2019 NTM & Bronchiectasis
Physician/Patient Conference

Patient Phenotypes in NTM & Bronchiectasis

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National Heart, Lung, and Blood Institute

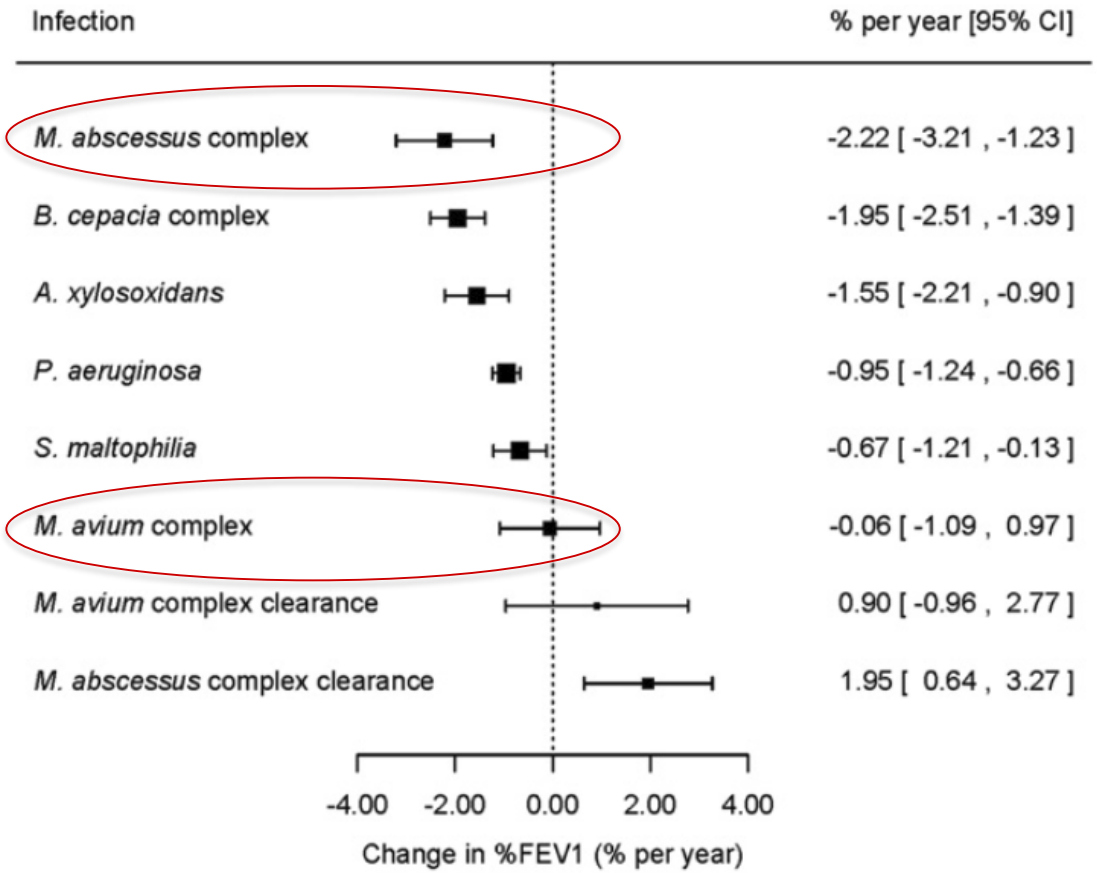
Disclosures

- Relationships with commercial interest:
  - Cooperative Research and Development Agreements
    - (NHLBI) with AIT Therapeutics
    - (NHLBI) with Matinas BioPharma
    - (Past NIAID) with Insmed
- External Grant Review Committee
  - Colorado Cystic Fibrosis Research & Development Program

NTM Phenotypes

- Why is this important?
  - Heterogeneity in clinical trials can lead to failures of promising Rx
    - Different phenotypes may respond differently to specific drugs
  - Different phenotypes can have different prognosis
- Phenotype categorizations for NTM
  - By organism
  - By radiographic presentation
  - By associated conditions/co-morbidities

MAC vs MABS



Qvist. J Cyst Fibros 2016

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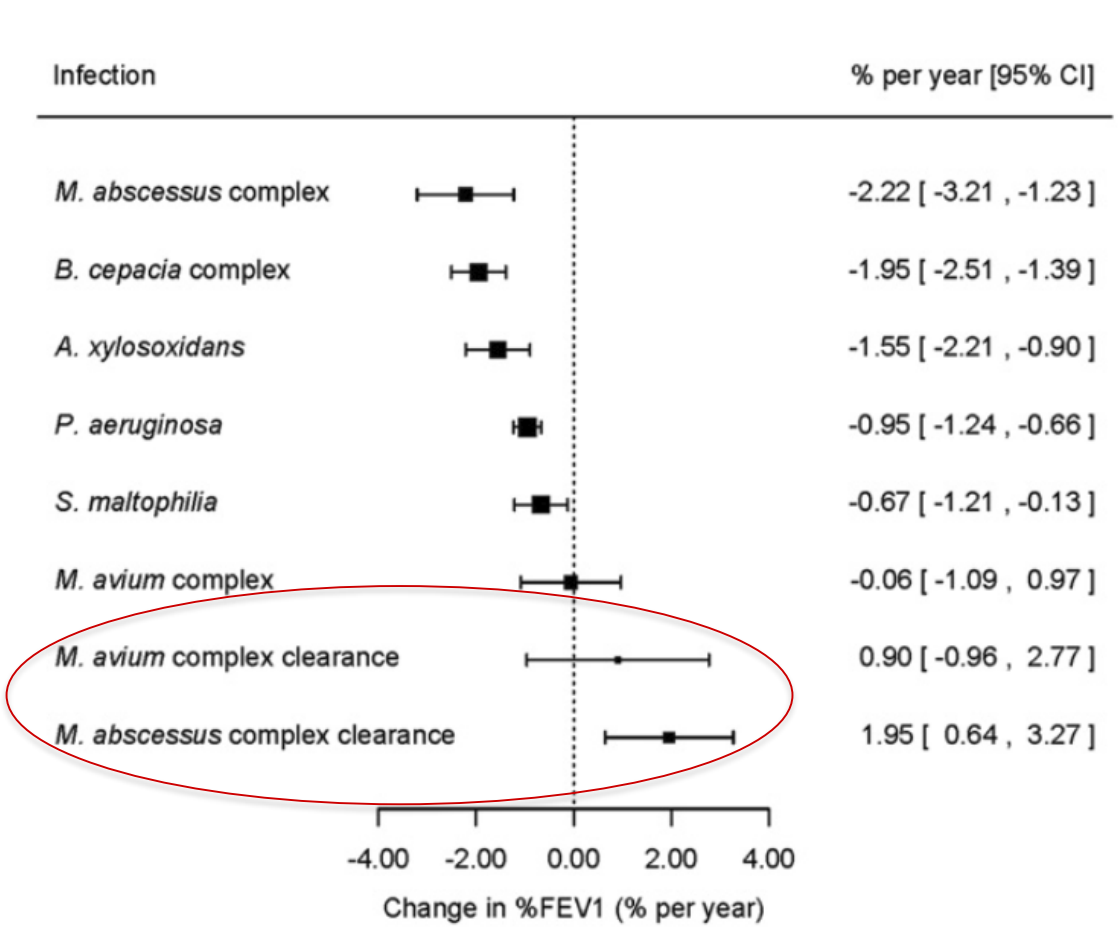

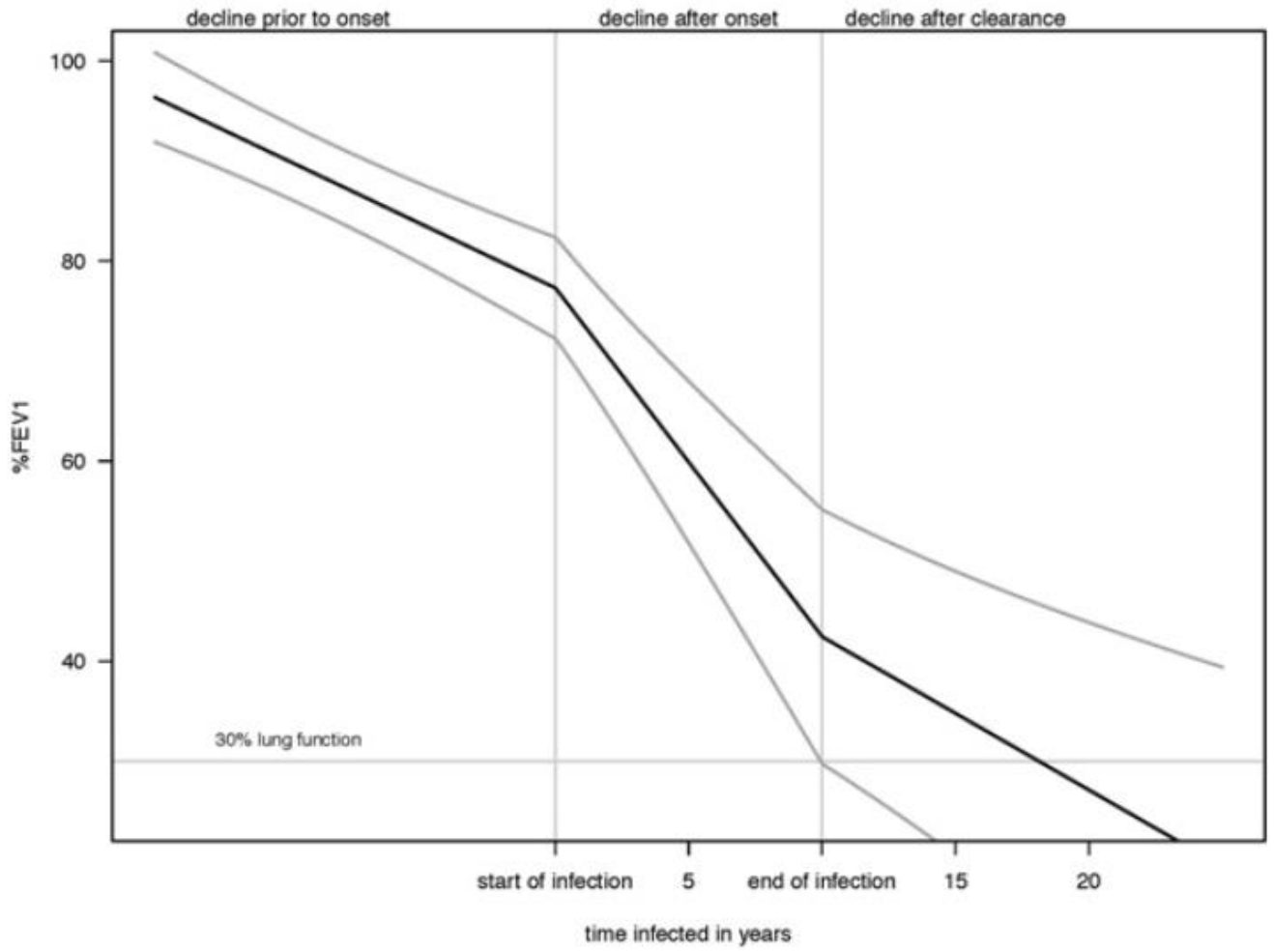

Qvist. J Cyst Fibros 2016

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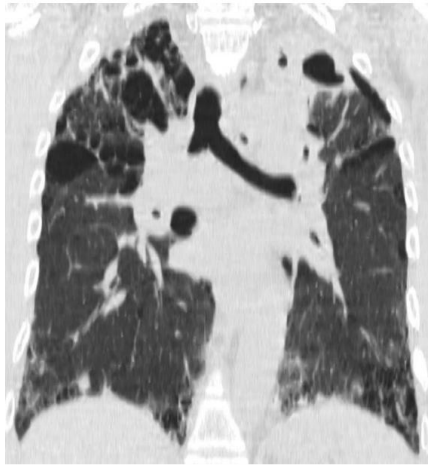
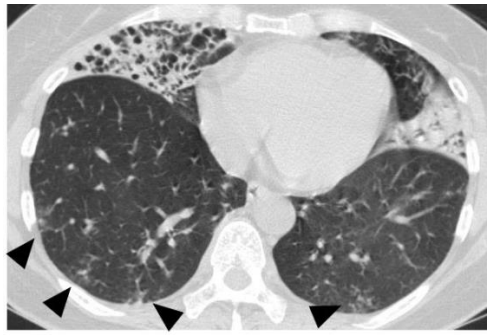
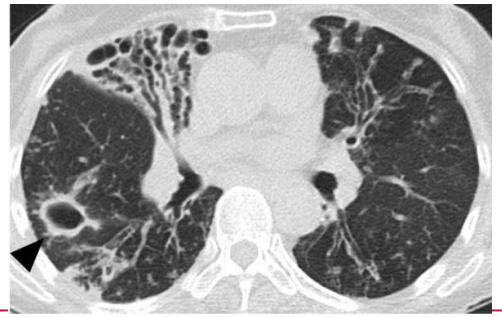
Nodular, bronchiectatic, cavitary, fibrocavitary…



- Fibrocavitary (FC)
  - Cavitary lesions, pleural thickening predominantly in upper lobes
  - Predominantly older males
    - Previous pulmonary tuberculosis
    - COPD
- Nodular bronchiectatic (NC-NB)
  - Bilateral bronchiectasis with multiple nodules (tree-in-bud opacities)
  - Predominantly postmenopausal, nonsmoking females
- Cavitary nodular bronchiectatic (C-NB)
  - Some NB also have small cavities





Koh. Eur Respir J 2017

Nodular, bronchiectatic, cavitary, fibrocavitary…

- Favorable outcome (culture conversion **+** ⩾12 mos (-) cultures) on ATS/IDSA regimen

	Favorable	Unfavorable	Univariate aOR	Multivariate aOR
Subjects	**402 (84%)**	79 (16%)		
Male sex	153 (38)	43 (54)	**1.94** (1.20, 3.16)	**1.80** (1.07, 3.02)
Disease Type				
NC-NB	246 (61)	32 (41)	**1.00** Ref.	**1.00** Ref.
C-NB	62 (15)	18 (23)	**2.23** (1.07–4.65)	**2.36** (1.24–4.52)
FC	94 (23)	29 (37)	**2.37** (1.26–4.48)	**1.99** (1.11–3.54)

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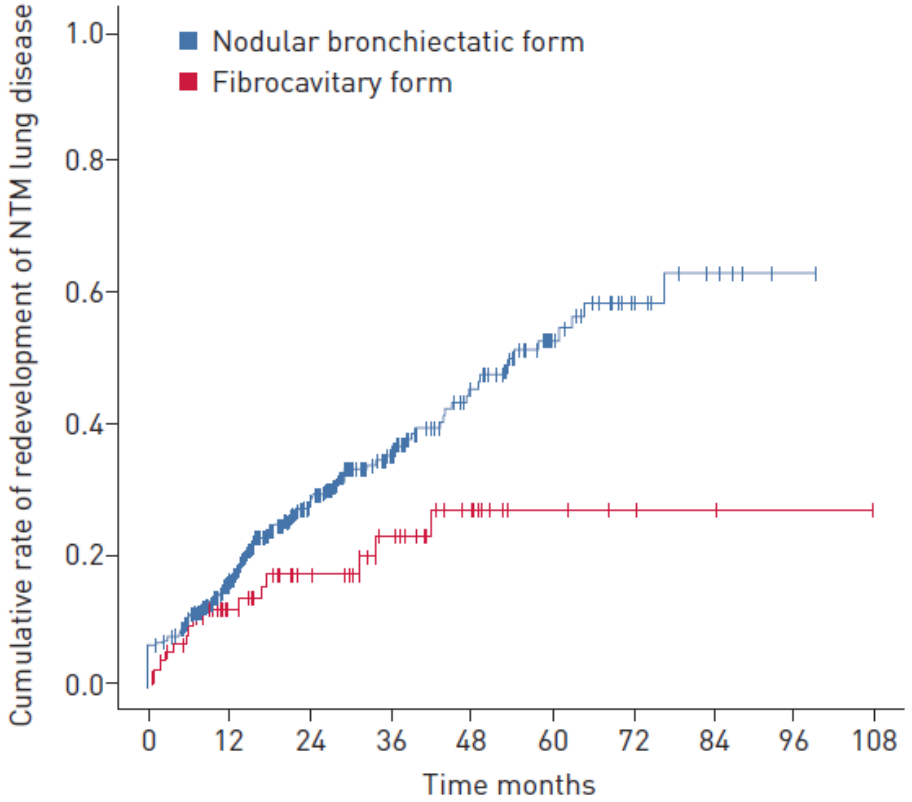

Koh. Eur Respir J 2017

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Cystic fibrosis vs “nonCF bronchiectasis”

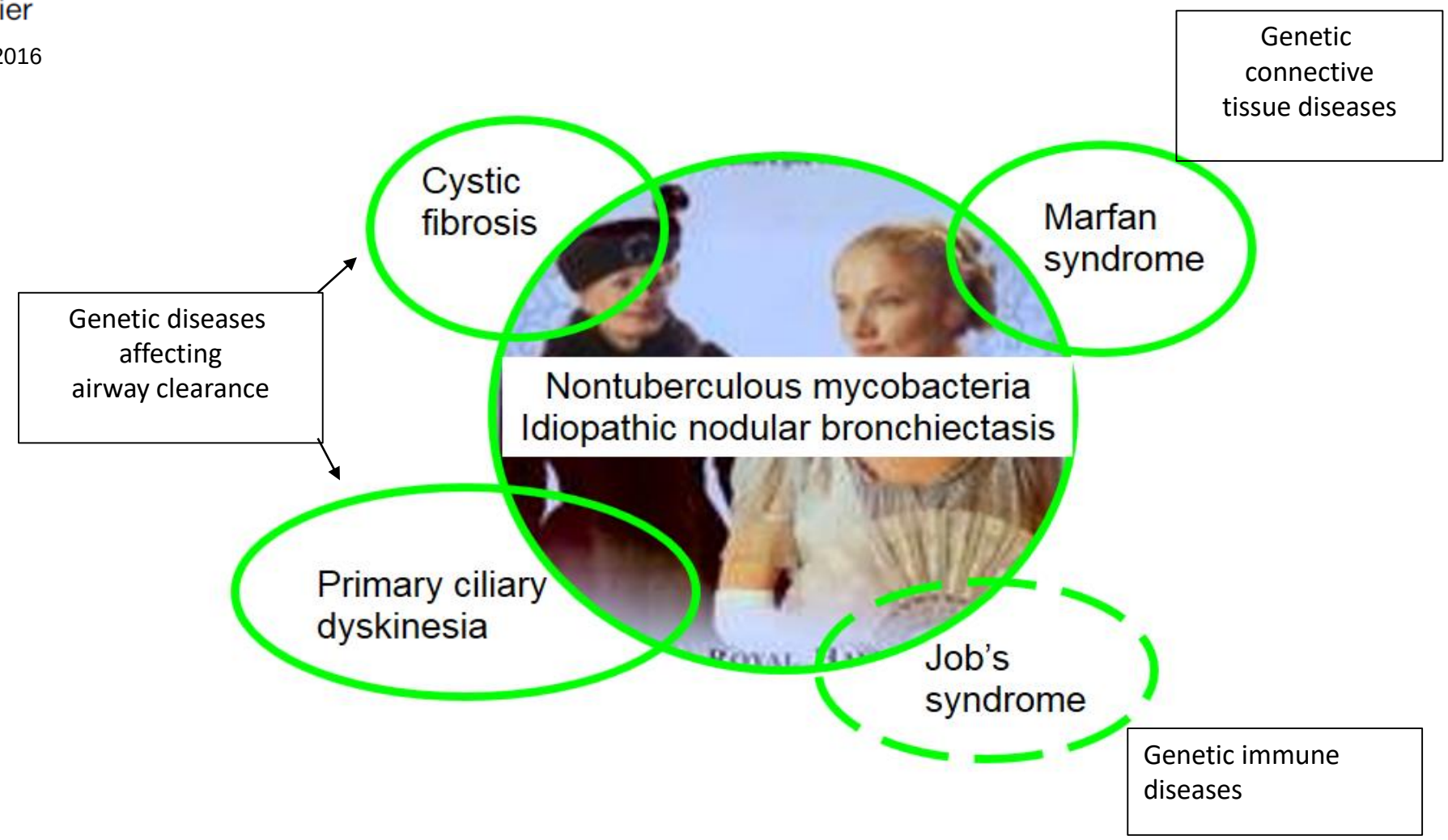
- NTM & CF
  - Monogenic disease with known mechanisms of pathogenesis
  - Relative skew toward younger age
  - Increasing prevalence of Mabs relative to Mac
  - FEV1 better predictor of disease course
  - More concomitant pathogens
  - Altered volume of distribution for some drugs
- NTM & nonCF BE
  - Multiple disorders, etiologies, potential mechanisms of pathogenesis
  - Skewed toward older women
  - Mac by far most prevalent NTM
  - FEV1 likely not a good predictor of disease course
  - ? Fewer exacerbations
  - Tends to distribute to mid lung zones

Aksamit. Chest 2017
Binder. Am J Respir Crit Care Med 2013

Lady Windermere Dissected: More Form Than Fastidious

Kenneth N. Olivier

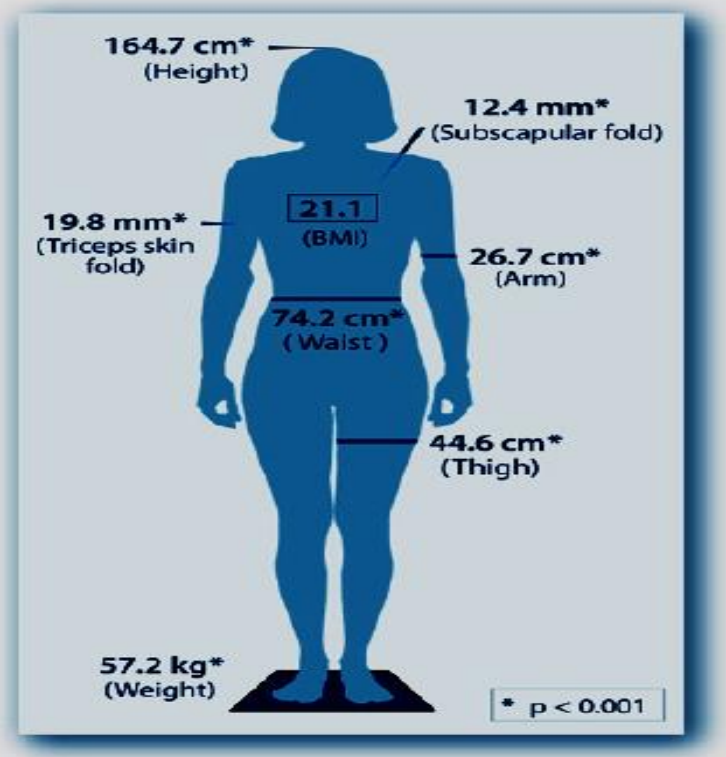
Ann Am Thorac Soc 2016

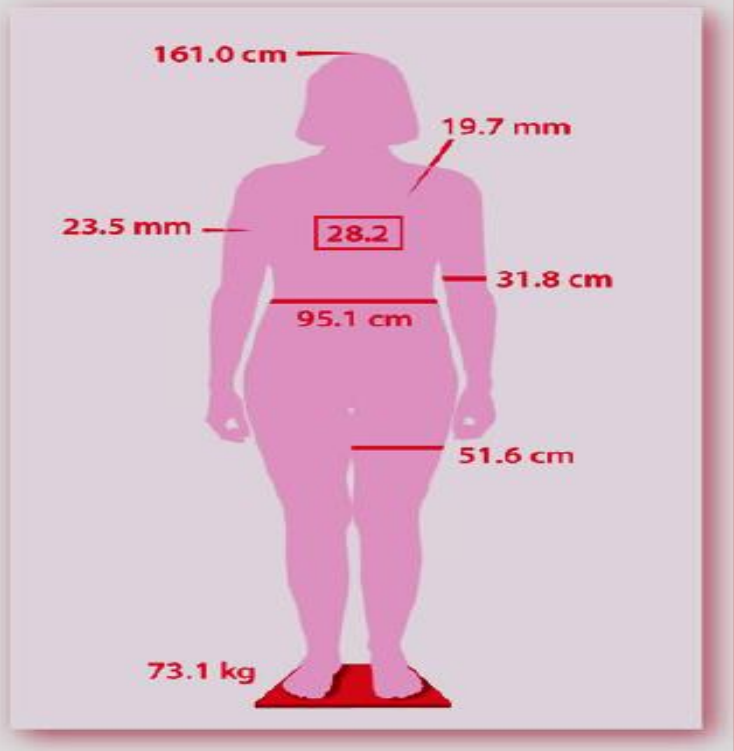


Distinct Phenotype

Kim. 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

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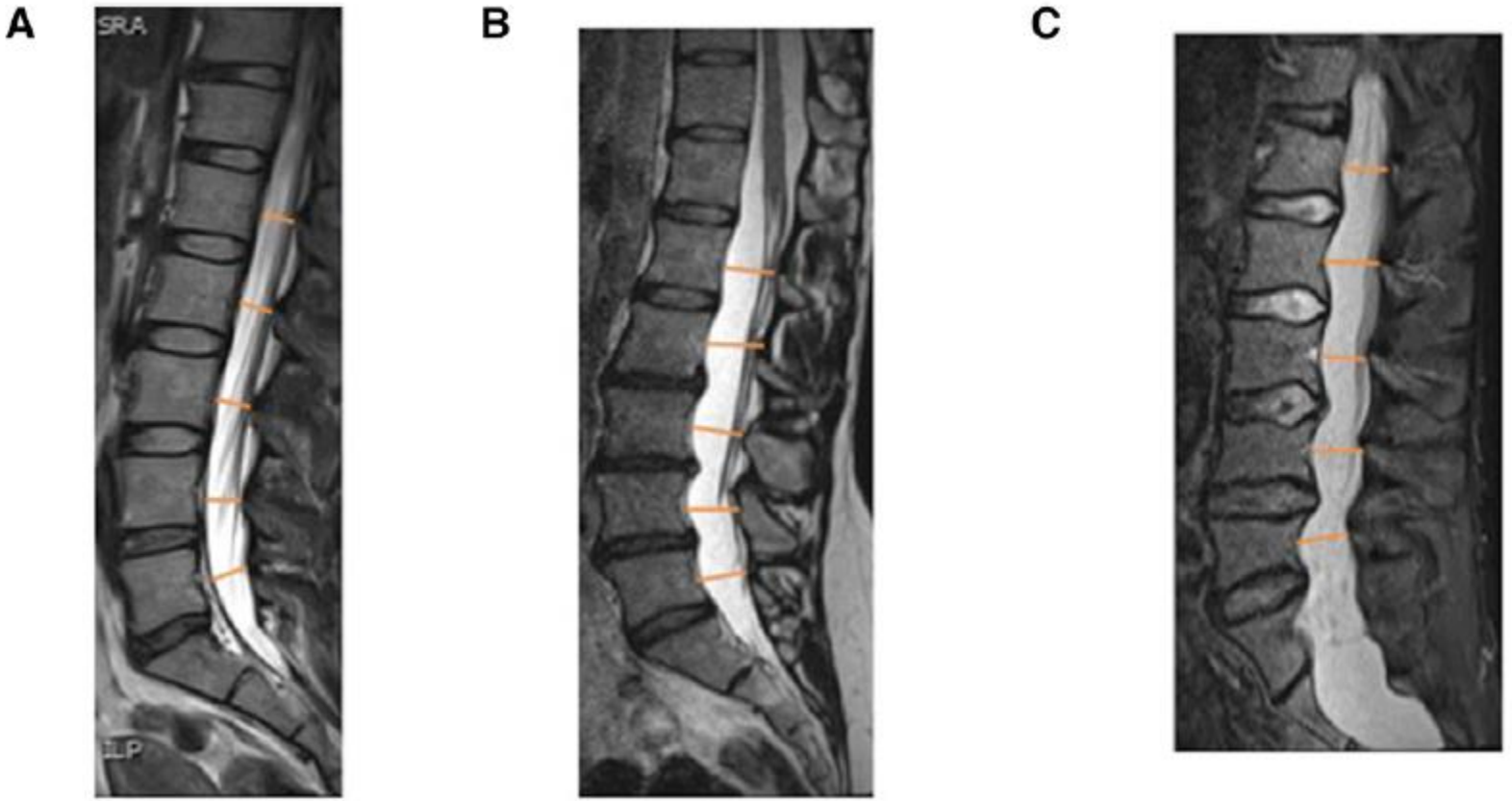
Enlarged Dural Sac in Idiopathic Bronchiectasis Implicates Heritable Connective Tissue Gene Variants

M. Leigh Anne Daniels[1], Katherine R. Birchard[2], Jared R. Lowe[3], Michael V. Patrone[4], Peadar G. Noone[1], and Michael R. Knowles[1]

Ann Am Thorac Soc 2016



Healthy control

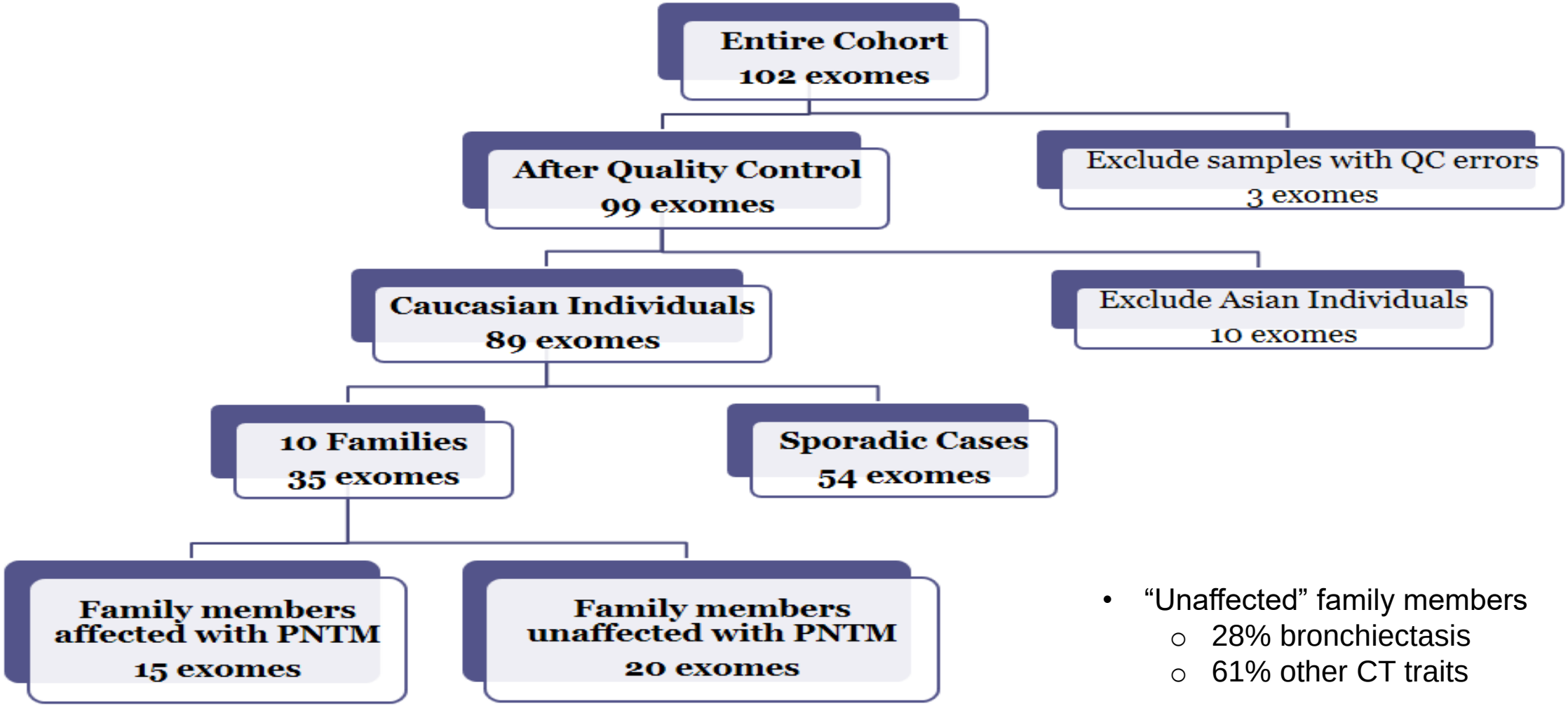
Idiopathic bronchiectasis

Marfan syndrome

Pulmonary Nontuberculous Mycobacterial Infection

A Multisystem, Multigenic Disease

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



- "Unaffected" family members
  - 28% bronchiectasis
  - 61% other CT traits

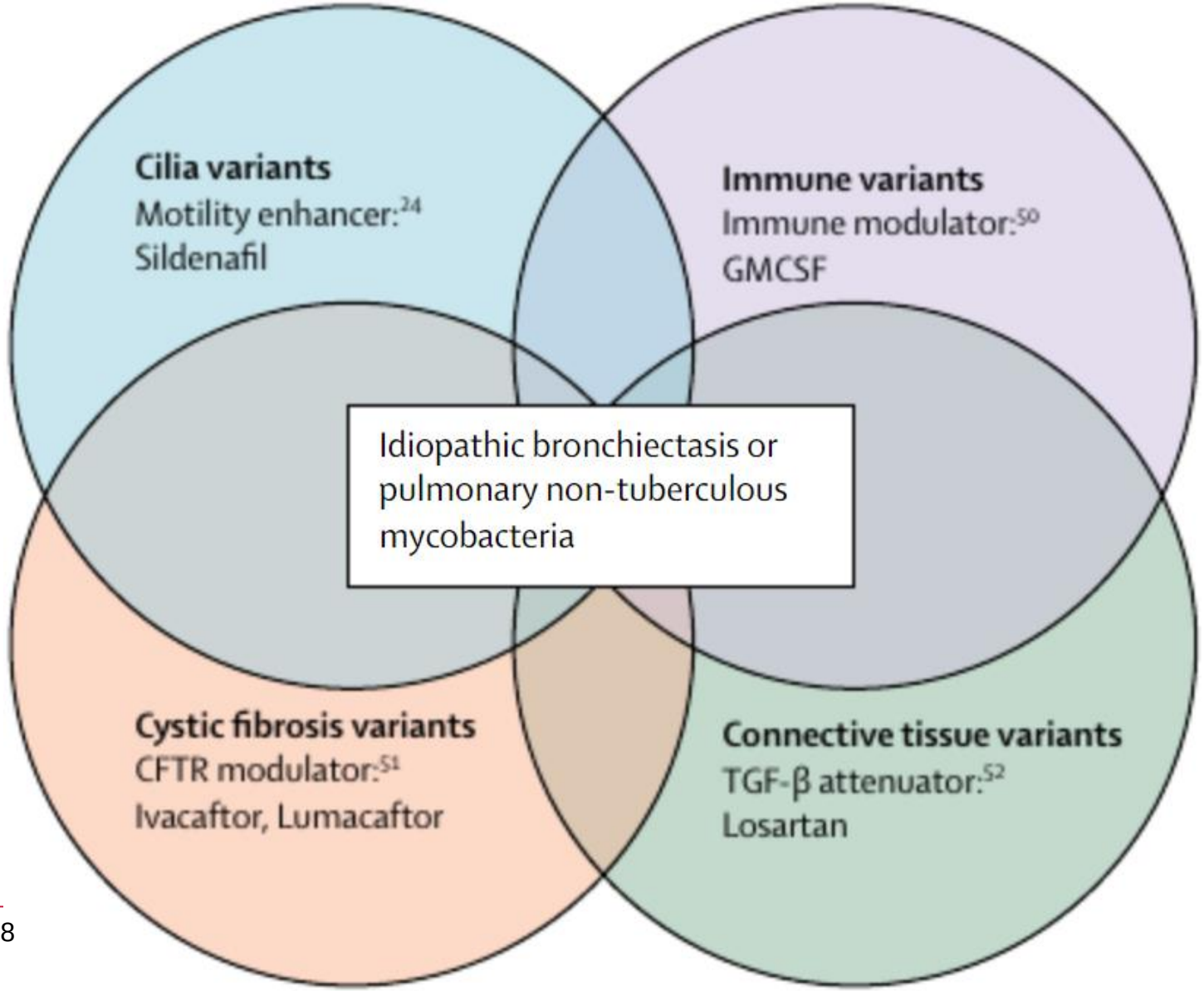
PNTM = Pulmonary Nontuberculous Mycobacterial Disease

Conclusions: Initial WES Analysis

- PNTM patients *&* “unaffected” family members
  - More variants in CF, cilia, & connective tissue genes vs. controls
  - Overlapping bronchiectasis & connective tissue disease features
- More *immune* variants only seen in *PNTM* affected
- Whole exome data support
  - “Susceptible persons” model of PNTM disease
  - Increased frequency of “mild” mutations from relevant gene categories increases risk of bronchiectasis and NTM infection

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

Endotyping/genetics → Modifiable disease targets



Flume PA. Lancet 2018

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