

IGRA Tests – A Wave of Change

What? When? Why? How?



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Learning Objectives

Participants will be able to:

- Give a basic explanation of how an IGRA works
- List the test requirements of each IGRA test
- List a population in which IGRA testing is preferred
- Identify IGRA tests available near their local health department

What is an IGRA?

- Blood test that measures an immune response that reflects prior contact with M.tb and a few other Mycobacteria
- There are two IGRAs currently produced:
 - QuantiFERON-TB Gold-in-Tube by Cellestis, Inc.
 - T-Spot.TB by Oxford Immunotec, Ltd.



How To Detect TB Infection

First, there was the TST

- Used for more than 100 years (since 1890)
- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- Induration in millimeters read 48-72 hours after injection



TST Limitations

- Variability in administration and reading
- > 1 visit needed
- False negative responses
- Boosting of the immune response with repeated TSTs
- False positive responses



What Do These Tests Measure?

- Different aspects of the immune response to antigens specific to *M. tb*
- Therefore:
 - A client still has to have a functioning immune system to get a valid result
 - Because different tests use different antigens and interpretation criteria, TEST RESULTS MIGHT NOT BE INTERCHANGEABLE!



Basic Principles of IGRAs

- Peripheral white blood cells from a person suspected of having tuberculosis infection are exposed to antigens (different from those in PPD/more specific) from *Mycobacterium tuberculosis*
- If person has been infected with *M. tuberculosis*, white blood cells will respond by producing IFN- γ (interferon gamma)
- The tests measure the total IFN- γ produced (QFT-GIT) or number of cells that produce IFN- γ (T.Spot TB)



Antigens Specific to *M. tuberculosis*

- Not found in BCG or most non-tuberculous mycobacteria
- Exceptions! *M. kansasii*, *M. szulgai*, *M. marinum*, and *M. riyadhense*



QuantIFERON TB Gold In-Tube

- Whole blood is collected in three special collection tubes, filled precisely to 1 ml line, and shaken vigorously for 5 seconds
- Tubes must begin incubation within 16 hours of the blood draw
- The tubes are incubated for 16-24 hours
- Usually requires blood draw at a patient service center to meet time deadlines or spin and incubate on-site
- Results usually available within 1 week

QuantIFERON TB Gold In-Tube



The Tubes:
Mitogen (positive)
TB Antigen
Nil (negative)

QuantIFERON TB Gold In-Tube



The black fill line

QuantIFERON TB Gold In-Tube

- The QFT-GIT can have a result of negative, positive, or indeterminate
- Available at commercial labs and some local medical facilities
 - T-Spot TB under state contract
 - Quest - QFT-GIT
 - Labcorp - QFT-GIT
 - Riverside in Newport News - QFT-GIT
 - Call your local resources to locate
- Cost – varies from \$48.50 to \$230 or more
- Covered by most insurances if testing indicated

QuantIFERON TB Gold In-Tube Sample Results

QuantIFERON TB Gold	Positive Abnormal	Negative
CFT Positive Criteria		
To be considered positive a specimen should have a TB Ag minus Nil value greater than or equal to 0.35 IU/mL and in addition the TB Ag value must be greater than or equal to 25 % of the Nil value. There may be insufficient information in these values to differentiate between some negative and some indeterminate test values.		
QuantIFERON TB Ag Value	>10.00	IU/mL
QuantIFERON Nil Value	0.43	IU/mL
QuantIFERON Mitogen Value	>10.00	IU/mL
CFT TB Ag minus Nil Value	>10.00	IU/mL

Interpretation:
The QuantIFERON TB Gold (in Tube) assay is intended for use as an aid in the diagnosis of TB infection. Negative results suggest that there is no TB infection. In patients with high suspicion of exposure, a negative test should be repeated. A positive test indicates infection with *Mycobacterium tuberculosis*. Among individuals without tuberculosis infection, a positive test may be due to exposure to *M. kansasii*, *M. szulgai* or *M. marinum*. On the Internet, go to cdc.gov/tb for further details.

T.Spot TB – Now under state contract!

- Available after signing a local agreement with Oxford Immunotec
- Local health department covers the cost of the test, which may be billed to the patient on a sliding fee scale
- WebVision test code is "TSpotTB"

T.Spot TB Testing

- Whole blood is collected in one or two green top tubes (lithium heparin), depending on presence immuno-compromising conditions



- Tubes must begin incubation within 32 hours of the blood draw



T.Spot TB

- Blood is shipped via. FedEx (or processed in-house if equipped)
- Oxford Immunotec provides shipping materials/mailling label with very clear directions.





T Spot Sample Result

T-SPOT.TB Positive

A patient's test result is positive when the difference between the number of spots present in patient's sample and the negative (NTL) control is ≥8. Note: Diagnosing or excluding tuberculosis disease, and assessing the probability of TB, requires a combination of epidemiological, historical, medical and diagnostic findings that should be taken into account when interpreting T-SPOT.TB test results. Refer to the most recent CDC guidance (<http://www.cdc.gov/ncidod/d/diseases/tb>) for detailed recommendations about diagnosing TB infection (including disease) and selecting persons for testing.

Ntl (Neg) Control Spot Count	1
Panel A Spot Count	>50
Panel B Spot Count	>50
Positive Control Spot Count	>20



Immune response being measured!

- There still is no way to detect M.tb bacteria directly while only infected
- **The test results should be used in combination with clinical assessment**



Which Test is Better?

- It depends on the population to be tested
- All are recommended to be used in high-risk populations only



Overview of the 2010 CDC Guidelines

Centers for Disease Control and Prevention

**Updated Guidelines for Using
Interferon Gamma Release Assays to
Detect Mycobacterium tuberculosis Infection-
United States, 2010**

MMWR 2010: 59(No. RR-5);1-26



General Recommendations for Use of IGRAs - 1

- TSTs and IGRAs should be used as aids in diagnosing infection with M. tuberculosis.
- IGRAs should be performed and interpreted according to FDA-approved guidelines.
- BOTH standard the test interpretation (positive or negative) AND the numerical measurements should be reported, along with the criteria used for test interpretation.



General Recommendations for Use of IGRAs - 2

- Arrange for IGRA testing prior to blood collection.
- Each institution and TB control program needs to evaluate the availability, overall cost, and benefits of IGRA use for their own setting. Consider your population!
- Select the most suitable test or combination of tests for detection of M.tb on the basis of the reasons and context for testing.
- As with TSTs, IGRAs generally should not be used for testing persons with a low risk for both infection and progression to TB disease.



Situation in Which an IGRA is Preferred but TST is Acceptable

- Testing persons with low rates of return for reading
 - the homeless
 - substance abusers
- Testing persons who have received BCG
 - as a vaccine
 - for treatment of bladder cancer therapy



Situations in which a TST is preferred but an IGRA is Acceptable

- TST is preferred for testing children less than 5 years of age.
- Some have advocated an IGRA in conjunction with a TST to increase diagnostic sensitivity in this group. The American Academy of Pediatrics states* that IGRAs may be useful in determining whether a BCG immunized child with a reactive TST more likely has LTBI or has a false-positive TST caused by the BCG.

*American Academy of Pediatrics, Red Book: 2009, pg. 687.



Situations in Which Either TST or IGRA May Be Used Without Preference

- To test recent contacts of persons known or suspected to have active TB disease.
 - IGRA with greater specificity than TSTs in this setting
 - Unlike TSTs they do not boost subsequent test results
 - Offer a single patient visit
 - Need to be repeated at 8-10 weeks after contact broken if first test is prior to that time, as with TSTs
- To conduct periodic screening of persons who might have occupational exposure to TB (HCWs)



Situations in Which Testing with Both an IGRA and a TST May BE Considered

- When the initial test (TST or IGRA) is negative and
 - When the risk for infection, progression and risk of poor outcome are increased (HIV or children aged < 5 years)
 - When clinical suspicion exists for active tuberculosis
- When more evidence of infection might encourage compliance with Tx for LTBI
- In healthy persons with low risk for both infection and progression to disease; to support conclusion of false positive test
- When initial IGRA result is indeterminate, borderline or invalid and a reason for testing persists



What to do with IGRA Results Medical Management

- Decisions about treatment include medical history, clinical picture, and epidemiologic information
- Persons with positive TST or IGRA should be evaluated for likelihood of M.tb infection, for risks for progression to active disease, and for symptoms of TB disease
- A diagnosis of LTBI requires that a diagnosis of active disease has been ruled out
- **Neither a TST nor IGRA can distinguish LTBI from active TB disease**



What to do with IGRA Results Medical Management – positive results

- In persons with symptoms or x-ray evidence of active TB who are at increased risk of progression to TB if infected, a positive result of either TST or IGRA should be taken as evidence of M. tuberculosis infection
- Negative results are NOT SUFFICIENT TO EXCLUDE INFECTION



What to do with IGRA Results Medical Management – negative results

- In healthy persons who have a low likelihood of both infection and progression to TB disease, a single positive TST or IGRA SHOULD NOT BE TAKEN AS RELIABLE EVIDENCE OF M.tuberculosis infection.
A false positive is more likely.
 - Reassess likelihood of infection and progression to disease
 - Repeat testing with the same or different test on a case-by-case basis
 - Can also assume, without additional testing, that the initial test is a false positive (Why were they tested?)



What to do with IGRA Results Medical Management-discordant results (+ and -)

- Decisions about management include:
 - Assessment of the quality and number value of each test result
 - The probability of infection
 - The risk for disease if infected
 - The risk for poor outcome if disease occurs



What to do with IGRA Results Medical Management – discordant results

- Taking a positive result from either test is reasonable when:
 - Clinical suspicion exists for active tuberculosis
 - The risks for infection, progression, and a poor outcome are increased
 - HIV +
 - Children aged < 5 years



What to do with IGRA Results Medical Management – discordant results

- For healthy persons with low risk for infection and progression to disease DISCOUNTING A POSITIVE RESULT IS REASONABLE. This choice will:
 - increase specificity of the test
 - Decrease unnecessary treatment



What to do with IGRA Results Medical Management – discordant results

- For persons who have received BCG who are not at increased risk of poor outcome if infected:
 - TST <15 mm may be discounted as a false positive when an IGRA is clearly negative
- In other situations, evidence is lacking in which to base recommendations
 - Diagnostic decisions can be deferred if no risk of progression or poor outcome



What is next??

- Your health department may selectively begin to use IGRA testing
- More studies are needed!
- Sites using either IGRA are encouraged to publish results



Questions??
