IGRAs in Children for the Detection of LTBI and Tuberculosis?

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Disclosure

- No shares of or fees from PPD or IGRA manufacturers
- No invitation to any of the three global symposia on IGRA by the sponsoring companies:
  - 21.02.-22.02.2007 Vancouver
  - 30.05.-01.06.2009 Dubrovnik
  - 12.01.-15.01.2012 Waikaloa, Hawaii
- Personalized attack from IGRA manufacturer subsequent to Nadal D. CID 2002 editorial
Evidence for IGRAs in Children?

- Children with microbiologically-confirmed TB disease – very few studies and low numbers of patients
- Children with clinically suspected TB disease
- Children identified as close contacts of TB cases
- Graduated risk in a contact investigation – e.g. schools
Use of TST or IGRA in children?

- Both tests have advantages and limitations, and they do not allow distinction active vs. latent TB
- IGRA may be more specific, but does cross-react in infections with non-tuberculous mycobacteria (NTM):
  - *Mycobacterium kansasii*
  - *Mycobacterium marinum*
  - *Mycobacterium szulgae*
  - *Mycobacterium flavescens*

**Recommendation:**
**Diligent use** of the tests, taking into consideration child’s age, immune status, epidemiologic situation, and vaccination status
Vaccine (BCG) or NTM

- Common mycobacterial genes
- Tuberculosis complex-specific genes
- Deleted region

**M bovis BCG**

**M tuberculosis**

**M avium**

Albert Calmette 1863-1933

Camille Guérin 1872-1961
IGRAs: Advantages for Children

– Enhanced specificity: optimal for BCG-immunized persons and exposure to environmental non-tuberculous mycobacteria (NTM)
– Help differentiating TB vs. NTM disease
– Decreased confusion about interpretation: one cut-off irrespective of age, immune status, and tuberculosis risk factors
– One visit: optimal if adherence issues
Mortality of Tuberculosis Disease in Relation to Age

Disseminated tuberculosis
Pulmonary tuberculosis

Years

Mortality per 100,000

0-1, 1-2, 3-5, 6-10, 11-15, 16-20, 21-30, 31-40, 41-50, 51-60, 61-70, over 70
Age-related and Sex-related Incidence of Tuberculosis

Donald PR et al. Lancet 2010;375:1852-4
Tuberculosis Disease: Child versus Adult

Atypical manifestations
Extrapulmonary tuberculosis
Secondary Immune Responses: Lymphatic Tissue and Metastatic Foci

- **Dendritic cell**
- **Memory CD4+ T-cell**
- γ2δ2 T cell
- **Macrophage**

**CD40** → **CD40L**

- **Memory CD4+ T-cell**
  - **TCR**
  - **MHC II**
  - **CD40L**
  - **CD40**
  - **IFN-γ**
  - **IL-2**
  - **IL-12**
  - **TNF-α**
  - **↑ Killing**

- **CD8+ T-cell**
  - **↑ IFN-γ**
  - **↑ Killing**

- **Infected cell**
  - **Cytolysis**
  - **Mycolic acid**
  - **LAM**

- **Activated macrophage**

- **↑ Killing**
High Rate of Indeterminate Results of IGRA in Children < 4 Years of Age

Interferon-$\gamma$ release assays do not identify more children with active tuberculosis than the tuberculin skin test

B. Kampmann, E. Whittaker, A. Williams, S. Walters, A. Gordon, N. Martinez-Alie, B. Williams, A.M. Crook, A-M. Hutton and S.T. Anderson
Conclusions: There was no clear evidence that IGRAs should replace TST for detecting LTBI in children. Sensitivity of the IGRA for TB disease was no different from TST, and a significantly reduced IGRA sensitivity was found in high-burden TB settings compared with low-burden TB settings. Further studies are needed to determine the value of IGRAs in LTBI and TB disease diagnosis in children.
IGRA: Limitations for Children

- Important pre-analytic obstacles (sampling, etc.)
- One cut-off irrespective of age, immune status, and TB risk factors
  - Is this appropriate across ages?
- Indeterminate results: decrease the utility of a screening tool
- Unknown dynamics of when assays become positive – “window” prophylaxis
- Discordance: interpretation if TST and IGRA provide different results
- Limited pediatric data: especially for the most vulnerable risk groups
TST preferred, IGRA acceptable

- Children < 5 years of age

**IGRA preferred, TST acceptable:**
- Children who have had BCG vaccine
- Children in a group with historically low rates of return for TST reading

**Note:** In Switzerland, routine BCG vaccination has been abandoned, and the vast majority of patients return for TST reading
Either TST or IGRA can be used

– Children identified in contact investigations

Nevertheless, in Switzerland a two-step approach using TST first is justified.
Both TST and IGRA should be considered for children when:

- The TST is positive and NTM disease is suspected
- The initial IGRA is indeterminate or borderline
- The initial test (TST or IGRA) is negative and:
  • Clinical suspicion for TB disease exists
  • Risk of infection, progression, and poor outcome are higher
- The initial test (TST or IGRA) is positive and:
  • Need additional evidence to increase compliance
  • Healthy with low risk for both infection and disease progression
What to do with discordant results between a TST and an IGRA?

- In patients in whom disease is suspected or at high risk for progression from infection, treat if any test positive
- For immunocompetent patients with low risk, treat if the more specific test is positive
- A positive TST and negative IGRA in a child with chronic lymphadenitis suggests NTM disease
Latent Tuberculosis Infection in the United States

C. Robert Horsburgh, Jr., M.D., and Eric J. Rubin, M.D., Ph.D.


<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Close contacts of persons with infectious TB</td>
<td>TST or IGRA, but not both</td>
<td>TST, with IGRA to confirm positive TST</td>
<td>TST, with IGRA to confirm positive TST</td>
</tr>
<tr>
<td>Persons who may not return for TST reading because of circumstances (e.g., homelessness or injection-drug use) or logistic difficulties</td>
<td>IGRA preferred</td>
<td>No specific recommendation</td>
<td>IGRA preferred</td>
</tr>
<tr>
<td>Immunosuppressed persons (e.g., those infected with HIV or receiving treatment with prednisone or TNF-α inhibitor)</td>
<td>TST or IGRA; use both if first is negative and suspicion is high</td>
<td>TST, followed by IGRA if TST is negative</td>
<td>TST or IGRA</td>
</tr>
<tr>
<td>Foreign-born persons</td>
<td>Screening only for those who have immigrated in past 5 yr; use TST or IGRA, but not both</td>
<td>Screening only for those &lt;15 yr old who have immigrated in past 2 yr; use TST, with IGRA to confirm positive TST</td>
<td>Screening for new immigrants only; use TST with IGRA to confirm positive TST for those 5-15 yr of age and IGRA for those 16-35 yr of age</td>
</tr>
<tr>
<td>BCG vaccine recipients (if they belong to another risk group)</td>
<td>IGRA preferred</td>
<td>No specific recommendation</td>
<td>TST or IGRA</td>
</tr>
<tr>
<td>Health care workers (screening program)</td>
<td>TST or IGRA, but not both</td>
<td>TST preferred</td>
<td>TST or IGRA, depending on specific circumstances</td>
</tr>
<tr>
<td>Children &lt;5 yr old</td>
<td>TST preferred</td>
<td>No specific recommendation</td>
<td>TST preferred</td>
</tr>
<tr>
<td>Other risk groups</td>
<td>TST or IGRA, but not both</td>
<td>TST, with IGRA to confirm positive TST</td>
<td>TST, with IGRA to confirm positive TST</td>
</tr>
</tbody>
</table>

Table 4. Screening Guidelines from the United States, Canada, and the United Kingdom for Selected Groups at Risk for Latent Tuberculosis (TB) Infection.
Algorithm for TB Testing in Children

*Either positive TST or IGRA considered significant if clinical suspicion of TB disease

Courtesy Jeffrey M. Starke, Baylor College of Medicine, Houston, TX
Studies Comparing the Performance of IGRA vs. TST in Children

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample Size</th>
<th>Age (yr)</th>
<th>Test Type</th>
<th>TB Burden</th>
<th>TST Cutoff (mm)</th>
<th>Overall Agreement Between TST and QFT ($\kappa$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada et al(^{10})</td>
<td>2008</td>
<td>Cambodia</td>
<td>195</td>
<td>&lt;5</td>
<td>QFT-G</td>
<td>High</td>
<td>10</td>
<td>0.63</td>
</tr>
<tr>
<td>Hesseling et al(^{15})</td>
<td>2007</td>
<td>South Africa</td>
<td>29</td>
<td>&lt;5</td>
<td>QFT-G</td>
<td>High</td>
<td>10</td>
<td>0.78</td>
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<tr>
<td>Nakaoka et al(^{12})</td>
<td>2006</td>
<td>Nigeria</td>
<td>207</td>
<td>&lt;5</td>
<td>QFT-G IT</td>
<td>High</td>
<td>10</td>
<td>0.50</td>
</tr>
<tr>
<td>Dogra et al(^{11})</td>
<td>2006</td>
<td>India</td>
<td>105</td>
<td>1–12</td>
<td>QFT-G IT</td>
<td>High</td>
<td>10</td>
<td>0.73</td>
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<tr>
<td>Tsiouris et al(^{13})</td>
<td>2006</td>
<td>South Africa</td>
<td>184</td>
<td>5–15</td>
<td>QFT-G IT</td>
<td>High</td>
<td>10</td>
<td>0.56</td>
</tr>
<tr>
<td>Lighter et al(^{16})</td>
<td>2009</td>
<td>United States</td>
<td>207</td>
<td>&lt;18</td>
<td>QFT-G</td>
<td>Low</td>
<td>10</td>
<td>0.17</td>
</tr>
<tr>
<td>Connell et al(^{18})</td>
<td>2006</td>
<td>Australia</td>
<td>106</td>
<td>&lt;18</td>
<td>QFT-G</td>
<td>Low</td>
<td>10</td>
<td>0.3</td>
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<tr>
<td>Dominguez et al(^{25})</td>
<td>2007</td>
<td>Spain</td>
<td>134</td>
<td>&lt;18</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>5</td>
<td>0.71</td>
</tr>
<tr>
<td>Bianchi et al(^{20})</td>
<td>2009</td>
<td>Italy</td>
<td>336</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
<td>0.53</td>
</tr>
<tr>
<td>Haustein et al(^{22})</td>
<td>2009</td>
<td>United Kingdom</td>
<td>237</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>6</td>
<td>0.71</td>
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<tr>
<td>Bergamini et al(^{19})</td>
<td>2009</td>
<td>Italy</td>
<td>496</td>
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<td>QFT-G</td>
<td>Low</td>
<td>10</td>
<td>0.35</td>
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<tr>
<td>Connell et al(^{16})</td>
<td>2008</td>
<td>Australia</td>
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<td>QFT-G IT</td>
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<tr>
<td>Nsutebu et al(^{26})</td>
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<td>United Kingdom</td>
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<td>13–14</td>
<td>QFT-G</td>
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<tr>
<td>Tavast et al(^{17})</td>
<td>2009</td>
<td>Finland</td>
<td>99</td>
<td>&lt;18</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
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<tr>
<td>Higuchi et al(^{27})</td>
<td>2009</td>
<td>Japan</td>
<td>61</td>
<td>8–12</td>
<td>QFT-2G</td>
<td>Low</td>
<td>10</td>
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<tr>
<td>Chun et al(^{21})</td>
<td>2008</td>
<td>South Korea</td>
<td>227</td>
<td>&lt;15</td>
<td>QFT-G IT</td>
<td>Low</td>
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<tr>
<td>Higuchi et al(^{29})</td>
<td>2009</td>
<td>Japan</td>
<td>313</td>
<td>&lt;16</td>
<td>QFT-G</td>
<td>Low</td>
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<tr>
<td>Bramford et al(^{24})</td>
<td>2009</td>
<td>United Kingdom</td>
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<td>QFT-G IT</td>
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<tr>
<td>Kampmann et al(^{23})</td>
<td>2009</td>
<td>United Kingdom</td>
<td>209</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
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<td>15</td>
<td>0.57</td>
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<tr>
<td>Hermann et al(^{28})</td>
<td>2009</td>
<td>France</td>
<td>131</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

*Year of publication.
†$\kappa$ values between 0.61 and 0.80 imply good agreement (adapted from Landis and Kock, 1977\(^{14}\)).
QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.

Machingaidze S et al. *PIDJ* 2011;30:694-700
# Studies Comparing Sensitivity of IGRA vs. TST in Active TB in Children

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Test Type</th>
<th>TB Burden</th>
<th>Age (yr)</th>
<th>Sample Size</th>
<th>No. TB Cases</th>
<th>TST Cutoff (mm)</th>
<th>Sensitivity (%) TST</th>
<th>Sensitivity (%) QFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada et al, 2008</td>
<td>QFT-G</td>
<td>High</td>
<td>&lt;5</td>
<td>195</td>
<td>19</td>
<td>10</td>
<td>79%</td>
<td>53%</td>
</tr>
<tr>
<td>Dogra et al, 2006</td>
<td>QFT-G IT</td>
<td>High</td>
<td>1-12</td>
<td>105</td>
<td>8</td>
<td>10</td>
<td>63%</td>
<td>63%</td>
</tr>
<tr>
<td>Bianchi et al, 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>336</td>
<td>15</td>
<td>10</td>
<td>86%</td>
<td>94%</td>
</tr>
<tr>
<td>Haustein et al, 2009</td>
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<td>Low</td>
<td>&lt;16</td>
<td>237</td>
<td>27</td>
<td>6</td>
<td>72%</td>
<td>78%</td>
</tr>
<tr>
<td>Bramford et al, 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>333</td>
<td>195</td>
<td>15</td>
<td>55%</td>
<td>52%</td>
</tr>
<tr>
<td>Kampmann et al, 2009</td>
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<td>Low</td>
<td>&lt;16</td>
<td>209</td>
<td>63</td>
<td>15</td>
<td>60%</td>
<td>63%</td>
</tr>
</tbody>
</table>

*Year of publication.

QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.
Meta-analysis of IGRA Sensitivity for Dx of Active (Culture+) TB in Children

Machingaidze S et al. PIDJ 2011;30:694-700
Meta-analysis of IGRA Sensitivity for Dx of Active (All Cases) TB in Children

Machingaidze S et al. PIDJ 2011;30:694-700