Testing for Tuberculosis Infection: Why, Who, How?

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Shu-Hua Wang, MD, MPH &TM, PharmD

Professor, Infectious Diseases

The Ohio State University

Medical Director, Ben Franklin TB Clinic

TB Consultant, Ohio Department of Health

The Ohio State University
Wexner Medical Center

- **Two billion people**, 1/3 - 1/4 of the world's total population, are infected with TB bacilli
- **One in 10** people infected with TB bacilli will become sick with active TB in their lifetime
- If not treated, each person with active TB infects ~ **10 to 15** people every year

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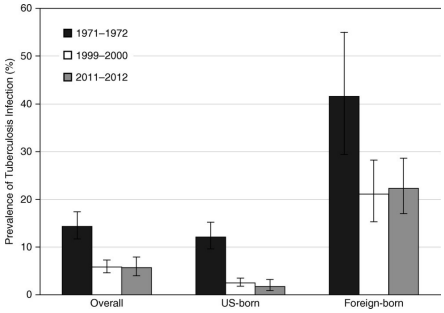
TB Infection in the US

- Up to 13 million people in US infected; ~ 4.5%
- 5-10% may go on to have active TB if untreated
- ~ 70% of LTBI in foreign born individuals
- 19% of US born with LTBI treated; 10% of foreign born
- Treatment 90% effective
- 80% active cases arise from prior infection
- No significant decline in TST or IGRA positivity over past decade



Mancuso et al, AJRCCM, 2016

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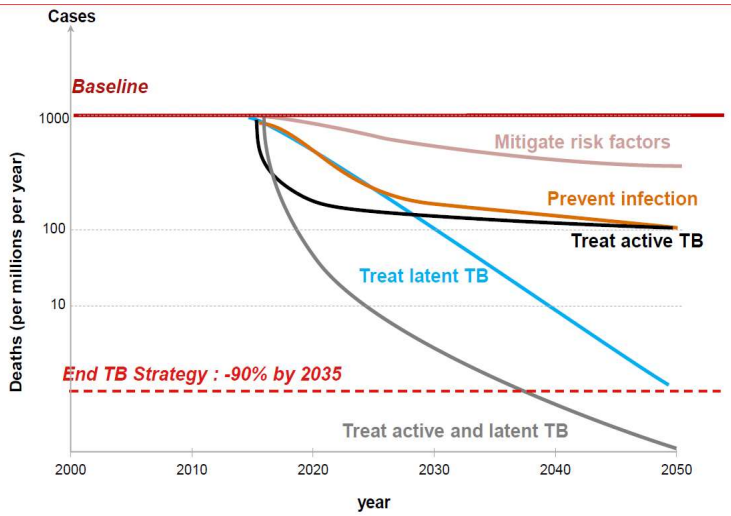
END TB Elimination: Treatment of Active TB Disease and Latent TB Infection



Dye C et al., Prospects for Tuberculosis Elimination. Ann Rev Public Health 2013. 34:271-86

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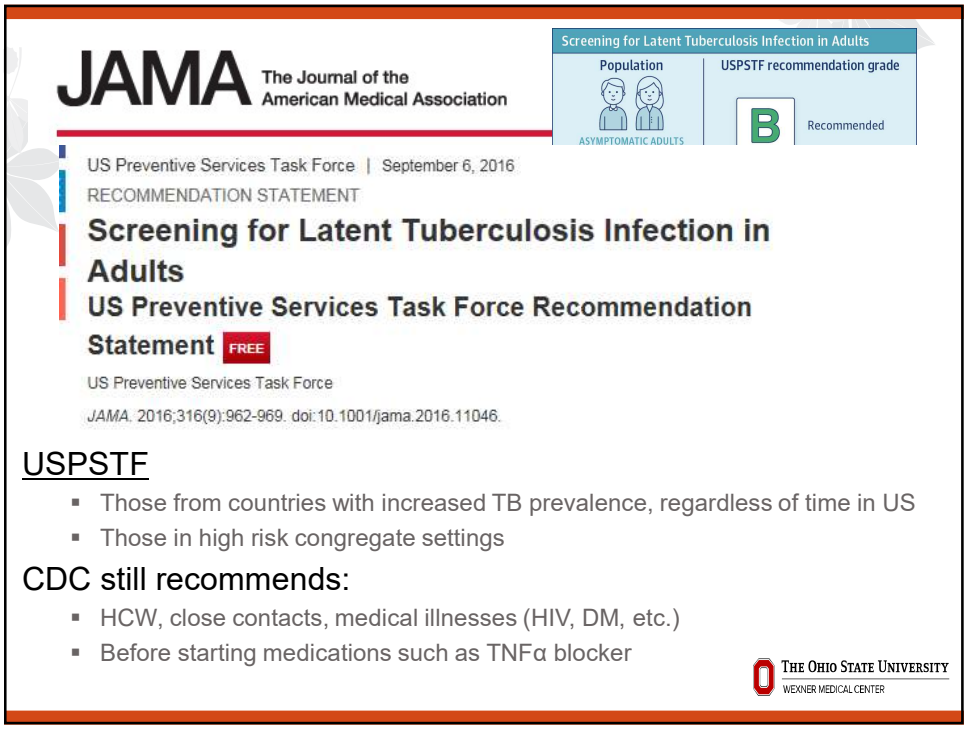

USPSTF

- Those from countries with increased TB prevalence, regardless of time in US
- Those in high risk congregate settings

CDC still recommends:

- HCW, close contacts, medical illnesses (HIV, DM, etc.)
- Before starting medications such as TNFα blocker

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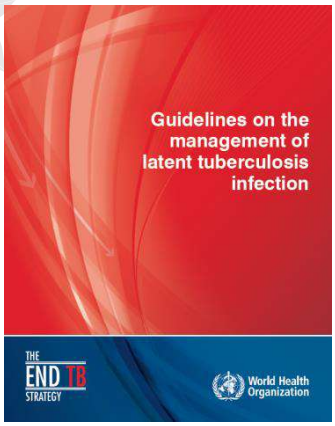

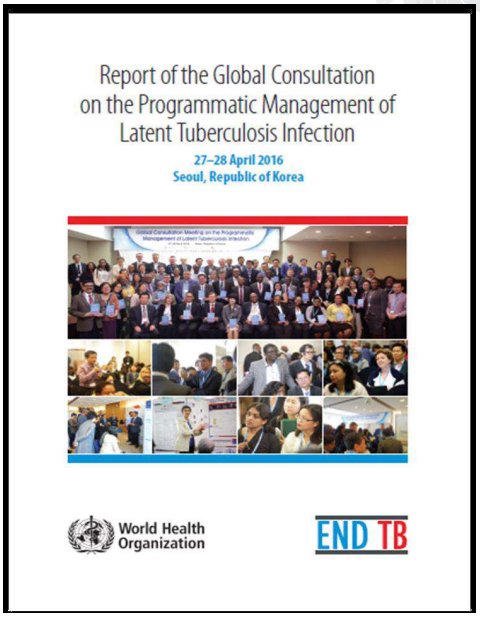

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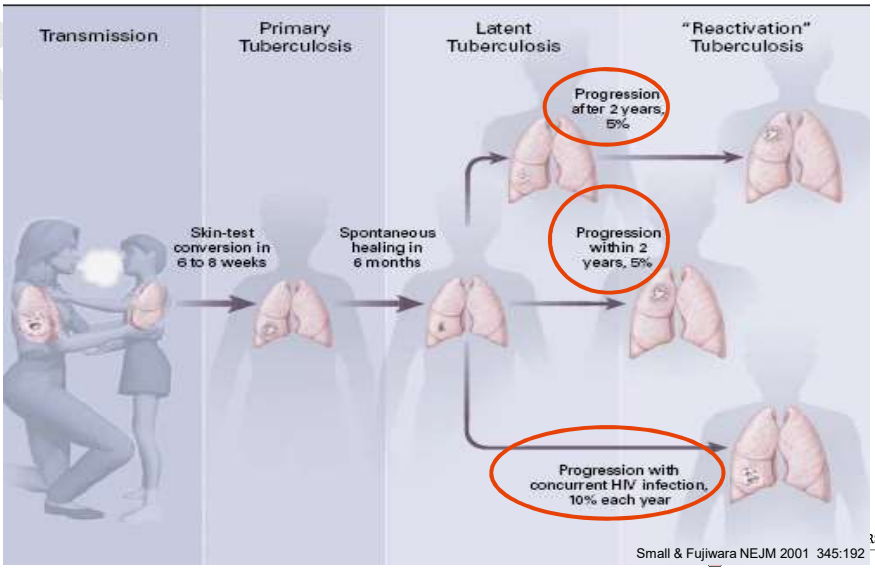
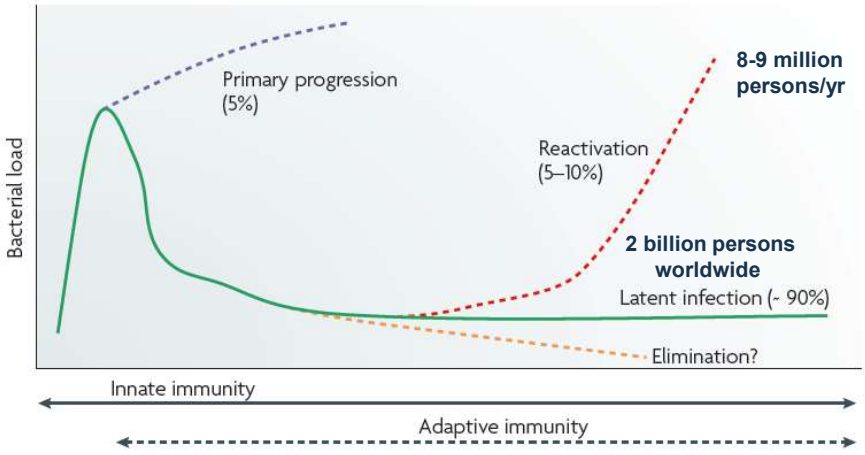
Risk Associated with Development of Active TB Disease



Small & Fujiwara NEJM 2001 345:192



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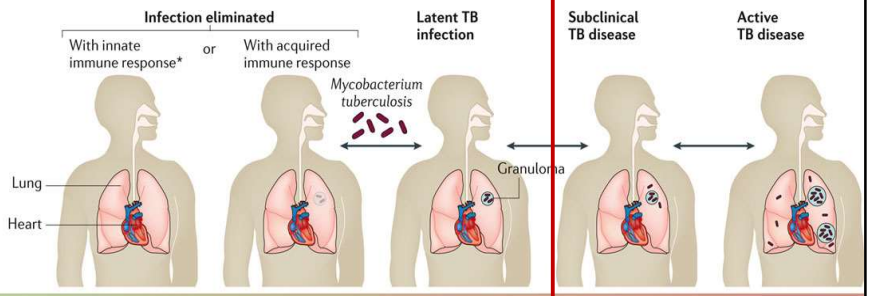
The Spectrum of TB: From *M. tuberculosis* Infection to Active (pulmonary) TB Disease



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Pai, M. et al. Nat. Rev. Dis. Primers 2016

Who Should be Screened for TB?

- **TB screening of general population is not recommended**

Who do we test?

- High risk of infection
  - Close contacts
  - Work/live high-risk settings
  - Those from countries where TB is common
- High risk of progression
  - HIV infection
  - Recently infected
  - Young children
  - Diabetes
  - Immunocompromised
  - Those not properly treated for TB disease in past

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Risk for Progression from TB Infection to TB Disease

Risk Factor and Study	Relative Risk (95% CI)
	%
Advanced, untreated HIV infection	
Moss et al.[10]	9.9 (8.7–11)
Pablos-Méndez et al.[16]	9.5 (3.6–25)
Close contact with a person with infectious tuberculosis†	
Ferebee[17]	6.1 (5.5–6.8)
Radiographic evidence of old, healed tuberculosis that was not treated	
Ferebee[17]	5.2 (3.4–8.0)
Treatment with ≥15 mg of prednisone per day‡	
Jick et al.[18]	2.8 (1.7–4.6)
Chronic renal failure	
Pablos-Méndez et al.[16]	2.4 (2.1–2.8)
Treatment with TNF-α inhibitor	
Askling et al.[19]	2.0 (1.1–3.5)
Poorly controlled diabetes	
Pablos-Méndez et al.[16]	1.7 (1.5–2.2)
Weight ≥10% below normal	
Palmer et al.[20]	1.6 (1.1–2.2)
Smoking	
Bates et al.[21]	1.5 (1.1–2.2)

Horsburgh and Rubin, NEJM, 2011

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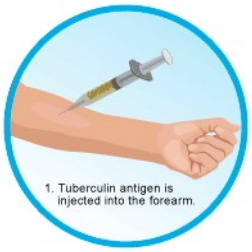
Approved Tests for LTBI

QuantiFERON®-TB Gold In-Tube (Cellestis) measures interferon gamma



Tuberculin Skin Test

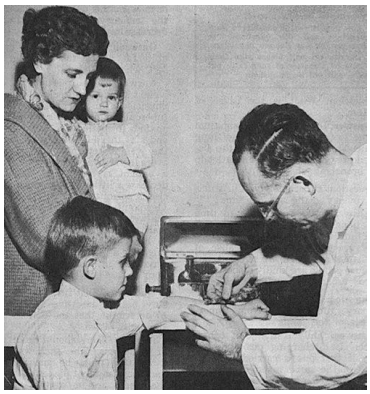
T-SPOT®.*TB* test (Oxford Immunotec) measures peripheral blood mononuclear cells that produce interferon gamma

Diagnostic Test for LTBI

- Tuberculin skin test (TST)
- >100-year old skin test

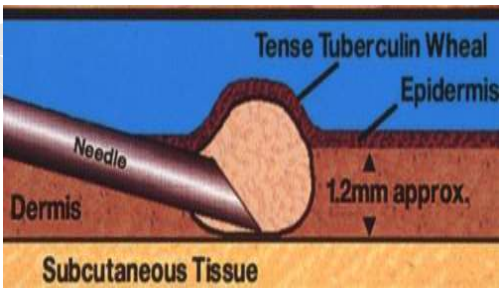
- Poor specificity:
  - Antigenic cross-reactivity of PPD with BCG and environmental mycobacteria

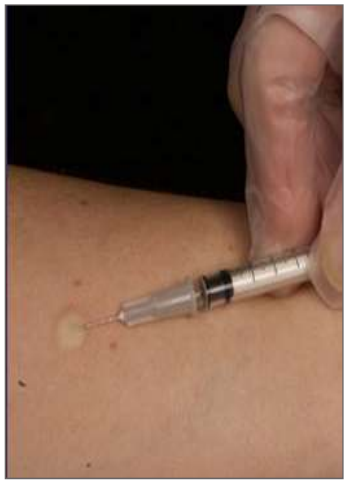
- Poor sensitivity:
  - 75-90% in active disease



The skin test enters its 6th decade of use.
(Canada 1957)

Tuberculin Skin Test (TST)-1





Administering TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution **intradermally** on volar surface of lower arm
- Produce a wheal 6 to 10 mm in diameter

No tape or bandaids

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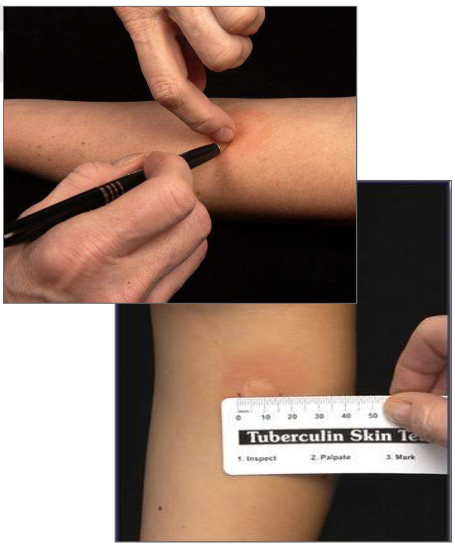
Tuberculin Skin Test (TST)-2



Reading TST

- Measure 48 to 72 hours
- Induration, not erythema
- Record reaction in mm, not "negative" or "positive"

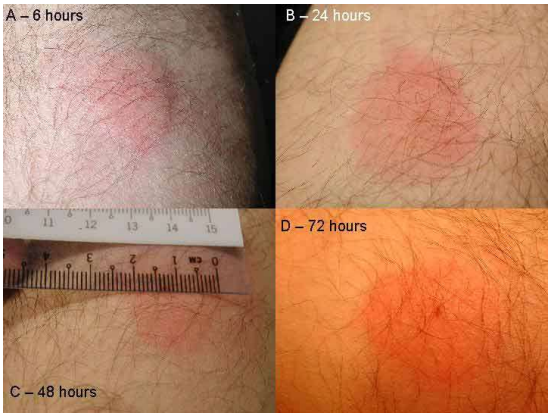
Tuberculin Skin Test (TST)-3

Biological limitations:

- Confounding by BCG
- Confounding by NTM

Operational limitations:

- Requires trained staff for administration and interpretation
- Requires second patient visit



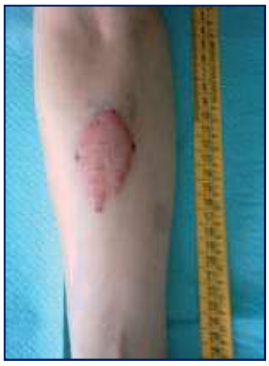
Interpretation of TST Results

INDURATION DIAMETER	INDIVIDUAL RISK FACTORS
≥5 mm	**Positive test result for:** ▪ Persons with HIV infection ▪ Recent contacts of persons with active TB disease ▪ Persons with evidence of old, healed TB lesions on chest X-rays ▪ Persons with organ transplants and other immunosuppressed persons, including those receiving prolonged corticosteroid therapy (the equivalent of >15 mg/d of prednisone for one month or more) and TNF-α blockers
≥10 mm	**Positive test result for:** ▪ Persons who have immigrated within the past 5 years from areas with high TB rates* ▪ Injection drug users ▪ Persons who live or work in institutional settings where exposure to TB may be likely, such as hospitals, prisons, homeless shelters, SROs, and nursing homes ▪ Mycobacteriology laboratory personnel ▪ Persons with clinical conditions associated with increased risk of progression to active TB, including: silicosis; chronic renal failure; diabetes; more than 10% below ideal weight or BMI < 18.5; gastrectomy/jejunoileal bypass; some hematologic disorders (such as leukemia and lymphomas); and certain cancers (such as carcinoma of the head, neck, or lung, leukemias, and lymphomas) ▪ Children < 5 years, and children or adolescents exposed to adults in high-risk categories ▪ Persons with prolonged stay in areas with high TB rates*
≥15 mm	**Positive test result for:** ▪ Persons at low risk for active TB disease for whom testing is not generally indicated

nyc.gov/health

TST Do's and Don'ts

- **Do test**:
  - Prior to immunosuppression
  - 8-10 weeks after prior negative TST for a contact
- **Don't test**:
  - Previous positive result (documented)
  - <6 weeks after live virus vaccine (can be done at same time as vaccine)
  - Prior severe reaction



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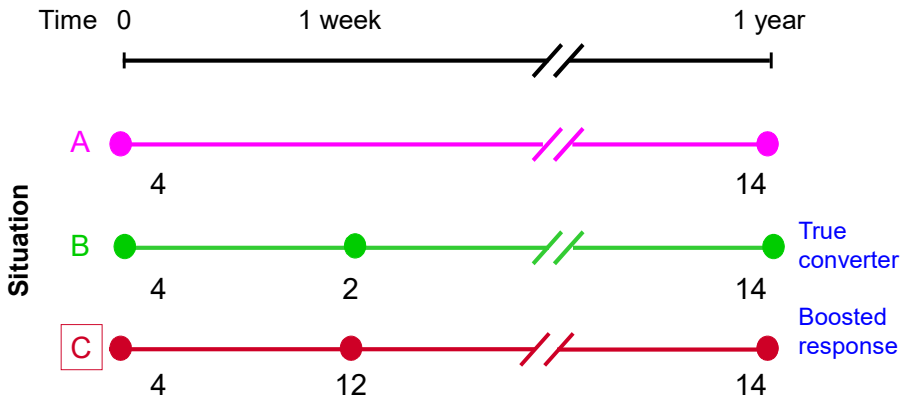
Two Step Testing

Use two step testing for initial skin testing of adults who will be retested periodically

- If first test positive, consider the person infected
- If first test negative, give second test 1-3 weeks later
- If second test positive, consider person infected
- If second test negative, consider person uninfected

Tuberculin Testing

True Infection vs. Booster Effect (mm induration)



Special Considerations When Using TST

Pregnant women

- TST is safe and reliable for mother and fetus throughout pregnancy
- Give TST to pregnant women who have risk factors for infection or disease

Prevention of Progression from Latent to Active TB

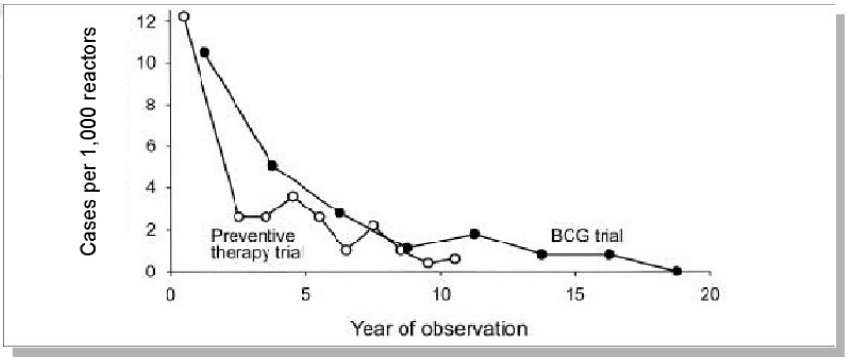


Figure 52. Incidence of tuberculosis among household contacts receiving placebo, compared to household contacts receiving preventive chemotherapy with isoniazid [134] and number of tuberculosis cases among unvaccinated persons with large tuberculin skin test reactions by time interval after beginning of observation in a controlled clinical trial on BCG vaccination in Great Britain [135].

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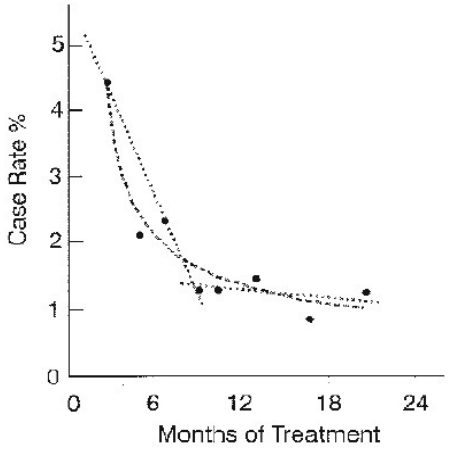
Reduction of Risk of Active TB After INH Treatment of Latent Infection



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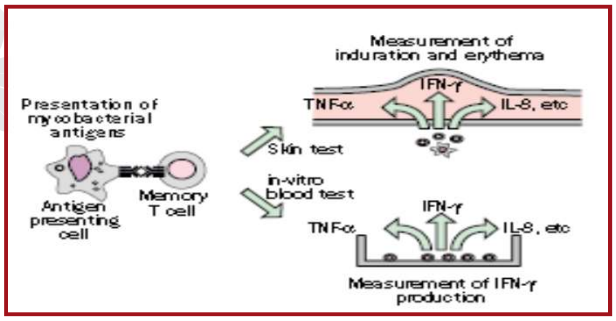
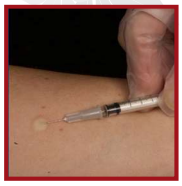
Diagnosis of LTBI





- Mantoux tuberculin skin test (TST)

Delayed-type hypersensitivity reaction in persons with *M. tb* infection

- Interferon gamma release assay (IGRA)

Blood test that measures and compares amount of interferon-gamma (IFN-γ) released by blood cells in response to antigens

QuantiFERON® and T-SPOT®.*TB* Test

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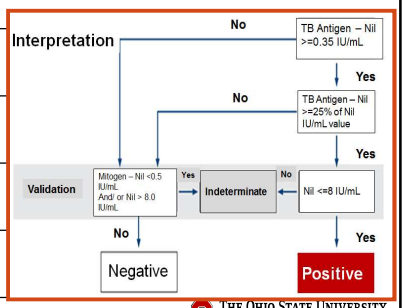
New: QuantiFERON (QFT) TB Gold Plus Implemented at OSU since August 13, 2018

Mitogen	**Positive Control** (Low response may indicate inability to generate IFNγ)
Nil	Negative Control (Adjusts for background IFNγ)
TB 1	Primarily detects CD4 T cell response
TB 2	Optimized for detection of CD4 and CD8 T cell responses

QFT-Plus Result	Test interpretation
Positive	*M. tuberculosis* infection is **likely**
Negative	*M. tuberculosis* infection is **NOT** likely
Indeterminate	Likelihood of *M. tuberculosis* infection **cannot** be determined



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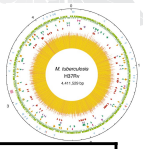
Species Specificity of ESAT-6 and CFP-10



Tuberculosis Complex	ESAT	CFP 10
M. tuberculosis	+	+
M. africanum	+	+
M. bovis	+	+
BCG substrains	-	-

Environmental strains	ESAT	CFP 10
M. kansasii	+	+
M. marinum	+	+
M. szulgai	+	+

QFT-TB Gold-In-Tube – additional TB 7.7Ag

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Overall Test Performance → More Specific

	Sensitivity**	Specificity (BCG vaccinated population)	Specificity (non-BCG vaccinated population)
TST	71-82%	*60%	97%
QFT	81-86%	> 95%	> 95%
T-SPOT.*TB*	90-95%		98%

IGRA Advantages:

- One visit, blood test, more specific
- Poor rates of return for TST reading
- Who have received BCG

* Variable, depends on when and how often BCG was given
**Sensitivity wanes in HIV or young children

Pai, M etal. Clinical Microbiology Reviews, 2014
King et al., AJRCCM, 2015

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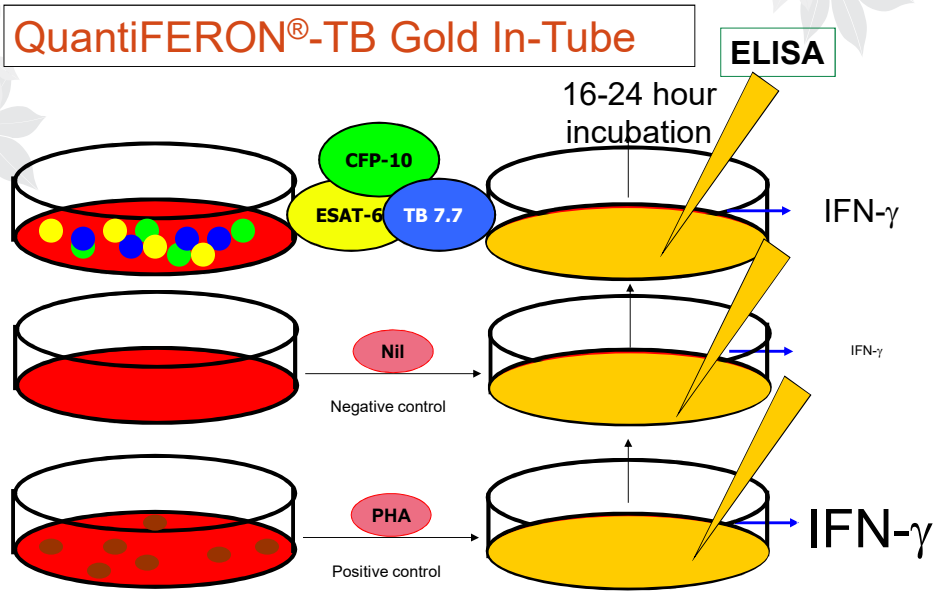
QuantiFERON®-TB Gold In-Tube



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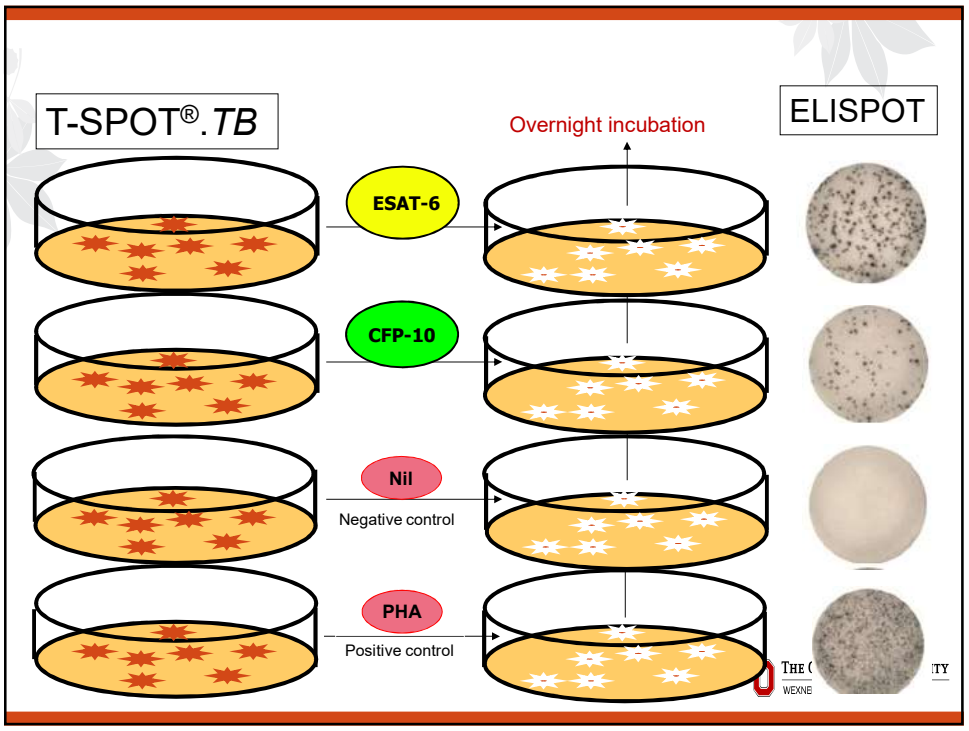

QFT-GIT Interpretation

TABLE 2. Interpretation criteria for the QuantiFERON-TB Gold In-Tube Test (QFT-GIT)

Interpretation	Nil*	TB Response†	Mitogen Response§
Positive¶	≤8.0	≥0.35 IU/ml and ≥25% of Nil	Any
Negative**	≤8.0	<0.35 IU/ml or <25% of Nil	≥0.5
Indeterminate††	≤8.0	<0.35 IU/ml or <25% of Nil	<0.5
	>8.0	Any	Any

Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection — United States, 2010. MMWR Vol 59, RR-5

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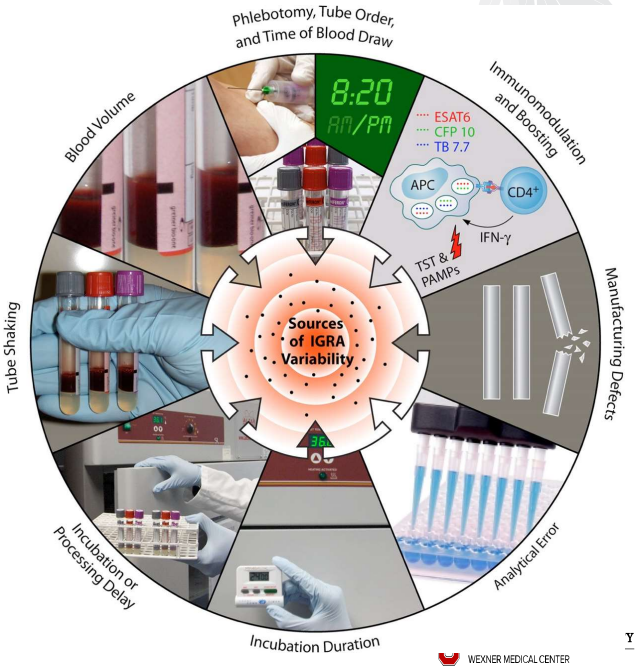

Pai, M.; Denkinger, C.M.; Kik, S.V.; Rangaka, M.X.; Zwerling, A.; Oxlade, O.; Metcalfe, J.Z.; Cattamanchi, A.; Dowdy, D.W.; Dheda, K.; Banaei, N. (2014). Gamma Interferon Release Assays for Detection of Mycobacterium tuberculosis Infection. Clinical Microbiology Reviews 27(1), 3-20.

T-Spot®.*TB* Interpretation

TABLE 3. Interpretation criteria for the T-SPOT.TB Test (T-Spot)			
Interpretation	**Nil***	**TB Response**	**Mitogen**
Positive	≤10 spots	≥8 spots	Any
Borderline**	≤10 spots	5, 6, or 7 spots	Any
Negative	≤10 spots	≤4 spots	
Indeterminate**	>10 spots	Any	Any
	≤10 spots	<5 spots	<20 spots

Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis Infection — United States, 2010. MMWR Vol 59, RR-5*

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TST Replacement Characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective
- *Can IGRAs achieve this standard?*

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TST Return Rates

- Return rates vary from 18% to 72% depending on the population*
- This is especially important in high risk groups

Population	LTBI screening completion rate	Source
HIV	57%	Cheallaigh et al. (2013) *Plos One*
Immigration employees	39%	De Perio et al. (2011) *J Occup Environ Health*
Children	< 50%	Jacono et al. (2006) *Arch Pediatr Adolesc Med*

Failure to come for result reading undermines the TST

* Cheng et al. (2011) *Pediatrics* 100;210

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TST Replacement Characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective
- *Can IGRAs achieve this standard?*

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IGRA Sensitivity and Specificity

Based on published meta-analyses:

- Overall sensitivity:
  - T-SPOT: **90%**
  - QFT-GIT: **80%**
  - TST: **80%**
- Specificity:
  - IGRAs: **>95%** in low-TB-incidence settings; not affected by BCG vaccination
  - TST: **97%** in populations not vaccinated by BCG; **~60%** in populations receiving BCG (varies depending on timing of BCG administration)

Summarized in Pai et al, Clinical Microbiology Reviews, 2014

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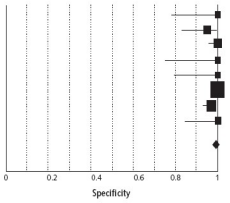
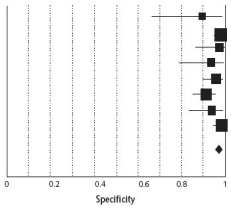
Specificity of QFT-Gold and QFT-GIT and Effect of BCG Vaccination



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	1.00 (0.78–1.00)
Brock et al., 2004 (36)	0.95 (0.83–0.99)
Taggart et al., 2006 (37)	1.00 (0.96–1.00)
Palazzo et al., 2008 (24)	1.00 (0.75–1.00)
Bua et al., 2007 (18)	1.00 (0.79–1.00)
Mazurek et al., 2007 (38)	1.00 (0.99–1.00)
Franken et al., 2007 (39)	0.97 (0.93–0.99)
Detjen et al., 2007 (25)	1.00 (0.85–1.00)

Pooled specificity = 0.99 (0.98–1.00)
Chi-square = 15.88; $P = 0.026$
Inconsistency $I^2 = 55.9\%$

BCG non-vaccinated
Pooled specificity **99%**



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	0.89 (0.67–0.99)
Mori et al., 2004 (7)	0.98 (0.95–0.99)
Ravn et al., 2005 (9)	0.97 (0.87–1.00)
Brock et al., 2004 (36)	0.94 (0.79–0.99)
Kang et al., 2005 (10)	0.96 (0.90–0.99)
Lee et al., 2006 (11)	0.92 (0.85–0.96)
Kobashi et al., 2006 (15)	0.94 (0.83–0.99)
Soborg et al., 2007 (40)	0.99 (0.95–1.00)

Pooled specificity = 0.96 (0.94–0.98)
Chi-square = 13.81; $P = 0.055$
Inconsistency $I^2 = 49.3\%$

BCG vaccinated
Pooled specificity **96%**

Pai M et al Annals Intern Med 2008

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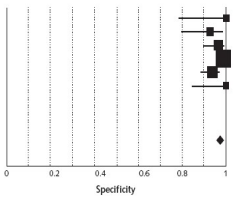
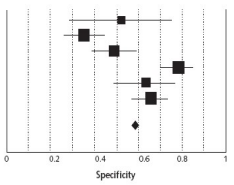
Specificity of the TST and Effect of BCG Vaccination



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	1.00 (0.78–1.00)
Brock et al., 2004 (36)	0.93 (0.80–0.98)
Taggart et al., 2006 (37)	0.96 (0.90–0.99)
Mazurek et al., 2007 (38)	0.98 (0.97–0.99)
Franken et al., 2007 (39)	0.94 (0.89–0.97)
Detjen et al., 2007 (25)	1.00 (0.85–1.00)

Pooled specificity = 0.97 (0.95–0.99)
Chi-square = 12.25; $P = 0.032$
Inconsistency $I^2 = 59.2\%$

BCG non-vaccinated
Pooled specificity **97%**



Study, Year (Reference)	Specificity (95% CI)
Brock et al., 2001 (35)	0.53 (0.29–0.76)
Mori et al., 2004 (7)	0.35 (0.27–0.45)
Kang et al., 2005 (10)	0.49 (0.39–0.60)
Lee et al., 2006 (11)	0.79 (0.71–0.85)
Kobashi et al., 2006 (15)	0.64 (0.49–0.77)
Soborg et al., 2007 (40)	0.66 (0.58–0.74)

Pooled specificity = 0.59 (0.46–0.73)
Chi-square = 55.69; $P < 0.001$
Inconsistency $I^2 = 91.0\%$

BCG vaccinated
Pooled specificity **59%**

Pai M et al Annals Intern Med 2008

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TST Replacement haracteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective
- *Can IGRAs achieve this standard?*

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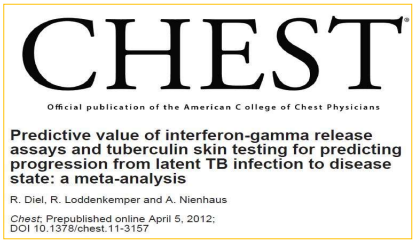
Can IGRAs Predict Disease? Latest Meta-Analysis

- **Pooled PPV for progression:**
- Commercial IGRAs was 2.7%
- TST was 1.5%


CHEST
Official publication of the American College of Chest Physicians

Predictive value of interferon-gamma release assays and tuberculin skin testing for predicting progression from latent TB infection to disease state: a meta-analysis

R. Diel, R. Loddenkemper and A. Nienhaus

Chest; Prepublished online April 5, 2012;
DOI 10.1378/chest.11-3157

- **PPV for progression in high risk groups:**
- **IGRAs was 6.8%.**
- TST 2.4%

- **Pooled values of NPV for progression**
- IGRAs: 99.7% (p<0.01)
- TST: 99.4%

Diel et al, Chest. 2012 Jul;142(1):63-75

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IGRAs and Contact Investigation

IGRAs better correlate to exposure

- Supersized supermarket investigation: 10,000 TSTs on 2 separate days; 285 BCG unvaccinated subjects had QFT-GIT and T-Spot done
- Exposure risk based on frequency and cumulative shopping time
- Results:
  - TST results correlated with age, NOT exposure
  - QFT and T-Spot results correlated with exposure time
  - IGRA-TST concordance correlated with large TST size

Arend, Am J Resp Crit Care 2007; 175: 618-27

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TST Replacement Characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective
- *Can IGRAs achieve this standard?*

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Cost effectiveness of IGRAs

IGRAs was cost saving compared to TST

*Linas B, et al. AJRCCM 2011; 184(**5**):590-601*

- Evaluated CDC-defined risk-groups referenced in current U.S. LTBI screening guidelines
  - Contacts
  - HIV
  - Immigrants – regardless of time living in the US
  - Base case cost used: IGRA - $52 and TST- $22

QFT-GIT more cost-effective for individuals referred to public health clinic for a positive TST

*Shah M, et al. BMC Infect Dis 2012; **12**:360*

- Additional QFT-GIT testing of individuals referred
- Conclusion: LTBI screening with TST in low-prevalence settings may lead to overtreatment and increased costs
  - Base case cost used: QFT-GIT - $43.5

TST Replacement Characteristics

- Convenient and efficient
- Higher specificity and sensitivity
- Higher predictive value
- Cost effective
- *Can IGRAs achieve this standard?*

TB testing: How good are our tests?

Facts:

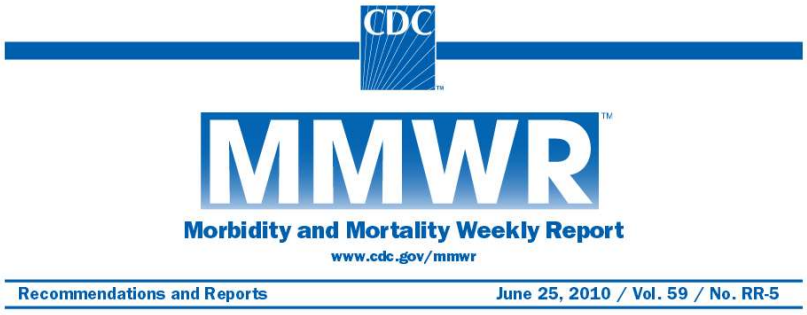
- TST and IGRAs are indirect methods and are dependent on a healthy immune system
- No gold standard to compare for LTBI
- Accuracy of tests depends on the prevalence of infection
- Association of IGRA to exposure risk and risk of progression are indirect but important measures

TST and IGRAs Are Similar in Some Ways

- Do not distinguish latent infection from active disease
- Do not provide any direct evidence of the presence of viable bacilli
- Determine that infection has at some point led to an acquired immune response that is detectable following re-challenge with antigen
- Are both affected by HIV infection

TST and IGRAs Are Dissimilar in Some Ways

- IGRAs are specific in all settings
- TST is specific in BCG unvaccinated or those who get BCG in infancy
- IGRAs have operational characteristics that are more advantageous
- IGRAs require more resources



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

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General Recommendations for Using IGRAs-1

- May be used in place of (*but not in addition to*) a TST in all situations for which CDC recommends tuberculin skin testing
- *IGRA preferred*
  - Hard to reach populations (e.g., homeless, migrant workers)
    - Only one visit required
  - People who have received BCG (either as vaccine or cancer therapy)
    - TB specificity higher

MMWR, June 25, 2010/59

General Recommendations for Using IGRAs-2

- *Both TST and IGRA may be considered*
  - At high risk for infection or progression (e.g., HIV)
  - Suspicion for TB disease exists
  - Further evaluation of positive TST results in individuals at low risk for infection and progression
    - Confirming questionable TST results
  - Other reasons:
    - Immediate hypersensitivity to PPD
    - Convincing high risk patient with strongly positive TST to take LTBI treatment
    - Indeterminate/borderline IGRA

MMWR, June 25, 2010/59

General Recommendations for Using IGRAs-3

- *Use either TST or IGRA*
  - Contacts
  - Periodic screening for those with occupational exposure, surveillance programs etc.
- *TST preferred*
  - Children < 5 yrs.

MMWR, June 25, 2010/59

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IGRAs in Special Populations

- Pediatrics

Stay tuned!

- HIV
- End stage renal disease
- Populations using biologic agents

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IGRAs in Special Populations

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Stay tuned!

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HIV IGRA Studies in Low incidence Countries-
Summary (proxy for other immunocompromised groups)

IGRA agreement with TST	Poor (1-4)
IGRA sensitivity compared to TST	Similar or higher (1-3)
Correlation of results to TB risk factors	Yes! (1-4)
Indeterminate rate	High with CD4 <200
Prediction of risk of progression	Data inadequate- available data says yes (4)

1.Cattamachi, Pai et al, JAIDS 2011
2. Ramos et al., BMC Infectious Diseases 2012, 12:169
3. Cheallaigh et al, PLoS 2013, Vol 8, Issue 1 e5330
4. Aichelburg M al, CID 2009:48 April 1

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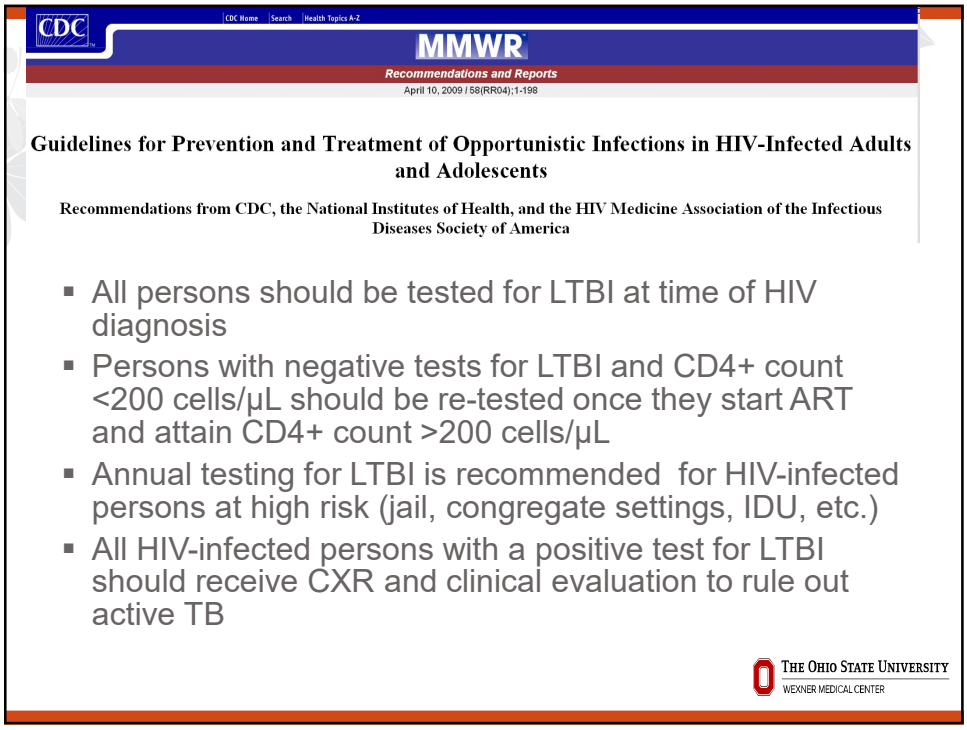

- All persons should be tested for LTBI at time of HIV diagnosis
- Persons with negative tests for LTBI and CD4+ count <200 cells/μL should be re-tested once they start ART and attain CD4+ count >200 cells/μL
- Annual testing for LTBI is recommended for HIV-infected persons at high risk (jail, congregate settings, IDU, etc.)
- All HIV-infected persons with a positive test for LTBI should receive CXR and clinical evaluation to rule out active TB

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IGRAs in Special Populations

- Pediatrics
- HIV
- End stage renal disease
- Populations using biologic agents

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New IGRA Systematic Review: End Stage Renal Disease

Rogerson et al. Am J Kidney Dis. 2013 Jan;61(1):33-43

- Major conclusions
  - *"ELISA-IGRA likely to be a more accurate diagnostic tool for LTBI in ESRD"*
  - Consistent with previous systematic reviews of general population showing better correlation of QFT results with TB exposure and independence from prior BCG
  - *"Propose that the ELISA-IGRA should be the test of choice"*

IGRAs in Special Populations

- Pediatrics
- HIV
- End stage renal disease
- Populations using biologic agents

Anti-TNF Agents: Summary

IGRA agreement with TST	Poor
IGRA sensitivity compared to TST	Similar or higher
Correlation of results to TB risk factors	Yes, unlike the TST
Indeterminate rate	Higher than in healthy controls
Effect of anti-TNF treatment	Lower quantitative response
Prediction of risk of progression	Yes. but data few
Guidance for Rheumatologic pts on DMARDs Arthritis Care & Research,Vol. 64, No. 5, May 2012, pp 625–639	IGRA preferred if BCG hx

Matulis G et al, Ann Rheum 2008: 67: 84-90, Schoepfer AM et al, Am J Gastroenterol 2008; 103:2799-806,

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Studies Show Significant Differences Between Tests

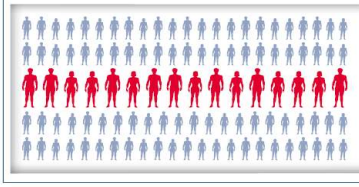
QFT is more accurate than TST in immune-suppressed patients (1, 2)

Moderate-to-severe psoriasis[11]

9 out of 50 patients were TST positive and QuantiFERON-TB Gold negative prior to TNF-α inhibitor

None developed active TB over 12 months

Rheumatic disease[12]



16 out of 107 patients were TST positive and QuantiFERON-TB Gold negative prior to TNF-α inhibitor

None developed active TB over 24.5 months

1. Matulis G et al. Ann Rheum Dis 2008; 67:84-90. 2.Ponce de Leon D et al. J Rheumatol 2008; 35:776-781.
3. Garcovich S et al. J Eur Acad Derm Venereol. 3. 2011. 4 Chang B et al. Clin Rheumatol 2011.

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Interferon-gamma release assays for diagnosis of latent tuberculosis infection: evidence in immune-mediated inflammatory disorders

Rachel Smith[a,*], Adithya Cattamanchi[b,*], Karen R. Steingart[c], Claudia Denkinger[d], Keertan Dheda[e], Kevin L. Winthrop[f] and Madhukar Pai[g]

Current Opinion in Rheumatology 2011

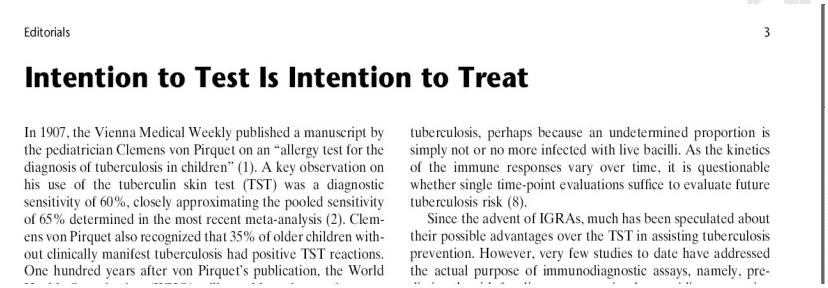
- Individuals with immune-mediated inflammatory disorders (IMIDs) are at increased risk of developing active TB
- Current evidence does not suggest that IGRAs >TST in identifying patients with IMID who could benefit from LTBI treatment
- Tendency for guidelines to prefer IGRA over TST in IMIDs or to recommend both tests
- If high index of suspicion for LTBI, perform both tests

Know IGRA Gray Areas

- Serial testing: No quantitative "converter" definition
- Unknown negative predictive value in:
  - Very young children under 5 years old
  - Immunocompromised individuals
- *Maximum sensitivity may be needed in these groups, especially if patient is symptomatic or have multiple risks*
- **Remember that IGRAs are tools, not a panacea**
- *IGRAs, like the TST, cannot definitively "rule out disease or LTBI", only a doctor can….*

Summary

- IGRAs are a significant advance because of their high specificity and operational advantages over the TST
- Findings among high risk groups show consistent performance: higher sensitivity and specificity of QFT
- In low prevalence countries like the US, negative predictive value has been outstanding across high risk asymptomatic groups
- Cost effective studies have demonstrated savings and effectiveness using QFT compared to TST and Tspot. among the most important TB risk groups
- Knew knowledge from IGRAs are being used to advance screening policies that will benefit individuals, communities and their providers



Editorials 3

Intention to Test Is Intention to Treat

In 1907, the Vienna Medical Weekly published a manuscript by the pediatrician Clemens von Pirquet on an "allergy test for the diagnosis of tuberculosis in children" (1). A key observation on his use of the tuberculin skin test (TST) was a diagnostic sensitivity of 60%, closely approximating the pooled sensitivity of 65% determined in the most recent meta-analysis (2). Clemens von Pirquet also recognized that 35% of older children without clinically manifest tuberculosis had positive TST reactions. One hundred years after von Pirquet's publication, the World

tuberculosis, perhaps because an undetermined proportion is simply not or no more infected with live bacilli. As the kinetics of the immune responses vary over time, it is questionable whether single time-point evaluations suffice to evaluate future tuberculosis risk (8).

Since the advent of IGRAs, much has been speculated about their possible advantages over the TST in assisting tuberculosis prevention. However, very few studies to date have addressed the actual purpose of immunodiagnostic assays, namely, pre-

"Although desirable, a substantially improved test to better define individuals at risk of future tuberculosis does not seem imminent. It is thus all the more important that only individuals are tested who are at a high risk of tuberculosis in the future and who are fully appraised of the treatment consequences."

Lange C and Rieder H, AJRCCM 2011

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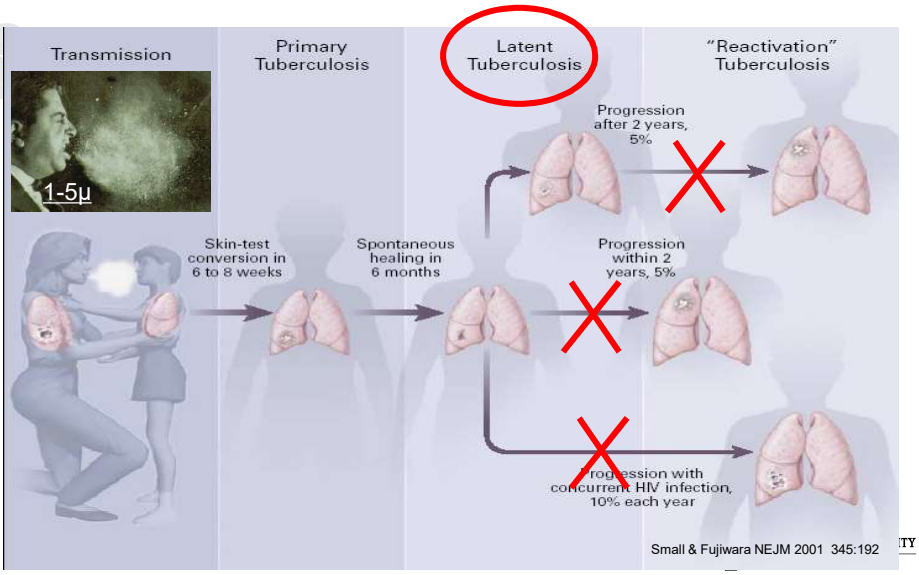
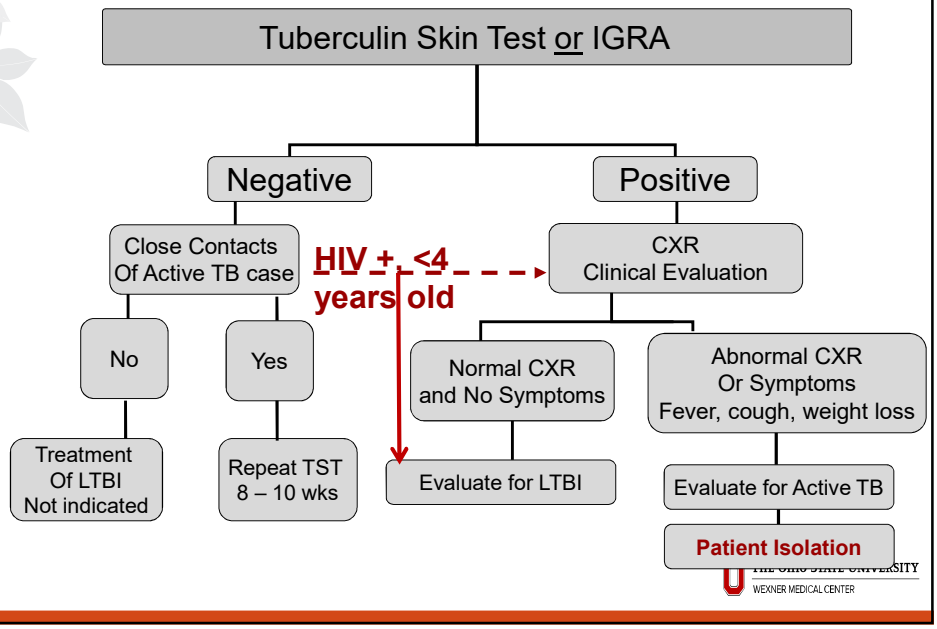
Treatment of LTBI to Prevent Reactivation TB Disease



US TB Screening Flowchart



TB Infection vs. TB Disease

TB Infection (LTBI)	TB Disease (in the lungs)
Inactive, contained tubercle bacilli in the body	**Active**, multiplying tubercle bacilli in the body
TST or blood test results usually positive	TST or blood test results usually positive
Chest x-ray usually **normal**	Chest x-ray usually **abnormal**
Sputum smears and cultures **negative**	Sputum smears and cultures may be **positive**
No symptoms	**Symptoms** such as cough, fever, weight loss
Not infectious	**Often infectious** before treatment
Not a case of TB	**A case** of TB

2 billion people

9 million people

References

- Systematic reviews on IGRAs and other TB diagnostics are available at Evidence-based tuberculosis diagnosis, www.tbevidence.org
- Barry C et al. Nature Reviews Microbiology | AoP, published online 26 October 2009; doi:10.1038/nrmicro2236
- American Academy of Pediatrics. Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009
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- Mack U et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009 May;33(5):956-73.
- Lange C and Rieder H. Am J Resp and Crit Care Med 2011

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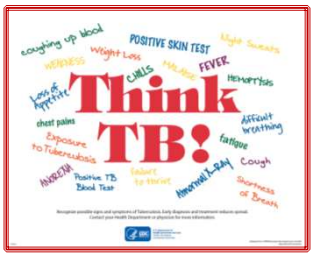

NO Test Can "RULE OUT" TB

Thank You!