Interferon gamma release assays for tuberculosis screening

Clinical Policy ID: CCP.1067

Recent review date: 12/2021

Next review date: 4/2023

Policy contains: automated real-time nucleic acid amplification, interferon-gamma release assays, Mantoux test, tuberculosis screening.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center'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 Sandhills Center 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. Sandhills Center 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. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Interferon-gamma release assays for diagnosis of tuberculosis is clinically proven and, therefore, medically necessary when the following criteria are met (Lewinsohn, 2017):

- Members over age five who meet the following criteria: (1) are likely to be infected with *Mycobacterium tuberculosis*, (2) have a low or intermediate risk of disease progression, (3) it has been decided that testing for latent tuberculosis infection is warranted, and (4) either have a history of Bacille Calmette-Guerin vaccination or are unlikely to return to have their tuberculin skin test read.
- Members over age five who are likely to be infected with *Mycobacterium tuberculosis*, who have a low or intermediate risk of disease progression, and in whom it has been decided that testing for latent tuberculosis infection is warranted.
- Members over age five who are likely to be infected with *Mycobacterium tuberculosis* who have a high risk of progression to disease and in whom it has been determined that diagnostic testing for latent tuberculosis infection is warranted (a tuberculin skin test may be used as well).
- If testing is obliged by law or credentialing bodies, for members over age five who are unlikely to be infected with *Mycobacterium tuberculosis* despite guidelines to the contrary, including a second test if the initial test is positive.

Limitations

Interferon gamma release assays for diagnosis of tuberculosis is not clinically proven and, therefore, not medically necessary, for:

- Members at low risk for *Mycobacterium tuberculosis* infection and disease progression.
- Healthy members under age five for whom it has been decided that diagnostic testing for latent tuberculosis infection is warranted; a tuberculin skin test should be used.

Alternative covered services

- Skin testing with a Mantoux test.
- Tuberculosis culture of sputum, when performed within the AmeriHealth Caritas 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, 8,920 new tuberculosis cases were reported in 2019 (Schwartz, 2020). 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).

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 (Theron, 2011).

Positive results of tuberculosis testing is a good predictor of elevated risk of the disease. In a systematic review/meta-analysis of 122 studies (n = 33,811), incidence of tuberculosis for participants with a positive result of interferon gamma release assay and T spot tuberculin testing were 17.0% and 8.4% per 1000 person years, respectively (Campbell, 2020).

Findings

A guideline from the American Thoracic Society, Infectious Diseases Society of America, and Centers for Disease Control and Prevention outlines criteria on medical necessity of screening for tuberculosis using interferon gamma release assays; see coverage section of this policy for more detail (Lewinsohn, 2017).

An evidence review for the U.S. Preventive Services Task Force found no studies evaluating the direct benefits and harms of screening for latent tuberculosis infection in adult populations; and that both tuberculin skin tests and interferon gamma release assays are moderately sensitive and highly specific within countries with low tuberculosis rates (Kahwati, 2016).

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 five, persons recently exposed to *M. tuberculosis*, immunocompromised persons, and serial assays. Testing may also be expensive.

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.

A systematic review and meta-analysis to compare the sensitivity and specificity of interferon gamma release assays and T-spot tuberculin testing for the prediction of progression to clinical tuberculosis concluded evidence following individuals who had undergone testing and progressed to clinical tuberculosis is sparse. The study was unable to judge which method was superior (Auguste, 2019).

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/meta-analysis showed no difference in accuracy of diagnosing tuberculosis between QuantiFERON-TB Gold Plus and QuantiFERON-TB Gold In-Tube (Oh, 2021).

A more recent systematic review/meta-analysis of 20 studies of patients with human immunodeficiency virus included QuantiFERON-TB Gold In-Tube and T-SPOT.TB tests. Pooled sensitivity and specificity were 75% and 82%, respectively, which authors state are “good diagnostic values” (Ma, 2021).

A systematic review/regression meta-analysis of 34 studies (581,956 person-years) using interferon gamma assays showed increased risk of progression from latent to active tuberculosis increased with higher levels of assay, based on 788 cases. Compared to 0 international units per milliliter, the relative risk of progression to active tuberculosis steadily rose from 1.64 (at 0.35 units) to 22.31 (at 20 units) (Ledesma, 2021).

A systematic review (Auguste, 2016) of 53 studies (n = 6,687) Found 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.

A systematic review/meta-analysis of 40 studies (n = 50,592) individuals in 41 cohorts) showed that pooled risk ratio for the rate of disease progression in untreated individuals who were positive by interferon gamma release assays and tuberculin skin tests were 9.35 and 4.24, respectively. Pooled positive predictive value for the two groups were 4.5% and 2.3%, while negative predictive values were 99.7% and 99.3%. Authors conclude that individuals positive from interferon gamma release assays, but not those positive from tuberculin skin tests, might benefit from preventive treatment (Zhou, 2020).

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 in the U.S., 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%, versus 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 meta-analysis of 15 studies evaluating efficacy of testing methods for active tuberculosis in immunocompetent children showed no significant differences in sensitivity between tuberculin skin test (88.2%), QuantiFERON-TB Gold In-Tube (89.6%), and T SPOT (88.5%). However, specificity for QuantiFERON (95.4%) and T-SPOT (96.8%) are significantly higher tuberculin skin test (86.3%) (Laurenti, 2016).

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 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.

References

On September 22, 2021, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “tuberculosis,” “interferon-gamma,” “tuberculosis screening,” and “gamma interferon assay tuberculosis.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

11/2013: initial review date and clinical policy effective date: 3/2014

11/2014: Policy references updated.

11/2015: Policy references updated.

11/2016: Policy references updated.

11/2017: Policy references updated.

11/2018: Policy references updated.

12/2019: Policy references updated. Policy ID changed to CCP.1067.

12/2020: Policy references updated.

12/2021: Policy references updated.