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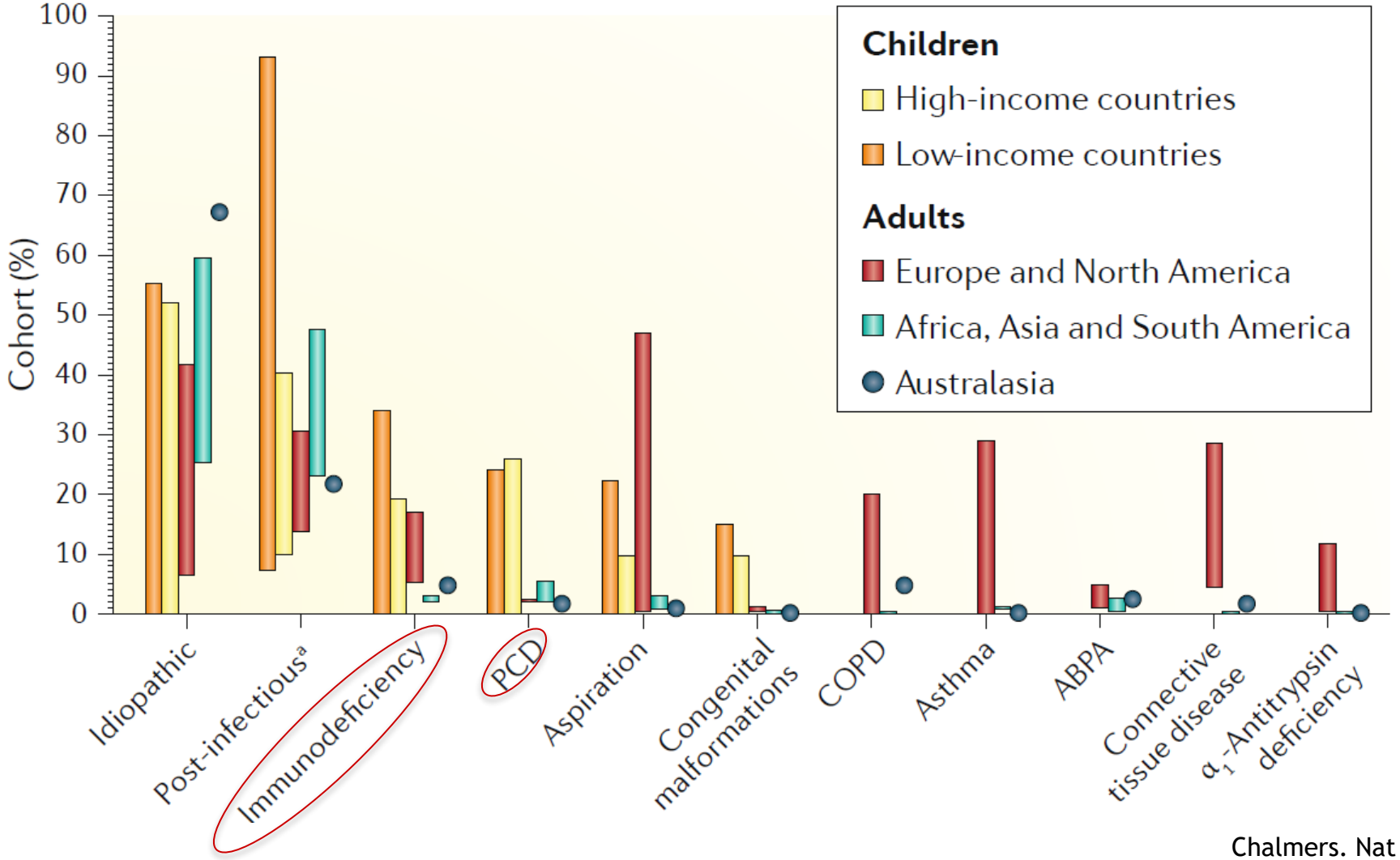
Co-Morbidities of NTM & Bronchiectasis

Kenneth N Olivier, MD, MPH
Chief, Pulmonary Branch, NHLBI

Disclosures

COI	Non FDA approved drugs
Cooperative Research & Development Agreement • AIT Therapeutics • Matinas Biopharma • Insmed (past) CF Foundation Advisory Committee • Colorado CF Research Development Program • MWCFC Sputum Biomarker Consortium	N/A

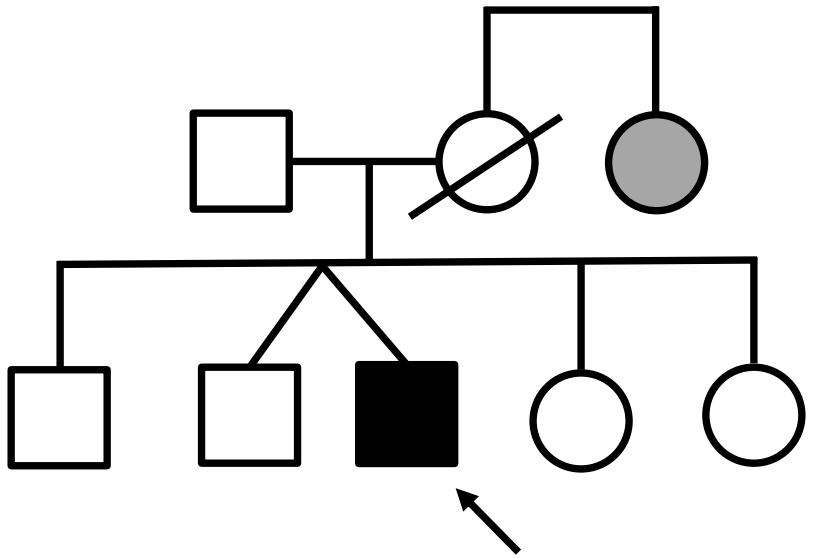
Bronchiectasis – etiologies beyond CF



Chalmers. Nat Rev Dis Primers 2018

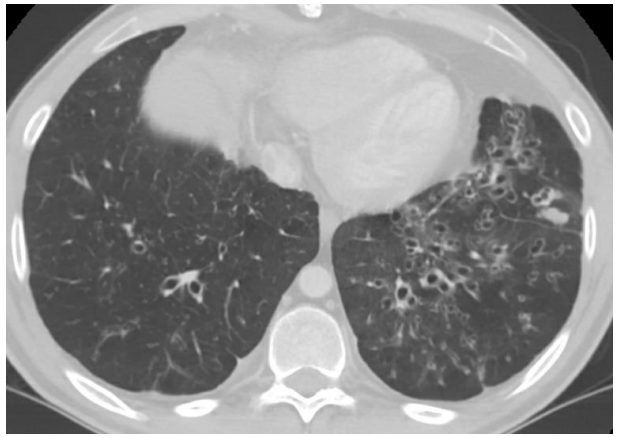
26 yo male recurrent resp tract infections

- Born at 32 weeks, significant resp distress
- No problems until age 7
  - Severe varicella infection
- Chronic productive cough since age 8
  - 15 episodes bronchitis/pneumonia
- 1-5 episodes sinusitis/year
  - Sinus surgery ages 15 & 21
- Sweat chloride 48 mmol/L; CF genetics (-)



26 yo male recurrent resp tract infections

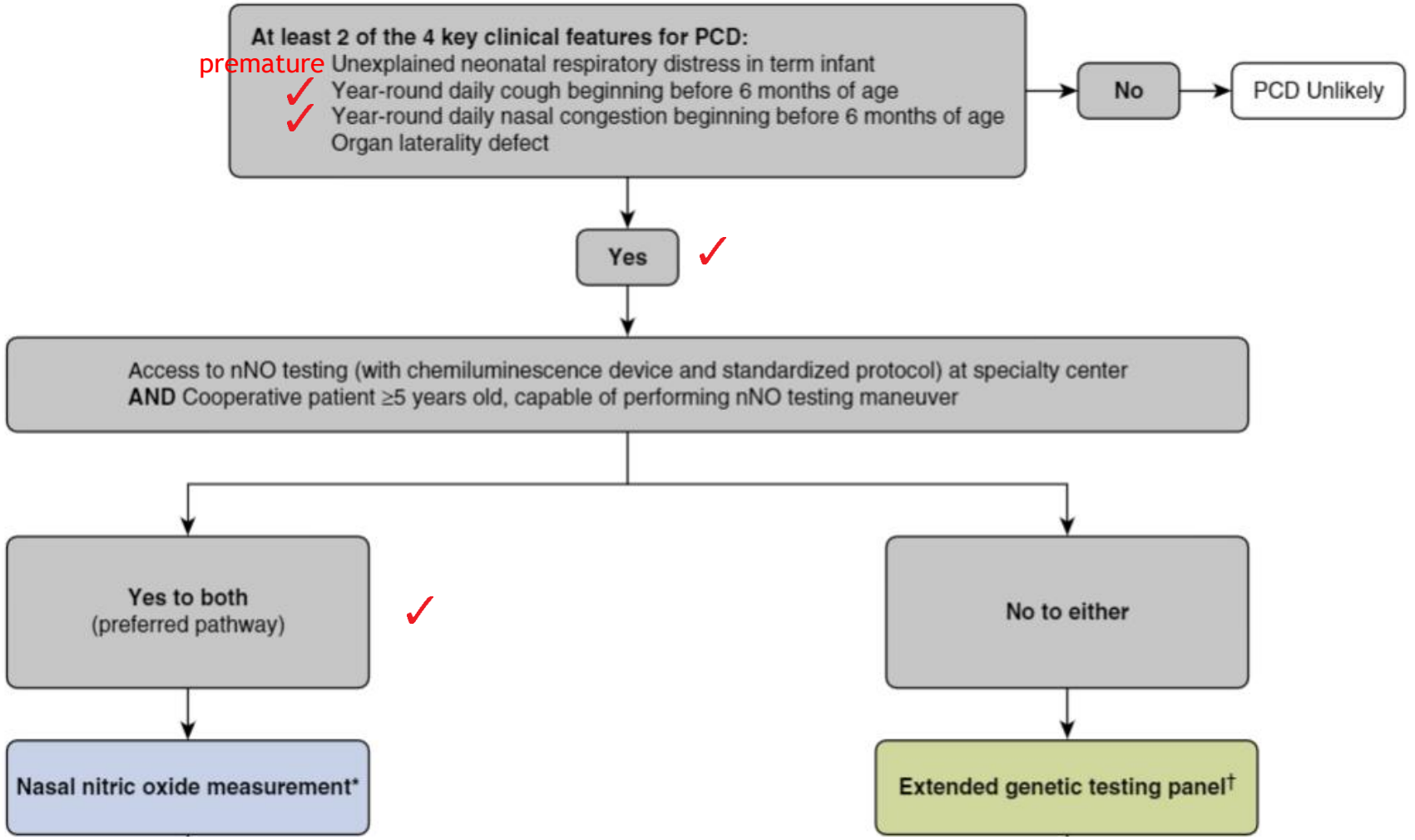
- WBC: 6.82
  - Abs Neut Count: 5006
  - Abs Lymph Count: 723
  - Abs Eos Count: 334
  - Abs Mono Count: 702
- Immunoglobulins:
  - IgG: 1140
  - IgA: 232
  - IgM: 83
  - IgE 7



- Cilia studies
  - Nasal NO: 13 nL/min (>77 nL/min)
  - Electron microscopy: Normal
  - Targeted sequencing - heterozygous missense variant in *DNAAF3*
- Plan: batched whole exome sequencing

Diagnosis of Primary Ciliary Dyskinesia

Shapiro AJ. Am J Respir Crit Care Med 2018



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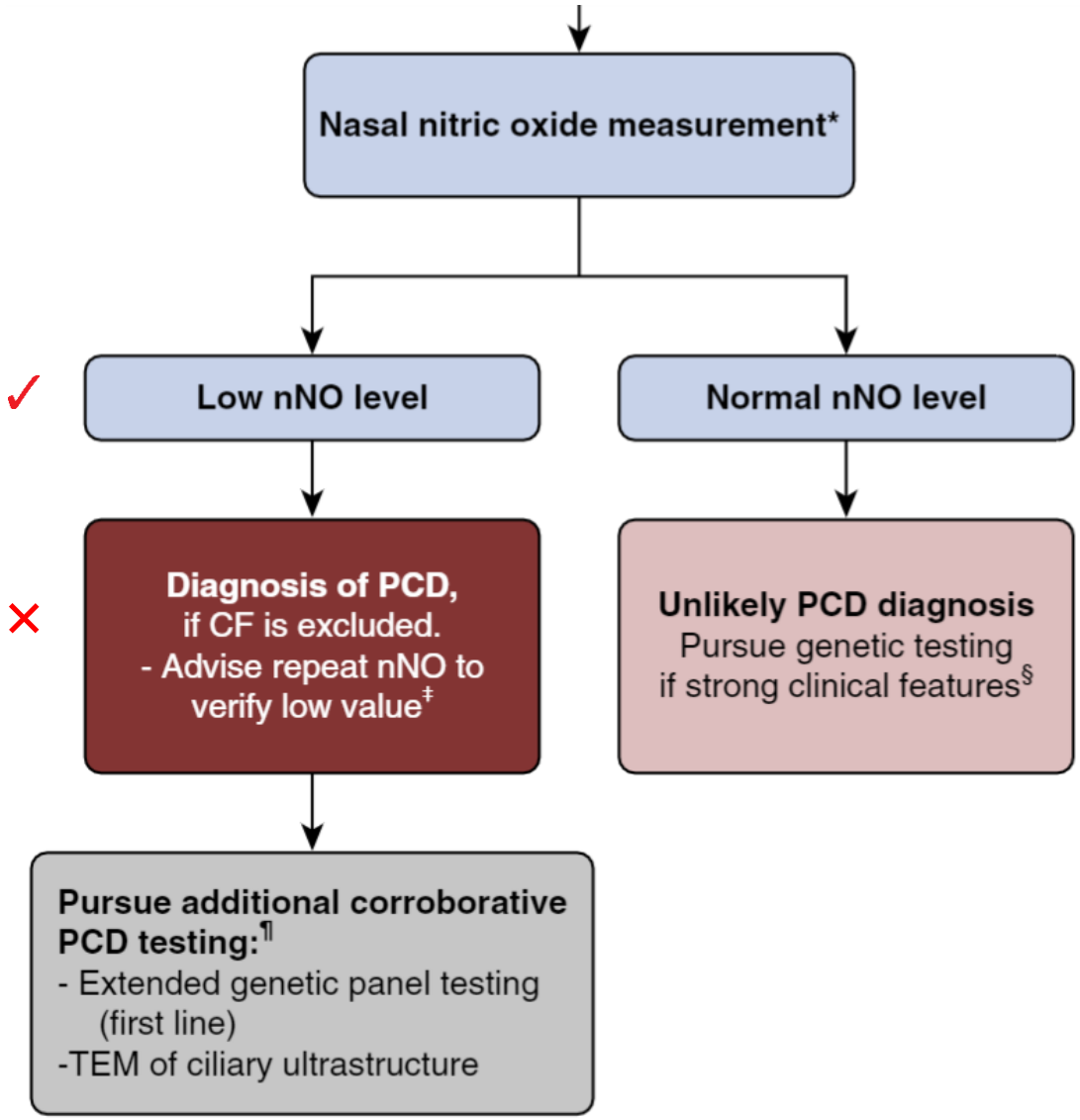
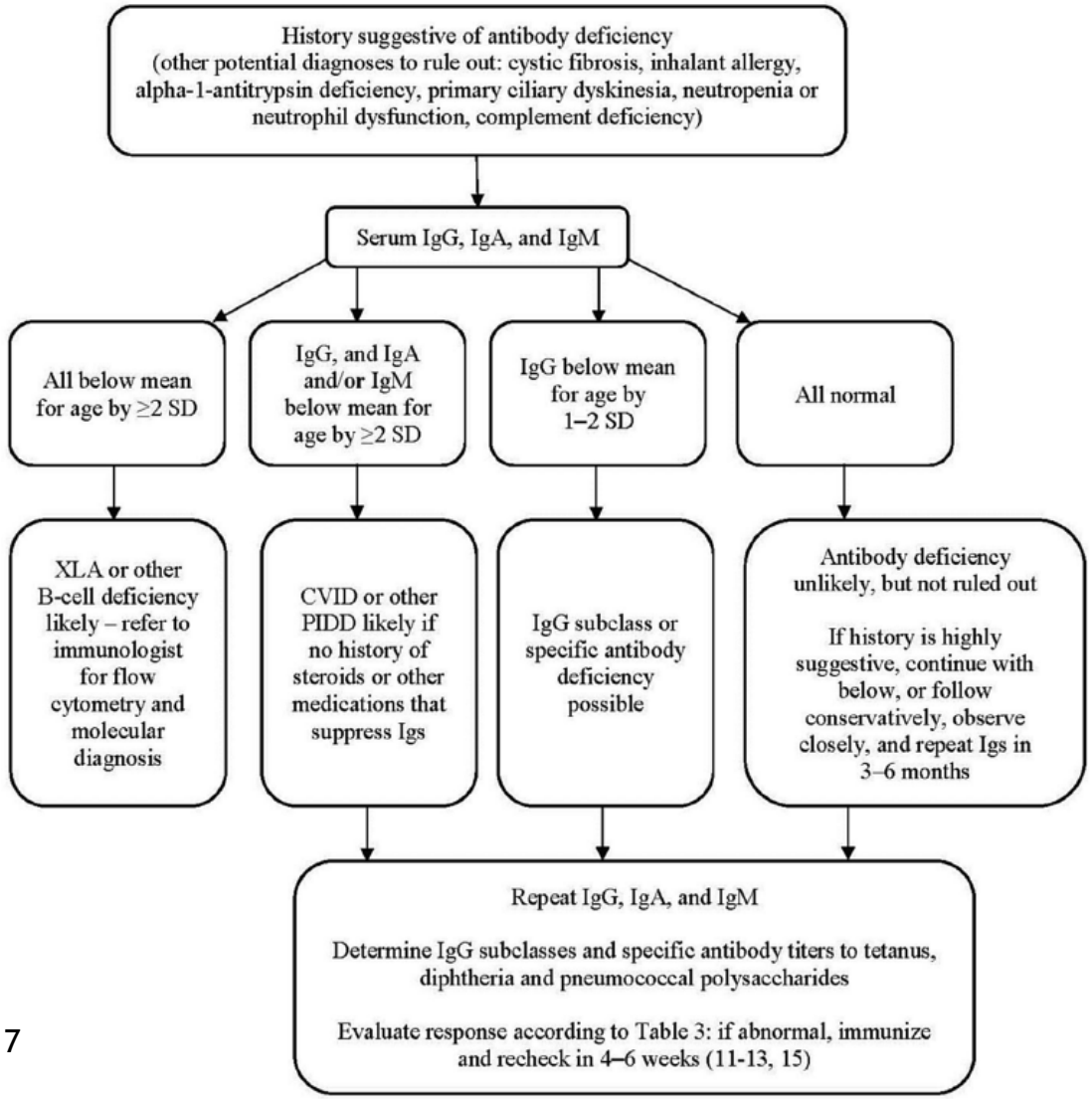


Approach to finding PID in respiratory disease



Berger. Resp Med 2017

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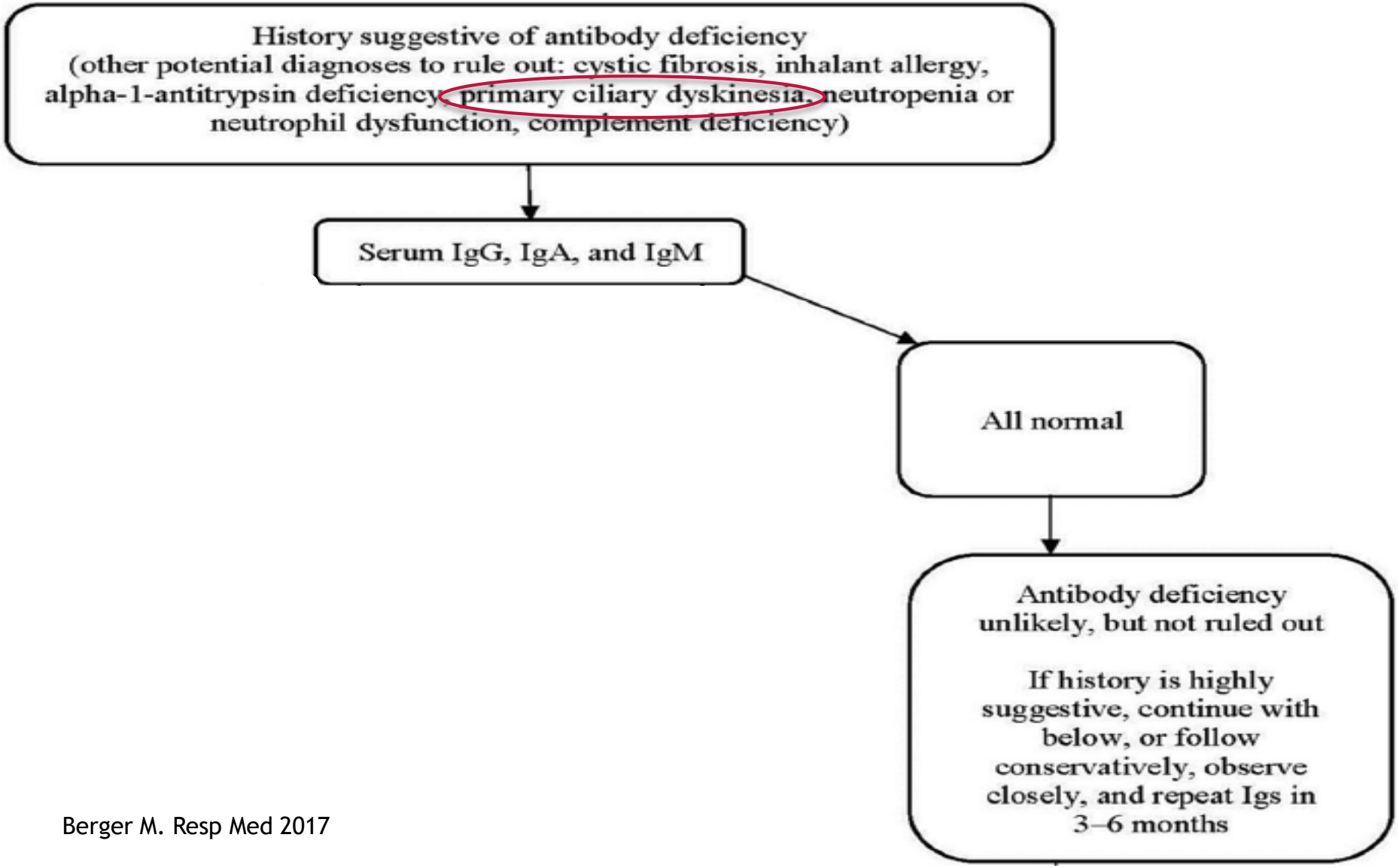
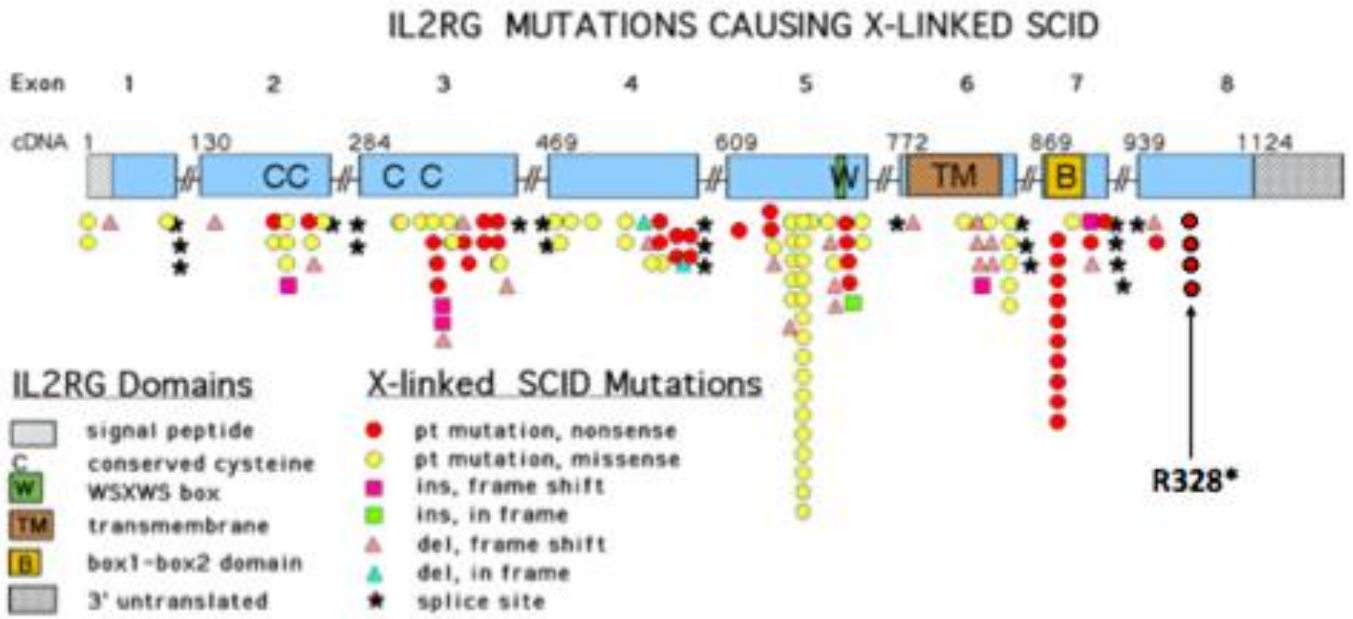


Berger M. Resp Med 2017

26 yo male recurrent resp tract infections

- Age 33: fatigue, fevers, rigors, night sweats
  - Pericardial effusion, mediastinal mass
  - Diffuse Large B cell Lymphoma
- Age 36: multiple sites of lymphoma, EBV+ lymphoproliferative disease
  - Failed chemotherapy, deemed not candidate for conventional HCT
- WES: *IL2RG* mutation (c. 982 C>T), predicted to cause premature termination consistent with hypomorphic variant of X-SCID



Notarangelo L. Personal communication

GDMCC – PID genes identified via WES

#	UNC ID #	Age[1]	Gender	Otitis Media[2]	Sinusitis	Nasal Congestion[3]	Cough/Sputum	Bronchitis/PNA[4]	Hosp./IV ATBs[5]	Respir Pathogens[6]	Bronchiectasis	FEV_1 (% Pred)	Nasal NO (nl/min)[7]	Genes (for subjects #1-22) (Variants in Table 2)
1	998	30	M	X	X	X	X	X	X	X	X	66	219	***RAG1***
2	2724	8	F	X	X	X	X	X	X	X	X	86	13	***RAG1***
3	1464	26	M	X	X	X	X	X	X	X	X	56	40	***IL2RG***
4	1425	11	F	X	X	X	X	X	X	X	X	80	20	***GATA2***
5	1210	17	M	X	X	X	X	X	X	X	X	54	107	***PIK3CD***
6	3174	15	M	X	X	X	X	X	?	X	X	49	100	***PIK3CD***
7	1217	44	F	X	X	X	X	X	X	X	X	54	177	***STAT3***
8	1222	39	F	X	X	X	X	X	X	X	X	61	402	***STAT3***
9	3011	28	F	X	X	X	X	X	X	X	X	-	7	***KMT2D***

Knowles MR. Personal communication

Bronchiectasis/Suppurative Airway Disease

- Textbook algorithms for ruling out genetic etiologies inadequate
- CF most common/relatively easy to evaluate
- Multi-gene panels may have some value
  - PCD (40 genes), PID (327 genes)

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- Textbook algorithms for ruling out genetic etiologies inadequate
- CF most common/relatively easy to evaluate
- Multi-gene panels may have some value
  - PCD (40 genes), PID (327 genes)
- Whole exome sequencing
  - GDMCC
  - NIAID Centralized Sequencing Initiative (#302; C105 Tues 2:15-4:15)

Back to our patient…

- Met 2018 Guidelines clinical diagnostic criteria for PCD in 2008
  - Single VUS in PCD associated gene, not causative
- Unexpected diagnosis of a PID that is almost always lethal in infancy without bone marrow transplantation
  - Emphasizes need for unbiased diagnostic approach
- Association of PID with treatment refractory lymphoma
  - Emphasizes critical need for early recognition of PID

NIH Clinical Center NATIONAL INSTITUTES OF HEALTH

- Training and Career Opportunities at the NIH
  - Post bac & Post doc Intramural Research Training Award
  - Pulmonary/Critical Care Medicine & ID Fellowship Programs
  - Lasker Clinical Research Scholars Program
    - Up to 10 years intramural/extramural career development funding
  - Tenure track/tenured investigator & staff clinician positions