



BlueCross BlueShield
of Alabama

Name of Blue Advantage Policy:

Gamma Interferon Blood Test for Diagnosis of Latent Tuberculosis

Policy #: 186
Category: Laboratory

Latest Review Date: September 2019
Policy Grade: **Effective May 26, 2011: Active Policy but no longer scheduled for regular literature reviews and updates.**

Background:

Blue Advantage medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
 - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
 - *Furnished in a setting appropriate to the patient's medical needs and condition;*
 - *Ordered and furnished by qualified personnel;*
 - *One that meets, but does not exceed, the patient's medical need; and*
 - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill **Original Medicare for covered services that are related to **clinical trials** that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

The presence of latent tuberculosis is routinely assessed by a tuberculin skin test (TST), which detects a cell-mediated immune response to the injected tuberculin purified protein derivative (PPD). Although TST has been in use for over a century, its limitations include poor specificity (i.e., numerous false positive results), the need to examine the site 48 to 72 hours after injection, and the subjective interpretation of results (i.e., estimation of the diameter of induration). For example, a negative result may indicate no exposure to the organism, or simply an inability of the lymphocytes to respond. A positive result may indicate acute current infection, past exposure without infection, or exposure to other mycobacterial antigens, including prior immunization with BCG. In addition, the underreporting of positive tuberculin skin tests by health care workers has been an ongoing concern that has led to an educational campaign - the National Tuberculosis Training Initiative sponsored by the Centers for Disease Control and Prevention and other national medical and nursing organizations.

The development of interferon-gamma release assays (IGRAs) is an important advance in the diagnosis of latent tuberculosis infection (LTBI). IGRAs are in vitro blood tests of cell-mediated immune response; they measure T cell release of interferon-gamma following stimulation by antigens unique to *Mycobacterium tuberculosis*. The assays, originally investigated in cattle, are based on the incubation of whole blood with PPD and the subsequent immunoassay of gamma interferon released from PPD-reactive T cells, if present. The production of gamma interferon represents activation of the cell-mediated immune system, similar in concept to the immunologic basis of the TST. However, the in vitro blood test avoids the problem of requiring a second office visit to interpret the TST, and the well-known variability in the subjective assessment of intradermal skin reaction. Another feature of the in vitro assay is its ability to distinguish between reactivity from *Mycobacterium tuberculosis* reactivity related to mycobacteria other than tuberculosis (MOTT). MOTT is a significant cause of false positive TST results.

Two types of IGRAs exist. Both are approved by the US Food and Drug Administration (FDA) and are also available in Canada, Europe, and many other countries.

- The QuantiFERON-TB Gold In-Tube (QFT-GIT). This test has replaced the second generation QuantiFERON-TB Gold (QFT-G)
 - This is an enzyme linked immunosorbent assay (ELISA)-based whole-blood test that uses peptides from three TB antigens (ESAT-6, CFP-10, and TB7.7) in an in-tube format; blood is drawn into three tubes containing either TB antigens, mitogen, or nothing (negative control). The result is reported as quantification of interferon-gamma in international units per mL. An individual is considered positive for *M.tuberculosis* infection if the interferon-gamma response to TB antigens is above the test cut-off (after subtracting the background interferon-gamma response in the negative control).
 - There is also a newer assay, the QuantiFERON-TB Gold Plus (QFT-Plus) that became available in the U.S. in July 2018. This test has two TB antigen tubes, unlike the older QFT-Gold assay (which has a single TB antigen tube). Both tubes contain peptide antigens ESAT-6 and CFP-10 (not TB7.7). A positive result from either tube is interpreted as a positive test.

- The T-SPOT.TB assay
 - This is an enzyme-linked immunospot (ELISPOT) assay performed on separated and counted peripheral blood mononuclear cells (PBMCs), which include circulating monocytes and lymphocytes. It uses ESAT-6 and CFP-10 peptides. The result is reported as a number of interferon-gamma-producing T cells (spot-forming cells in antigen wells minus negative control wells). An individual is considered positive for M.tuberculosis infection if the spot counts in the TB antigen wells exceed a specific threshold relative to the control wells.

Policy:

Effective for dates of service on or after August 1, 2014:

Blue Advantage will treat **interferon-gamma release assays (QuantiFERON-TB test (QFT) or the T-SPOT TB test)** as a **covered benefit** as a technique to diagnose latent tuberculosis infection in patients considered at high risk for latent tuberculosis infection, including but not limited to HIV-infected patients and intravenous drug abusers.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

IGRAs have specificity >95% for diagnosis of latent TB infection. The sensitivity for T-SPOT.TB appears to be higher than for QFT-GIT or TST (approximately 90, 80, and 80%, respectively). The higher sensitivity of T-SPOT.TB may be useful for evaluating individuals with immunosuppressive conditions. TST specificity is high in populations not vaccinated with BCG (97%). Among populations where BCG is administered, it is much lower although variable (approximately 60%). IGRA sensitivity is diminished by HIV infection. Lower CD4 counts have been associated with higher rates of indeterminate IGRA results; this is especially the case with QFT-GIT. TSPOT appeared to be less affected by immunosuppression than QFT-GIT, likely because the testing procedure requires that an adequate number of peripheral blood mononuclear cells are placed in each test well, even if the overall peripheral blood lymphocyte count is low.

For the diagnosis of active TB, IGRA sensitivity and specificity are poor, particularly in high TB incidence settings. Specificity is poor because these populations will have high prevalence of LTBI and the immune-based tests cannot distinguish between active disease and latent infection. Sensitivity is reduced because of the temporary anergy of the acute illness. Therefore, IGRAs should not be used for diagnosis of active TB.

Active Disease

Neither IGRAs nor the TST have high accuracy for the prediction of active TB, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment. Several longitudinal studies show that incidence rates of active TB, even in IGRA-positive individuals in high TB burden countries, are low, suggesting that a vast majority (>95%) of IGRA-positive individuals do not progress to TB disease during follow-up. This is similar to the TST. Thus, further research is needed to identify biomarkers that are highly predictive and can identify latently infected individuals who are at highest risk of disease progression.

Monitoring Therapeutic Response

IGRAs should not be used to monitor response to therapy, given potential problems with reproducibility, conversions, and reversions. Some data suggest that a large percentage of active TB patients become IGRA-negative by the end of TB therapy, while other studies do not support this. Some data suggest that TB patients can remain IGRA-positive, even years after TB treatment. One study noted that changes in IGRA results were not associated with smear and culture conversion to negative results, reinforcing the lack of utility for active TB treatment monitoring. In a clinical trial among contacts with LTBI, isoniazid (INH) therapy played no role in observed decreases in *Mycobacterium tuberculosis* (MTB) antigen-specific T cell responses over time.

Testing Population

In order to minimize false-positive IGRA results, testing should be risk-based; ordinarily, testing for TB infection should not be performed on low-risk individuals.

Summary

Interferon gamma release assays (IGRAs) are diagnostic tools for latent tuberculosis infection (LTBI). They are in vitro blood tests of cell-mediated immune response to *Mycobacterium tuberculosis* and measure T cell release of interferon (IFN)-gamma following stimulation by antigens specific to *M. tuberculosis*. IGRAs are not affected by Bacille Calmette-Guérin (BCG) vaccination status. Therefore, they are superior to the tuberculin skin test (TST) for evaluation of LTBI in BCG-vaccinated individuals, since TST specificity varies depending on the timing and number of BCG vaccination.

IGRAs cannot distinguish between latent infection and active TB disease and should not be used for diagnosis of active TB in adults. In children, IGRA may be used as a supplementary diagnostic tool for evaluation of active TB disease, although evidence for use of IGRAs in children is limited. A negative IGRA does not rule out active TB at any age.

For serial testing in populations exposed to TB, data are insufficient for interpretation of IGRA conversions and reversions, and several studies suggest poor assay reproducibility. Until more definitive evidence and consensus emerges, laboratories should report both quantitative results and qualitative results, and all quantitative IGRA results should be interpreted with caution. To reduce assay variability, laboratories should ensure standardization of preanalytical procedures such as tube agitation, time interval between specimen collection and incubation, and duration of incubation.

Practice Guidelines and Position Statements Centers for Disease Control and Prevention (CDC)

The CDC 2010 guidelines address both T-SPOT.TB and the QuantiFERON-TB Gold In-Tube (QFT-GIT). The guidelines indicate that 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 Mycobacterium tuberculosis infection. This includes contact investigations, testing during pregnancy, and screening of healthcare workers and others undergoing serial evaluation for M. tuberculosis infection. However, subsequent data has noted poor reproducibility for serial IGRA testing in healthcare workers, and several groups have called for revised guidance. Populations in which IGRAs are preferred over TST include individuals who have received BCG (either as a vaccine or for cancer therapy) and individuals from groups that historically have poor rates of return for TST reading. TST is preferred over IGRAs for testing children less than five years of age. Despite the preferences noted, use of either TST or IGRA is acceptable in these groups; each institution should evaluate the availability and benefits of IGRAs in prioritizing their use. 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 (whichever test was used first) is **negative** and the risk for infection, progression to disease, and/or poor outcome is high (e.g., HIV-infected individuals or children under five years of age who are exposed to a person with infectious TB); or
- When the initial test is **positive, AND:**
 - Additional evidence of infection would be helpful to encourage adherence to latent tuberculosis infection (LTBI) treatment (for example, in the setting of foreign-born healthcare workers [HCWs] who believe their positive TST is due to BCG).
 - The person has a low risk of infection and progression from infection to TB disease. A positive result from the second test 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.

Repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate and there is a persistent reason for testing. Multiple negative results from any combination of these tests cannot exclude M. tuberculosis infection. 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 cost of testing.

National Institute for Health and Clinical Excellence (NICE)

NICE guidelines were published in 2006. In April 2011, the updated NICE guidelines were published. The main recommendations are:

- TST should be used as the first-line test for LTBI in contacts of infectious cases and new entrants from high-incidence countries. Those with positive TST results may be considered for IGRA testing, depending on BCG status and results of the TST.

- In persons with HIV infection and low CD4 counts (<200), IGRA plus concurrent TST is recommended.
- In persons with HIV infection and CD4 counts of 200 to 500, IGRA alone or IGRA plus concurrent TST is recommended.
- In persons with immunocompromising conditions (other than HIV), IGRA alone or IGRA plus concurrent TST is recommended.
- IGRA testing may be used as the sole test for LTBI in hard-to-reach groups and in an outbreak situation when a large number of people might need to be screened.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (USPSTF) published on September 6, 2016, a B-recommendation for the screening for latent tuberculosis infection in at risk adults. Screening tests included are recommended the Mantoux tuberculin skin tests (TSTs) and interferon-gamma release assays (IGRAs). The USPSTF found no evidence on the optimal frequency of screening for latent tuberculin infection. Depending on specific risk factors, screening frequency could range from one-time only screening among persons who are at low risk for future tuberculosis exposure to annual screening among those who are at continued risk of exposure.

Key Words:

Tuberculosis, QuantiFERON-TB[®], QFT, tuberculin skin test (TST), HIV, latent tuberculosis infection, QuantiFERON[®]-TB, QFT-G, T-Spot[®]-TB, QuantiFERON[®]-TB Gold In-Tube (QFT-GIT), T-SPOT.TB assay, QuantiFERON-Gold, QuantiFERON-Gold Plus

Approved by Governing Bodies:

FDA premarket approval on November 28, 2001 as a diagnostic device intended as an aid in the diagnosis of latent tuberculosis infection, and to aid in the evaluation of individuals suspected of having M. tuberculosis infection.

QuantiFERON[®]-TB Gold Test was approved by the FDA May 2, 2005

T-Spot[®]-TB was FDA approved in July 2008

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:

CPT codes:

86480	Tuberculosis test, cell mediated antigen response measurement; gamma interferon
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Policy History:

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This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plans contracts.