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What Are the Differences Between the Tuberculin Skin Test and the QuantiFERON-TB Gold Test?

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Tuberculosis (TB) continues to be a major cause of morbidity and mortality in the world today. After decades of decline in reported TB cases and deaths, the resurgence of TB in the mid-1980s and early 1990s has resulted in its increased prevalence in the community and in the occupational setting.[1] Public health and health care workers, as well as others employed in occupational settings where populations served have a high prevalence of infection with TB, are at increased risk of acquiring the disease. Not only is undiagnosed active TB a potential source of infection but undiagnosed latent infection is also a potential future source of infection. Hence recognizing and reducing the pool of latently infected individuals, which can go on to active disease is of public health benefit.[2,3] The need to accurately diagnose TB infection is important in the occupational setting.

The QuantiFERON-TB Gold (QFT-G) test has been used with increasing frequency in occupational settings as a diagnostic aid for detecting *Mycobacterium tuberculosis* infection since the Federal Drug Administration approved its use in May 2005.[4] It has been used in solo or in conjunction with the traditional tuberculin skin test (TST) that is approximately 100 years old. The TST and the QFT-G differ in several ways. The QFT-G measures a cell-mediated immune response in TB-infected individuals rather than an antibody response to *M. tuberculosis* antigens as does testing with the tuberculin purified protein derivative.

The TST assesses in vivo delayed-type hypersensitivity (Type IV) and uses a polyvalent antigenic mixture of proteins and protein fragments that have homologs shared with many other bacteria, environmental mycobacteria, and Bacillus Calmette-Guérin (BCG) vaccine strains. The QFT-G on the contrary is an indirect, laboratory test for detection of immune response to TB infection in whole blood measuring in vitro release of the cytokine interferon-gamma (IFN-γ). As T-cells of infected individuals are sensitized to the tubercle bacillus, they respond to stimulation with peptides that simulate those expressed by the TB. This results in bacteria secreting IFN-γ. The QFT-G test uses synthetic peptides from two proteins made almost exclusively by mycobacteria of the TB complex (*M. tuberculosis, Mycobacterium africanum,* and *Mycobacterium bovis*) and are highly specific to *M. tuberculosis*, helping to render this test more specific than the TST. These proteins, namely the early secretory antigenic target-6 and the culture filtrate protein-10, are absent from most non-TB mycobacteria, with the exception of *Mycobacterium kansasii, Mycobacterium szulgai,* and *Mycobacterium mariuum*.[5] Studies have shown that QFT-G is an effective diagnostic test in the diagnosis of active TB and in patients in whom TB is suspected.[6–8] The QFT-G has also been found to be accurate for the detection of active pulmonary TB and extrapulmonary TB.[9]

In executing the QFT-G test, the patient's blood is first incubated in special blood collection tubes coated with the TB antigenic proteins. An enzyme-linked immunosorbent assay test detects and quantifies the amount of IFN-γ released from an infected blood sample. Individuals free of infection are not expected to release IFN-γ. The production of IFN-γ is subsequently measured by a rapid single-step enzyme-linked immunosorbent assay.[4]

The Centers for Disease Control guidelines for using the QuantiFERON-TB Gold test for detecting *M. tuberculosis* infection notes that studies have found the QFT-G to be more specific than the TST[4] and to have a sensitivity of approximately 80% in detecting *M. tuberculosis* infection in persons with untreated, culture confirmed TB. Indeterminate QFT-G responses were found to be common (21%) among patients who had a negative TST "although most of these patients could have been immunocompromised."[4,10,11] The Centers for Disease Control guidelines indicate that the QFT-G test can be used in all situations in which the TST is currently being used including contact investigations, evaluation of recent immigrants, and sequential-testing surveillance programs for infection control such as for health care workers, where a single QFT-G test can be used in place of two-step TST for serial screening programs.[4] The QFT-G can also be used to detect active TB disease or latent TB infection in place of the TST. The guidelines note that positive QFT-G results should prompt the same evaluation and management as positive TST results in that, persons with positive QFT-G results should be evaluated for TB disease before latent TB infection is diagnosed. As recommended with the TST, for recent contacts with individuals who have contagious TB, a negative QFT-G result should be confirmed with a repeat test 8 to 10 weeks after the last known exposure.[4,12]

There are several advantages associated with the use of QFT-G. For example, it necessitates a single visit where a blood sample is collected, eliminating the need for a return visit in 48 to 72 hours as is necessary after administration of the TST. This also mitigates the issue of tests not being brought to completion due to lack of follow-up as is the case when individuals do not return to have their TST read subsequent to placement. In addition, as a laboratory-based test, the QFT-G is more objective than the TST, for which the interpretation depends on the skill and experience of the individual

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measuring the skin induration during test interpretation. Unlike the TST, the QFT-G also has the advantage of not being subject to the boosting effect of BCG vaccination and of some environmental nontuberculous mycobacteria as it does not expose the individual to an antigen.[5,8,13]

Although cost varies among different sites, screening for active TB using the QFT-G test can significantly lower testing costs depending on whether or not it is combined with sequential TST testing.[14] Indeed, the QFT-G might be a cost-effective alternative in testing programs in settings where there is a high prevalence of BCG vaccinated individuals or where returning for the TST to be read poses a problem such as homeless shelters.[4] In patients with prior BCG vaccinations, using QFT-G alone was found by Harada et al to be more cost effective than with TST-alone or TST followed by QFT.[15]

One of the disadvantages of the QFT-G is that it is subject to errors in collecting or transporting blood specimens, as well as in running and interpreting the assay. Specimens need to be properly obtained, handed, and processed prior to and after arrival in the laboratory. Errors in this process can reduce its accuracy. In addition, its' use also necessitates the need for drawing blood and for delivery of the specimen to a qualified laboratory within a specified time period.[4] The QFT-G can also lead to an indeterminate result as to the presence of *M. tuberculosis.* In this case, recommended options include repeating the QFT-G or administering the TST, especially if the likelihood of disease is high. Another option recommended is for no further testing.[4] If the QFT-G is positive, the Centers for Disease Control recommendation is that there is no need to follow with a TST. Having laboratories report the reason for the QFT-G indeterminate result may help elucidate the matter and allow for a more informed next step. Neither the QFT-G nor the TST can differentiate between latent TB infection and active TB disease. Further medical evaluation is necessary for exclusion of active TB disease. Furthermore, neither a negative TST nor a negative QFT-G can exclude *M. tuberculosis* in persons with signs and symptoms of TB. Again further medical evaluation is necessary.

A newer version of the IFN-γ release assay called QuantiFERON-Gold-In-Tube was approved by the FDA in October 2007. The In-Tube version removes the need to transport the blood tubes to a laboratory, and the enzyme-linked immunosorbent assay analysis can be done on-site thereby decreasing the logistic burden. A study by Harada et al[16] compared the sensitivity and specificity of the QuantiFERON-Gold and QuantiFERON-Gold-In-Tube diagnostic test for mycobacterium TB infection and reported that the QuantiFERON-Gold-In-Tube had enhanced sensitivity for detection of TB infection over the QFT-G test, while maintaining equivalent high specificity. We await further studies examining the parameters of these tests including cost-benefit analysis of the QFT-GIT compared with QFT-G.

Despite the new advances in the diagnosis of latent and active TB infection, culture remains the gold standard for confirming TB infection. The diagnosis of active TB cannot be made on the basis of an immunological test only. Appropriate microbiological investigation and alternate diagnostic procedures such as chest radiograph and review of symptoms are still needed to adequately diagnose individuals suspected of having active TB.[4]

The QFT-G test shows promise and is being increasingly used in occupational settings. It is indicated for diagnosing Mycobacterium TB infection, both TB disease and latent TB[4]. The relative ease of testing makes it more desirable than the TST and its sensitivity and specificity are encouraging. It does have its own disadvantages including giving indeterminate results and inaccurate results if improper collection and testing methods are used. However, given that its use is becoming more widespread in occupational and other health care settings as experiences are reported and its use studied, we will be able to see its real impact over time.

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