

IGRAs: Can They Replace the TST?

Frequently Asked Questions

From the National Web-based Seminar
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The following questions were submitted by participants in the above IGRA training event, the responses below have been provided by the faculty members and relate to information presented during the training. To view the archived recording of the 1/28/09 training, please visit the following website:

www.nationaltbcenter.ucsf.edu/training/arch_igras.cfm

Employee Health

What do you think about occupational health facilities who specialize with EMS/Fire personnel using IGRAs as their only test?

Current national guidelines state that QFT-G can be used for serial testing. When using IGRAs exclusively, start up costs, cost of the tests, time lost from work, and follow-up evaluation should be considered. Protocols to evaluate converters need to be in place to avoid false conversions and estimate the likelihood of new infection. At the moment, a better definition for an IGRA-converter is needed. Some programs verify new positives by repeating the test, looking at the quantitative results and evaluating the risk of TB exposure in the interim.

Regarding the notion that TST is better at detecting old infection, please note that in a recent German study, QFT-IT was better at detecting old infections than the TST (Nienhaus A, PLoS ONE, July 2008, Vol.3, Issue 7, e2665). The jury is out on this question.

Do you recommend IGRA testing of healthcare personnel who had received BCG as part of routine testing?

IGRAs consistently show better specificity in BCG vaccinated populations in contact investigation and population studies.

What is the recommended TB screening of staff at homeless shelters, where incidence in the area is low?

Although the TB incidence of an area may be low, homeless populations are notoriously mobile and constantly changing. They have significantly higher rates of TB that can be brought into a low incidence area. Hence, TB screening of staff at homeless shelters

are recommended. Screening shelter clients is more important however and here is where IGRAs can be useful because a result can be obtained with a single visit.

Have there been studies as to whether IGRA testing has many advantages to TST testing within correctional facilities (inmates, employees, volunteers)?

I'm not sure if there are any published studies but if there are, I'm not aware of them. Cook County Jail in Chicago, Illinois piloted the original QFT-TB in 2003 and found it feasible in a report to ACET.

Cook County Jail is the largest single-site detention facility in the United States and has an average daily population of 11,000, an average yearly admission of 100,000 and an average daily intake of 300-350.

How would you handle a new hire HCW who had a negative IGRA 6 months prior to hire, and is being hired by a facility that is not able to perform IGRA testing?

The new HCW can be followed throughout employment with the available TST, following the employer's algorithm for routine screening. A new baseline upon hire with the skin test would be advisable to document whether discordant results exist prior to beginning work.

I work in an employee health setting; currently we are mainly using TST for screening and exposure follow-up. IF a HCW had hx of PPD positive with ?BCG hx, and went outside to obtain an IGRA and the QFT-G test was negative. What is your recommendation for future f/u? Serial IGRA testing?

Yes, serial IGRA for this scenario would avoid confusion and potentially identify a future conversion.

What is your opinion regarding swapping out TSTs for IGRAs in HCW surveillance programs? Is it feasible to use a mix of TST and IGRA depending on TST status?

Using both TST and IGRA tests can be done within the same surveillance programs, but can cause significant confusion in terms of protocol design and response for discordant results if used in a random fashion. There have been studies that have looked at using IGRAs as confirmatory tests for all positive TST results which suggest that this may be more cost-effective, while others have shown that an IGRA alone in this group is most cost-effective (see questions above).

For surveillance of Mycobacterial lab personnel, how might you use IGRA? Would you recommend a hybrid strategy of using IGRA after a positive TST? Or would the single strategy approach of only using IGRAs be preferable? Is CXR also necessary if the IGRA is negative and there are no identified risk factors other than occupation?

IGRA testing for this group could have a theoretical advantage if there is an increased risk of false-positive TB test results due to handling and exposure to non-tuberculous mycobacterium. Either testing strategy would work and the cost benefit would be dependent on local circumstances. Certainly, the IGRA only approach is the most time efficient for employees.

The need for a CXR is the same whether you use a TST or IGRA – in an otherwise healthy individual, a CXR is recommended only after a positive TB test to look for evidence of active disease.

Serial Testing

In the serial testing, was INH used in between testing?

All of the studies referenced for serial testing did not involve treatment with INH between tests.

In serial testing, if TST positive and QFT negative what should be done annually after that (symptom check or annual QFT)?

If the plan is to use QFT testing annually at the institution, I would place that person in the pool of “negatives” for repeat QFT. We are still learning how to use these new tests, but we are finding that a lot of our “old-positives” are negative on both TST and IGRA. We don’t know exactly what that means.

I have several concerns that were nicely pointed out by the speakers -- such as the use of these tests in serial testing programs, given the wobble of the test around the cut point (for QFT-IT) and lack of a "conditional zone." Also since there is no standard for LTBI (all studies to date use TB disease as a surrogate for TB infection -- not really a correct assumption since LTBI is a very different thing, at least in some situations), there really is no way to know what the real sensitivity might be.

The only gold-standard for LTBI that matters is the risk of progression to active TB associated with a test result. Even that standard is difficult since the populations with various results that have to be followed for years may be exposed during follow-up so those with a “negative” baseline test may develop TB because the test was not sensitive or because of exposure after baseline. What we know with the TST is that populations with different TST indurations have different rates of progression to active TB. For an individual, we can never know exactly what their test means. We have to make an individual decision based on the population-based data and their individuals and clinical and epidemiological risk factors.

I understand that IGRA may one day be useful in determining adequate TB treatment in both LTBI and active TB cases (QFT reverts to negative). This would

be especially beneficial to determine adequate treatment for resistant TB cases and their contacts who are put on medications without any real known ideal duration of treatment. Is this true and are there any articles or studies?

So far the studies that have looked at follow-up testing after treatment of latent or active TB do not look encouraging (one example referenced below). Values tend to go down but there is considerable variability. Some recent references include:

Pollock NR, Kashino SS, Napolitano DR, Sloutsky A, Joshi S, Guillet J, Wong M, Nardell E, Campos-Neto A. *Evaluation of the Effect of Treatment of Latent Tuberculosis Infection on QuantiFERON-TB Gold Assay Results*. Infect Control Hosp Epidemiol. 2009 Feb 23. [Epub ahead of print]

TST studies years ago suggested recent converters often revert. Interesting result but of uncertain significance. I suggest such “follow-up” tests be done only as part of a research study for now – otherwise, you will incur more cost and have results that can’t be used.

Is it possible for an individual who was infected with TB in the remote past to clear the infection so that a QFT-IT would be negative because there was insufficient time for incubation of the antigens with blood cells i.e., effector T-cells were not able to recognize the antigens whereas memory T-cells would be able to respond if the incubation time was longer?

This is certainly possible and from my perspective it is an interesting immunological and pathophysiological theory, but it remains unproven. The idea that TST measures remote infections more than IGRA is a theory. It is equally plausible that older people TST/IGRA positive/negative because of cumulative exposure to other antigens leading to more false positive TST.

A client comes to us reporting prior positive PPD and treatment in the 1980s, due to known exposure to a close contact. There is no documentation. We have skin tested again with 20 mm result. We sent for QFT. If positive, should we re-treat? (No known exposure since prior treatment, but no documentation of prior treatment).

(See response to previous question) We have quoted the dogma that a TST remains positive for life and shouldn’t be repeated, but it is not true. However, we don’t know what a positive or negative TST and/or IGRA means after treatment. Old data before INH suggests lower risk of TB among prior positive vs. negative TST following exposure (nursing student in PA). I would suggest not basing re-treatment on the TST result in this patient. If there was recent extensive exposure or if immunosuppression is planned now, I might consider treating again.

Discordant Results

What if you get 2 discordant QFT-IT results?

The risk of exposure and disease progression should always be assessed when discordant results are found. Reviewing the quantitative results can also be helpful in determining false positives from high background nil results or wobblers around the cut point. Sometimes a 3rd test is needed to break the tie. Clinical decision making should always be done with full disclosure to the patient.

Are you doing TST and IGRAs in Class B immigrants and which result are you following?

The SF TB Control Program is using IGRAs and TSTs in assessing Class B immigrants (old TI classification). If TST and IGRA results are discordant (usually TST positive/QFT negative), LTBI treatment decisions are being made based on the clinician's assessment which always includes sputum culture results, serial CXRs, and history of prior TB disease and treatment.

In a QFT-IT test, if we get a mitogen positive and TB antigens negative, what has been your experience with this?

The mitogen is the positive control and tells you if the patient is capable of making gamma interferon. If the mitogen result is valid and TB antigen – nil value is below .35, the result is negative. A negative result should always be interpreted in the context of whether the patient is a TB suspect or not. In a suspect or immunocompromised individual, a negative result does not rule out active TB or LTBI. In a healthy, asymptomatic individual, the negative result should mean “no TB infection.”

Employee health. Prior positive TST, now has negative QFT. Are these individuals considered LTBI and need annual symptom reviews/QFT? In these individuals who have documentation of adequate LTBI treatment, might the QFT suggest adequate treatment and that the individual no longer is LTBI? Or, does the employee still remain with an LTBI status. In this case, might the QFT suggest remote infection and rule out any recent TB infection?

Discordant results are always difficult and confusing, especially when you don't know which test to believe. Remember, false positives and negative occur with both the TST and IGRAs. No test is perfect and IGRAs are certainly not panaceas. If you are using a QFT result in a serial testing setting, my advice is to disregard prior TST results and make clinical decisions based on the result you have at hand. You should manage an IGRA result as you would a TST result. In regards to treatment, quantitative IGRA results may change with treatment, some to negative but these findings are too preliminary to generalize what they mean (cure, need for more treatment, etc.) Again, until more research is done, the most prudent approach is to treat an IGRA result like

you would treat a TST result. For example, once a patient is positive by IGRA, do not retest them.

We have been told previously that the recommendation is not to do both TST and IGRAs due to the possibility of conflicting results. Can you please clarify?

In general, using both tests is unnecessary, more time consuming for patients and expensive. Conflicting results add another layer of confusion, especially when there is a lack of expertise in using IGRA results. However, when maximum sensitivity is needed to make critical clinical decisions in TB suspects, very young children or immunocompromised individuals, serial testing with the TST and IGRA can be helpful. In these situations, any test result that is positive should be interpreted as evidence of TB infection. On the contrary, negative results would not rule out infection or disease.

With routine TST that is positive, IGRA negative and repeat IGRA positive. When would you anticipate a change in IGRA? Guidelines say that after 8-10wks TST testing should be done for post exposure.

Research shows that gamma interferon production can occur as early as 2 weeks. Based on what we know, the current TST guidelines of retesting 8-10 weeks post-exposure is more than adequate for IGRAs.

What is the recommendation for patient follow-up for TST negative, QFT positive? What is the recommendation for an adult BCG vaccinated patient that is QFT positive, CXR negative?

At the moment, because of lack of data, we should follow a patient with a positive QFT the same as we would a patient with a positive TST. LTBI treatment should be recommended to individuals with a positive QFT per ATS guidelines (e.g., contacts, converters, newcomer to the US <5 yrs, diabetic, HIV, end-stage renal disease, immunosuppressed persons, etc).

Contact Investigation

Contact investigations. All contacts were tested with a TST. The foreign born contacts were positive. These contacts had no other conditions that would increase risk of disease progression. QFT was done to r/o current transmission, r/o BCG, and all QFTs were negative. Understanding that there is not enough research to corroborate this use, the contacts were offered LTBI treatment. Is this correct?

The research shows that IGRAs correlate better with exposure than TST in BCG vaccinated contacts, highlighting the specificity of current IGRAs. If the IGRA results are not being used to make clinical decisions, there is no point to using them.

I understand that QFT is not sensitive to remote TB infection. Can QFT be used to determine LTBI as a result of recent transmission? Are there studies being done to support this? It would be very beneficial in contact investigations.

Remember, the goal in contact investigation to find those who are newly infected because they carry a much higher risk of disease progression than those with remote infection. Less QFT sensitivity to remote TB infection is an unproven theory. In a recent German study by Nienhaus (PLoS ONE, July 2008, 3(7), e2665), TST was not more likely to detect old infection than the QFT. QFT-IT appeared more sensitive to remote infection in the elderly than TST. Clearly, more research is needed in this area.

Immune Compromised/Children

The test maker for T-Spot.*TB* would have us believe that their test is less influenced by immunosuppression and by young age. Some of the data presented today do not support this. What are your thoughts about differences between QuantiFERON and T-Spot.*TB* in these specific populations?

Pediatric experts all agree that there is too little data to make conclusions on any IGRA in children under 5 years old. There is even less data with T-Spot.*TB* than QFT-G. So until then, I would be cautious about what you are being told.

In our HIV clinic we have been using TB QuantiFERON for screening all patients. In the past 2 months we've had a rash of positive tests. We've repeated eight positives and six were negative on retest. How do we know who is really positive, what is false positive and how do we proceed with these patients?

When results are not making sense, it is important to investigate for trends to determine if it is a laboratory issue or a clinical issue. It is quite possible that the six positives were false positives due to bad collection tubes with higher nil backgrounds, contaminated wells that had both mitogen and antigen or other issues. Looking at quantitative gamma interferon values and clustering of positives by dates or batched runs can help you. Clinically, you can expect more wobblers in HIV infected individuals because of immunosuppression and fluctuating immune status. There is no easy answer (especially with HIV patients) but if these individuals are at low risk of TB infection and have not had recent exposure, working with your laboratory and reviewing the quantitative data on these patients should be helpful.

Am I understanding that IGRA's can be used for children less than 5?

The data currently available is very helpful and encouraging but is considered inadequate by most pediatric experts on this subject. The big dilemma is unknown sensitivity of IGRAs in this age group and how to interpret and manage the negative IGRA result. The revised CDC guidelines on IGRAs will be available soon. It is unclear what the recommendations will be.

Is the volume of blood required for the IGRAs a barrier for screening small children?

The amount of blood needed by the second generation QFT-IT is only 3 cc. Six cc is needed for T-Spot. *TB*. Hence, there is less of a barrier than with the QFT-G which required at least 7-8 cc.

Would you suggest IGRA on a 9 month old, 17 lb. baby girl whose mother, who is a recent immigrant from the Philippines, was recently treated for active TB. Child had a 15 mm. TST and a negative Chest x-ray? If the result is negative...would you still recommend treatment for LTBI?

This child does not need an IGRA to confirm recent transmission from her mother. The large size of the TST is evidence enough. Even if the result were negative, window prophylaxis would be the standard of care in the U.S. The risk of progression in this age group is 40-50%. Why take a chance?

In a situation with a patient who is reluctant to take LTBI treatment because they believe that the BCG vaccine is responsible for a positive TST, would it be appropriate to use an IGRA test to possibly persuade the client that the positive result is not related to BCG, even though this may lead to a false negative with the IGRA? In this situation, the child was younger than 5, but had not had any known contact with a TB case.

If the parent is refusing to give a healthy asymptomatic child LTBI treatment, you are better off using an IGRA, despite the young age. If it is positive, it will provide the evidence to better persuade the parent to provide the LTBI treatment. If it is negative, you can follow the child clinically and carefully explain to the parent that a negative result does not rule-out LTBI.

Cost

Will there be funding support for state public health labs to offer IGRA testing? Will CDC provide funding to designated regional laboratories for provision of QFT-IT testing so local jurisdictions/providers can submit specimens via mail for testing? Many hospital labs located in rural areas will not be able to justify start-up and personnel costs to offer these tests.

Currently there are no plans that we know of for specific CDC funding to support IGRA testing in regional/local laboratories.

There are some regional/local health department and private labs that will take outside specimens but require reimbursement. Cellestis (maker of QFT) has a locator tool at www.quantiferon.com.

In Washington State, we have not been very successful getting Medicaid to reimburse for QFT-IT. Any feedback?

Medicare reimbursement for IGRA testing varies state by state. I would consider working with your state TB Control Program to advocate for your region.

We have a waived laboratory. Is there any way that we could begin using the QFT-IT in our local health department. At his time, the only other option we have is to send out to the local lab and the cost is \$75 a test.

The issues should be raised with your local health department and laboratory as to whether they are able to support bringing on a new test. The laboratory process itself is a relatively straightforward automated ELISA. Local resources and level of demand will likely determine the outcome.

What is the average cost of the IGRA's compared to the TST? What type of "training" in the interpretation of IGRA's is required? Are there large numbers of "mentors" around the country that are proficient in reading the IGRA's? Could your next presentation show a sample of a positive and negative IGRA interpretation?

Help for interpreting IGRA results for specific cases can be obtained from your regional training and medical consultation centers (RTMCC). See our website www.nationaltbcenter.ucsf.edu for more information on how to contact our "Consult Warmline" or your own local RTMCC.

Other resources:

- CDC Div. of TB Elimination has a QFT Fact Sheet and will be posting new guidelines soon [www.cdc.gov/tb/publications/factsheets/default.htm].
- More IGRA educational material may be found at the www.findtbresources.org site maintained by the CDC.

Cellestis (makers of QFT) also has a FAQ for healthcare providers located on their website www.cellestis.com

What is the average cost of the IGRA's compared to the TST? What is the cost per QFT-IT for the San Francisco program?

Cost per test will vary based on the volume of testing (lower cost when bought in larger quantities) and lab/personnel costs. The San Francisco Department of Health lab estimates that with large volume test purchasing and local high-level salary costs, the laboratory cost runs approximately \$50/test (fully recovered via Medicare reimbursement).

Cost comparison between TST and IGRA?

Cost analyses done via mathematical modeling in the literature offer variable results. A recent analysis in healthcare workers (de Perio, Arch Intern Med Jan 2009) suggests either QFT-G or QFT-IT would be more effective and less costly compared with TST regardless of prior history of BCG and prevalence of LTBI in the community. Other studies suggest that the most cost-effective use of QFT is in BCG-vaccinated individuals (contact screening; Marra, Int J Tuberc Lung Dis, Dec 2008) or as a confirmatory test after a positive TST result (Oxlade, Int J Tuberc Lung Dis, Jan 2007; and Diel, CHEST, May 2007).

Miscellaneous/Other

Does San Francisco repeat IGRA when a person changes shelters? Is there a standard such as do one IGRA per year even if they have gone to a new location that requires a new test?

No, SF requires TB screening initially and annually, regardless of how many shelters a homeless individual may stay in in a year. Entry screening prevents active TB from entering the shelter system. Remember screening is more than an IGRA. It includes a risk factor assessment, symptom review and a CXR when results cannot be relied upon (HIV or immunocompromised).

Why would a test type affect the initiation and completion of treatment?

Many physicians and patients believe the TST is positive because of prior BCG vaccination or because the test was read wrong. If the physician, NP, RN or health worker is more confident in the result, there is naturally more conviction on their part to start and convince their patient that treatment is needed. From a patient perspective, a less subjective and more accurate test result would motivate them towards treatment completion.

Can you describe specific difficulties you experienced in the early phase of implementation of QFT-IT?

We had a defective batch of mitogen tubes and had unusually high rates of indeterminates. Once we switched the tubes out, the problem went away.

The statement that additional testing adds sensitivity has not been our experience as QFT-IT positives are more often found to be TST-negative and would not have been candidates for additional screening. San Francisco TB Control Section mentioned that they have automated the QFT-IT, by what method? What is the impact of out-of-range volumes of blood on the test result (<0.8ml - >1.2ml) -- in our hands such specimens represented over 37% of our specimens and the indeterminants clustered in these out of range specimens.

Using an additional diagnostic for added sensitivity should only be applied to special situations when patients are very immunocompromised and neither test can be relied upon. Here, any positive result can “rule- in” TB or LTBI. (examples: TB meningitis suspect with negative TST or Asian rheumatoid arthritis patient on prednisone and methotrexate with a negative QFT)

Using both tests in low-risk scenarios is not advised. However, false positives can occur with either the TST or QFT, especially when testing low-risk persons. This will happen much more often with the TST because of its lower specificity.

Full automation eliminates manual pipetting and can be accomplished by purchasing the laboratory tools to do so. All major commercial labs have these tools.

The impact of out-of range volumes is exactly what you found, indeterminate results. Hence, it is important not to over or under fill the tubes.

How many sites are using PPD's as follow-up to indeterminate QFT? Logically, it makes some sense, and is much less expensive than a repeat QFT.

I don't know the answer to that question. However, in our experience, repeating the QFT will yield valid results two-thirds of the time regardless of whether the initial indeterminate result was due to mitogen failure or high nil background. Regarding the decision to use the TST or QFT after an indeterminate result should involve the patient.

It sounds like Dr. Kawamura is recommending sequential testing to increase sensitivity for LTBI. Can you elaborate on this, or correct me.

No, that is not correct. Sequential testing to maximize sensitivity should only be used when patients are very immunocompromised and neither test can be relied upon. Here, any positive result, even a granuloma on a CXR can “rule- in” LTBI. (example: Asian rheumatoid arthritis patient on prednisone and methotrexate about to be placed on TNF blockers)

What is your clinical experience with QuantiFERON-TB Gold or Gold In-Tube in patients with known *M. bovis* infections or contacts of those cases?

There are almost no data regarding the utility of IGRA in detecting infection with *M. bovis* in humans. The antigens used in the assays are secreted by *M. bovis* however, so that theoretically there is a possibility and likelihood that persons with active *M. bovis* disease could test positive with IGRA. However, the sensitivity of IGRA in this setting is unknown.

Do you have any information on how test performance characteristics of QuantiFERON-TB Gold or Gold In-Tube in populations with higher *M. bovis* to *M. tuberculosis* ratios than what we have in the US would compare to those in US populations?

Although IGRA should be able to detect *M. bovis* infection, there are no data regarding the different performance characteristics of the tests in populations with higher exposure to *M. bovis* than occurs in the U.S. As there is no gold standard for detecting asymptomatic *M. bovis* infection (much less latent *M. tuberculosis* infections) such studies would be nearly impossible to carry out.

How long will you need to wait to do the TST and the QFT?

Current recommendations suggest waiting 6-10 weeks following possible exposure before performing a TST. There are no firm recommendations for IGRA, but at present it would seem prudent to wait a similar period of time.

When do we repeat the QFT or T-Spot. TB after providing the initial test? For example, the current recommendation for TST is to repeat the test 8 to 10 weeks after the initial TST

There are no specific data regarding the “window” period after TB exposure and IGRA testing, however, current CDC guidelines state that IGRA can be used in all circumstances in which TST is done, so it makes sense to repeat IGRA a similar length of time following exposure.

Can you give us any prediction of the acceptability of the QuantiFERON as a testing method for civil surgeon exams?

My guess is that civil surgeons would readily accept IGRAs over the skin test if they had access to it and if it became part of the technical instructions. It would reduce radiology costs significantly for applicants.

We have several of our LTBI patients in Texas who have a history of BCG or live in areas with prevalent non-MTB mycobacterias. It would appear that the QFT-IT offers a more specific means of detecting MTB and an estimated 50-75% reduction in our LTBI caseload? Is this consistent with your data analysis?

You can expect an estimated reduction in the LTBI case load of 50-75% as you predict. San Francisco, San Diego, and New York City TB programs testing BCG vaccinated populations are seeing declines precisely in that range.

We understand that Immigration does not accept IGRA test results. What are your thoughts or recommendations?

Overseas panel physicians have to comply with the U.S. Technical Instructions which uses TST as the method for testing. However, once the immigrant is in the U.S., IGRAs are being used by some programs to verify LTBI status (e.g., San Diego TB Control).

Have there been any studies looking at the effects of alcohol abuse on the results of the IGRAs?

No, there have not been any studies.

There were multiple references to BCG vaccination, were there cutoff times for when the BCG vaccine was given? In other words, was the test run >1yr, 5yr, etc. after vaccination?

BCG metanalysis have shown that vaccination can impact TST results for up to 15 years. IGRA results are not affected by BCG vaccination because the antigens are specific to *M. tuberculosis*, *M. kansasii* and *M. szulgai* and NOT to any of the BCG strains. You can be sure that if you have a positive IGRA result, it is not because of BCG vaccination. This is a significant advantage when screening BCG-vaccinated contacts in an investigation.

Do any of the noted differences in sensitivities or concordance diminish in QuantiFERON if the lymphocyte count of individual tests are incorporated in the assay of IFN?

Low T-cell counts (<100) in HIV infected patients correlate to higher indeterminate rates. I'm not aware of any studies that address your question specifically.

We would very much like to receive the teaching materials used during the presentation because, as a public health agency, we are in a position to provide public education re TB and LTBI.

All the course materials, in the PDF format, as well as the recording of the IGRA training are available on the Curry Center website on the "Archived Web-based Training" page. www.nationaltbcenter.ucsf.edu/training/arch_webtrain.cfm