Published in final edited form as:

JAMA. 2014 October 8; 312(14): 1460–1461. doi:10.1001/jama.2014.4928.

Interferon- γ Release Assays for the Evaluation of Tuberculosis Infection

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A woman in her 20s presents for follow-up of a tuberculin skin test (TST) placed 2 days earlier. The patient is from India and arrived in the United States 1 month ago for graduate studies. She reports no significant medical history and is unaware of any tuberculosis (TB) exposures. She has no symptoms. She received the BCG vaccine as a child. Laboratory testing showed normal chemistry and hematology values and a negative HIV test. The TST reveals an induration of 20 mm. Because of the TST result, the patient has a chest radiograph performed, which was unremarkable. Treatment for latent TB infection (LTBI) was recommended based on the positive TST, negative chest radiograph, and recent US arrival from a high-TB-incidence country. The patient asks whether the positive TST result could be due to her BCG vaccination and wants further testing before beginning therapy. Blood is drawn for an interferon- γ release assay (IGRA; see Figure for results).

Test Characteristics

A major challenge in diagnosing LTBI is lack of a gold standard test.¹ Latent *Mycobacterium tuberculosis* cannot be directly detected.² The commercially available US Food and Drug Administration–approved tests (TST and IGRA) rely on measuring host immune responses to *M tuberculosis* and cannot discriminate between LTBI and active TB. TST is a cutaneous delayed-type hypersensitivity response to purified protein derivative (PPD), a mixture of more than 200 *M tuberculosis* proteins,³ and it cross-reacts with BCG and nontuberculous mycobacteria. The 2 commercially available IGRAs, the QuantiFERON-TB Gold In-Tube test (Qiagen) and the T-SPOT. TB test (Oxford Immunotec), are more expensive than the TST (about \$50–\$100 each) and use 2 or 3 relatively TB-specific antigens that do not cross-react with BCG and are less likely to cross-react with nontuberculosis mycobacteria. The QuantiFERON uses an ELISA assay to measure the amount of interferon- γ released following in vitro stimulation of whole blood. The T-SPOT uses an ELISPOT assay to count the number of interferon- γ –producing cells.^{1, 4} Both IGRAs can yield indeterminate results if there is an inadequate mitogen response or a high nil (negative control) response. Discordance among LTBI tests is common.⁴ Estimated sensitivity and specificity of diagnostic tests for LTBI⁵ are shown in Table.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Application of Test Result to This Patient

The QuantiFERON IGRA was positive (Figure), suggesting previous infection with *M tuberculosis*, most likely in India. Active TB should be ruled out in people with a positive test for LTBI. In this patient, active TB was excluded given the absence of symptoms such as fever, night sweats, cough, or fever and a normal chest radiograph. If the patient had symptoms suggestive of TB or an abnormal chest radiograph, then further evaluation for active TB disease, including obtaining sputum samples for smear and culture for *M tuberculosis*, would be indicated.

What Are Alternative Diagnostic Approaches?

The Centers for Disease Control and Prevention guidelines indicate that a TST or an IGRA may be used to test for LTBI.⁴ An IGRA is preferred over the TST when testing people who are BCG vaccinated or are unlikely to return for TST reading. The TST is preferred for serial testing programs such as those involving health care workers because the IGRA has a high false-positive rate in this setting in the United States.⁷ The TST, vs an IGRA, is also recommended by the American Academy of Pediatrics for children.^{4, 8}

Performing the TST and an IGRA in this patient increased the number of office visits and health care costs.

Patient Outcome

The patient completed a course of treatment for LTBI. More than 80% of active TB in the United States is due to reactivation of LTBI and could be prevented by treating those with LTBI.² The highest-risk period for developing reactivation TB among foreign-born persons with LTBI is within the first 2 years of US arrival. Therefore, patients from high-TB–endemic areas should be targeted for testing and treatment of LTBI.⁹ Due to the limitations of currently available diagnostic tests for LTBI^{1, 5} and the low positive predictive value of a positive test in low-prevalence populations, testing for LTBI should be restricted to persons at high risk for LTBI and progression to active TB.⁸ This includes those with recent infection, including contacts of active TB cases, persons living with HIV, and immunocompromised persons.

Acknowledgments

Funding/Support: Supported in part by grants from the National Institutes of Health: National Center for Advancement of Translational Science (UL1TR000454), and the National Institute of Allergy and Infectious Diseases (K23AI103044).

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HOW DO YOU INTERPRET THESE TEST RESULTS?

- A.** The patient has active TB.
- B.** The patient has LTBI.
- C.** The patient does not have LTBI. No further evaluation is needed.
- D.** The patient needs further evaluation for active TB disease.

Answer

- B.** The patient has LTBI

Clinical Bottom Line: Interferon- γ Release Assays

- Testing for LTBI (whether an IGRA or TST is used) should be targeted and restricted to persons at high risk for LTBI and progression to active TB disease.
- An IGRA is preferred over the TST when testing people who are BCG vaccinated.
- Active TB should be ruled out in patients with a positive diagnostic test for LTBI prior to the initiation of therapy for the treatment of LTBI.

IGRA Test Results, IU/mL					
	Nil Result ^a	TB Antigen Result	Mitogen Result	TB Antigen Minus Nil ^a	Mitogen Minus Nil ^a
Patient Values	0.12	1.42	5.52	1.30	5.40

IGRA Results Interpretation ^b			
Nil, IU/mL ^a	TB Antigen Minus Nil, IU/mL ^a	Mitogen Minus Nil, IU/mL ^a	Result ^c
≤8.0	<0.35	≥0.5	Negative
	≥0.35 and <25% of Nil value	≥0.5	
	≥0.35 and ≥25% of Nil value	Any	Positive
	<0.35	<0.5	Indeterminate
	≥0.35 and <25% of Nil value	<0.5	
>8.0	Any	Any	

Figure.

IGRA indicates interferon- γ release assay; TB, tuberculosis.

^aExplanation of values: nil (the interferon- γ concentration in plasma from blood incubated without antigen [negative control]); TB antigen minus nil (the interferon- γ concentration in plasma from blood stimulated with 3 relatively specific TB peptides) minus nil; and mitogen minus nil (the interferon- γ concentration in plasma from blood stimulated with mitogen minus nil). The mitogen tube contains a mitogen (phytohaemagglutinin-P) that is a nonspecific stimulator of T-cells. It is used as a positive control to ensure the capacity to respond to antigens and also serves as a control for correct blood handling and incubation.

^bFor this IGRA, 1 mL of blood is drawn into each of 3 tubes (nil [negative control], mitogen [positive control], and TB antigens tube). The TB response (TB antigen minus nil) is calculated as the difference in interferon- γ concentration in plasma from blood stimulated with TB antigens minus the interferon- γ concentration in plasma from blood incubated without antigen (nil). A positive IGRA test result occurs when all of the following criteria are met: (1) the nil value is less than 8 IU/mL; (2) the TB antigen minus nil response is greater than or equal to both 0.35 IU/mL and 25% of the nil value; and (3) there is a positive mitogen response. Data are based on package insert available at <http://www.quantiferon.com/irm/content/PI/QFT/2PK/US.pdf>.

^cFor negative, positive, and indeterminate results, the probability of *Mycobacterium tuberculosis* infection is not likely, likely, and uncertain, respectively.

Table

Sensitivity and Specificity of the TST and IGRA Among BCG-Vaccinated and Non-BCG-Vaccinated Persons for Latent TB Infection^a

Test Characteristic	QuantiferON-TB Gold In-Tube	T-SPOT.TB, %	TST, %
Sensitivity ^b	≈ 80	≈ 90	≈ 80
Specificity, % ^b			
Non-BCG-vaccinated	>95	>95	>95
BCG-vaccinated	>95	>95	≈ 60

Abbreviations: IGRA, interferon-γ release assay; TB, tuberculosis; TST, tuberculin skin test.

^aData were adapted.⁵

^bIn immunocompromised persons, sensitivity of diagnostic tests is less than that shown.⁶ Because there is no gold standard test for latent TB infection, sensitivity is estimated among culture-confirmed TB cases while specificity is estimated among low-risk individuals in low-incidence settings with no known TB exposure.