A gamma interferon blood test is considered *medically necessary* as a technique to diagnose latent tuberculosis infection in patients considered at high risk, including but not limited to HIV-infected patients and intravenous drug abusers.

**DESCRIPTION:**

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 TSTs 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 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 tuberculin skin test. 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.

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 U.S. Food and Drug Administration (FDA) in the United States with the following indication:

"The QuantiFERON-TB test is intended as an aid in the detection of..."
GAMMA INTERFERON BLOOD TEST FOR DIAGNOSIS OF LATENT TUBERCULOSIS
MED207.120
POSTED DATE: 6/11/2003
EFFECTIVE DATE: 8/15/2003

latent Mycobacterium tuberculosis infection."

RATIONALE:

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. The participants in the study were categorized into 6 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 the gamma interferon blood test may be more sensitive than the TST, 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 TST. 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 skin test, is also perceived as a potential advantage.

2002 Update

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 TST 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 their 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."

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 care givers 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.

PRICING:
None
REFERENCES:

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

DISCLAIMER:

State and federal law, as well as contract language, including definitions and specific inclusions/exclusions, takes precedence over Medical Policy and must be considered first in determining coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Any benefits are subject to the payment of premiums for the date on which services are rendered. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically. HMO Blue Texas physicians who are contracted/affiliated with a capitated IPA/medical group must contact the IPA/medical group for information regarding HMO claims/reimbursement information and other general polices and procedures.