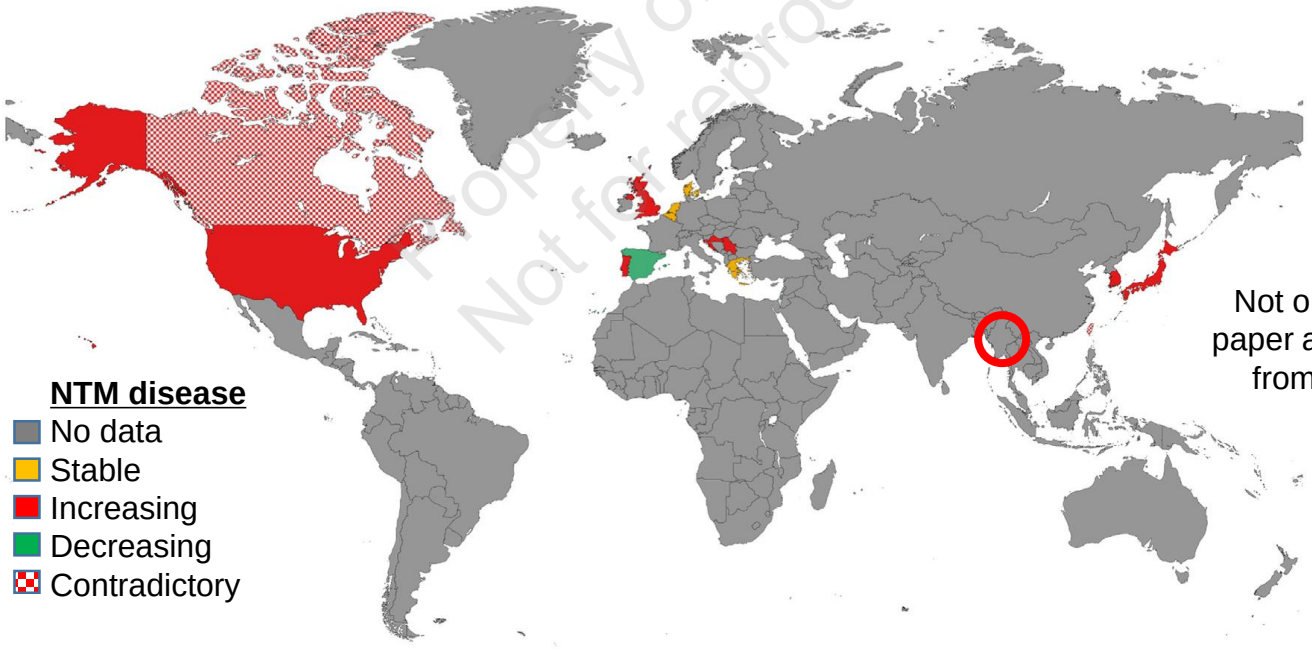
NTM Lecture Series
No conflict of interests

Goals: identify host risk factors for:
- Skin-soft tissue infections
- NTM lung disease
- Disseminated NTM infections

Host Risk Factors for NTM Infections

Ed Chan, M.D.
April 27, 2023, 11:00-11:45 AM
ChanE@NJHealth.org



Not one single paper about NTM from Burma

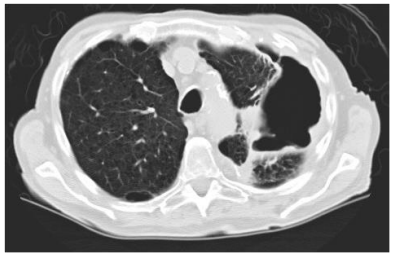
Dahl VN et al.
Int J Infect Dis 2022

The type of NTM disease reflects the underlying host risk factor

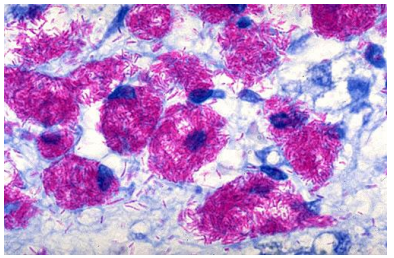
Skin, soft tissue, and/or traumatic orthopedic NTM infection
(most have normal immunity)


After liposuction

Isolated NTM lung disease
(structural lung abnormality)


Underlying COPD

Extrapulmonary visceral or disseminated NTM infection (essentially all have underlying severe immunodeficiency)

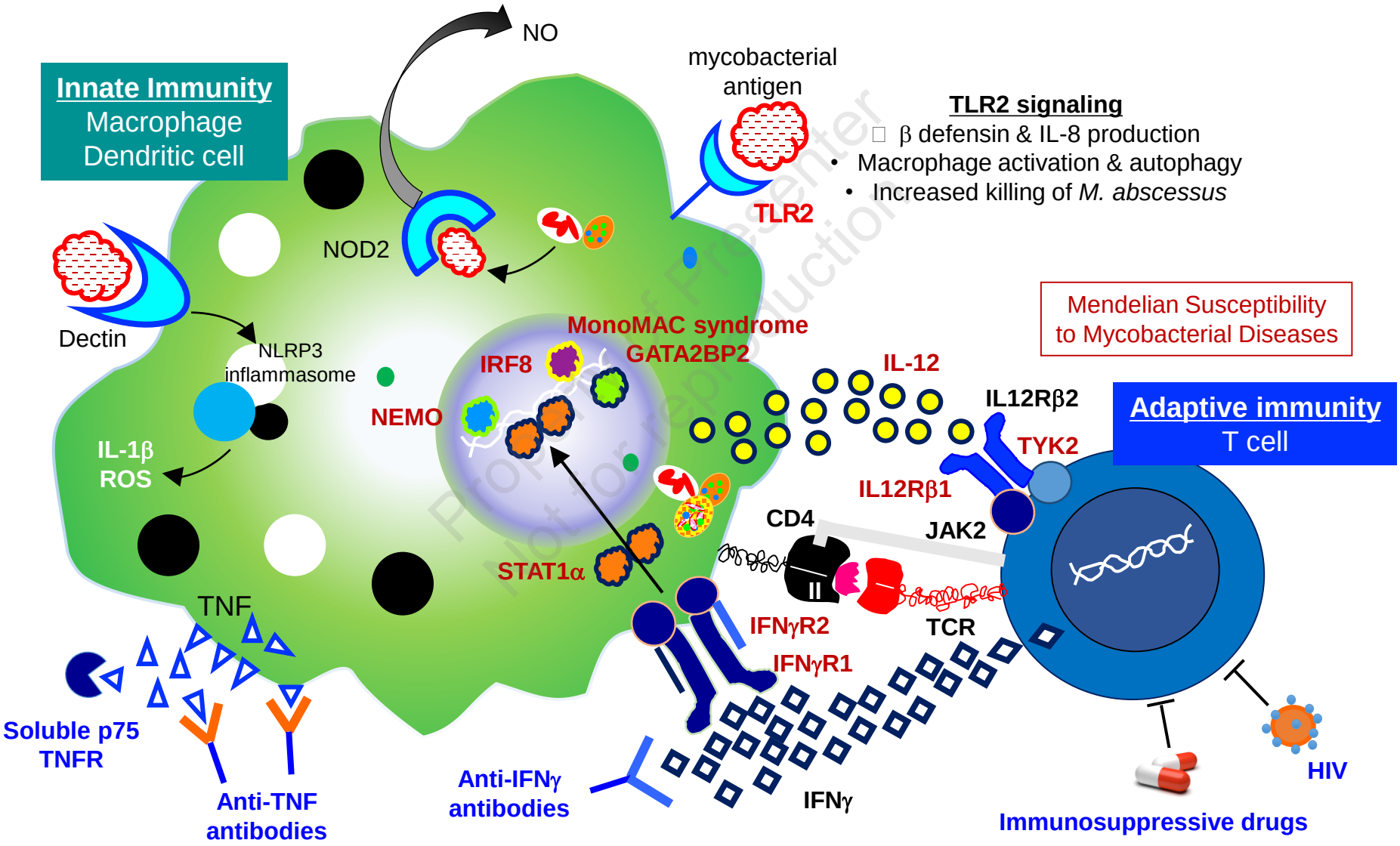

AIDS

What medical condition am I alluding to with this blood collection tube?

Dupont isolator

AIDS

Acquired and inherited disorders that predisposes to disseminated mycobacterial infection



Risk factors for skin, soft tissue, and traumatic orthopedic NTM infections

- **Breach of skin** – accidental trauma, foot salons, medical procedures with contaminated water, instrument, or medications.

After cosmetic surgery

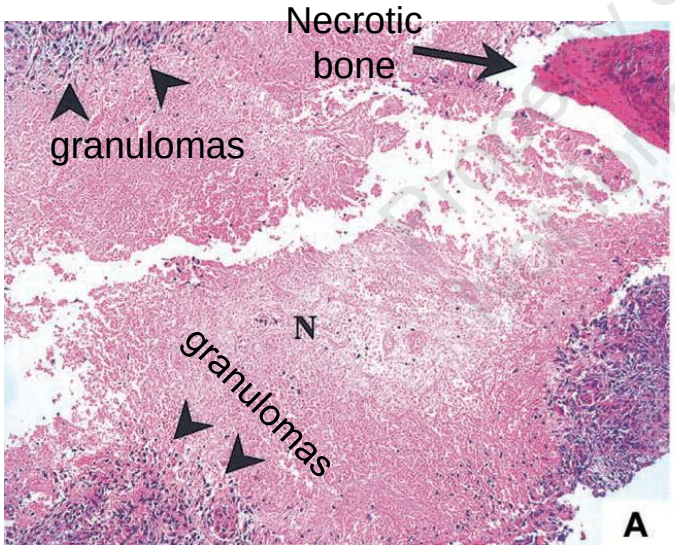
After liposuction

After bunionectomy

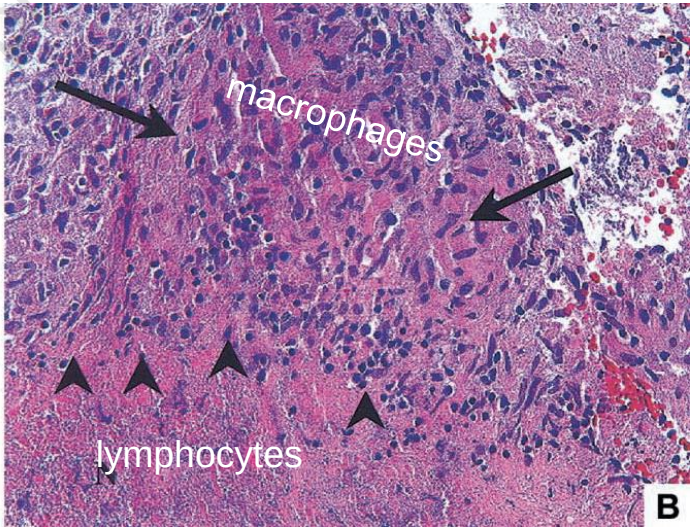
- Most cases occur in those with normal host immunity…but we contend that physical trauma itself may be immunocompromising.

Why did this healthy teenager get a localized NTM infection of the spine?

- A 16-year-old girl suffered multiple falls from competitive roller skating, resulting in abrasions, MSK pains, and recalcitrant backache.
- MRI revealed an enhancing signal in T9 with anterior paraspinal soft tissue mass from T8-T10.
- Biopsy of T9 revealed necrotizing granulomas and culture was +ve for *M. abscessus.*



T9 vertebra biopsy



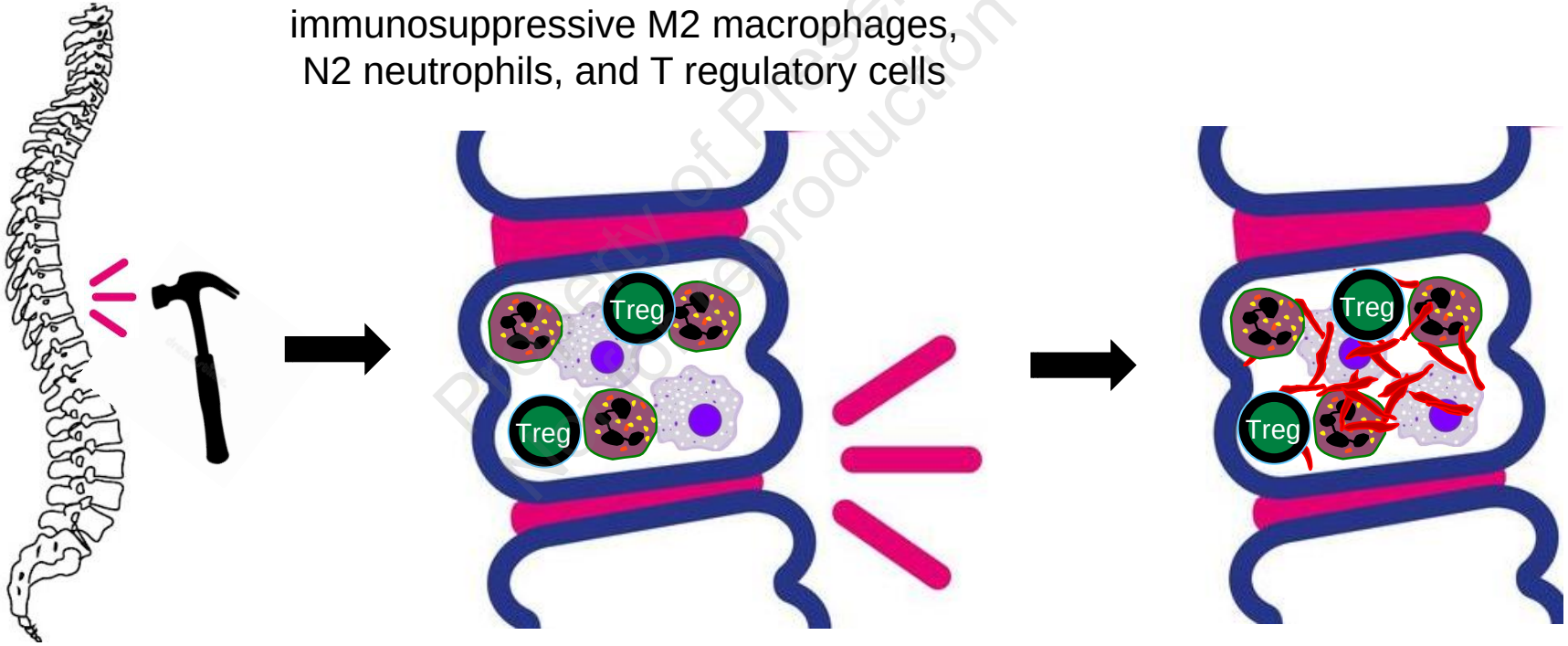
Higher power of granuloma

Mike Iseman, MD

We hypothesized that the site of trauma is “fertile soil” for seeding of infection

“locus minoris resistentiae”

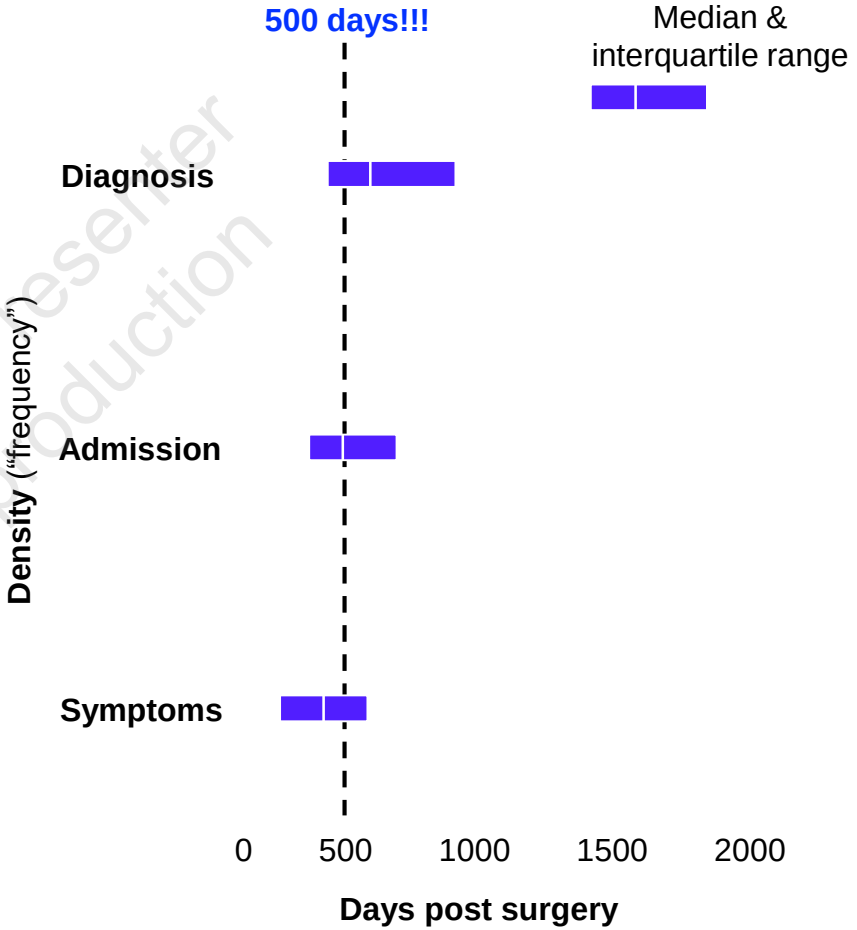
Migration of wound-healing & immunosuppressive M2 macrophages, N2 neutrophils, and T regulatory cells



Trauma “Fertile soil” “Seeding”

M. chimaera and open-chest heart surgery

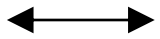
- In 2013, *M. chimaera* infections were reported in patients who underwent open-chest heart surgery.
- Infections involved the **implanted hardware**, **surgical wounds**, and/or **internal organs**.
- *M. chimaera* was traced to **contaminated heater-cooler units** (“heart-lung machine”) and the bioaerosols generated, which contaminated the surgical sites.



Scriven JE et al. Clin Microbiol Infect 2018

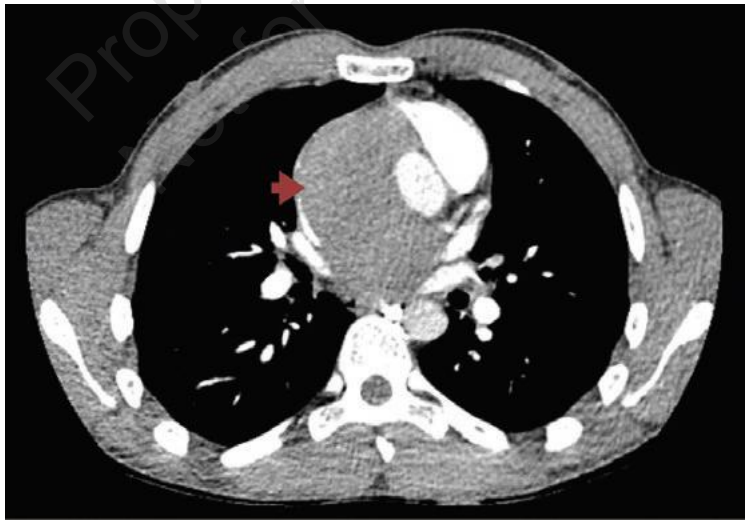
M. chimaera and open-chest heart surgery

AORTIC & AORTIC VALVE SURGERY are HIGHEST RISK



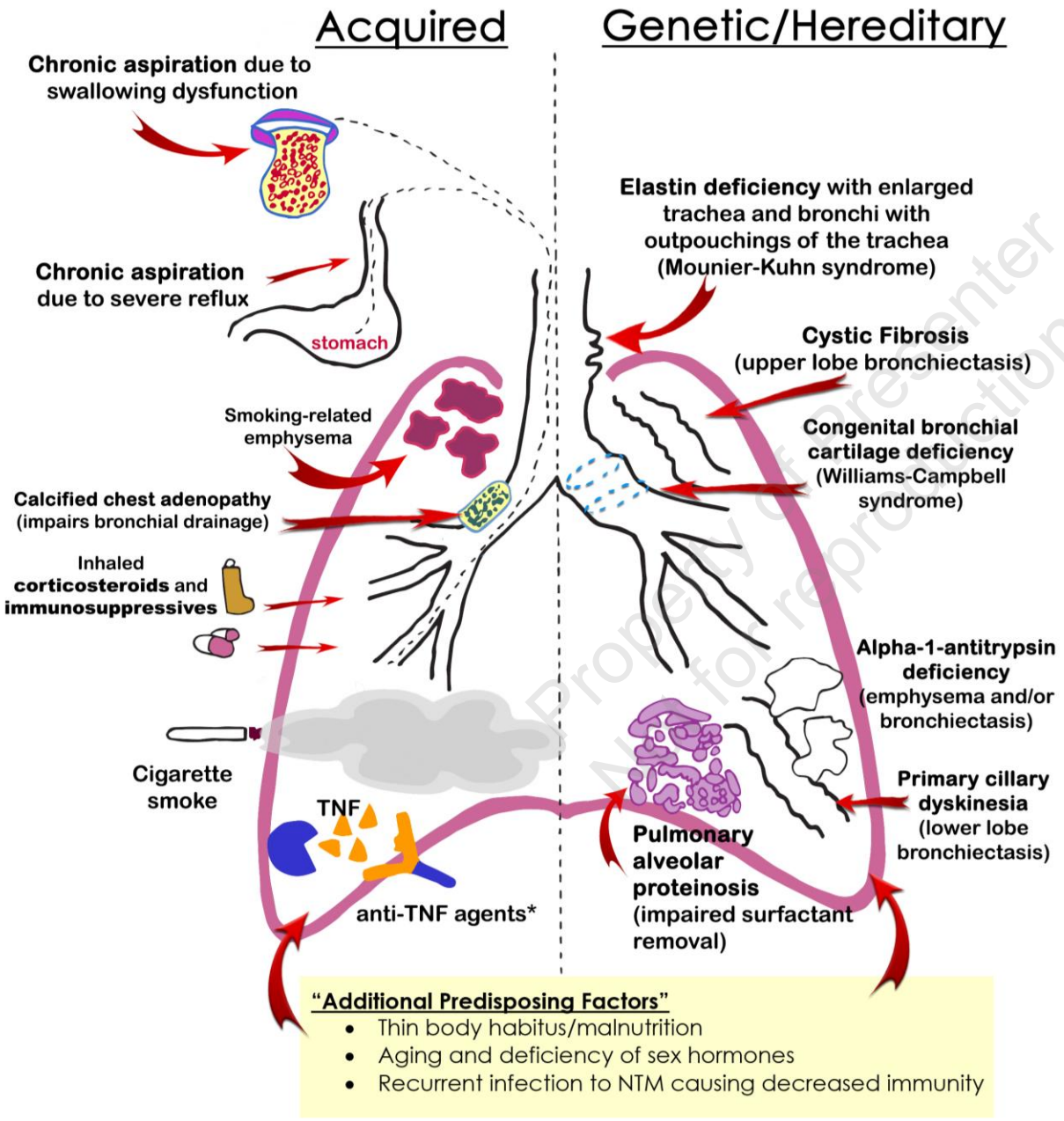
Coronary artery bypass graft surgery is lowest risk

- A 22-year-old man had undergone mechanical aortic valve replacement.
- He presented **~1.5 years later** with drenching night sweats & chest pains.
- Aortic dissection with pseudoaneurysm with false lumen (red arrow).
- Underwent prosthetic aortic grafting with intraoperative tissues +ve for *M. chimaera*.

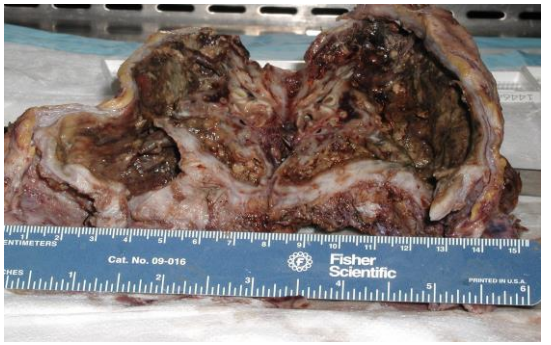


O'Neil CR et al. OFID 2018

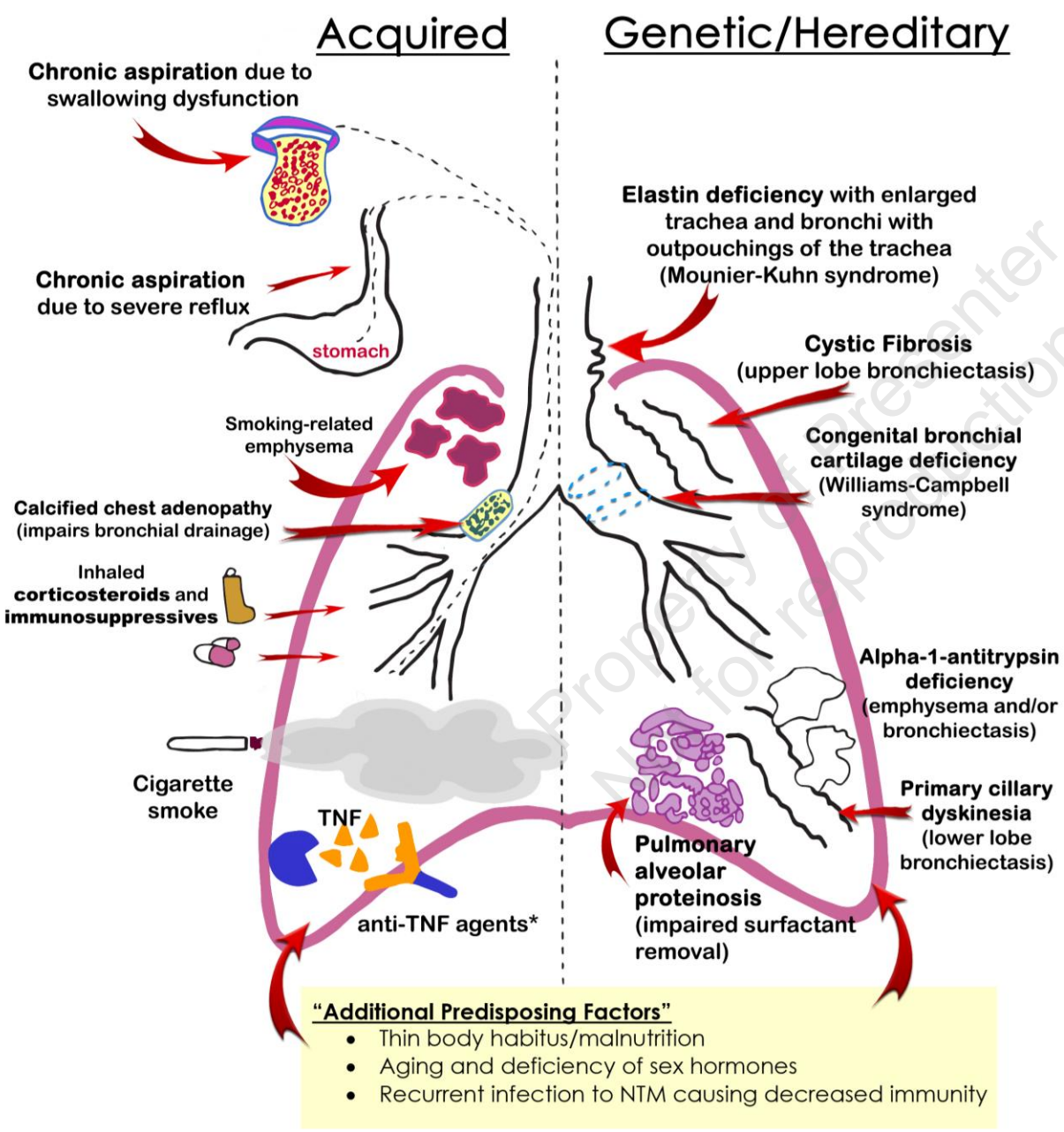
Risk factors for NTM lung disease

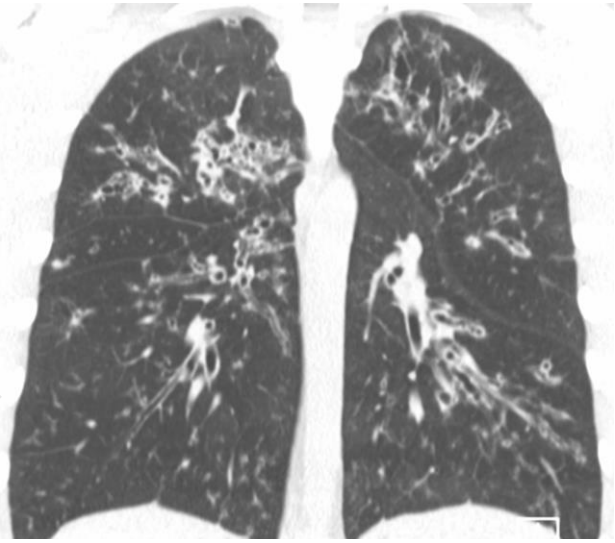


55-year-old Asian woman from Hawaii with remote history of TB

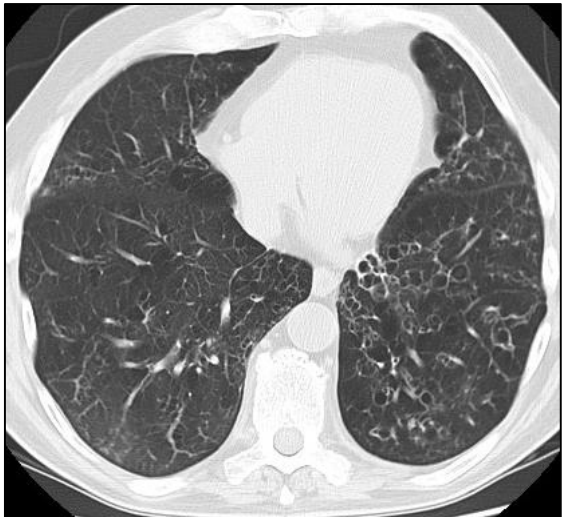


Q1: What are the underlying causes for BXSIS ± NTM-LD ?



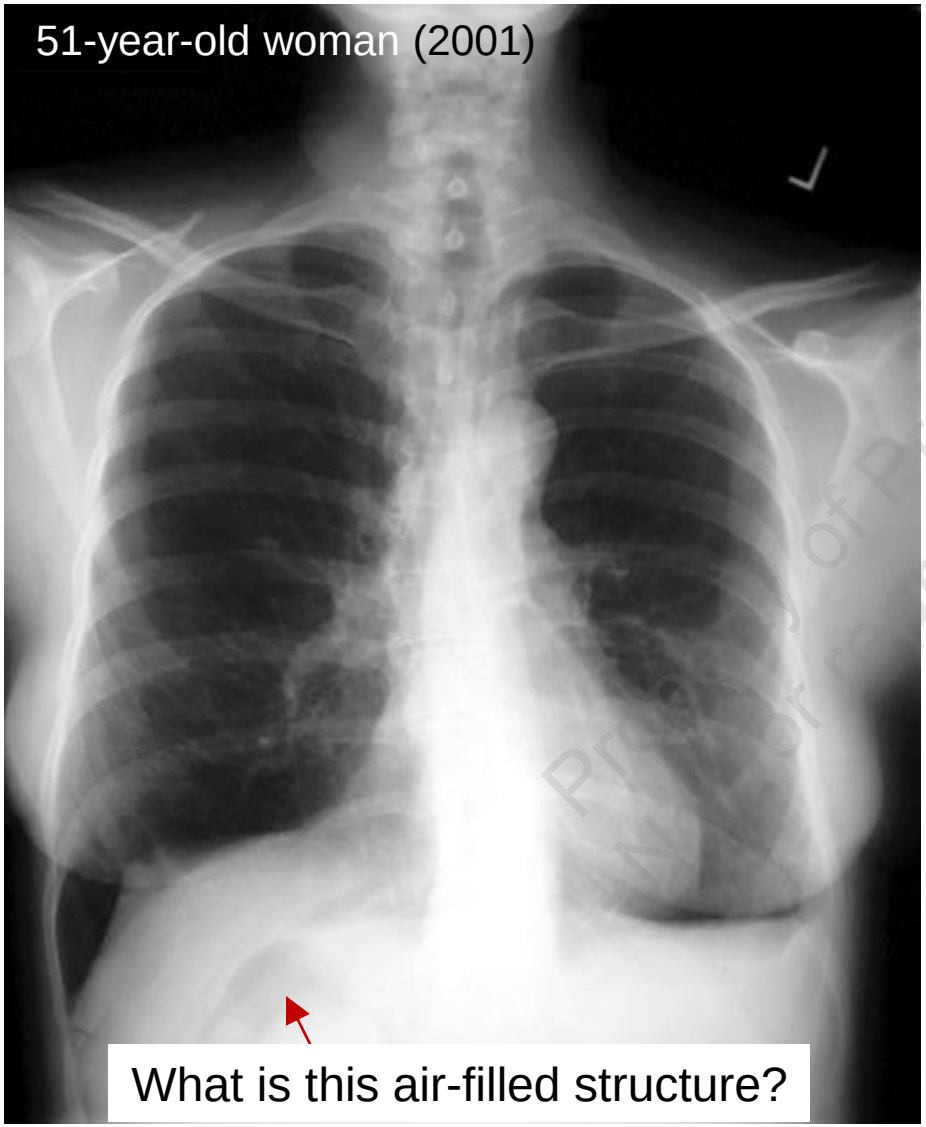


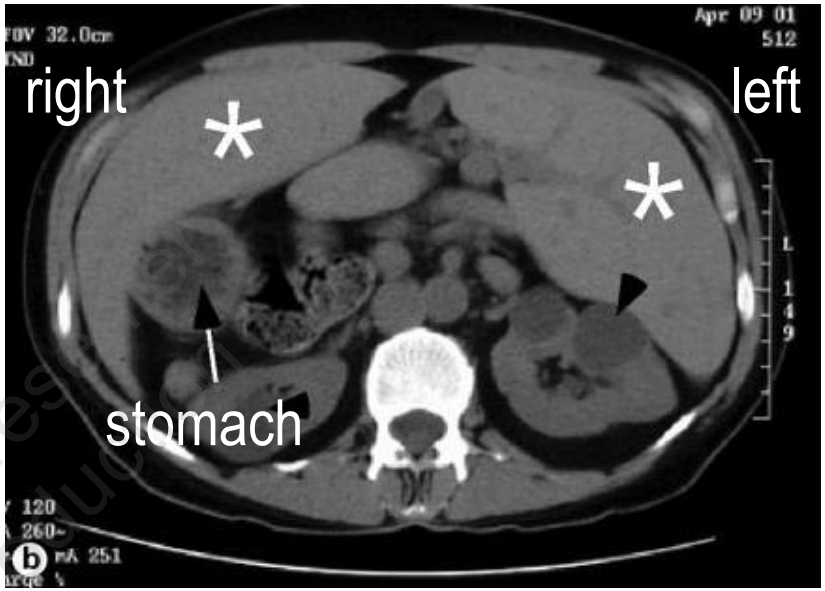
A 66 –year-old woman with CF

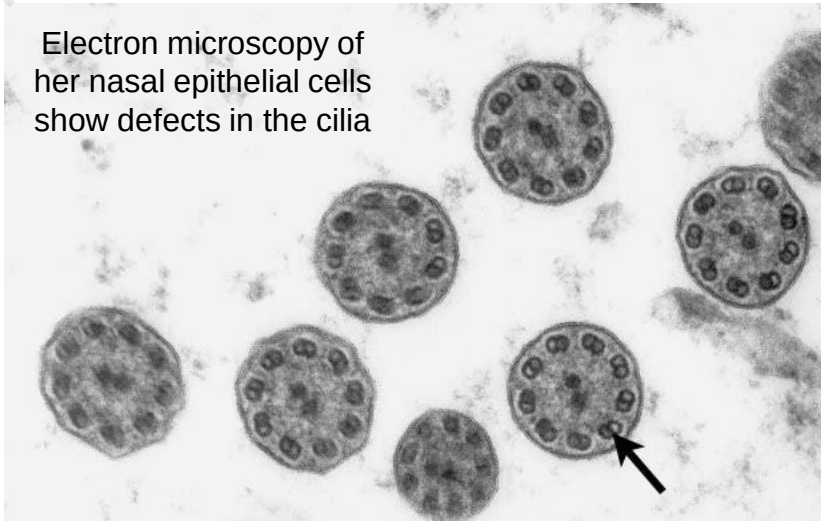


A 65 –year-old man with alpha-1-antitrypsin deficiency

Q2: What is the underlying cause for the BXSIS + NTM-LD?

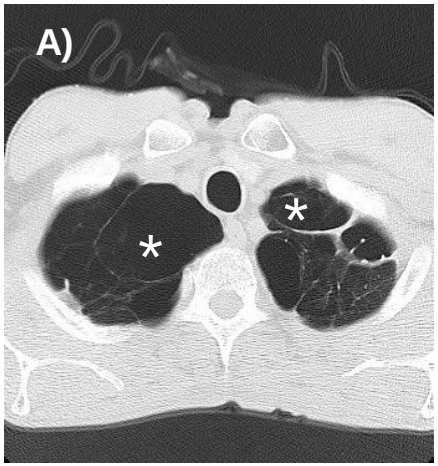


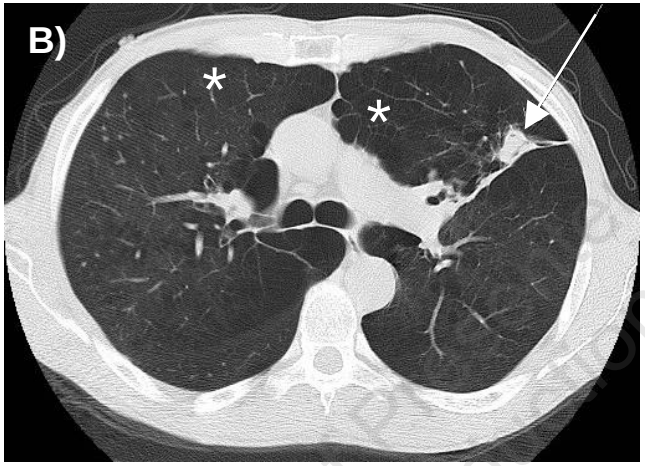


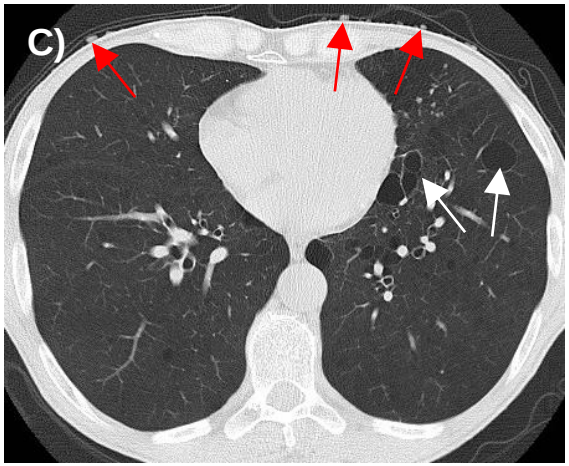


She has **primary ciliary dyskinesia** resulting in situs ambiguous of her internal organs

Q3: What is the underlying cause for the emphysema, lung cysts, and *M. avium* complex-LD in a 63-year-old male veteran?





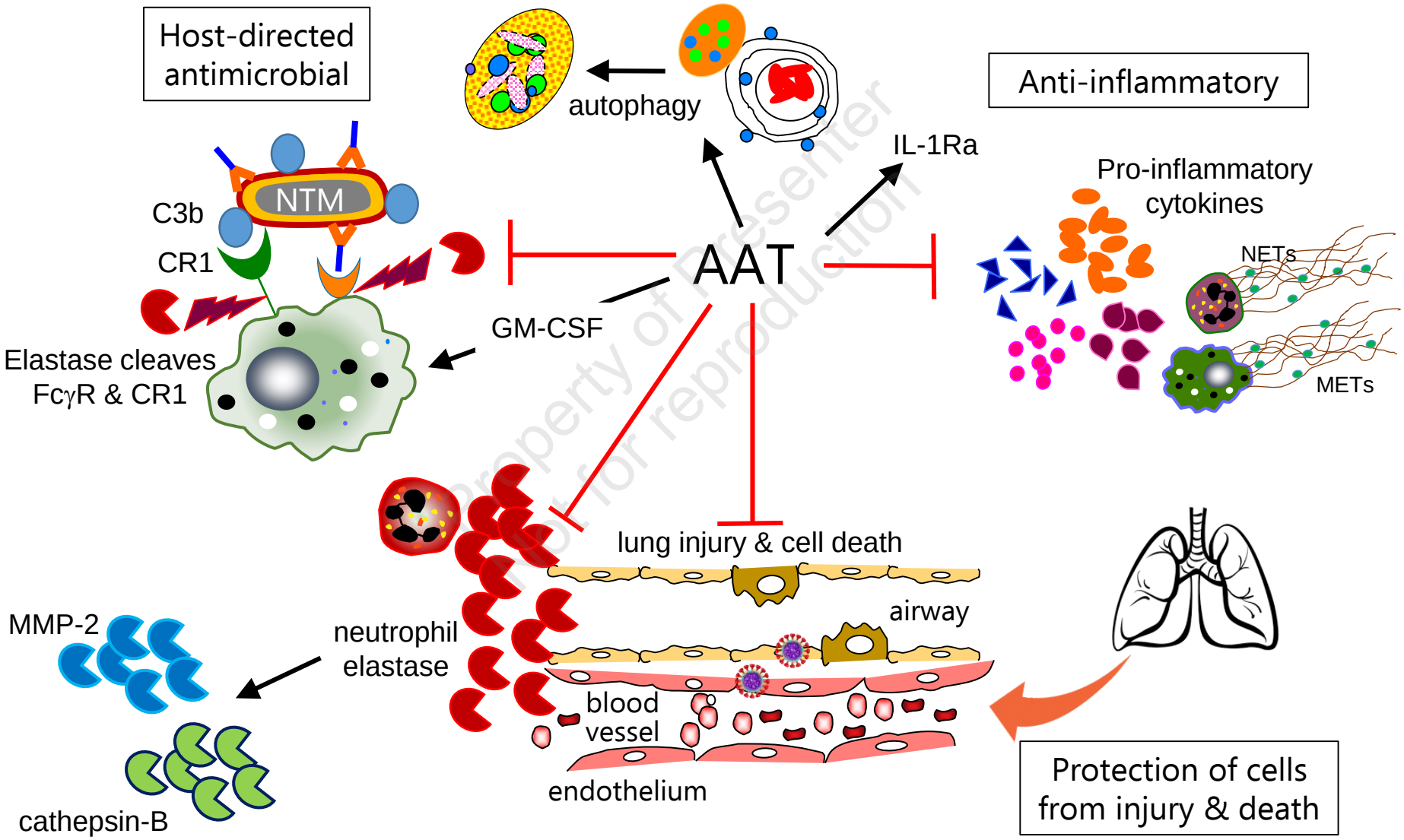


Not the same patient

Not the same patient

Neurofibromatosis
(von Recklinghausen's disease)

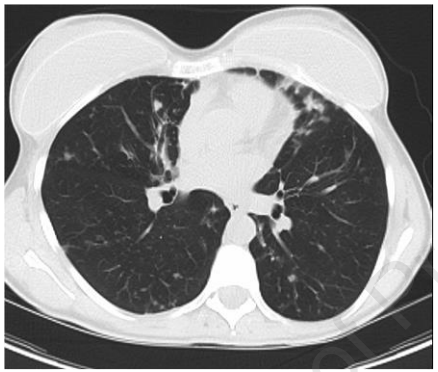
Why patients with AAT deficiency have increased vulnerability to NTM lung disease

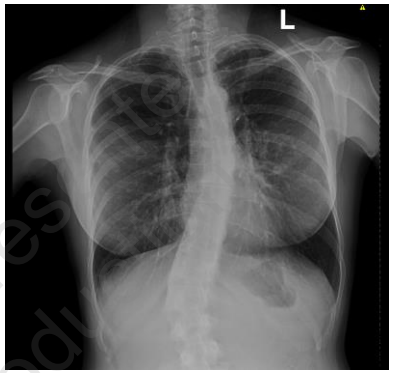


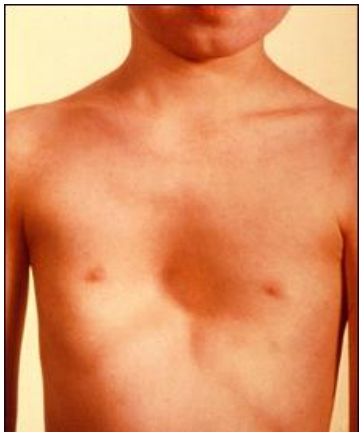
What about those without obvious risk factors?

- A significant number have a life-long slender body habitus, scoliosis, & pectus excavatum.

A 41-year-old previously healthy woman life-long slender body habitus, severe scoliosis, and NTM lung disease



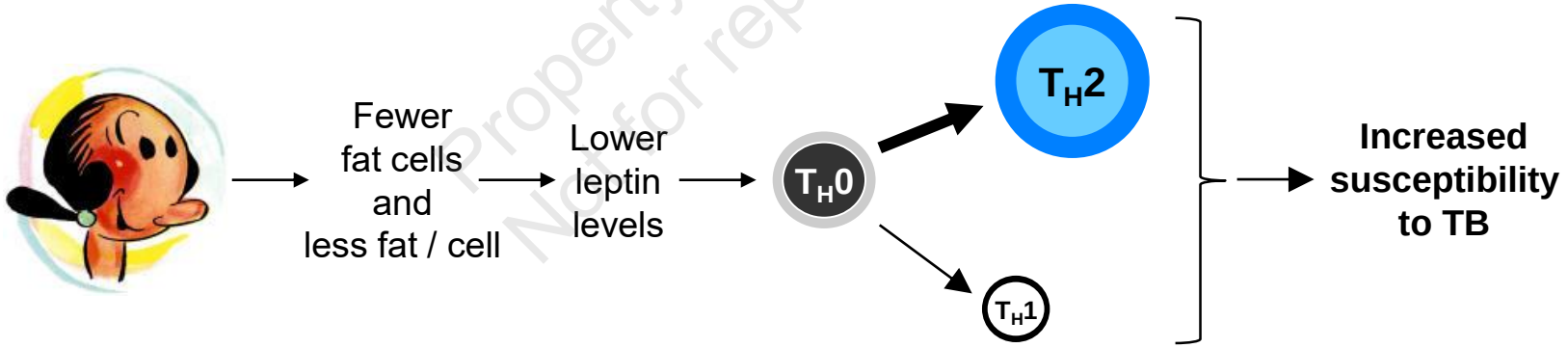




- Reich and Johnson described 29 patients (all women with no obvious risk factors) with NTM lung disease, localized mostly in the right middle lobe and lingula (Chest 1992).
  - They coined the eponym “Lady Windermere syndrome” because they posited that some women are more vulnerable to NTM-LD because of “voluntary cough suppression.”
  - While they did not allude that these patients have slender body habitus or thoracic cage abnormalities, “Lady Windermere syndrome” has become synonymous with women with NTM-LD with this body phenotype.

If thin individuals are more susceptible (as has well documented with TB), why could that be?

- Hypothesis: due to a relative deficiency of leptin.
- Leptin is a satiety hormone produced by fat cells: the more fat one has → the more leptin is produced.
- Leptin also skews the adaptive immunity toward the host-protective T_H1 (IFNγ-producing) phenotype.
- Thus, thin individuals → less leptin → less IFNγ-producing T_H1 cells.



- Leptin-deficient mice are more susceptible to *M. tuberculosis* and *M. abscessus*.

Wieland CW et al. Int Immunol 2005
Ordway D et al. J Leuk Biol 2008

Another hypothesis of why patients without obvious risk factors get NTM-LD

Mutation of *FIBRILLIN-1 (FBN-1)* gene
(Marfan or Marfanoid syndrome)

Increased tissue TGFβ → Decreased tissue IFNγ

Abnormal connective tissue → Increased predisposition to bronchiectasis

Increased vulnerability to NTM-LD

Tun MH et al. J Thorac Dis 2021

Mitral valve prolapse
Aortic dissection
Retinal detachment
Fibrillin-1 mutation
Arachnodactyly
Near-sightedness
Scoliosis

Dilated dural sac

- Dural sac diameter measured in 4 groups: no lung disease, idiopathic bronchiectasis, CF, and Marfan.
- The L1-L5 dural sac diameter was significantly larger in idiopathic bronchiectasis compared to controls and CF.
- Dural sac diameter correlated with the presence of NTM-LD and long fingers.

Daniels ML et al. Ann ATS 2016

Whole Exome Gene Sequencing of 11 NTM-LD patients with PEX/scoliosis

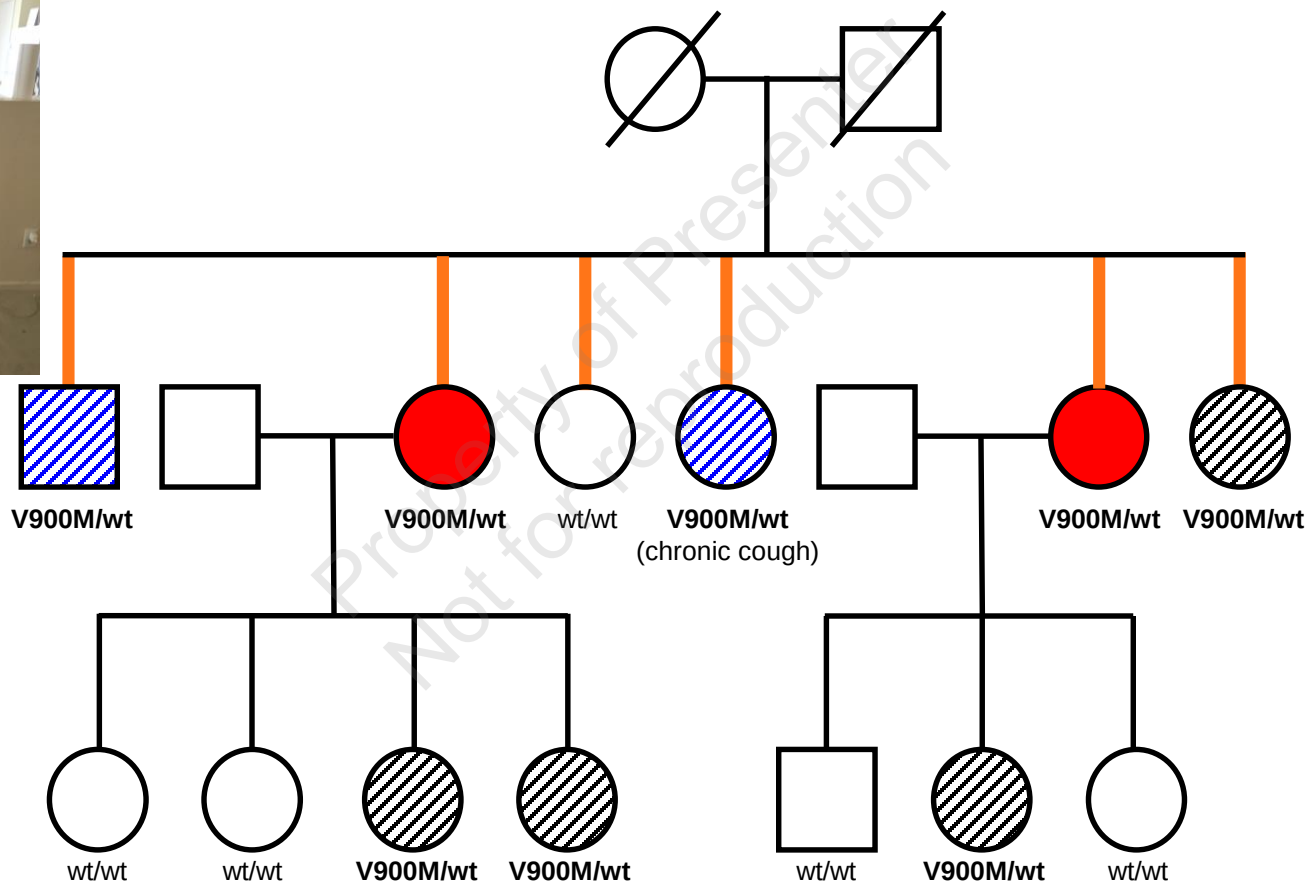
Patient number	Study No.	%body fat or BMI	PEX	Scoliosis	Key gene variant found
1	63682	21%	Yes	Yes	Δ*fibrillin-1*, Δ*IFNγR1*
2	63690	21%	Yes	Yes	***ΔMST1R***
3 (sister of 2)	63685	17.5 kg/m^2	Yes	Straight back	***ΔMST1R***
4	63688	25%	Yes	Yes	
5	63683	21.5 kg/m^2	Yes	Yes	*ΔTGFβ-induced*
6	63687	28%	Yes	Yes	
7	63684	25%	Yes	Yes	
8	63686	27%	Yes	Yes	
9	63692	25%	Yes	Yes	***ΔMST1R***
10	63691	21 kg/m^2	Yes	Yes	***ΔMST1R***
11	63689	23 kg/m^2	Yes	Yes	

MST1R = Macrophage Stimulating-1 Receptor, aka RON (recepteur d'origine nantais)

Targeted Sanger sequencing of 29 pNTM patients without PEX or scoliosis do NOT have ΔMST1R

Familial analysis of two sisters (Patients 2 and 3) with *ΔMST1R*

PEX
Recurrent pneumonia
Throat clearing



Summary: 5 of 6 sibs have ΔMST1R; 4 of 5 with ΔMST1R have chronic respiratory symptoms

MST1R is known to enhance airway ciliary function!

- MST1R is a **cell surface receptor with tyrosine kinase activity**, expressed on the apical surface of human ciliated airway and fallopian tubes.
- Macrophage-stimulating protein (MSP) is the ligand to MST1R. Addition of MSP to human nasal ciliated epithelium significantly increases ciliary beat frequency.

Sakamoto O et al. Role of macrophage-stimulating protein and its receptor, RON tyrosine kinase, in ciliary motility. J Clin Invest 1997.
Takano Y et al. Elevated levels of macrophage-stimulating protein in induced sputum of patients with bronchiectasis. Respir Med 2000.
Becker K et al. MST1R mutation as a genetic cause of Lady Windermere syndrome. Eur Respir J 2017

Hypothesized mechanisms of how *FBN-1* and *MST1R* mutations may predispose to NTM

ΔFBN-1

↑TGFβ activity

↑Bronchiectasis

↓IFNγ activity

ΔMST1R

↓Ciliary beat frequency

↓IFNγ activity

Vulnerability to NTM lung disease

Multigenic disorder increasing vulnerability to NTM-LD: Mutation of multiple minor genes

- Whole exome sequencing (WES) of 15 NTM-LD patients (from 9 families), 18 unaffected family members, and 54 sporadic NTM-LD patients.
- Compared their WES data to control sequencing data from the 1000 Genomes Project of 300+ Caucasian subjects.
- No dominant gene variant ("mutation") found.
- Candidate gene analysis using the following gene categories:
  - **Connective tissue gene mutations (including FBN-1 and FBN-2 genes)**: NTM-LD = family members **>** controls
  - **Ciliary gene mutations**: NTM-LD **>** family members ≥ controls
  - **Immune gene mutations**: NTM-LD **>** family members = controls
  - ***CFTR* gene mutations**: Family members > NTM-LD **>** controls

"**>**" signifies statistical significance ($p<0.05$)

Szymanski EP et al. Am J Respir Crit Care Med 2015

Take home points

Skin, soft tissue, and/or traumatic orthopedic NTM infection

Most have normal underlying immunity but trauma itself is immunosuppressive

Isolated NTM lung disease

Most have underlying structural lung abnormality (BXSIS or emphysema): e.g., CF, AAT deficiency, multigenic

Extrapulmonary visceral or disseminated NTM infection

Essentially all have underlying severe immunodeficiency & one should search for it

Q4: Which of the following patients is likely to have a functional defect in IFNγ signaling / function?

a. 60-year-old man with COPD and cavitary *M. avium* lung disease.

b. 60-year-old woman with isolated *M. avium* lung disease of the lingula, RML, and RUL.

c. 4-year-old girl with disseminated *M. avium*.

d. 25-year-old man with surgical wound foot infection after bunionectomy.

Q5: Which of the following are risk factors for isolated NTM lung disease? *More than one may be correct*.

a. Pulmonary alveolar proteinosis

b. Emphysema

c. Auto-antibodies to IFNγ

d. Idiopathic bronchiectasis

Q6: Greater consumption of which of the following is *least* likely to help fight NTM-LD in a person with Lady Windermere syndrome?

Bonus points: who makes the three burgers?

a. Baconator  Wendy's

b. Three-quarter Pounder  McDonald's

c. El Diablo Thick Burger  Carl's Jr

d. Celery (yummy) 

Extra bonus points: which franchise was founded first?

Carl's Jr: July 17, 1941
McDonald's: April 15, 1955
Wendy's: November 15, 1969