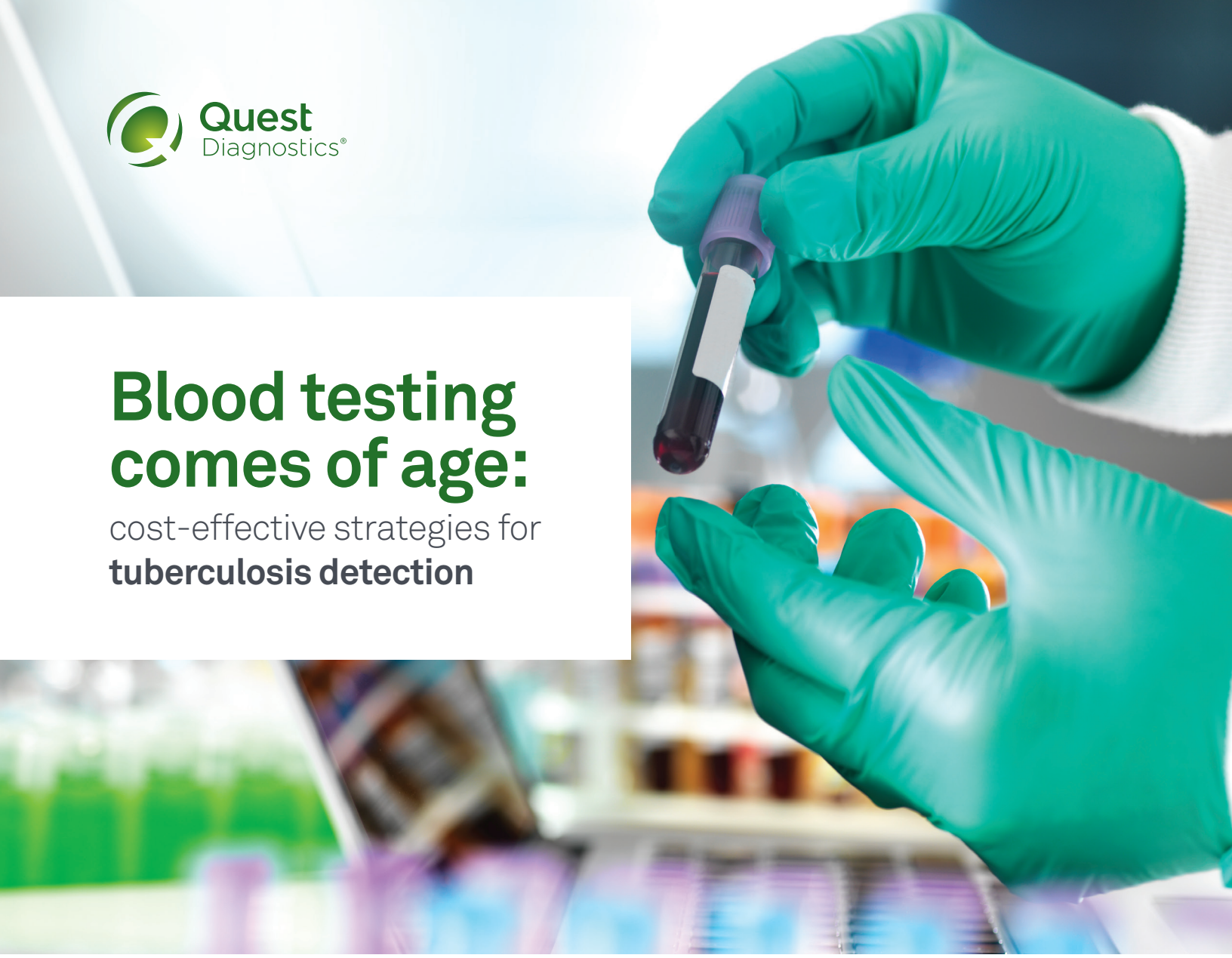
Quest Diagnostics®

Blood testing comes of age:

cost-effective strategies for **tuberculosis detection**



Abstract

Tuberculosis (TB) is one of the leading causes of infectious disease morbidity and mortality worldwide,[1] and is an ongoing concern for public health professionals. The tuberculin skin test (TST) was developed, between 1907-1908, to help detect latent tuberculosis infection (LTBI) and has remained the most commonly used test today, despite the availability of newer blood testing options that are easy to perform with more accuracy in the Bacillus Calmette-Guérin (BCG) vaccinated population. Physicians acknowledge the superior performance of the interferon-gamma release assay (IGRA), or TB blood test, and yet do not universally utilize this option for their patients due to a perceived higher cost. Here we explore the short- and long-term cost savings associated with TB blood testing compared with TST. Although per test costs are lower for TST, additional costs accumulate to make IGRA blood testing more cost effective. Specifically, with less false-positives delivered via IGRA blood testing programs, fewer unnecessary follow-up procedures need to be scheduled; and unlike TST, patients do not have to return days later to have their results read by a clinician. Furthermore, costs associated with a missed diagnosis are not easily quantified, but studies evaluating the quality-adjusted life years support the use of blood testing over skin testing to minimize missed diagnoses.[2,3] Finally, when considering the overall healthcare and societal costs of TB, it makes good financial sense to invest in a more robust testing system—with more accurate results—that will save you real money in the long run. This paper outlines the medical evidence supporting expanded use of IGRA blood tests for more cost-effective TB screening with significant clinical benefits for patients.

Evolution of tuberculosis (TB) testing

When *Mycobacterium tuberculosis*, the bacteria that causes TB, was first identified more than a century ago, the disease killed 1 out of every 7 people living in the US and Europe.[4] **TB remains a leading cause of infectious disease morbidity and mortality worldwide,[1] and therefore is an ongoing concern for public health professionals seeking to prevent its transmission.**

Individuals infected with *M. tuberculosis* may develop symptoms of TB with an active infection and risk transmitting the highly contagious airborne disease. However, approximately 30% of people exposed to the pathogen will develop LTBI, exhibiting no symptoms of the disease.[5] Some people have a higher risk of progressing to an active case including the immunocompromised, HIV patients, and people with diabetes. In fact, people living with HIV are 18 times more likely to develop active TB disease than people without HIV.[6] Left untreated, about 5% to 10% of people with LTBI will develop TB disease at some time in their lives.[7] Even with active screening and treatment, as many as 13 million Americans are estimated to have LTBI.[8] Certain groups are at higher risk for exposure to or infection with TB, such as those who live and/or work in congregate settings, healthcare workers, those who may travel frequently to places where TB is common, and those exposed to people in any of these groups. People who are already vulnerable face even higher risk, including those who are medically underserved, low-income, living with a chronic condition, persons whose TB has been treated inadequately or not at all, and children under the age of 5.[9] Therefore, identifying and treating LTBI is crucial to preventing both new cases and progression to highly contagious, active TB.[10]

For this purpose, TSTs were developed at the turn of the century to measure a person's immune response to a small amount of tuberculin fluid placed into the skin. Two to 3 days later, the extent of an induration at the insertion site is interpreted by a clinician to determine whether the individual was positive for LTBI.

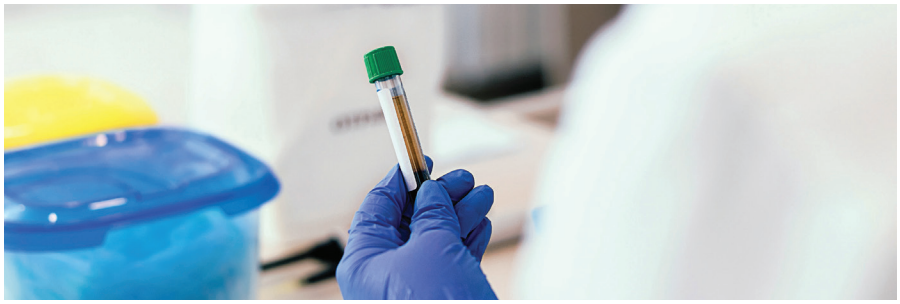
Skin testing today has remained virtually unchanged for over 100 years. However, TSTs have a number of disadvantages including the subjective nature of the readings, as test readers sometimes mistake erythema, or redness, for a positive reaction leading to a high rate of false positives. Secondarily, the need for 2 visits—the first to place the tuberculin and the second to interpret the reaction—may result in incomplete testing due to patients not returning for the reading and, therefore, becomes an administrative burden for the healthcare provider. In rare occasions, TST has also led to anaphylaxis.[11] Lastly, TSTs may register a false-positive result if the individual has had a BCG vaccine or if they experience a "booster" phenomenon from repeated testing with TSTs (as can be the case with healthcare workers).[12] Likewise, immunosuppressed patients risk receiving false-negative results from TST.[13]

~30%
of people exposed to the pathogen will develop LTBI, exhibiting no symptoms of the disease[5]

People living with HIV are
18x
more likely to develop active TB than people without HIV[6]

5%-10%
of people with LTBI will develop TB disease at some time in their lives[7]

13M
Americans are estimated to have LTBI[8]



Two TB blood testing methods, or interferon-gamma release assays (IGRAs), have been approved for use by the US Food and Drug Administration (FDA): the **QuantiFERON®-TB Gold Plus** (QFT-Plus) and the **T-SPOT®.*TB***[a] test (T-Spot). With either assay, healthcare personnel draw a patient's blood and send it to a laboratory for analysis and results.

Alternatively, the physician may send the patient to a laboratory patient service center for the blood draw. The test requires only 1 patient visit to draw blood and there is no risk of anaphylaxis. The results are not subject to reader bias and generally ready within 48 hours of receipt into the lab. Most importantly, the results of IGRAs are not affected by prior BCG vaccination. Therefore, fewer false positives are observed within this population as compared with TST.

With these advantages in mind, the Centers for Disease Control and Prevention (CDC) guidelines promote the advantages of blood testing.[10] However, TSTs have not been universally replaced by the more accurate blood testing technologies in the 2 decades since their introduction. Instead, healthcare providers use both methods to diagnose TB infection, preferring blood tests for specific patient populations, such as people who are BCG-vaccinated. Despite significant clinical evidence to the contrary (see listing to the right), there is a misconception that blood testing is relatively cost-prohibitive for patients. Therefore, many providers view blood testing only as an ancillary tool to be used on a selective basis or as a confirmatory test after a positive TST.

Table 1 IGRA vs TST: 2 types of tests for active TB infections

	Blood test	TST
1 blood draw or testing appointment	✓	✗
Low false-positive rates compared to skin tests in individuals who received a BCG vaccine[14]	✓	✗
Objective results	✓	✗
Preferred by the CDC for certain patient populations[15]	✓	✗
Not affected by BCG vaccine	✓	✗
Cost savings and practice efficiency (1 blood draw vs multiple office visits, no follow-ups due to false positives, costs of missing LTBI)	✓	✗

[a] Quest Diagnostics has validated the use of this assay under CLIA for processing specimens more than 8 hours after collection, up to 54 hours.

Clinical evidence

A selection of studies supporting the cost-effectiveness of IGRA testing over TSTs:

- Nijhawan AE, Iroh PA, Brown LS, Winetsky D, Porsa E. Cost analysis of tuberculin skin test and the QuantiFERON-TB Gold In-tube test for tuberculosis screening in a correctional setting in Dallas, Texas, USA. *BMC Infect Dis*. 2016;16(1):564.
- Nienhaus A, Schablon A, Costa JT, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Serv Res*. 2011;11:247.
- Kowada A. Cost effectiveness of interferon-gamma release assay for tuberculosis screening of rheumatoid arthritis patients prior to initiation of tumor necrosis factor-alpha antagonist therapy. *Mol Diagn Ther*. 2010;14:367-373.
- Pooran A, Booth H, Miller RF, et al. Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost effectiveness analysis. *BMC Pulmonary Medicine*. 2010; 10:7.
- de Perio MA, Tsevat, J, Roselle GA, et al. Cost-effectiveness of interferon gamma release assays vs tuberculin skin tests in healthcare workers. *Arch Intern Med*. 2009;169:179-187.
- Diel R, Lampenius N, Nienhaus A. Cost effectiveness of preventative treatment for tuberculosis in special high-risk populations. *Pharmacoeconomics*. 2015 Aug;33(8):783-809.

Illuminating the reality of TB testing costs

A comparative characterization of skin vs blood tests, including the short-term and long-term costs incurred for both patients and healthcare providers

Cost perception vs reality

In 2016, health economics researchers conducted a meta-analysis assessing the comparative economics of TB testing methods. They identified 28 studies which met strict inclusion criterion. All but 3 of the multifactorial studies concluded that testing with IGRAs, either alone or sequentially after a positive TST result, was more cost-effective than a single TST.[16] The relative costs can be broken down into short-term and long-term financial impact.

Short-term costs

Although the cost for the test reagent and laboratory time required to perform a blood test is higher compared to a TST,[17] the immediate costs to the healthcare provider are higher with TSTs due to the expense to administer the test. A trained clinician is needed to properly inoculate the skin and read the result. Results are also reliant on the patient's return visit to have the test read. With a blood test, the process is simplified to one-time blood collection. The specimen is sent to a lab and results are generally available within 48 hours after receipt at the lab.

In terms of direct patient out-of-pocket costs, based on the recommendations of the US Preventive Services Task Force, routine TB screenings should be covered without any cost-sharing obligations, although Medicare benefits may limit how frequently this test can be administered in a calendar year. For privately insured patients, incurred cost is likely limited to a nominal copay. And for uninsured patients, regional health departments generally offer the tests at variable, yet affordable rates (see Table 2). The greater cost to patients lies in the necessary time commitment for the TST, as patients must schedule and attend a second office visit for test interpretation.

Table 2

Sample pricing for TB testing
(San Francisco Department of Public Health)

Test	Cost
Skin test for TB (includes return visit for reading)	$49
2-Step skin test for TB (includes return visits for 2 readings)	$98
Blood test (which may include additional $29 venipuncture fee)[b]	$77

Source: https://www.sfcdcp.org/aitc/aitc-regular-prices-low-cost-or-free-vaccines/

[b] This study utilizes the QuantiFERON TB-Gold In-Tube test which is no longer commercially available; we are using this as a proxy for QuantiFERON-TB Gold Plus and TSPOT.*TB* since costs are comparable.

Table 3 Testing process and cost comparison

	Step		TST	Blood test
Short-term costs	1 Test visit		• Healthcare worker (HCW) time • Ongoing training in proper inoculation	If drawn in the office: • HCW time • Phlebotomist time If drawn in a patient service center, no HCW/phlebotomist time is needed
			• Copay or out-of-pocket expense • Patient time • Transportation costs	• Copay or out-of-pocket expense • Patient time • Transportation costs
	2 Interpretation visit		• HCW time • Ongoing training in proper interpretation • Patient reminders to return	N/A
			• Copay or out-of-pocket expense • Patient time • Transportation costs	N/A
Long-term costs	3 Follow-up visits/tests (due to false positives)		• HCW time	Low risk
			• Copay or out-of-pocket expense for physician visit, chest X-ray • Transportation costs	Low risk
	4 Costs of missing LTBI		• Costs for treatment of advanced disease • Disease transmission	Low risk

Provider Patient Society

In general, the medical practice incurs administrative and staff costs for both visits when TST is used (see Table 3). For the test provider, blood testing may result in lower overall costs due to improved efficiency stemming from a single visit, elimination of the need to train and maintain staff competency in administering and interpreting the TST, higher patient compliance, and more rapid results.

Long-term costs

Skin testing produces a higher rate of false-positive results (15%-40%) among those who have received the BCG vaccination.[5] As such, these individuals must undergo further testing such as chest X-ray, which can be avoided if IGRA is initially used. Likewise, a positive TST or IGRA indicates only that a person has been infected with TB bacteria. It cannot be used to stage the progression of TB disease. For diagnosis, other tests are needed. At a minimum, a chest X-ray is required to assess lung abnormalities consistent with TB disease. A chest X-ray is typically covered fully by health insurance or requires only a modest copay. For patients not covered by health insurance, a chest X-ray may cost approximately $110-$700,[18] depending on the provider and the number of views taken. Additional evaluation might depend on patient history including exposure to infectious TB and physical examination. Thus, patient expense grows exponentially if a false-positive result leads to additional testing or the initiation of counseling or treatment for LTBI.

Furthermore, TST relies on the patient to return for interpretation. Initial loss to follow up (LTFU) among TB patients is high, varying between 14.9% and 18%.[19] In most cases, this noncompliance simply requires the process to start anew. But, in the worst-case scenario, failure to complete the interpretation could lead to a missed diagnosis and future risk of active TB disease progression—with loss of productivity and income due to illness, and potential for TB transmission. This is also a concern for immunosuppressed patients who are at high risk for false-negative results even when LTBI is present.

Superior blood test sensitivity, specificity, and objectivity reduce both unnecessary follow-up and missed diagnoses in the BCG-vaccinated population. For a healthcare organization or employer that must test all incoming workers and maintain a program of serial screening, blood testing may yield significant cost reductions. And, when quality-adjusted life years—a measure inclusive of long-term effects—are compared, blood testing is significantly more cost effective than TST.[20]

Cost avoidance

The universal financial benefit gained from effective screening that limits the spread of TB cannot be overstated. The cost of TB treatment to the patient and healthcare system is significant. In 2020, CDC reported that the average cost of treating a person with TB disease increases with greater resistance. Direct costs average from $20,000 to treat drug-susceptible TB to $568,000 to treat the most drug-resistant form of the disease (XDR TB).[21] In addition, there are high societal costs due to the reduction in remaining lifetime productivity for patients who survive, and especially for those who die prematurely (see Table 4). Public health efforts to control TB spread, through effective and relatively low-cost screening programs, work hand-in-hand with healthcare workplace and private screening programs to keep LTBI relatively stable. Should screening efforts wane, resultant spikes in active TB and/or in TB drug resistance would strongly impact the economics of healthcare in the US.

Table 4 Average cost per TB case (2020 US dollars)[22]

	Non-multidrug-resistant TB	Multidrug-resistant TB	Extensively drug resistant TB
Direct treatment costs	$20,211	$182,186	$567,708
Societal w/o deaths	$24,661	$347,324	$729,039
Societal w/ deaths	$67,337	$419,530	$801,245

Conclusion

Today, TB screening programs that utilize advanced IGRA technology can provide more accurate detection at lower overall cost to the program than antiquated skin tests. Now, more than ever before, reliable TB testing is paramount to public health. New data suggest that the pandemic has had a substantial effect on TB trends. In the US, reported TB disease diagnoses fell 20% in 2020 and remained 13% lower in 2021 than TB disease diagnoses made prior to the COVID-19 pandemic.[23]

Therefore, it is time to assess the relative value of TB testing methods. While the legacy TST is cheaper in terms of materials, it requires more staff time, and a greater commitment on the part of the patient. The superior test sensitivity and specificity of IGRA assays greatly reduce unnecessary follow-up visits and out-of-pocket costs associated with false-positive results, as well as avoid false-negative results in immunosuppressed patients. Savings in labor and resources, 1 patient visit, and clinical accuracy, as evidenced in the medical literature, make the widespread replacement of skin tests with IGRA blood tests a cost-effective transition for US healthcare providers, with significant clinical benefits for patients.

20%
decline in reported TB diagnoses in 2020 vs prepandemic levels[23]

13%
decline in reported TB diagnoses in 2021 vs prepandemic levels[23]

Quest Diagnostics®

Visit **TBBloodTesting.com** to learn more about TB blood testing

The T-SPOT®.*TB* test is an in vitro diagnostic test for the detection of effector T cells that respond to stimulation by *Mycobacterium tuberculosis* antigens ESAT-6 and CFP-10 by capturing interferon gamma (IFN-γ) in the vicinity of T cells in human whole blood collected in sodium citrate or sodium or lithium heparin. It is intended for use as an aid in the diagnosis of *M tuberculosis* infection. The T-SPOT.*TB* test is an indirect test for *M tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

Up-to-date relevant warnings, precautions, side effects, and contraindications can be found at: http://www.oxfordimmunotec.com/north-america/

QuantiFERON-TB Gold Plus. This test is a blood-based interferon-gamma release assay (IGRA) used as an aid in the diagnosis of *Mycobacterium tuberculosis* infection. It is an immune response-based, indirect test for *M tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations. Additional testing is needed to determine if a person who has tested positive has latent tuberculosis (TB) infection or TB disease.

This in vitro diagnostic test uses a peptide cocktail simulating ESAT-6, CFP-10, and TB7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-γ (IFN-γ) by ELISA is used to identify in vitro responses to those peptide antigens that are associated with *Mycobacterium tuberculosis* infection.

References

1. CDC. Tuberculosis. Published April 6, 2020. Accessed August 25, 2022. https://www.cdc.gov/globalhealth/newsroom/topics/tb/index.html
2. Nienhaus A, Schablon A, Torres Costa J, et al. Systematic review of cost and cost-effectiveness of different TB-screening strategies. *BMC Health Serv Res*. 2011; 11:247. doi:10.1186/1472-6963-11-247
3. Diel R, Nienhaus A, Loddenkemper R. Cost-effectiveness of interferon-gamma release assay screening for latent tuberculosis infection treatment in Germany. *Chest*. 2007;131(5): 1424-1434. doi:10.1378/chest.06-2728
4. CDC. History of World TB Day. Updated December 12, 2016. Accessed October 19, 2022. https://www.cdc.gov/tb/worldtbday/history.htm
5. US Preventative Services Task Force. Final recommendation statement. Latent tuberculosis infection: screening. Published September 6, 2016. Accessed October 19, 2022. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/latent-tuberculosis-infection-screening
6. World Health Organization. Tuberculosis: key facts. Published October 14, 2021. Accessed October 25, 2022. https://www.who.int/news-room/fact-sheets/detail/tuberculosis
7. CDC. Questions and answers about tuberculosis. Reviewed June 22, 2021. Accessed October 27, 2022. https://www.cdc.gov/tb/publications/faqs/tb-qa.htm
8. CDC. Latent TB infection in the US—Published Estimates. Updated January 21, 2022. Accessed October 27, 2022. https://www.cdc.gov/tb/statistics/ltbi.htm
9. CDC. TB in specific populations. Updated October 25, 2021. Accessed October 19, 2022. https://www.cdc.gov/tb/topic/populations/default.htm
10. CDC. Latent tuberculosis infection: A guide for primary health care providers. Department of Health and Human Services; 2020. Accessed October 19, 2022. https://www.cdc.gov/tb/publications/ltbi/pdf/LTBIbooklet508.pdf
11. Youssef E, Wooltorton E. Serious allergic reactions following tuberculin skin tests. *CMAJ*. 2005;173(1):34. doi:10.1503/cmaj.050710
12. Al-Orainey IO Diagnosis of latent tuberculosis: can we do better? *Ann Thorac Med*. 2009; 4(1):5-9. doi:10.4103/1817-1737.44778.
13. Lee J, Choi HJ, Park I-N, et al. Comparison of two commercial interferon-gamma assays for diagnosing Mycobacterium tuberculosis infection. *Eur Respir J*. 2006:28(1):24-30. doi: 10.1183/09031936.06.00016906.
14. CDC. Tuberculin skin testing fact sheet. Updated November 2, 2020. Accessed August 29, 2022. https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm
15. CDC. Who should be tested for TB? Reviewed April 14, 2016. Accessed September 21, 2022. https://www.cdc.gov/tb/topic/testing/whobetested.htm
16. Koufopoulou M, Sutton AJ, Breheny K, et al. Methods used in economic evaluations of tuberculin skin tests and interferon gamma release assays for the screening of latent tuberculosis infection: a systematic review. *Value Health*. 2016;19(2):267-276. doi:10.1016/j.jval.2015.11.006.
17. Relias Media. Blood test vs. skin test: are hospitals ready for the TB 'gold standard'? Published February 1, 2006. Accessed October 19, 2022. https://www.reliasmedia.com/articles/126716-blood-test-vs-skin-test-are-hospitals-ready-for-the-tb-gold-standard
18. New Choice Health. Chest X-ray cost and procedure information. Accessed October 27, 2022. www.newchoicehealth.com/Directory/Procedure/77/Chest%20X-Ray
19. Mwansa-Kambafwile JRM, Chasela C, Ismail N, et al. Initial loss to follow up among tuberculosis patients: the role of ward-based outreach teams and short message service (SMS) technology (research proposal). *BMC Res Notes*. 2019;12(1): 737. doi:10.1186/s13104-019-4757-3.
20. Kowada A. Cost effectiveness of interferon-gamma release assay for tuberculosis screening of rheumatoid arthritis patients prior to initiation of tumor necrosis factor-α antagonist therapy. *Mol Diagn Ther*. 2010;14(6):367-373. doi:10.1007/BF03256394.
21. CDC. Drug-resistant TB. Reviewed October 13, 2022. Accessed October 27, 2022. https://www.cdc.gov/tb/topic/drtb/default.htm
22. CDC. Estimates for TB treatment costs (in 2020 US dollars). Reviewed October 21, 2021. Accessed October 27, 2022. https://www.cdc.gov/tb/publications/infographic/appendix.htm
23. CDC. Effect of COVID-19 on TB in the US. Updated March 24. 2022. Accessed August 29, 2022. https://www.cdc.gov/media/releases/2022/s0324-tuberculosis-covid-19.html

Image content features models and is intended for illustrative purposes only.

QuestDiagnostics.com