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

Clinical Policy Number: 07.01.02

Effective Date: March 1, 2014
Initial Review Date: November 20, 2013
Most Recent Review Date: November 18, 2015
Next Review Date: November 2016

Policy contains:
- Tuberculosis screening.
- Mantoux test.
- Interferon-gamma release assays.
- Automated real-time nucleic acid amplification.

Related policies:
None

ABOUT THIS POLICY: Arbor Health Plan has developed clinical policies to assist with making coverage determinations. Arbor Health Plan’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 Arbor Health Plan 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. Arbor Health Plan’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. Arbor Health Plan’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Arbor Health Plan will update its clinical policies as necessary. Arbor Health Plan’s clinical policies are not guarantees of payment.

Coverage policy

Arbor Health Plan considers the use of interferon-gamma release assays for tuberculosis (TB) to be clinically proven and, therefore, medically necessary when all of the following criteria are met:

- The individual being screened meets the appropriateness guidelines for age from the CDC or the American Academy of Pediatrics Report of the Committee on Infectious Diseases/Red Book

Limitations:

- All other uses of interferon-gamma release assays and automated real-time nucleic acid amplification technology for tuberculosis screening are not medically necessary.
- The use of interferon-gamma release assays 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.
- TB culture of sputum, when performed within the Arbor Health Plan network.

**Background**

Tuberculosis (TB) remains a worldwide health concern. Caused by infection with mycobacterium tuberculosis (M. tuberculosis), active or latent TB affects some two billion people. It is the eighth leading cause of death across the globe. However, the United States has experienced a decline in the prevalence of tuberculosis since its peak in 1992. The Centers for Disease Control and Prevention (CDC) reports a 2012 case rate in the United States of 3.2 active cases of TB per 100,000 people. Rates of infection are higher among individuals who are foreign-born, infected with human immunodeficiency virus (HIV) or in close contact with individuals with active TB.

**Current methods of screening for tuberculosis:**

Key to control of tuberculosis is cost-effective screening of the identified high-risk populations for case-finding. Over the past century, such screening has been performed with the use of tuberculin skin test (TST), also termed Mantoux skin testing. This involves the intradermal injection of purified protein derivative (PPD) on an initial encounter with a second encounter required for measurement of any subsequent area of induration which would reflect delayed hypersensitivity reaction of tuberculin antigen within the individual.

During infection with M. tuberculosis, circulating T cells release interferon gamma in regulating cellular immune response. The Food and Drug Administration (FDA) has approved two new interferon-gamma release assays (IGRA) are blood studies 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 the production of interferon gamma in the blood. The second test, T-SPOT®.TB assay (Oxford Immunotec, Marlborough, MA), is an ELISA immunospot test measuring the number of cells releasing interferon gamma. The specific interferon-gammas measured in both tests are selective for M. tuberculosis, and are not found in the BCG vaccine strains or most nontuberculosis mycobacteria.

All current testing methods (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, determinations of accuracy of any of these tests suffer from the inability to have a direct control for comparison. Recognizing that there are cost differences among all testing methods, the strategy employed takes into account the specific advantages of each type. For example, studies cited by the CDC suggest TST is a better predictor of older TB exposure, whereas the blood tests are more likely to be positive in very recent infection. Few studies have been performed with blood studies in children less than five years of age, a time of life when the child’s immune responses differ from those of more mature individuals. All methods of testing may provide borderline results, making interpretation difficult.
New test for rifampicin-resistant tuberculosis:

In the face of an increasing number of individuals harboring multi-drug resistant tuberculosis, there has been a need for a rapid determination of rifampicin resistance for individuals suspected of having active tuberculosis. The National Institutes of Health (NIH) funded research to develop TB-specific, cartridge-based nucleic amplification assay for detection in sputum samples of M. tuberculosis with rifampicin-resistant mutations. Current tests require culturing TB from sputum samples and performing drug sensitivity testing. This may require several months before the results can be obtained and used in treatment decisions.

The Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA) can provide results from sputum within one day from receipt in an appropriate laboratory. Compared to sputum cultures this test has a negative predictive value of more than 99 percent with a positive predictive value of more than 90 percent in populations in whom more than 15 percent of isolates demonstrate multi-drug resistance. The positive predictive value is significantly reduced when the incidence of rifampicin resistance is lower. The pretest probability of a positive test being truly positive is predicated upon the prevalence of resistant organisms in the community.

In 2010, the World Health Organization (WHO) released evidence-based guidelines on the use of the Xpert MTB/RIF system:

1. Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB. (Strong recommendation).
2. Only sputum has been tested. The use of other sources, such as urine or tissue, is still investigational.
3. The recommendations are based upon a single sputum sample and not multiple samples for testing.
4. This test may be used in children as it is a test of the tuberculosis bacillus and not of the immune system.
5. Conventional monitoring should be done. This test is used as a monitoring test.

Because of the low incidence of rifampicin-resistant tuberculosis in the United States, the CDC is not recommending the use of Xpert MTB/RIF in this country currently as the “positive predictive value is low for a rare disease” such as rifampicin-resistant TB.

Searches

Arbor Health Plan 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 November 9, 2014 and November 9, 2015. 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 interferon-gamma release assay 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. Furthermore, 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.

**Policy updates:**

We identified one WHO policy update on the use of the Xpert MTB/RIF assay (WHO, 2015). These findings do not change the conclusions of the original policy. Therefore, no changes to the policy are warranted.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mazurek (2010)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>CDC</td>
<td>• Selection of test should be based upon reason and context of testing, availability, and cost-effectiveness.</td>
</tr>
<tr>
<td></td>
<td>• Sensitivity and specificity vary among all testing methods since no direct test of M. tuberculosis.</td>
</tr>
<tr>
<td></td>
<td>• IGRA preferred for persons with low rates of returning to have TST reading, e.g., homeless or drug users.</td>
</tr>
<tr>
<td></td>
<td>• IGRA preferred for testing BCG vaccine recipients.</td>
</tr>
<tr>
<td></td>
<td>• TST preferred for children &lt; 5 years of age.</td>
</tr>
<tr>
<td></td>
<td>• Combining both TST and IGRA should be considered when an indeterminate test is obtained by either testing method.</td>
</tr>
<tr>
<td>Nienhaus (2011)</td>
<td><strong>Key points:</strong></td>
</tr>
<tr>
<td>Cost and cost-effectiveness of different TB-screening strategies</td>
<td>• Meta-analysis.</td>
</tr>
<tr>
<td></td>
<td>• Available studies on cost effectiveness provide strong evidence in support of IGRAs in screening high-risk groups.</td>
</tr>
<tr>
<td></td>
<td>• High-risk groups include immigrants from endemic countries, individuals with close contacts, health care workers.</td>
</tr>
<tr>
<td></td>
<td>• Until the body of research in this area is broadened, recommendations concerning this</td>
</tr>
</tbody>
</table>
Con

should be regarded with caution.

Dai (2012)  
IGRAs for TB  

**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.

CDC (2013)  
Xpert MTB/RIF assay Assay for Detecting Mycobacterium tuberculosis, Including Rifampin-Resistant Strains  

**Key points:**

- CDC continues to recommend following published U.S. guidelines for TB diagnosis and infection control practices, including the use and interpretation of nucleic acid amplification-based test results.
- There is generally a low rate of multi-drug resistance in the U.S., currently at 1.8%, so the Xpert MTB/RIF should have limited use.

WHO (2011, updated 2015)  
Policy statement  

**Key points:**

- 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).
- 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).
- 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).

**Glossary**

**Automated real-time nucleic acid amplification 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** — 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** — Blood tests for tuberculosis based upon the release of interferon-gamma from T cells in response to mycobacterium tuberculosis infection.

**Latent tuberculosis (TB)** — 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.

**PPD** — Another name for the Mantoux test as cited above.

**References**

**Professional society guidelines/other:**


**Peer-reviewed references:**


T-Spot.TB. TB—P070006. Inspections, Compliance, Enforcement and Criminal Investigations. FDA Web site. 


**Clinical trials:**

Searched clinicaltrials.gov on November 9, 2015 using terms "Interferon-gamma release assay" | Open Studies | tuberculosis. 10 studies found, 2 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>
</thead>
<tbody>
<tr>
<td>86480</td>
<td>Tuberculosis test, cell mediated immunity antigen response measurement; gamma interferon.</td>
<td></td>
</tr>
<tr>
<td>86481</td>
<td>Enumeration of gamma interferon-producing T cells in cell suspension.</td>
<td></td>
</tr>
<tr>
<td>86580</td>
<td>Skin test; tuberculosis, intradermal.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>V74.1</td>
<td>Screening for tuberculosis.</td>
<td></td>
</tr>
<tr>
<td>042</td>
<td>Human immunodeficiency virus (HIV).</td>
<td></td>
</tr>
<tr>
<td>V60.0</td>
<td>Lack of housing (homeless).</td>
<td></td>
</tr>
<tr>
<td>V60.2</td>
<td>Inadequate material resources (medically underserved, low-income populations).</td>
<td></td>
</tr>
<tr>
<td>V60.6</td>
<td>Person living in residential institution (correctional institutions, nursing homes, mental institutions, other long-term residential facilities, homeless shelters).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A15.0</td>
<td>Tuberculosis of lung</td>
</tr>
<tr>
<td>A15.4</td>
<td>Tuberculosis of intrathoracic lymph nodes</td>
</tr>
<tr>
<td>A15.5</td>
<td>Tuberculosis of larynx, trachea and bronchus</td>
</tr>
<tr>
<td>A15.6</td>
<td>Tuberculous pleurisy</td>
</tr>
<tr>
<td>A15.7</td>
<td>Primary respiratory tuberculosis</td>
</tr>
<tr>
<td>A15.8</td>
<td>Other respiratory tuberculosis</td>
</tr>
<tr>
<td>A15.9</td>
<td>Respiratory tuberculosis unspecified</td>
</tr>
<tr>
<td>B20</td>
<td>Human immunodeficiency virus [HIV] disease</td>
</tr>
<tr>
<td>Z59.0</td>
<td>Homelessness</td>
</tr>
<tr>
<td>Z59.3</td>
<td>Problems related to living in residential institution</td>
</tr>
<tr>
<td>Z59.4</td>
<td>Lack of adequate food and safe drinking water</td>
</tr>
<tr>
<td>Z59.5</td>
<td>Extreme poverty</td>
</tr>
<tr>
<td>Z59.6</td>
<td>Low income</td>
</tr>
<tr>
<td>Z59.7</td>
<td>Insufficient social insurance and welfare support</td>
</tr>
<tr>
<td>Z59.9</td>
<td>Problem related to housing and economic circumstances, unspecified</td>
</tr>
<tr>
<td>Z63.6</td>
<td>Dependent relative needing care at home</td>
</tr>
<tr>
<td>Z63.79</td>
<td>Other stressful life events affecting family and household</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>HCPCS Level II</th>
<th>Description</th>
<th>Comment</th>
</tr>
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</table>


FIG 3.13. GUIDANCE ON STRATEGY FOR USE OF TST AND IGRA BY AGE AND BCG-IMMUNIZATION STATUS

- If BCG vaccinated?
  - Yes: Age <5 y?
    - Yes: TST preferred
    - No: IGRA preferred
  - No: Likely to return for TST reading?
    - Yes: Either TST or IGRA acceptable
    - No: IGRA preferred
- If BCG vaccinated?
  - Yes: Age <5 y?
    - Yes: TST preferred
    - No: IGRA preferred
- Negative TST: Testing complete unless criteria A are met, then IGRA
- Positive TST: Testing complete unless criteria B are met, then IGRA

Criteria A
1. High clinical suspicion for TB disease and/or
2. High risk for infection, progression, or poor outcome

Criteria B
1. Additional evidence needed to ensure adherence and/or
2. Child healthy and at low risk and/or
3. NTM suspected
### Table 3.79. Tuberculin Skin Test (TST) and IGRA Recommendations for Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children for whom immediate TST or IGRA is indicated:</td>
</tr>
<tr>
<td>• Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)</td>
</tr>
<tr>
<td>• Children with radiographic or clinical findings suggesting tuberculosis disease</td>
</tr>
<tr>
<td>• Children immigrating from countries with endemic infection (eg, Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees</td>
</tr>
<tr>
<td>• Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries</td>
</tr>
</tbody>
</table>

| Children who should have annual TST or IGRA:                                   |
| • Children infected with HIV infection (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.

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IGRA indicates interferon-gamma release assay; HIV, human immunodeficiency virus; LTBI, latent *M. tuberculosis* infection.

*Beginning as early as 3 months of age for TST, 3 years of age for IGRA for LTBI and disease.*

*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.*