

Interferon Gamma Release Assay (IGRA): Frequently Asked Questions

Why use the IGRA Tuberculosis (TB) blood test?

Both the tuberculin skin test (TST) and IGRAs are aids in the diagnosis of TB infection and active TB disease. Neither test type can definitively rule TB in or out. An IGRA has the advantage over the TST of not requiring the patient to return for test result determination, and current IGRAs do not cross react with most non-TB mycobacteria, including Bacille Calmette-Guerin (BCG) strains. This makes IGRAs more specific for TB infection in some situations and thus better able to identify those most likely to benefit from TB infection treatment.

Who should be tested for TB with the IGRA?

The two test types for TB are the TST and IGRA, which are both useful in detecting TB infection in people who are at risk for having TB infection. In Los Angeles County (LAC), the Tuberculosis Control Program (TBCP) determined that the groups at highest risk for TB infection are people who are:

- Foreign born from countries with high rates of TB
- Immunosuppressed
- A contact to a person with TB disease
- Homeless or have a history of incarceration

To determine the risk for TB infection, please see the LAC TB Risk Assessments

(<http://publichealth.lacounty.gov/tb/TBTesting.htm>). Generally, patients at risk for TB infection who will benefit most from an IGRA are those who are foreign born and have been BCG vaccinated or are unlikely to return for TST reading.

Which test should persons with impaired immune function (including HIV infection) receive?

Maximum sensitivity for detection of TB infection is preferred in patients with the highest risk of reactivation TB, which include those with impaired immune function. Because the sensitivity of the IGRA in patients with impaired immune function is reduced, and these patients are more likely to progress to active TB disease if they have TB infection, LAC TBCP recommends that both TST and IGRA tests be performed whenever possible. A chest X-ray is recommended even if TST and IGRA are both negative as well. Patients with discordant results, e.g. (TST+/IGRA-) or (TST-/IGRA+), should be managed as if they are infected with TB, unless some overriding concern exists for false positive TST results (e.g. active non-tuberculous mycobacteria disease).

When can a patient receive both an IGRA and TST?

As above, unless they have impaired immune function, patients should not routinely receive both IGRA and TST. If you already have a test result from either TST or QuantiFERON-TB (QFT), it is reasonable to act based on information of one test. Persons with history of BCG vaccination should ideally be tested with an IGRA instead of TST to avoid dual testing.

My patient has a negative IGRA can they still be a person who may have active TB disease, or are they cleared?

Anyone with TB symptoms or TB risk factors and a new abnormal chest radiograph may be a person who could have TB disease, regardless of the IGRA or TST result. Like the TST, the IGRA is a useful but

imperfect diagnostic aid; it should never replace clinical judgment. Patients with a negative TST, as well as patients with a negative IGRA, can have active TB. Remember: contacts to active TB cases who are newly infected with TB can take up to 8 weeks to convert their IGRA or TST to a positive test.

Can I confirm a positive TST with an IGRA?

You can, however, there is no gold standard for the diagnosis of TB infection. False negative tests can also occur with the IGRA. A confirmatory IGRA, i.e. IGRA after a positive TST, is most useful in BCG vaccinated individuals or patients refusing treatment for TB infection. Please note, however, that a TST may cause boosting that may result in a subsequent positive IGRA.

The QFT result is indeterminate or T-Spot is borderline. What do we tell the patient and what do we do?

Indeterminate or borderline results can be caused by high background level of interferon-gamma (failure of the negative control), or lack of response to the mitogen (failure of the positive control). Repeat IGRA or TST placement should depend on patient and provider preference. The optimal follow-up of persons with indeterminate test results has not been determined, however, any follow-up strategy should include education to the patient as to what the indeterminate result means (either technical or host factor). When an indeterminate result is obtained, the medical provider should reassess the client for dates of live virus vaccinations. As per CDC recommendations, IGRAs should have a 4-6 week window after the administration of any live virus vaccine. Recommended follow-up on an indeterminate could include one of the following:

Retesting options:	Suggested Interval:
Retesting using the same IGRA	Waiting 4 weeks after the initial test may increase valid results although NYC and SF TB programs report >70% valid IGRA results when retesting within 1 week. Discuss urgency of results with patient.
Retesting using different IGRA	Immediately
Retesting with a TST	Immediately

My patient was IGRA-positive OR indeterminate/borderline, but he/she never came back for their results. What do I do?

Provide routine follow up per your clinic protocol. For patients with abnormal chest radiology, please submit a Confidential Morbidity Report by phone at 213-745-0800 or by fax at 213-744-0926. If your patient is associated with an outbreak or high risk group, e.g. living with HIV or homeless with unknown chest radiology status or normal chest radiology, you can report these patients and they will be prioritized for follow up.

How should an IGRA conversion (initial IGRA test negative with subsequent IGRA test positive) be evaluated when there is no documented TB exposure?

When using any test for TB infection, patients should be assessed for their individual risk of TB exposure and disease progression. Low risk patients should be discouraged from being tested in order to reduce false positive results. Reviewing the quantitative results can be helpful in determining false positives from high background nil results or wobblers (http://www.ctca.org/fileLibrary/file_481.pdf) around the cutoff point of 0.35 IU. In other situations a 3rd test is needed to further evaluate true conversion or the possibility of a false positive. Clinical decision making should always be done with full disclosure to the patient.

How should we use quantitative data in interpreting IGRA results?

Generally, quantitative results should not be used if they will not change clinical decisions and should not be used to determine therapeutic response to TB infection or active TB treatment. Although CDC recommends that laboratories report both qualitative and quantitative IGRA results, the use of quantitative values in routine clinical practice has not been established or evaluated. Situations where providers may benefit from reviewing quantitative results, include:

- a. Low risk of exposure and evaluating potential false positive IGRA results.
- b. Evaluating high-risk persons with negative IGRA results (e.g., immunocompromised persons, contacts with significant exposure to TB, and foreign-born children who are less than 5 years old with discordant positive TB skin test results).
- c. Evaluating a test conversion in an individual receiving serial testing, particularly in low risk transmission settings and when there is no history of TB contact.
- d. The evaluation of unexpected large proportions of results, such as indeterminate rates, exceeding 5% or high numbers of converters at a single location.

If you have any additional questions regarding the IGRA blood test, please contact:

LAC TBCP: (213) 745-0800 or the Curry International TB Center Warmline (for general, non-LA County related questions): (415) 502-4700

References:

1. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, Desmond E, Keane J, Lewinsohn DA, Loeffler AM, Mazurek GH, O'Brien RJ, Pai M, Richeldi L, Salfinger M, Shinnick TM, Sterling TR, Warshauer DM, Woods GL. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. 2017; 64(2):111-115. doi: 10.1093/cid/ciw778
2. Interferon Gamma Release Assays Clinical Guidelines in California. California Tuberculosis Controllers Association Web site. http://www.ctca.org/filelibrary/IGRAfinalchangessavedv5_1.pdf Updated 2012.
3. Interferon-Gamma Release Assays (IGRAs) – Blood Tests for TB Infection. Centers for Disease Control and Prevention Web site. <https://www.cdc.gov/tb/publications/factsheets/testing/igra.htm> Updated August 17, 2015.
4. Ma KC, Mathad JS, Wilkin T, Wu X, Li A, Singh H. Treat or Repeat? Variability of Interferon Gamma Release Assays in the Detection of Latent TB Infection among HIV-positive Patients, abstract: ID Week 2015. 2015. <https://idsa.confex.com/idsa/2015/webprogram/Paper51507.html>