Diagnosing TB Infection and Disease

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Diagnosing TB Infections and Disease

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WILLIAMSON COUNTY AND CITIES HEALTH DISTRICT

Special Thanks!

- Dr. Lisa Armitige, M.D., Ph. D and Dr. Barbara Seaworth, M.D., F.I.S.DA., F.A.C.P.
- The Team at Heartland
- The TB eliminators at WCCHD
- Our Public Health Nurses and Public Health Prevention Specialists

Who do we test?

Who do we test?

- Testing is usually risk based (meaning, what is the likelihood someone is infected?)

- Just a note about HCW: in 2019, guidelines changed to state that routine TB screens on HCW are not recommended

USPSTF updates and what it means for us!

Recommendation Summary

Population	Recommendation	Grade
Asymptomatic adults at increased risk of latent tuberculosis infection (LTBI)	The USPSTF recommends screening for LTBI in populations at increased risk. See the "Assessment of Risk" section for additional information on adults at increased risk.	B

Pathway to Benefit

To achieve the benefit of screening, it is important that persons who screen positive for LTBI receive followup and treatment.

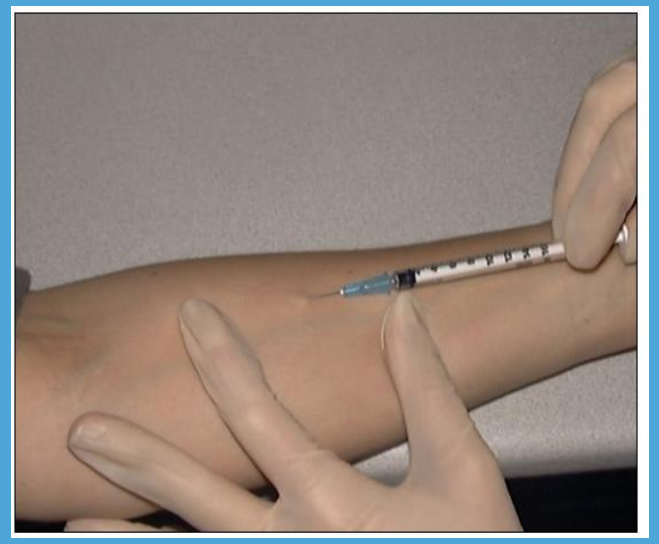
So…how do we test for TB?- 1) TSTs

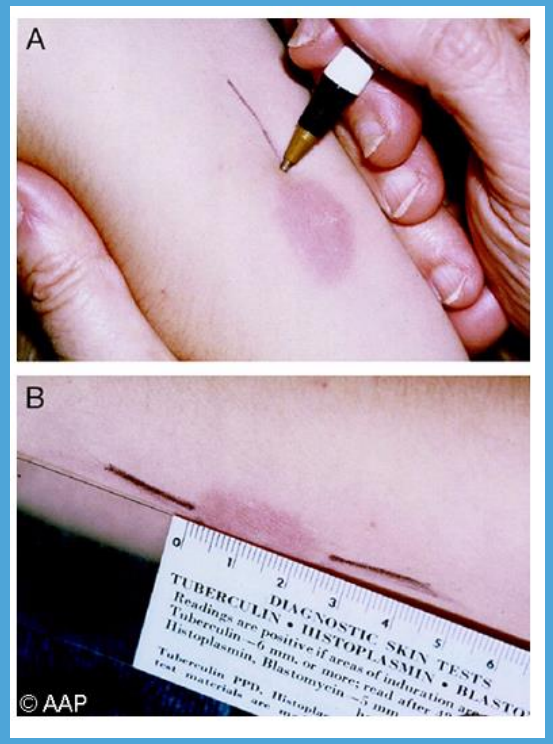
1) One option is via a Tuberculin Skin Test (TST)

-0.1 ml of 5 Tuberculin Units (TU) injected **intradermally**

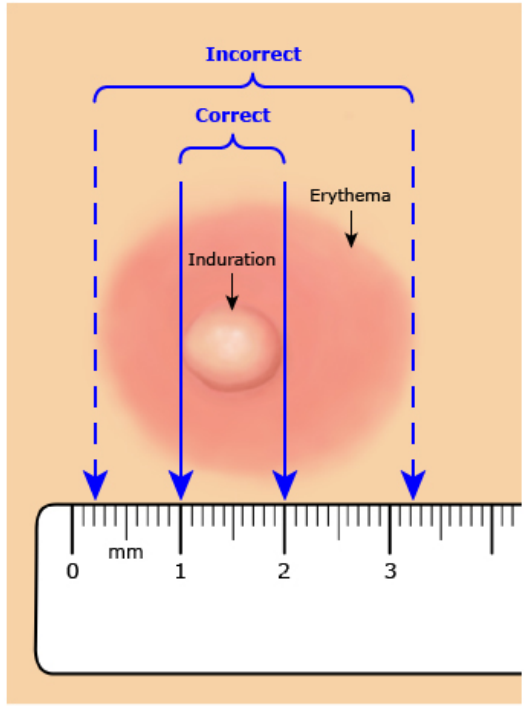
- Patient returns 48-72 after placement for reading

- Read is done in millimeters
- Read is of **induration, NOT erythema**





Measuring a reaction to the tuberculin skin test



This figure shows the correct method for measuring a reaction to the tuberculin skin test. The size of the reaction is measured by the width of induration, not erythema. In the example shown, the reaction measures 10 mm.

Modified from: Testing for tuberculosis infection and disease. In: Core Curriculum on Tuberculosis: What the Clinician Should Know, 6th ed, Centers for Disease Control and Prevention 2013. https://www.cdc.gov/tb/hcp/education/core-curriculum-on-tuberculosis.html (Accessed on July 16, 2024).

How to Measure

- reading a ppd - UpToDate

1) TST- what number is positive?

- Like many things TB related, there is no one answer to this.
- Positive Tests are defined based on a patient's individual risk factors.
- From smallest to largest…
  - * An induration of 5mm is **positive** for High risk individuals such as
    - HIV/Immunocompromised
    - Recent contact (8 or fewer weeks) to a person with active TB
    - History or Imaging suggestive of old disease
  - * An induration of 10 mm is **positive** for individuals in high-risk settings
    - Immigrants from countries with high TB burden (>20/100,000)
    - Residents or Employees of congregate settings (jails, shelters, etc)
  - * An induration of 15 mm is **positive** for ANY individual

Interpretation of tuberculin skin test

Tuberculin skin test reaction size (mm)	Situation in which reaction is considered positive*
<5	HIV infection plus close contact of active contagious case¶
≥5	HIV infection
	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)
≥10	Persons with clinical conditions that increase the risk of reactivation, including silicosisΔ, chronic renal failure requiring dialysisΔ, diabetes mellitus, some malignancies (leukemias, lymphomas, carcinoma of the head, neck, or lung), underweight (by ≥10% ideal body weight), jejunoileal bypass, injection drug users
	Children age <4 years◇
	Foreign-born from countries with incidence >25/100,000§
	Residents and employees in high-risk settings, such as prisons, jails, health care facilities, mycobacteriology labs, and homeless shelters
≥15	Healthy individuals age ≥4 years with low likelihood of true TB infection¥

The table summarizes the approach to interpretation of initial TST; issues related to interpretation of repeat TST are discussed separately (refer to UpToDate topic on diagnosis of TB infection).

TB: tuberculosis; TNF: tumor necrosis factor; TST: tuberculin skin test.

* The goal of testing for TB infection is to identify individuals who are at increased risk for the development of TB disease and therefore would benefit from treatment of TB infection. Only those who would benefit from treatment should be tested, so a decision to test presupposes a decision to treat if the test is positive. Refer to the UpToDate topic on diagnosis of TB infection for discussion of issues related to interpretation of repeat TST.

¶ The risk of active TB is high among human immunodeficiency virus (HIV)-positive patients who are close contacts of active contagious cases and are anergic.

Δ The United States Centers for Disease Control and Prevention (CDC) recommends a 10 mm induration definition for patients with silicosis or chronic renal failure. However, population-based studies demonstrate that the relative risk for development of tuberculosis disease in this category is high (≥10× that of healthy individuals). For this reason, many favor a lower threshold for a positive test (≥5 mm).

◇ The American Academy of Pediatrics (AAP) favors a threshold of 10 mm for otherwise healthy children <4 years of age with no risk factors (and a threshold of ≥15 mm for healthy children ≥4 years of age)[1]. This threshold differs from the CDC which favors a threshold of 10 mm for otherwise healthy children <5 years of age (and a threshold of ≥15 mm for healthy children ≥5 years of age)[2].

§ The United States Preventive Services Task Force recommends screening of adults at risk for TB infection (implying all foreign-born adults from countries with high TB incidence), regardless of time since immigration[3]; this approach is based on a 2023 systematic review[4]. Previously, the CDC favored testing only for foreign-born individuals (regardless of age) who immigrated within the past five years, given the higher risk of disease within the first five years after immigration.

¥ Individuals with a low likelihood of true TB infection should not be tested routinely unless they are entering a high-risk setting such as starting employment at a healthcare facility. A threshold of 15 mm is used in the United States and is appropriate for healthy individuals with low likelihood of true TB infection and high likelihood of exposure to nontuberculous mycobacteria (eg, southern United States). However, Canadian guidelines use a threshold of 10 mm for healthy individuals given the lower likelihood of exposure to nontuberculous mycobacteria. (Refer to the UpToDate topic on epidemiology of nontuberculous mycobacterial infections.)

References:

1. *American Academy of Pediatrics. Red Book: 2024-2027 Report of the Committee on Infectious Diseases, 33rd ed, Kimberlin DW, Banerjee R, Barnett ED, et al (Eds), American Academy of Pediatrics 2024.*
2. *Tuberculin skin testing fact sheet: Information for health care providers. Centers for Disease Control and Prevention. https://www.cdc.gov/tb/hcp/mantoux/skin-test-fact-sheet.html (Accessed on June 20, 2024).*
3. *Mangione CM, Barry MJ, Nicholson WK, et al. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. JAMA 2023; 329:1487.*
4. *Jonas DE, Riley SR, Lee LC, et al. Screening for latent tuberculosis infection in adults: Updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2023; 329:1495.*

Chart Form of Positive PPD reads

reading a ppd - UpToDate

1) TST- pros and cons

- PROS
  - *Cheap!
  - * Easy! ….kind of

- CONS
  - * Mandatory return visit (48-72 hours)
  - * The art of interpretation can be tricky
  - * Potential for false negatives
  - * Potential for false positives

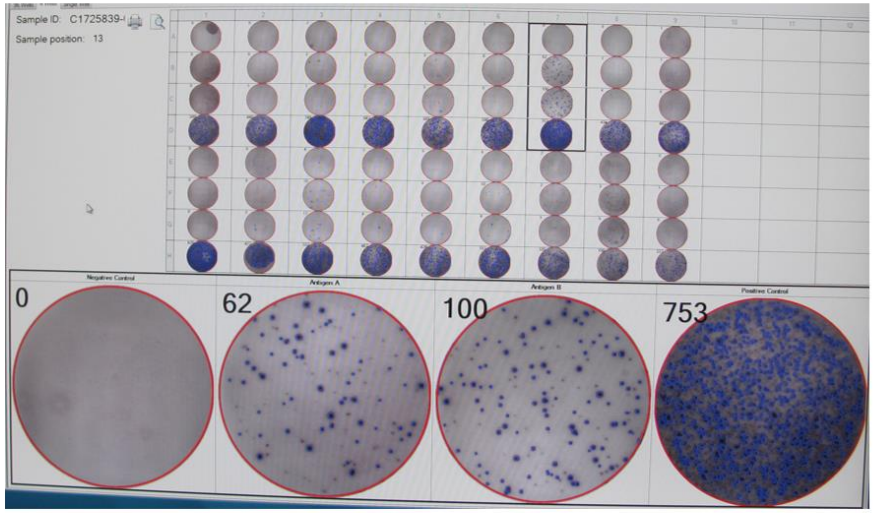
So…how do we test for TB?- 2.) IGRAs

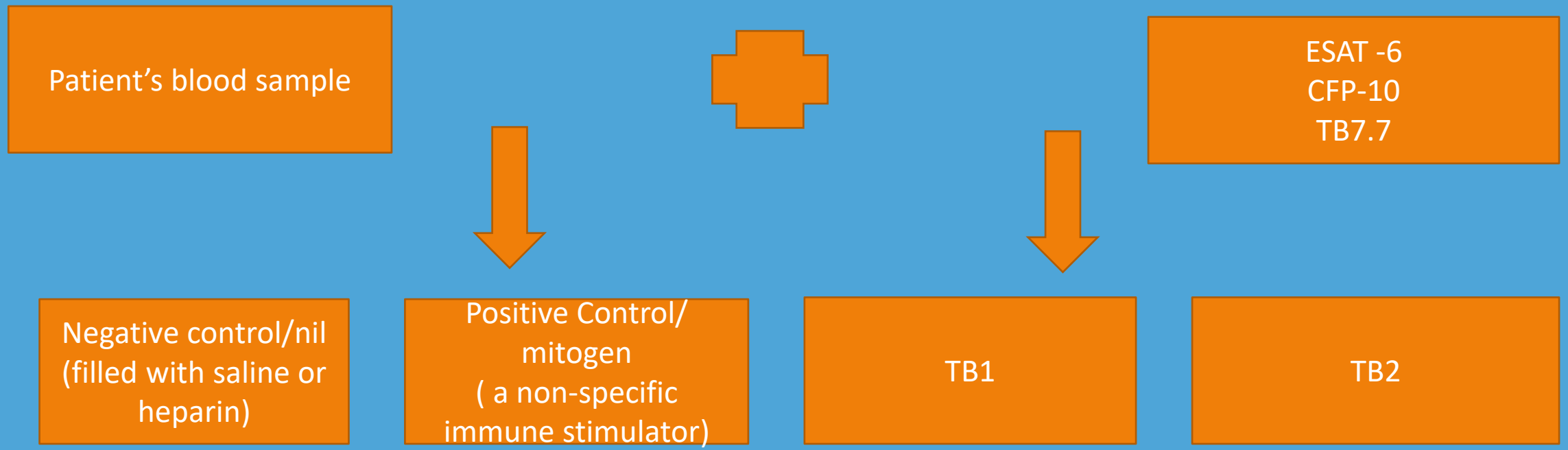
QuantiFERON®-TB Gold Plus

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	

- Essentially 2 tests in one blood draw
- TB1 and TB2 should be close in value

T-Spot.*TB*





Initial process of evaluating for TB via IGRAs

2.)IGRAs - what number is positive for a QFT

Interpretation Criteria for the QFT-Plus Test

Nil (IU/mL)	TB1 or TB2 Antigen minus Nil (IU/mL)	TB1 or TB2 (IU/mL)	Mitogen	Interpretation
≤ 8.0	≤ 0.35 or < 25% of Nil value	Negative	≥ 5.0	*M. tuberculosis* infection **unlikely**
≤ 8.0	≥ 0.35 and ≥ 25% of Nil value	Positive	ANY	*M. tuberculosis* infection **likely**
≥ 8.0	ANY	Indeterminate	ANY	Indeterminate
≤ 8.0	≤ 0.35 and or < 25% of Nil value	Indeterminate	< 5.0	Indeterminate

immunization or past orcurrent infection with rubella virus.

QuantiFERON-TB Gold Plus				
	MITOGEN-NIL	9.88	IU/ml	
	NIL	0.05	IU/ml	
	QUANTIFERONA (R)-TB GOLD PLUS,1T	Positive		Negative

In healthy persons who have a low likelihood ofM. tuberculosis infection, a single positive QFTresult should not be taken as reliable evidenceof M. tuberculosis infection. Repeat testing, witheither the initial test or a different test, maybe considered on a case-by-case basis.

	TB1-NIL	0.55	IU/ml
	TB2-NIL	0.87	IU/ml

2.)IGRAs - what number is positive for a QFT

QuantiFERON-TB Gold

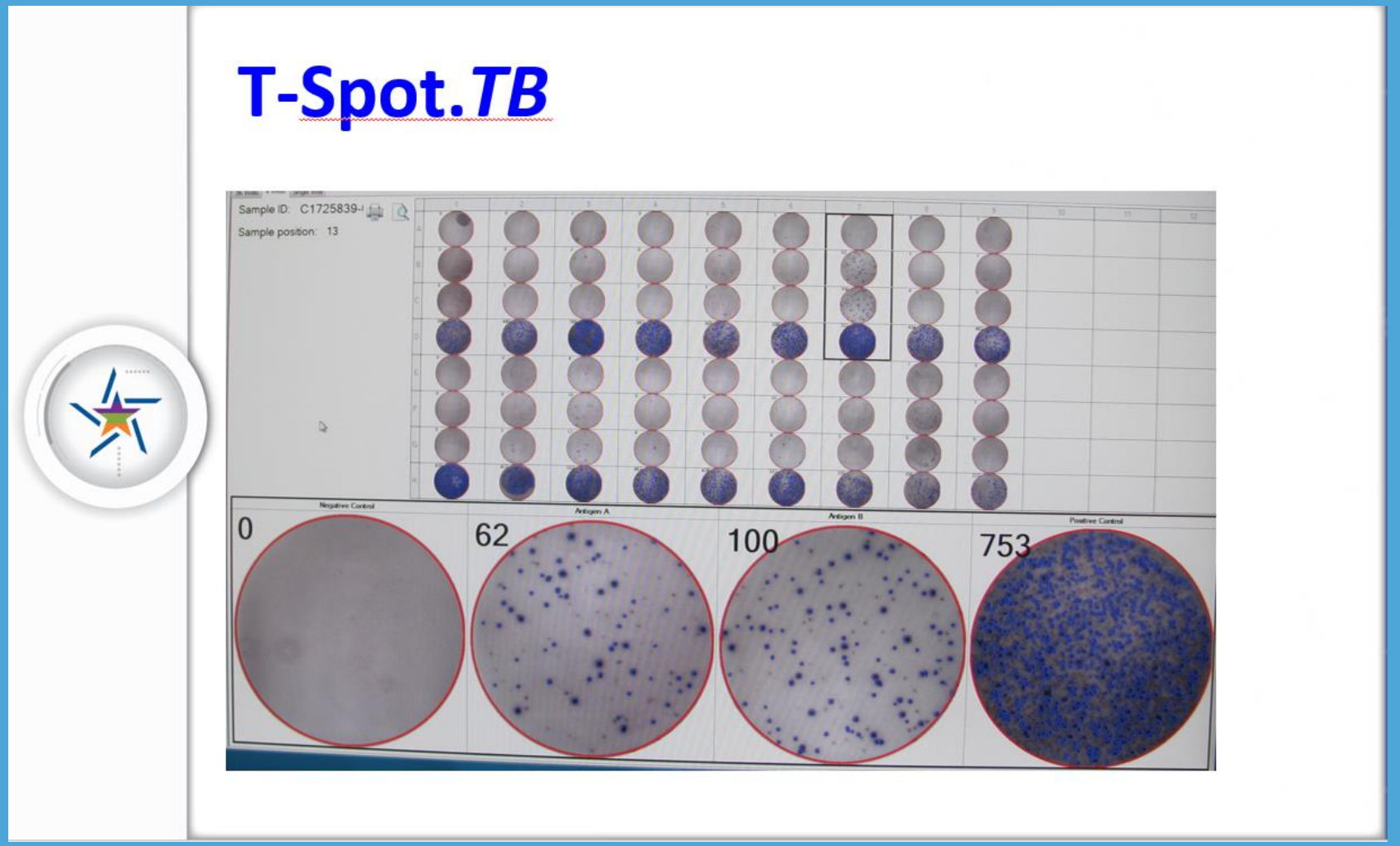
TABLE 2. TEST SENSITIVITY AND SPECIFICITY FOR CFP-10 AND ESAT-6 AT VARIOUS CUTOFFS IN WHOLE-BLOOD IFN-γ ASSAY

Cutoff, IFN-γ	CFP-10		ESAT-6		CFP-10 and/or ESAT-6	
(*IU/ml*)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)
0.05	92.5	81.4	94.8	94.9	89.4	97.5
0.10	94.4	77.1	96.2	90.7	92.0	95.8
0.15	95.8	72.9	97.6	88.1	93.9	93.2
0.20	96.7	71.2	99.1	86.4	96.2	91.5
0.25	97.2	67.8	99.1	84.7	96.7	91.5
0.30	97.7	66.9	99.1	83.1	97.2	89.8
0.35	**98.6**	**65.3**	**99.5**	**81.4**	**98.1**	**89.0**
0.40	98.6	61.9	99.5	79.7	98.1	88.1
0.45	98.6	60.2	100.0	78.8	98.6	86.4
0.50	99.1	60.2	100.0	75.4	99.1	83.9

Sensitivity was determined on the basis of data from 118 patients with culture-positive tuberculosis, and specificity was determined on the basis of data from 213 low-risk subjects. The chosen cutoff (0.35) is in boldface.

Mori et al 2004 Am J Respir Crit Care Med ,170: 59–64

2.)IGRAs - what number is positive for a TSpot



2.)IGRAs - what number is positive for a TSpot

Interpretation Criteria for the T-Spot.TB

Result	Nil*	TB Response##	Mitogen++	Interpretation+
Positive	≤ 10 spots	≥ 8 spots	Any	*M.tuberculosis* infection likely
Borderline	≤ 10 spots	5, 6, or 7 spots	Any	Uncertain likelihood of *M. tuberculosis* infection
Negative	≤ 10spots	≤ 4 spots		M Tb infection unlikely
Indeterminate	> 10 ≤ 10	Any < 5 spots	Any < 20 spots	Uncertain likelihood of *M. tuberculosis* infection

⚠ T-SPOT®.TB (FINAL)

Lab: V6O

Analyte	Value		
⚠ **T-SPOT.TB** (71773-6)	**POSITIVE**	Reference Range: SeeBelow	FINAL

Normal Value: Negative
Diagnosing or excluding tuberculosis (TB) disease and assessing the probability of latent TB infection (LTBI) requires a combination of epidemiological, historical, medical and diagnostic findings that should be taken into consideration when interpreting T-SPOT.TB test results. A positive test result does not rule in active TB disease caused by Mycobacterium tuberculosis (M. tuberculosis); active TB disease should be confirmed by other tests such as sputum smear and culture, PCR, and chest radiography. Uncommonly, a positive T-SPOT.TB result may be due to infection with other Mycobacterium species including M. kansasii, M. szulgai, M. gordonae, or M. marinum. Alternative tests would be required if these infections are suspected. The T-SPOT.TB test is qualitative and results are reported as positive, borderline or negative, given that the test controls perform as expected. In line with the Centers for Disease Control and Prevention's 2010 recommendation to report quantitative measurements alongside the qualitative result, the laboratory provides spot counts for informational purposes only. The T-SPOT.TB test should not be interpreted as a quantitative test.

PANEL A SPOT COUNT CORRECTED FOR NEG CONTROL (74278-3)	>50		FINAL
PANEL B SPOT COUNT CORRECTED FOR NEG CONTROL (74277-5)	42		FINAL
NEGATIVE CONTROL (74279-1)	Passed		FINAL
POSITIVE CONTROL (74280-9)	Passed		FINAL

2.) IGRAs- Pros and Cons

- Pros
  - * Objective
  - * (Should) only require one visit
  - * Is not impacted by BCG vaccine status

- Cons
  - * Though per the AAP IGRAs can now be performed on age, a *negative* IGRA cannot be trusted until the child is at least 6m
  - * A more expensive test/ study
  - * Though results are more objective, can be indeterminate/ borderline, creating a need for further testing and potential for confusion for your patient

So we have a positive test- now what?

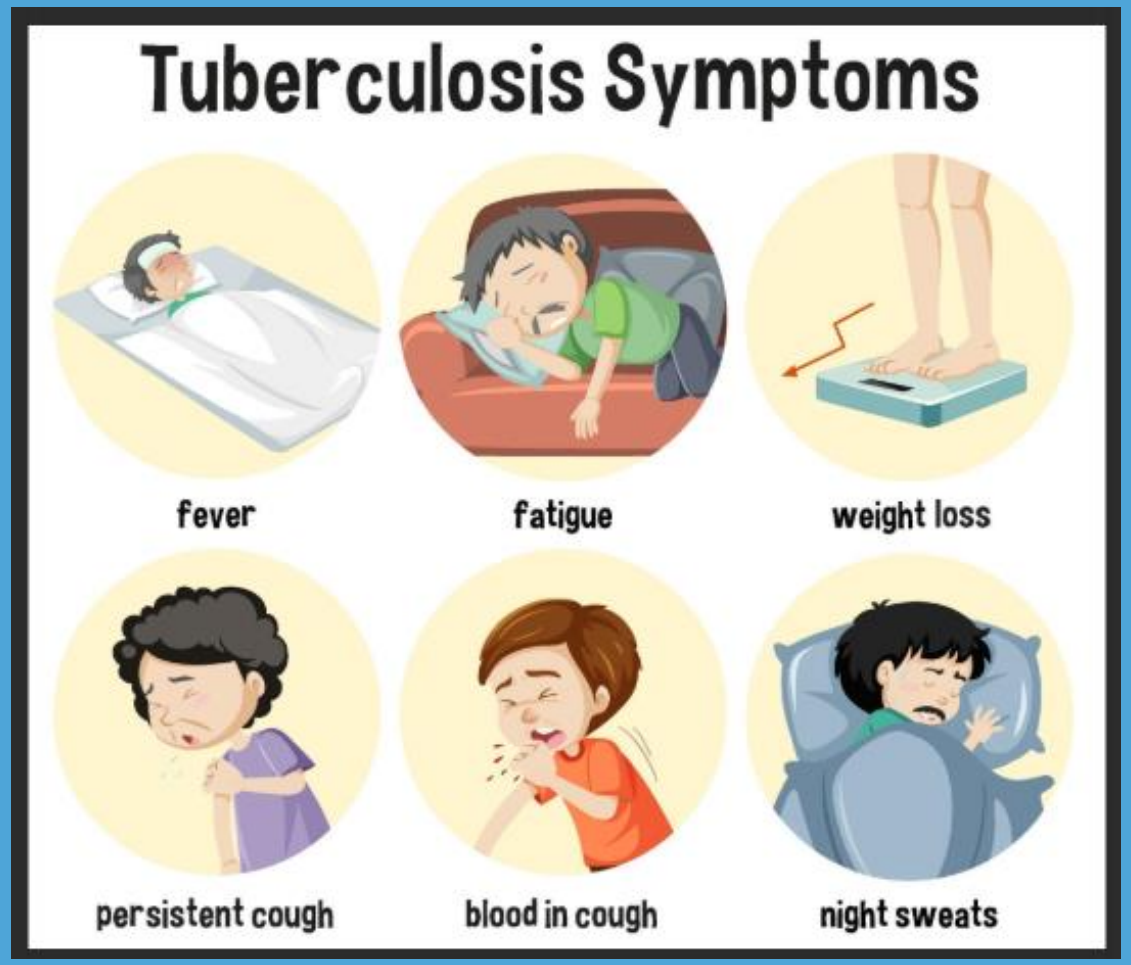
- The 3 main components of determining TB disease (after a positive test or a negative test result in a patient of high risk) are:

    * History

    *Physical

    *Chest X-Ray

History


Tuberculosis Symptoms
fever
fatigue
weight loss
persistent cough
blood in cough
night sweats

Physical Exam

Observation

*Are they frail? Cachectic? Clammy? Coughing?

Lungs

*Wheezing? Rhonchi? Rales?

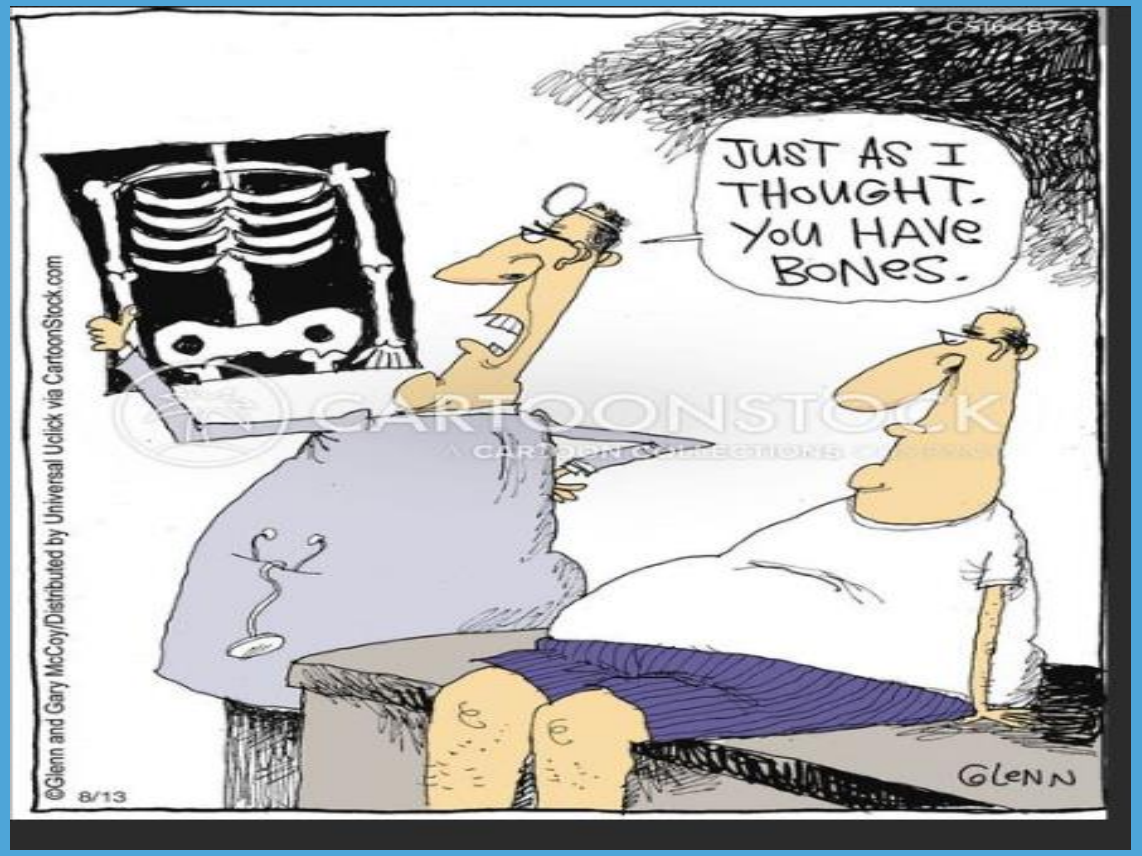
Lymph nodes

* Any lymphadenopathy?

Abdomen

*With a focus on the liver

Imaging


JUST AS I THOUGHT. YOU HAVE BONES.
GLENN
8/13
©Glenn and Gary McCoy/Distributed by Universal Uclick via CartoonStock.com

Imaging

Typically a chest xray or CT of the chest (without contrast)

*Looking for evidence of active disease

*Looking for clear imaging

* Looking for evidence of old disease/ stable abnormalities over a 3 month period

Additional (ie, always get a chest xray!) imaging may be needed if concern for extrapulmonary disease

* Sites include: bone and joints, lymph, skin, kidneys, miliary (disseminated)

Imaging- but what if they are pregnant!

- Being pregnant and having TB is not safe for the mom or the baby
- Therefore, priority is to evaluate for TB

Imaging- but what if they are pregnant!

Yes! You can X-ray a pregnant patient!

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 723 • October 2017 (Replaces Committee Opinion Number 656, February 2016)

Committee on Obstetric Practice

This document is endorsed by the American College of Radiology and the American Institute of Ultrasound in Medicine. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. Member contributors included Joshua Copel, MD; Yasser El-Sayed, MD; R. Phillips Heine, MD; and Kurt R. Wharton, MD. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	**Effects**	**Estimated Threshold Dose***
8–15 weeks	Severe intellectual disability (high risk)†	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).
†Because this is a period of rapid neuronal development and migration.
Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. Radiographics 2007;27:1705–22.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations

Type of Examination	Fetal Dose* (mGy)
Very low-dose examinations (<0.1 mGy)	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
Low- to moderate-dose examinations (0.1–10 mGy)	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
Higher-dose examinations (10–50 mGy)	
Abdominal CT	1.3–35
Pelvic CT	10–50
^{18}F PET/CT whole-body scintigraphy	10–50

Putting it all together…

- Assume a patient has a positive IGRA/ TST
- Now they have a positive/concerning CXR
- What next?
- *Depends….do they have symptoms?*

- If NO symptoms- collect 3 sputum samples for both smears and cx
    - if smear and culture negative, can repeat imaging (this is approx. 2-3 months wait).
    - MTB PCR or NAAT can be of great benefit here!

-If YES symptomatic, refer to PHD

- We may consider fast start on RIPE after sputum collected

Now You Are a Pro!

- Now you know how to test for TB exposure via blood or skin test
- If positive, pursue imaging and an exam
- If imaging or exam is suspicious, pursue sputum collection (assuming pulmonary site)
- If sputa are positive- treat for TB!

Questions?

- Contact us any time!
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- WCCHD TB team:

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