Review: Commercial interferon-γ release assays have high specificity but suboptimal sensitivity for detecting latent TB

Menzies D, Pai M, Comstock G. **Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research.** Ann Intern Med. 2007;146:340-54.

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QUESTION

In healthy or immunosuppressed persons, what is the diagnostic accuracy of commercially available interferon-γ release assays (IGRAs) for diagnosing latent tuberculosis (TB)?

METHODS

Data sources: MEDLINE (to October 2006), bibliographies of relevant studies, and handsearches of the *International Journal of Tuberculosis and Lung Disease.*

Study selection and assessment: English-language studies that used QuantiFERON (QFT) or Elispot tests with overnight incubation of peripheral blood lymphocytes stimulated with RD1 antigens. No gold standard exists for testing latent TB. Studies of sensitivity had to include persons with active TB or contact with a person with TB (exposure had to be graded with ≥ 2 categories). Studies of specificity had to include healthy lifelong residents of low-incidence countries who had a mean age < 40 years and did not have occupational, travel, or other exposure to TB. Studies were excluded if use of a second test depended on the results of a first test. The review included 22 studies evaluating sensitivity with active TB as a surrogate for latent TB, 10 studies evaluating sensitivity with gra-dient of exposure as an indication of latent TB, and 11 studies evaluating specificity. The quality of study methods was assessed (e.g., blinding and microbiologic or histologic confirmation of diagnosis). Studies were pooled using a fixed-effects model.

Outcomes: Sensitivity and specificity.

MAIN RESULTS

In persons with newly diagnosed active TB, pooled sensitivity was 71% for tuberculin skin testing, 76% for QFT, and 88% for Elispot tests (Table). In persons from low-incidence countries, pooled specificity was 66% for tuberculin skin testing, 97% for QFT, and 92% for Elispot (Table). In studies that used gradient of exposure to indicate latent TB, the prevalence of positive test results in the high-exposure group ranged from 22% to 100% for Elispot (7 studies) and from 44% to 74% for QFT (3 studies). Relative to the tuberculin skin test, a greater prevalence of positive IGRA test results among highly exposed persons was seen for 3 of 7 Elispot studies and 1 of 3 QFT studies.

CONCLUSION

Commercial interferon-γ release assays have high specificity but less than optimal sensitivity for detecting latent tuberculosis in healthy or immunosuppressed persons.

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Commercially available interferon-γ release assays for detecting latent TB*

Test	Number of studies	Pooled sensitivity (95% CI)†	Number of studies	Pooled specificity (CI)
Tuberculin skin testing	14	71% (65 to 74)	8	66% (46 to 86)
QuantiFERON	13	76% (70 to 83)	9	97% (95 to 99)
Elispot or T-SPOT.TB	12	88% (81 to 95)	4	92% (88 to 95)

*TB = tuberculosis. Diagnostic terms defined in Glossary. Studies were pooled using a fixed-effects model.
†Patients with active TB were used as surrogates for latent TB.

COMMENTARY

Despite the availability of effective treatment methods, TB continues to be a major public health problem. About one third of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (1); this huge burden of latent TB infection poses a global threat to TB control. Latent TB infection is also an occupational risk for health care workers who are constantly exposed to infectious patients. Prophylaxis with isoniazid is the accepted method of treatment, and its appropriate use is dependent on accurate diagnosis of latent TB infection. Tuberculin skin testing remains the mainstay of diagnosis of latent TB in the world, regardless of endemicity.

The new IGRAs seem to be promising alternatives to the tuberculin skin test for latent TB diagnosis. These commercially available assays are T-cell–based, enzyme-linked immunosorbent assays that measure antigen-specific production of interferon-γ. They overcome the limitations of tuberculin skin testing, including crossreactivity to Bacille Calmette-Guérin, booster effect (anamnestic recall of immunity due to repeated testing), and false-negative results in patients with active TB and immunocompromised (HIV) persons. Despite these advantages, the newer IGRAs do not distinguish between latent and active TB, which is an ongoing challenge in clinical practice. Due to the lack of a gold standard for diagnosis of latent TB, active TB has been used as a surrogate for latent infection.

The review by Menzies and coworkers suggests that IGRA response generally decreased with treatment in patients with active TB. This finding could have serious implications for using the test to diagnose latent TB in populations where empirical treatment for tuberculosis is widespread. As these assays are resource-intensive, they would be more useful in low-incidence, high-income settings and are of limited value in highly endemic, resource-limited settings.

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Reference

1. **World Health Organization.** Global Tuberculosis Control. Surveillance, Planning, Financing. WHO Report 2005. Geneva: WHO; 2005.