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Is It Time to Replace the Tuberculin Skin Test With a Blood Test?

Philip A. LoBue, MD and **Kenneth G. Castro, MD**

Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

Effective Diagnosis and Treatment of Latent Tuberculosis infection (LTBI) to prevent progression to tuberculosis (TB) disease is one of the priority strategies for control, prevention, and eventual elimination of TB in the United States. Recent mathematical TB transmission modeling has shown that substantial improvements in addressing LTBI will be needed to eliminate TB before the 22nd century.[1] Effective management of LTBI has been hampered by limitations of both treatment regimens and diagnostic tools. The advent of medication regimens with much shorter durations (eg, 12 weekly doses of isoniazid and rifapentine) than the current standard of 9 months of isoniazid is likely to lead to higher rates of treatment completion. Efforts have also been directed at finding a replacement for the tuberculin skin test (TST), which despite its many limitations has been the mainstay of LTBI diagnosis.

Beginning in the 1990s, interferon-γ–release assays (IG-RAs) were developed to diagnose LTBI. Currently, 2 US Food and Drug Administration-approved IGRAs are commercially available, QuantiFERON TB Gold In-Tube (Cellestis/Qiagen) and T-SPOT.*TB* (Oxford Immunotec). These blood tests detect ex vivo interferon-γ production by peripheral blood mononuclear cells exposed to peptides designed to simulate *Mycobacterium tuberculosis* antigens. Interferon-γ–release assays offer several practical and theoretical advantages over TST. Interferon-γ–release assays require only 1 patient visit as opposed to 2 for TST (1 visit for placement and 1 visit for reading 48-72 hours later). Interferon-γ–release assays use an objective measurement of interferon-7 production as opposed to human measurement of induration for TST. Also, IGRAs use peptides simulating specific *M tuberculosis* antigens (early secretory antigenic target 6 [ESAT-6], culture filtrate protein 10 [CFP-10], TB7.7), whereas TST uses purified protein derivative. Purified protein derivative contains numerous *M tuberculosis* antigens that cross-react with bacille Calmette-Guérin (BCG) and many nontuberculous mycobacteria. ESAT-6, CFP-10, and TB7.7 are found in very few nontuberculous mycobacteria and not found in BCG.

Corresponding Author: Philip A. LoBue, MD, Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Rd, Mail Stop E-10, Atlanta, GA 30333 (plobue@cdc.gov).

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Numerous reports and a number of systematic reviews have examined the performance of IGRAs, largely in comparison with TST. Studies have encompassed many populations including children, persons with human immunodeficiency virus, immigrants, contacts of patients with TB, and health care workers. However, research in this area has been subject to at least 2 important methodological limitations. First, there is no gold standard for diagnosing LTBI. Sensitivity has usually been measured using persons with TB disease, and specificity has been measured using persons with no identifiable TB risk factors as surrogate standards. Second, studies of certain populations (eg, young children, immunocompromised persons) have been confined to relatively small sample sizes with inadequate statistical power. Despite these limitations, in general IGRAs appear to be no less sensitive and specific than TST and more specific than TST in persons vaccinated with BCG.[2]

The most important property of diagnostic tests for LTBI is predicting which patients will eventually progress to TB disease. In this regard, TST performs poorly, with only 5% to 10% of persons with positive TST results developing TB disease.[3] Evaluating the ability of IGRAs to predict development of TB disease has been difficult. Analogous data for TST were collected in large prospective studies starting in the 1950s (eg, untreated control groups in early isoniazid LTBI treatment trials). It is not possible to replicate such studies for IGRAs because of the ethical necessity to offer LTBI treatment to persons with positive test results. Therefore, prospective IGRA studies have often focused on persons refusing or not completing LTBI treatment, which limits sample size and statistical power and introduces potential bias.

Although no study or combination of studies has been definitive because of these issues, the available data suggest IGRAs are at least as good as TST in predicting future incident TB and may be slightly better. A recent meta-analysis on this subject stated: “Neither IGRAs nor the TST have high accuracy for the prediction of active tuberculosis, although use of IGRAs in some populations might reduce the number of people considered for preventive treatment. Until more predictive biomarkers are identified, existing tests for latent tuberculosis infection should be chosen on the basis of relative specificity in different populations, logistics, cost, and patients’ preferences rather than on predictive ability alone.”[4]

In addition, there have been expected and unexpected potential obstacles to widespread use of IGRAs. The testing materials for IGRAs are substantially more costly than for TST. Even including labor costs, the cost of a single IGRA may be 3 times as high as the cost of a TST.[5] Analyzing cost-effectiveness is more complex because the results vary with many factors including the population being tested. Among populations in which there is substantial TST-positive/IGRA-negative discordance, for example, costs of follow-up evaluation and treatment will be lower if IGRAs are used, assuming persons with IGRA-negative results are at low risk for future TB disease. A number of cost-effectiveness studies have been performed in different populations and, not surprisingly, the results are inconsistent. Various studies have found IGRA alone, IGRA limited to persons with positive TST results, or IGRA in BCG-vaccinated persons/TST in non-BCG-vaccinated persons to have varying cost-effectiveness profiles.[5,6]

A more unexpected finding has been some reports of unusually high rates of initial positive IGRA results and high IGRA conversion rates (ie, from a negative test to a positive test) among health care workers who undergo periodic testing in relatively low TB risk settings.[7,8] Preliminary results from a multicenter center study sponsored by US Centers for Disease Control and Prevention appear to confirm these reports.[9] With additional testing (either TST or repeat IGRA), these unexpected initial positive test results and conversions have usually been determined to be false-positive results. Various explanations have been proposed to explain these false-positive results, including laboratory error and inherent assay variability. Although the full extent and nature of this issue has yet to be determined, it raises questions of whether a single cutoff for a positive result is optimal for all populations and whether defining a conversion as simply going from a negative to positive result is adequate. By comparison, the TST has 3 cutoffs for a positive test result based on pretest TB risk, and conversion requires a change of at least 10-mm induration.

Interferon-γ–release assays are welcome new diagnostic tools that provide certain advantages over TST. However, those advantages may incur additional costs and the diagnostic improvement of IGRAs over TST is incremental rather than transformational. Therefore, TST has not outlived its usefulness. Consistent with this conclusion, the Centers for Disease Control and Prevention issued updated recommendations for use of IGRAs in 2010.[10] The fundamental recommendation is that IGRAs can be used in place of TST in all situations in which TST is currently used. Interferon-γ– release assays are preferred and TST is an acceptable alternative in persons who have been BCG vaccinated or who are in groups that historically have low rates of return for TST reading (eg, homeless persons). Tuberculin skin test is preferred and IGRAs are an acceptable alternative for young children because of the lack of data for this population. For all other groups, there is no preference for IGRA or TST. Each institution and TB control program should evaluate the availability, overall cost, and benefits of IGRAs vs TST for their target populations in deciding which test to use.

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