Clinical Policy Title: Interferon-gamma release assays for tuberculosis screening

Clinical Policy Number: 07.01.06

Effective Date: March 1, 2014
Initial Review Date: November 20, 2013
Most Recent Review Date: November 16, 2016
Next Review Date: November 2017

Related policies:
None.

ABOUT THIS POLICY: AmeriHealth Caritas District of Columbia has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas District of Columbia’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas District of Columbia when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas District of Columbia’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas District of Columbia’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas District of Columbia will update its clinical policies as necessary. AmeriHealth Caritas District of Columbia’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas District of Columbia considers the use of interferon-gamma release assays (IGRA) for diagnosis of tuberculosis (TB) to be clinically proven and, therefore, medically necessary when the following criteria are met:

- The individual being screened meets the appropriateness guidelines from the Centers for Disease Control and Prevention (CDC) Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection (Appendix A), OR
- The individual being screened meets the appropriateness guidelines from the American Academy of Pediatrics (AAP) Report of the Committee on Infectious Diseases/Red Book Tuberculosis (Appendix B).

Limitations:

All other uses of IGRA and automated real-time nucleic acid amplification technology for tuberculosis screening are not medically necessary.
The use of IGRA for tuberculosis screening is not medically necessary when a standard Mantoux test would have similar efficacy.

TB screening as a requirement of employment is not a covered benefit under state Medicaid programs.

The use of automated real-time nucleic acid amplification technology in communities with a low incidence of multi-drug resistance is not medically necessary.

Alternative covered services:

Skin testing with a Mantoux test and TB culture of sputum, when performed within the AmeriHealth Caritas District of Columbia network.

Background

Tuberculosis remains a significant health concern in both the developed and developing world. Caused by infection with *mycobacterium tuberculosis* (*M. tuberculosis*), active or latent TB affects some 2 billion people across the globe. Patients with renal failure undergoing dialysis are at an increased risk of TB due to attenuated cellular immunity.

Key to control of TB is cost-effective screening of high-risk populations. Over the past century such screening has been performed with the use of tuberculin skin test (TST), or Mantoux skin test. This involves the intradermal injection of purified protein derivative (PPD) and measurement of any subsequent area of induration (a delayed hypersensitivity reaction of tuberculin antigen within the individual) at the test site.

Interferon-gamma release assays are blood studies for active and latent tuberculosis infection (LTBI) based upon the release of interferon-gamma. The QuantiFERON®-TB Gold In-Tube (QFT-GIT) (Cellestis Inc., Valencia, CA) test employs enzyme-linked immunosorbent assay (ELISA) to measure interferon gamma in the blood. The T-SPOT®.TB test (Oxford Immunotec, Marlborough, MA) is an ELISA immunospot test measuring the number of cells releasing interferon gamma.

All current blood testing methods for TB (TST, QFT-GIT, and T-SPOT) are indirect tests that measure the body’s response to tuberculosis and do not assay the causative organism directly. As such, the accuracy of these tests suffers from the inability to have a direct control for comparison. Studies cited by the CDC suggest TST is a better predictor of older TB exposure, whereas IGRA is more likely to be positive in recent infection.

A parallel concern in testing for TB is the increasing prevalence of the multi-drug resistant (MDR) *M. tuberculosis* organism. The National Institutes of Health (NIH) has funded research to develop a TB-specific, cartridge-based nucleic amplification assay (NAA) for detection of *M. tuberculosis* with rifampicin-resistant mutations. The Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA) can provide culture and sensitivity results from sputum within one day. The test has a negative predictive value of more than 99 percent with a
positive predictive value of more than 90 percent in populations in which more than 15 percent of isolates demonstrate MDR.

**Searches**

AmeriHealth Caritas District of Columbia searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on October 26, 2016. Search terms were: "tuberculosis" [Mesh], "interferon-gamma" [Mesh], “tuberculosis screening,” and “gamma interferon assay tuberculosis.”

We included:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

The use of IGRA has been increasing in use because it does not require a follow-up visit; however, the technical aspects of the testing may result in lost data, and costs are significantly higher. For these reasons, this technology is finding an appropriate use for those for whom follow-up visits may not occur reliably and in those with CD4 cell counts at a low level. Because of the low incidence of rifampicin-resistant tuberculosis in the United States, the CDC does not currently recommend the routine use of Xpert MTB/RIF in this country.

**Policy updates:**

Gudjónsdóttir (2016) conducted a prospective trial of testing with QFT-GIT in 762 children/adolescents (median age 14 years) with TST ≥10 mm. A total of 163/492 (33 percent) of the children with a Bacillus Calmette–Guérin (BCG) vaccine scar had a positive QFT-GIT, whereas 205/270 (76 percent) without a BCG scar had a positive QFT-GIT (p < 0.0001). The median TST was 12 mm in QFT-GIT negative and 18 mm in QFT-GIT positive children (p < 0.0001) but with considerable overlap. Median TST was the same (12 mm) in QFT negative children with and without a BCG scar. Among the QFT positive children, 25/368 had chest X-ray changes compared to 2/393 among the QFT-GIT negative children (p < 0.0007). The authors concluded
that a previous BCG vaccination had an effect on the TST diameter so an IGRA is recommended to diagnose LTBI.

Kwong (2016) refuted Canadian guidelines that suggest BCG vaccination does not result in a false-positive TST, citing a growing body of evidence that IGRA may be a more suitable alternative in identifying LTBI in vaccinated populations. Of the 11 children who underwent routine screening at 14 years of age for LTBI, seven had a positive TB skin test (≥10 mm). All seven children received the BCG vaccine as newborns and all had a negative TB skin test during their routine screening at 4 years of age. No potential exposure to active TB could be identified. Chest radiographs were normal, and none of the children had symptoms suggestive of active TB. The seven children underwent IGRA testing using QFT-GIT. All seven tests were negative, suggesting that neonatal BCG vaccination may contribute to a false-positive skin test in youth at 14 years of age.

Shu (2016) studied interferon-gamma release assay (IGRA) in 157 hemodialysis patients (age ≥20 years) using QFT-GIT. Of the participants who had initially positive QFT-GIT, 82 had persistent positivity and 75 had negative conversion. The persistently positive group was younger, had more current smokers, and had higher plasma levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and QFT-GIT responses than the negative conversion group. Smoking had borderline significance. The authors concluded that dialysis patients with persistent QFT-GIT positivity status may be associated with a young age, high plasma sTREM-1, initial strong QFT-GIT response, current smoking, and TB contact history, and that these findings may help focus screening on those most likely to evidence positivity.

Recent guidelines from the CDC (Appendix A) and the AAP (Appendix B) grant that IGRA is a helpful diagnostic test for the identification of M. tuberculosis infection and LTBI. All agree that the usage experience of IGRA in children <5 years old is insufficient to make conclusions about test efficacy in this cohort; however, IGRA performs well in children age 5 years or older. The sensitivity of IGRA for detecting TB infection in children is similar to TST, while IGRA specificity seems to be higher than TST. The AAP goes on to point out that:

"At this time, neither an IGRA nor the TST can be considered 'the gold standard' for diagnosis of LTBI. Children with a positive result from an IGRA should be considered infected with M. tuberculosis complex. A negative IGRA result cannot be interpreted universally as absence of infection. Indeterminate IGRA results have several possible causes that could be related to the patient, the assay itself, or its performance. Indeterminate results do not exclude M. tuberculosis infection and may necessitate repeat testing, possibly with a different test. Indeterminate IGRA results should not be used to make clinical decisions."

Guidelines from the World Health Organization (WHO, 2013) recommend that Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of MDR-TB or human immunodeficiency virus (HIV)-associated TB (strong recommendation; high-quality evidence for adults, very low-quality evidence for children). They also suggest that Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in individuals suspected of having TB (conditional recommendation
acknowledging resource implications; high-quality evidence for adults, very low-quality evidence for children); and that Xpert MTB/RIF may be used as a follow-on test to microscopy in adults suspected of having TB but not at risk of MDR-TB or HIV-associated TB, especially when further testing of smear-negative specimens is necessary (conditional recommendation acknowledging resource implications, high-quality evidence).

The CDC did not expressly endorse an MDR testing method in screening for TB, but its expert panel on the subject (CDC, 2012) encouraged the body to:

“...develop a system with sufficient testing capacity to enable molecular DR testing for one acid-fast bacillus (AFB) smear-positive or NAA-positive respiratory specimen or one *M. tuberculosis* culture from each TB patient or TB suspect and specimens or isolates from persons that the local or state TB Control Program designates as high priority for testing.”

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gudjónsdóttir (2016)</td>
<td>Relation between BCG vaccine scar and an interferon-gamma release assay in immigrant children with &quot;positive&quot; tuberculin skin test (≥10 mm).</td>
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<tr>
<td></td>
<td><strong>Key points:</strong></td>
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<td>• Trial with QFT-GiT in 762 healthy children/adolescents (median age 14 years) with TST ≥10 mm.</td>
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<td>• A total of 163/492 (33%) of the children with BCG vaccine scar had a positive QFT-GiT, whereas 205/270 (76%) without a BCG scar had a positive QFT (p &lt; 0.0001).</td>
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<td>• Among the QFT positive children, 25/368 had chest X-ray changes compared to 2/393 among the QFT-GiT negative children (p &lt; 0.0007).</td>
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<td>• The authors concluded that a previous BCG vaccination had an effect on the TST diameter so an IGRA is recommended to diagnose LTBI.</td>
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<td>Inflammatory markers and clinical characteristics for predicting persistent positivity of interferon gamma release assay in dialysis population.</td>
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<td>• These findings may help focus screening to those most likely to evidence positivity.</td>
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<td>Kwong (2016)</td>
<td>Potential role for interferon-y release assays</td>
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<tr>
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<td><strong>Key points:</strong></td>
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<td></td>
<td>• Refuted doctrine suggesting BCG vaccination does not result in a false-positive TST.</td>
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<tr>
<td></td>
<td>• Concluded that IGRA may be a more suitable alternative in identifying LTBI in BCG.</td>
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</tbody>
</table>
### Citation

in tuberculosis screening in a remote Canadian community: a case series.

### Content, Methods, Recommendations

- Vaccinated populations.
  - Of 11 children who underwent routine screening at 14 years of age for LTBI, seven had a positive TB skin test ($\geq 10\ mm$).
  - The seven children underwent IGRA testing using QFT-GIT. All seven tests were negative, suggesting that neonatal BCG vaccination may contribute to a false-positive skin test in youth at 14 years of age.

### Key points:

- IGRA can be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing M. tuberculosis infection.
- This includes contact investigations, testing during pregnancy, and screening of health care workers and others undergoing serial evaluation for M. tuberculosis infection.
- Populations in which IGRA are preferred for testing:
  - Persons who have received BCG (either as a vaccine or for cancer therapy); and
  - Persons from groups that historically have poor rates of return for TST reading.
- TST is preferred over IGRA for testing children less than 5 years of age.
- As with TST, IGRA 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.
- Routine testing with both TST and IGRA is not recommended. However, results from both tests might be useful in the following situations:
  - When the initial test is negative and:
    - The risk for infection, the risk for progression to disease, and the risk for a poor outcome are high (e.g., HIV-infected persons or children under 5 years of age who are exposed to a person with infectious TB).
    - There is clinical suspicion for TB disease (e.g., signs, symptoms, and/or radiographic evidence suggestive of TB disease) and confirmation of M. tuberculosis infection is desired.
    - Taking a positive result from a second test as evidence of infection increases detection sensitivity.
  - When the initial test is positive and:
    - Additional evidence of infection is required to encourage acceptance and adherence (e.g., foreign-born health care workers who believe their positive TST is due to BCG). A positive IGRA might prompt greater acceptance of treatment for LTBI as compared with a positive TST alone.
    - The person has a low risk of both infection and progression from infection to TB disease. Requiring a positive result from the second test as evidence of infection increases the likelihood that the test reflects infection. An alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results.
    - In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.
- Multiple negative results from any combination of these tests cannot exclude M. tuberculosis infection. Steps should be taken to minimize unnecessary and misleading testing of persons at low risk.
- 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
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<td><strong>Red Book (2015)</strong>&lt;br&gt;Red Book: 2015 Report of the Committee on Infectious Diseases.</td>
<td><strong>Key points:</strong>&lt;br&gt;- AAP (2015) recommends TST alone in children younger than 5 years and before initiation of immunosuppressive therapy.&lt;br&gt;- AAP recommends that BCG vaccinated children (&gt;5 years of age), patients who may not be inclined to return for reading of a TST, and those anticipating immunosuppressive therapy undergo testing with IGRA alone.&lt;br&gt;- Both TST and IGRA are recommended where the initial TST is positive and the child is &gt;5 years of age and received BCG vaccine, non-tuberculous mycobacterial disease is suspected, or additional evidence is needed to increase compliance.</td>
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<td><strong>WHO (2013)</strong>&lt;br&gt;Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children.</td>
<td><strong>Key points:</strong>&lt;br&gt;- Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation; high-quality evidence for adults, very low-quality evidence for children).&lt;br&gt;- Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in individuals suspected of having TB (conditional recommendation acknowledging resource implications; high-quality evidence for adults, very low-quality evidence for children).&lt;br&gt;- Xpert MTB/RIF may be used as a follow-on test to microscopy in adults suspected of having TB but not at risk of MDR-TB or HIV-associated TB, especially when further testing of smear-negative specimens is necessary (conditional recommendation acknowledging resource implications, high-quality evidence).</td>
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<td><strong>CDC (2012)</strong>&lt;br&gt;Report of Expert Consultations on Rapid Molecular Testing to Detect Drug-Resistant Tuberculosis in the United States</td>
<td><strong>Key points:</strong>&lt;br&gt;- CDC should develop a system with sufficient testing capacity to enable molecular DR testing for one AFB smear-positive or NAA-positive respiratory specimen or one M. tuberculosis culture from each TB patient or TB suspect and specimens or isolates from persons that the local or state TB Control Program designates as high priority for testing.&lt;br&gt;- CDC should evaluate existing molecular DR testing services to identify best practices.&lt;br&gt;- CDC should use a phased approach to implementing a universal molecular DR testing service.&lt;br&gt;- CDC should immediately establish an interim service to provide molecular DR testing for persons at high-risk of having MDR TB and those deemed high priority by the local TB program. CDC is encouraged to explore using supplements to existing cooperative agreements to provide sufficient new funds to existing, proficient molecular DR testing laboratories to allow them to expand their capacities to meet this need. The interim service could serve as a pilot project to inform the development of a universal molecular DR testing service.&lt;br&gt;- CDC should establish and fund regional laboratories to provide molecular DR testing for state and local TB programs. Funds in the current TB Elimination Cooperative Agreements should not be redirected to the molecular DR testing program. The molecular DR testing laboratories should:&lt;br&gt;  - Coordinate molecular DR testing services with the medical consultation and training</td>
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<td>services of the TB Regional Training and Medical Consultation Centers (RTMCCs),</td>
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<td></td>
<td>- Provide six-day-a-week service,</td>
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<td>- Use validated molecular methods to detect rifampin and isoniazid resistance,</td>
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<td>- Implement molecular DR testing for anti-TB drugs other than rifampin and isoniazid (e.g., fluoroquinolones) as the tests are developed and validated,</td>
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<td>- Report results electronically within two business days of specimen receipt,</td>
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<td>- Report detection of drug resistance in specimen or isolate by telephone to facilitate prompt action by the program and clinician,</td>
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<td>- Ensure notification of appropriate individuals (e.g., local program, laboratory, clinician) of the need for expedited testing of rifampin-resistant samples for susceptibility to first-line and second-line anti-TB drugs, and</td>
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<td>- Participate in an external quality assurance program.</td>
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</table>

**Dai (2012)**

Evaluation of interferon-gamma release assays for the diagnosis of tuberculosis: an updated meta-analysis

**Key points:**
- Though IGRAs showed good sensitivity and specificity for the detection of tuberculosis in this meta-analysis, the decision to use an IGRA should be based on the local prevalence of the disease and the country guidelines, as well as resources and logistical considerations.

**Nienhaus (2011)**

Systematic review of cost and cost-effectiveness of different TB-screening strategies.

**Key points:**
- Meta-analysis.
- Available studies on cost effectiveness provide strong evidence in support of IGRAs in screening high-risk groups.
- High-risk groups include immigrants from endemic countries, individuals with close contacts, health care workers.
- Until the body of research in this area is broadened, recommendations concerning this should be regarded with caution.

**Mazurek (2010)**

Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection.

**Key points:**
- Selection of test should be based upon reason and context of testing, availability, and cost-effectiveness.
- Sensitivity and specificity vary among all testing methods since no direct test of M. tuberculosis.
- IGRA preferred for persons with low rates of returning to have TST reading, e.g., homeless or drug users.
- IGRA preferred for testing BCG vaccine recipients.
- TST preferred for children <5 years of age.
- Combining both TST and IGRA should be considered when an indeterminate test is obtained by either testing method.


Glossary

**Automated real-time nucleic acid amplification (NAA) technology for rapid and simultaneous detection of tuberculosis** — Test of sputum sample for evidence of the presence of and mutation in mycobacterium tuberculosis for drug resistance.

**Bacillus Calmette-Guerin (BCG)** — Also abbreviated as BCG. A vaccine against tuberculosis made from an attenuated strain of a bovine tuberculosis bacillus. This is used in some endemic countries to control tuberculosis. However, it confers a positive TB skin test result.

**Interferon-gamma release assays (IGRA)** — Blood tests for tuberculosis based upon the release of interferon-gamma from T cells in response to mycobacterium tuberculosis infection.

**Latent tuberculosis infection (LTBI)** — Inactive tuberculosis with caseation containing the organism so as to prevent active TB disease.

**Mantoux Test** — Named for the French physician, Dr. Charles Mantoux, who invented the test. This skin test involves the intradermal inoculation of purified protein derivative. A delayed hypersensitivity response with erythema and induration at 48 to 72 hours indicates an immune response to tuberculosis bacillus as with latent or active TB.

**Purified protein derivative (PPD)** — Another name for the Mantoux test as cited above.

References

**Professional society guidelines/other:**


Centers for Disease Control and Prevention (CDC). TB Elimination. Interferon-Gamma Release Assays (IGRAs) – Blood Tests for TB Infection. CDC website:  


Peer-reviewed references:


**Clinical trials:**

Searched clinicaltrials.gov on October 26, 2016, using terms "Interferon-gamma release assay." | Open Studies. Thirteen studies found, 1 relevant.


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
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<tbody>
<tr>
<td>86480</td>
<td>Tuberculosis test, cell mediated immunity antigen response measurement; gamma interferon.</td>
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<tr>
<td>86481</td>
<td>Enumeration of gamma interferon-producing T cells in cell suspension.</td>
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Appendix A

The CDC (2015) has published a fact sheet and list of recommendations regarding the use of IRGA (i.e., QFT-GIT and T-SPOT):

- IGRAs can be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection.
- This includes contact investigations, testing during pregnancy, and screening of health care workers and others undergoing serial evaluation for *M. tuberculosis* infection.
- Populations in which IGRAs are preferred for testing:
  - Persons who have received BCG (either as a vaccine or for cancer therapy); and
  - Persons from groups that historically have poor rates of return for TST reading.
- TST is preferred over IGRAs for testing children less than 5 years of age.
- As with 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*.
- Routine testing with both TST and IGRA is not recommended. However, results from both tests might be useful in the following situations:
  - When the initial test is negative and:
- The risk for infection, the risk for progression to disease, and the risk for a poor outcome are high (e.g., HIV-infected persons or children under 5 years of age who are exposed to a person with infectious TB).
- There is clinical suspicion for TB disease (e.g., signs, symptoms, and/or radiographic evidence suggestive of TB disease) and confirmation of *M. tuberculosis* infection is desired.
- Taking a positive result from a second test as evidence of infection increases detection sensitivity.
  - When the initial test is positive and:
    - Additional evidence of infection is required to encourage acceptance and adherence (e.g., foreign-born health care workers who believe their positive TST is due to BCG). A positive IGRA might prompt greater acceptance of treatment for LTBI as compared with a positive TST alone.
    - The person has a low risk of both infection and progression from infection to TB disease. Requiring a positive result from the second test as evidence of infection increases the likelihood that the test reflects infection. An alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results.
  - In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.

The CDC advises that multiple negative results from any combination of these tests cannot exclude *M. tuberculosis* infection. Steps should be taken to minimize unnecessary and misleading testing of persons at low risk.

The CDC also advises that the 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 overall cost of testing.

**Appendix B**

**Recommendations of the AAP/Red Book 2015**

- Children for whom immediate TST or IGRA is indicated:
  - Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation).
  - Children with radiographic or clinical findings suggesting tuberculosis disease.
  - Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees.
  - Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries.
- Children who should have annual TST or IGRA:
- Children infected with HIV (TST only).
- Children at increased risk of progression of LTBI to tuberculosis disease:
  - Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists deserve special consideration. Without recent exposure, these people are not at increased risk of acquiring *M. tuberculosis* infection. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. A TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged systemic corticosteroid administration, organ transplantation, use of TNF-alpha antagonists or blockers, or other immunosuppressive therapy in any child requiring these treatments.

### Table 3.79. Tuberculin Skin Test (TST) and IGRA Recommendations for Infants, Children, and Adolescents

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<td>• Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries^c</td>
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**Children at increased risk of progression of LTBI to tuberculosis disease:** Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists deserve special consideration. Without recent exposure, these people are not at increased risk of acquiring *M. tuberculosis* infection. Underlying immune deficiencies associated with these conditions theoretically would enhance the possibility for progression to severe disease. Initial histories of potential exposure to tuberculosis should be included for all of these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. A TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged systemic corticosteroid administration, organ transplantation, use of TNF-alpha antagonists or blockers, or other immunosuppressive therapy in any child requiring these treatments.

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*IGRA indicates interferon-gamma release assay; HIV, human immunodeficiency virus; LTBI, latent *M. tuberculosis* infection.
^b Bacille Calmette-Guérin immunization is not a contraindication to a TST.
^c Beginning as early as 3 months of age for TST, 3 years of age for IGRA for LTBI and disease.
^d If the child is well and has no history of exposure, the TST or IGRA should be delayed for up to 10 weeks after return.