Quest Diagnostics®

IGRA Blood Testing:

Possibly the best kept secret in tuberculosis testing

Abstract

More than 100 years ago, healthcare professionals first used the Mantoux Tuberculin Skin Test (TST) to screen their patients for possible tuberculosis (TB). The test consisted of injecting a tiny amount of tuberculin fluid under the patient's skin; 2 to 3 days later, a trained clinician would examine the extent of skin induration and decide if it was caused by an immune response to TB.

Today, about 75% of America's modern healthcare professionals still rely on variations of the original TST technique to diagnose patients suspected of having TB—with mixed results.[1]

In 2005, the Interferon Gamma Release Assay (IGRA) was first introduced as a means to provide evidence of an immune response to TB. This revolutionary new technology enabled healthcare professionals to screen a patient for possible TB through the testing of a standard blood sample. The innovations introduced through IGRA blood testing solved many of the shortcomings of TSTs.

However, nearly 2 decades later, IGRAs have yet to replace traditional TSTs as the leading tool for screening patients for possible TB. The following is a look at some of the myths and misconceptions that may have slowed the adoption of IGRAs in the fight to test for—and thereby, hopefully, one day — eradicate TB.

Myths and misconceptions surrounding IGRAs

Some misunderstandings about IGRAs have stunted their widespread adoption.

Myth: IGRAs are…a luxury item

When they were introduced in 2005, IGRAs were quickly recognized as a more efficient method of TB testing—but being new can be expensive. Currently, IGRA and TST are comparably cost effective—when savings from the extra benefits of IGRAs (described below) are factored in.[2]

Myth: IGRAs are…not field proven

When first introduced, IGRAs were revolutionary, experimental, and edgy. Almost 2 decades later, IGRAs are now a fully refined, polished, industry-leading technology—in fact, when the American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), and Centers for Disease Control and Prevention (CDC) revised their guidelines for tuberculosis screening, they recommended that healthcare professionals select an IGRA over a "TST for persons at least 5 years of age who are likely to have *M. tuberculosis* infection."[3]

Myth: IGRAs are…not covered by insurance

Back when IGRAs were originally introduced, most healthcare insurance providers did not reimburse for the new procedure (which is common for many new technologies). This disincentive may have kept many healthcare providers from adopting the new technology. However, in 2016, the US Preventive Services Task Force (USPSTF) changed its screening guidelines to include IGRA technology, thus mitigating this disincentive to use the newer technology.[4]

Myth: IGRAs are…difficult to adopt

Hardly any special training or devices are necessary to collect a blood specimen for IGRA testing. Like any normal phlebotomy procedure, peripheral blood samples can be processed at your regular testing laboratory. In fact, IGRA specimen collection does not require the specialized training and subjective expertise that TST demands—such as knowing how and where to inject the tuberculin fluid and the experience to interpret the size, shape, and hardness of the resulting skin induration.*

* The CDC requires 6 hours of lecture and demonstration and 16 hours of supervised practice before an HCP is qualified to place and read TSTs.[5]

IGRA advantages over TST

In the following areas, IGRAs demonstrate advantages over TST:

Only one healthcare visit is required

A major drawback of TST is that the procedure requires at least 2 office visits—which must be scheduled between 48-72 hours apart. The extent of the patient's tuberculin skin induration response must be examined by a trained clinician within this time window, otherwise the results will be invalid, and the entire test will need to be reinitiated. It is not uncommon for patients to miss the follow-up exam, resulting in wasted office time and inconclusive TB tests. One study found that of 5,443 TSTs placed, 24% of patients did not return for the reading.[6] IGRAs, on the other hand, only require a blood sample, and the results are usually available in approximately 2-3 days, eliminating the need for a follow-up clinical reading of TST-induced skin induration.

Unaffected by BCG vaccinations

The Bacillus Calmette–Guérin (BCG) vaccine is used around the globe to stave off TB—outside of the US, it is estimated that 90% of children receive it. However, between 15%-40% of those vaccinated with BCG will display a false positive result skin test when they receive a TST.[7] These high false positivity results associated with TST lead to additional follow-up visits and testing (such as X-rays) that ultimately increase costs and tie up resources. IGRA tests, on the other hand, are not affected by this vaccine; that is why, in 2018, US immigration guidelines were modified to recommend the use of IGRAs over TSTs.[8]

> Between 15%-40% of those vaccinated with BCG will display a false positive result skin test when they receive a TST[7]

Ideal for nearly all patient populations

As mentioned earlier, the CDC, in its 2010 guidelines, stated that IGRA tests can be substituted for TST to screen for tuberculosis infections in all situations, but suggested that children, under 5 years of age, use TST if possible.[3] However, in its 2018 guidelines, the American Academy of Pediatrics (AAP) lowered the minimum age for IGRA testing from 5 years old to 2 years old.[9]

Objective results > subjective results

Since IGRA tests are objective by design—the results are obvious—approximately 97% are returned conclusively (either positive or negative).[10] TST results, on the other hand, are subjective. TST results must be deciphered by a trained clinician who manually measures the size of the skin bump, and then—taking the patient's medical history into consideration—must make an educated guess deciding if the size and texture of the skin induration indicates a tuberculosis infection.

IGRA tests are objective—approximately 97% are returned conclusively[10]

Seamless EMR updates

Being products of the 21st century, IGRA test results can be fed automatically into a patient's Electronic Medical Record (EMR), avoiding transcription errors, and ensuring that the results are available as soon as the test is complete. Meanwhile, TST results must be manually entered into an EMR system.

Better sensitivity and specificity

Sensitivity rates, or the lack of producing false negative results, rank in the mid-90% range for IGRAs yet do not quite reach 80% for TST. Specificity rates, or the lack of false positive results, for both IGRA and TST register at around 97%. However, those same specificity rates for TST can dip as low as 59% when tests are conducted on BCG-vaccinated patient populations (see Table 1 for more information).

Leading IGRA Products[11]

There are 2 types of TB blood tests approved by the FDA: the T-SPOT®.*TB* test, and the QuantiFERON®-TB Gold Plus (QFT-Plus) test. Quest Diagnostics is the only lab that offers both options for its clients.

T-SPOT®.*TB* (T-SPOT)

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. It is intended for use as an aid in the diagnosis of *M tuberculosis* infection. Refer to the **https://www.questdiagnostics.com/healthcare-professionals/clinical-education-center/faq/faq215** for more information.

QuantiFERON®-TB Gold Plus (QFT-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 current or prior *M tuberculosis* infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.

This in vitro diagnostic test uses a peptide cocktail simulating the TB ESAT-6, CFP-10, and TB7.7 proteins to stimulate cells in heparinized whole blood. Detection of interferon-γ (IFN-γ) by enzyme-linked immunosorbent assay (ELISA) is used to identify in vitro responses to these peptide antigens that are associated with *Mycobacterium tuberculosis* infection. Additional testing is needed to determine if a person who has tested positive has latent tuberculosis infection (LTBI) or TB disease. Refer to the **https://www.questdiagnostics.com/healthcare-professionals/clinical-education-center/faq/faq204** for more information.

Table 1 Comparison of T-SPOT, QFT-Plus, and TST[7]

	T-SPOT	QFT-Plus	TST
Required visits	1		2
Results reporting	Can be automatically reported to EMR		Results must be manually entered
Sensitivity	95.6%	94%	79%
Specificity	97.1%	97%	97% (as low as 59% with BCG-vacinated patients)

Conclusion

IGRAs are an efficient, convenient, and accurate way to test for evidence of an immune response to TB. This cutting-edge technology has been used successfully in the field since 2005. It is endorsed by key regulatory and medical organizations, and it's associated cost is covered by even the most basic insurance plans. If you have access to a laboratory, no extra equipment or training is required to take advantage of all the extras IGRAs have to offer.

And the perks to healthcare professionals are substantial. For example, the number of office visits required for testing is literally cut in half. Test results are available sooner (and digitally updated across the EMR in real time) with better sensitivity and specificity. This yields improved accuracy and reduces the costs of rescheduled appointments, unnecessary follow-up testing, and the premature launch of costly treatments on "false-positive" patients.

Finally, IGRAs have been declared safe for virtually anyone over 2 years of age, and testing results are not skewed—unlike TSTs—by patients who have had BCG vaccinations. At first pass the cost of TST may still be less expensive, but once the savings from IGRA's various benefits are accounted for, the true cost-effective champion becomes clear.

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. O'Connor L. Anticipating TB skin test antigen shortage, CDC proposes switch to IGRA lab tests. *360dx*. June 28, 2022. https://www.360dx.com/business-news/anticipating-tb-skin-test-antigen-shortage-cdc-proposes-switch-igra-lab-tests
2. Nienhaus A, Schablon A, Costa JT, 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. Hauk L. Tuberculosis: Guidelines for diagnosis from the ATS, IDSA, and CDC. *Am Fam Physician*. 2018;97(1):56-58. https://www.aafp.org/pubs/afp/issues/2018/0101/p56.html
4. Szkwarko D, Kim S, Carter EJ, et al. Primary care providers' and nurses' knowledge, attitudes, and skills regarding latent TB infection testing and treatment: A qualitative study from Rhode Island. *PLoS One*. 2022:17(4):e0267029. doi:10.1371/journal.pone.0267029
5. Blood test vs. skin test: Are hospitals ready for the TB 'gold standard'? *Hospital Employee Health*. February 1.2001. https://www.reliasmedia.com/articles/126716-blood-test-vs-skin-test-are-hospitals-ready-for-the-tb-gold-standard
6. Foroushani S., Crawford A., Woodbridge A, et al. Evaluating patient profile, follow-up rates and barriers to follow-up at a student-run, community-based tuberculosis testing program. *Journal of Student-Run Clinics*. 2022;8(1):1-8. https://journalsrc.org/index.php/jsrc/article/view/263
7. US Preventive 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
8. CDC. Intercountry (international) adoption tuberculosis FAQs. Updated August 6, 2019. Accessed January 25, 2023. https://www.cdc.gov/immigrantrefugeehealth/adoption/tuberculosis-faqs.html
9. Campbell J, Tabatneck M, Sun M, et al. Increasing use of interferon gamma release assays among children ≥2 years of age in a setting with low tuberculosis prevalence. *Pediatr Infect Dis J*. 2022;41(12) e534-e537. doi:10.1097/inf.0000000000003685
10. Takwoingi Y, Whitworth H, Rees-Roberts M, et al. Interferon gamma release assays for diagnostic evaluation of active tuberculosis (IDEA): test accuracy study and economic evaluation. *Health Technol Assess*. 2019;23(23):1-152. doi:10.3310/hta23230
11. Quest Diagnostics. Powering affordable care with an efficient way to test for tuberculosis fact sheet. Retrieved from https://provider.questdiagnostics.com/tbbloodtesting.

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

QuestDiagnostics.com