1, 2, 3s to Diagnose Tuberculosis

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The Ohio State University
Wexner Medical Center

Objective:

- Diagnosis of TB (Not including pediatrics)
  - 1. Importance good history and physical:
    - Symptom screen
    - Prior TB exposure or history of prior treatment
    - Physical exam
    - Presumptive diagnosis of TB
- Work-up
  - 2. Excluding the possibility of extrapulmonary TB
  - 3. Chest radiography:
    - PA/LAT, landmarks, common findings
  - 4.Tests for TB – (not include TST/IGRA)
    - Lab: smear, NAAT/PCR, culture, and drug susceptibility
  - 5. Report to Health Department
    - Even if it is presumed TB.

- History
- Symptom Screening
- Physical Examination

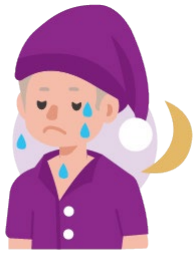
1

Clinical Case

- 54 year old male, US born
- Seen at Emergency Department with complaints of productive cough, discolored, non-bloody, worse at night
- Associated with fevers, chills, shortness of breath
- feeling well and lost 30 pounds

- What are some possible symptoms of TB?

Possible TB Disease Symptoms



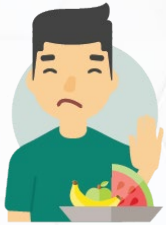
Night Sweats

Fever

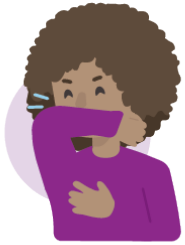
Chills

Weakness
or fatigue

Weight loss

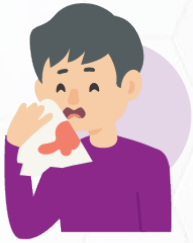


No appetite



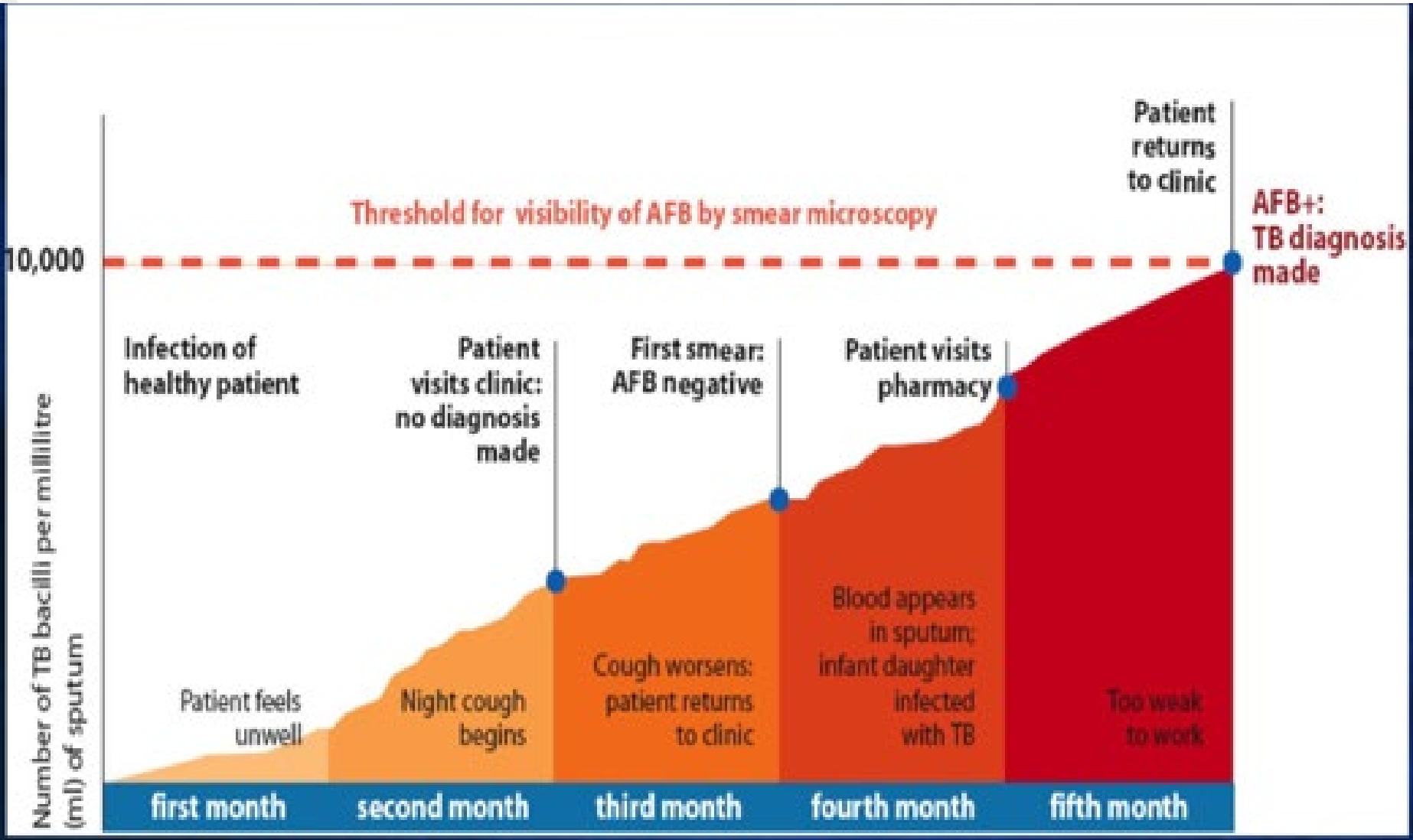
Cough lasting
longer than
3 weeks

Pain in
the chest



Coughing up
blood or sputum
(phlegm from inside
the lungs)

Delayed Diagnosis and Increased Transmission



Hopewell, Presentation entitled "Global Challenges in TB Care and Control"

People at high risk for developing TB disease generally fall into two categories:

- Those who have been **recently infected with TB germs**
- Those with **medical conditions that weaken the immune system**, such as:

HIV infection

Substance abuse

Specialized treatment for rheumatoid arthritis or Crohn's disease

Organ transplants

Severe kidney disease

Head or neck cancer

Diabetes

Medical treatments such as corticosteroids

Silicosis

Low body weight

Clinical Case

Past Medical History

Past Surgical History

Allergy

Medication

Review of System

Social History

Clinical Case

Past Medical History

Chronic obstructive pulmonary disease (COPD)
Hypertension
Diabetes
Hepatitis C
Alcoholism
Pneumonia - 6 months prior

Clinical Case

Social History

Homeless - ? Street

Sister, shelter, jail/prison

Smokes ½ Pack per day

Alcohol abuse: drinks daily ~ 40oz beer/day

No illicit drug use

Review of System
Physical Examination

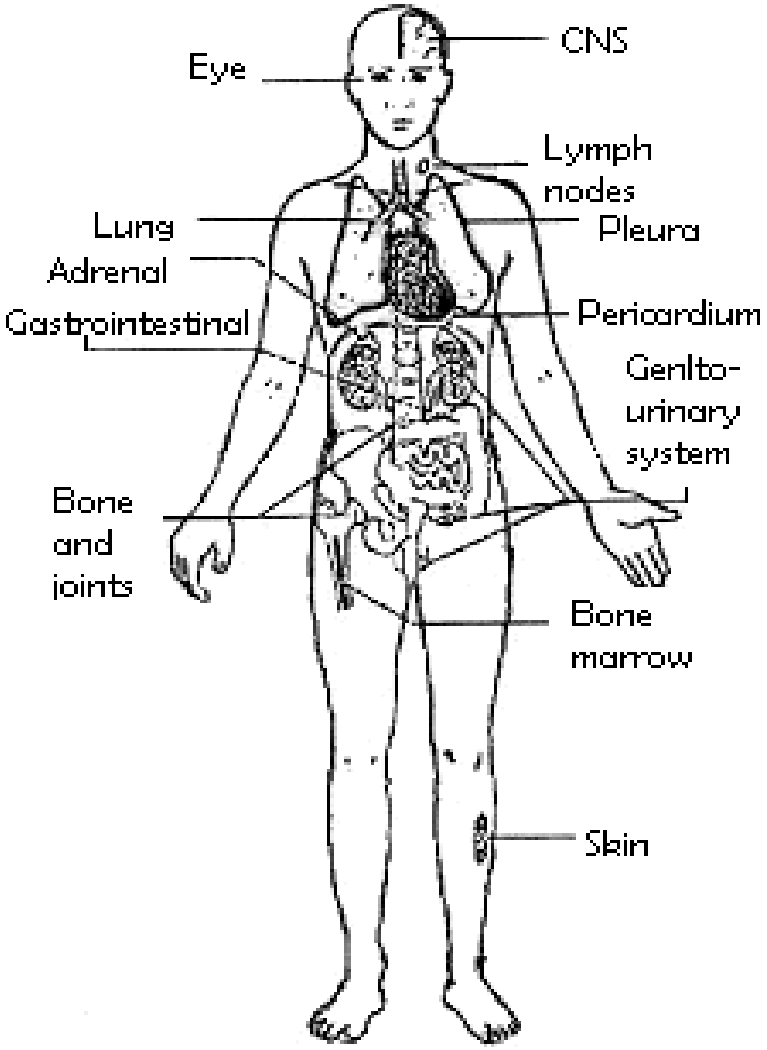
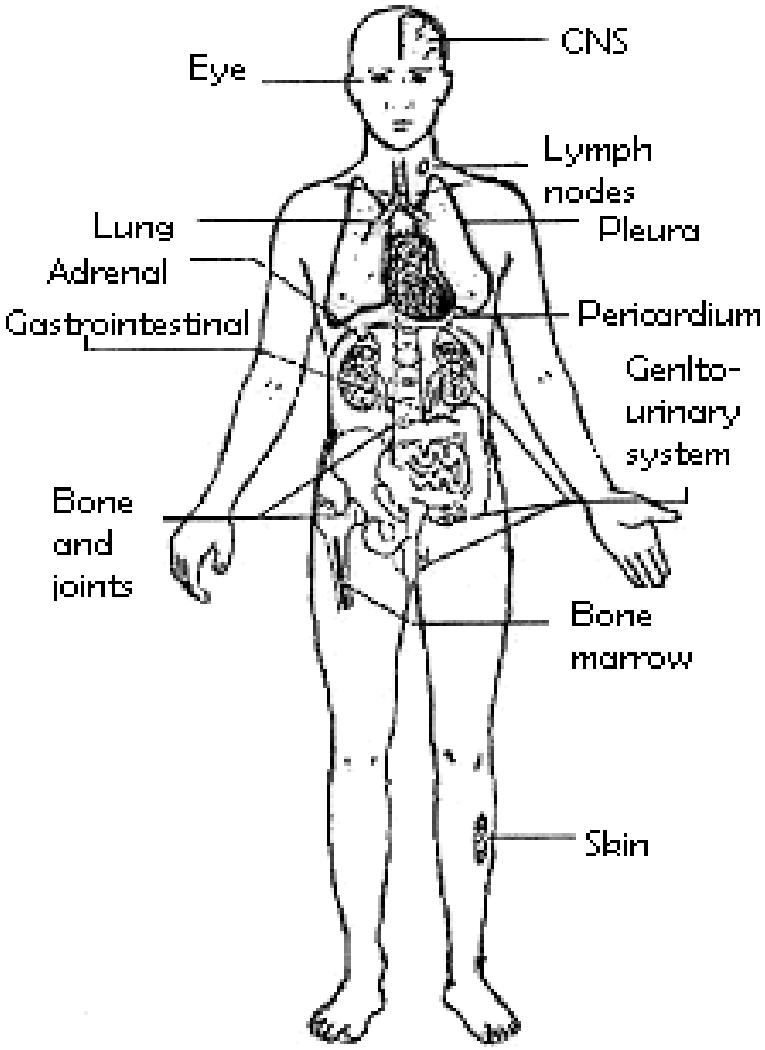
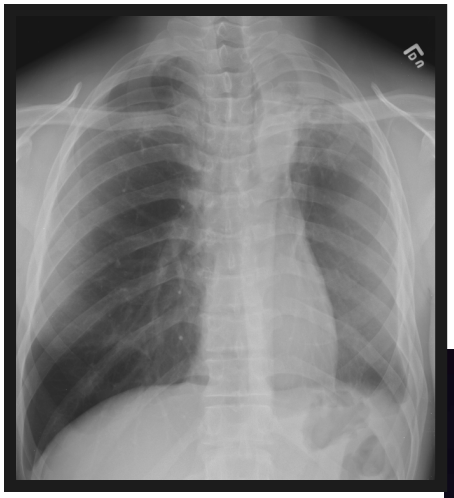
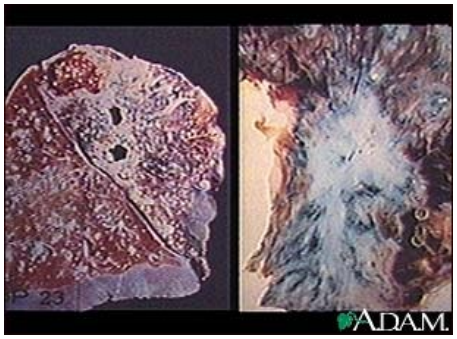


Photo CDC and ADAM

Common Sites of Active TB Disease







THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Photo CDC and ADAM

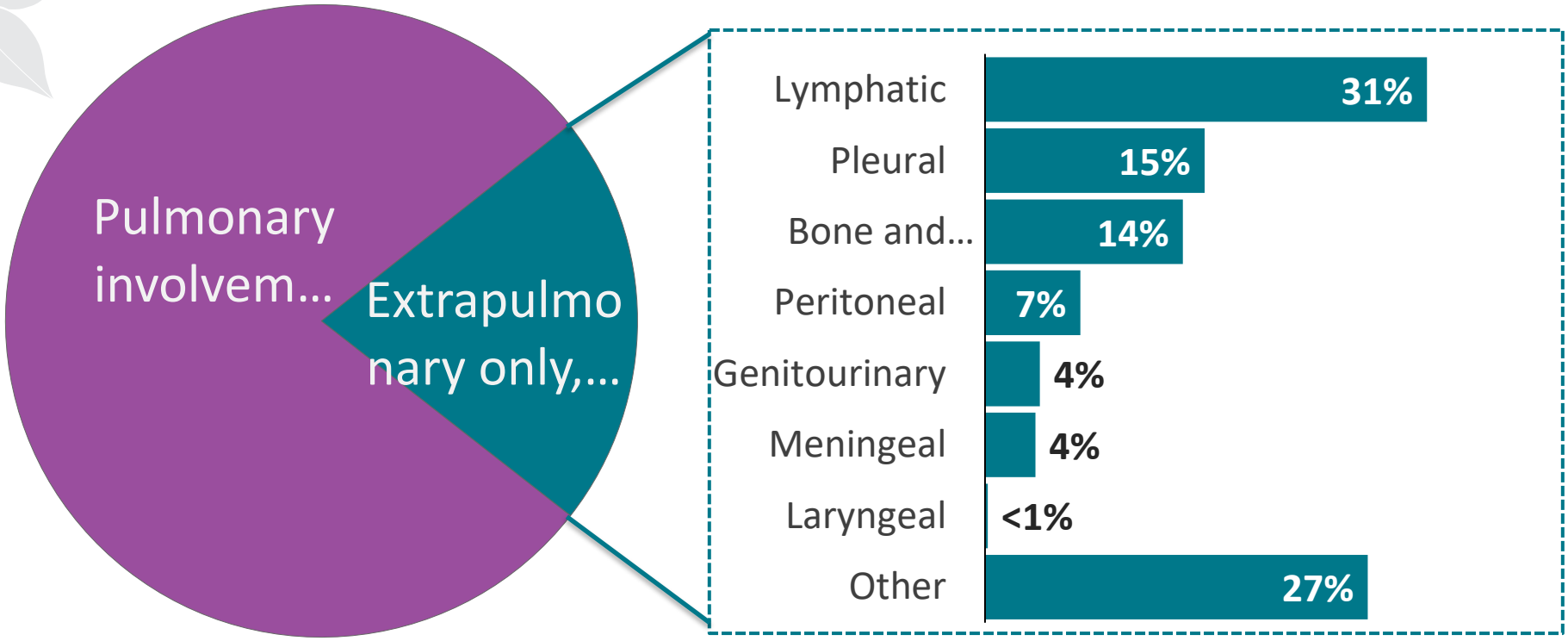
- Rule out - Extrapulmonary TB
- compare symptoms of pulmonary vs extra-pulmonary TB

2

Not Everyone Who Is Infected with TB Becomes Sick

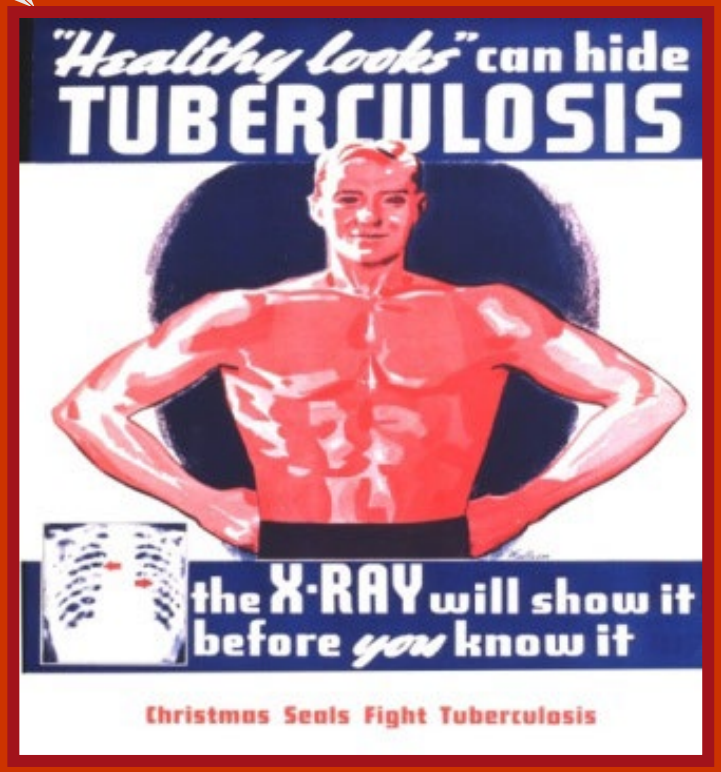
 Person with **Latent TB Infection**	 Person with **TB Disease**
Has a small amount of TB germs in his/her body that are alive but inactive	Has a large amount of active TB germs in his/her body
Cannot spread TB germs to others	May spread TB germs to others
Does not feel sick, but may become sick if the germs become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a positive TB skin test or TB blood test result indicating TB infection	Usually has a positive TB skin test or TB blood test result indicating TB infection
Should consider treatment for latent TB infection to prevent TB disease	Needs treatment for TB disease

Percentage of TB Cases by Site of Disease,* United States, 2021



*Patients may have more than one disease site but are counted in mutually exclusive categories for surveillance purposes.
†Any pulmonary involvement which includes cases that are pulmonary only and both pulmonary and extrapulmonary.

- Chest radiography – common views ordered and review some of the radiographic manifestations



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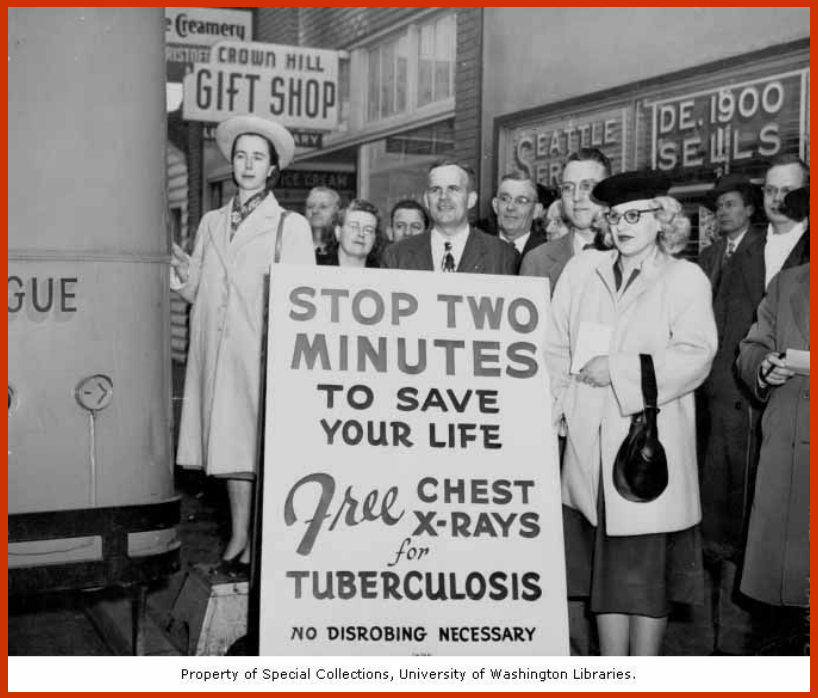

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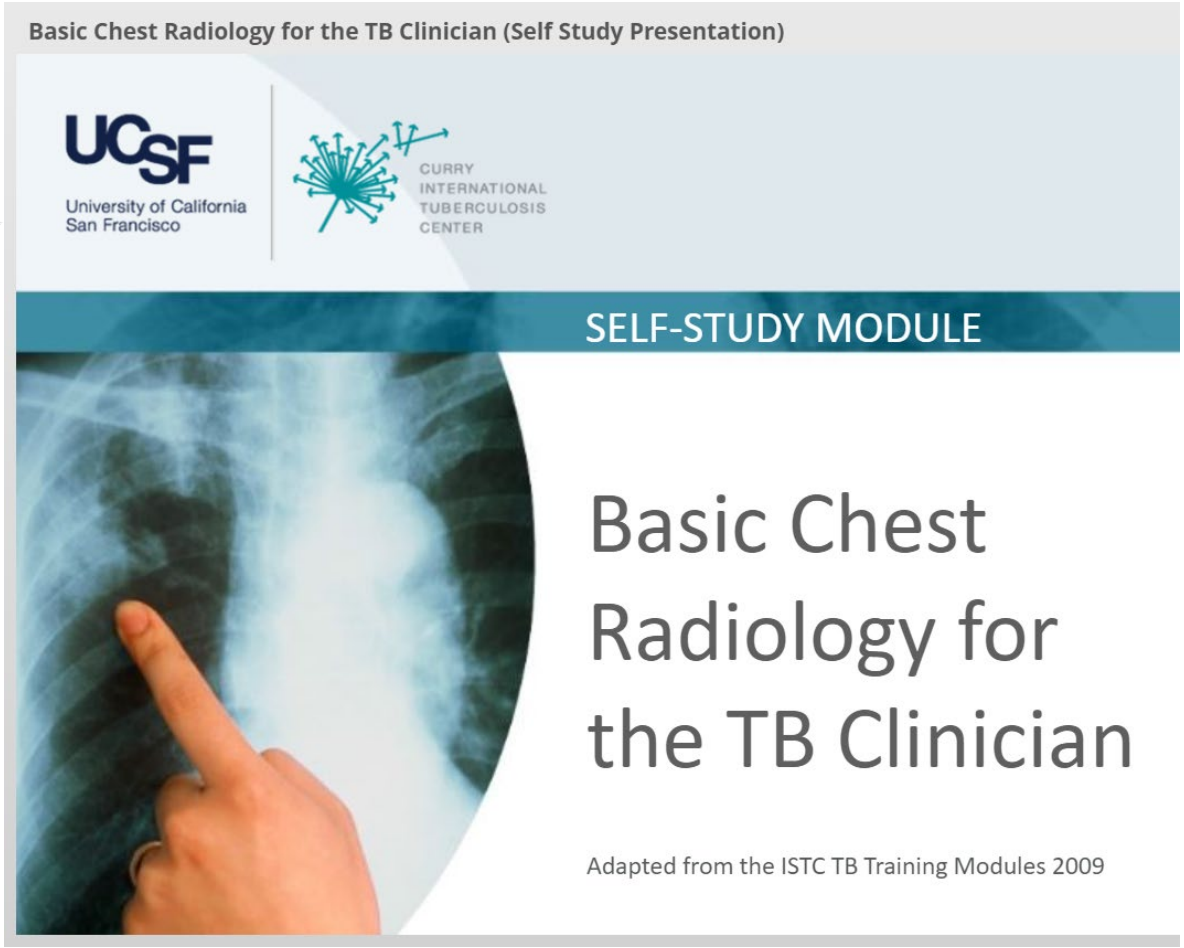


https://www.currytbcenter.ucsf.edu/sites/default/files/product_tools/chest_radiology/story.html

Basic Radiology for the TB Clinician

A systematic approach to reading a CXR

Image Credit: Lung Health Image Library/Gary Hampton

Basic CXR Anatomy

Frontal and Lateral Views

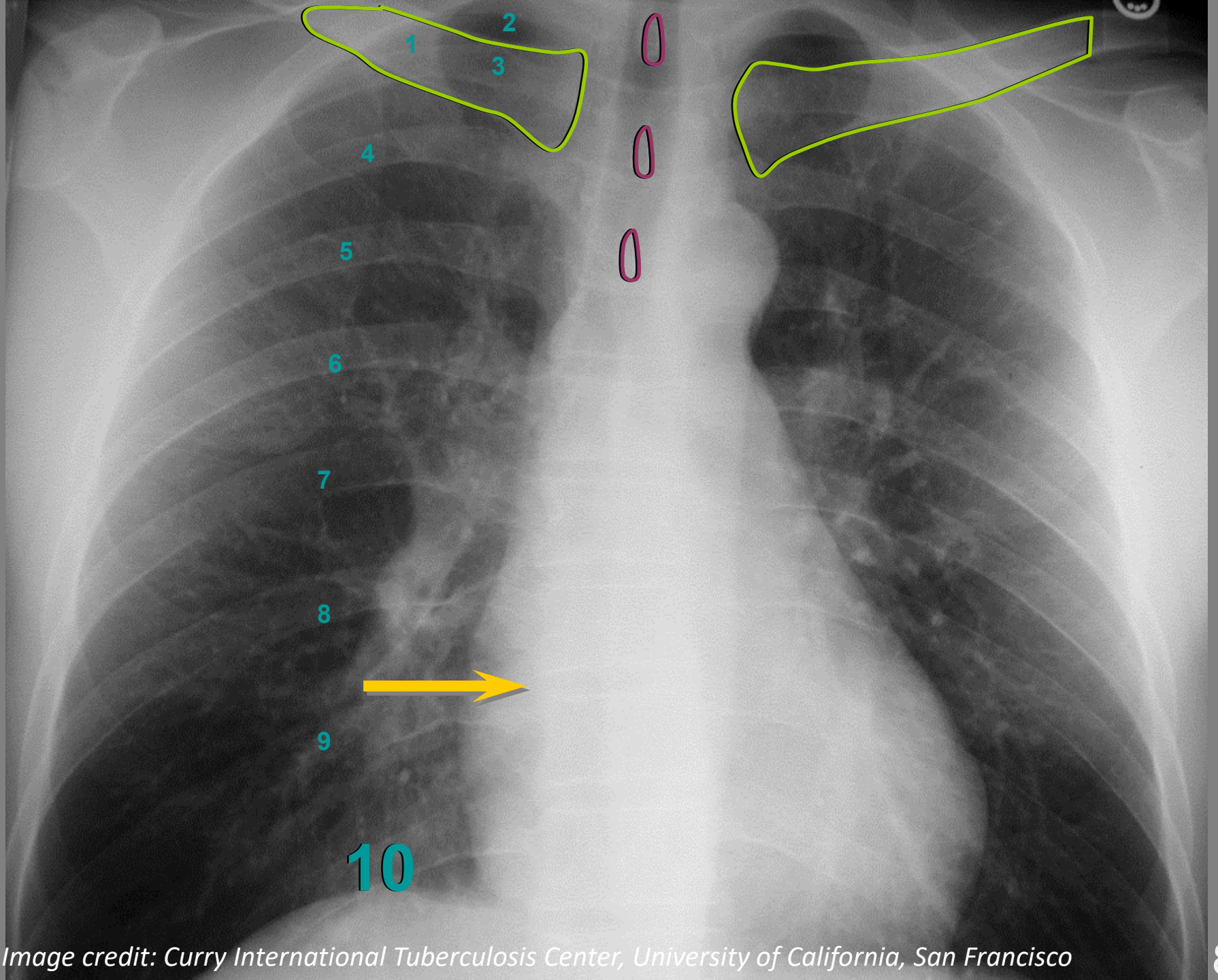
- Heart
- Aorta
- Pulmonary arteries
- Airways

Image Credit: Lung Health Image Library/Pierre Virot

Approach to Reading a CXR

- **Be Systematic**
- Lungs
- Pleural surfaces
- Cardiomediastinal contours
- Bones and soft tissues
- Abdomen

Image credit: Curry International Tuberculosis Center, University of California, San Francisco



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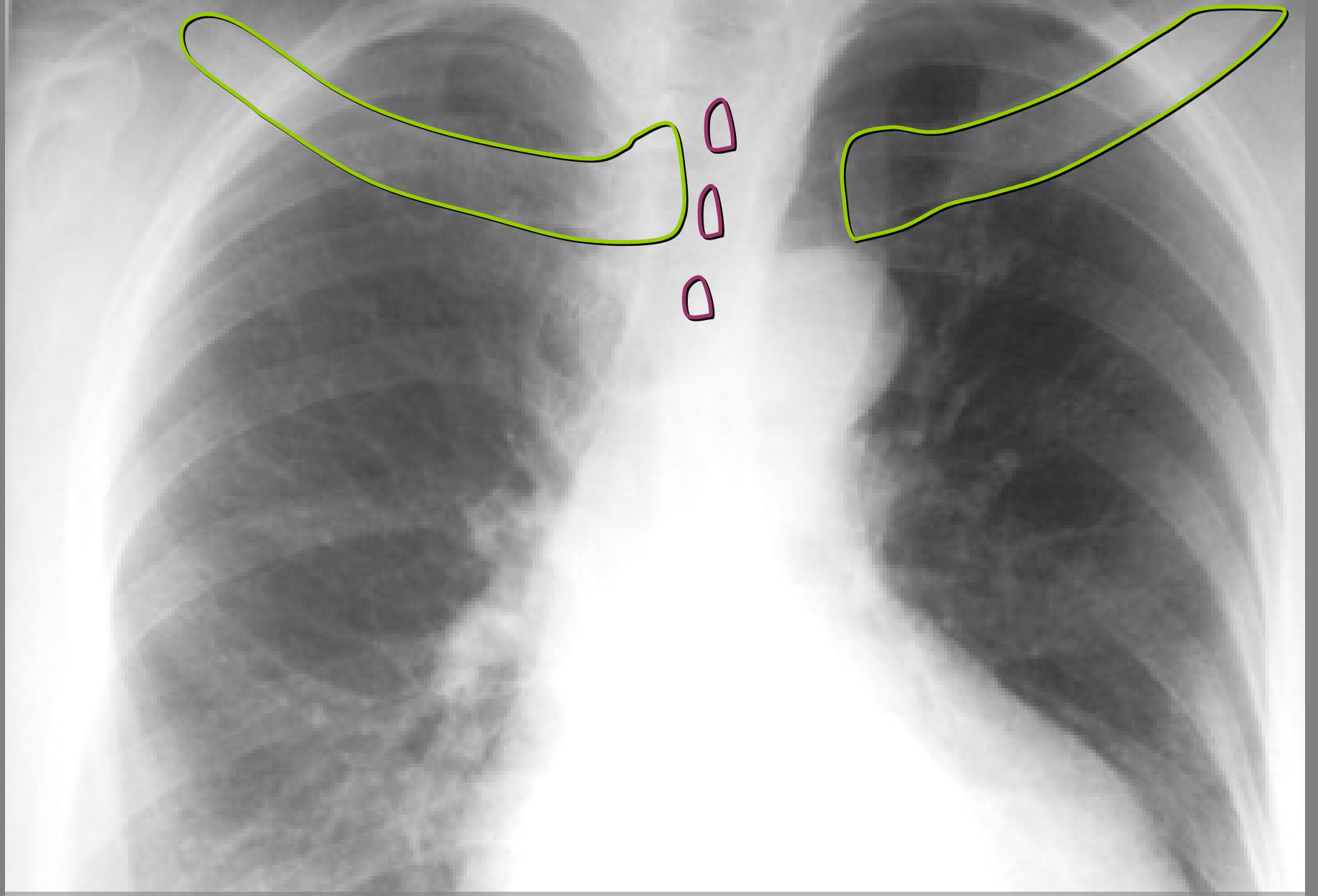


Rotated (Oblique)

Image credit: Curry International Tuberculosis Center, University of California, San Francisco


ZYGOTE

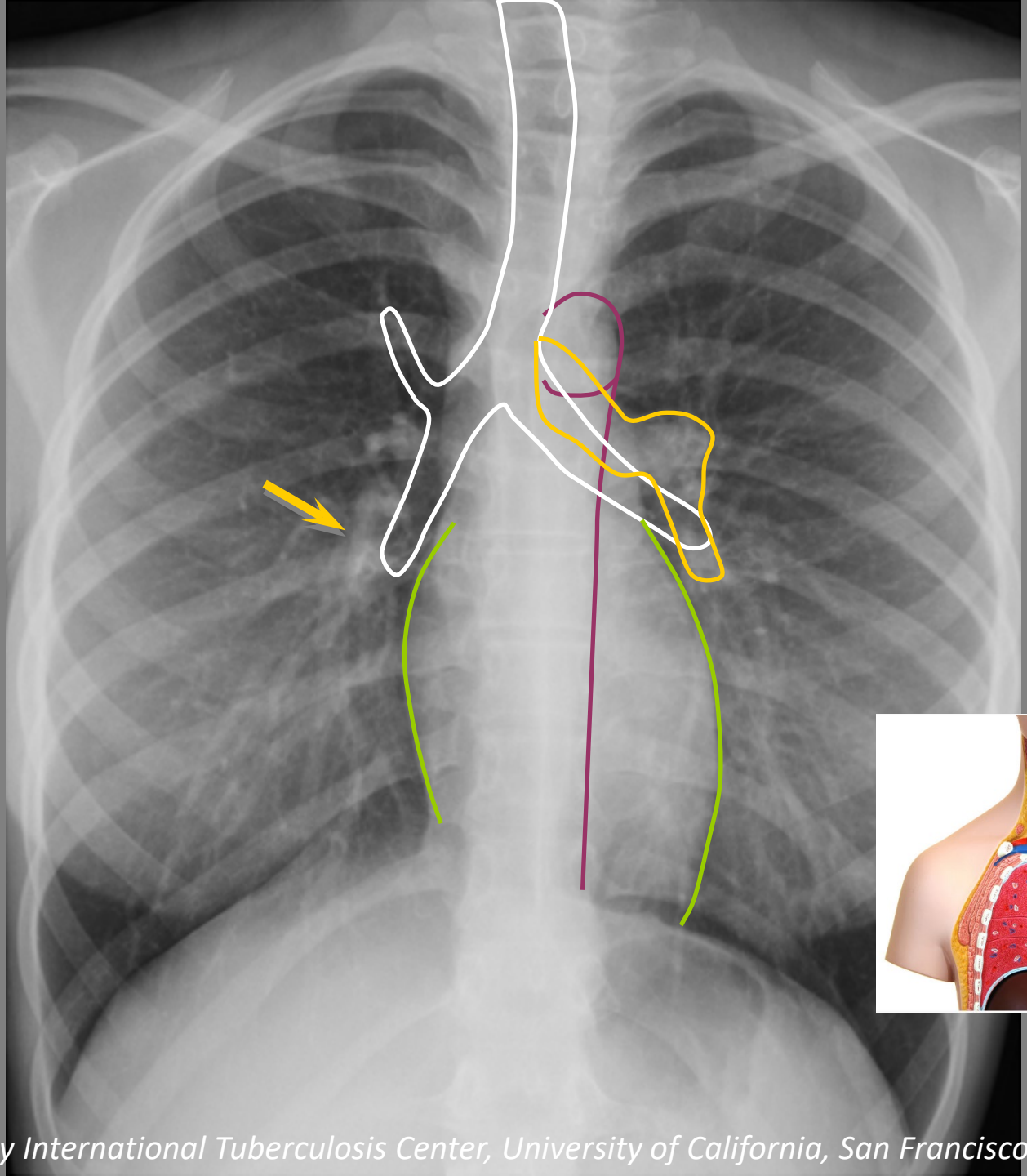


Image credit: Curry International Tuberculosis Center, University of California, San Francisco

- Aortic arch

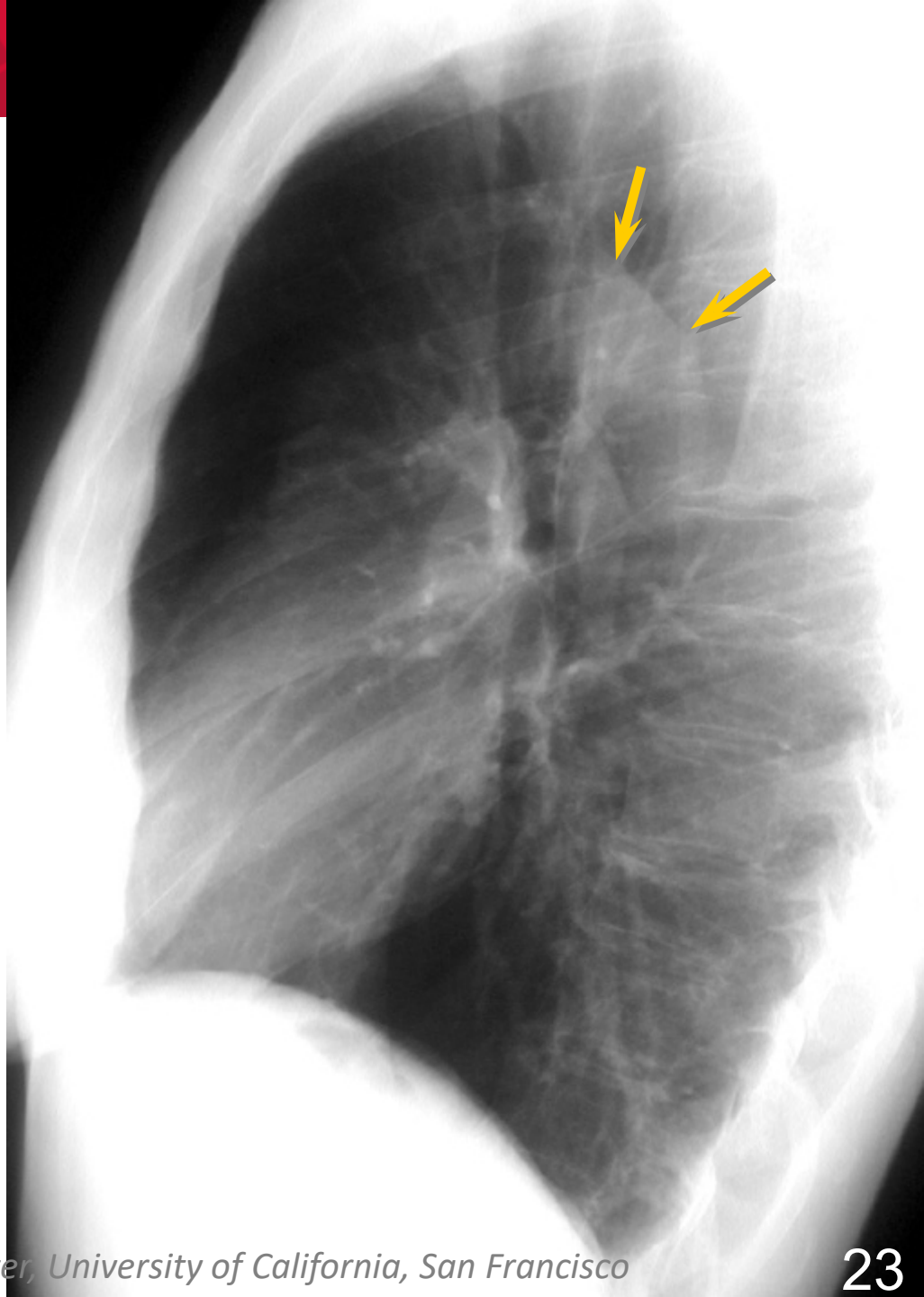


Image credit: Curry International Tuberculosis Center, University of California, San Francisco

- Aortic arch
- Right pulmonary artery

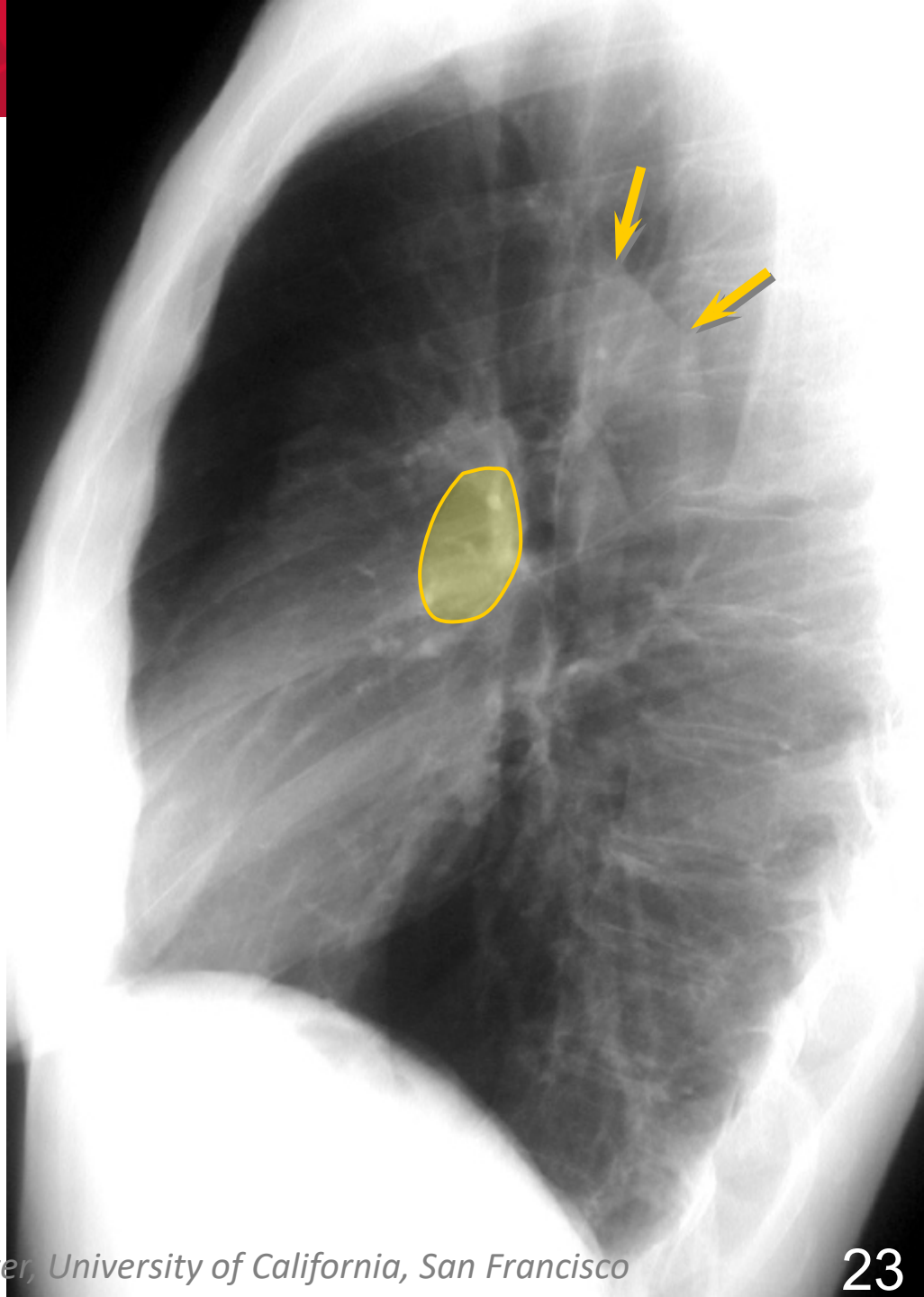


Image credit: Curry International Tuberculosis Center, University of California, San Francisco

- Aortic arch
- Right pulmonary artery
- Left pulmonary artery

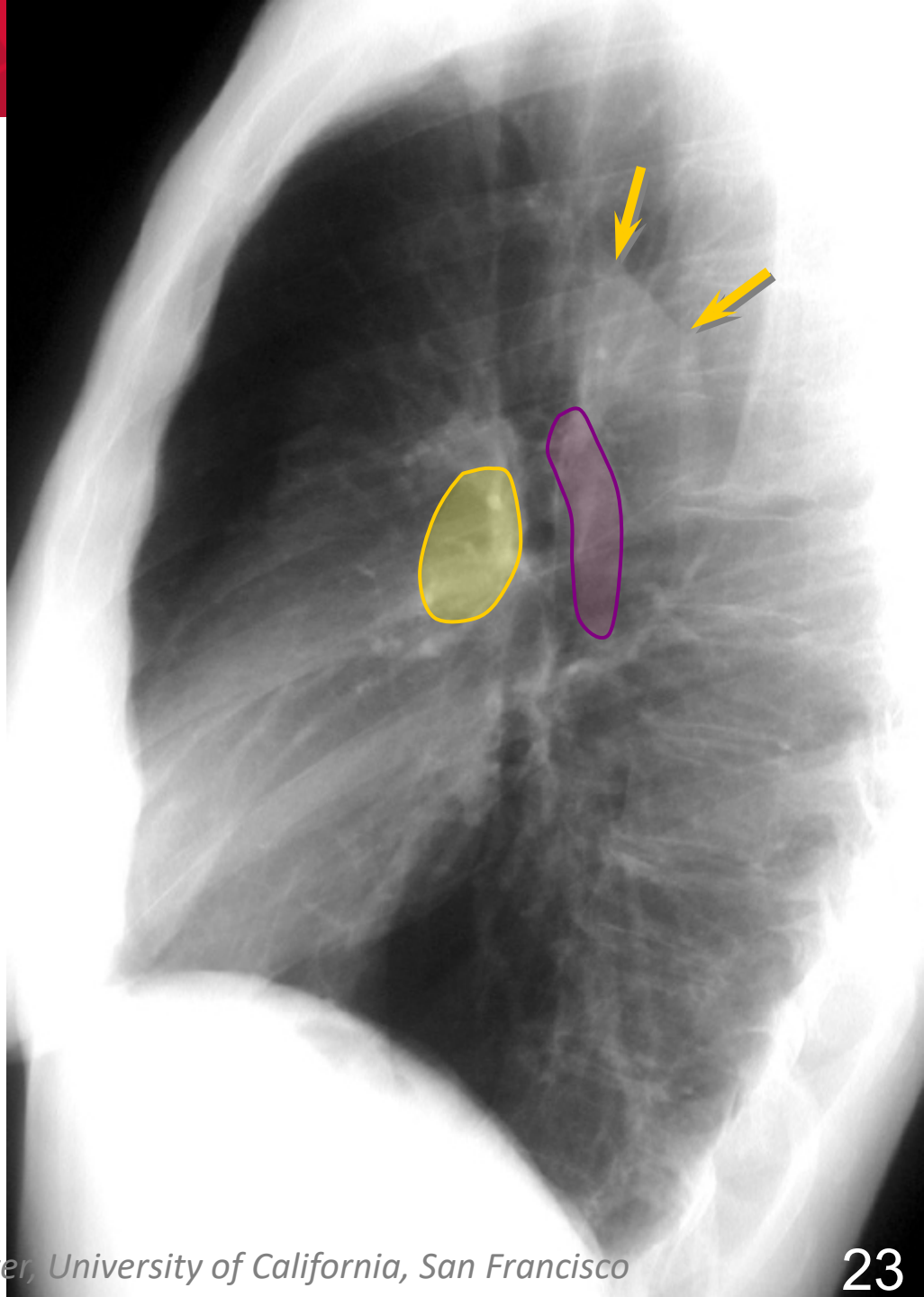


Image credit: Curry International Tuberculosis Center, University of California, San Francisco

- Aortic arch
- Right pulmonary artery
- Left pulmonary artery
- Trachea & bronchi

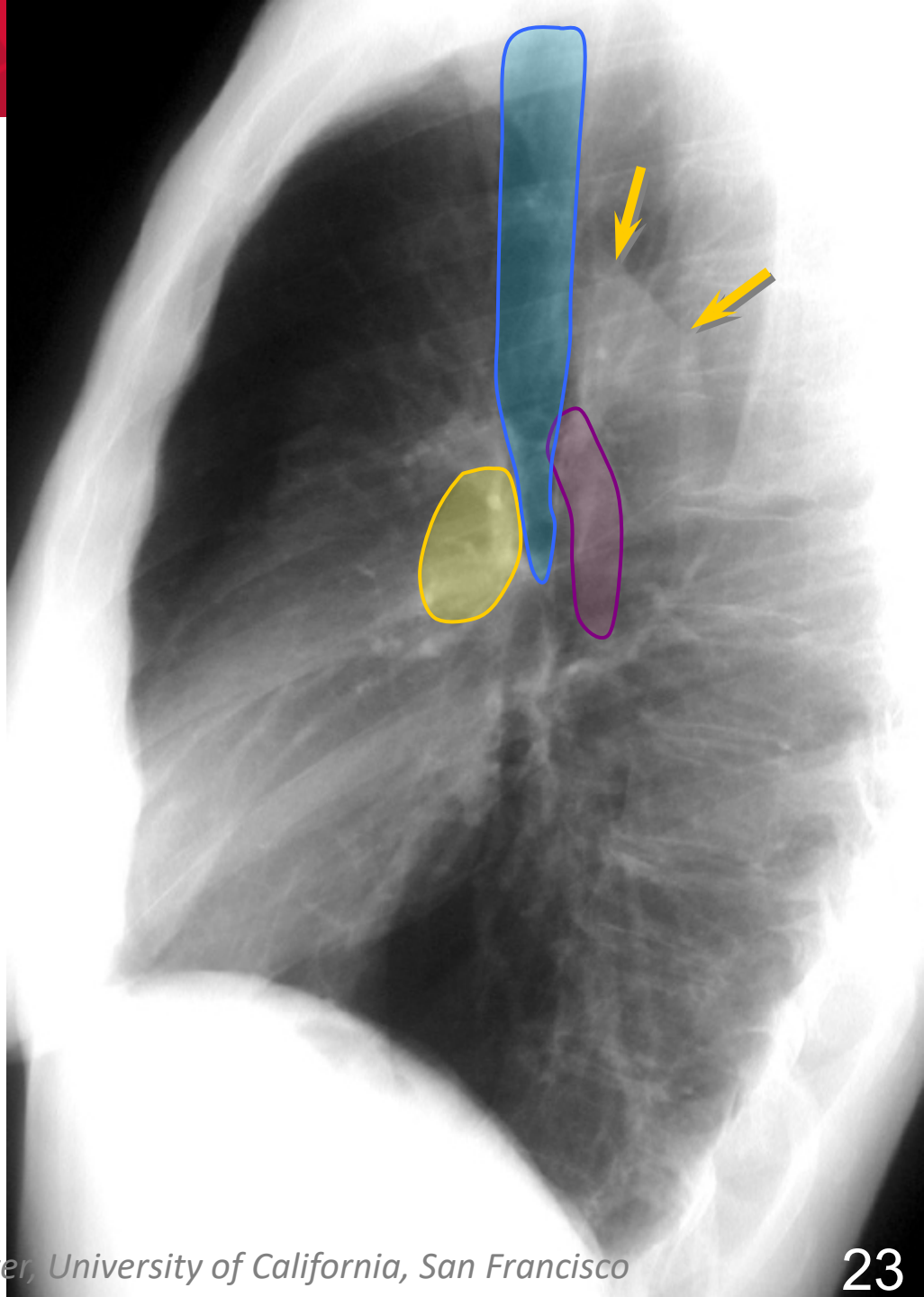
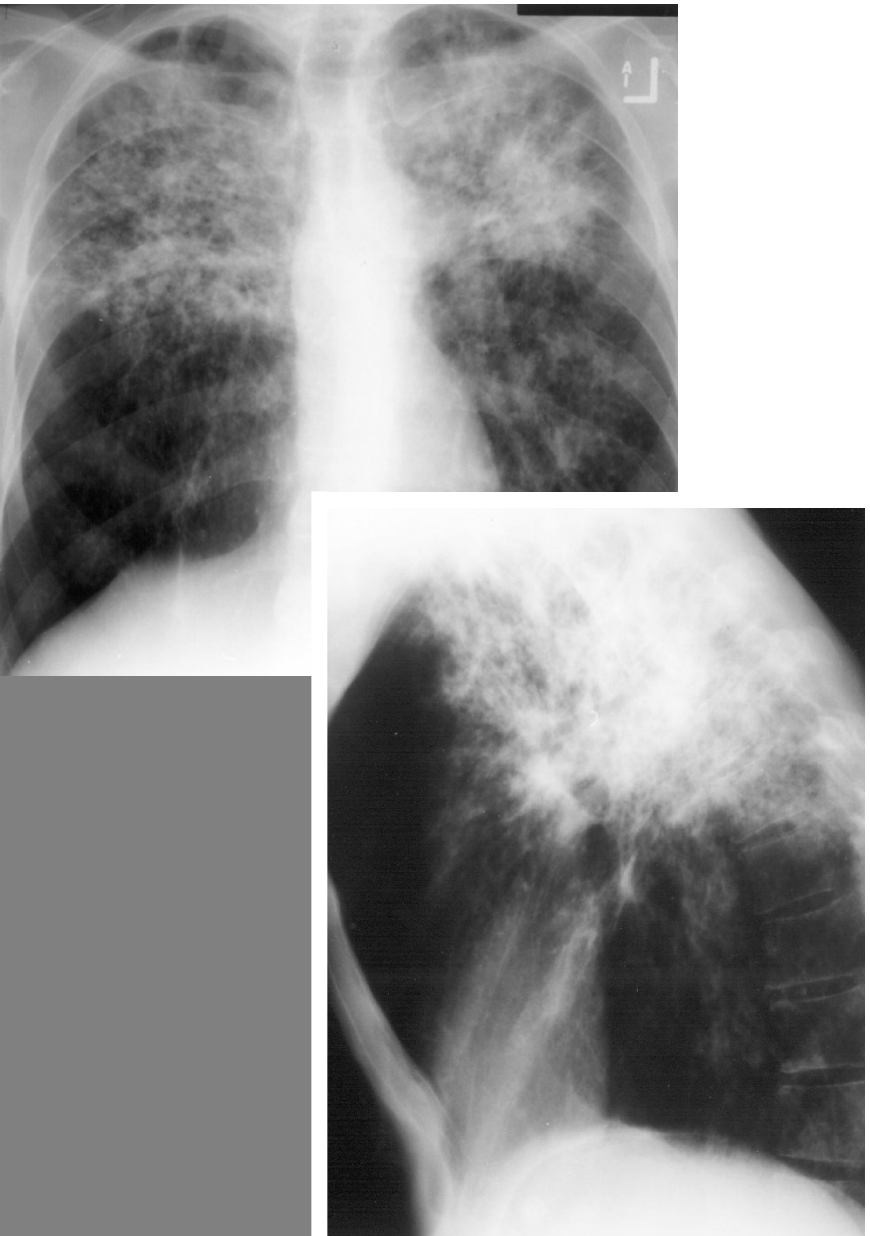


Image credit: Curry International Tuberculosis Center, University of California, San Francisco

Basic Radiology for the TB Clinician

Radiographic Manifestations of TB

Can this be TB?



"Typical Pattern":

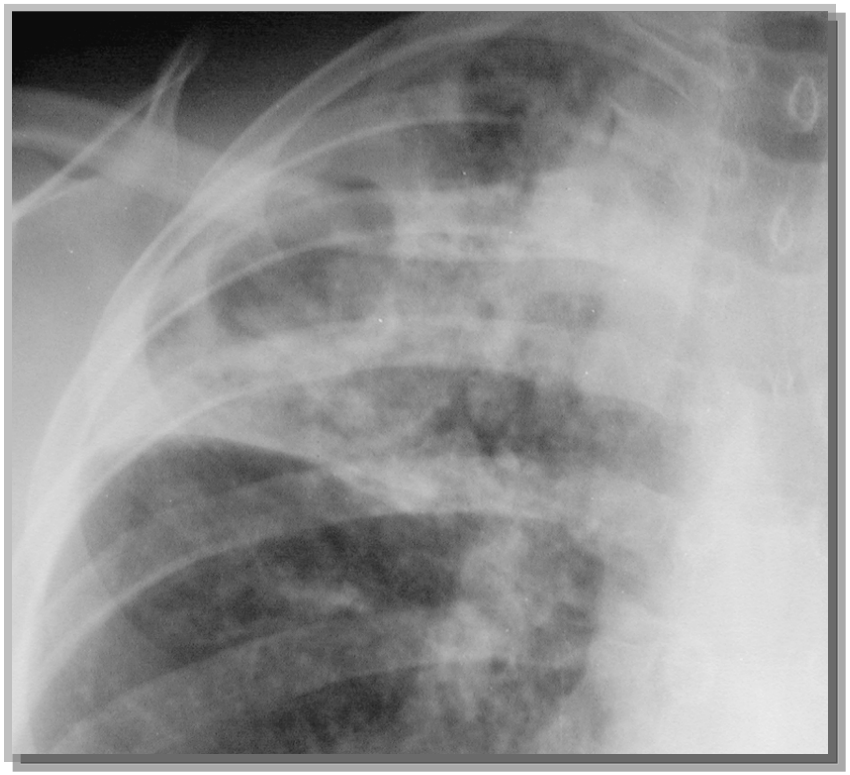
Post-primary TB

- Distribution
  - Apical / posterior segments of upper lobes
  - Superior segments of lower lobes
  - Isolated anterior segment involvement unusual for *M.tb* (think *M. avium* complex)

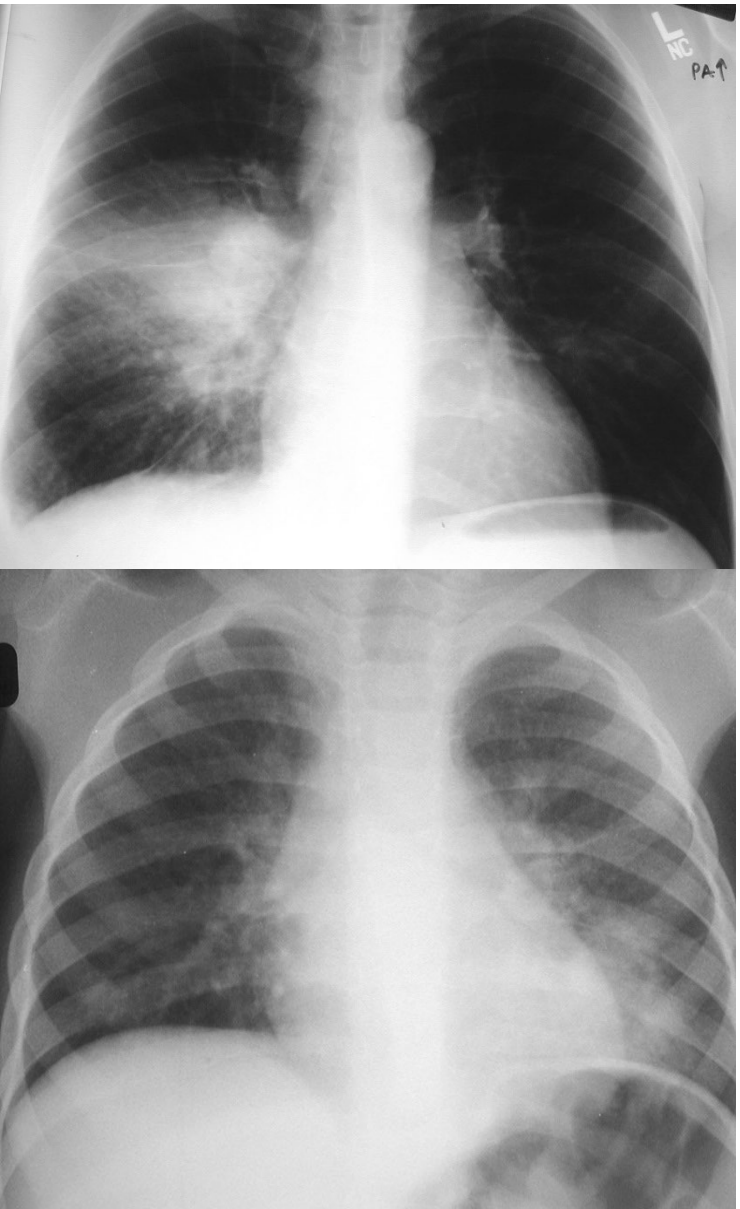
"Typical pattern": Post-Primary TB

Patterns of disease

- Air-space consolidation
- Cavitation, cavitary nodule
- Endobronchial spread
- Miliary
- Bronchostenosis
- Tuberculoma
- Pleural effusions (empyema most likely in post-primary disease)



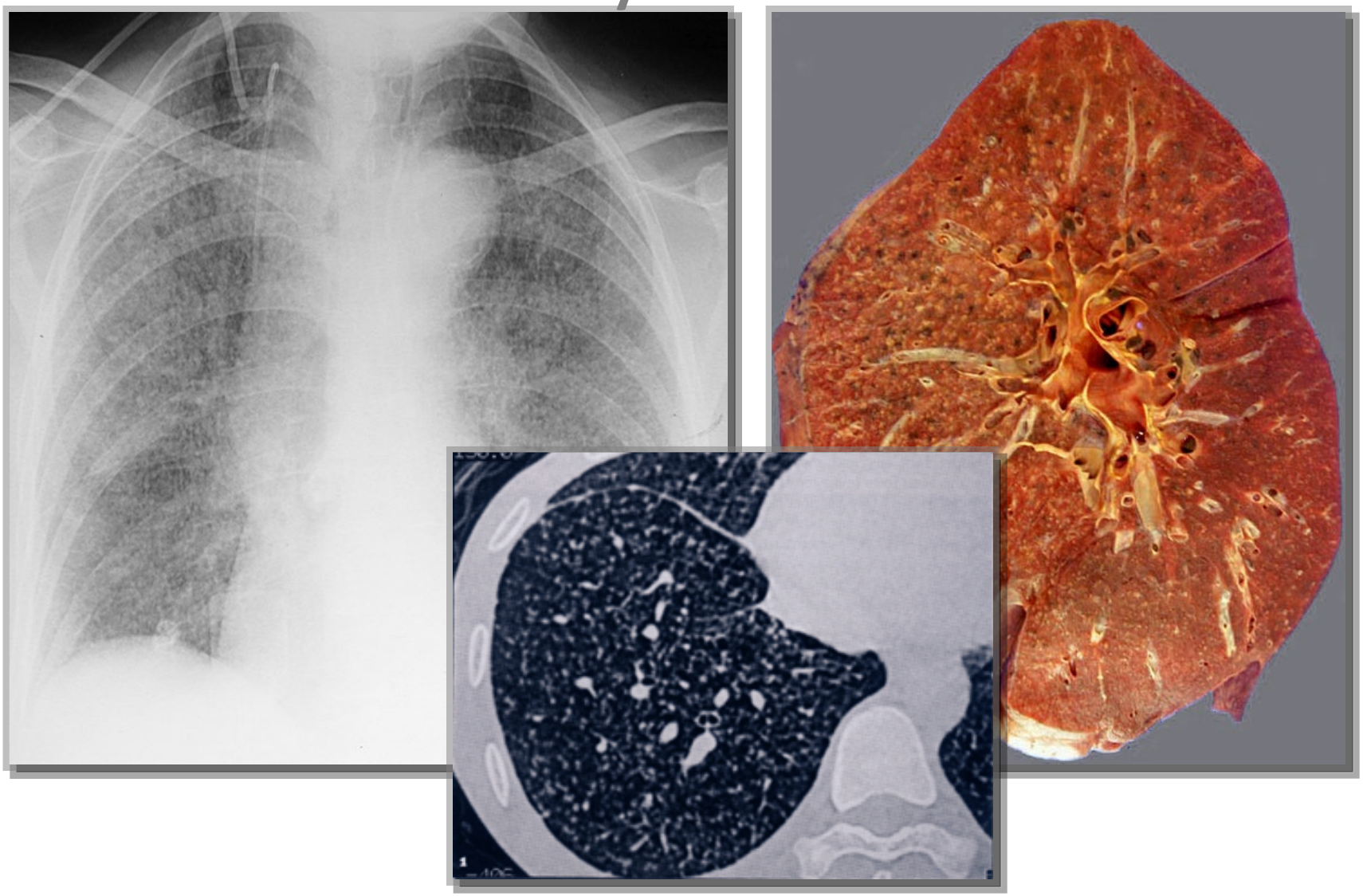
Can this be TB?



“Atypical pattern”: Primary TB

- Distribution : any lobe involved (slight lower lobe predominance)
- Air-space consolidation
- Cavitation is uncommon (<10%)
- Adenopathy is common (esp. children and HIV), predilection for right side
- Miliary pattern
- Pleural effusions

Can this be TB? Miliary TB



Radiographic Patterns: Pulmonary TB

TB Pattern	"Typical" (Post-Primary)	"Atypical" (Primary)
Infiltrate	85% upper	Upper : Lower 60 : 40 Usually upper in children
Cavitation	Common	Uncommon
Adenopathy	Uncommon	Children common Adults ~30% Unilateral > bilateral
Effusion	May be present	May be present

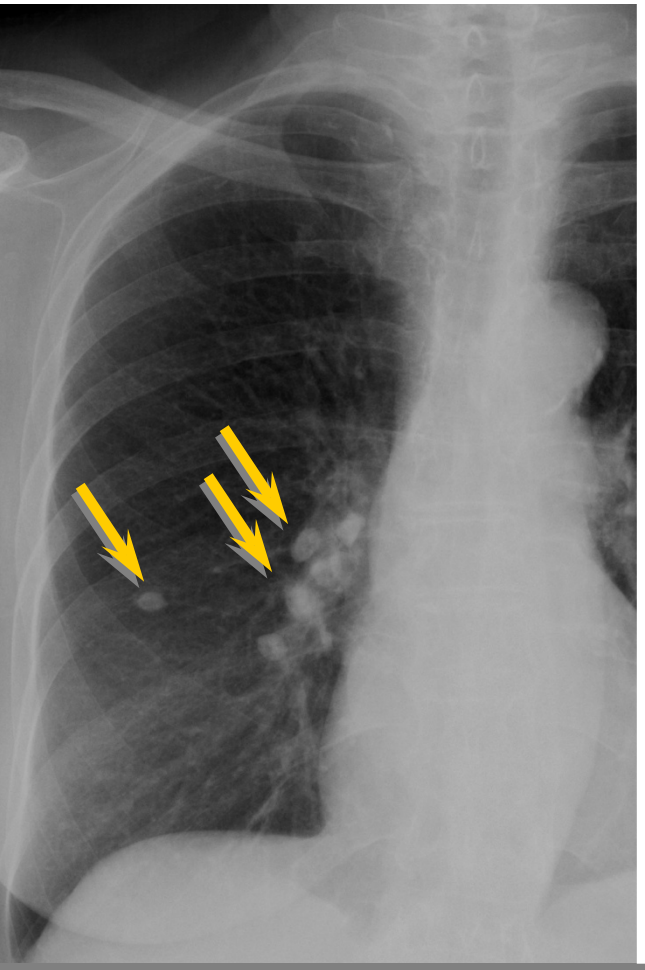
CXR Pattern: Early vs. Advanced HIV

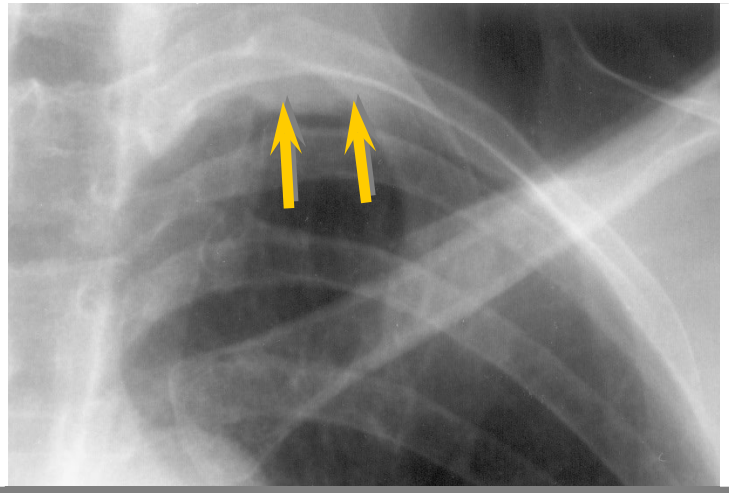
	Early HIV (CD4>200)	Advanced HIV (CD4<200)
Pattern	"Typical" (Post-primary)	"Atypical" (Primary)
Infiltrate	Upper lobes	Lower lobes, multiple sites, or miliary
Cavitation	Common	Uncommon
Adenopathy	Uncommon	Common
Effusion	Uncommon	More common

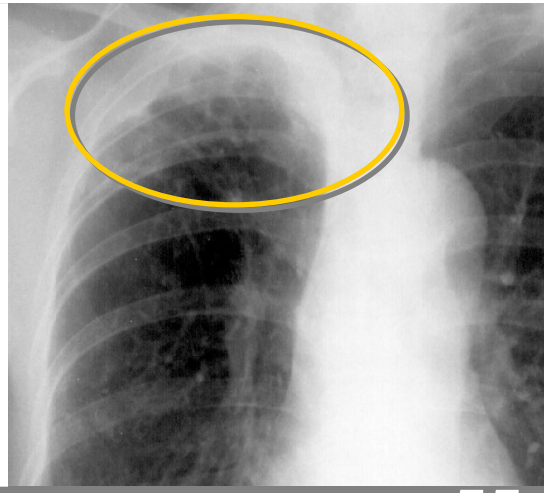
Can this be TB?

"Old / Healed" TB

- Ca^{++} granuloma–Ghon lesion
- Ca^{++} granuloma and hilar node calcification–Ranke complex
- Apical pleural thickening
- Fibrosis and volume loss





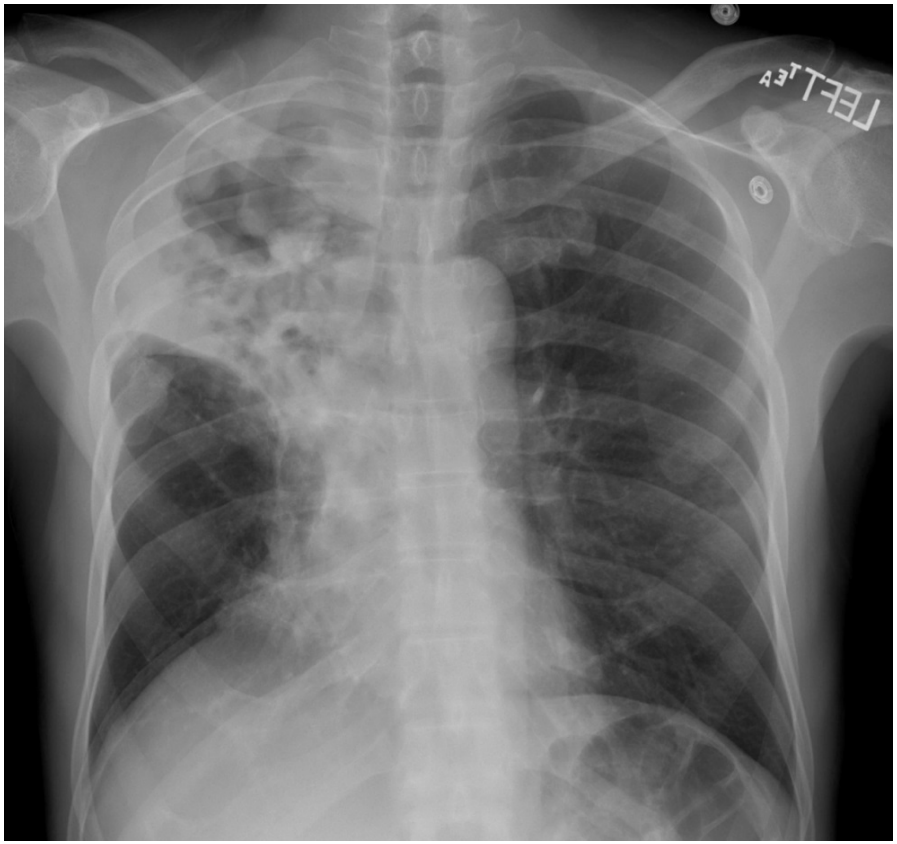


Basic Radiology for the TB Clinician

Summary:

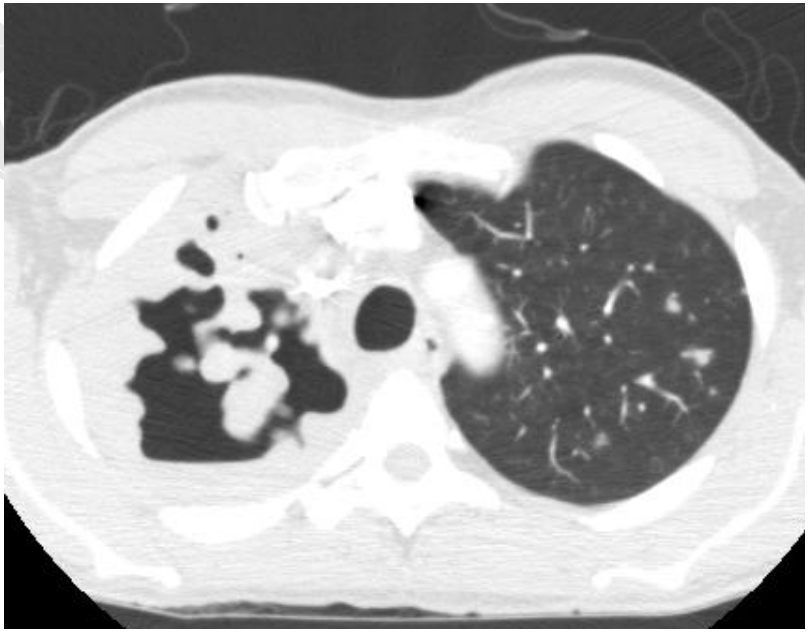
- Remember: Technical quality can significantly impact your CXR interpretation
- Develop a systematic approach (and use it every time!)
- Practice identifying **normal** CXR anatomy
- Important to characterize and describe lesions—this can help with your differential diagnosis
- Whether typical or atypical
  - ➡ TB can always fool you!

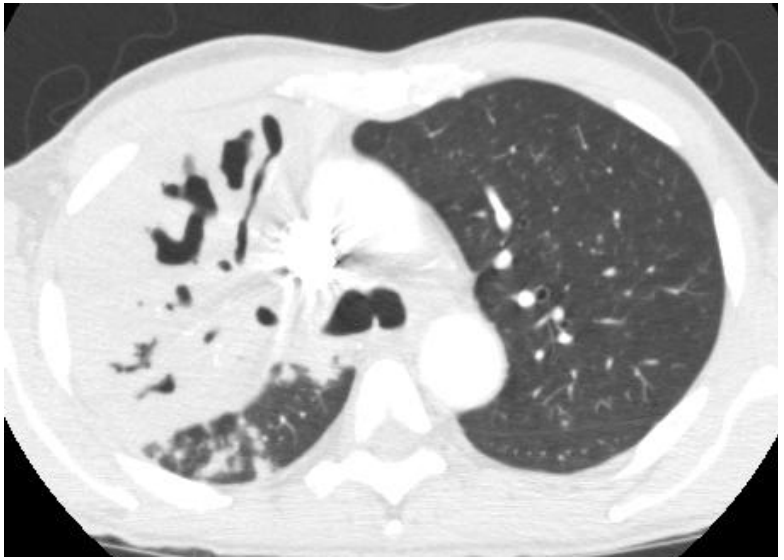
Clinical case - Radiologic Findings



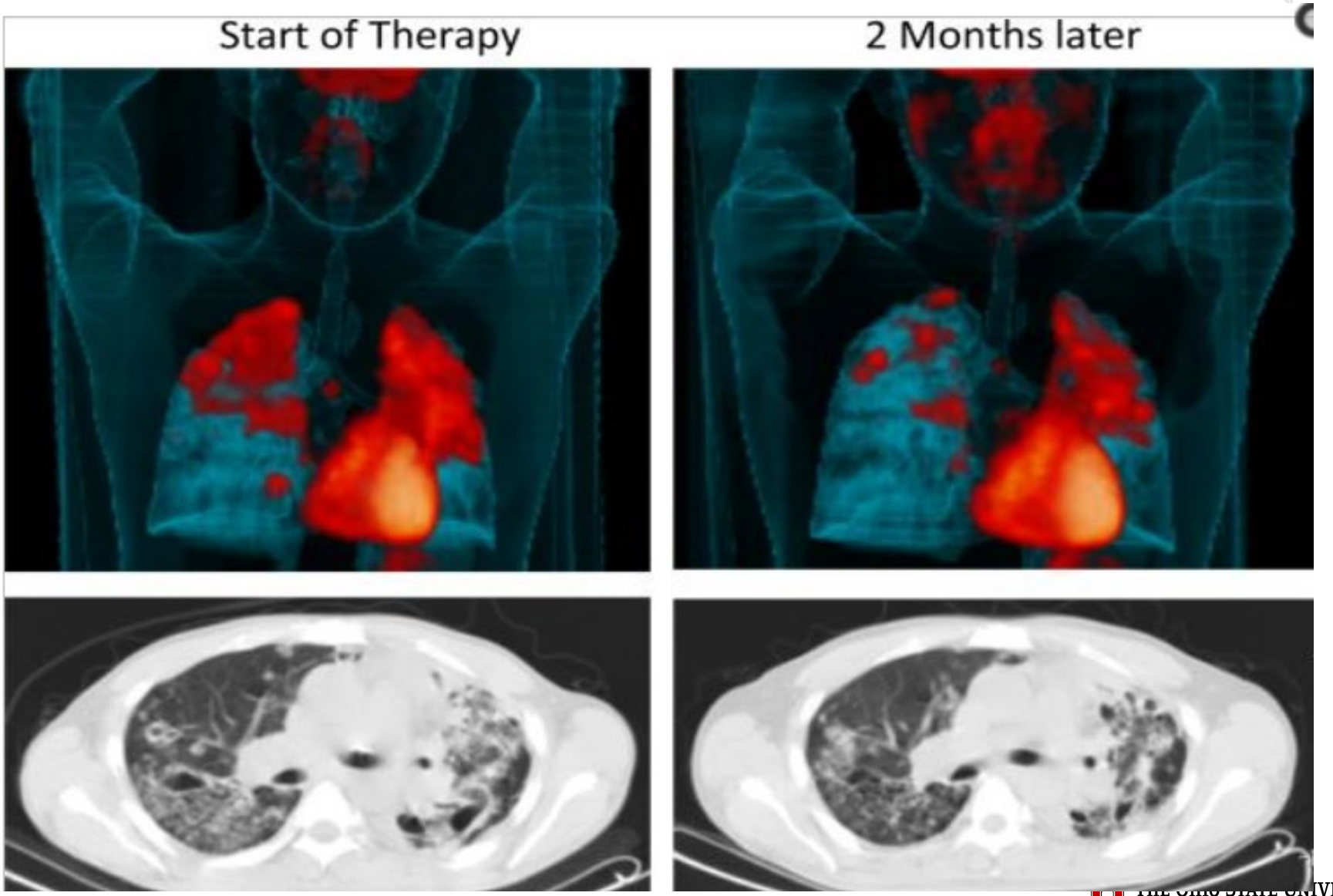
RUL cavitary lesion
RLL consolidation

Clinical case - Radiologic Findings





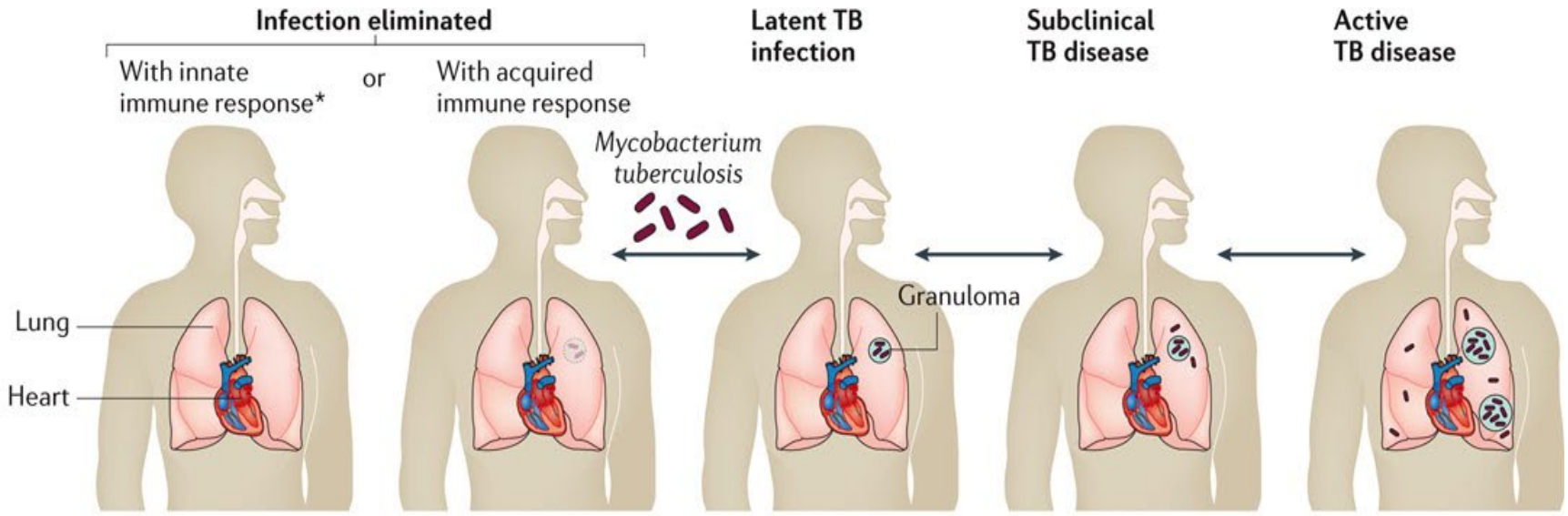
Disease progression in humans



- Diagnosis of TB
- Tests for TB – (not include TST/IGRA)
- Lab: smear, NAAT, culture, and DST

4

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,

International Guidelines for Examination and Reporting Acid-Fast Smears

Organism Count at Specific Magnifications

Report	Number of AFB Observed	
	200x, 250x	400x, 450x
No AFB seen	0	0
Doubtful: repeat	1-2/30F*	1-2/70F
1+	1-9/10F	2-18/50F
2+	1-9/F	4-36/10F
3+	10-90/F	4-36/F
4+	>90/F	>36/F

* number of acid-fast bacilli observed per microscopic field

Laboratory Diagnosis – Active TB Disease

Specimen collection and processing

AFB Smear

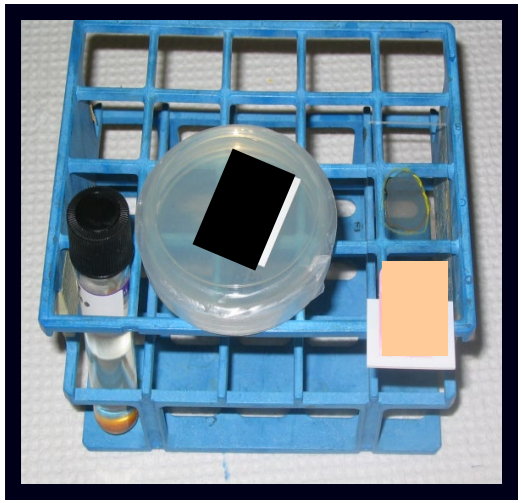
MGIT
(Liquid medium, automated system)

Agar Plate
M H 711

No Growth
Incubate for 6 weeks

Positive Growth

No Growth
Incubate for 4 weeks



Gen-Probe

MTB, MAC, M kansasii, M gordonae

MTB Susceptibility Testing
RIF, INH, EMB, PZA, Strep

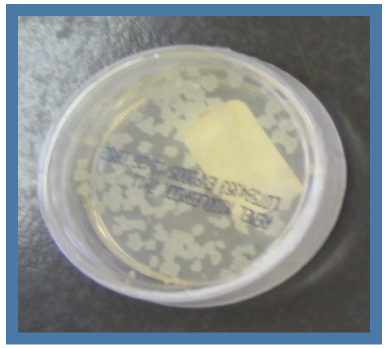
MGIT= mycobaterial growth indicator tube

AFB SMEAR and CULTURE

Ziehl-Neelsen
X 1,125

AFB smear
< 24 hours

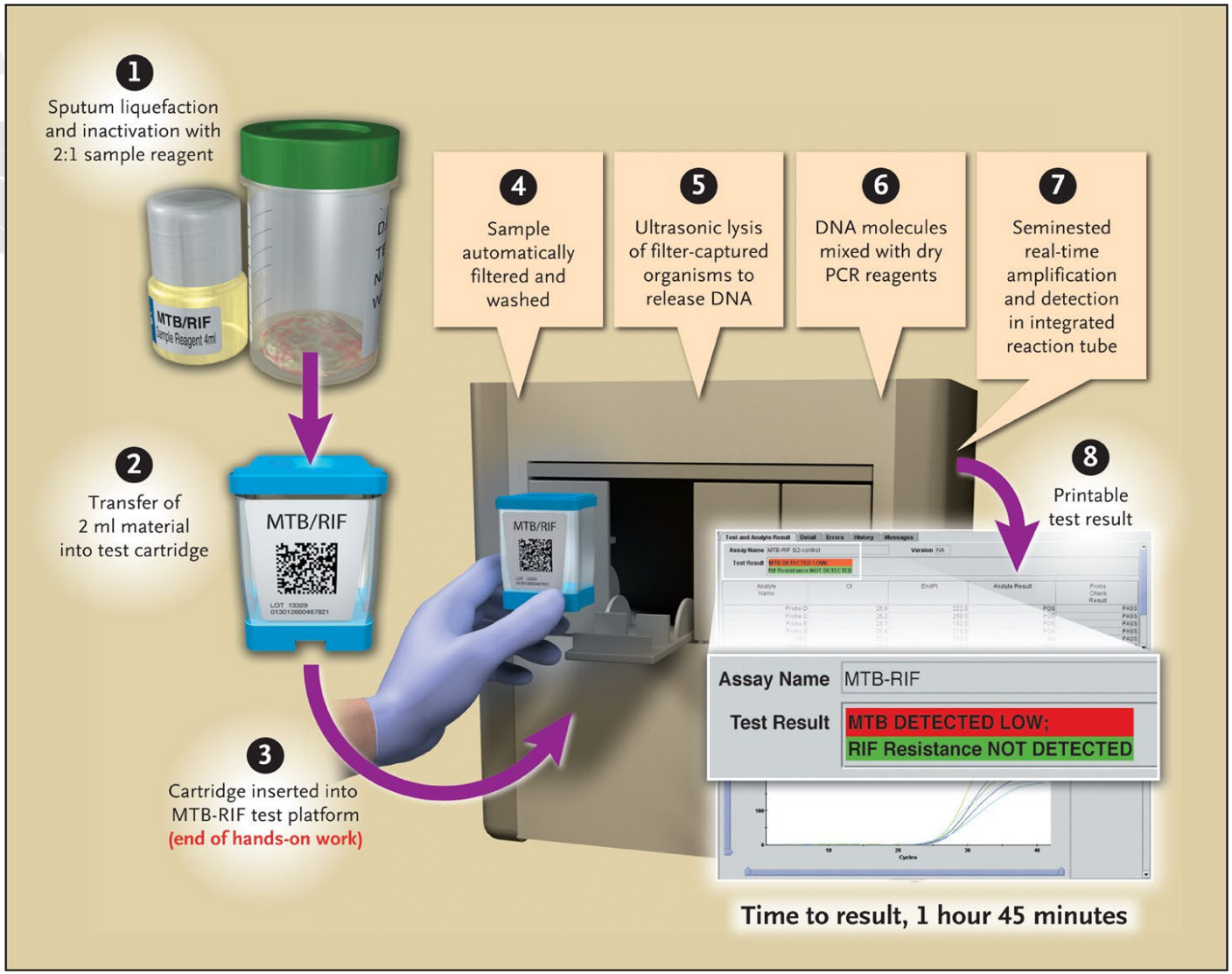
X 1440

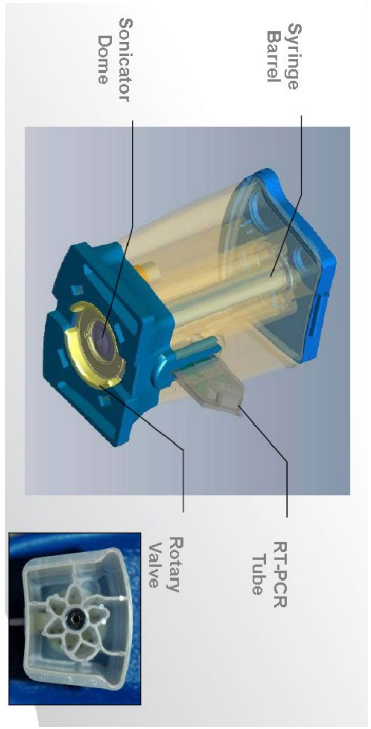


Solid Culture
3 – 8 weeks

Liquid Culture
7 – 21 days

GeneXpert Assay Procedure for the MTB/RIF Test





Boehme CC et al. N Engl J Med 2010;363:1005-1015.

AFB Smear

Ziehl-Neelsen
X 1,125

X 1440

AFB smear
< 24 hours

- Variable sensitivity
  - 40-70% for pulmonary TB (less in miliary TB, late HIV, children)
  - Limit of detection (LOD):

    >10^4 AFB/ml by Ziehl-Neelsen;

    >10^3/ml fluorochrome
  - Correlates with disease severity and infectiousness
- Not specific for *M.tb* complex
  - *Red snappers*
- Inexpensive and quick
  - Turnaround time (TAT) <24hr

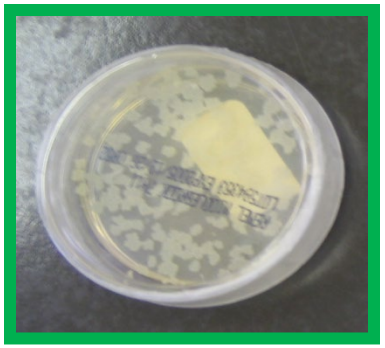
AFB Smear and Culture

Ziehl-Neelsen
X 1,125

AFB smear
< 24 hours

X 1440

Liquid Culture
7 – 21 days



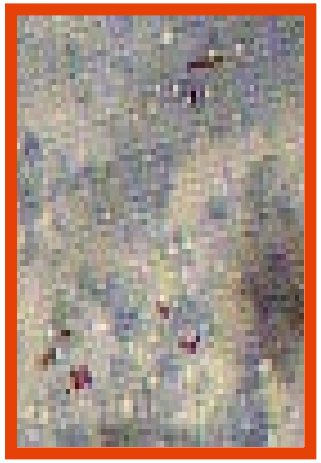
Solid Culture
3 – 8 weeks

- Importance of reporting to the health department even if it's presumed TB

5

Bacteriology

Sputum Specimen	AFB Smear	Culture
Hospital day 1	Positive 2+	
Hospital day 2	Positive 3+	
Hospital day 6	Positive 3+	
Hospital day 11	Positive 2+	
Hospital day 20	Positive 2+	



Is this *M.tb* for certain?

What about if his QFT is positive- then is it *M.tb*?

Laboratory Diagnosis – Active TB Disease

Specimen collection and processing

AFB Smear

MGIT
(Liquid medium, automated system)

Agar Plate
M H 711

NAA

No Growth
Incubate for 6 weeks

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Gen-Probe
M.tb, MAC, M kansasii, M gordonae

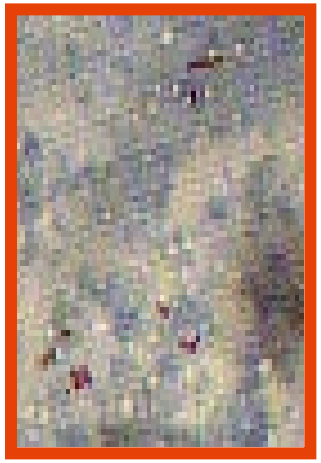
M.tb Susceptibility Testing
RIF, INH, EMB, PZA, Strep

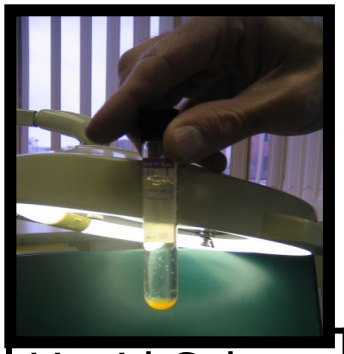
MALDI-TOF

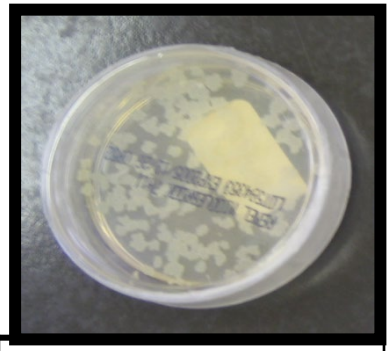
MGIT = mycobaterial growth indicator tube

Bacteriology

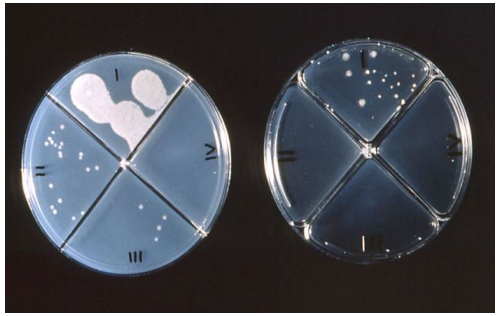
Sputum Specimen	AFB Smear	Culture
Hospital day 1	Positive 2+	*M. tuberculosis*
Hospital day 2	Positive 3+	*M. tuberculosis*
Hospital day 6	Positive 3+	*M. tuberculosis*
Hospital day 11	Positive 2+	
Hospital day 20	Positive 2+	





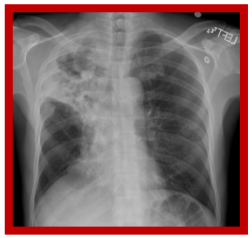


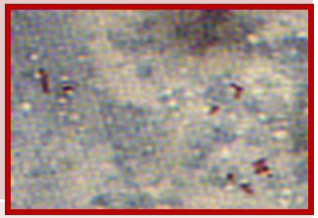
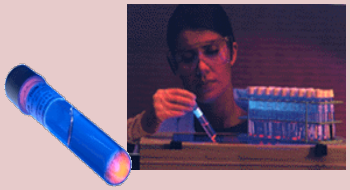
Liquid Culture	Solid Culture
7 – 21 days	3 – 8 weeks



Drug Susceptibility Test

Summary Hospital Course

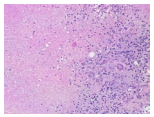


Tuberculin skin test	**Reactive** ?mm 
AFB sputum smear:	**Smear Positive**  
Anti-TB therapy:	**Started on 4 drugs** 
AFB Culture	**Culture Positive**  

In the Absence of a Culture Isolate

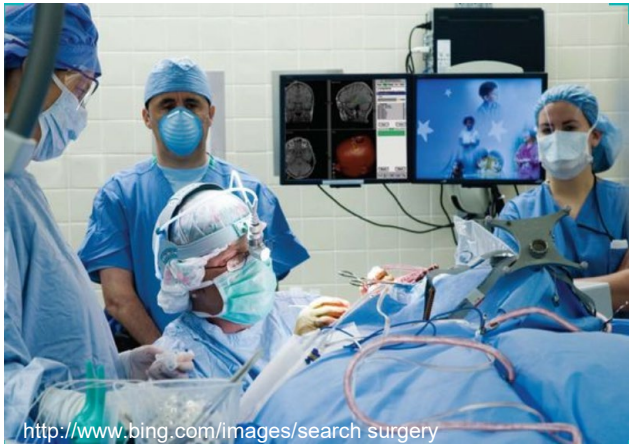
- Culture confirmed diagnosis of TB
  - 7,171 (77%) of 9,253 US +affiliated cases (2017) were culture-confirmed

  - Clinical diagnosis of TB (no culture confirmation)
    - Evidence of TB infection (positive TST)
    - Supporting clinical information: symptoms, signs
    - Supporting epidemiological information:
    - Supporting radiography
    - Supporting pathology
    - Clinical/radiographic improvement with therapy



- The U.S.-affiliated areas include: American Samoa, Northern Mariana Islands, Federated States of Micronesia, Guam, Marshall Islands, Palau, Puerto Rico, and U.S. Virgin Islands. Total 512 cases, 242 culture positive

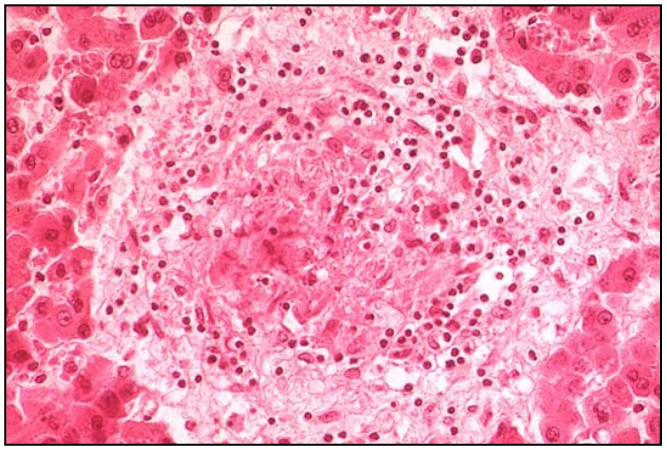
Pathology - Laboratory Diagnosis



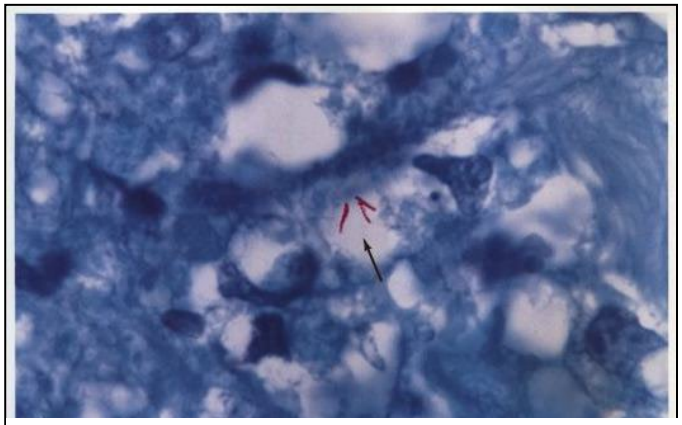
- **ALL** specimen sent to path
- **NO** specimen for culture

Univ of Wash – Molecular DX

Histology



H&E 400x



Acid fast stain 1000x

- Importance of reporting to the health department even if it’s presumed TB

6

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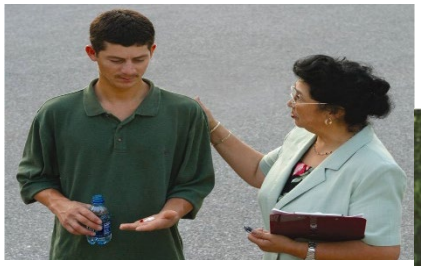
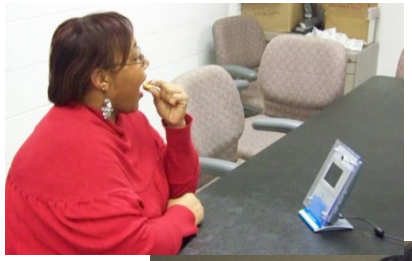
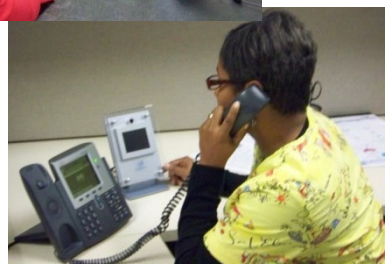
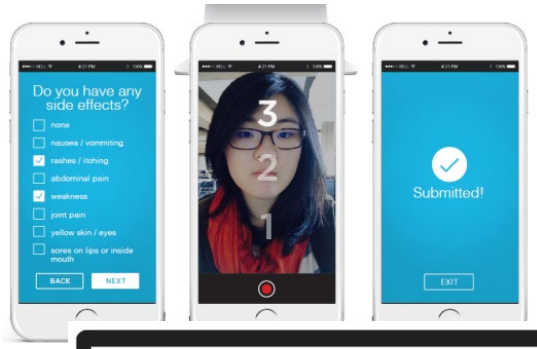
Directly Observed Therapy (DOT)

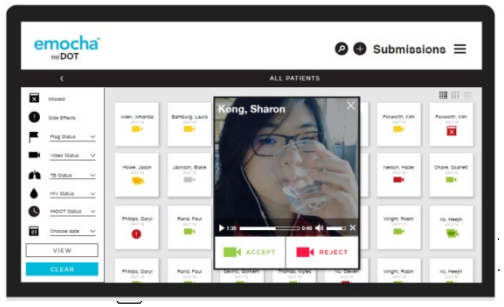
- Health care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse





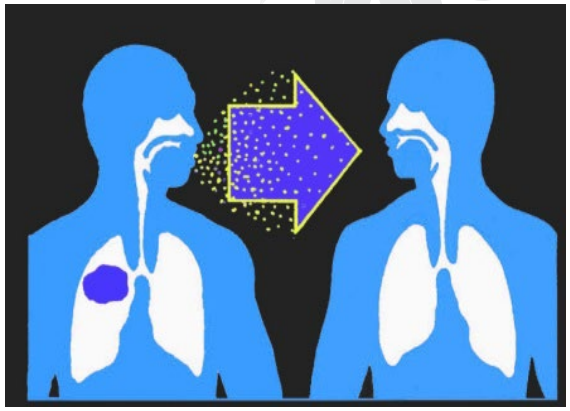


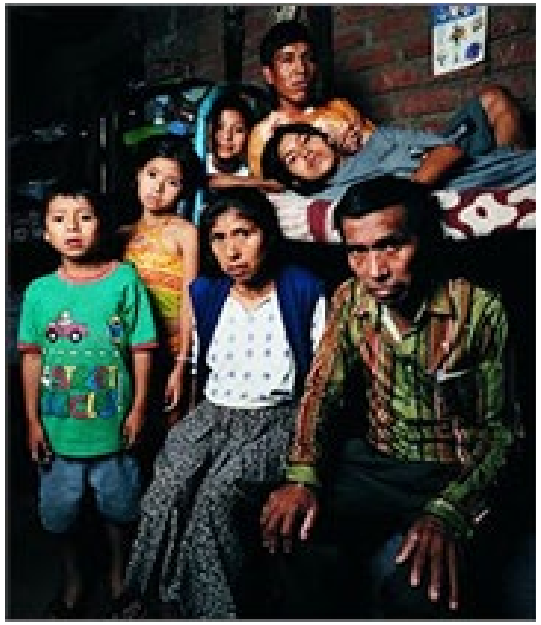




Transmission of TB

- Transmission is **airborne** from patients with **active** pulmonary TB
- **Vehicle:** droplet nucleus (coughing, talking, sneezing); size (1-5 μm)
- **Quantity** of organisms; high with cavitary disease
- **Environment:** spread is enhanced by crowded, poorly ventilated conditions
- Bottom line: duration of exposure and concentration of organisms in the air





Slide courtesy Dr Lee Reichman

- History, Examination, Symptom Screening

1

Clinical Case

History of Present Illness:

- 28 year old Chinese female
- Presented to Emergency Room with hemoptysis
- Complaints of cough x2 days, associated with mild shortness of breath

Clinical Case

Past Medical History

Past Surgical History

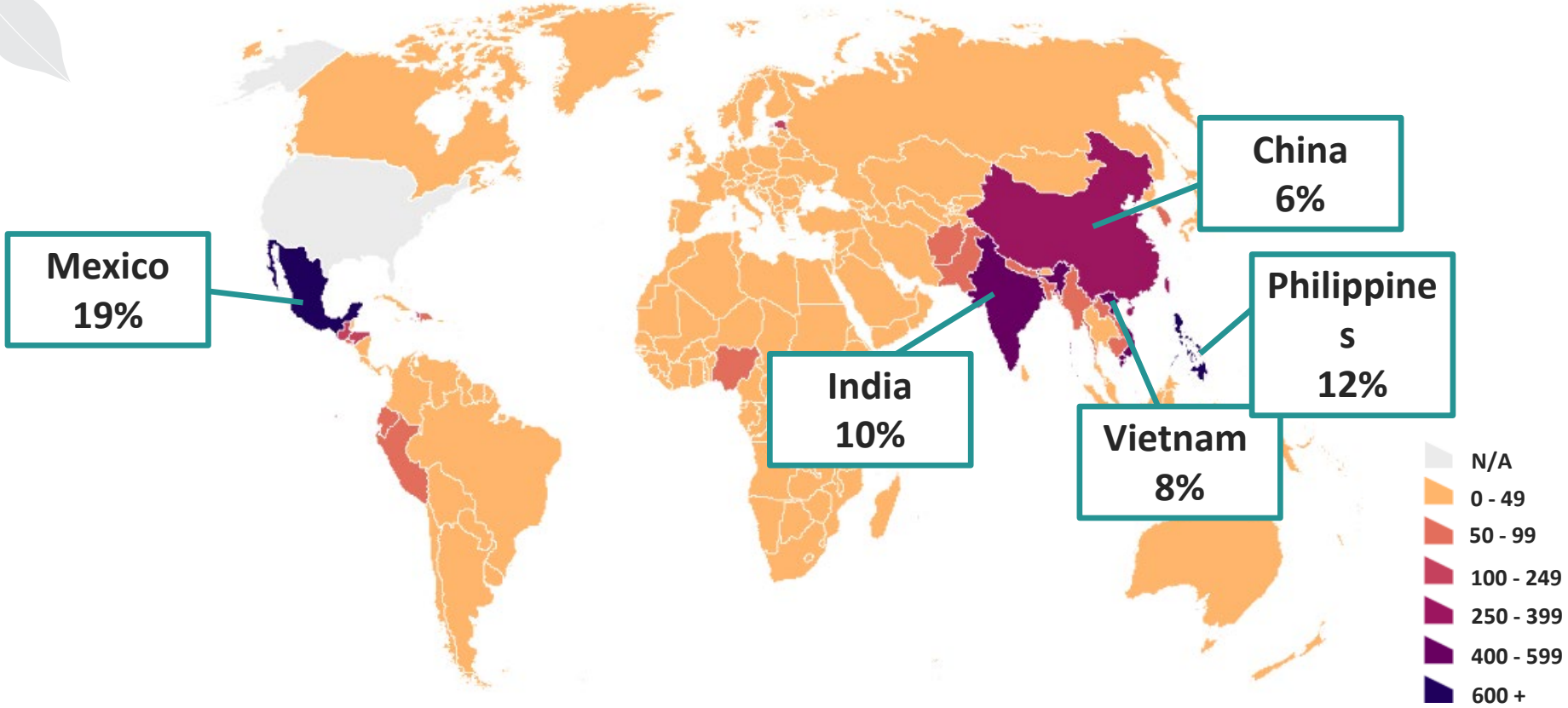
Allergy

Medication

Review of System

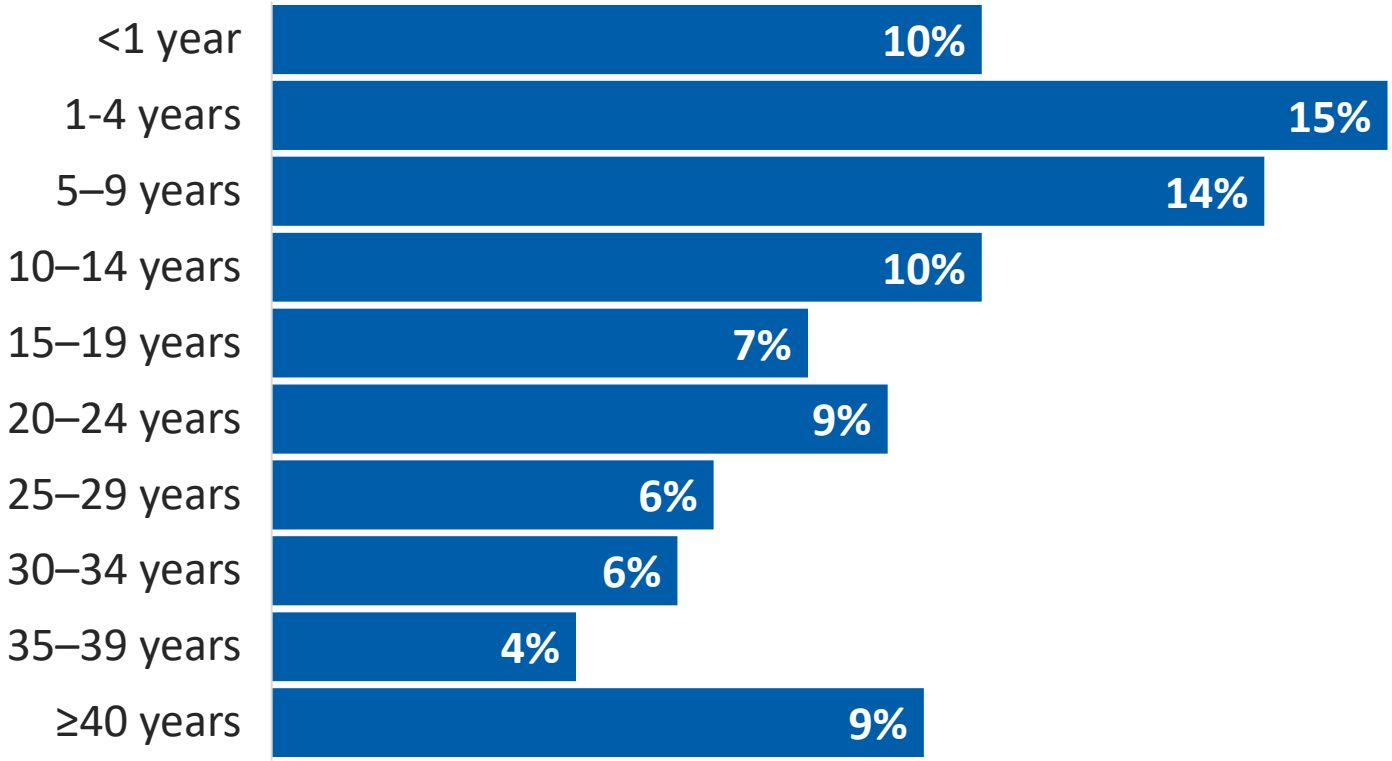
Social History

TB Cases by Countries of Birth Among Non-U.S.–Born* Persons with TB, United States, 2021 (N=5,626)



*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

Percentage of TB Cases Among Non-U.S.–Born* Persons by Years Since Initial Arrival in the United States at Diagnosis,† 2021 (N=5,626)



*Persons born in the United States, certain U.S. territories, or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.
†The number of years since initial arrival in the United States at diagnosis was unknown or missing for 11% of non-U.S.–born persons. These persons were included in the denominator when calculating percentages.

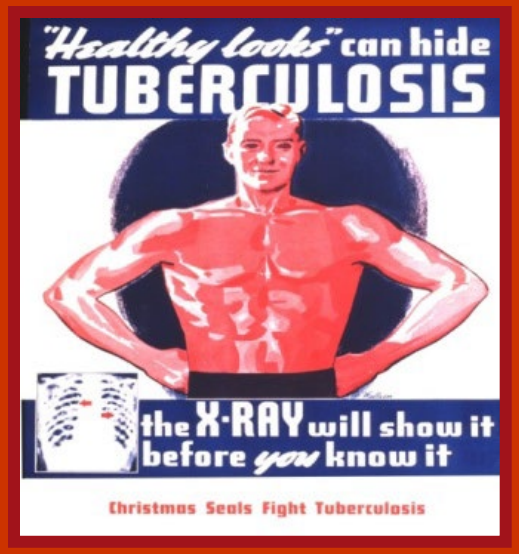
Clinical Case

- No other symptoms
- Denies any h/o TB or known contacts
- History positive TST – No LTBI TX
- BCG vaccine in China as a child
- 32 weeks pregnant

- Rule out - Extrapulmonary TB
- compare symptoms of pulmonary vs extra-pulmonary TB

2

- Chest radiography – common views ordered and review some of the radiographic manifestations

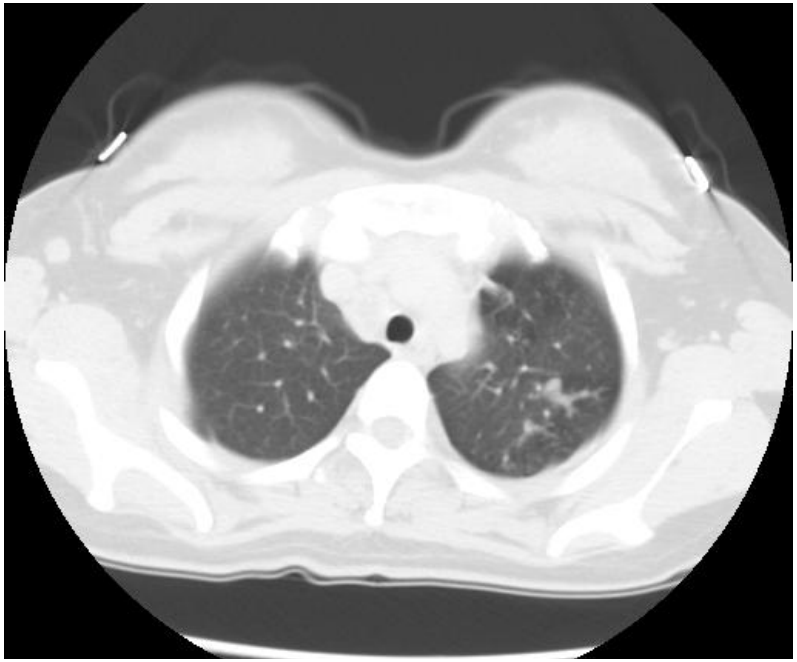


3

CXR

Mild asymmetric patchy opacity in the left upper lobe

CT Scan



- Diagnosis of TB
- Tests for TB – (TST/IGRA)
- Lab: smear, NAAT, culture, and DST

4

- Airborne isolation unit
- TST 17mm
- QuatiFERON TB Test: Positive

Specimen	Smear	Culture
Sputum day 1	**Negative**	
Sputum day 2	**Negative**	
Sputum day 3	**Negative**	
BAL day 4	**Negative**	

• Discharge home on INH for Latent TB infection (LTBI) treatment

• Follow up at TB Clinic

- TST 17mm QFT: Positive
- Nucleic acid amplification test:
  - Positive for *M. tuberculosis complex*

Specimen	Smear	Culture
Sputum day 1	Negative	***M. tb***
Sputum day 2	Negative	***M. tb***
Sputum day 3	Negative	***M. tb***
BAL day 4	Negative	Negative
Sputum day 9*	Negative	Negative

Drug susceptibility:

Resistant to Rifampin, Isoniazid, and Streptomycin

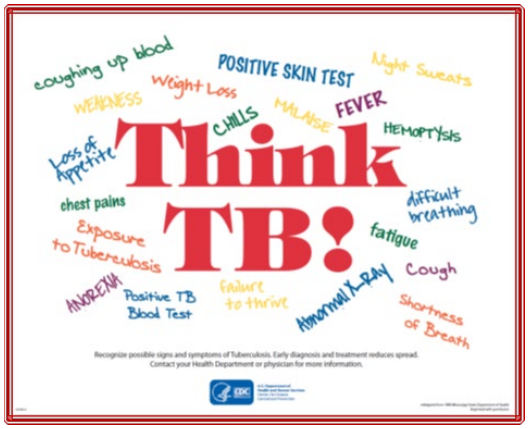
Using MDDR to Rapidly Identify Drug-Resistant TB

Smear- positive, cultures still pending (needed before conventional DST)

Locus	Result	Interpretation
rpoB	**Mutation**	**RIF R**
inhA	No mutation	**INH R**
katG	**Mutation**	
embB	**Mutation**	**EMB R**
pncA	**Mutation**	**Cannot rule out PZA resistance**
gyrA	No mutation	**Cannot rule out fluoroquinolone resistance**
rrs	**Mutation**	**AMK and KAN resistance, possible Capreo resistance**
eis	No mutation	
tlyA	No mutation	

- Importance of reporting to the health department even if it's presumed TB

5



- *A negative TST/QFT **does not** exclude TB*
- *A positive smear **does not** establish diagnosis*
- *A negative smear **does not** exclude TB*
- *A negative GeneXpert does not exclude TB*
- *A negative culture does not exclude TB*
- ***NO Test Can "RULE OUT" TB***
  - ***TB is still a clinical diagnosis***

What to do if you suspect TB?

- Airborne Infection Isolation (AII)/precautions –
- CXR
- Respiratory AFB smear and culture, GeneXpert
- Tuberculin skin test/ QuantiFERON-TB Test
- HIV Test, Hepatitis serology, HgA1c, pregnancy test
- AFB Smear and culture from other sites
- Rapid molecular drug susceptibility test, conventional drug susceptibility test
- REPORT ALL Possible TB Patients to TB Program
- Hotline: 614 645-1823

TB detection by Giant Rats

TB Detection by Giant Rats

https://www.youtube.com/watch?v=ZvUUadKKQ1s

- **Thank you!**
- شكرًا لك
- በጣም፡እናመሰግናለ ን።
- Muito Obrigado!
- Asante Sana!
- ć Źńč Ĺ ŘЄĆ
- Muchas gracias!
- Merci Beaucoup!
- شكرا جزيلا
- 谢谢
- Terima Kasih
- நன்றி