Gamma Interferon Blood Test for Diagnosis of Latent Tuberculosis
Archived Medical Policy

Archived medical policies are no longer subject to periodic review, are maintained for reference, and may be returned to active status if the need is identified.

Policy # 00044
Original Effective Date: 06/05/2002
Archived Date: 09/14/2011

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider a gamma interferon blood test 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, to be eligible for coverage.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers a gamma interferon blood test for all other indications to be investigational.*

Background/Overview
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 48–72 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.

Recently, an in vitro assay has been investigated as an alternative to TST. The assay, originally investigated in cattle, is based on the incubation of whole blood with antigens specific for TB and the...
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subsequent immunoassay of gamma interferon released from 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 tuberculin skin test. However, the in vitro blood test avoids the problem of requiring a second office visit to interpret the tuberculin skin test, 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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
The QuantiFERON-TB® assay (CSL Biosciences, Australia) for detection of gamma interferon production is a blood test that has been used in humans in Australia. In November 2001, this test received approval from the FDA in the United States for the following indication:

- “The QuantiFERON-TB test is intended as an aid in the detection of latent Mycobacterium tuberculosis infection.”

In December of 2004, QuantiFERON-TB GOLD received FDA approval for the detection of latent TB. This test differs from the first generation test in that instead of using PPD as the stimulus for interferon production, two antigens, ESAT-6 and CFP-10, are used. These antigens are present in mycobacterium tuberculosis, but are not present in those exposed to BCG or non-tuberculous mycobacteria.

Rationale/Source
The published medical literature regarding the QuantiFERON-TB test consists of several articles comparing the sensitivity and specificity of the gamma interferon blood test with the TST in various populations of patients. Streeton and colleagues compared the results of a tuberculin skin test and a gamma interferon blood test in 952 Australian volunteers, including both a group of military recruits and those attending a specialist respiratory medicine practice. The purpose of the study was to determine appropriate cut-off levels for interpreting the results of the gamma interferon TB blood test such that the blood test would be equivalent to the TST. Using the designated cut-off point, the specificity of the gamma interferon blood tests was 98% (407/417 individuals with no known exposure to tuberculosis were negative) and sensitivity was 90% (163/182 untreated patients with positive TST results were positive). The gamma interferon blood test was also positive in 43% (55/128) of those with known exposure to TB but TST negative. These results suggest that the blood test may be more sensitive than the TST, but the investigators did not pursue microbiological or histopathologic confirmation of these results.

Converse and colleagues compared the results of the gamma interferon blood test with the TST in a high-risk population of 67 patients, consisting of HIV seropositive and HIV seronegative intravenous drug users.

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The participants in the study were categorized into six groups according to their HIV status, TST status, and presence of anergy. The results of the gamma interferon test were then compared with the results of the TST for each group. The gamma interferon blood test agreed 89%–100% of the time with a positive TST in both HIV positive and negative subjects, but the blood test was positive 52% of the time among those with a negative TST or with anergy. Similar to the Streeton study above, these results suggest that the gamma interferon blood test may be more sensitive than the tuberculin skin test, although further investigation is needed to assess the clinical significance of discordant results.

The available data suggest that the gamma interferon blood test can be calibrated to produce results comparable to the tuberculin skin test. Whether or not the blood test will be more sensitive than the skin test requires further research. Aside from the diagnostic performance, an advantage of the blood test is that only one office visit is required, unlike the skin test in which a repeat office visit to assess results of the skin test may be required. While a repeat office visit may not be considered necessary in screening reliable, low-risk patients, a second office visit is considered more important in high-risk patients, i.e., in HIV-positive patients or intravenous drug users. In some studies, the call-back rates of these patients have been below 50%. The objective interpretation of the blood test, compared to the subjective interpretation of the skin test, is also perceived as a potential advantage.

Further data are available from the FDA Summary of Safety and Effectiveness, representing the data presented to the FDA as part of the FDA-approval process. The clinical data included 1,042 individuals undergoing screening for latent M. tuberculosis infection. Patients underwent both a tuberculin skin test and a QuantiFERON-TB test. The results of this trial have also been published in the peer-reviewed literature.

Agreement of the QuantiFERON-TB with the TST was 84.8%. Within this group agreement was 88.1% for subjects with no history of BCG vaccination and 70% for those who had. Reactivity to mycobacteria other than M. tuberculosis (MOTT) can also cause false positive TST reactions. Of the 80 individuals with TST positive discordant results, 13 were classified as QuantiFERON negative due to reactivity to MOTT. The authors concluded that QuantiFERON-TB was equivalent to TST in its ability to detect latent M. tuberculosis infection. As noted in the discussion section, a patient only needs to be seen once for the QuantiFERON-TB test, whereas for TST the patient needs to self-evaluate or return for evaluation at 48 to 72 hours later to have his or her adverse reaction measured. In some situations, as many as 65% of individuals fail to return to have their TST read. As noted in the FDA summary of safety and effectiveness, "Whatever the merits of accuracy of the TST itself, the failure to obtain a result for the test in such a large proportion of individuals has considerable public health implications. A test for latent TB infection, which has equivalent performance to the TST and does not require subject to return to have the test read, has obvious public health benefits and can only lead to more truly infected individuals being treated than is currently the case."
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It should be noted that for many patients undergoing routine screening for TB, such as the routine screening of schoolchildren with no other known risk factors, self-assessment of the skin reaction by parents or caretakers is considered adequate. In contrast, patients at high risk for latent TB infection, such as patients with HIV infection or intravenous drug use, are typically called back to have formal interpretation of the skin reaction. This population of patients would probably derive the most benefit from an in vitro assay.

Results of large clinical trials using the QuantiFERON-TB GOLD diagnostic test (see Background/Overview section) have not been published in the peer-reviewed literature, but are available on the manufacturer’s Web site. The specificity of this test was assessed in a population of over 300 patients considered to be at low risk of TB; 80% of them had undergone previous vaccination with BCG. The specificity was estimated at 98.7%; in contrast, more than 30% of the BCG-vaccinated subjects had positive skin tests (i.e., a false positive result). The sensitivity was evaluated in untreated patients with active TB; in this population the sensitivity was approximately 90%. As noted above, the test is indicated in patients with suspected latent TB; however, it is difficult to study this population due to the lack of readily available gold standard diagnostic tests. However, QuantiFERON-TB GOLD was performed in contact investigations and in a large healthcare work study. In all cases, positive results were significantly related to well known risk factors for TB, such as length of exposure of a contact, past history of working with TB patients, etc. Mori and colleagues reported on the sensitivity and specificity of an interferon gamma assay using the same antigens CFP-10 and ESAT-6 in BCG immunized patients (i.e., low risk) and in patients with newly diagnosed active infection. The specificity was estimated at 98.1%, and the sensitivity was 89.0%.

References
5. FDA Summary of Safety and Effectiveness: www.fda.gov/ohrms/dockets/ac/01/briefing/3795b2 01.pdf

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines (BCBSLAMPCG) are obtained from Current Procedural Terminology (CPT®), copyright 2010 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.
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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<th>Code Type</th>
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Policy History

Original Effective Date:  06/05/2002
04/18/2002  Medical Policy Committee review
06/05/2002  Managed Care Advisory Council approval
06/24/2002  Format revision. No substance change to policy.
06/01/2004  Medical Director review
06/15/2004  Medical Policy Committee review. Policy change from investigational to eligible for coverage.
06/28/2004  Managed Care Advisory Council approval
09/07/2005  Medical Director review
09/22/2005  Quality Care Advisory Council approval
07/07/2006  Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
11/07/2007  Medical Director review
11/15/2007  Medical Policy Committee review. No change to coverage eligibility.
12/03/2008  Medical Director review
12/17/2008  Medical Policy Committee review. No change to coverage eligibility.
12/04/2009  Medical Policy Committee approval
12/01/2010  Medical Policy Committee approval
09/01/2011  Medical Policy Committee approval
09/14/2011  Medical Policy Implementation Committee approval. Policy archived.

Next Scheduled Review Date:  Archived Medical Policy

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Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. in accordance with nationally accepted standards of medical practice;

B. clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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