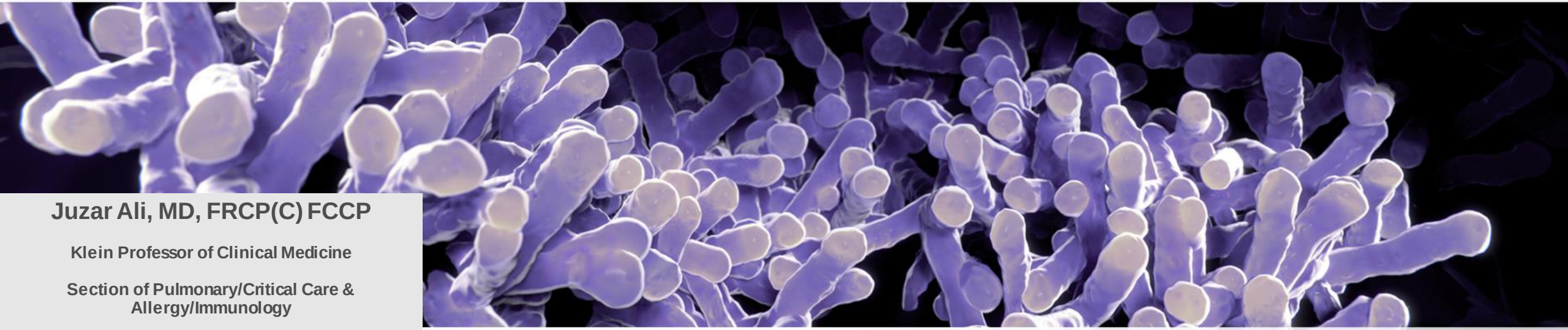
Rheumatology Practice & Mycobacterial Diseases

Awareness, Screening, Treatment and Sequelae



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Disclosures & Affiliations**

- **Medical Director Wetmore – LSU TB and Mycobacterial Diseases program
- **Klein Professor of Medicine, Section of Pulmonary/CC Medicine/Allergy & Immunology
- LSUHSC/SOM New Orleans
- **Speaker/Consultant to Oxford Immunotec

- Basis of this presentation: Rheumatology feedback

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Objectives

At the end of the presentation, the participants will be able to:

1. Update their knowledge of identification, screening, and management of TB and NTM in non-HIV immune compromised patients seen specially in Rheumatology practices

2. Engage in the discussion of practical issues faced by physicians taking care of patients being treated with immune suppressive medications and biologic agents

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Public Health Classification

- 0 No exposure; not infected
- 1 Exposure; not infected
- 2 Infected; no disease Dx?
- 3 Active disease Pulm / EP Dx?
- 4 Old disease or “UDA”
- 5 Under evaluation Dx?
- 6 Atypical/NTM Dx ?
- 7 Associate involvement
- 8 Exposed contacts Dx ?

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Tuberculosis Surveillance

Risk factors for TB activation

Relative risk of TB compared to the general population.

Risk Factor	Relative Risk
High-risk factors	
HIV/AIDS	10–100
Close contacts	15
Organ-transplant recipients	20–70
Chronic renal failure requiring dialysis	6.9–52.5
TNF-alpha blockers	1.6–25.1
Silicosis	2.8
Moderate-risk factors	
Fibronodular disease on chest x-ray	6–19
Immigrants from high-TB-prevalence countries	2.9–5.3
Healthcare workers	2.55
Low-risk factors	
Diabetes mellitus	1.6–7.83
Smoking	2–3.4
Use of corticosteroids	2.8–7.7
Low body weight	2–3

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Ai J-W, Ruan Q-L, Liu Q-H, Zhang W-H. Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect. 2016;5(2):e10.

US Immunocompromised Population

Condition	Estimated # of US Persons Living with Condition
HIV infection	1.2 million
Rheumatoid arthritis	1.5 million
Inflammatory bowel disease	1.1 million
Systemic lupus erythematosus	320,000
Systemic sclerosis	49,000
Spondyloarthropathies	2.4 million
Vasculitis	1.0 million
End-stage renal disease	0.87 million
Hematologic malignancies	1.0 million
Solid organ transplant candidates	120,000
Total	**10 million**

JA Note: something missing!!

Double jeopardy
(Disease and Rx)

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Redelman-Sidi G, Sepkowitz KA. IFN-gamma release assays in the diagnosis of latent tuberculosis infection among immunocompromised adults. *Am J Respir Crit Care Med*. 2013;188(4):422-431.

Audience Response Question 1

1. Why is there a higher probability of progression of TB infection to disseminated and active TB or Mycobacterial disease in patients treated with anti-TNF biologics and immunosuppressive drugs?

    a. This is an overstated concern and keeps us in business ☺☺

    b. This is related to decrease in Immunoglobulin G levels in patients with rheumatological disease and those prone to TB

    c. This is due to disruption and breakdown of granulomas in mycobacterial disease

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Pathway of pathogenesis in non-immune compromised patients with a connection and yet…. a disconnect between infection, immune response and disease

- Inhalation and then reaction of Physiologic, Innate and Adaptive immunity or lack thereof
- Macrophage phagocytosis
- Shedding and macrophage turnover
- Alveolar dendritic cell migration to regional lymph node
- MTB antigens ESAT-6; CFP-10 with CD4/CD8 interaction
- Differentiate into INF-G, TNF, Th1 or cytotoxic Tc1 cells respectively IL-12, IL-21, and IL-22
- Delayed-type hypersensitivity (DTH) response, positive TST with intragranulomatous necrosis called "Ghon Complex"
  - Ghon Complex is not necessarily limited to lung
- Post Primary IL-4, IL-13, Th2 response with central caseation
  - Granulomas are dynamic lesions with a continuous turnover and variable bacillary activity presenting as disease or dormancy
- **No clinical activity and signs hence called "LATENT TB" (LTBI) or now TB Infection (TBI)
- What's in a name ?? ** LTBI: TB Infection or is it Lasting TB Immunity?

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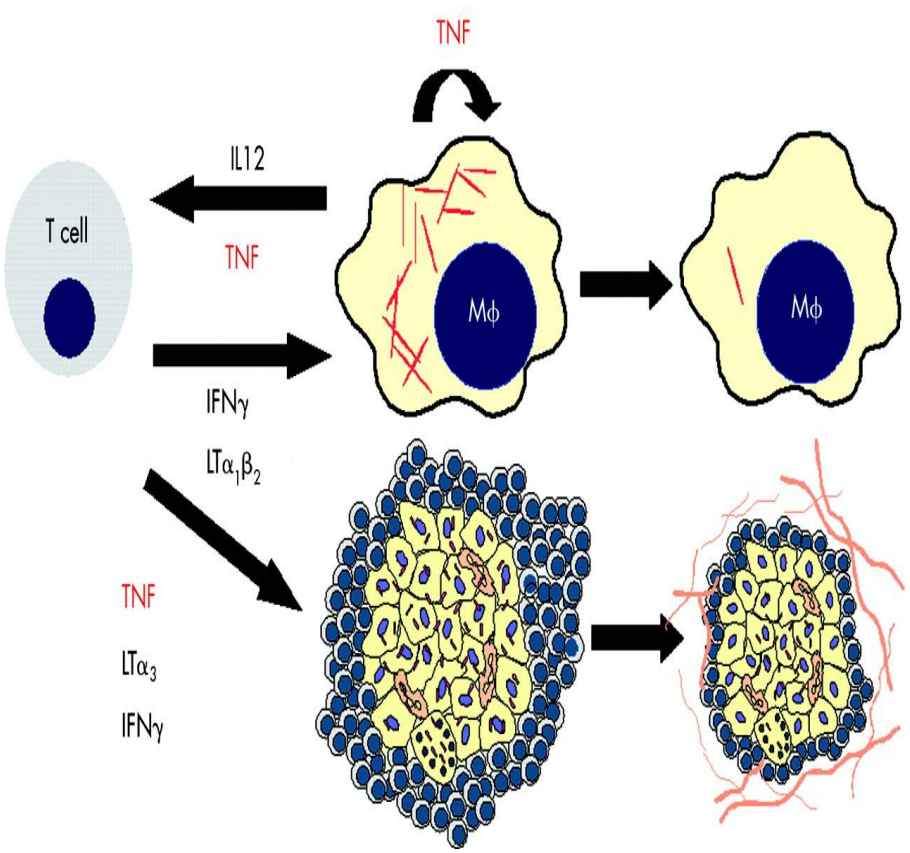
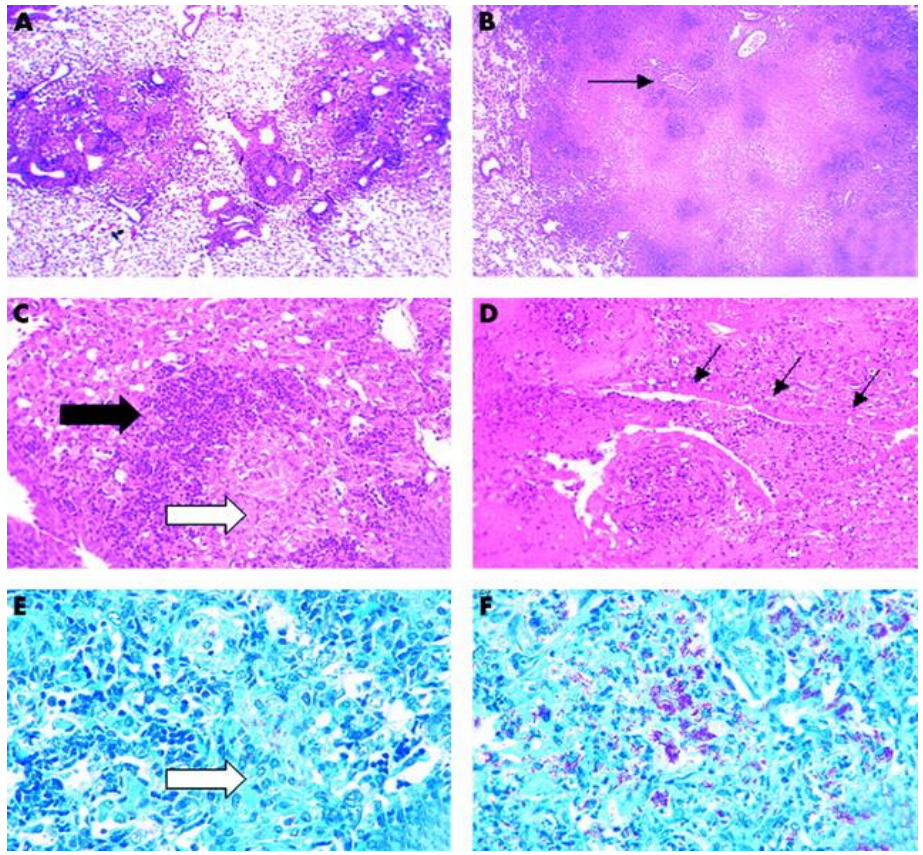
Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009;33(5):956-973.

Tumor Necrosis Factor – Alpha

Macrophage to Inflammation to Granuloma





"TNF is involved at multiple steps in antibacterial and inflammatory responses to *M tuberculosis* infection. It is a macrophage activating cytokine and is necessary for the sustained recruitment of inflammatory cells into granulomatous lesions. It is produced by macrophages and T cells, and it strongly synergises with interferon-γ in containing tuberculous infection by inducing bacterial killing and granuloma development."

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Ehlers S. Role of tumor necrosis factor (TNF) in host defense against tuberculosis: implications for immunotherapies targeting TNF. *Ann Rheum Dis*. 2003;62(Suppl 2):ii37-ii42.

Immune Response

TB Skin Testing

- ***In vivo*** **measurement of cell-mediated immunity to mycobacterium antigens in the form of a delayed-type hypersensitivity reaction**
- Previous exposure to mycobacterium results in production of **sensitized lymphocytes**
- Sensitized lymphocytes secrete cytokines to attract neutrophils, **memory CD4 T cells, CD8 T cells,** which cause induration and erythema
- Induration measured 48−72 hours post implantation
- Sensitivity of the tuberculin skin test is limited in **immunocompromised** individuals
- Specificity is limited because of cross-reactivity due to prior infection with **environmental mycobacteria or BCG vaccination**

Interferon-Gamma Release Assay

- ***In vitro*** **measurement of INF-gamma released by effector T cells responding to specific TB antigen stimulation, such as ESAT-6 and CFP10**
- Previous exposure to *M. tuberculosis* results in production of **sensitized T cells**
- **Sensitized T cells secrete IFN-γ (cytokine) when they reencounter specific *M. tuberculosis* antigens**
- IFN-γ secreted by effector T cells measured ~20 hours poststimulation
- **Antigens used in IGRAs (CFP10, ESAT-6, TB7.7) are not present *M. bovis* BCG and in most environmental mycobacteria**

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Mack U, Migliori GB, Sester M, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. *Eur Respir J*. 2009;33(5):956-973.

Issues Affecting the Use of TST

Limitations

- Need for trained personnel to administer the intradermal injection and also interpret the test
- Inter- and intrareader variability in interpretation
- Need for a return visit to have the test read
- False-positive results due to cross-reactivity of antigens within the PPD to both BCG and nontuberculous mycobacteria
- False-negative results due to infections and other factors, rare adverse effects, and complicated interpretation

False-Positive Results

- Repeat TST can restore reactivity in persons whose TST reactivity has decreased over time
- Cross-reactivity with BCG vaccine
- Cross-reactivity for non-tuberculous mycobacteria (NTM) is increased for persons living in areas where nontuberculous mycobacteria is common
- Errors in TST placement or reading

False-Negative Results

- In persons with clinical conditions associated with immunosuppression or overwhelming illness
- After recent viral and bacterial infections
- In association with treatment with immunosuppressive drugs

Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. December 2016:ciw694.

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Audience Response 2

A positive IGRA test result indicates all EXCEPT:

1. Infection with *M.TB*
2. Infection with *M.Avium Complex*
3. Infection with *M.Kansasii*
4. Infection with *M.Szulgai*

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TB-Specific Antigens Used in IGRAs

- Produce measureable immunologic responses in TB-infected persons
- Are **present** in
  - *Mycobacterium tuberculosis* complex organisms, including *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*
  - *M. kansasii*, *M. szulgai*, and *M. marinum* (nontuberculous mycobacteria)
- Are **absent** in and do not cross-react with
  - *M. bovis* BCG substrains
  - *M. avium* and most other nontuberculous mycobacteria

Oxford Immunotec. T-SPOT.TB Package Insert PI-TB-IVD-UK-V3. Abingdon, UK. March 2016.
QuantiFERON-TB Gold (QFT) ELISA Package Insert, 1075116 Rev. 02. Cellestis, Inc. Valencia, CA., April 2015.

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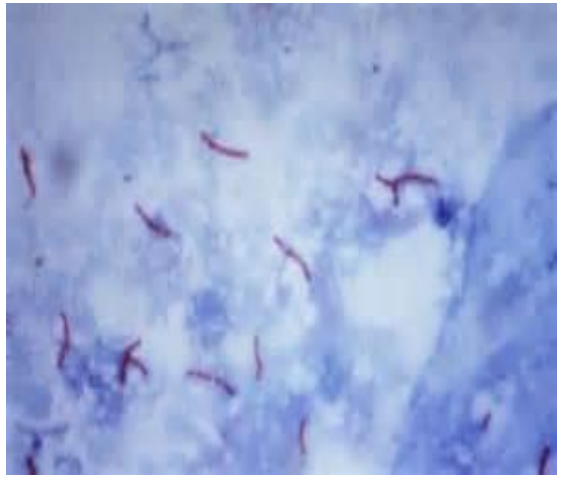
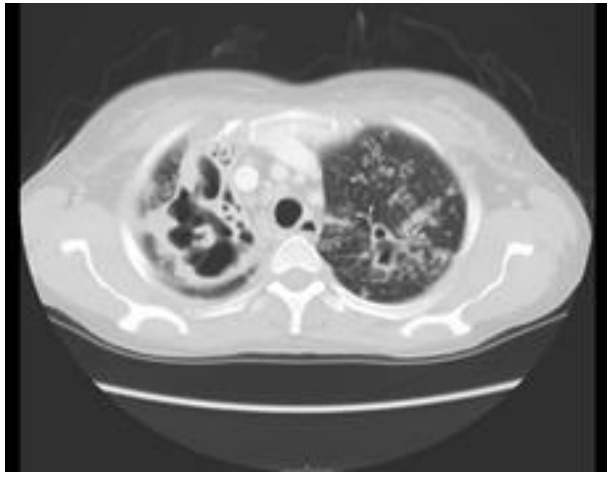
“To Be or not To Be…”

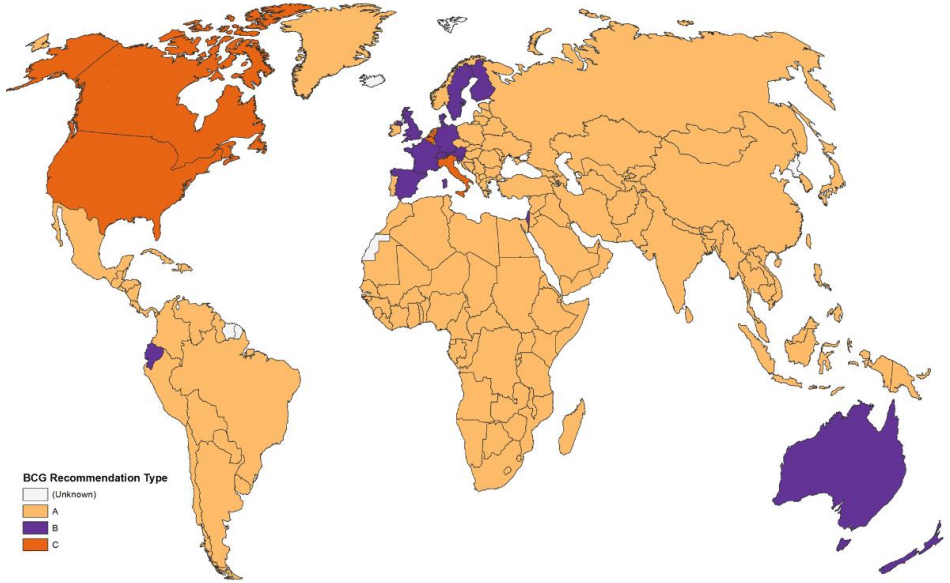
Looks like a duck, walks like a duck, must be…..





….BUT IS IT?

BCG - is it a big issue?
NTM - so what?



BCG Recommendation Type

- (Unknown)
- A. Country currently has universal BCG vaccination program
- B. Country used to but currently does not have universal BCG program
- C. Country never had universal BCG vaccination programs

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No Cross-Reactivity to BCG & Most NTMs

Tuberculosis Complex	ESAT-6	CFP10
M. tuberculosis	+	+
M. africanum	+	+
M. bovis	+	+
BCG substrain		
gothenburg	-	-
moreau	-	-
tice	-	-
tokyo	-	-
danish	-	-
glaxo	-	-
montreal	-	-
pasteur	-	-

Environmental Strains	ESAT-6	CFP10
M. abcessus	-	-
M. avium	-	-
M. branderi	-	-
M. celatum	-	-
M. chelonae	-	-
M. fortuitum	-	-
M. gordonii	-	-
M. intracellulare	-	-
M. kansasii	+	+
M. malmoense	-	-
M. marinum	+	+
M. oenavense	-	-
M. scrofulaceum	-	-
M. smegmatis	-	-
M. szulgai	+	+
M. terrae	-	-
M. vaccae	-	-
M. xenopii	-	-

ESAT-6 Early Secreted Antigenic Target
CFP-10 Culture Filter Protein

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Andersen P, Munk ME, Pollock JM, Doherty TM. Specific immune-based diagnosis of tuberculosis. *Lancet*. 2000;356(9235):1099-1104.

Major studies reporting prevalence of NTM pulmonary disease

Study/Lead author	Dates	Location	Study population	Measure	Prevalence- start of study period (per 100,000 person-years)	Prevalence- end of study
Marras	1997-2003	Ontario, Canada	Population-based	Isolation	9.1	14.1
Winthrop	2005-2006	Oregon, USA	Population-based	Disease	n/a	8.6
Winthrop	2000-2008	Northern California	Integrated health system	Disease	n/a	4.1
Prevots	2004-2006	California, Colorado, Pennsylvania, and Washington	Integrated health system In four US states	Disease	n/a	5.5
Adjemian	1997-2007	USA	Medicare beneficiaries	Disease	20	47
Moore	1995-2006	England, Wales, and Northern Ireland	Population-based	Isolation	0.9	2.9
Lai	2000-2008	Taiwan	University hospital	Disease	1.3	7.9
Thomson	1999, 2005	Queensland, Australia	Population-based	Disease	2.2	3.3

*Study population limited to patients ≥ 65 years of age

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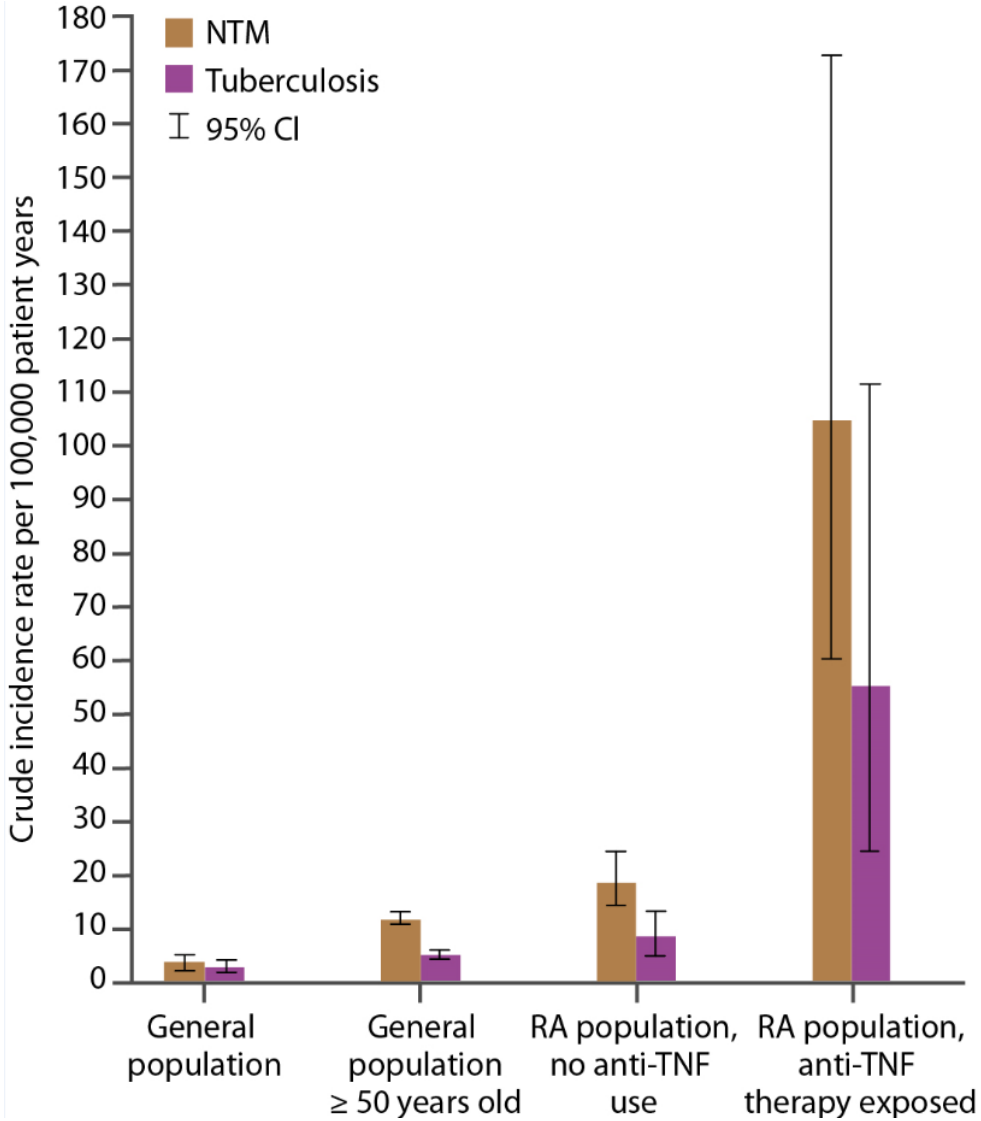
Kendall B, Winthrop K. Update on the Epidemiology of Pulmonary Nontuberculous Mycobacterial Infections. *Seminars in Respiratory and Critical Care Medicine*. 2013;34(01):087-094.

Tuberculosis and nontuberculous mycobacteria in the general population and in patients with rheumatoid arthritis

Crude incidence rates of TB and NTM disease observed in the general population and in patients with rheumatoid arthritis in a large northern California health maintenance organization 2000 to 2008. Patient TB screening results were not reported in this study.



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Winthrop KL, Baxter R, Liu L, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. *Ann RheumDis*. 2013;72(1):37-42.

TST and IGRA Comparison

TST	
Visits	2 *(minimum)*
Method	*in vivo (intradermal injection)*
BCG	results affected
NTM	can affect results
Results	48–72 hours
Results	subjective
Costs	variable

IGRAs	
Visits	1
Method	*in vitro (blood draw)*
BCG	results not affected
NTM	not affected by most NTM
Results	≤ 48 hours
Results	objective
Costs	defined

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Commercially Available IGRAs

Variables	QuantiFERON-TB Gold	T-SPOT.*TB* Test
Technology	ELISA	ELISPOT Enzyme linked imm Spot
Test Substrate	Whole blood	Peripheral blood mononuclear cells
Sample Collection	3 specialized tubes (new 4)	1 standard tube
Adjusted Cell Count	No	Yes
Cell Wash	No	Yes
Cell Targets	CD4 (new version CD 8 also)	CD4, CD8
Sample Stability	16 hours	32 hours
Diagnostic Performance	Package Insert: sensitivity, 88.7%; specificity, 99.2%	Package Insert: sensitivity, 95.6%; specificity, 97.1%
Readout	Interferon-gamma concentration (international units per mL)	Individual spots representing captured interferon-gamma
Result Interpretation	Positive, Negative, Indeterminate	Positive, Borderline, Negative, Invalid Includes FDA-approved borderline category
Accessibility	In-house lab or available through reference laboratories	In-house lab or available through Oxford Diagnostic Laboratories®

Oxford Immunotec. T-SPOT.TB Package Insert PI-TB-IVD-UK-V3. Abingdon, UK. March 2016.
QuantiFERON-TB Gold (QFT) ELISA Package Insert, 1075116 Rev. 02. Cellestis, Inc. Valencia, CA., April 2015.

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Comparison of T-SPOT.*TB* and TST Test Sensitivity and Specificity in Rheumatic Disease Patients

- 311 subjects with rheumatic disease or probable rheumatic disease
  - 83.9% BCG-vaccinated
  - 256 patients (82.3%) on glucocorticoid or immunosuppressant therapy
  - 28 patients (9.0%) clinically diagnosed with TB disease
  - overall positivity rates
    - TST test 37.8% (42/111)
    - T-SPOT.*TB* test 14.2% (44/311)

	T-SPOT.*TB* test n/N (%)	TST n/N (%)
Sensitivity	92.9% (26/28)	81.8% (9/11)
Specificity	93.6% (265/283)	67.0% (67/100)

"As a new immunoassay for TB diagnosis, the sensitivity and specificity of [T-SPOT.*TB* test] is higher than TST. It is of great importance in the diagnosis of active or latent TB infection in rheumatic disease patients."

Jiang B, Ding H, Zhou L, Chen X, Chen S, Bao C. Evaluation of interferon-gamma release assay (T-SPOT. TB™) for diagnosis of tuberculosis infection in rheumatic disease patients. *International Journal of Rheumatic Diseases*. 2015. http://onlinelibrary.wiley.com/doi/10.1111/1756-185X.12772/full. Accessed March 1, 2016.

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Comparison of T-SPOT.*TB* Test and QFT® Indeterminate Rates in Patients with Rheumatic Disease

- 108 pediatric patients with rheumatic disease
  - tested by IGRA before initiating or changing treatment with biologics or immunosuppressants
  - 81 tested by QFT-GIT and 27 by T-SPOT.*TB* test
- 7/8 (87.5%) patients with QFT-GIT indeterminate results patients given >0.5 mg/kg prednisolone
- Significantly higher numbers of WBCs/neutrophils and CRP value in QFT-GIT indeterminate group

	T-SPOT.*TB* test n/N (%)	QFT-GIT n/N (%)
Indeterminate [invalid] result	0/27 (0)	8/81 (9.9)

"T-SPOT.*TB* test was suitable for evaluating latent tuberculosis infection even under immunosuppression where TB tests are generally hard to perform."

Nozawa T, Mori M, Nishimura K, et al. Usefulness of two IFN-γ release assays for patients with rheumatic disease. *Pediatr Int*. December 2015.

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CDC Guidelines (2010) and by others- 2017

Testing with both IGRA and TST may be considered when initial test result (by IGRA or TST) is:

Negative	Positive	Indeterminate, Invalid, or Borderline
and risks for infection, progression, and poor outcome are increased	and additional evidence of infection is required to encourage compliance	repeating IGRA or performing the TST might be useful
and clinical suspicion exists for TB disease and confirmation of *M. tuberculosis* infection is desired	in a healthy person who has a low risk for both infection and progression	

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Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recomm Rep*. 2010;59(RR-5):1-25.

American College of Rheumatology Recommendations (2015)

Recommendations for TB screening in patients being considered for or receiving biologics or tofacitinib

- **All patients** being considered for **biologics or tofacitinib**, **regardless of the presence of risk factors**, should be screened with an IGRA or the TST
- **IGRA recommended** over the TST in patients who have previously received a **BCG vaccination**, due to the high false-positive test rates for TST
- **Repeat** TST or IGRA could be considered after an **initial negative test result** in immunosuppressed **RA patients with risk factors for LTBI**

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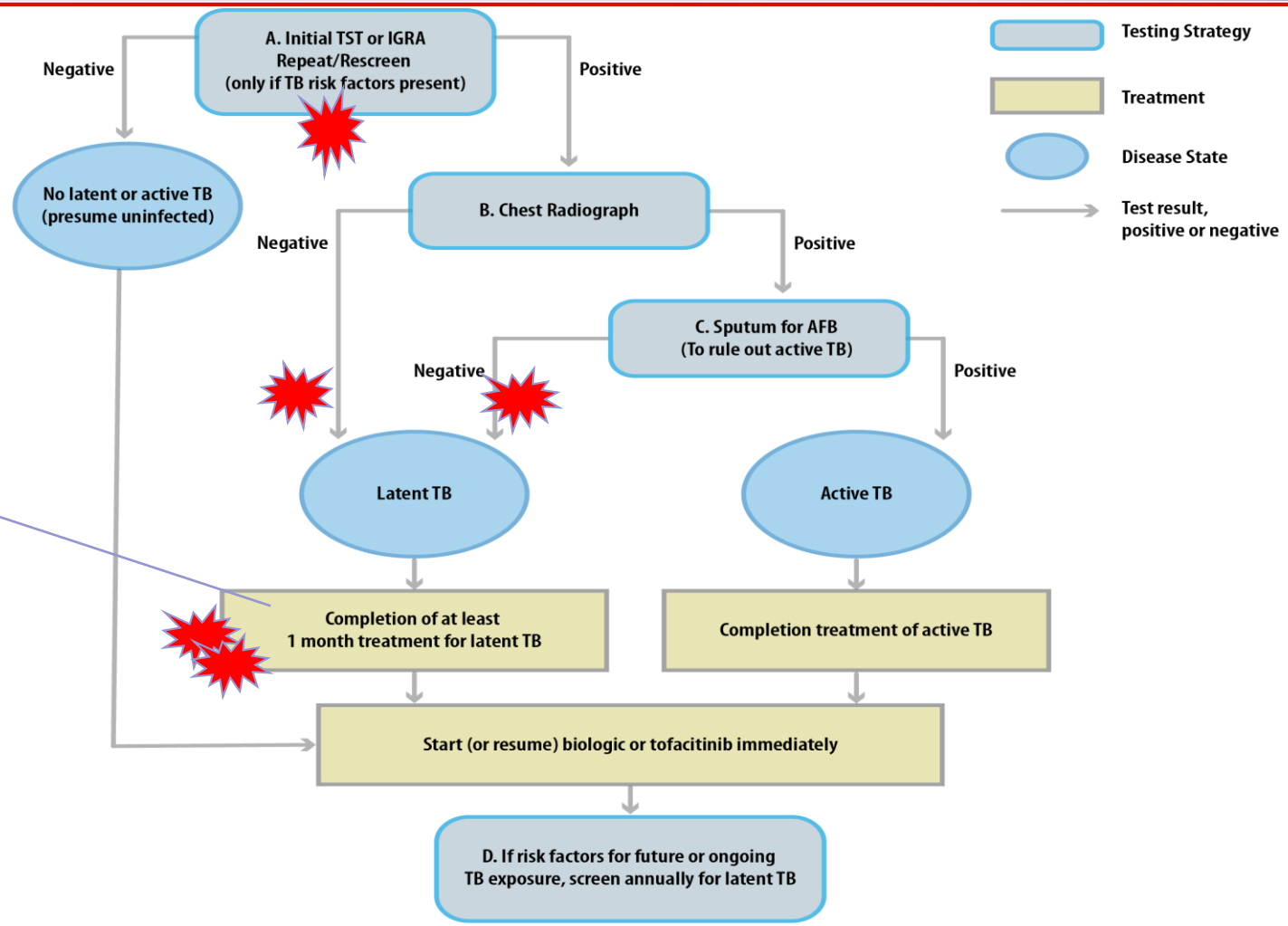
Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis: ACR RA Treatment Recommendations. *Arthritis Care & Research.* 2016;68(1):1-25.

TB Screening Algorithm for Biologics and Tofacitinib (2015)



INH + B 6
or Rif/Rpt –
INH/other options
but with caution

JA remarks

Adapted from Singh, JA, Saag, KG, Bridges, SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis & Rheumatology. 2015;68(1):1–26 doi:10.1002/art.39480

Adapted from Singh, JA, Saag, KG, Bridges, SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis & Rheumatology*. 2015;68(1):1–26 doi:10.1002/art.39480

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1. How soon after start of LTBI treatment with negative CXR and no evidence of active TB or active NTM, can a biologic be re-started?

   0-1-3 months

2. If a patient on a biologic already has LTBI, how long would it take granulomas to form?

   ~3 months (animal data)

3. If a patient treated with a biologic for a year converts and develops a positive IGRA on annual re-testing, does the biologic need to be stopped and patient assessed as discussed for TB/NTM/LTBI

   Yes

WIDE RANGE OF DATA & GENERAL CONSENSUS

Furst DE, Keystone EC, Kirkham B, et al. Updated consensus statement on biological agents for the treatment of rheumatic dise ases, 2008. Ann Rheum Dis. 2008;67(Suppl 3):iii2-iii25.
Lee SW, Oh DK, Lee SH, Kang HY, Lee CT, Yim JJ. Time interval to conversion of interferon-gamma release assay after exposure to tuberculosis. *Eur Respir J*. 2011;37(6):1447-1452.

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“Issues” and debate about IGRAs

- Cost/front end load vs down stream cost
- Invalid T-SPOT.*TB* test meaning
- Indeterminate QFT meaning
- Borderline T-SPOT.*TB* test significance
- Variations in serial testing related to conversions and reversion
- Collection / Technical / Logistical issues
- Inter-observer variation 6 -15 % variation on spot counting
- Need for more closer look with ……
  - Quantitative Assessment?
  - Antigen Specificity?
  - Spot / PHA Ratio?

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Identification of False-positive QuantiFeron-TB Gold In-Tube Assays by Repeat Testing in HIV-Infected Patients at Low Risk of Tuberculosis

- N= 1364; with 94 (6.9%) with positive results
- Repeat testing in 49 of 94 (52 %)

- Of the 49 repeated QFT tests, 35 (71.4%) reverted to negative
- 12 (24.5%) remained positive, and 2 (4.1%) were indeterminate

Gray J et al CID 2012:54 (I Feb)

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King *et al.*, Am J Respir Crit Care Med 2015
T-SPOT.*TB* HCW Serial Screening Study

Summary of Publications Reporting Conversion and Reversion Rates in North American HCWs

Study	Setting	IGRA Used	Number of Subjects Tested	Conversion Rate (%)	Reversion Rate (%)
This study	19 U.S. hospitals	T-SPOT.*TB*	19,630	0.8	17.6
Dorman et al. (3)	4 large urban U.S. hospitals	T-SPOT.*TB*	2,418	8.3	63.9
Dorman et al. (3)	4 large urban U.S. hospitals	QFN	2,418	6.1	56.8
Fong et al. (9)	Cleveland Clinic, OH	QFN	1,857	2.8	80.0
Zwerling et al. (10)	McGill University Health Centre, Montreal, Canada	QFN	258	5.3	61.5
Joshi et al. (4)	Central Arkansas Veterans Healthcare System	QFN	2,303	3.2	45.0
Slater et al. (6)	Stanford University Medical Center, Palo Alto, CA	QFN	9,153	4.4	38.7

Definition of abbreviations: HCW = healthcare workers; IGRA = interferon-gamma release assay; QFN = QuantiFERON.

King TC, Upfal M, Gottlieb A, et al. T-SPOT.TB Interferon-γ Release Assay Performance in Healthcare Worker Screening at Nineteen U.S. Hospitals. *Am J Respir Crit Care Med*. 2015;192(3):367-373. doi:10.1164/rccm.201501-0199OC.

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King Study conclusion:

- 79.8% of borderline test results resolved as positive or negative upon retesting

- 23% retesting as positive, suggesting that the borderline is useful in maintaining test sensitivity and specificity

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Our Data part of IGRA T-SPOT.*TB* study (n=1937) in HIV clinic
(poster presentation done and manuscript sent for publication)
Ige, Frontini, Ali

Table 3. Results with Serial Repeat T-SPOT.*TB* Test During Study Period (n=34) of the 68 patients with either positive or borderline tests studied

Group1 : 19 were repeated after initial positive

Group 2: 15 were repeated after initial borderline

Group 1		
Reversion positive to negative	11/19	58%
Remained positive	8/19	42%
Group 2		
Borderline to negative	10/15	67%
Borderline to positive	2/15	13%
Remained Borderline	3/15	20%)

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General consensus of all studies to date on this topic:

1. Awareness of Reversion
2. Need for targeted screening
3. Unclear on reasons

MULTIFACTORIAL (Pt/Technical/Logistics)

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Issues with Reproducibility

- Pre-analytical processing QFT ELISA
- Analytical testing EQUAL
- Assay manufacturing EQUAL
- Immunemodulation PPD BOOSTING (more than 3 days gap) / DRUGS / Pathogen Associated Molecular atterns (PAMP)
- Release of Interferon Gamma by other cells

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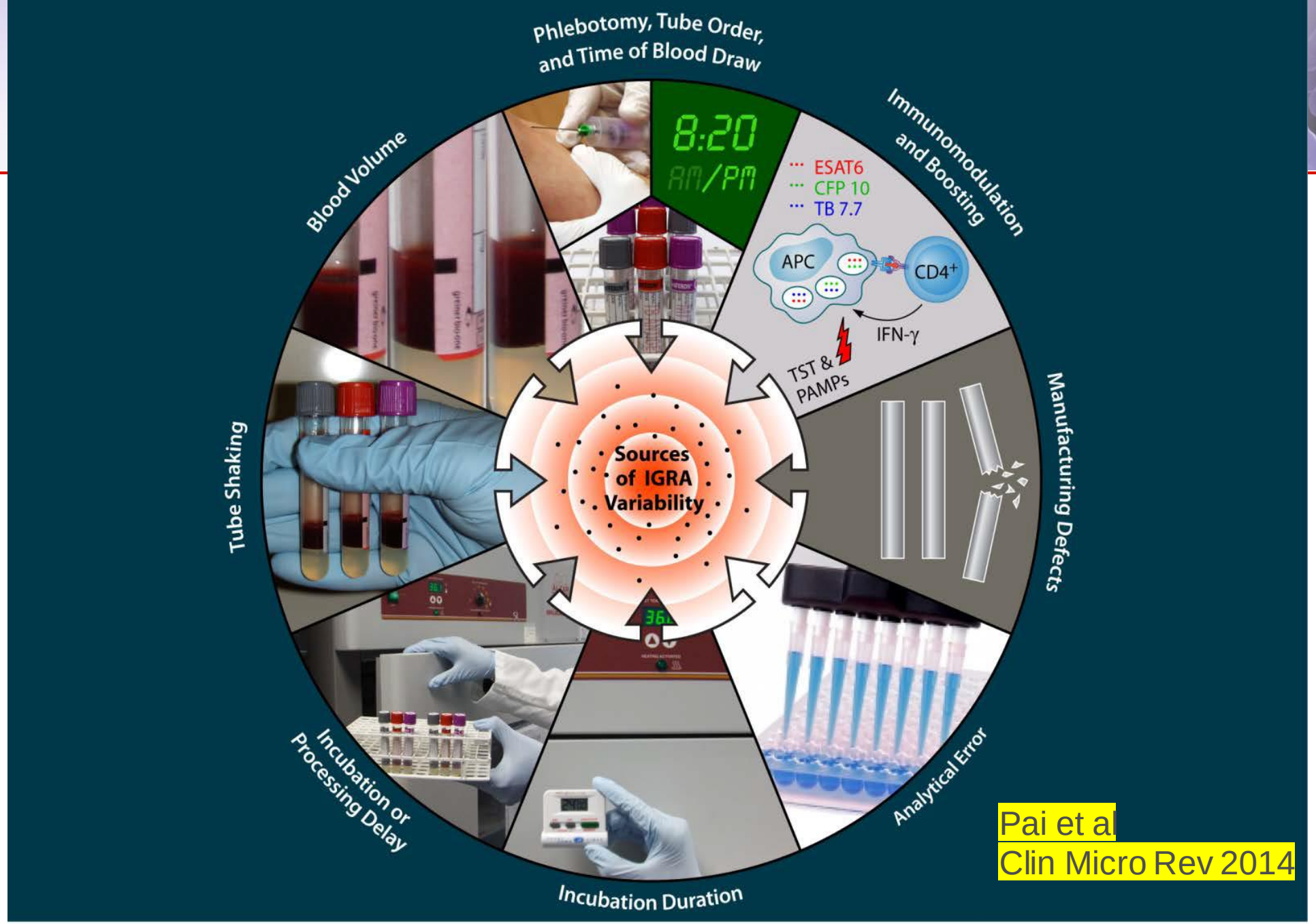
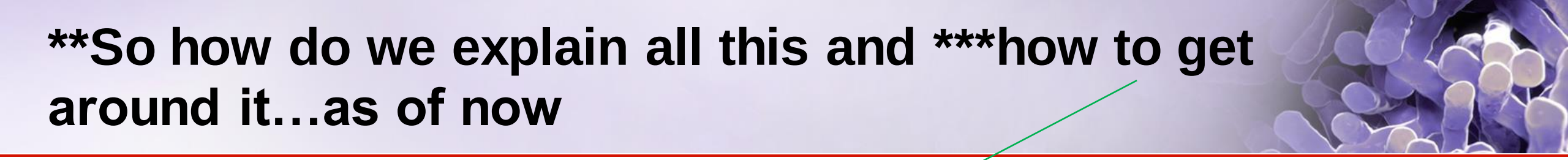


Pai et al
Clin Micro Rev 2014

Oxford Immunotec

**So how do we explain all this and ***how to get around it…as of now



- ***Risk stratification of subject or cohort / population
- ***Incorporate TST data if applicable, timely and available
- ***Appropriate two step testing (TST–IGRA) with acceptable interval between the two (see international and national guidelines)
- ***Using borderline category and quantification data of positive and borderline results as a guide
- *** “CClinicalS” ☺

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Positive TST/IGRA:

Jeopardy Question 1 response

What do you do before starting treatment for latent TB/TB Infection?

…Remember the one definitive contraindication**

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Jeopardy 1

Must check for active TB

Do not forget to look for Extrapulmonary TB

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“Positive” TST/IGRA: Suggested Traffic Light Plan*

Driving Path

A: DATA	B: EVALUATE	C: SCAN	D: RECAP	E: TREAT
Quantify Assess Borderline Indeterminate Discordant Results	Rule Out Active Disease	Rule out Extra-Pulmonary Disease	Size of TST: Is it helpful? In Children; Degree of IGRA?	**Dx; TB Infection Should we Offer Rx? Based on Many Factors**
Document	Symptoms H/P	ROS **“101”** LN Exam	Go Back to Steps B&C if in Doubt	**Risk of ADR***
Check HIV	CXR CT Scan if needed	Correlate with Chest imaging		**Pre-Lab Check**
Stratify Risk, Check Source Case **Why?**	Sputum Induce if needed REMEMBER ‘DOSE”	Pre-Test Probability?	If Sure go to Step E	Treat for TB Infection; Assess Risk Benefit Ratio
Conclude after Full Evaluation: if Positive Steps B-E	Pre-Test Probability? Treat for Active TB REMEMBER DOT	Treat for TB ?		**Monitor Side Effects* and Rx**

*ATS 2006 DILI consensus statement

* JA)

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"Case" Finding: The Real "TST" is

- Risk Stratification , Targeted Screening and Site and Focus of Team Efforts
- Identifying Active & Latent TB and the steps in diagnosis and Treatment
- **Role of Primary Care and lack thereof ****
- **Care Coordination and Continuity of Care and Closing the Loop**

Coordination of Community Care/Specialists
Academics, Clinical and Public Health
& Case Management

**Ref: JAMA Editorial Case Finding in TB 1941;116
****PICO based Case Management Paradigm & Strategy**
*ATS/CDC/IDSA Clinical Practice Guidelines for Drug Susceptible TB CID Advanced Access Aug 10.2016
**JAMA 2016 ;316(9):970-983 Kahwati et al Cochrane Analysis on Primary Care Screening & US Preventive Services Task Force

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Thank you for your kind attention

Juzar Ali