NTM and Bronchiectasis Physician/ Patient Conference
Georgetown University Medical Center

Why Do I (and so many others) Have NTM Lung Infections?

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Disclosures

- No conflict of interest disclosures
- No discussion of nonFDA approved drugs

Overview – Why so much NTM disease?

- We’re looking for it more
- The bug
- The environment
- The host

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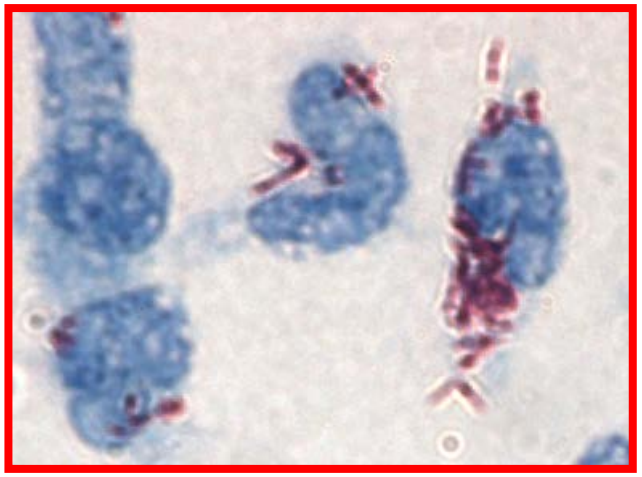
Nontuberculous Mycobacteria



- Common environmental bugs
  - Water including potable, soil
- >150 species
  - *M. avium* complex
  - *M. abscessus* group
  - *M. kansasii*
- Clinical
  - Lung (85%)
  - Skin, soft tissues
  - Disseminated

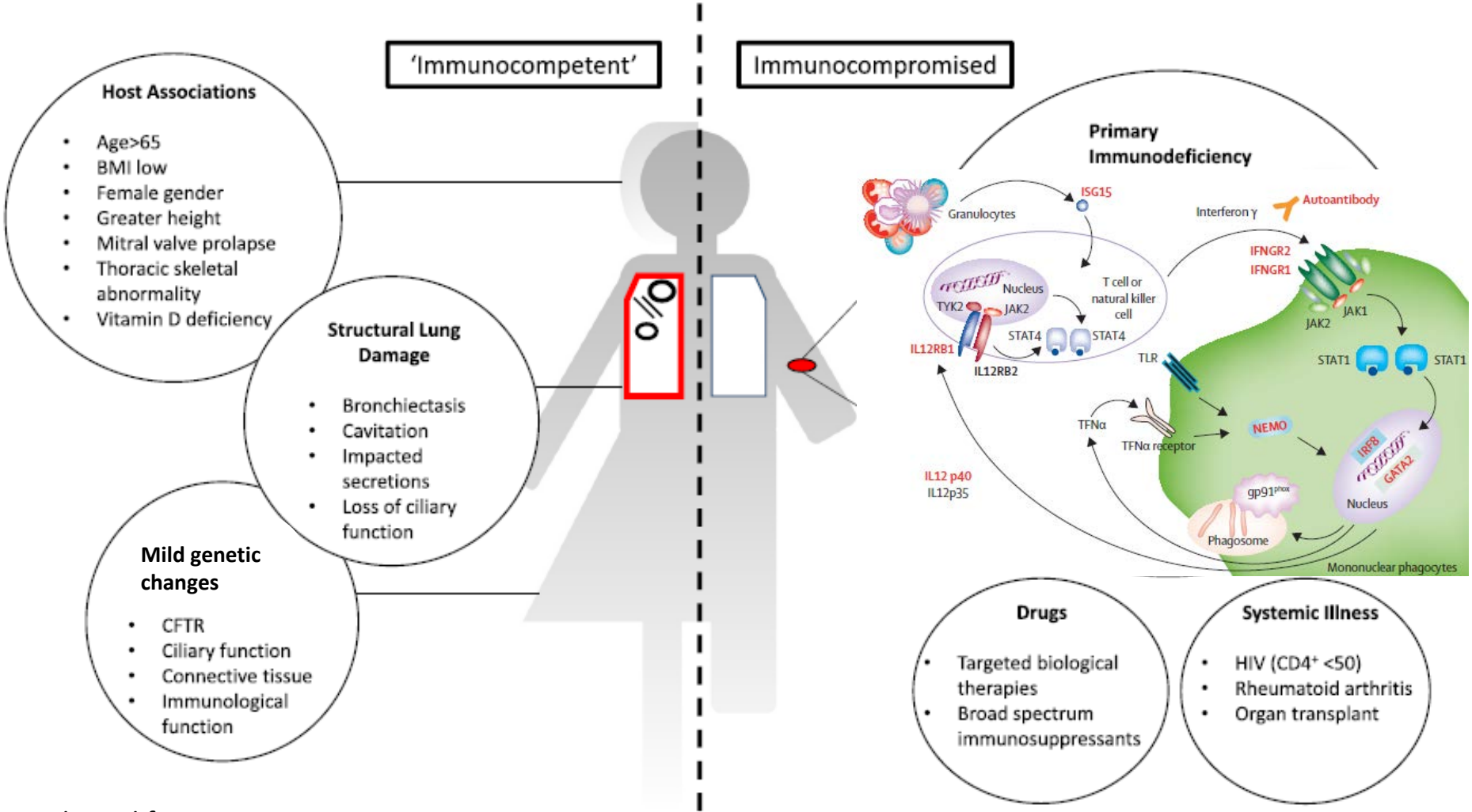
“Unusual dose” vs. “Susceptible host”

vs.

“Hot Tub Lung”

“Lady Windermere”

NTM Host Risk Factors



Adapted from:
Lake. BMC Medicine 2016
Wu. Lancet Infect Dis 2015

Host Susceptibility

- Varies by organism & anatomic location of infection

Disease Severity *or* Treatment Refractory ≠ **Immunodeficiency**

Susceptibility to NTM Pulmonary Disease

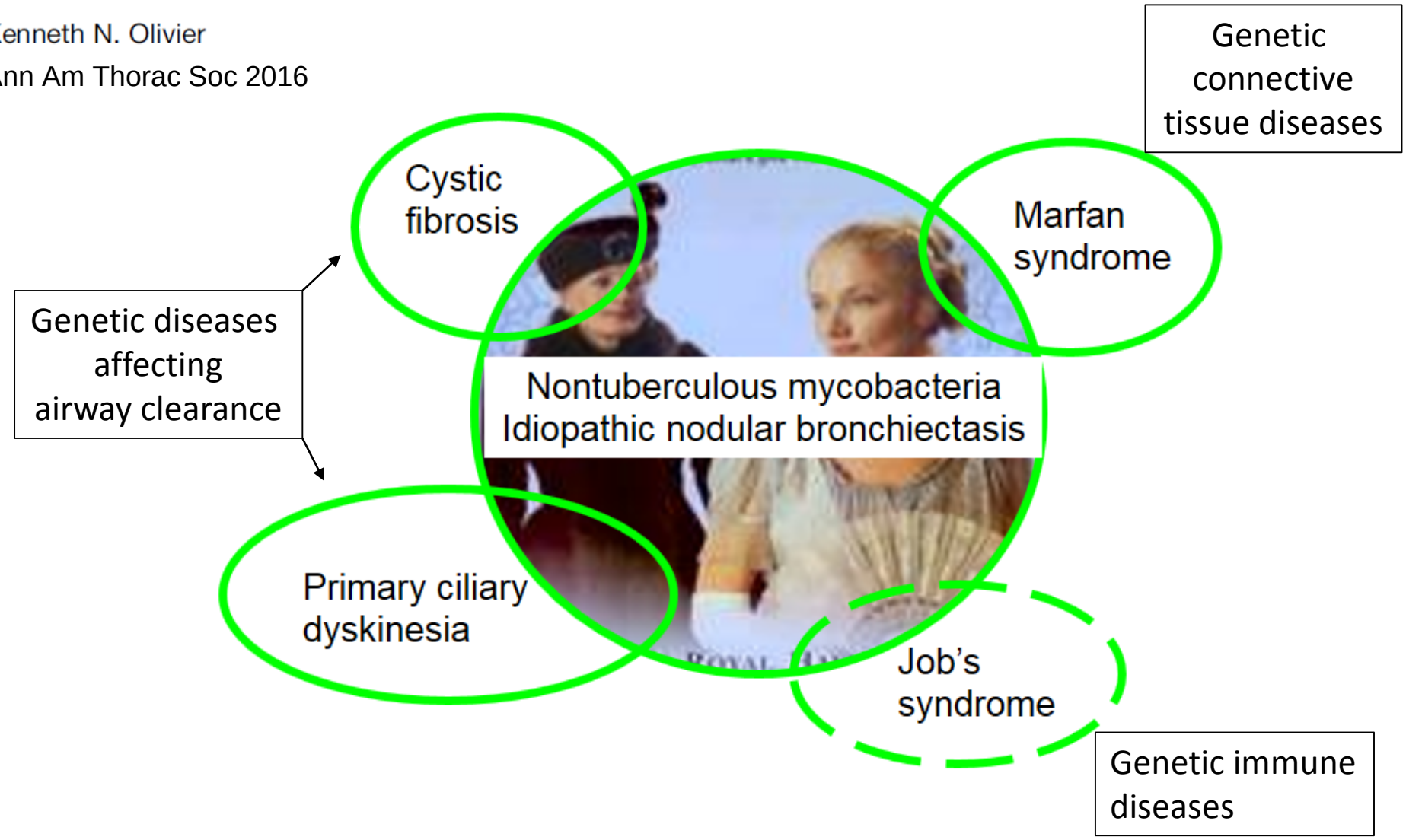
Impaired local defenses Bronchiectasis, COPD, coal/gold miners, sand blasters, previous cavitary tuberculosis	Clinical history, chest imaging, pulmonary function tests
Alpha-1 antitrypsin deficiency	A1AT phenotype, level, genetic testing
Cystic fibrosis	Sweat chloride test, genetic testing
Alveolar proteinosis	Chest imaging, bronchoscopy or biopsy, anti-GMCSF antibody levels
Primary ciliary dyskinesia	Measurement of nasal nitric oxide, cardinal clinical features, biopsy for electron microscopy (cilia structure), genetic testing (38+ genes)
Impaired systemic immunity Job's syndrome	Total IgE, cardinal clinical features & family history, genetic testing
Immunosuppressant use Tumor necrosis factor-α blockers	Drug history
Lady Windermere syndrome	Clinical history with exclusion of above risk factors, unique physical features

Adapted from Wu. Lancet Infect Dis 2015

Lady Windermere Dissected: More Form Than Fastidious

Kenneth N. Olivier

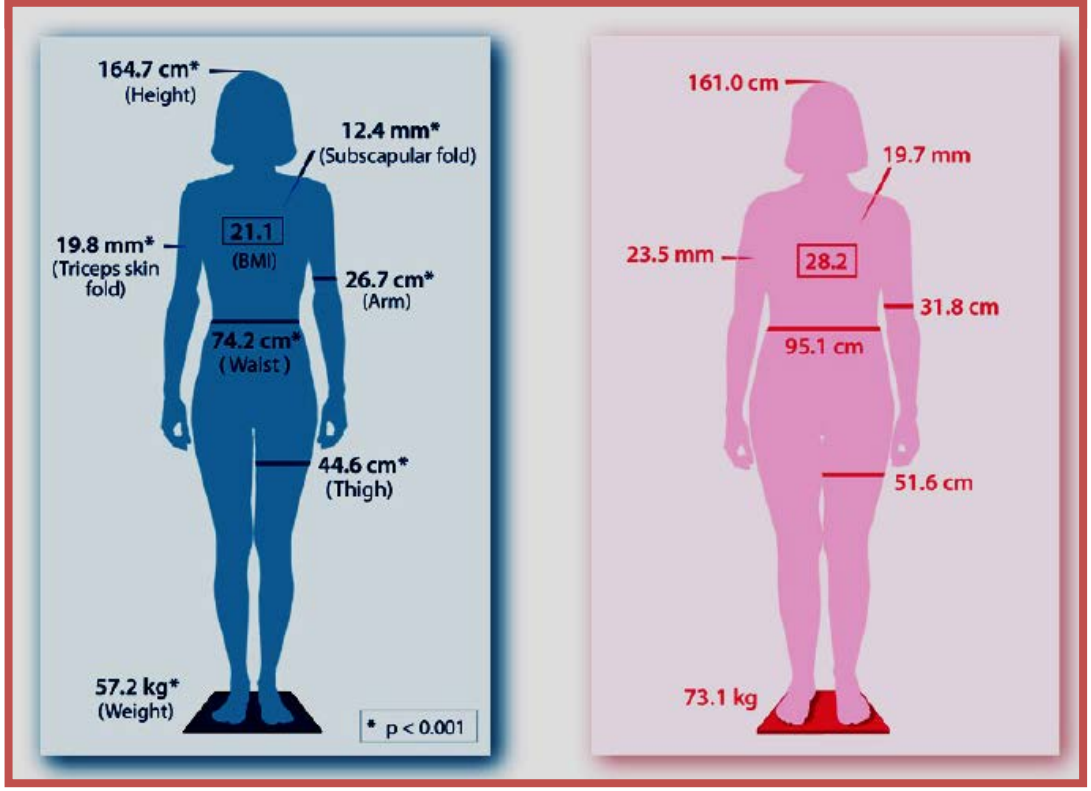
Ann Am Thorac Soc 2016



Physical Features

Kim RD, et al. Am J Resp Crit Care Med 2008

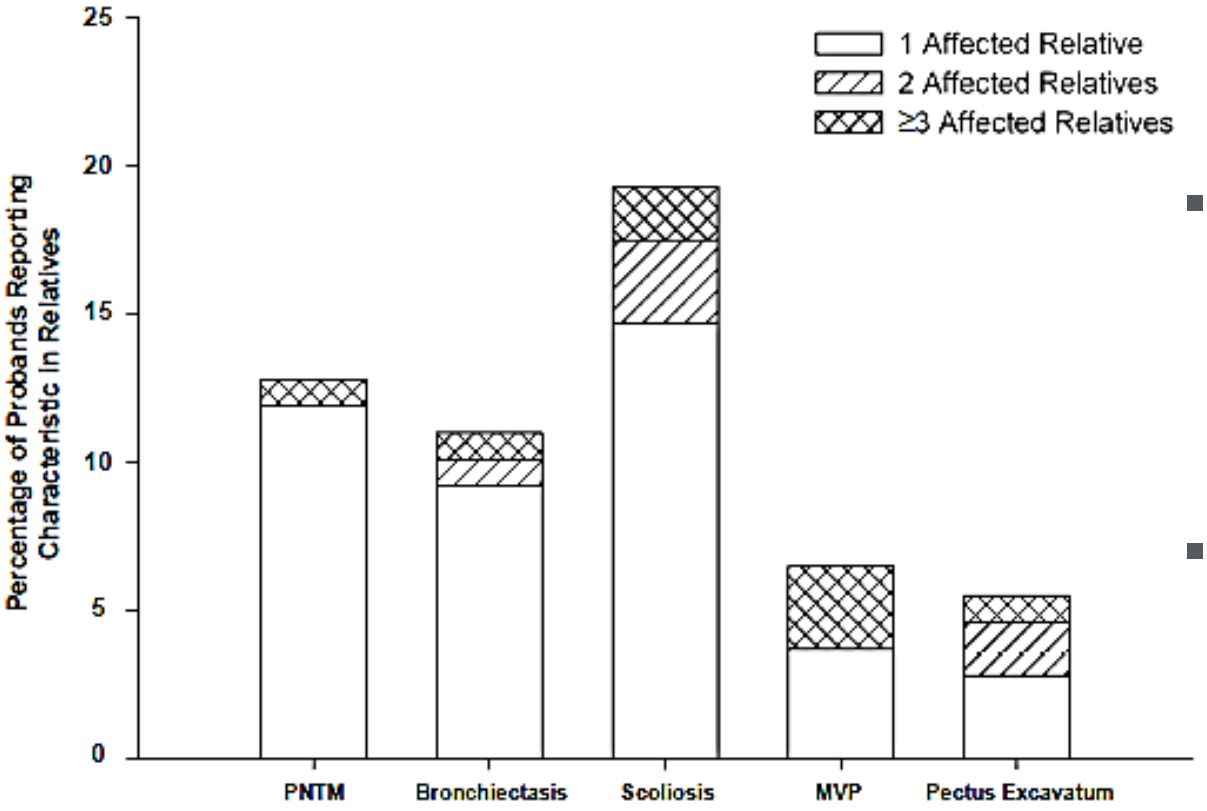
Measurement	% PNTM (n=63)	% General Population	P values
Scoliosis	51 (23)	1.9	<0.001
Pectus excavatum	11 (7)	1	<0.001
Mitral valve prolapse	9 (5/56)	2.4	0.004



Pulmonary Nontuberculous Mycobacterial Disease

NHANES Controls

Familial traits

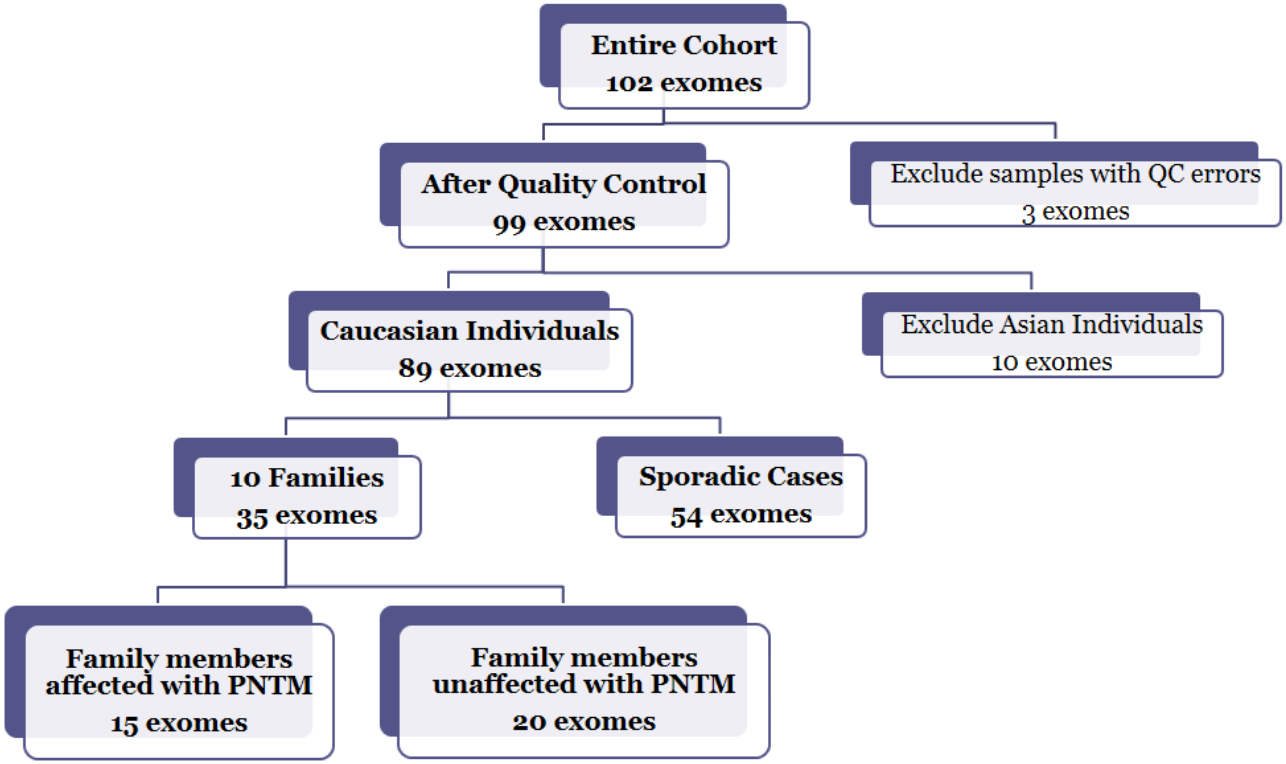


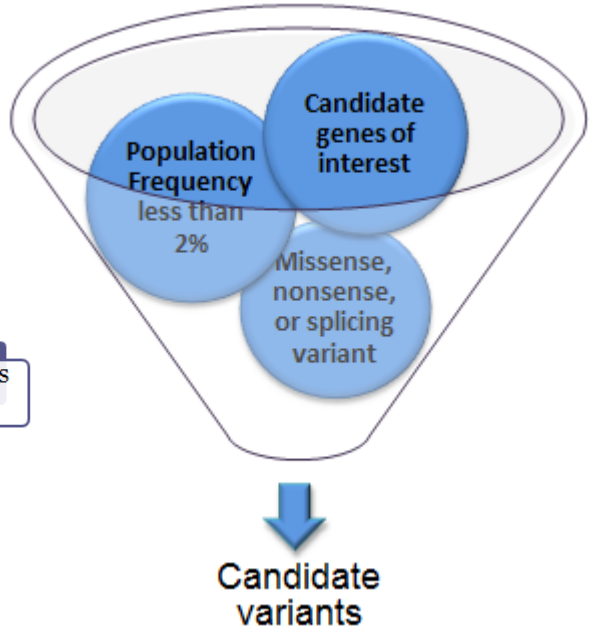
- 14 (12.8%) at least 1 relative with PNTM
  - 8 sibling pairs
  - 4 parent-child
  - 2 aunt-niece
- 13 (11.9%) had relatives with bronchiectasis

Leung. Am J Respir Crit Care Med 2013

PNTM Exome Sequencing Study*

*Looking for rare, protein-altering gene changes that may increase risk of developing PNTM disease





1. CF
2. Cilia
3. Connective tissue
4. Immune

Szymanski EP. Am J Respir Crit Care Med 2015

NIH National Heart, Lung, and Blood Institute

Whole Exome Analysis Results

- PNTM patients *&* unaffected family members vs. controls
  - More changes in CF, cilia, & connective tissue genes
  - No difference - PNTM patients & unaffected family members
- What about “unaffected” family members?
  - Many had bronchiectasis and/or overlapping physical features
- More *immune gene* changes only in *PNTM* affected
- Whole exome data support
  - “Susceptible persons” model of PNTM disease
  - The more “mild” changes you have in relevant gene categories, the greater risk of developing bronchiectasis and PNTM

Host-Environment-Pathogen