberculin Testing

True Infection vs. Booster Effect (mm induration)

<table>
<thead>
<tr>
<th>Situation</th>
<th>Time 0</th>
<th>1 week</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>B</td>
<td>4</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>C</td>
<td>4</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>
Special Considerations When Using TST

Pregnant women

• TST is safe and reliable for mother and fetus throughout pregnancy

• Give TST to pregnant women who have risk factors for infection or disease
Interferon γ Release Assays
Presentation of mycobacterial antigens

Antigen presenting cell

Memory T cell

Measurement of induration and erythema

IFN-γ

TNF-α

IL-8, etc

Skin test

in-vitro blood test

Measurement of IFN-γ production

IFN-γ

TNF-α

IL-8, etc

Lancet 2000; 356: 1099-104
Interferon Gamma Release Assays (IGRAs)

- Approved by FDA
  - QuantiFERON®-TB GOLD In Tube (QFT-GIT)
  - T-SPOT®.TB

- *In vitro* blood test

- Use antigens not found in BCG or most nontuberculous mycobacteria (ESAT-6, CFP-10, TB7.7)

- More specific, less cross-reaction with NTM

- Can cross-react with *M. kansasii, M. marinum, M. szulgai*
QuantiFERON®-TB Gold In-Tube

16-24 hour incubation

ELISA

IFN-γ

Nil

Negative control

PHA

Positive control

CFP-10

ESAT-6

TB 7.7

IFN-γ
T-SPOT®. TB

Overnight incubation

ELISPOT

Positive control

Negative control

PHA

ESAT-6

CFP-10

Nil
QFT-GIT Interpretation

**TABLE 2. Interpretation criteria for the QuantiFERON-TB Gold In-Tube Test (QFT-GIT)**

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil*</th>
<th>TB Response†</th>
<th>Mitogen Response§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive†</td>
<td>≤8.0</td>
<td>≥0.35 IU/ml and ≥25% of Nil</td>
<td>Any</td>
</tr>
<tr>
<td>Negative**</td>
<td>≤8.0</td>
<td>&lt;0.35 IU/ml or &lt;25% of Nil</td>
<td>≥0.5</td>
</tr>
<tr>
<td>Indeterminate††</td>
<td>≤8.0</td>
<td>&lt;0.35 IU/ml or &lt;25% of Nil</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;8.0</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

# T-Spot®. TB Interpretation

**TABLE 3. Interpretation criteria for the T-SPOT.TB Test (T-Spot)**

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil*</th>
<th>TB Response†</th>
<th>Mitogen§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive†</td>
<td>≤10 spots</td>
<td>≥8 spots</td>
<td>Any</td>
</tr>
<tr>
<td>Borderline**</td>
<td>≤10 spots</td>
<td>5, 6, or 7 spots</td>
<td>Any</td>
</tr>
<tr>
<td>Negative††</td>
<td>≤10 spots</td>
<td>≤4 spots</td>
<td>Any</td>
</tr>
<tr>
<td>Indeterminate**</td>
<td>&gt;10 spots</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>≤10 spots</td>
<td>&lt;5 spots</td>
<td>&lt;20 spots</td>
</tr>
</tbody>
</table>

* ≥10 spots is considered abnormal.
† Mitogens include: PPD, PHA, PWM, and ConA.
§ Mitogens include: PPD, PHA, PWM, and ConA.

TST replacement characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective

*Can IGRAs achieve this standard?*
TST Return rates

- Return rates vary from 18% to 72% depending on the population*
- This is especially important in high risk groups

<table>
<thead>
<tr>
<th>Population</th>
<th>LTBI screening completion rate</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>57%</td>
<td>Cheallaigh et al. (2013) <em>Plos One</em></td>
</tr>
<tr>
<td>Immigration employees</td>
<td>39%</td>
<td>De Perio et al. (2011) <em>J Occup Environ Health</em></td>
</tr>
<tr>
<td>Children</td>
<td>&lt; 50%</td>
<td>Jacono et al. (2006) <em>Arch Pediatr Adolesc Med</em></td>
</tr>
</tbody>
</table>

Failure to come for result reading undermines the TST

* Cheng et al. (2011) Pediatrics 100;210
TST replacement characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective

*Can IGRAs achieve this standard?*
IGRA Sensitivity and Specificity

Based on published meta-analyses:

• Overall sensitivity:
  – T-SPOT: 90%
  – QFT-GIT: 80%
  – TST: 80%

• Specificity:
  – IGRA: >95% in low-TB-incidence settings; not affected by BCG vaccination
  – TST: 97% in populations not vaccinated by BCG; ~60% in populations receiving BCG (varies depending on timing of BCG administration)

Summarized in Pai et al, Clinical Microbiology Reviews, 2014
Specificity of QFT-Gold and QFT-GIT and effect of BCG vaccination

BCG non-vaccinated
Pooled specificity 99%

Study, Year (Reference)  Specificity (95% CI)
Brock et al., 2001 (35)  1.00 (0.78–1.00)
Brock et al., 2004 (36)  0.95 (0.83–0.99)
Taggart et al., 2006 (37)  1.00 (0.96–1.00)
Palazzo et al., 2008 (24)  1.00 (0.75–1.00)
Bian et al., 2007 (18)  1.00 (0.79–1.00)
Mazurek et al., 2007 (38)  1.00 (0.99–1.00)
Franken et al., 2007 (39)  0.97 (0.93–0.99)
Dejne et al., 2007 (25)  1.00 (0.85–1.00)

Pooled specificity = 0.99 (0.98–1.00)
Chi-square = 15.88; P = 0.026
Inconsistency $I^2$ = 56.9%

BCG vaccinated
Pooled specificity 96%

Study, Year (Reference)  Specificity (95% CI)
Brock et al., 2001 (35)  0.89 (0.67–0.99)
Mori et al., 2004 (7)  0.98 (0.95–0.99)
Ravn et al., 2005 (9)  0.97 (0.87–1.00)
Brock et al., 2004 (36)  0.94 (0.79–0.99)
Kang et al., 2005 (10)  0.96 (0.90–0.99)
Lee et al., 2006 (11)  0.92 (0.85–0.96)
Kobashi et al., 2006 (15)  0.94 (0.83–0.99)
Soborg et al., 2007 (40)  0.99 (0.95–1.00)

Pooled specificity = 0.96 (0.94–0.98)
Chi-square = 13.81; P = 0.095
Inconsistency $I^2$ = 49.3%

Specificity of the TST and effect of BCG vaccination

BCG non-vaccinated
Pooled specificity 97%

BCG vaccinated
Pooled specificity 59%

Discordant Results
What do they mean? What should one do?

• Discordant results = IGRA+/TST- or IGRA-/TST+
• Consider positive result of *either* IGRA or TST as evidence of TB infection when
  – Clinically suspect active TB
  – Risks for infection, progression, and poor outcome are increased (HIV infection, children <5 yrs)
• In BCG-vaccinated persons (not at risk for poor outcome), can discount TST result <15 mm when IGRA is negative
TST replacement characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective

*Can IGRAs achieve this standard?*
German contact study:

Predictive power of QFT for development of active TB

*Diel, Loddenkemper et al., AJRCCM, 27 August 2010*

954 close contacts

198 QFT-positive

- 142 QFT-positive/TST-positive
  - Not treated
  - 17 developed active TB

- 5 QFT-positive TST-negative
  - Not treated
  - 2 developed active TB

- 51 QFT-positive (49 TST-positive)
  - Chemoprophylaxis: RIF and/or INH
  - No active TB

756 QFT-negative

- 413 TST positive
  - Not treated
  - No active TB

- 343 TST negative
  - Not treated
  - No active TB

Mean follow-up >3.5 yr
Can IGRAs predict disease? Latest meta-analysis

- **Pooled PPV for progression:**
  - Commercial IGRAs was 2.7%.
  - TST was 1.5%.

- **PPV for progression in high risk groups:**
  - IGRAs was 6.8%.
  - TST 2.4%

- **Pooled values of NPV for progression**
  - IGRAs: 99.7% (p<0.01)
  - TST: 99.4%

Diel et al, Chest. 2012 Jul;142(1):63-75
IGRAs and Contact Investigation

IGRAs better correlate to exposure

- Supersized supermarket investigation: 10,000 TSTs on 2 separate days; 285 BCG unvaccinated subjects had QFT-GIT and T-Spot done
- Exposure risk based on frequency and cumulative shopping time
- Results:
  - TST results correlated with age, NOT exposure
  - QFT and T-Spot results correlated with exposure time
  - IGRA-TST concordance correlated with large TST size

TST replacement characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective

*Can IGRAs achieve this standard?*
Cost effectiveness of IGRAs

**IGRAs was cost saving compared to TST**

*Linas B, et al. AJRCCM 2011; 184(5):590-601*

- Evaluated CDC-defined risk-groups referenced in current U.S. LTBI screening guidelines
  - Contacts
  - HIV
  - Immigrants – regardless of time living in the US
  - Base case cost used: IGRA - $52 and TST- $22

**QFT-GIT more cost-effective for individuals referred to public health clinic for a positive TST**


- Additional QFT-GIT testing of individuals referred
- Conclusion: LTBI screening with TST in low-prevalence settings may lead to overtreatment and increased costs
  - Base case cost used: QFT-GIT - $43.5
TST replacement characteristics

• Convenient and efficient

• Higher specificity and sensitivity

• Higher predictive value

• Cost effective

• *Can IGRAs achieve this standard?*
TB testing: How good are our tests?

**Facts:**

- TST and IGRAs are indirect methods and are dependent on a healthy immune system

- No gold standard to compare for LTBI

- Accuracy of tests **depends on the prevalence** of infection

- Association to exposure risk and **risk of progression** are indirect but important measures

- The published literature of IGRAs is massive and continues to grow
TST and IGRAs are similar in some ways

- Do not distinguish latent infection from active disease
- Do not provide any direct evidence of the presence of viable bacilli
- Determine that infection has at some point led to an acquired immune response that is detectable following re-challenge with antigen
- Are both affected by HIV infection
TST and IGRAs are dissimilar in some ways

- IGRAs are specific in all settings
- TST is specific in BCG unvaccinated or those who get BCG in infancy
- IGRAs have operational characteristics that are more advantageous
- IGRAs require more resources
General Recommendations for Using IGRAs

• May be used in place of (*but not in addition to*) a TST in all situations for which CDC recommends tuberculin skin testing

• *IGRA preferred*
  – Hard to reach populations (e.g., homeless, migrant workers)
    • Only one visit required
  – People who have received BCG (either as vaccine or cancer therapy)
    • TB specificity higher
General Recommendations for Using IGRAs

- Both TST and IGRA may be considered
  - At high risk for infection or progression (e.g., HIV)
  - Suspicion for TB disease exists
  - Further evaluation of positive TST results in individuals at low risk for infection and progression
    - Confirming questionable TST results
  - Other reasons: immediate hypersensitivity to PPD, convincing high risk patient with strongly positive TST to take LTBI treatment, indeterminate/borderline IGRA
General Recommendations for Using IGRAs

• *Use either TST or IGRA*
  – Contacts
  – Periodic screening for those with occupational exposure, surveillance programs etc.

• *TST preferred*
  – Children < 5 yrs
IGRAs in special populations

- Pediatrics – stay tuned…
- HIV
- End stage renal disease
- Populations using biologic agents
IGRAs in special populations

- Pediatrics
- HIV
- End stage renal disease
- Populations using biologic agents
Interferon-Gamma Release Assays for Active Pulmonary TB Diagnosis in Adults in Low- and Middle-Income Countries: Systematic Review and Meta-Analysis, Metcalfe J et al, J of Infection, 2011

<table>
<thead>
<tr>
<th>author/year</th>
<th>country</th>
<th>Sensitivity (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT-GIT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aabye 2009</td>
<td>Tanzania</td>
<td>81 (71, 88)</td>
<td>15.15</td>
</tr>
<tr>
<td>Chegou 2009</td>
<td>South Africa</td>
<td>96 (78, 100)</td>
<td>12.81</td>
</tr>
<tr>
<td>Chen (a) 2009</td>
<td>China</td>
<td>85 (71, 94)</td>
<td>12.02</td>
</tr>
<tr>
<td>Dheda (d) 2009</td>
<td>South Africa</td>
<td>73 (45, 92)</td>
<td>5.26</td>
</tr>
<tr>
<td>Katiyar 2008</td>
<td>India</td>
<td>95 (87, 99)</td>
<td>17.83</td>
</tr>
<tr>
<td>Pai 2007</td>
<td>India</td>
<td>74 (60, 84)</td>
<td>11.80</td>
</tr>
<tr>
<td>Raby 2008</td>
<td>Zambia</td>
<td>84 (68, 94)</td>
<td>11.09</td>
</tr>
<tr>
<td>Tahereh 2010</td>
<td>Iran</td>
<td>77 (59, 90)</td>
<td>9.02</td>
</tr>
<tr>
<td>Tsiouris 2006</td>
<td>South Africa</td>
<td>77 (46, 95)</td>
<td>5.02</td>
</tr>
<tr>
<td>Subtotal (I-squared = 59.8%, p = 0.011)</td>
<td></td>
<td>84 (78, 91)</td>
<td>100.00</td>
</tr>
<tr>
<td>TSPOT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dheda (c) 2009</td>
<td>South Africa</td>
<td>93 (68, 100)</td>
<td>15.47</td>
</tr>
<tr>
<td>Ozekinci (a) 2007</td>
<td>Turkey</td>
<td>93 (76, 99)</td>
<td>26.13</td>
</tr>
<tr>
<td>Shao-ping 2009</td>
<td>China</td>
<td>91 (71, 99)</td>
<td>18.95</td>
</tr>
<tr>
<td>Soysal (a) 2008</td>
<td>Turkey</td>
<td>81 (72, 88)</td>
<td>39.45</td>
</tr>
<tr>
<td>Subtotal (I-squared = 27.5%, p = 0.247)</td>
<td></td>
<td>88 (81, 95)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

HIV uninfected
Pooled sensitivity
QFT-GIT 84%, TSPOT 88%

HIV infected
Pooled sensitivity
QFT-GIT 65%, TSPOT 68%
HIV 3-way analysis of TST-QFT-T-Spot

Cheallaigh et al, PLoS 2013, Vol 8, Issue 1 e5330

• Irish prospective study: 8/2008 – 2/2010

• N=256 (40% foreign born with 14% CD4<100)

• Positive rate:
  – TST (+) =10% (69/162 - 43% failed to return)
  – QFT (+) = 18%
  – T-Spot (+)= 11%

• Significant associations
  – Low CD4 associated with negative QFT result or insufficient T-Spot specimen
  – Foreign birth associate with positive IGRAs
HIV 3-way analysis of TST-QFT-T-Spot

*Chealligh et al, PLoS 2013, Vol 8, Issue 1 e5330*

**Indeterminate rates** – significantly lower for QFT (p< 0.002):

- TST  43% (did not return for reading)
- QFT  2.0% (associated with CD4<200)
- T-Spot 7.0% (11% if insufficient sample included)

**Conclusions of author:**

- QFT-GIT yields more positive results and less indeterminate results compared to other methods
- Both IGRAs affected by low CD4
- No clear superiority of one IGRA over the other
- Interpret negative results with caution when CD4 counts are low
HIV IGRA studies in low incidence countries - Summary (proxy for other immunocompromised groups)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>IGRA agreement with TST</td>
<td>Poor (1-4)</td>
</tr>
<tr>
<td>IGRA sensitivity compared to TST</td>
<td>Similar or higher (1-3)</td>
</tr>
<tr>
<td>Correlation of results to TB risk factors</td>
<td>Yes! (1-4)</td>
</tr>
<tr>
<td>Indeterminate rate</td>
<td>High with CD4 &lt;200</td>
</tr>
<tr>
<td>Prediction of risk of progression</td>
<td>data inadequate-available data says yes (4)</td>
</tr>
</tbody>
</table>

2. Ramos et al., BMC Infectious Diseases 2012, 12:169
4. Aichelburg M et al, CID 2009:48 April 1
Case 1

- 40-year-old male living with HIV
- CD4 count of 337 cells/mm³
- On antiretroviral therapy with undetectable HIV RNA level
- Presents for routine follow-up, asymptomatic
- States that his partner was recently diagnosed with active pulmonary TB and is currently receiving TB treatment
- How would you evaluate this patient?
- Would you do anything different if CD4 count were 100 cells/mm³?
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

• All persons should be tested for LTBI at time of HIV diagnosis
• Persons with negative tests for LTBI and CD4+ count <200 cells/µL should be re-tested once they start ART and attain CD4+ count >200 cells/µL
• Annual testing for LTBI is recommended for HIV-infected persons at high risk (jail, congregate settings, IDU, etc)
• All HIV-infected persons with a positive test for LTBI should receive CXR and clinical evaluation to rule out active TB
IGRAs in special populations

- Pediatrics
- HIV
- End stage renal disease
- Populations using biologic agents
New IGRA Systematic Review: End Stage Renal Disease


- 9 studies compared IGRA with TST
  - 3 TST vs QFT (n=347)
  - 2 TST vs T-Spot (n=418)
  - 4 3-way studies (n=361)

- Results compared to TST by risk association:
  - +QFT more strongly associated with clinical risk:
    - Radiologic evidence of past TB (OR 4.29, p=0.001)
    - Contact to TB (OR 3.36, p=0.001)
  - Negative QFT associated with BCG (OR .30 p=0.002)
  - T-Spot: no statistical differences for any clinical risk factor
New IGRA Systematic Review: End Stage Renal Disease


– Major conclusions

• “ELISA-IGRA likely to be a more accurate diagnostic tool for LTBI in ESRD”

• Consistent with previous systematic reviews of general population showing better correlation of QFT results with TB exposure and independence from prior BCG

• “Propose that the ELISA-IGRA should be the test of choice”
IGRAs in special populations

- Pediatrics
- HIV
- End stage renal disease
- Populations using biologic agents
Use of biologic agents that impact cell-mediated immunity: TNF-\(\alpha\) inhibitors

TNF-\(\alpha\) plays a central part in the host response against tuberculosis including granuloma formation and containment of disease.(1)

Keane J., et al. (2001) NEJM 345(15), 1098-104

Granuloma formation and maintenance

with TNF-\(\alpha\) inhibitors

No granuloma – no containment
## Anti-TNF agents: Summary

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>IGRA agreement with TST</td>
<td>Poor</td>
</tr>
<tr>
<td>IGRA sensitivity compared to TST</td>
<td>Similar or higher</td>
</tr>
<tr>
<td>Correlation of results to TB risk factors</td>
<td>Yes, unlike the TST</td>
</tr>
<tr>
<td>Indeterminate rate</td>
<td>Higher than in healthy controls</td>
</tr>
<tr>
<td>Effect of anti-TNF treatment</td>
<td>Lower quantitative response</td>
</tr>
<tr>
<td>Prediction of risk of progression</td>
<td>Yes, but data few</td>
</tr>
</tbody>
</table>

**Guidance for Rheumatologic pts on DMARDs**

- Arthritis
- IGRA preferred if BCG hx

Studies show significant differences between tests

QFT is more accurate than TST in immune suppressed patients

- Matulis G et al
  - Prospective study in 142 consecutive patients with chronic inflammatory rheumatoid conditions
  - Low incidence setting / high BCG vaccination (83%) (Switzerland)

Key findings – in patients with inflammatory rheumatoid conditions:
- QFT correlates better with TB risk than TST
- QFT is unaffected by BCG vaccination
- QFT is less affected by conventional DMARDs and corticosteroids than the TST

Studies show significant differences between tests

QFT is more accurate than TST in immune-suppressed patients (1, 2)

Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders
Rachel Smith\textsuperscript{a}, Adithya Cattamanchi\textsuperscript{b}, Karen R. Steingart\textsuperscript{c}, Claudia Denkinger\textsuperscript{d}, Keertan Dheda\textsuperscript{e}, Kevin L. Winthrop\textsuperscript{f} and Madhukar Pai\textsuperscript{g}

- Individuals with immune-mediated inflammatory disorders (IMIDs) are at increased risk of developing active TB
- Current evidence does not suggest that IGRAs > TST in identifying patients with IMID who could benefit from LTBI treatment
- Tendency for guidelines to prefer IGRA over TST in IMIDs or to recommend both tests
- If high index of suspicion for LTBI, perform both tests
Two strategies to detect LTBI in patients with IMID

**Strategy 1:** either test positive to maximize sensitivity; best used in areas that have not used BCG vaccine. **Benefit:** fewer false negatives. **Drawback:** in areas that do use BCG vaccine, some patients with discordant TST+/IGRA- will be incorrectly classified as LTBI

**Strategy 2:** maximize specificity; best used in areas that have used BCG vaccine. **Benefit:** fewer false positives. **Drawback:** false negative IGRA results are possible and more likely in IMID patients

Smith, Current Opinion Rheumatol 2011
Case 2

- Patient is referred for possible LTBI
- 55-year-old female emigrated from El Salvador to Texas in 1985
- Employed at a poultry processing plant for 15 years
- Diagnosed with rheumatoid arthritis
- Prescribed prednisone 20 mg twice daily, methotrexate and Humira® (adalimumab - a tumor necrosis factor alpha antagonist)

- How would you evaluate this patient?
Case 3: Does this remicade candidate have LTBI? (also on prednisone 20mg QD)

55 y/o Filipino female in US
35 yrs

TST (−)
QFT (−)
Asymptomatic
Know IGRA gray areas

• **Serial testing:** No quantitative “converter” definition

• **Unknown negative predictive value in:**
  – Very young children under 5 years old
  – Immunocompromised individuals

• **Maximum sensitivity may be needed in these groups, especially if patient is symptomatic or have multiple risks**

• **Remember that IGRA**s are tools, not a panacea.

• **IGRAs, like the TST, cannot definitively “rule out disease or LTBI”, only a doctor can….**
Summary

• IGRAs are a significant advance because of their high specificity and operational advantages over the TST

• Findings among high risk groups show consistent performance: higher sensitivity and specificity of QFT

• In low prevalence countries like the US, negative predictive value has been outstanding across high risk asymptomatic groups

• Cost effective studies have demonstrated savings and effectiveness using QFT compared to TST and Tspot. among the most important TB risk groups

• Knew knowledge from IGRAs are being used to advance screening policies that will benefit individuals, communities and their providers
Intention to Test Is Intention to Treat

In 1907, the Vienna Medical Weekly published a manuscript by the pediatrician Clemens von Pirquet on an “allergy test for the diagnosis of tuberculosis in children” (1). A key observation on his use of the tuberculin skin test (TST) was a diagnostic sensitivity of 60%, closely approximating the pooled sensitivity of 65% determined in the most recent meta-analysis (2). Clemens von Pirquet also recognized that 35% of older children without clinically manifest tuberculosis had positive TST reactions. One hundred years after von Pirquet’s publication, the World tuberculosis, perhaps because an undetermined proportion is simply not or no more infected with live bacilli. As the kinetics of the immune responses vary over time, it is questionable whether single time-point evaluations suffice to evaluate future tuberculosis risk (8).

Since the advent of IGRA, much has been speculated about their possible advantages over the TST in assisting tuberculosis prevention. However, very few studies to date have addressed the actual purpose of immunodiagnostic assays, namely, pre-

“Although desirable, a substantially improved test to better define individuals at risk of future tuberculosis does not seem imminent. It is thus all the more important that only individuals are tested who are at a high risk of tuberculosis in the future and who are fully appraised of the treatment consequences.”

Lange C and Rieder H, AJRCCM 2011
Can we afford not to use the most specific test we have for LTBI?

<table>
<thead>
<tr>
<th>US accepted treatments</th>
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<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>6-9 months</td>
</tr>
<tr>
<td><strong>Rifampin</strong></td>
<td>4-6 months</td>
</tr>
<tr>
<td><strong>Rifampin/INH</strong></td>
<td>4 months</td>
</tr>
<tr>
<td><em><em>New</em> 12 dose INH/rifapentine</em>*</td>
<td>3 months (once weekly – DOT)</td>
</tr>
</tbody>
</table>
References

- Systematic reviews on IGRAs and other TB diagnostics are available at Evidence-based tuberculosis diagnosis, www.tbevidence.org
- Barry C et al. Nature Reviews Microbiology | AoP, published online 26 October 2009; doi:10.1038/nrmicro2236
- ATS/CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 2000 ;49(RR-6)
Thank you!