TB Diagnosis, Prevention, and Treatment

Ten things you need to know now

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Disclosure

I have received stipends for speaking at continuing medical education events sponsored by Oxford Immunotec, maker of T.Spot*TB*. This relationship, relevant to the content of this activity, has been investigated. The content of this presentation does not relate to any product of a commercial interest.

1. Participants will be able to define LTBI guidance regarding diagnosis using TST, QuantiFERON and TSpot.*TB*
2. Participants will be able to define risk and benefit of the currently approved LTBI treatment regimens with patients
3. Participants will be able to describe TB diagnosis, treatment strategies including new agents bedaquiline and delaminid, and transmission prevention strategies.

2017 Global TB Epidemiology

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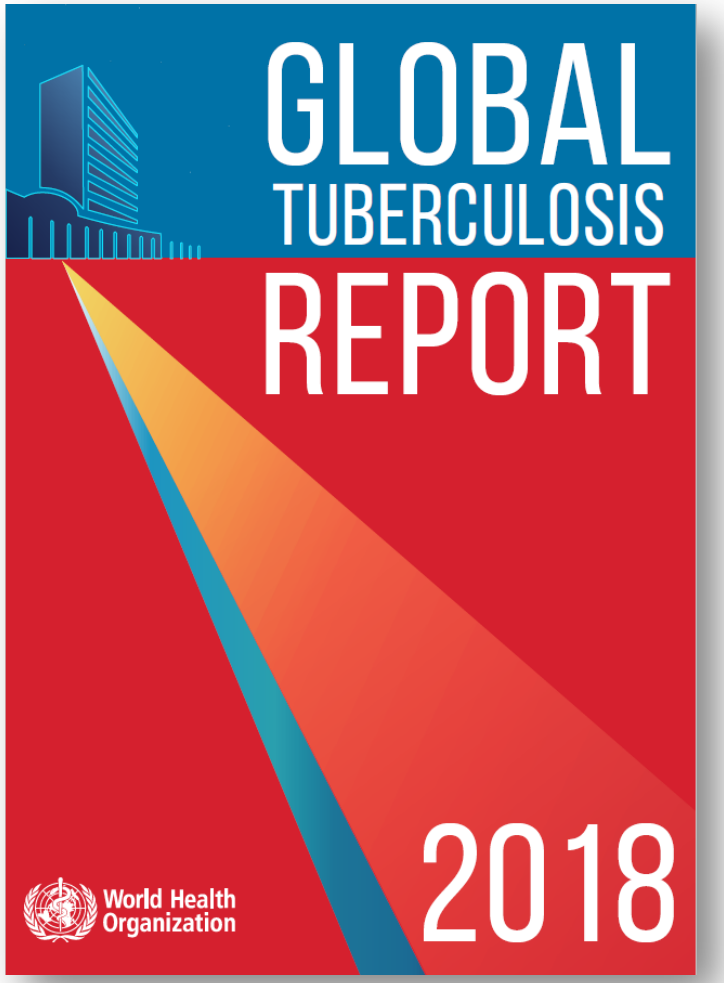
- Released in preparation for first UN High Level Meeting
- ~10M new cases (2% decrease)
  - 5.8M men, 3.2M women, 1M children
  - ~1.6M died from TB
    - 9th leading cause of death
    - 1st cause of death among IDs
- 558k RR-TB, 82% MDR
- 1.7B (23%) with LTBI*

6.4M (64%) notified

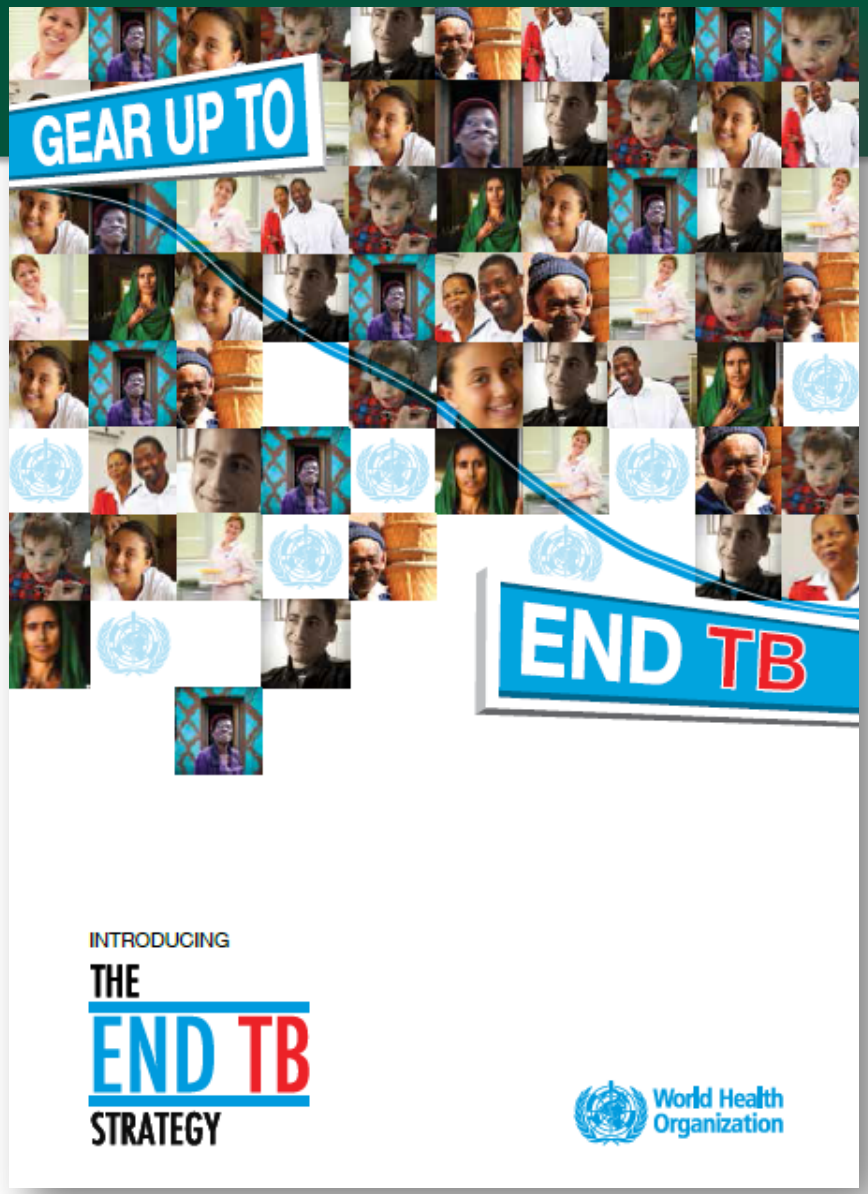
161k (28%) detected
139k (25%) treated



WHO/HTM/TB/2017.22

*Houben RM et al. Global burden of LTBI . . PLoS Med 2016;13:e1002152.
RR-TB is rifampin resistant TB, phenomenon of Xpert; MDR is res to INH+RMP

LTBI Reservoir

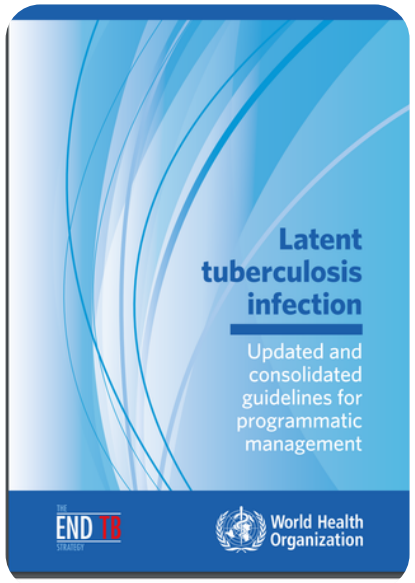


WHO/HTM/GTB/2015.09, Image used with permission

- In low-incidence countries most TB is from reactivation
  - In US >80%
- 4.2% of US pop 1999-2000 have TBI
  - Reservoir of untreated TBI ~8.8M
- TBI dx/tx in high-risk groups is **priority action** for TB elimination strategy

2018 WHO LTBI Updates

- **Expand groups for LTBI testing and treatment**
  - Continue PLWH, child contacts <5, immunocompromised, HD, transplant, silicosis
  - HIV-neg children ≥5, adolescent, adult contacts
    - Including contacts of patients with MDR-TB
  - Low TB incidence settings: HCWs, prisoners, immigrants, homeless, drug use
- **Expand testing options:** TST or IGRA in all settings
- **Expand treatment options:** besides 6-9INH
  - RFP-INH qw 3m for both adults and children



LTBI: updated and consolidated guidelines for programmatic management. Geneva: WHO; 2018. License: CC BY-NC-SA 3.0 IGO

Your Perspective

- What is your most important rationale for not testing and treating LTBI?

Challenge #1: LTBI Test and Treat Hesitancy

Testing too complicated
- Clinicians dread false positive
- Public health fears false negative
- Patients suspect either

→ Testing too expensive → Treatment too dangerous → "Tx can engender DR"

Targeted Testing

- Mass screening and treatment?
- Identify, evaluate, and treat persons at high risk for either
  - LTBI and/or
  - Progression LTBI to TB

TB "Risk"

- Plea for clarity with reference to "high risk"
  - High risk for being infected with *M. tuberculosis* or progressing to TB disease

High Risk for TB Infection

- Close contacts to TB patients
- Non-US-born persons
- Low-income groups and homeless persons
- Individuals who live and/or work in high risk settings
- Healthcare workers who serve high-risk groups
- People who inject drugs

It's all about risk of TB contact

High-Risk for Progression to TB Disease

- People living with HIV
- People with medical conditions known to increase the risk for TB
- People infected with *M. tuberculosis* within past 2 years
- Infants and children <4 years old
- People who inject drugs

It's all about host factors for progression

Who to Test for LTBI?

- Use this tool to identify asymptomatic **adults** for latent TB infection (LTBI) testing.
- Re-testing should only be done in persons who previously tested negative, and have new risk factors since the last assessment.
- For TB symptoms or abnormal chest x-ray consistent with active TB disease → Evaluate for active TB disease

  Evaluate for active TB disease with a chest x-ray, symptom screen, and if indicated, sputum AFB smears, cultures and nucleic acid amplification testing. A negative tuberculin skin test or interferon gamma release assay does not rule out active TB disease.

Check appropriate risk factor boxes below.

LTBI testing is recommended if any of the 3 boxes below are checked.

If LTBI test result is positive and active TB disease is ruled out, LTBI treatment is recommended.

☐ **Foreign-born** person from a country with an elevated TB rate

- Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe
- If resources require prioritization within this group, **prioritize** patients with at least one medical risk for progression (see User Guide for list)
- Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for foreign-born persons

☐ **Immunosuppression**, current or planned

HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) or other immunosuppressive medication

☐ **Close contact** to someone with infectious TB disease at any time

www.ctca.org

How to Test for LTBI?

- Methods
  - Tuberculin skin test (TST)
  - Interferon gamma release assays (IGRA)
    - T-SPOT.*TB* test
    - QuantiFERON Plus
- Limitations of testing: indirect tests
  - Testing detects acquired cell-mediated immune response to *M. tuberculosis* antigens as surrogate of infection
  - Limited (-to-no) data on predictive ability of these tests to identify persons likely to progress to TB disease

QuantiFERON-TB Gold Plus

2

- Removed TB7.7 antigens
  - Implicated in reduced specificity
- Adds tube of shorter peptides
  - Targets CD8 > CD4 response
- Postulated for recent LTBI or active TB

Comparing New and Old QFT

- 162 TB+ vs 212 *M. tuberculosis*-uninfected
  - Cut-off still 0.35 IU/mL, but Plus had lower sensitivity (91.1%) compared to optimum cut-off 0.168 IU/mL (96.2%) with no compromised specificity
  - Among 162 cx-confirmed TB patients, IFN-γ concentration of QFT-Plus lower than QFT-GIT
  - QFT-Plus IFN-γ values less impacted by age than GFT-GIT
- 19 healthy, 58 LTBI, 33 cured TB, 69 active TB
  - Similar sensitivity (~90%) for Plus and GIT for active TB
  - Selective response to TB2 associated with TB (9%)

Yi L et al. Eval of QFTG Plus for Detection of MTB infection in Japan. Sci Rep 2016; 6: 30617
Petruccioli E et al. Analytical eval of Q-Plus and Q-GIT . . . Tuberculosis 2017;106:38-43.

QFT Plus Better for Recent Infx?

- Prospective recruitment of TST+ adult contacts comparing Plus and GIT
- Strong agreement, but 12 discordants Plus positive
  - All but one of which also had TST>10
  - Stronger infection risk association based on time and proximity to source case
- TB2 minus TB1 may be proxy for recent infection
  - 15% QFT Plus positive contacts had values >6 IU/mL
    - Associated with proximity to index case

Barcellini L et al. Eur Resp J 2016; 47: 1587-90

TST and IGRA Similarities

3

- Cost money
- Compromised sensitivity in immunocompromised
- Specificity
  - TST: nor G history
  - IGRA: lo
- Quantitativ
- Cannot differentiate between LTBI and active TB
- Neither predicts risk for progression to active TB

Altet et al. Ann Am Thor Soc 2015; 12(5):680; Andrews J et al. Serial QFT . . . Lancet 2017.

TST or IGRA?

4

- Either, if likely LTBI and high risk of progression
- Perform IGRA rather than TST* in individuals ≥5 years who:
  - Are likely to be infected,
  - Have low or intermediate risk of disease progression,
  - Testing for LTBI is warranted, and
  - Either have history of BCG vaccination or are unlikely to return to have their TST read
- *Strong recommendation, moderate-quality evidence*

* TST is an acceptable alternative

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases.* 2017;64(2):e1-e33.

Positive IGRA in Low TBI Risk Patient

- Farmer from northern Maine who never left his farm needs an IGRA because he will start TNF-alpha inhibitor for steroid-resistant RA
- QuantiFERON Plus comes back as positive:
  - TB1-nil=0; TB2-nil=0.36

A very frequent curbside!

Q. WHAT DO YOU DO ABOUT A POSITIVE IGRA IN LOW TBI RISK PATIENT?

Options

1. Nothing – probably false positive
2. Repeat same IGRA
3. Do the other IGRA
4. Place TST
5. Call the State

LTBI: Low Risk for LTBI

5

- Do NOT test. But …
- Suggest performing an IGRA instead of TST*
  - *Conditional recommendation, low-quality evidence*
- If initial test is positive, suggest second diagnostic test, either IGRA or TST
  - When such testing is performed, person is considered infected only if both tests are positive
  - *Conditional recommendation, very low-quality evidence*

* TST is an acceptable alternative

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases.* 2017;64(2):e1-e33.

Unexpected Positive IGRA in HCW

- Recent hire who had multiple negative TSTs in course of her healthcare career gets an IGRA with no obvious TB exposure risk
- QuantiFERON Plus positive:
  - TB1-nil=0; TB2-nil=0.36

A very frequent curbside!

Q. WHAT DO YOU DO ABOUT A POSITIVE IGRA DURING SERIAL TESTING IN LOW TBI RISK?

Serial LTBI Testing

6

- Insufficient evidence to make specific recommendation
  - For TST, criteria boosting and conversions established
  - For IGRAs, criteria for conversions and reversions not established
- Among 2,563 HCWs, IGRA showed poor reproducibility
  - Most conversions not confirmed on repeat testing
- Therefore, TST and IGRA are both acceptable
  - May consider confirmatory (dual) testing in this setting

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official ATS/IDSA/CDC. Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases*. 2017;64(2):e1-e33.

A Need for Definitions

Concordance

- Negative result followed by a negative result
- Positive result followed by a positive result

Conversion

- Negative result with a subsequent positive result

Reversion

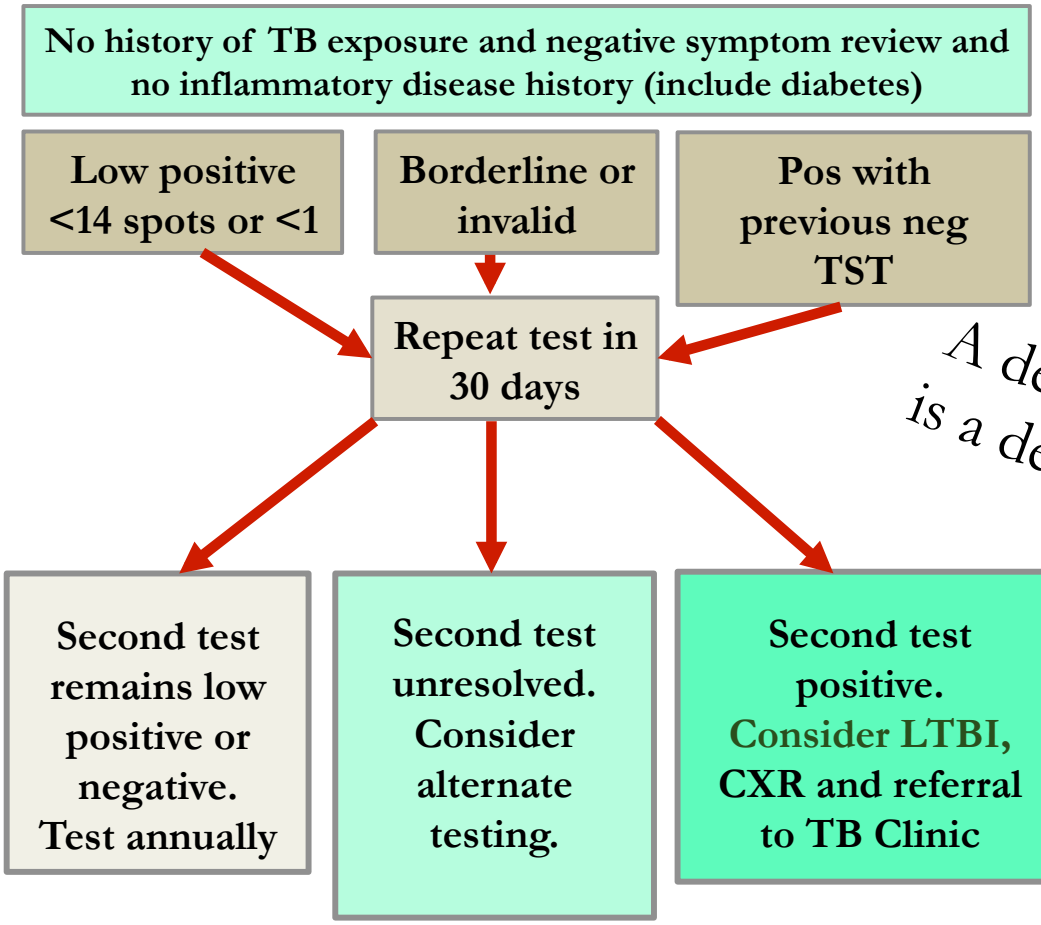
- Positive result with a subsequent negative result

The TBES HCW Serial Testing Study

- Prospective study of serial IGRAs in low risk HCWs
  - 4 sites: Denver, Houston, Baltimore, NYC
- TST+IGRAs q6m over 3 years Feb 2008–Mar 2011
- Conversions occurred in all 3 tests
  - TST: 21 of 2293 (0.9%)
  - QFT: 138 of 2263 (6.1%)
    - 76.4% reverted – less likely if contact to TB
  - T-SPOT.*TB* test: 177 of 2137 (8.3%)
    - 77.1% reverted
  - IGRAs less likely to revert if higher baseline values

Dorman SE, Belknap R, Graviss EA et al. IGRA and TST for Diagnosis of LTBI in HCW in the US. *Am J Respir Crit Care Med.* 2014;189(1):77-87;

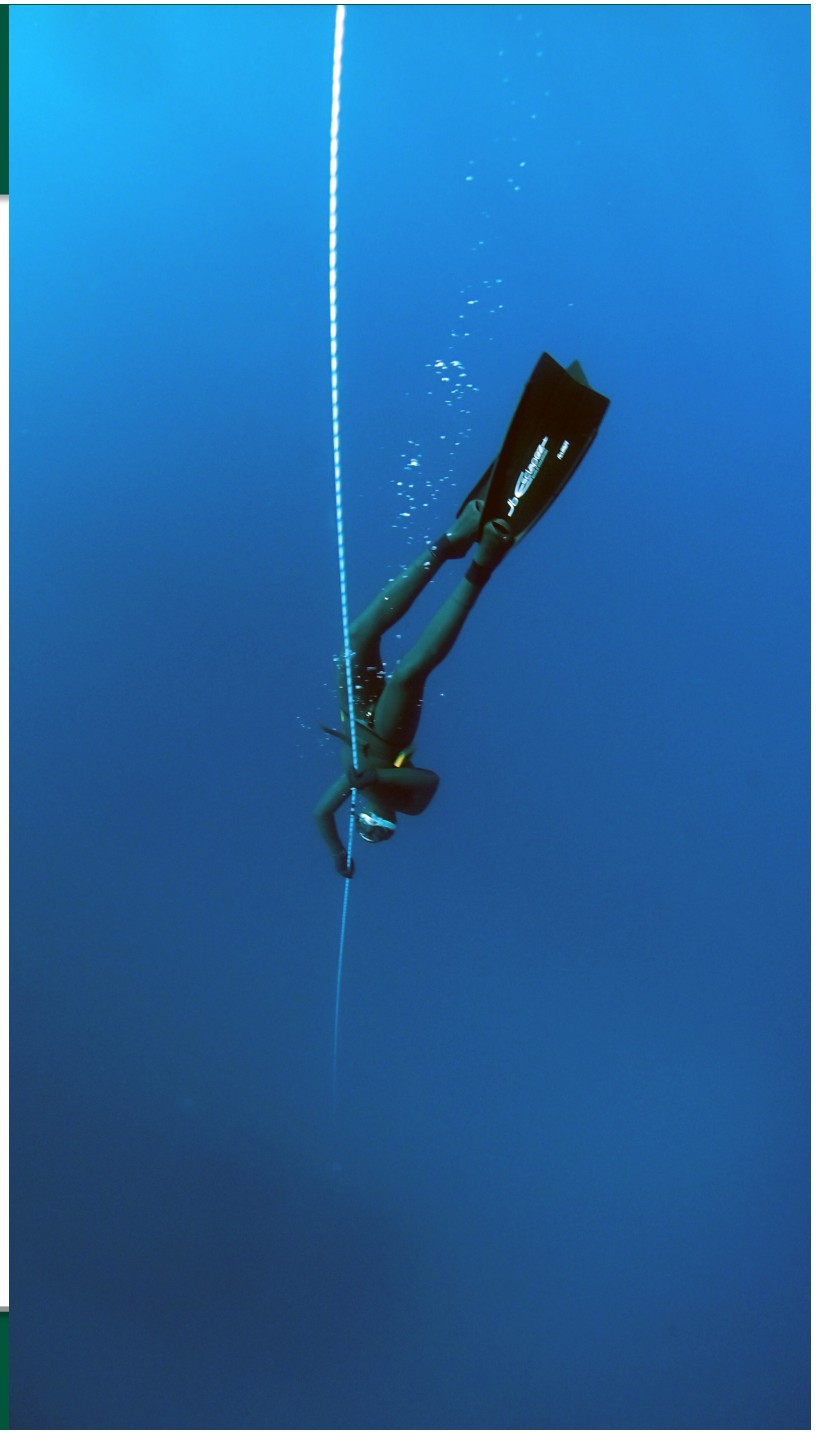
Serial Testing Algorithm



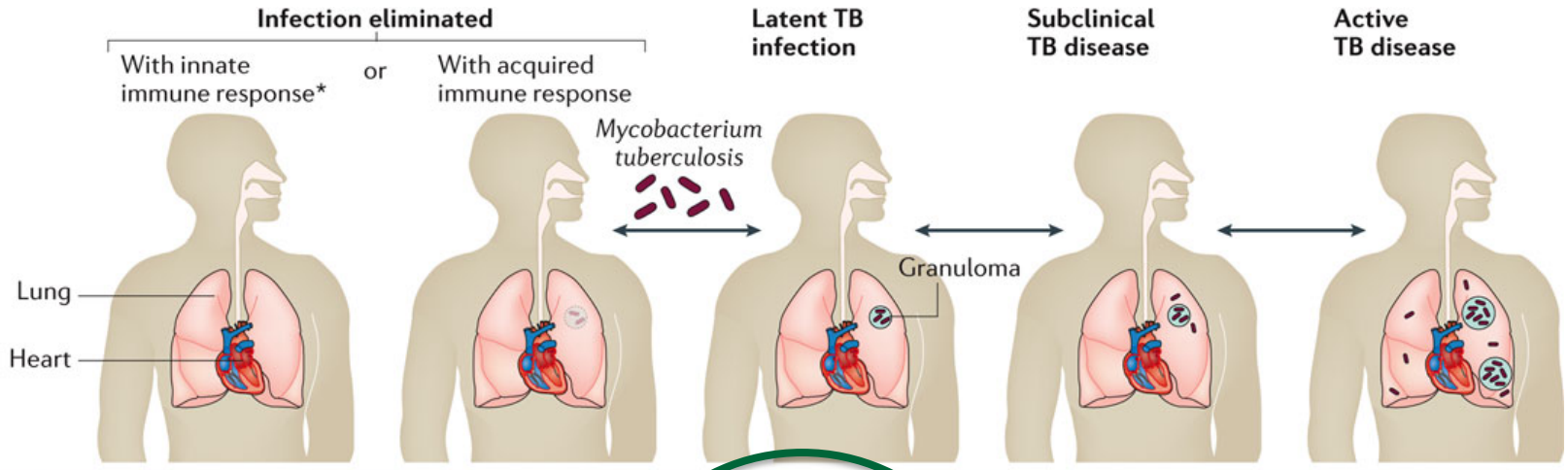
A decision to test is a decision to . . . think

A Deeper Dive

LTBI



LTBI vs TB: Not Binary



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

Nature Reviews | Disease Primers

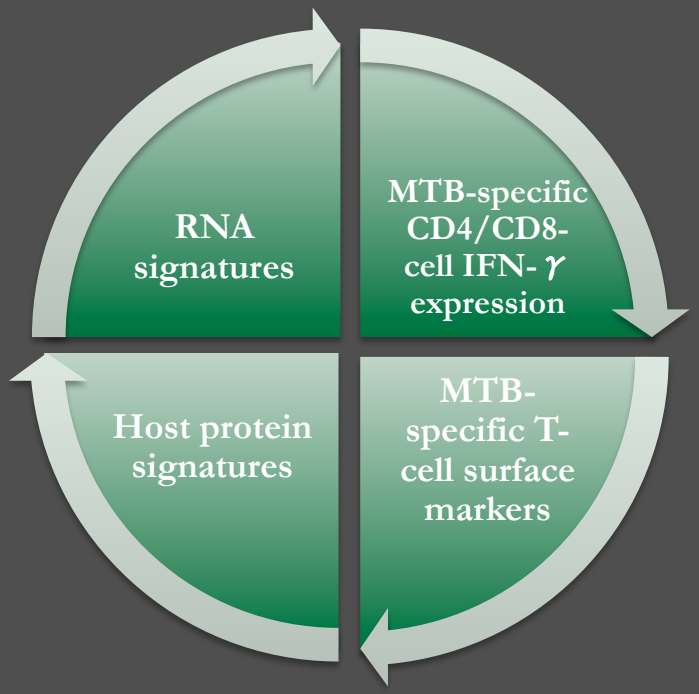
Pai M. *et al.* (2016) Tuberculosis. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

WHO: Unmet LTBI Test Needs

1) Better at identifying TB disease or response to TB therapy
   - *'Neither TST nor IGRA can be used to diagnose active TB disease nor for diagnostic workup of adults suspected of having active TB.'*
   - Why? All *M. tuberculosis* infected individuals positive. Test must differentiate active from latent – esp in mid/high burden countries
2) Identify those with LTBI who will progress to TB
   - *'Diagnostic tests with improved performance and predictive value for reactivation of TB are critically needed.'*
   - Why? PPV of IGRAs is 2.7% = too many test-positive individuals get treated to prevent 1 case of TB disease

LTBI: Updated and consolidated guidelines for programmatic management. Geneva: WHO; 2018. CC BY-NC-SA 3.0 IGO

Better Tests in Pipeline



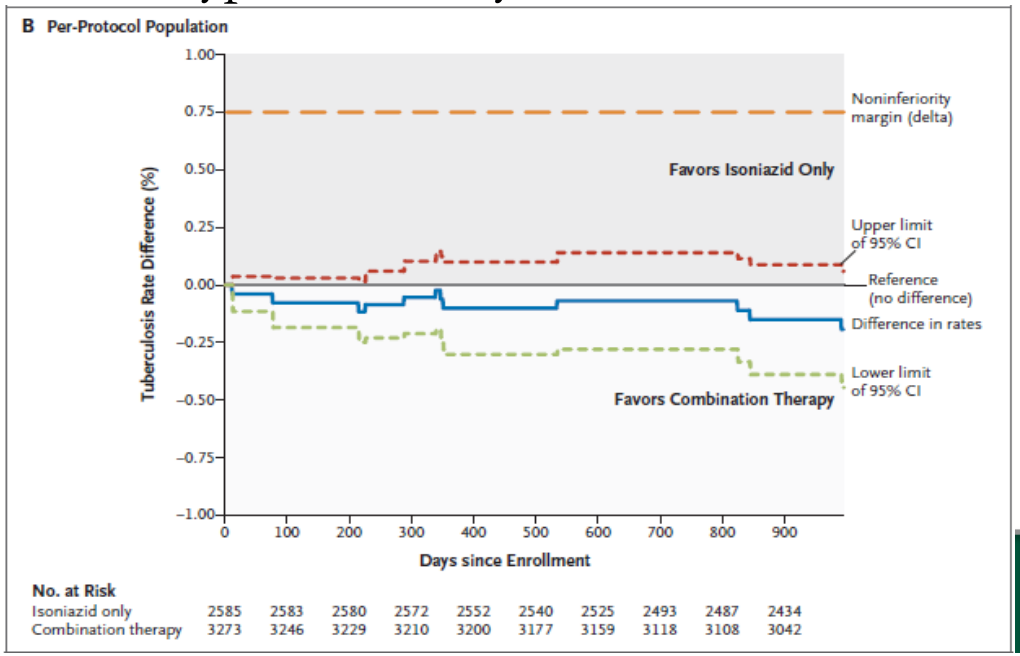
Treatment Regimens for LTBI

Drugs	Months of Duration	Interval	Minimum Doses
INH	9*	Daily	270
		2x wkly**	76
INH	6	Daily	180
		2x wkly**	52
RIF	4	Daily	120
INH-RPT	3	Weekly**	12

*Preferred, ** Intermittent treatment only with DOT

INH and Rifapentine for 12 weeks

- Efficacy similar: 0.19% v 0.43% developed TB disease
- Completion 82% in INH-RPT vs. 69% in INH
- Permanent drug discontinuation due to AEs in INH-RPT group, although fewer AEs in INH-RPT
  - More hepatotoxicity in INH alone group
  - More 'possible hypersensitivity' reactions in INH-RPT



NEJM 2011; 365(23)

3HP Recommendations

- Equivalent to 9 months INH in otherwise healthy individuals ≥ 12 years old + high risk for progression to TB disease:
  - Close contact
  - Converter
  - Fibrotic changes on CXR
  - *HIV not on ART, otherwise healthy*
- Children 2-11 years old esp if unlikely to complete 9m + high risk to progress to TB disease
- Recent study showed self-administered 3HP noninferior to DOT in US

Rec for Use of INH-RPT Regimen with DOT to Treat LTBI. MMWR / December 9, 2011 / Vol. 60 / No. 48
Villarino et al., JAMA Pediatrics, 2015; Belknap R. CROI 2015. Abstract 827LB.

"ARE WE EVER GOING TO GET BETTER LTBI REGIMENS?"

Short Course Treatment for LTBI

- 15 regimens indirectly compared from 53 studies and > 130,000 subjects
- Rifamycin containing regimens (without PZA) are as (or more) effective as 9H or 6H and safer
- PZA containing regimens not preferred due to hepatotoxicity

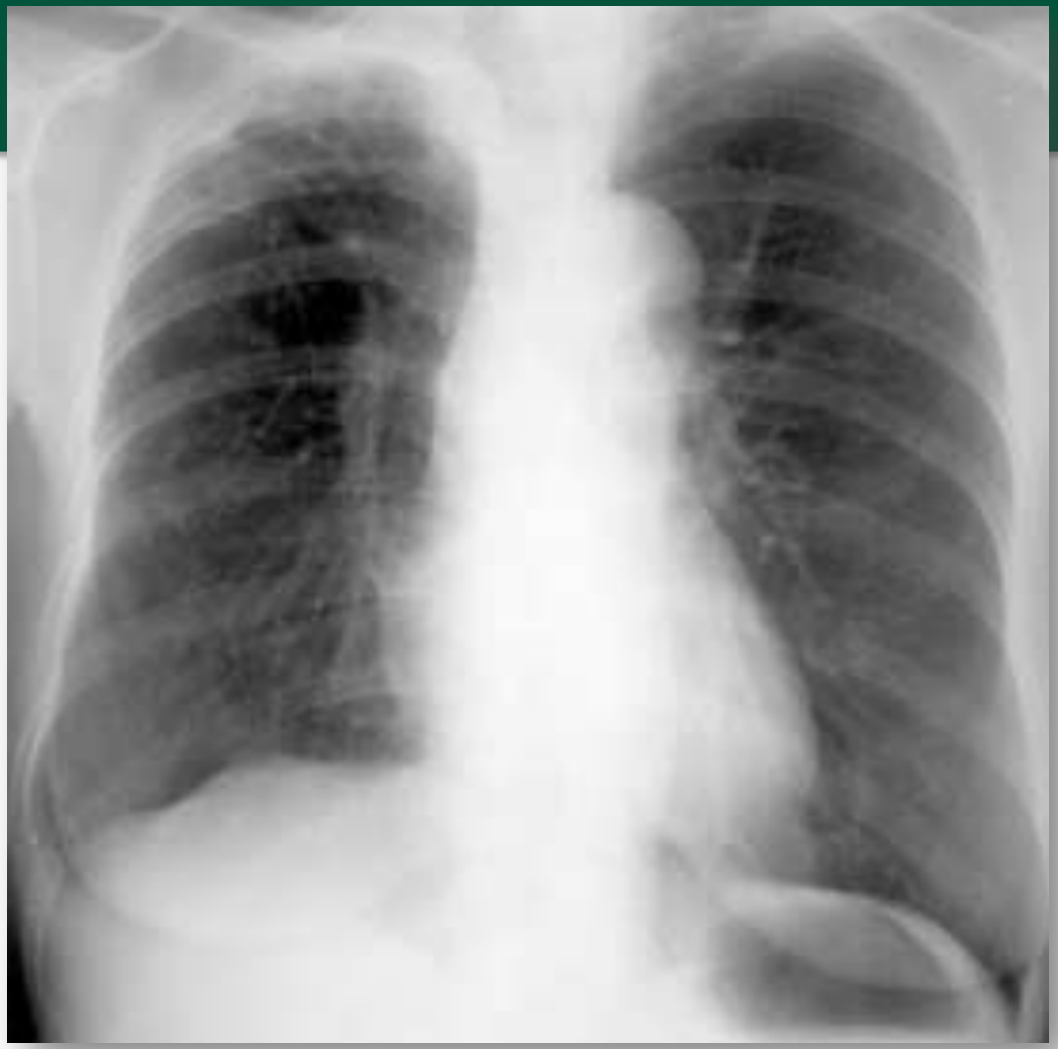
Stagg et alk. Ann Intern Med. 2014;161(6):419-428. doi:10.7326/M14-1019

BRIEF TB

- INH+RPT 450-600mg qd 1 month vs INH 9m
- Multicenter 10 countries, PLWH ≥13y
- Follow up ~3 years
- Rate of TB same
  - In low CD4, TB more common in 1m INH+RPT
- Both regimens safe, with fewer AEs in 1m regimen
- Treatment adherence better with INH+RPT

African Refugee with Abnormal CXR

- 51W referred to your outpatient clinic for evaluation for active TB
- From Somalia, but she immigrated from Dukwe, Botswana, 1 month ago
  - No h/o of TB or PMH
  - Asymptomatic
- TST 13 mm (no previous)
- Abnormal CXR



Right upper lobe fibronodular opacities with volume loss and hilar retraction. Right apical pleural thickening.

Multiple options, but what gets you closer to rule out?

Q. WHAT IS YOUR NEXT BEST STEP TO DISTINGUISH TB AND LTBI?

Options

1. Interferon gamma release assay (IGRA)
2. No more testing necessary – this is TB
3. No more testing necessary – this is LTBI
4. Get sputum for Xpert to distinguish LTBI and TB
5. Call the State

TB: Nucleic Acid Amplification

- Rec 7: A diagnostic NAAT should be performed on initial respiratory specimen from patients suspected of having pulmonary TB (*Conditional recommendation, low quality evidence)*
  - Appropriate NAATs include the Hologic Amplified Mycobacteria Tuberculosis Direct (MTD) test (San Diego, California) and the Cepheid Xpert® MTB/Rif test (Sunnyvale, CA)
  - References are pre-Xpert
- Comments:
  - AFB smear-pos, NAAT-neg sputum makes TB disease unlikely
  - In AFB smear-neg patients with an intermediate to high level of suspicion for disease, positive NAAT can be used as presumptive evidence of TB disease

Xpert is a registered trademark of Cepheid

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. *Clinical Infectious Diseases.* 2017;64(2):e1-e33.

Xpert MTB/RIF (Cepheid)

- Automated, real-time PCR
  - 100 mins to TB and rifampin resistance
    - 92% sensitivity for TB
    - 95% sensitivity for rifampin resistance
- Simple, modular system
  - Cartridges for other diseases
- 2010 WHO, Aug 2013 FDA
- 2013 WHO policy expanded for all *instead of* AFB sm and culture
  - MDR, HIV-TB and CNS TB suspects

http://www.cdc.gov/mmwr/pdf/wk/mm6241.pdf;
WHO/HTM/TB/2013.14

Xpert Omni, Ultra, Xtend

- Omni is GeneXpert platform improvement
  - Portable, 4 hour battery for point of care
- Ultra cartridge improves sensitivity
  - Lower specificity? "Trace calls" in paucibacillary disease
    - Detects dead organisms (decreased specificity for TB diagnosis)
  - Improved rifampin resistance specificity
- Xtend XDR cartridge for INH, FQ, SLIDs

http://www.pipelinereport.org/sites/default/files/TB%20Diagnostics.pdf

Alland D, et al. Xpert MTB/RIF Ultra: A New Near-Patient TB Test With Sensitivity Equal to Culture. CROI Feb 23-26, 2015, Seattle WA Abstract #91

Pipeline: Presumptive TB

- Hard to get sputum
  - A young child or infant who can't expectorate
  - An adult with dry or ineffective cough
    - With reasons not to do bronchoscopy to obtain specimen
    - Setting with no bronchoscopy available
- Dangerous to get sputum
  - Aerosolizing droplet nuclei
- Time consuming and dangerous to process sputum for culture
  - BSL3 not widespread

5 Studies of Stool as Sample for Xpert

Noninvasive alternative specimens for Xpert

Oral swabs, string test, urine, and stool

1. 0.15g stool from 115 children with presumptive pTB: vortexed with 2.4mL PBS, allowed to sediment, used 2mL supernatant processed
   - 47% of 17 confirmed TB
2. Stool from 91 children <15y with presumptive pTB: direct method vs DNA extraction step (commercial Qiagen kit)
   - 100% of 6 confirmed TB
3. Stool from 48 sputum AFB smear-positive adults with confirmed TB
   - 100% sensitivity, 100% specificity in 37 nonTB controls
     - 8 smear-negative: 50% sensitivity

1. Nicol MP et al. Xpert MTB/RIF Testing of Stool Samples for the Diagnosis of PTB in Children. CID 2014;59(1):145
2. Welday SH et al. Stool as an Appropriate Sample . . . Open J Respir Diseases 2014;4:83-89
3. Kokuto H et al. Open Forum ID 2015;2(2): ofv074.

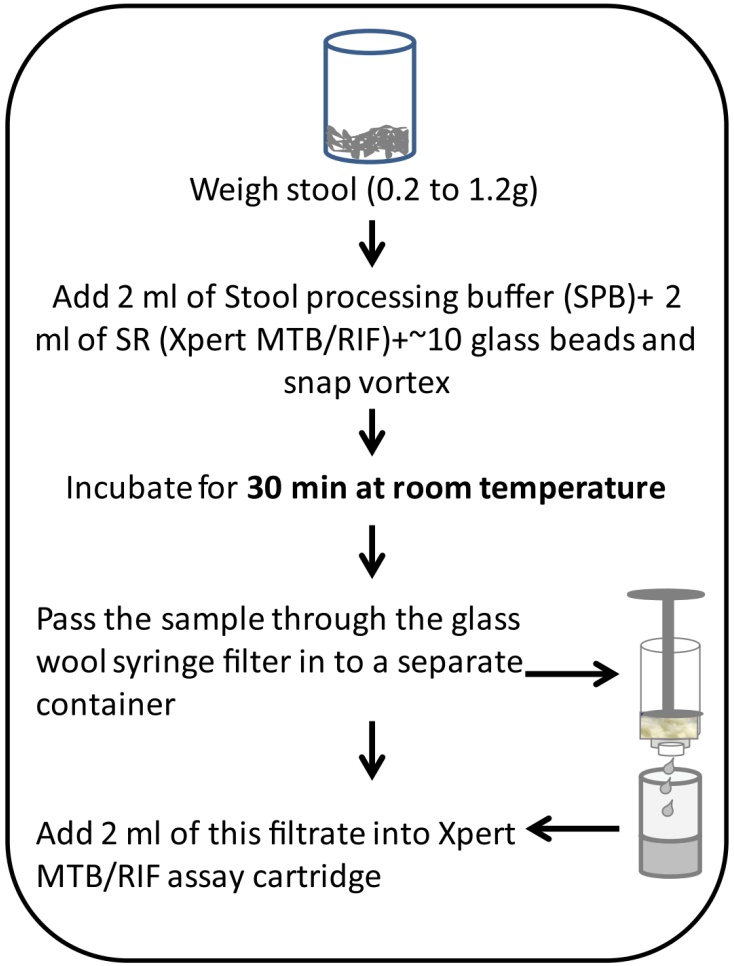
Stool Processed for Xpert

4. 379 children <13y with presumptive TB
   - 31.9% and 99.7% sens/spec
5. 218 children >5y with presumptive TB
   - 68% of 19 confirmed TB detected

- Confirmation costly, technically challenging, so these sensitivities with excellent specificity are appealing
- Stool processing needs simplification, automation
- March 2018, FIND and SA MRC announced trial of cost-negotiated, disposable stool processing kit for molecular tests

4. Walters E, et al. Pediatr ID J 2017; 35(9):837; 5. Chipinduro M et al. Stool Xpert test for diagnosis of childhood pulmonary TB at primary care clinics in Zimbabwe. Int JTBLD 2017

Novel Stool Sample Processing



- No need for centrifugation
- Simple and standardized
- Fewer errors from
  - Sample particulate
  - PCR inhibitors
- Larger allowed sample seems to increase sensitivity

Banada PP, et al. A Novel Sample Processing Method for Rapid Detection of TB in the Stool of Pediatric Patients Using the Xpert MTB/RIF Assay. PLoS ONE 11(3): e0151980. doi:10.1371/journal.pone.0151980

Smell as a Diagnostic Technology

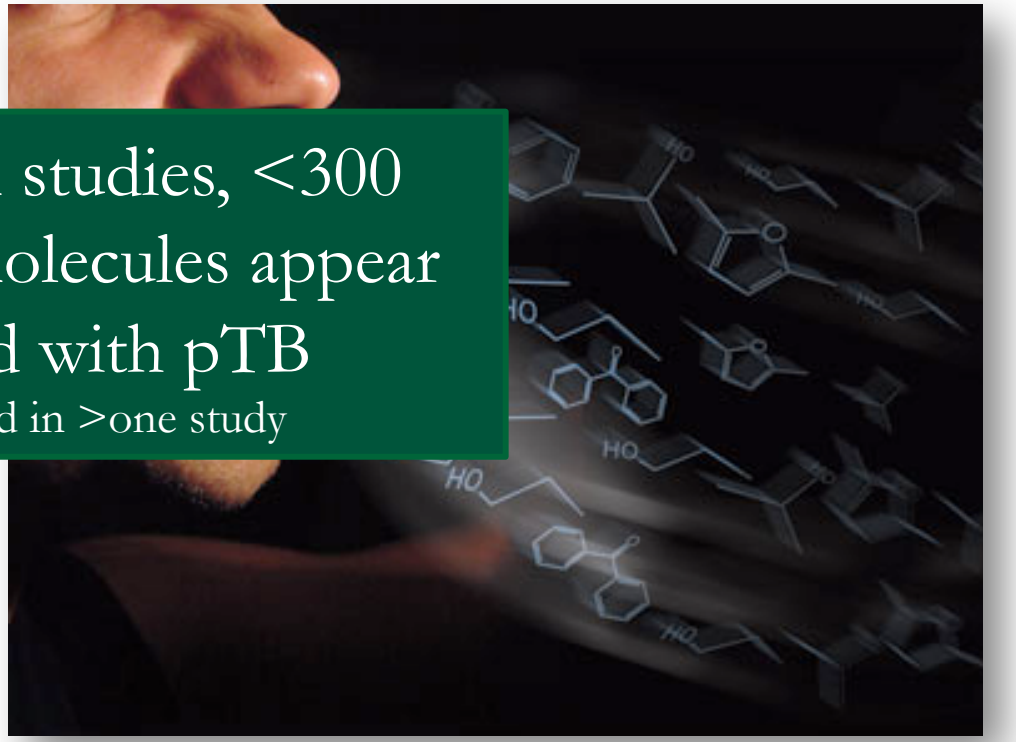
- Hippocrates
  - DKA=rotten apples
  - Renal failure=urine odor
  - Liver failure=fetor hepaticus
  - Lung abscess=sewer
- Since 1950's, breathalyzers
  - Alcohol
  - *H. pylori*
  - Heart transplant rejection
  - Breast and lung cancer
  - Malabsorption, bacterial overgrowth

Breath-based TB Diagnosis Complexities

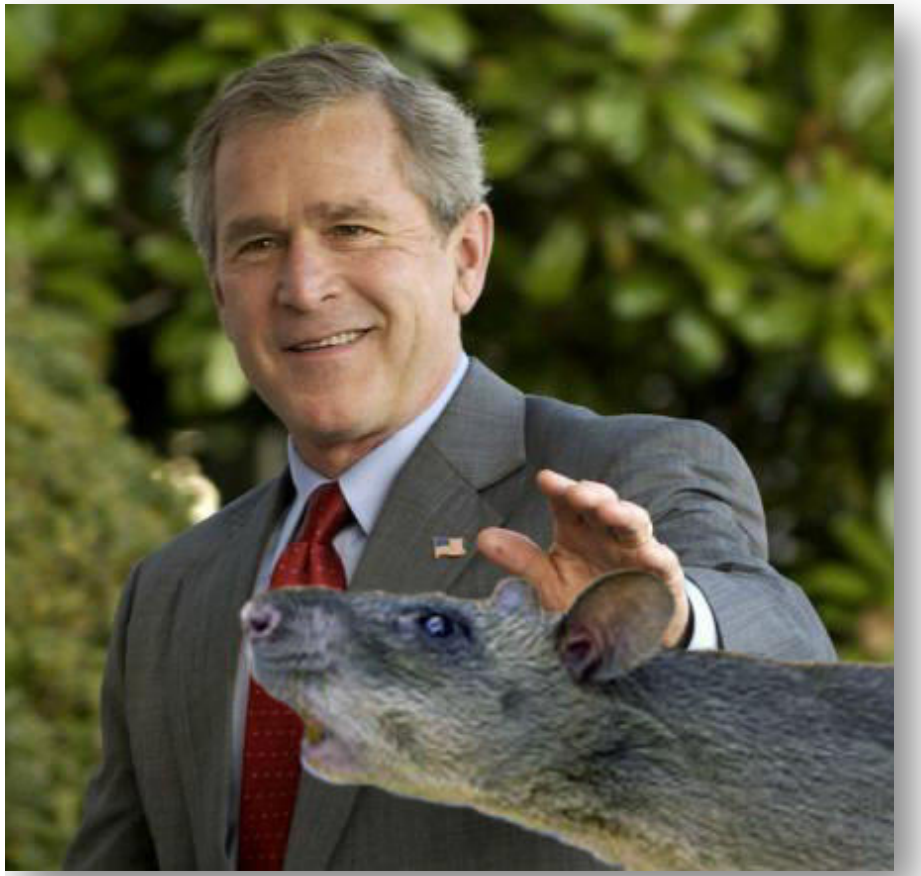
- Desirable because of biosafety, complexity of culture and challenge obtaining
- But questi
  - Breath f
  - Collecti storage
  - Approach as to whether pattern analysis or specific molecules
  - Detection systems e.g., sensor arrays or GCMS

Of 6 human studies, <300 patients, 47 molecules appear associated with pTB

1/47 reported in >one study



HeroRATS: Proof of Principle



- APOPO: Belgian NGO Anti-Persoonmijnen Ontmjinende Product Ontwikeling
  - Collaboration with Sokoine University of Agriculture
- 1996 established in Morogoro Tanzania to train giant Gambian rats to detect landmines

Why Rats?

- For landmine detection, excellent detection of volatile TNT from increasingly dilute water solutions
  - 4 rats evaluate 100 samples/d for 6 days
    - Detect 1 femtogram of TNT/liter of air
      - 1.3E-03 parts per trillion
    - Average sensitivity 80% and 4% false positive
- Friendly, easy to breed, easy to train (4-10m), live 4y
- Can they also detect TB?

HTTPS://WWW.YOUTUBE.COM/WATCH?V=VRZPEFCUNJC

6 Pubs on 53,668 Sputa from >24k Patients

- Weetjens BJ et al. *African pouched rats for the detection of pulmonary tuberculosis in sputum samples.* Int J Tuberc Lung Dis, 2009. 13(6): p. 737-43.
- Mgode GF et al. *Diagnosis of Tuberculosis by Trained African Giant Pouched Rats and Confounding Impact of Pathogens and Microflora of the Respiratory Tract.* Journal of Clinical Microbiology, 2012. 50(2): p. 274-280.
- Mgode GF et al. *Mycobacterium tuberculosis volatiles for diagnosis of tuberculosis by Cricetomys rats.* Tuberculosis (Edinb), 2012. 92(6): p. 535-42.
- Mgode GF et al. *Ability of Cricetomys rats to detect Mycobacterium tuberculosis and discriminate it from other microorganisms.* Tuberculosis, 2012. 92(2): p. 182-186.
- Mahoney A et al. *Pouched Rats' Detection of Tuberculosis in Human Sputum: Comparison to Culturing and Polymerase Chain Reaction.* Tuberculosis Research and Treatment, 2012.
- Reither K et al. *Evaluation of Giant African Pouched Rats for Detection of Pulmonary Tuberculosis in Patients from a High-Endemic Setting.* PLoS ONE, 2015. 10(10): p. e0135877.

Efficiency, Accuracy

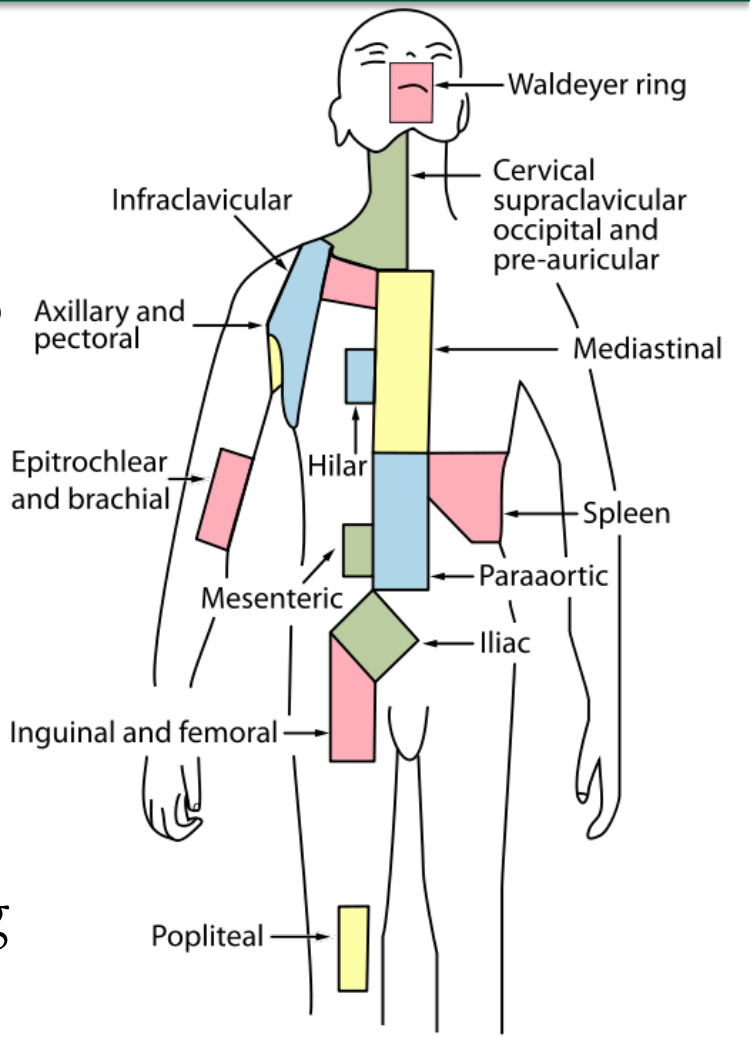
- Analyze 70 samples in <20 minutes
  - Microscopists do not exceed 20/d
  - Xpert module 16/day
- Sensitivity and specificity
  - Microscopy: 91-96% and 74-97%
  - Culture and/or Xpert: 56.9-86.6% and 72.4-89.1%
- Performance impacted by coinfection with other bacteria or fungi and number on "diagnostic rat team" (2-4)
  - No impact by HIV status

HeroRATS: Operational

- Programmatic use in Tanzania, Mozambique, Ethiopia
- Proof of principle
  - Identification of specific molecules and patterns
  - Hand held machine development for point of care

Case: Globus with History of LTBI

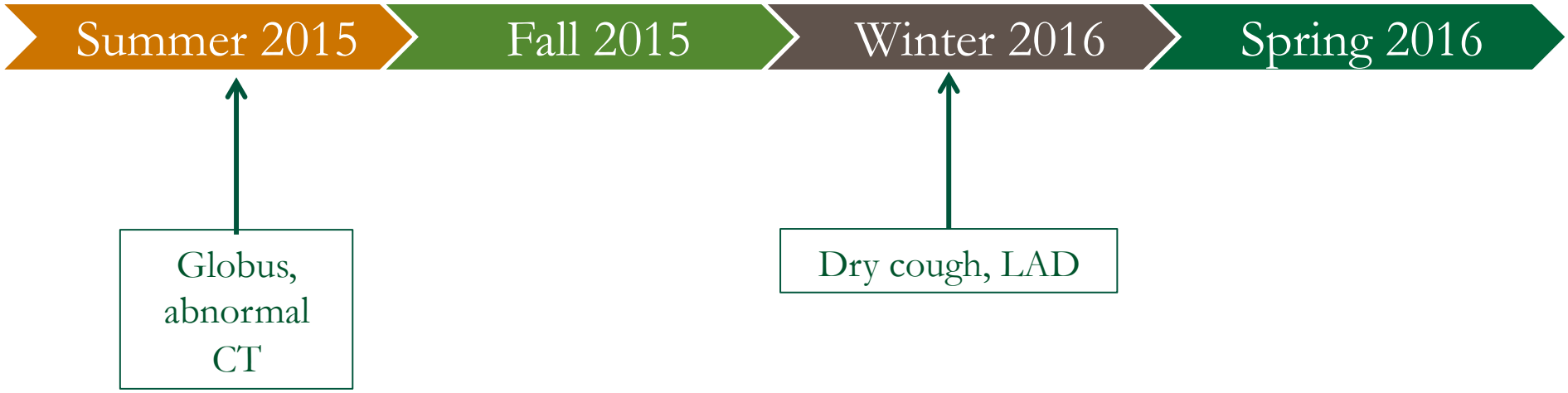
- 41M from Bhutan via Nepal
  - 1996 purulent right cheek lump resected in Nepal
  - 2009 came to US
    - TST positive, neg CXR[1]
    - 9m INH through July 2010
- July 2015 develops globus
  - CT#1 prominent Waldeyer ring



By Lymph_node_regions.jpg: http://training.seer.cancer.gov/ss_module08_lymph_leuk/lymph_unit02_sec02_reg_lns.htmlderivative work: Fred the Oyster - Lymph_node_regions.jpg, Public Domain, https://commons.wikimedia.org/w/index.php?curid=9828280

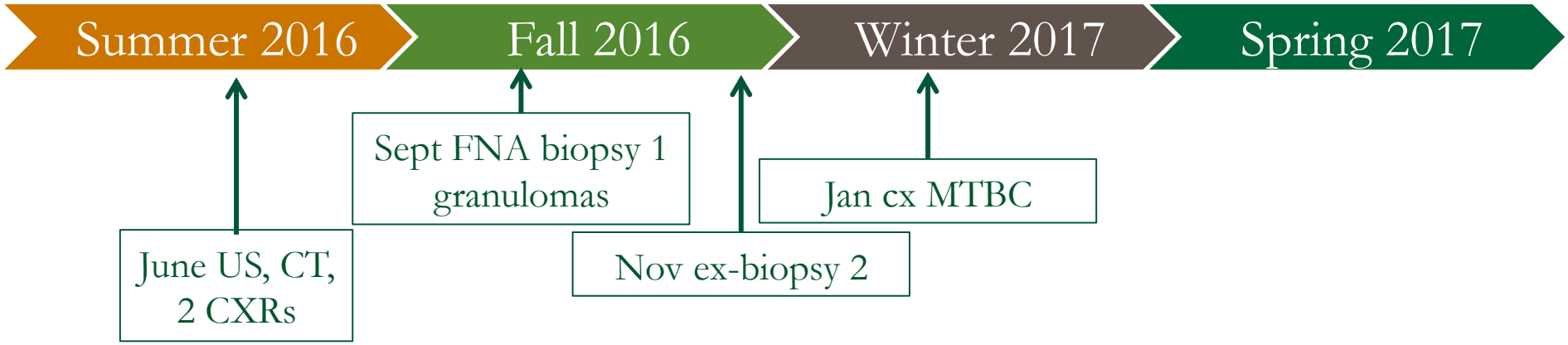
Patient, Clinician Delay

In patient at high risk for TB, previously LTBI treated:



Patient, Clinician, Organism Delay

In patient at high risk for TB, previously LTBI treated:



Most important MDR TB question in northeast US

"COULD THIS BE MDR TB?"

Why Does He Have TB?

1. He did not complete treatment
2. He's been re-infected
3. 9m INH treatment not effective
   - He got poor quality, wrong dose *or*
   - He had MDR LTBI so INH had no power to prevent TB

Victor Hugo's character Fantine (*Les Miserables*)
1886 painting by Margaret Bernadine Hall

Risk Factors for MDR TB

- Caused when TB drugs are misused or mismanaged
  - Patient does not complete full course of TB treatment
  - Providers prescribe wrong treatment (drug, dose or duration)
  - Drugs are not available or of poor quality
- Drug-resistant TB is more common in people who
  - Do not take their TB drugs regularly or completely
  - Have spent time with someone with drug-resistant TB
  - Develop TB disease after being treated for TB disease
  - Come from areas where drug-resistant TB is common
    - Nepal 2.2% new and 15% retreatment cases have MDR
    - Bhutan 38% retreatment cases have MDR

Corollary topic for public health and clinicians in the northeast US

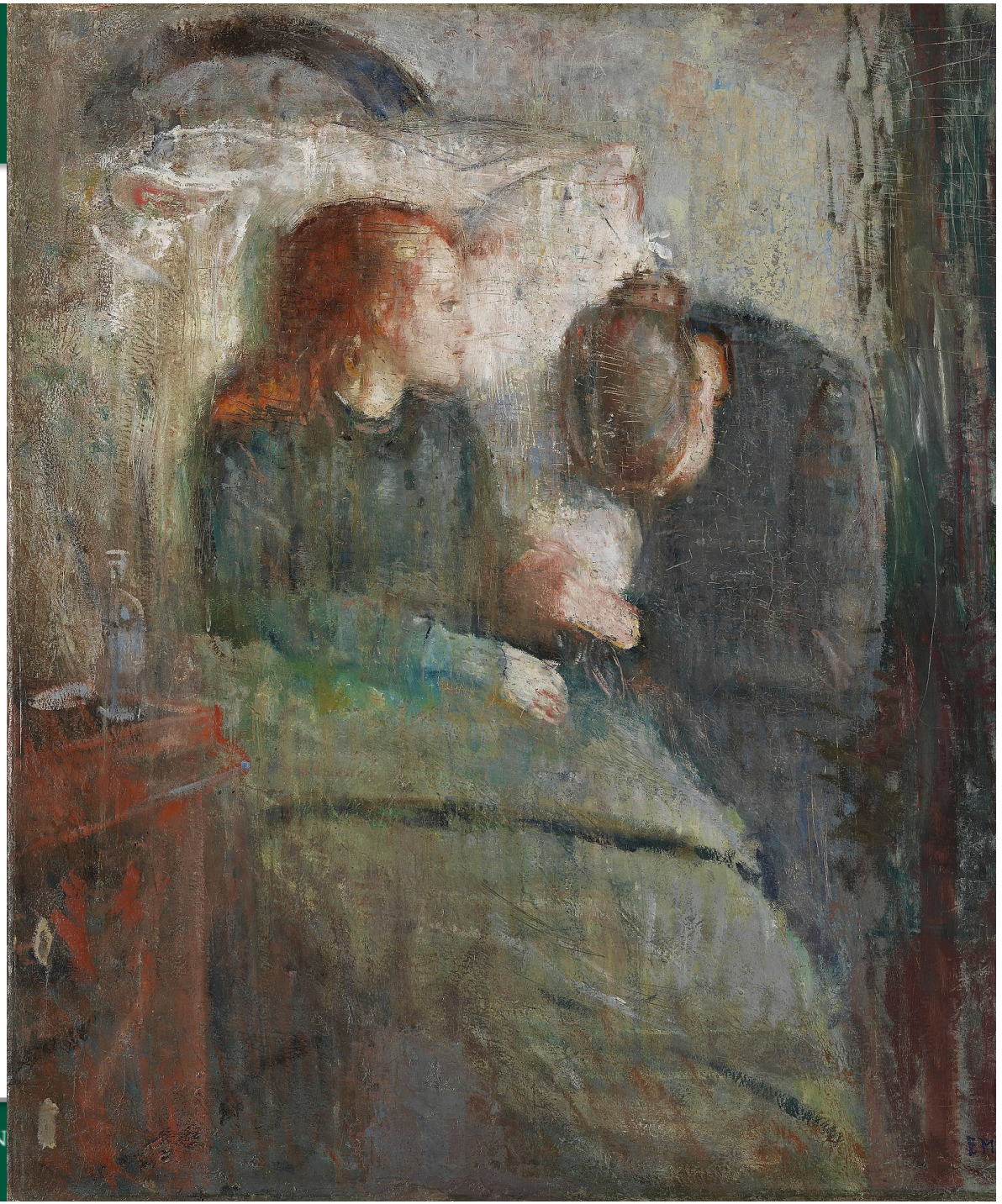
HOW DO I DIAGNOSE MDR TB?

Detecting MDR TB in the U.S.

Method	Description	Advantages	Disadvantages	Sens/Spec	Time
Proportion method	Solid (agar) culture	Conventional	Expertise, BSL3, time	(Reference)	<42d
MGIT DST	Liquid culture DST	Automated or manual	Expertise, BSL3, time, cost, contamination (10%)	100/99	10-22d
Cartridge-based NAAT (GeneXpert)	Automated modular PCR	Fast, simple, accurate, RR	Cost, only rifampin resistance	TB: 88/98 RIF: 94/98	90min
Line Probe Assay (Hain, INNO LiPA)	Molecular probes for detection of DR mutations	Fast, accurate, cost less than MGIT	Expertise, culture isolate or sm+ sputum, lab space, still need culture capacity	85-98 sens 99 specif	6h
MDDR	Probe for genes known associated with DR	MDR confirmation, SLD info	Approval through TB program, not all mutations identified yet	Varies	Few days
Sequencing	Whole or targeted genome	Surveillance method	Not practical as clinical tool	Varies	Few days

Next Steps?

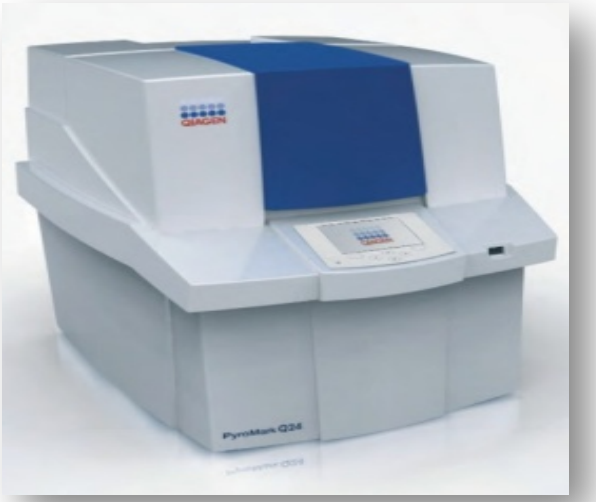
- Clinicians delay treatment until phenotypic DST
- NH DHHS sent specimen for Molecular Detection of Drug Resistance (MDDR)



Edvard Munch, *The Sick Child*, 1885–86, Nasjonalgalleriet, Oslo

Molecular Detection of Drug Resistance

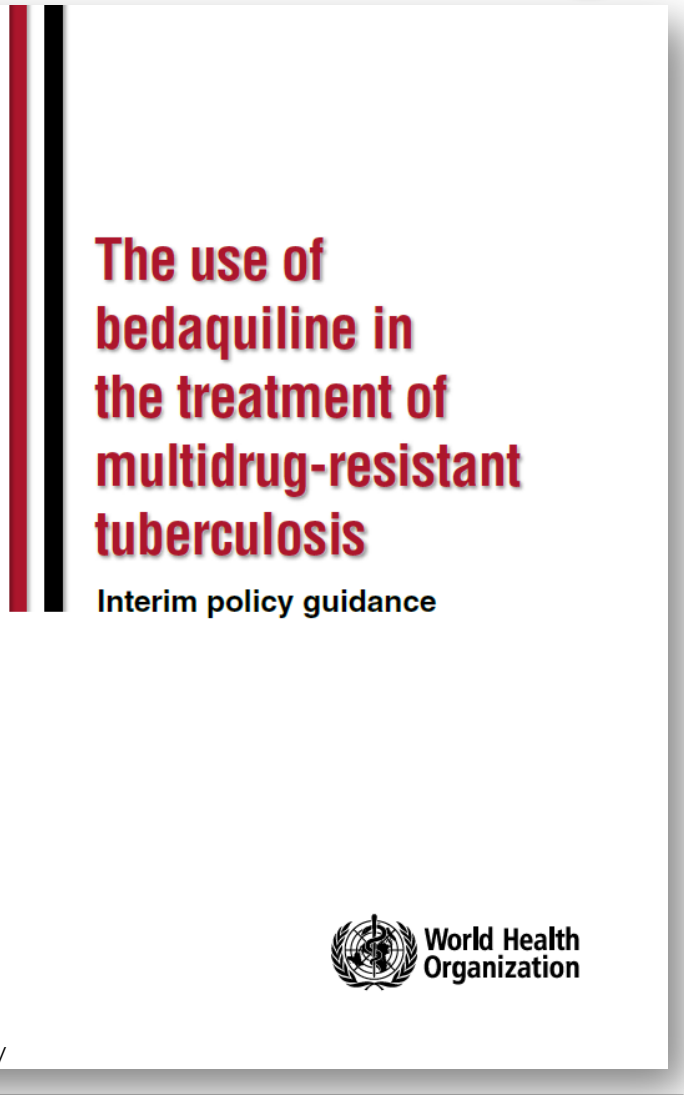
- Examine DNA of specific genes for mutations known to be associated with phenotypic resistance
  - Not all mechanisms of resistance are known
    - Absence of mutation does not necessarily mean susceptible
- Since 2009, available to TB control programs
  - Rapid MDR TB confirmation
  - Second line drug resistance
- (Easy) approval process



Pyrosequencing instrument used for MDDR

Sirturo (Bedaquiline, J+J)

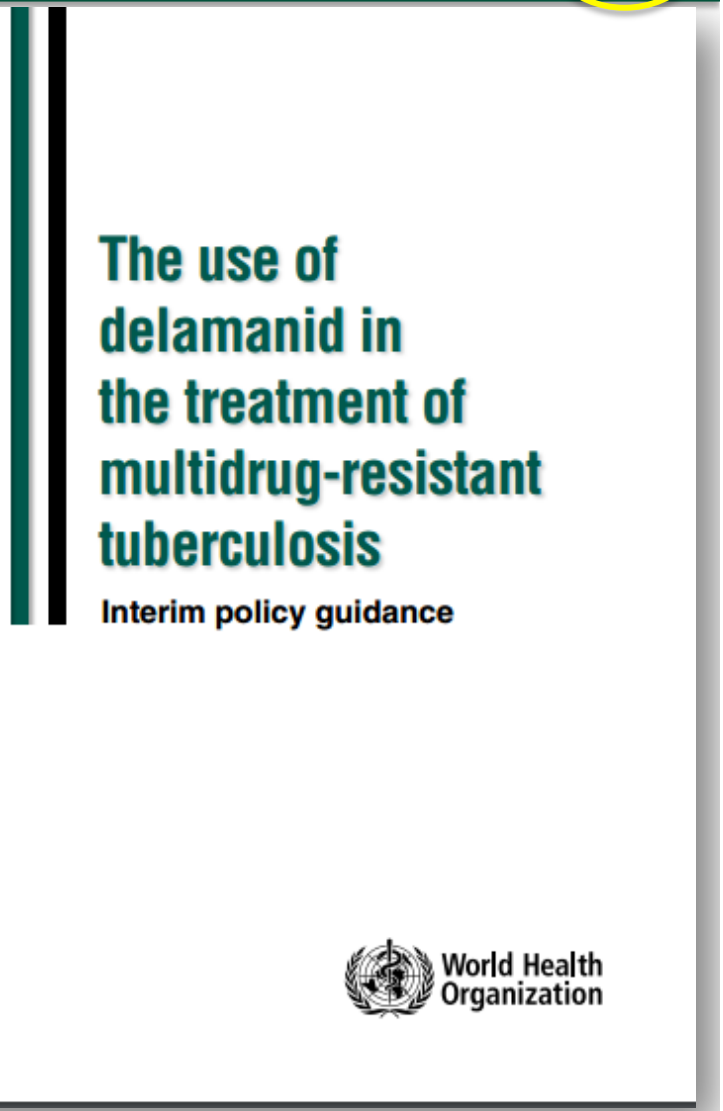
- Approved 2012
  - First new TB drug since 1970
- Diarylquinolone: inhibits ATP synthase
- First in its class, no resistance
- Common side effects nausea, joint pain, HA
  - QTc prolongation



www.who.int/tb/challenges/mdr/**bedaquiline**/en/

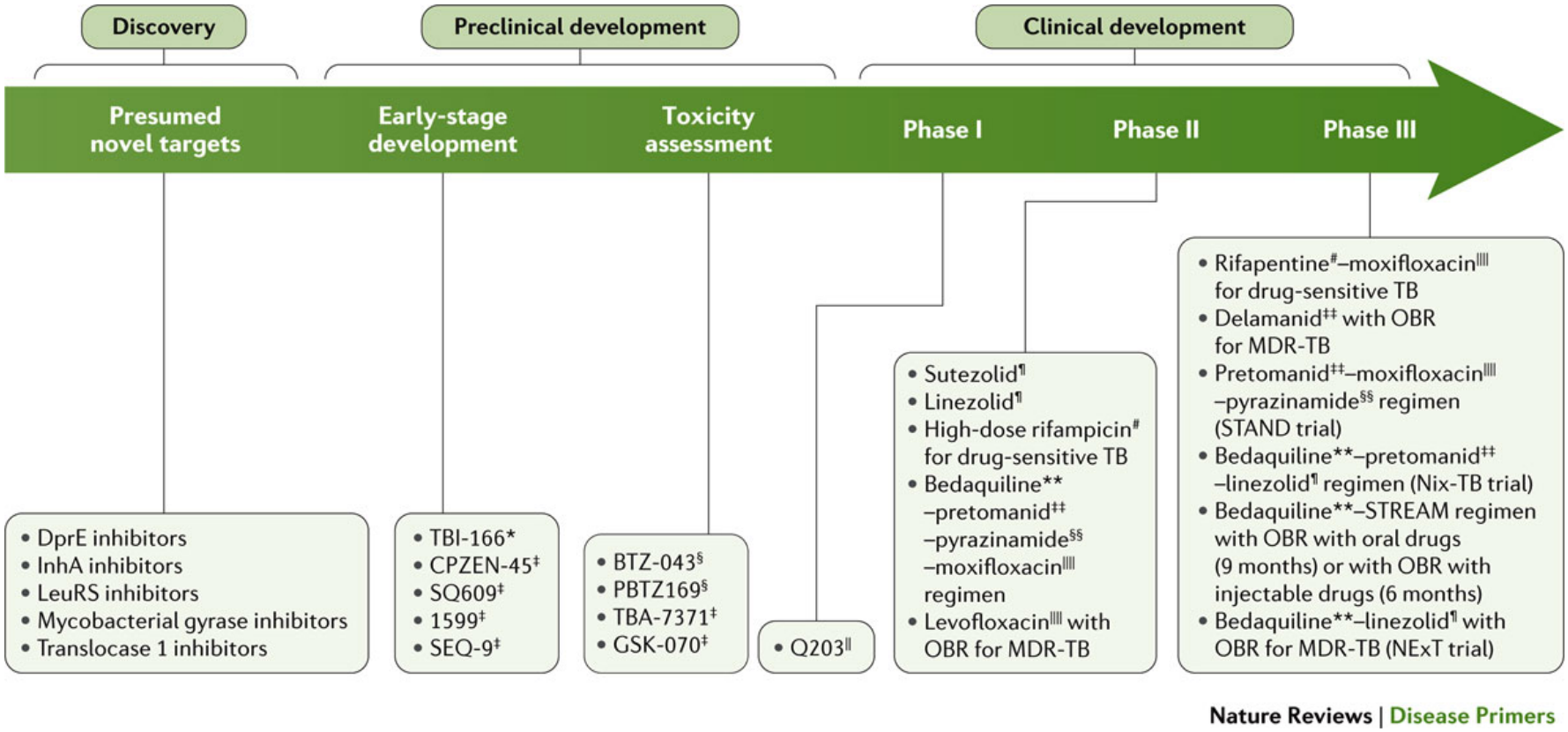
Delaminid (Otsuka)

- Nitro-dihydroimidazooxazole derivative: inhibits mycolic acid synthesis
- April 2014 approval
- No resistance yet
  - No tests either!
- Boxed Warning: QT prolongation
- Common side effects HA, nausea and dizziness



WHO_HTM_TB_2014.23_eng.pdf

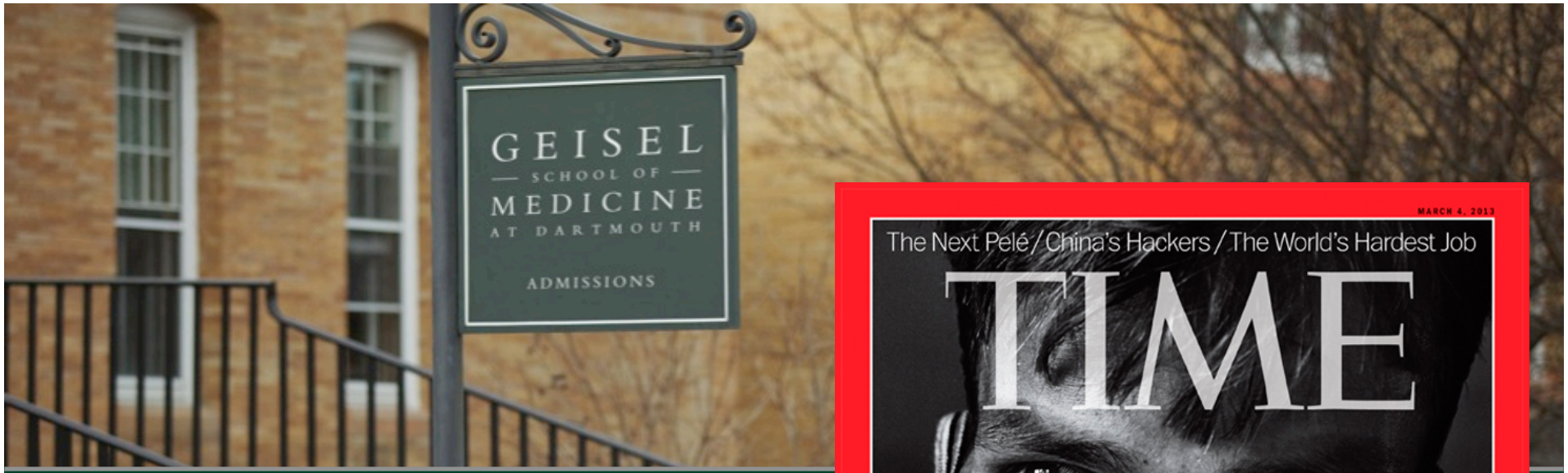
Global TB Drug Pipeline



Pai, M. *et al.* (2016) Tuberculosis. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

Conclusion

- We must be ready to assist in efficient diagnosis of LTBI, TB and MDR-TB
- New guidelines available
- Both TST and IGRAs have issues of specificity
- Xpert improving, underutilized
- M/XDR TB awareness
- Xpert, MDDR, other methods available


GEISEL
SCHOOL OF
MEDICINE
AT DARTMOUTH
ADMISSIONS

THANKS!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TIME
CONTAGION
Why drug-resistant tuberculosis threatens us all
BY KRISTA MAHR WITH PHOTOGRAPHS BY JAMES NACHTWEY
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