

TB Infection Testing Options, TB Infection Testing Nuances

DE TB Update

Ed Zuroweste MD
TB Medical Consultant
PA Department of Health
Founding Medical Director
Migrant Clinicians Network

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Disclosure and Disclaimer

Faculty:

Ed Zuroweste, MD

Disclosure: I have no real or perceived vested interests that relate to this presentation nor do we have any relationships with pharmaceutical companies, biomedical device manufacturers, and/or other corporations whose products or services are related to pertinent therapeutic areas.



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TB infection testing interpretation, PPD, TST, Mantoux test (created in 1907)

- Intradermal injection of tuberculin material
- Stimulates a delayed-type hypersensitivity response mediated by T lymphocytes
- In patients with prior mycobacterial exposure, causes induration at the injection site within 48 to 72 hours



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TB infection testing interpretation, PPD, TST, Mantoux test

- Interpretation depends on the **risk for TB infection** and the **risk for progression to active TB disease**

≥ 5mm	HIV + (any CD4 count)	Close contact of active contagious case	Abnormal chest radiograph with fibrotic changes consistent with old TB	Immunosuppressed patients: -TNF-alpha inhibitors -chemotherapy -organ transplantation -glucocorticoid treatment (equivalent of ≥15 mg/day prednisone for ≥1 month)
≥ 10mm	Certain conditions that increase the risk of reactivation -HD -Silicosis -Certain malignancies -DM -Malnutrition -Jejunal bypass -IVDU	Residents and employees in high-risk settings -Prisons -Jails -Healthcare facilities - Mycobacteriology labs -Homeless shelters	Children < 4 yrs age	Foreign born from countries with high incidence TB, in particular those immigrated in past 5 years
≥15mm	Healthy individuals age 4 years and older with low likelihood of true TB infection			

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TB infection testing interpretation, booster phenomenon vs. conversion

- **Booster response:**
 - Positive PPD performed 1-4 weeks after an initial negative PPD in the absence of TB exposure
 - Sometimes done in a person who is planned for serial testing, ie.. health care workers
 - May be a sign of a remote TB infection
 - Helps to avoid misclassifying someone as a new conversion
- **Conversion:**
 - An increase in induration of ≥ 10 mm since the previous test in the setting of ongoing risk of exposure to TB
- **Remember: serial PPDs will not lead to a false + PPD!**

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TB infection testing interpretation, PPD false +

- **Non-TB mycobacteria**
 - Remember TB is not the only mycobacteria- in fact there are approximately 200 NTM species out there!
- **BCG vaccine, made from *Mycobacterium bovis***
 - More likely if received a booster BCG after infancy
 - Effect on the PPD wanes with time (12mm PPD in a 8 yr old vs. 12mm PPD in a 60 yr old)
 - Can look for the scar on the upper lateral arm
- **Misreading**
 - Should read horizontally across the forearm
 - Read induration, not erythema! Close your eyes!

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TB infection testing interpretation, PPD false -

- Immunosuppression
 - HIV (esp low CD4), steroids, malignancy, TNF alpha
 - Malnourished
 - CRI
- Any active infection including active TB!
- Recent infection
 - Close contact of an active case repeat PPD in 8 wks to look for conversion
- Recent live vaccine, MMR
- Improper storage, improper administration, improper reading

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TB infection testing interpretation, IGRAs

- Blood tests
- Measure T cell release of interferon-gamma following stimulation by antigens more specific to *Mycobacterium tuberculosis*
- 2 IGRA tests:
 - QuantiFERON gold (plus)
 - enzyme-linked immunosorbent assay (ELISA)
 - T-spot
 - enzyme-linked immunospot (ELISPOT) assay

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TB infection testing interpretation, IGRAs

- Main advantages over PPD
 - Do not cross react to a prior BCG vaccine and most other NTM
 - One stop shop
 - More automated (ie... less room for error)
 - Built in measure of immune function
- Main disadvantage over PPD
 - Not well studied children < 2 yr old

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TB infection testing interpretation, Quantiferon gold plus

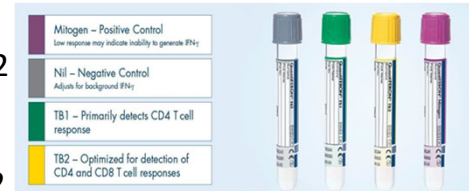
Mitogen – Positive Control
Low response may indicate inability to generate IFN- γ
Nil – Negative Control
Adjusts for background IFN- γ
TB1 – Primarily detects CD4 T cell response
TB2 – Optimized for detection of CD4 and CD8 T cell responses



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TB infection testing interpretation, Quantiferon gold plus

- Results in IU/ml
- Positive result
 - + Mitogen, - Nil, + result in EITHER tube 1 or tube 2
 - tube 1 or tube 2 minus nil > 0.35 IU/ml
- Negative result
 - + Mitogen, - Nil, - result in BOTH tube 1 and tube 2
- Indeterminate result
 - - Mitogen: immunosuppression
 - + Nil: high background noise
 - Improper testing technique
- Remember: no test is perfect!
 - False -
 - Window period after TB infection, up to 8-12 wks
 - False +
 - *M bovis* (but NOT BCG)
 - *M kansasii*, *M szulgai* and *M marinum*



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LabCorp	PATIENT INFORMATION	REPORT STATUS: FINAL
SPECIMEN INFORMATION		ORDERING PHYSICIAN
Lab ref no:	GENDER: Male	CLIENT INFORMATION
	FASTING: Yes	
COLLECTED: 02/18/2022 07:51AM LOCAL	Clinical Info:	
RECEIVED: 02/18/2022		
REPORTED: 02/20/2022 04:07PM ET		
Test Name	Result	Flag
QuantIFERON®-TB Gold Plus		
QuantIFERON Incubation	Incubation performed.	NORMAL
QuantIFERON-TB Gold Plus	Positive	ABNORMAL
Chemiluminescence immunoassay methodology		Negative
QuantIFERON-TB Gold Plus		
QuantIFERON Criteria	Comment	NORMAL
The QuantIFERON-TB Gold Plus result is determined by subtracting the Nil value from either TB antigen (Ag) tube. The mitogen tube serves as a control for the test.		
QuantIFERON TB1 Ag Value	1.77	NORMAL
QuantIFERON TB2 Ag Value	1.79	NORMAL
QuantIFERON Nil Value	0.08	NORMAL
QuantIFERON Mitogen Value	>10.00	NORMAL
Performing Laboratory Information:		
01: Labcorp Dublin, 6370 Wilcox Road, Dublin OH, 430161269, phone: 800-282-7300, Director: Ph Vincent Ricchiuti		

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Results

QUANTIFERON TB GOLD PLUS [LAB3522] (Order: 693690631)

Lab Collection Information

Specimen ID: [REDACTED]

Specimen: Blood

Specimen: Blood, Venous
Venipuncture

Collection Date and Time: 2/3/2022 4:06 PM

Collected By: [REDACTED]

Received: 2/3/2022 4:06 PM

QUANTIFERON TB GOLD PLUS

Order: [REDACTED]

Status: Final result Visible to patient: Yes (not seen) Next appt: None Dx: Sacroiliitis (HCC)

QUANTIFERON-TB PLUS,1T	Ref Range & Units	5 d ago
	NEGATIVE	POSITIVE ?

Comment: In healthy persons who have a low likelihood both of M. tuberculosis infection and of progression to active tuberculosis if infected, a single positive QFT result should not be taken as reliable evidence of M. tuberculosis infection. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis.

NIL	IU/mL	0.06
MITOGEN-NIL	IU/mL	>10.00
TB1-NIL	IU/mL	0.39
TB2-NIL	IU/mL	0.37

Comment: The Nil tube value reflects the background interferon

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QUANTIFERON (R) - TB GOLD PLUS, 1 TUBE

POSITIVE NEGATIVE

In healthy persons who have a low likelihood both of M. tuberculosis infection and of progression to active tuberculosis if infected, a single positive QFT result should not be taken as reliable evidence of M. tuberculosis infection. Repeat testing, with either the initial test or a different test, may be considered on a case-by-case basis.

NIL	0.04	IU/mL
MITOGEN-NIL	>10.00	IU/mL
TB1-NIL	0.47	IU/mL
TB2-NIL	0.27	IU/mL

The Nil tube value reflects the background interferon gamma immune response of the patient's blood sample. This value has been subtracted from the patient's displayed TB and Mitogen results.

Lower than expected results with the Mitogen tube prevent false-negative Quantiferon readings by detecting a patient with a potential immune

CLIENT SERVICES: [REDACTED]

SPECIMEN: [REDACTED]

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12/08/2021 3:12PM (GMT-05:00)

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TB infection testing interpretation, Quantiferon gold plus

QFT PLUS INTERPRETATION INDETERMINATE



Comment:

An Indeterminate interpretation can be caused by a number of factors, including sample collection. Testing should be reordered and a new sample collected on patients with indeterminate results. Samples with a low mitogen response (<0.5) may be due to anergy or immune suppression. Samples with a high Nil response (>8.0) may be due to interferon gamma production independent of TB stimulation or heterophile antibodies. For more details, please see TB Testing Guidance on Staffnet.

QFT PLUS NIL VALUE	10.000	IU/mL
QFT PLUS TB AG1 MINUS NIL	0.000	IU/mL
QFT PLUS TB AG2 MINUS NIL	0.000	IU/mL
QFT PLUS MITOGEN MINUS NIL	0.000	IU/mL

QUANTIFERON TB GOLD

Collected: 11/19/15 1021

Resulting lab: LABCORP

Reference range: Negative

Value: **Indeterminate !**

Comment: Mitogen (positive control) gave low response. This may indicate anergy or immune suppression. Early draws and extended transit time may also result in low positive control and indeterminate results. The specimen received for QuantiFERON testing was incubated by the ordering institution. Specific procedures outlined in our Directory of Services and in the package insert for the QuantiFERON Gold (In Tube) test must be followed to enable for proper stimulation of cells for the production of interferon gamma.

QFT TB AG VALUE	0.04
QFT NIL VALUE	0.04
QFT MITOGEN VALUE	0.14
QFT TB AG MINUS NIL VALUE	0.00
QFT INTERPRETATION	

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TB infection testing interpretation, T spot

- Results are interpreted by subtracting the spot count in the negative (Nil) control from the spot count in Panels A and B
- Positive:** if Panel A minus Nil and/or Panel B minus Nil is ≥ 8 spots
- Negative:** if both Panel A minus Nil and Panel B minus Nil is ≤ 4 spots
- Equivocal:** if the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6, or 7 spots

	Negative Result	Positive Result
Nil Control		
ESAT-6 Panel A		
CFP10 Panel B		
Positive Control		

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TB infection testing interpretation

- Remember
 - Neither PPD or IGRAs differentiates b/w latent or active TB infection
 - Neither is used to follow response the treatment in a patient with active TB
 - After TB infection both should remain + for life

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TB infection testing interpretation, Context matters!

- + PPD, - IGRA test
 - 8 yr old healthy girl from Brazil, PPD 10MM, IGRA neg
 - 60 yr old female from Brazil, uncontrolled DM and CRI, PPD 10mm, IGRA neg
 - 60 yr old female from Brazil, PPD 10mm, IGRA neg, getting ready to start TNF alpha inhibitor
 - 60 yr female from Brazil, PPD 0mm 2 yrs ago, now a contact of an active smear + case, current PPD 10mm, IGRA neg
 - 8 yr old healthy girl from Brazil, PPD 30mm, IGRA neg
 - 40 yr healthy male from Brazil, PPD 10mm, IGRA neg, works in a neonatal ICU

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TB infection testing interpretation, Context matters!

- -PPD, + IGRA (not as common)
 - 30 yr old healthy patient from Haiti, PPD 2 yrs ago 0 mm. Now IGRA +
 - 30 yr old patient from Haiti with RA. PPD 2 yrs ago 0 mm. Now IGRA+
 - 30 yr old patient from Haiti with HIV. PPD 2 yrs ago 0 mm. Now IGRA +
 - 18 yr US born patient, healthy, no h/o international travel or known exposures to TB, TB testing done b/c demanded for entry to college, PPD 0mm, quant gold plus Positive in 1 of the tubes at 0.35 IU/ml

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TB infection testing interpretation, Context matters!

- Indeterminate IGRA
 - 30 yr male from Haiti, on 40mg prednisone for RA, IGRA indeterminate due to low mitogen response
 - 30 yr male from Haiti, healthy, IGRA indeterminate due to high nil

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TB infection testing interpretation

Most important take home message

- When interpreting results of PPD or IGRA, always interpret in context of the patient
- No gold standard to diagnose latent TB infection, pre-test probability matters!
- Ask yourself:
 - what risk factors does this patient have for being infected with TB?
 - what risk factors does this patient have for reactivation of a latent TB infection?
 - what are the consequences of TB reactivation?
 - what are the possible reasons for a false + or a false - PPD or IGRA?

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