

PRACTICE ALERT

Public health issues influencing your practice

When, and when not, to use the interferon-gamma TB blood test

Consider the following cases of patients needing testing for tuberculosis:

1. A 55-year-old nurse returns to work after 10 years. Her pre-employment evaluation requires a test for tuberculosis.
2. A 35-year-old woman has lupus. Her physician is considering placing her on prednisone and wants to know if she has latent TB infection.
3. A homeless man presents to the clinic stating he has lost his TB medications that he has taken over the past 2 months. His diagnosis of TB was made in another city; he cannot remember its name. The physician wants to confirm the diagnosis of TB.
4. A 5-year-old from Mexico with a history of BCG vaccination presents for a preschool health evaluation.
5. A 35-year-old immigrant from Africa is pregnant and presents for prenatal care.

Patients 1 and 2 above are logical candidates for the newer interferon-gamma blood test to detect tuberculosis (TB). Patients 3, 4, and 5 are not; They should be evaluated with the conventional TB skin test.

The advantages and disadvantages of both kinds of testing are described in this review.

■ Is a better test at hand?

The TB skin test, using an intradermal injection of purified protein derivative, has been used to assist in the detection of active and latent TB for more than a century. However, this test has its problems: difficulty in accurately measuring and interpreting the reaction; low sensitivity in those with depressed cell-mediated immunity and those with early infections; lower specificity in those with a history of bacille Calmette-Guérin (BCG) vaccination and infection with other Mycobacteria; the need for 2 visits within 48 to 72 hours for test interpretation; and boosting of immune response caused by the TB skin test itself (see **Boosting phenomena**).

Those who work in TB control programs have sought better diagnostic tools. Two that are available today are the interferon-gamma blood tests QuantiFERON-TB (QFT) and QuantiFERON-TB GOLD (QFTG). The QFT and QFTG measure the release of interferon-gamma by sensitized lymphocytes when exposed to antigens of *Mycobacterium tuberculosis*.

The QFTG, licensed in 2004, is an improvement over the earlier QFT, licensed in 2001, which included antigens that *M tuberculosis* shares with other commonly encountered Mycobacteria. The QFTG is more specific to *M tuberculosis*, although it does cross-react with several relatively uncommon

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TABLE 1

Advantages/disadvantages of the QFTG

Advantages of QFTG compared with the TB skin test

- Improved sensitivity and specificity for latent TB infection
- Unaffected by prior BCG vaccination
- Only 1 patient visit required
- No effect on repeat tests or on skin tests through immune boosting
- Less subject to measurement bias and error

Disadvantages of QFTG

- Phlebotomy required
- May not be offered by all laboratories
- Costs \$80–\$100 per test
- Blood samples must be processed within 12 hours of collection

Boosting phenomena

In those who have had prior Mycobacteria infections or BCG vaccine, cell-mediated immunity can wane and a TB skin test can therefore be negative. However, the skin test can boost the person’s immunity, and a second skin test can then be positive as a result of the immune boost. This can cause someone who is actually a reactor (someone who reacts positively to a skin test because of prior Mycobacteria infection) to look like a converter (someone who has a negative skin test at a recent point in time followed by a positive skin test, indicated recent infection with Mycobacteria). It is recommended that adults who have not had a skin test within 12 months and who will need repeated skin tests should receive a 2-step skin test on initial evaluation. A 2-step skin test involves an initial test followed by a second one 1–2 weeks later.

nontuberculous Mycobacteria. These tests have several advantages over the older skin test (TABLE 1).

■ **Factors to keep in mind when considering the QFT**

In spite of the theoretical advantages of the QFT, research on its use is at an early stage. It can be considered a testing option for persons identified in TABLE 2. It may ultimately prove to be the test of choice for patients who have previously received a BCG vaccine, and in other

instances where specificity is the predominant consideration. However, the Centers for Disease Control and Prevention (CDC) does not recommend it over a TB skin test in any situation.

Whether a skin test or QFTG is used, testing is recommended only for those at high risk of having latent TB infection and for those at high risk of developing active TB disease, if infected. Targeted testing along with treatment of active and latent TB remains the basis of TB control activities in the US.

When QFTG is unwarranted. The QFTG appears to be less sensitive than a TB skin test in those with symptoms of active TB, with the exception of those who are HIV-positive.¹ In addition, the QFTG is not recommended for use with patients who are being treated for active TB. Current information is inadequate to recommend any QFTG use in children and pregnant women.

Gray areas. While there is some indication that QFTG is more sensitive for detecting TB infection in those exposed to an infectious patient, it is unknown whether it will predict as well as a skin test which patients are at risk of developing active disease.² Therefore, it is not clear at this time if all those who have a positive QFTG should be considered candidates for treatment of latent TB infection, or if this should be offered only to those who have both a positive QFTG and TB skin test.

Level of risk influences interpretation. The current CDC recommendations, which have not been updated since QFTG was licensed, state that low-risk patients with a positive QFT and negative TB skin test should not receive treatment for latent infection.³ However, clinical judgment and perceived risk should be the basis for deciding on treatment in those at increased risk who have a positive QFT and negative TB skin test.

It is also not clear what effect a recent TB skin test has on QFTG results, and performing a QFTG soon after a TB skin test is not recommended by the

US Food and Drug Administration or the manufacturer.

How to interpret QFTG results. If the QFTG result is positive, the patient needs clinical evaluation and a chest x-ray to rule out active disease. The diagnosis and treatment of active and latent TB has been covered in a previous Practice Alert.⁴ If the QFTG result is negative, no further evaluation is indicated unless symptoms of TB exist. The QFTG can have an indeterminate result, in which case a skin test can be useful.

Weighing the cost. The cost of a QFTG (about \$80–\$100 per test) needs to be compared with cost of staff time to read and interpret a skin test and to follow up with patients who fail to return for a skin test measurement.

■ Conclusion

The QFTG test is relatively new; as more evidence becomes available, its place among the tools available for the diagnosis of latent and active TB will clarify. Check with your state and local public health departments to find out the situations for which they are recommending this new diagnostic tool, as practice varies across the country.

REFERENCES

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3. Centers for Disease Control and Prevention. Guidelines for using QuantiFERON-TB test for diagnosing latent Mycobacterium tuberculosis infection. *MMWR Recomm Rep* 2003; 52(RR-2):15–18.
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TABLE 2

Recommendations for use of the QFT

SITUATIONS WHERE QFT IS RECOMMENDED AS A POSSIBLE DIAGNOSTIC TOOL

Persons at increased risk for latent TB infection

- Recent immigrants from countries with high rates of endemic TB
- Injection drug users
- Residents and employees in correctional institutions
- Homeless persons
- Some health care workers

Persons at increased risk of TB infection if exposed

- HIV-positive persons
- Those receiving other immunosuppressive medications

Persons with conditions that cause increased risk of TB disease if infected, including those with:

- Diabetes
- Chronic renal failure
- Silicosis
- Malnutrition
- Renal dialysis
- Chest x-ray consistent with old TB
- Immunosuppressive conditions and treatments

Persons at low risk of TB infection who require initial or periodic testing

- Most health care workers
- When required for school or work
- Members of the military
- Some emergency first-responders

SITUATIONS WHERE QFT IS NOT CURRENTLY RECOMMENDED

- Patients receiving anti-TB medications for active TB disease
- Children aged <17 years
- Pregnant women

SITUATIONS WHERE QFT IS PROMISING BUT FUTURE VALUE IS UNCERTAIN

- Testing contacts of persons with infectious TB
- Confirmation testing after a positive skin test

FAST TRACK

Cost of QFTG (\$80–\$100 per test) should be weighed with the cost of staff time to read and follow-up a skin test