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Research Article

# The Overview of the Clinical Significance of Interferon-Gamma Release Assays for the Diagnosis of Tuberculosis

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## Abstract

Due to lack of the practical application guidelines for Interferon-Gamma Release Assays (IGRAs), the testing result of IGRAs may be misinterpreted in clinical practice in China. Therefore, we clarify some important issues related to IGRAs based on the available evidences in this review. The available data reveals that IGRAs can be used to assist the diagnosis of Latent TB Infection (LTBI) and combined with HIV infection; while for the definite diagnosis and therapeutic monitoring of active TB have no value. In addition, IGRAs showed no better performance than TST in low income countries. It should make practical guidelines to TB diagnostic tools and further strengthen the training and guide for the clinicians the low income countries, so as to more scientifically manage TB.

## Introduction

As a novel potential tool to diagnose the Tuberculosis (TB) infection, the Interferon-Gamma Release Assays (IGRAs), mainly including Quanti FERON-TB Gold and T-SPOT.TB, have been widely used all around the world. In China, T-SPOT.TB has more commonly been applied to TB diagnosis in clinical practice in recent years. Compared with other TB tests, the assay costs more (about $100-$130) in China. However, due to lack of the practical guidelines for (IGRAs) in some countries, some clinicians don't understand its exact clinical significance. Sometimes, the positive result of IGRAs is misinterpreted as a robust diagnostic criterion for active TB, resulting in an inappropriate anti-TB treatment. Therefore, it is essential to clarify some important issues related to IGRAs based on the available evidences as follows.

### The clinical value in the diagnosis of Latent TB Infection (LTBI)

The meta-analysis results show that T-SPOT.TB appears to be more sensitive both Tuberculin Skin Test (TST) and QuantiFERON Gold in the diagnosis of TB infection. The pooled sensitivity was 78% (95% CI, 73% to 82%) for QuantiFERON-TB Gold and 90% (CI, 86% to 93%) for T-SPOT.TB [1]. The pooled specificity for both QuantiFERON and T-SPOT.TB was higher among non-BCG-vaccinated participants and among BCG-vaccinated participants. And thereby, IGRAs can be used to assist the diagnosis of LTBI [1] Especially in these regions with a high BCG vaccination rate, TST has a poor specificity due to false-positive responses, its advantages is more obvious [2].

### The clinical value in the diagnosis and treatment of active TB

IGRAs for the definite diagnosis of active TB have no value [3]. Especially in high TB burden regions and settings, there are a high proportion of TB contacts among population, and the positive rate of IGRA is very high. Due to the inference of the false positive results caused by these TB contacts, the diagnostics performance of IGRA for active TB is low [4]. However, because IGRAs has a high sensitivity, it could be suitable for screening of TB. That is to say, if its result is negative, we may rule out the possibility of TB, which can reduce some unnecessary treatment.

[4]. As almost 20% of non-TB patients would be erroneously treated for TB and 25% of patients with tuberculous pleurisy would be missed, pleural fluid IGRA are not useful for the clinical diagnosis of tuberculous pleurisy [5]. IGRAs have limited value as diagnostic tools to screen and rule out Extra Pulmonary Tuberculosis (EPTB), especially in low/middle-income countries. The immune status of patients does not affect the diagnostic accuracy of IGRAs for EPTB [6].

However, because of poor diagnostic performance, consuming time and cost resources, IGRAs for therapeutic monitoring (reversion from positive to negative) didn't show a clinical significance according to the previous data. [7]. Another study suggested that serial IGRA had limited use in children receiving antitubercular treatment [8].

### The clinical value in the diagnosis of TB infection in HIV-infected patients

A prospective study that has been carried out in Spain revealed that IGRAs were more sensitive than TST for diagnosis of TB infection in HIV-infected patients, and dual sequential testing with TST and IGRAs may be the optimal approach for LTBI screening in this population [9].

However, another study believed that IGRAs perform similarly to the TST at identifying HIV-infected individuals with LTBI, and given that both tests have modest predictive value and suboptimal sensitivity, the decision to use either test should be based on country guidelines and resource and logistic considerations [10].

### The clinical value in the diagnosis of TB infection in children

A meta-analysis in 2013 included in 31 studies calculated pooled estimates of sensitivities and specificities of QFT-G-IT, T-SPOT. TB, and TST. In this study, several sub-analysis were performed: stratification by background (low income *vs*. high income countries); including only microbiological confirmed TB cases; including only studies performing a simultaneous three-way comparison of the three tests, and including immunocompromised children. The results showed that both IGRAs showed no better performance than TST in low income countries [11].

## Prospective Strategies

Currently some clinicians have a misunderstanding for IGRAs in some countries, it should make practical guidelines to TB diagnostic tools and further strengthen the training and guide for the doctors in the future, so as to more scientifically manage TB.

However, currently available data on IGRAs is mainly from developed countries with low burden of TB, and the useful reports from the high burden countries is less available. The situation is different between them, and thereby it is urgent to perform large-scale and better design studies to assess the clinical value of IGRAs in these regions.

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