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

Clinical Policy Number: CCP.1067

Effective Date: March 1, 2014
Initial Review Date: November 20, 2013
Most Recent Review Date: December 3, 2019
Next Review Date: April 2021

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

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’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 Prestige Health Choice 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. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

The use of interferon-gamma release assays for diagnosis of tuberculosis is clinically proven and, therefore, medically necessary when the following criteria are met (American Academy of Pediatrics, 2015; Mazurek, 2010; World Health Organization, 2013):

- The individual being screened meets the appropriateness guidelines from the Centers for Disease Control and Prevention Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium Tuberculosis Infection (Mazurek, 2010) (Appendix A), or

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.

Tuberculosis 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 multidrug resistance is not medically necessary.

Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website may be accessed at [http://ahca.myflorida.com/Medicaid/](http://ahca.myflorida.com/Medicaid/).

**Alternative covered services:**

- Skin testing with a Mantoux test.
- Tuberculosis culture of sputum, when performed within the Prestige Health Choice 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 tuberculosis affects about 1.7 billion people across the globe. Patients with renal failure undergoing dialysis are at an increased risk of tuberculosis due to attenuated cellular immunity (Houben, 2016).

In the United States, 9,093 new tuberculosis cases were reported in 2017, up to 80% of which are associated with long-standing latent infection. Up to 13 million Americans, many of whom were born outside the United States in areas where the disease is common, have latent tuberculosis infections. Of these, 5 to 10% will progress to infectious tuberculosis at some point in their lifetime. The Centers for Disease Control and Prevention (2018) estimates that up to 300,000 cases of the disease have been prevented in the past 20 years.

Key to control of tuberculosis is cost-effective screening of high-risk populations. Over the past century such screening has been performed with the tuberculin skin test, or Mantoux skin test. This involves the intradermal injection of purified protein derivative 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 based upon the release of interferon gamma. The QuantiFERON®-Tuberculosis Gold In-Tube (Cellestis Inc., Valencia, California) test employs enzyme-linked immunosorbent assay to measure interferon gamma in
the blood. The T-SPOT® tuberculosis test (Oxford Immunotec Inc., Marlborough, Massachusetts) is an enzyme-linked immunosorbent assay immunospot test measuring the number of cells releasing interferon gamma (Centers for Disease Control and Prevention, 2011).

All current blood testing methods for tuberculosis (tuberculin skin test, QuantiFERON®-Tuberculosis Gold In-Tube, 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 Centers for Disease Control and Prevention suggest tuberculin skin testing is a better predictor of older tuberculosis exposure, whereas interferon-gamma release assay is more likely to be positive in recent infection.

Interferon-gamma release assays can be taken in a single visit, and results are available within 24 hours. The assay does not alter responses to future tuberculosis tests, and is unaffected (i.e., not subject to false positive tests) from earlier bacille Calmette-Guérin vaccinations. Drawbacks of the assays include reduced accuracy of results after any errors in sample collection, transportation, running, or misinterpretation. It is not known if positive results of interferon-gamma release assays predict later development of tuberculosis (Centers for Disease Control and Prevention, 2011).

The Centers for Disease Control and Prevention (2011) does not recommend giving tuberculin skin tests and interferon-gamma release assays at the same time. Limited data exists on results for these assays on children under age 5, persons recently exposed to *M. tuberculosis*, immunocompromised persons, and serial assays. Testing may also be expensive.

A parallel concern in testing for tuberculosis is the increasing prevalence of the multidrug resistant *M. tuberculosis* organism. The National Institutes of Health has funded research to develop a tuberculosis-specific, cartridge-based nucleic amplification assay for detection of *M. tuberculosis* with rifampicin-resistant mutations. The Xpert® MTB/RIF assay (Cepheid, Sunnyvale, California) can provide culture and sensitivity results from sputum within one day. The test has a negative predictive value of more than 99% with a positive predictive value of more than 90% in populations in which more than 15% of isolates demonstrate multidrug resistance (Centers for Disease Control and Prevention, 2016; Theron, 2011).

**Searches**

Prestige Health Choice searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.
- The Cochrane Library.

We conducted searches on September 25, 2019. Search terms were “tuberculosis,” “interferon-gamma,” “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**

Recent guidelines from the Centers for Disease Control and Prevention (Appendix A) and the American Academy of Pediatrics (Appendix B) grant that interferon-gamma release assay is a helpful diagnostic test for the identification of *M. tuberculosis* infection and latent tuberculosis. All agree that the usage experience of interferon-gamma release assay in children younger than age five is insufficient to make conclusions about test efficacy in this cohort; however, interferon-gamma release assay performs well in children ages five years and older. The sensitivity of interferon-gamma release assay for detecting tuberculosis infection in children is similar to that of the tuberculin skin test, while interferon-gamma release assay specificity seems to be higher than that of the tuberculin skin test. A systematic review (Overton, 2018) of 32 studies (n = 4,856) compared the ability of interferon-gamma release assays and tuberculosis skin tests to accurately diagnose tuberculosis in persons with human immunodeficiency virus. The QuantiFERON-Tuberculosis Gold In-Tube assay detected the same number of latent tuberculosis cases as did the skin test. All interferon-gamma release assays detected more positive tuberculosis cases than the skin test in subjects with active tuberculosis. Authors concluded that robust evidence for the superiority of interferon-gamma release assay testing was lacking.

Another systematic review and meta-analysis of the ability of interferon-gamma release assays to detect tuberculosis in persons with human immunodeficiency virus included 11 studies (Huo, 2016). Sensitivity rates of QuantiFERON-Tuberculosis Gold In-Tube and the T-SPOT tests were 69% and 89%, while specificity rates were 76% and 87%. While the new assays are not optimal for detecting tuberculosis in this population, T-SPOT testing appears to be more effective.

A large analysis (Doan, 2017) of 157 studies found that in testing immune-competent adults, the sensitivity of tuberculin skin testing (84%) was far greater than that of QuantiFERON-Tuberculosis Gold In-Tube (52%). Specificity of QuantiFERON in persons with and without bacille Calmette-Guérin vaccination (93% and 97%) compared favorably with specificity for skin testing (79% and 100%). In immune-competent adults, T-SPOT sensitivity is superior to that of QuantiFERON-Tuberculosis Gold In-Tube (68% versus 52%) and comparable in specificity (97% each). In non-vaccinated children, results are the same (sensitivity 98% versus 82%; specificity 98% each). Authors state that the results challenge the belief that interferon-gamma release assays are more accurate than skin tests.
A systematic review (Auguste, 2016) of 53 studies (n = 6,687) included 10 studies reporting evidence on cost-effectiveness of interferon-gamma release assays and tuberculosis skin tests. In immunocompromised populations, the most cost-effective strategy was the QuantiFERON-Tuberculosis Gold In-Tube followed by the tuberculin skin test; in children, the most cost-effective approach was the reverse. In children recently arrived from countries with a high prevalence of tuberculosis, the skin test only was less costly and more effective than a combination.

The same research team also performed a systematic review (Auguste, 2017) of 17 studies, including five in children, 10 in immunocompromised people, and two in persons recently arrived, and compared the effectiveness of interferon-gamma release assays with tuberculin skin tests. The studies of children and persons recently arrived documented mixed results, while the studies of immunocompromised persons showed no difference between interferon-gamma release assays and tuberculin skin tests. The quality of the data was substandard — highly uncertain, a high risk of bias, and highly heterogeneous.

A systematic review and meta-analysis (Lu, 2016) compared the accuracy of three methods of tuberculosis testing. The sensitivity for nine studies of QuantiFERON-Tuberculosis Gold In-Tube, 12 studies for T-SPOT, and 16 studies for tuberculin skin tests showed sensitivity of 0.842, 0.840, and 0.665, respectively, and specificity of 0.745, 0.658, and 0.633. Authors concluded that the two types of interferon-gamma release assays were superior to tuberculin skin testing.

A systematic review and meta-analysis (Ruan, 2016) of 11 studies (n = 1,940) of rheumatic patients found that the two interferon-gamma release assays had pooled agreements of 72% and 75% compared with the tuberculin skin test. Authors concluded that the two assays are more effective at identifying latent tuberculosis infection than conventional skin tests.

A systematic review and meta-analysis (Ferguson, 2015) of 102 studies (17 included in the meta-analysis) determined that in hemodialysis patients, the two interferon-gamma release assay tests had sensitivities of 53% and 50%, compared to just 31% for tuberculin skin tests. Specificities were roughly equivalent (69% and 67% versus 63%). Authors question the practice of using tuberculin skin tests on persons undergoing hemodialysis.

A systematic review (DeKeyser, 2014) of 19 studies showed that the T-SPOT test was significantly more sensitive than the tuberculin skin test (90% to 64%) in detecting tuberculosis, and insignificantly higher in specificity (77% to 57%). Similar patterns were observed for QuantiFERON-Tuberculosis Gold In-Tube (75% to 64% for specificity; 71% to 70% for specificity). Authors point out that the added cost of the two newer tests has added value.

A systematic review and meta-analysis (Laurenti, 2016) of 15 studies assessed the efficacy of diagnosing active *M. tuberculosis* in immunocompetent children under age 18. No differences were detected in sensitivity of QuantiFERON-Tuberculosis Gold In-Tube (89.6%), T-SPOT (88.5%), and tuberculin skin tests (88.2%). Specificity was greater for the two interferon-gamma release assays (95.4% and 96.8%) compared to 86.3% for skin tests.
A systematic review (Sollai, 2014) included 31 studies (n = 6,183 children) for QuantiFERON-Tuberculosis Gold In-Tube, 14 studies (n = 2,518 children) for T-SPOT, and 34 studies (n = 6,439 children) for tuberculin skin tests. In high-income countries, sensitivity rates for the two interferon-gamma release assays were 0.79 and 0.67 for all studies. In low-income nations, comparable rates were 0.57 and 0.61. In microbiologically confirmed cases, no difference existed between high- and low-income countries. Higher specificity for interferon-gamma release assays compared to tuberculin skin testing was observed in high-income countries (97 – 98% versus 92%) but not in low-income countries (85 – 93% versus 90%).

A systematic review (Chiappini, 2012) of 11 studies of children with active tuberculosis found sensitivity detected by QuantiFERON-Tuberculosis Gold In-Tube to be 0.79, higher than T-SPOT with 0.74 and lower than tuberculin skin tests at 0.82. Respective specificity rates were 0.95, 0.96, and 0.83, with the new interferon-gamma release assay showing greatest effectiveness.

A systematic review (Clifford, 2015) of 30 studies, mostly in countries with a low incidence of tuberculosis, reviewed results of interferon-gamma release assay tests at the end of treatment for active or latent tuberculosis. Most results remained positive, and thus these tests are not likely to be useful for monitoring effectiveness of tuberculosis treatment.

A systematic review and meta-analysis (Aggarwal, 2015) of 34 studies (n = 1,812) assessed the ability of interferon-gamma release assays to diagnose tuberculous pleural effusion. The pooled sensitivity and specificity for the blood assays were 0.77 and 0.71, respectively, and 0.72 and 0.78 for pleural fluid assays, both considered to have poor diagnostic accuracy for patients suspected to have tuberculous pleural effusion.

A systematic review (Zwerling, 2012) of 24 studies found that testing for tuberculosis among health care workers in low-prevalence areas was no more effective when interferon-gamma release assays were used as opposed to tuberculin skin tests.

A review (Owusu-Edusei, 2017) of 43 million Americans with employer-based private health insurance revealed that 1.4% had at least one outpatient claim for tuberculosis testing in 2013. The tuberculosis skin test was most commonly performed (86% of claims). The average cost ranged from $9 for the tuberculosis skin test to $106 for the T-SPOT test. Of the total cost of $53 million, employees paid $9 million, or 17%.

Prior to 2009, skin tests were the only type of tuberculosis testing allowed by the Centers for Disease Control and Prevention in the Medical Examination of Aliens screening process (Department of Homeland Security, 2009). On November 1, 2009, the Centers updated its policy by also allowing both interferon-gamma release assays during screening.

**Policy updates:**
A total of four guidelines/other and 16 peer-reviewed references were added to this policy in September 2018, and one guideline/other and nine peer-reviewed references were removed.

In 2019, we updated one reference and added four references. No policy changes are warranted at this time.

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

No Local Coverage Determinations identified as of the writing of this policy.

**Appendix A**

The Centers for Disease Control and Prevention (2015) has published a fact sheet and list of recommendations regarding the use of interferon-gamma release assays (i.e., QuantiFERON-Tuberculosis Gold In-Tube and T-SPOT):

- Interferon-gamma release assays can be used in place of (but not in addition to) tuberculin skin tests in all situations in which Centers for Disease Control and Prevention recommends tuberculin skin tests 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 interferon-gamma release assays are preferred for testing:
  - Persons who have received bacille Calmette-Guérin (either as a vaccine or for cancer therapy).
o Persons from groups that historically have poor rates of return for tuberculin skin test reading.

• Tuberculin skin testing is preferred over interferon-gamma release assays for testing children less than 5 years of age.

• As with tuberculin skin tests, interferon-gamma release assays 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 tuberculin skin tests and interferon-gamma release assays is not recommended. However, results from both tests might be useful in the following situations:
  o 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., human immunodeficiency virus-infected persons or children under 5 years of age who are exposed to a person with infectious tuberculosis).
    ▪ There is clinical suspicion for tuberculosis disease (e.g., signs, symptoms, or radiographic evidence suggestive of tuberculosis disease) and confirmation of *M. tuberculosis* infection is desired.
    ▪ Taking a positive result from a second test as evidence of infection increases detection sensitivity.
  o 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 tuberculin skin test is due to bacille Calmette-Guérin). A positive interferon-gamma release assay might prompt greater acceptance of treatment for latent tuberculosis infection as compared with a positive tuberculin skin test alone.
    ▪ The person has a low risk of both infection and progression from infection to tuberculosis 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 interferon-gamma release assay or performing a tuberculin skin tests might be useful when the initial interferon-gamma release assay result is indeterminate, borderline, or invalid and a reason for testing persists.

The Centers for Disease Control and Prevention 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 Centers 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


Table 3.79. Tuberculin Skin Test (TST) and IBRA Recommendation for Infants, Children, and Adolescents

<table>
<thead>
<tr>
<th>Children for whom immediate TST or IGRA is indicated:</th>
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<tbody>
<tr>
<td>• Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)</td>
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<tr>
<td>• Children with radiographic or clinical findings suggesting tuberculosis disease</td>
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<tr>
<td>• Children immigrating from countries with endemic infection (e.g., Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees</td>
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<tr>
<td>• Children with travel histories to countries with endemic infection and substantial contact with indigenous people from such countries³</td>
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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.

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

³Bacille Calmette-Guerin immunization is not a contraindication to a TST.

³Beginning 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.