Pediatric Grand Rounds

Text: 608-260-7097

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Need support? Email Kate Dougherty at catherine.dougherty@wisc.edu

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Pediatric Grand Rounds: Clinicopathological Conference (CPC)

Tyler Sternhagen, MD

February 29, 2024

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Conflict of Interest

The planner and speaker of this CE activity has no relevant financial relationships with ineligible companies to disclose.

The speaker does not intend to discuss any unlabeled or unapproved use of drugs or devices.

Please take a moment at the end of the session to complete your evaluation.

Thank you!

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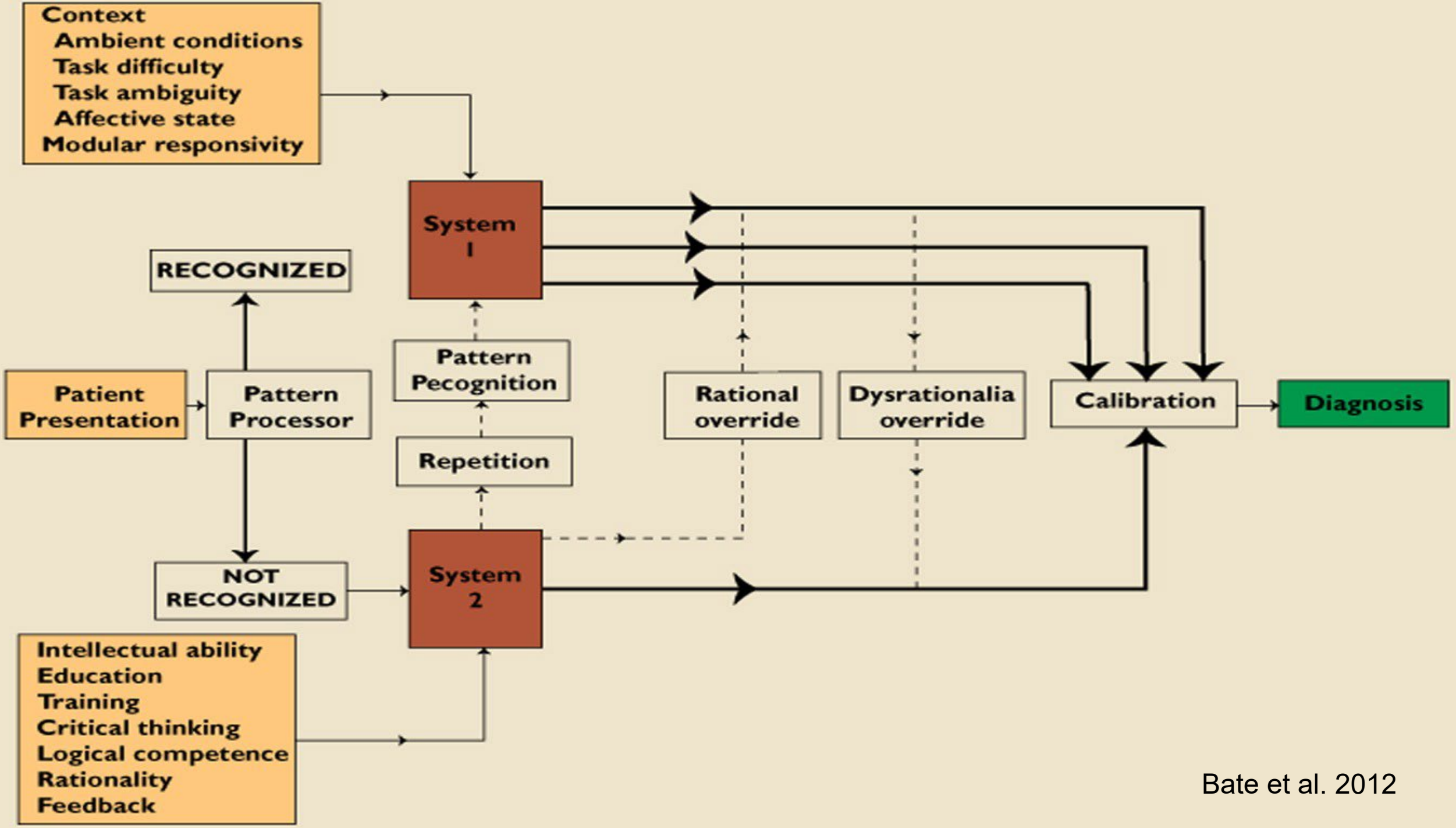
Objectives

- Explain the process of diagnostic reasoning through an interesting clinical case.
- Organize diagnostic thinking in difficult cases using this case as an example.
- Demonstrate how to evaluate a patient with oto-sino-pulmonary disease.

Disclosure

- No PHI, as defined by HIPAA, will be discussed in this fully de-identified case presentation



Bate et al. 2012

Diagnosis

Presentation

Let’s meet today’s patient

- 9-year-old male with history of recurrent otitis media with effusion s/p multiple tympanostomy tubes presenting with “chronic nasal congestion and cough”
- Runny and stuffy nose for years without typical allergy symptoms
  - Nasal irrigation and antibiotics only temporize symptoms
  - Nasal drainage persists despite sinus surgery 5 years ago

History Highlights

- Chronic “chunky” and wet cough that is year round
  - Worse with exercise
- No recurrent upper respiratory tract infections

- Born late preterm with a 7-day NICU course for NEC
- Twin with allergies

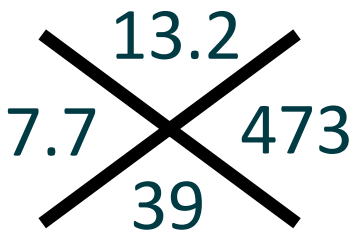
Exam Highlights

- Vitals

  BP 90/55 | Pulse 85 | Ht 54.69" (138.9 cm), 74th percentile | Wt 63 lb 11.2 oz (28.9 kg), 47th percentile | BMI 14.98 kg/m2, 21st percentile. SpO2 98%.

- Pale nasal mucosa and cobblestoning in pharynx
- Coarse breath sounds without wheeze

Our patient's work-up



41% neutrophils, 46% lymphocytes, 8% monocytes, 4% eosinophils, 1% basophils

- Normal Newborn Screen
- C3: 128 (80-170), C4: 17 (14-44), CH50: 95 (39-90)
- IgA: 96 (42-223), IgG: 1,012 (610-1,577), IgM: 118 (40-180), IgE: <25 (<90)
- Normal response to pneumococcal titers
- Negative ANCA testing
- Negative allergy testing

Age specific norms

Our patient's work-up

Sweat Chloride testing: 17mmol/L x2

CXR: Bronchial wall thickening and airspace opacities within the right middle lobe and lingula

Sinus pathology (from age 4): Mucosa: Biopsy: Cilia with focal disorganization, favor reactive-type changes.

	LLN	Pred	Baseline	%Pred	POST	%Chg	%Pred Post
FVC	2.57	3.16	2.76	87	2.78	1	88
FEV1	2.17	2.69	2.29	85	2.43	6	90
FEV1/FVC	75	86	72	84	73	1	
PEF	4.12	5.73	5.82	102	5.37	-8	
FEF 25/75	2.04	3.06	2.35	77	2.95	25	
FET			3.81		3.8	0	
V backextrap.			0.05		0.11	125	

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Case Review

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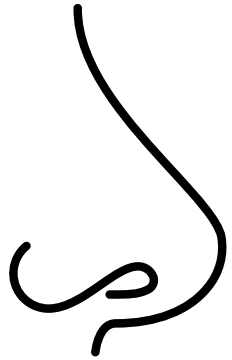
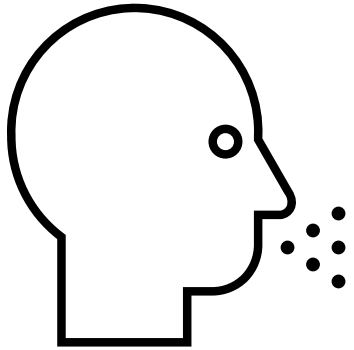
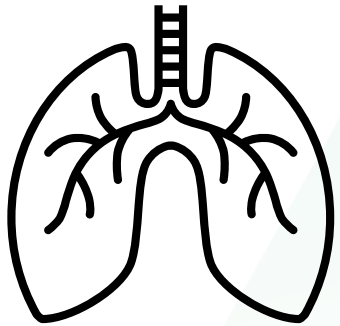
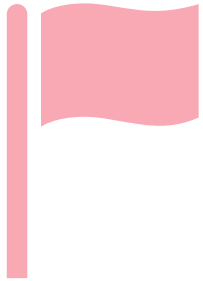
Pattern Recognition









Focused Differential

- Unifying
  - Primary Immunodeficiencies
    - X-Linked Agammaglobulinemia (XLA)
    - Common Variable Immunodeficiency (CVID)
    - IgA Deficiency
    - C3 Deficiency
  - Genetic/Ciliary Structural Abnormalities
    - Cystic Fibrosis
    - Primary Ciliary Dyskinesia
  - ANCA-associated vasculitidies
    - Granulomatosis with polyangiitis
- Other Considerations
  - Asthma + allergic rhinitis + chronic sinusitis

Turn 1: Chronic Sinusitis

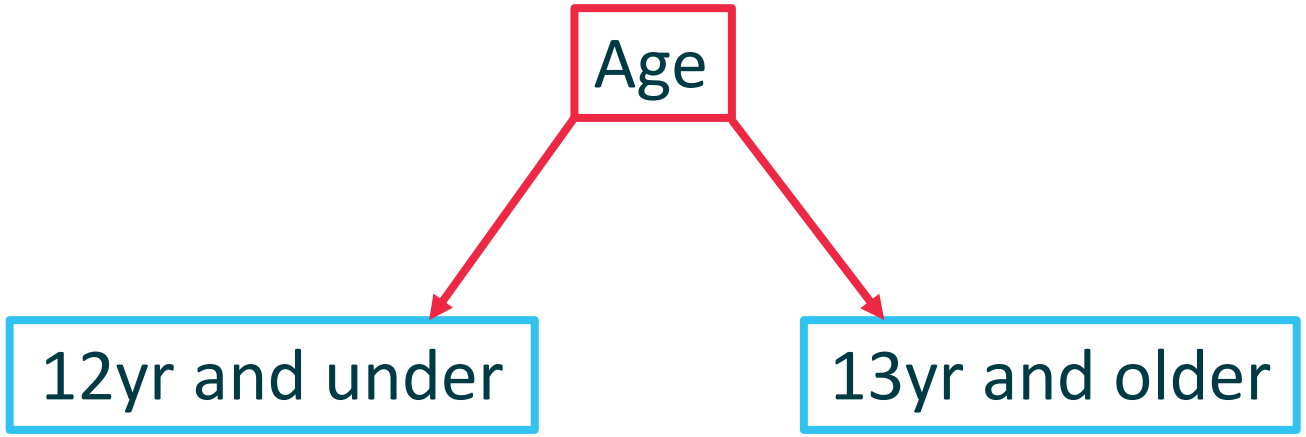
Chronic Rhinosinusitis (CRS)

- Diagnosis of CRS is 2 or more of the following symptoms for at least 12 weeks
  - Nasal obstruction
  - Facial Pressure/pain
  - Purulent rhinorrhea
  - Cough

Factors contributing to pediatric CRS
Frequent viral URIs
Anatomical abnormalities of sinus/ostia
Immune immaturity or deficiency
Biofilm formation
Adenoid Enlargement
Allergy
Impairment of mucociliary clearance

Hamilos 2015

Treatment Considerations:



- Adenoid Disease

- Allergic Rhinitis

Treatment Options: Non-operative

- **Intranasal Steroids**
- Nasal Saline Irrigation
- Antibiotics
- Biologics

Treatment Options: Non-operative

Intranasal Steroids

Nasal Saline Irrigation

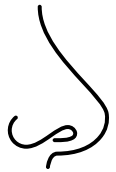
Antibiotics

Biologics

Treatment Options: Non-operative

Intranasal Steroids

Nasal Saline Irrigation



Antibiotics

Biologics

Treatment Options: Non-operative

Intranasal Steroids

Nasal Saline Irrigation

Antibiotics

Biologics

“Sinus Surgery”

- Adenoidectomy
- Balloon catheter dilation
- Functional endoscopic sinus surgery

“Sinus Surgery”

- **Adenoidectomy**
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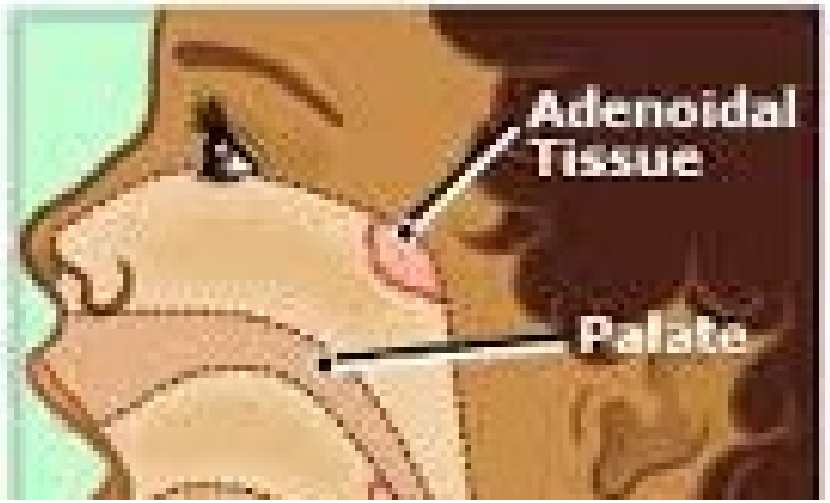
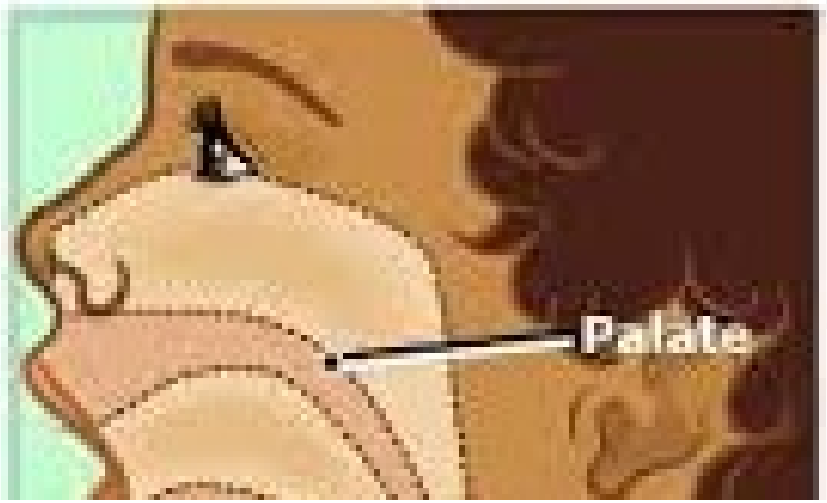
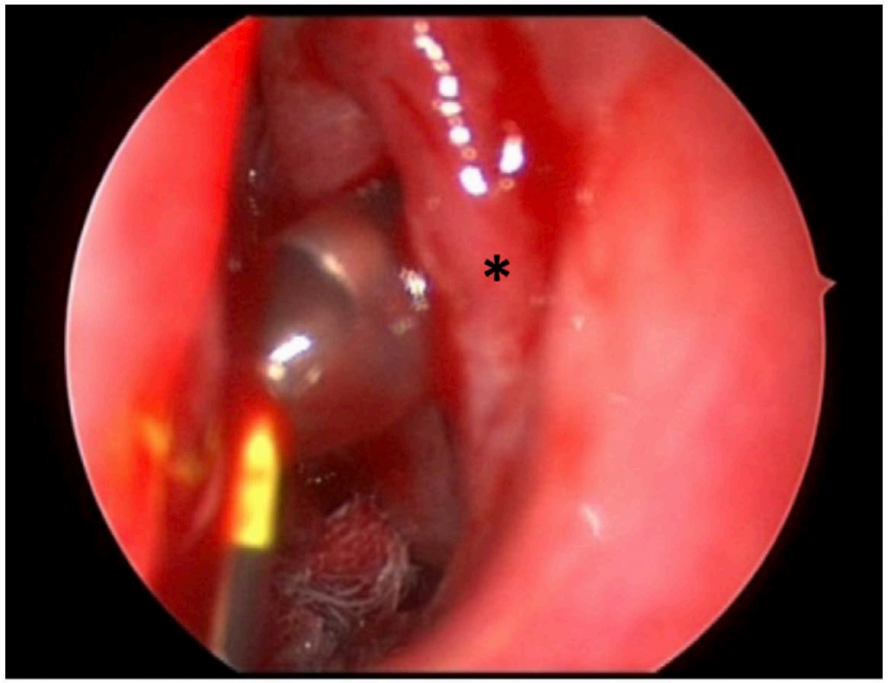




“Sinus Surgery”



Adenoidectomy

Balloon catheter dilation

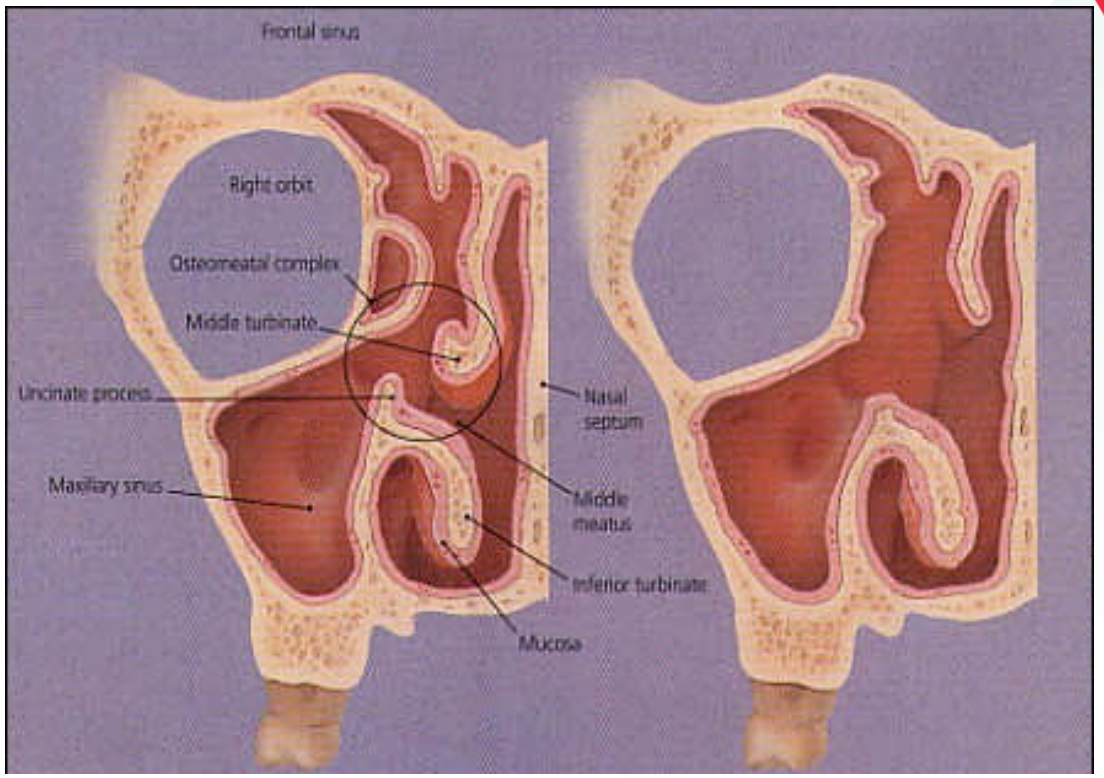
Functional endoscopic sinus surgery

“Sinus Surgery”

Adenoidectomy

Balloon catheter dilation

Functional endoscopic sinus surgery



What do we know about our patient?

Our patient: Oto-**Sino**-Pulmonary Disease

- Chronic snoring and nasal congestion with purulent discharge
  - Adenoidectomy performed (uncertain age)
  - Sinus surgery at age 4 (presumably FESS)
    - Mucosa Pathology: “cilia with focal disorganization, favor reactive-changes”
  - No relief with allergic rhinitis management and negative allergy testing

- Where do we go with this information?

Factors contributing to pediatric CRS
Frequent viral URIs
Anatomical abnormalities of sinus/ostia
Immune immaturity or deficiency
Biofilm formation
Adenoid Enlargement
Allergy
Impairment of mucociliary clearance

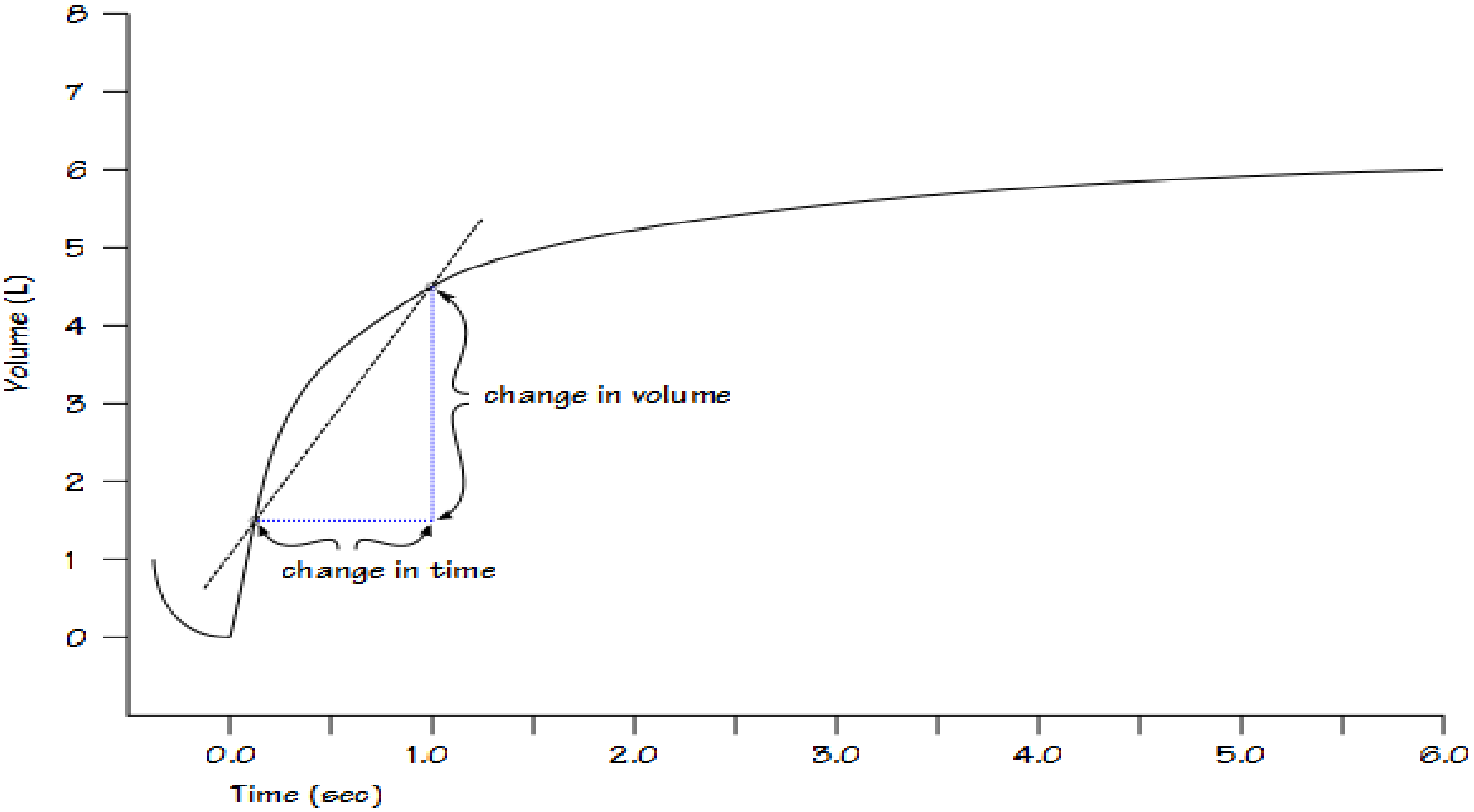
Turn 2: Recurrent AOM

Turn 3:
Lower Airway Disease

What do we know about our patient?

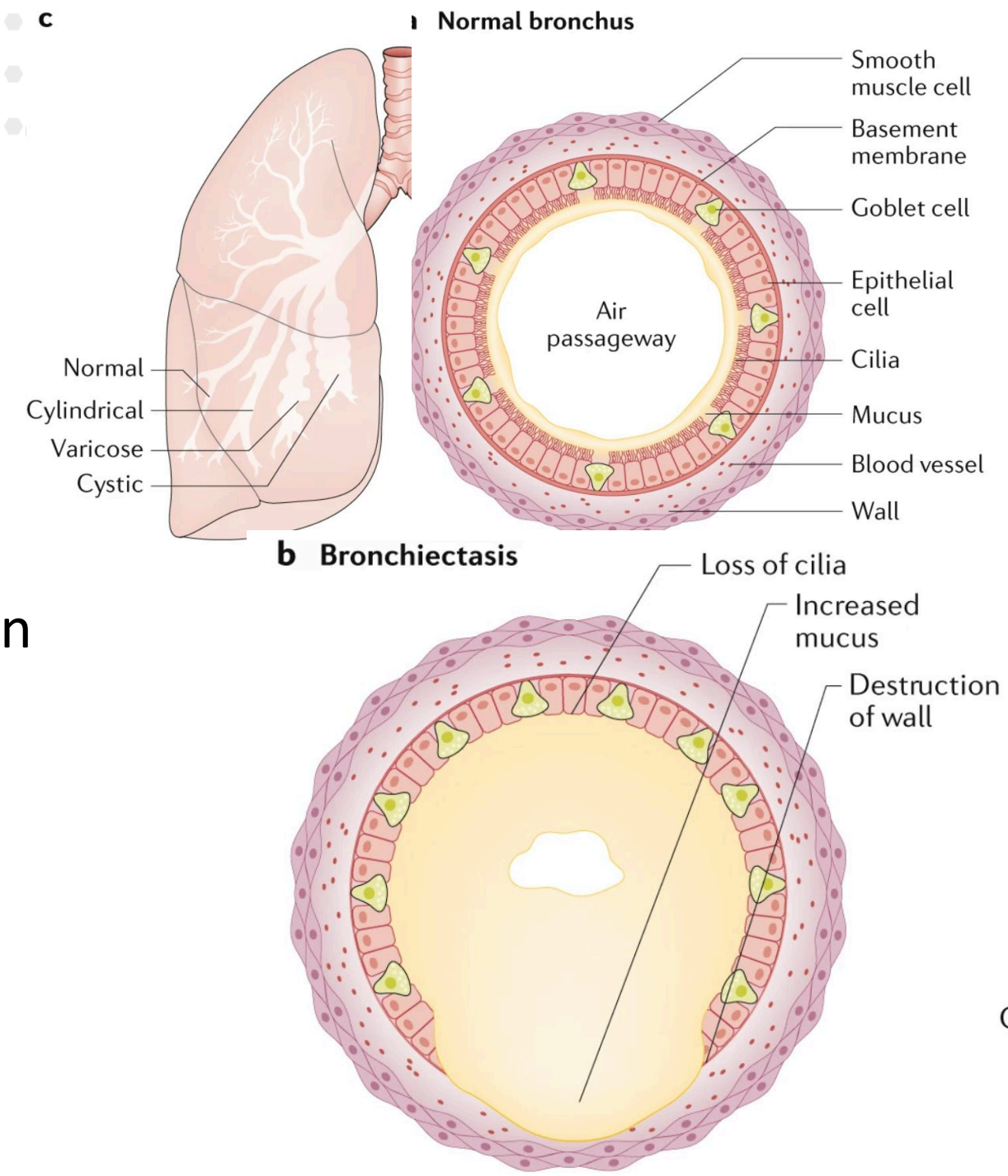
Our patient: Oto-Sino-**Pulmonary** Disease

- Chronic cough
  - Wet, productive, and worsens with exercise
- Consider
  - Post-nasal drip?
  - Cardiac etiology?
  - Lower respiratory tract disease?


8
7
6
5
4
3
2
1
0
Volume (L)
change in volume
change in time
0.0
1.0
2.0
3.0
4.0
5.0
6.0
Time (sec)

Bronchiectasis

- Characterized by wet productive cough, recurrent infections, and/or dyspnea
- Diagnosis is made with high-resolution computed tomography (HRCT) evidence of bronchial dilation
- Spirometry has limited sensitivity or specificity



Bronchiectasis

- Chronic lung condition that is an endpoint of a variety of conditions
    - Cystic Fibrosis
    - Primary Immunodeficiencies
    - Acquired Immunodeficiency
    - Congenital Malformations
    - Recurrent Infections (including aspiration)
    - Primary Ciliary Dyskinesia
- Management is generally supportive
    - Treat acute exacerbations
    - Airway clearance measures
        - chest physiotherapy, hypertonic saline, chronic antibiotics (in select patients)

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Turn 4: Immunodeficiencies

Antibody Deficiency Disorders

When to Suspect

Recurrent bacterial infections of the sinopulmonary tract

- otitis media, sinusitis, and pneumonia

May have:

- Diarrhea
- Autoimmune conditions

Common Considerations

Selective IgA Deficiency

Common Variable Immunodeficiency

Congenital Agammaglobulinemias

Starting Work-up

Measure major immunoglobulin classes (IgG, IgA, IgM, and IgE)

Measurement of specific antibody responses (vaccines)

T-Cell or Combined T- and B-Cell Disorders

When to suspect

Growth faltering and recurrent infections with opportunistic pathogens

- Candida albicans
- Pneumocystis jiroveci
- cytomegalovirus (very early in life)

Diarrhea and Skin rashes are common

Common Considerations:

DiGeroge (thymic aplasia)

Hyper IgM

SCID

WAS

Immunodeficiency with ataxia-telangiectasia

Starting Work-up

Cell count with differential (severe lymphopenia)

Lymphocyte subpopulation evaluation

Phagocyte Dysfunction Syndromes

When to suspect

Recurrent bacterial and fungal infections of the skin, lymph nodes, lung, liver, and bone

Common Considerations

Chronic granulomatous disease (CDG)

Leukocyte adhesion deficiency (LAD)

Starting Work-up

Leukocyte count (with differential) and morphologic review

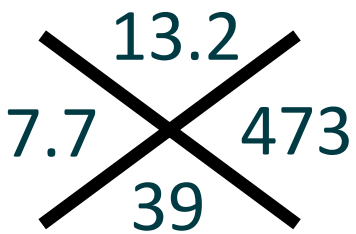
Consider direct assays

Complement Disorders

When to suspect	Common Considerations	Starting Work-up
SLE-like illness	C3 Deficiency	C3
Frequent sinopulmonary infections	Membrane Attack Complex Deficiency	C4
Recurrent infections with encapsulated organism		CH 50

What do we know about our patient?

Our patient: **Oto-Sino-Pulmonary** Disease



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~~T-Cell and Combined B&T-Cell Disorders~~

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- IgA: 96 (42-223), IgG: 1,012 (610-1,577), IgM: 118 (40-180), IgE: <25 (<90)
- Normal response to pneumococcal titers ~~Antibody Deficiency Disorders~~

Age specific norms

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The Destination

Diagnosis

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Focused Differential

- Unifying
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Final Differential

- Unifying
  - ~~Primary Immunodeficiencies~~
    - ~~X-Linked Agammaglobulinemia (XLA)~~
    - ~~Common Variable Immunodeficiency (CVID)~~
    - ~~IgA Deficiency~~
    - ~~C3 Deficiency~~
  - Genetic/Ciliary Structural Abnormalities
    - ~~Cystic Fibrosis~~
    - **Primary Ciliary Dyskinesia**
  - ANCA-associated vasculitidies
    - ~~Granulomatosis with polyangiitis~~
- Other Considerations
  - ~~Asthma + allergic rhinitis + chronic sinusitis~~

Primary Ciliary Dyskinesia

- Genetically heterogeneous disorder of motile cilia
- Typical phenotype
  1. Neonatal respiratory distress (usually term)
  2. Chronic, persistent lower respiratory symptoms
  3. Chronic, persistent upper respiratory symptoms
  4. Laterality defects (situs inversus or situs ambiguous)

Primary Ciliary Dyskinesia

- Relatively low prevalence
- Recently identified clinical sensitivity and specificity (Leigh et al 2016)
    1. Year-round daily productive cough
    2. Year-round, daily/non-seasonal rhinosinusitis
    3. Neonatal respiratory distress (without known source)
    4. Laterality defects
    - 2 or more symptoms has a sensitivity of 80% and specificity of 72%
- Management is generally supportive
    - Gene therapy on the horizon

The Unexpected Speed Bump

Diagnostic Dilemma

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Diagnostic Tools

- No current “gold standard”
- Emerging Options
  - Nasal nitric oxide (nNO) measurement
  - High-speed video microscopy with ciliary beat pattern analysis (HSVM)
  - Immunofluorescence imaging of axonemal proteins

Diagnostic Tools

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Dell 2008

Diagnostic Tools

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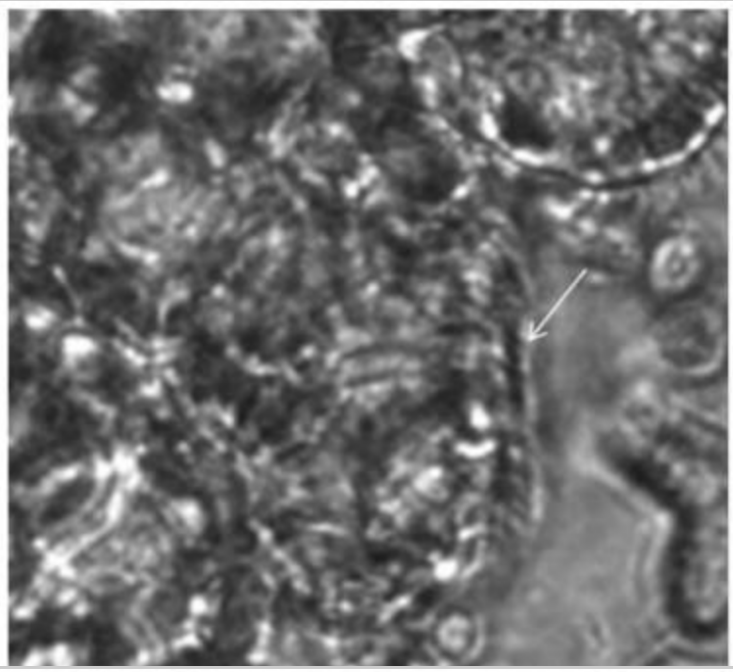

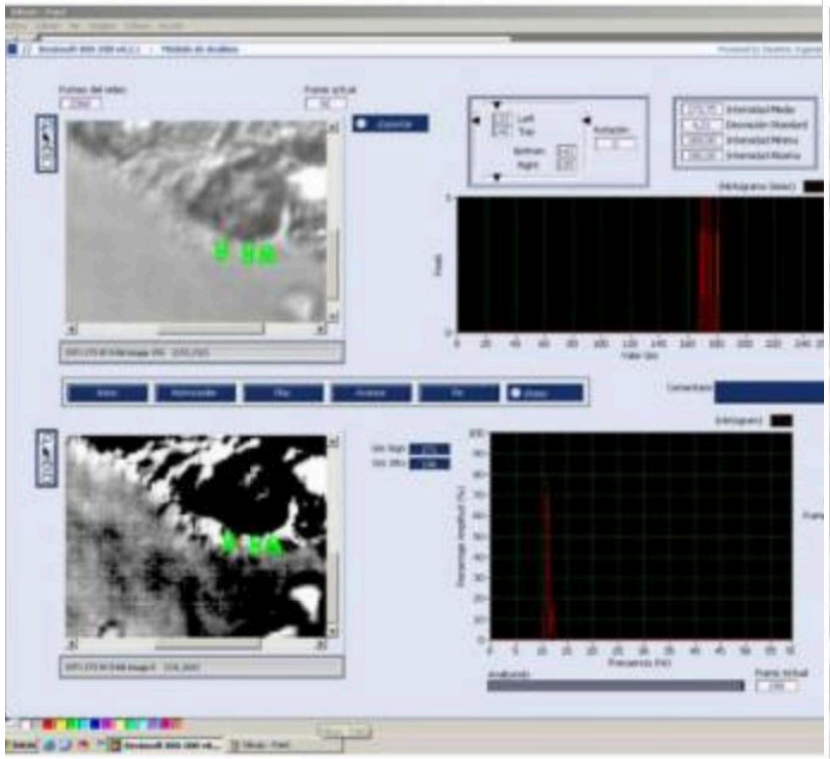

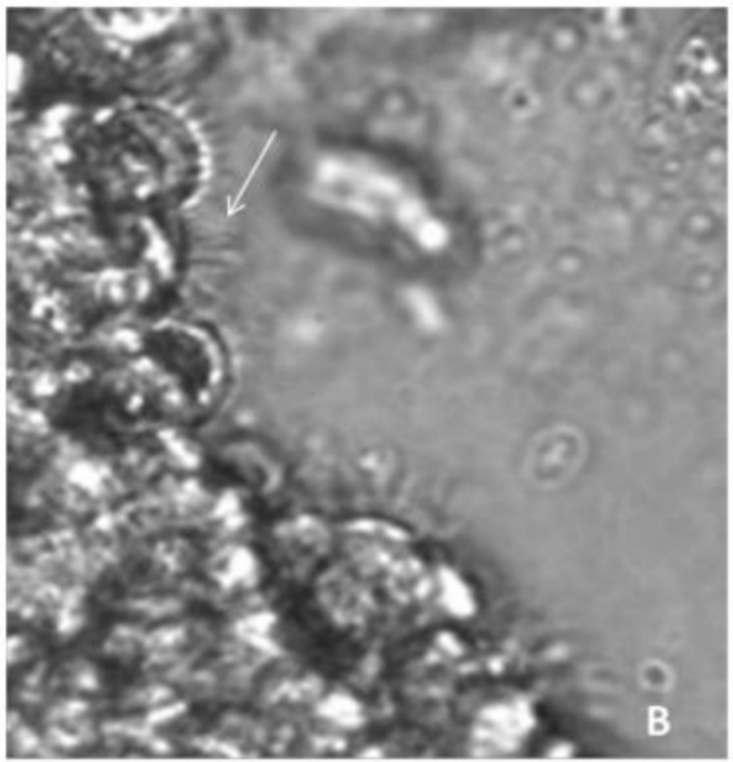

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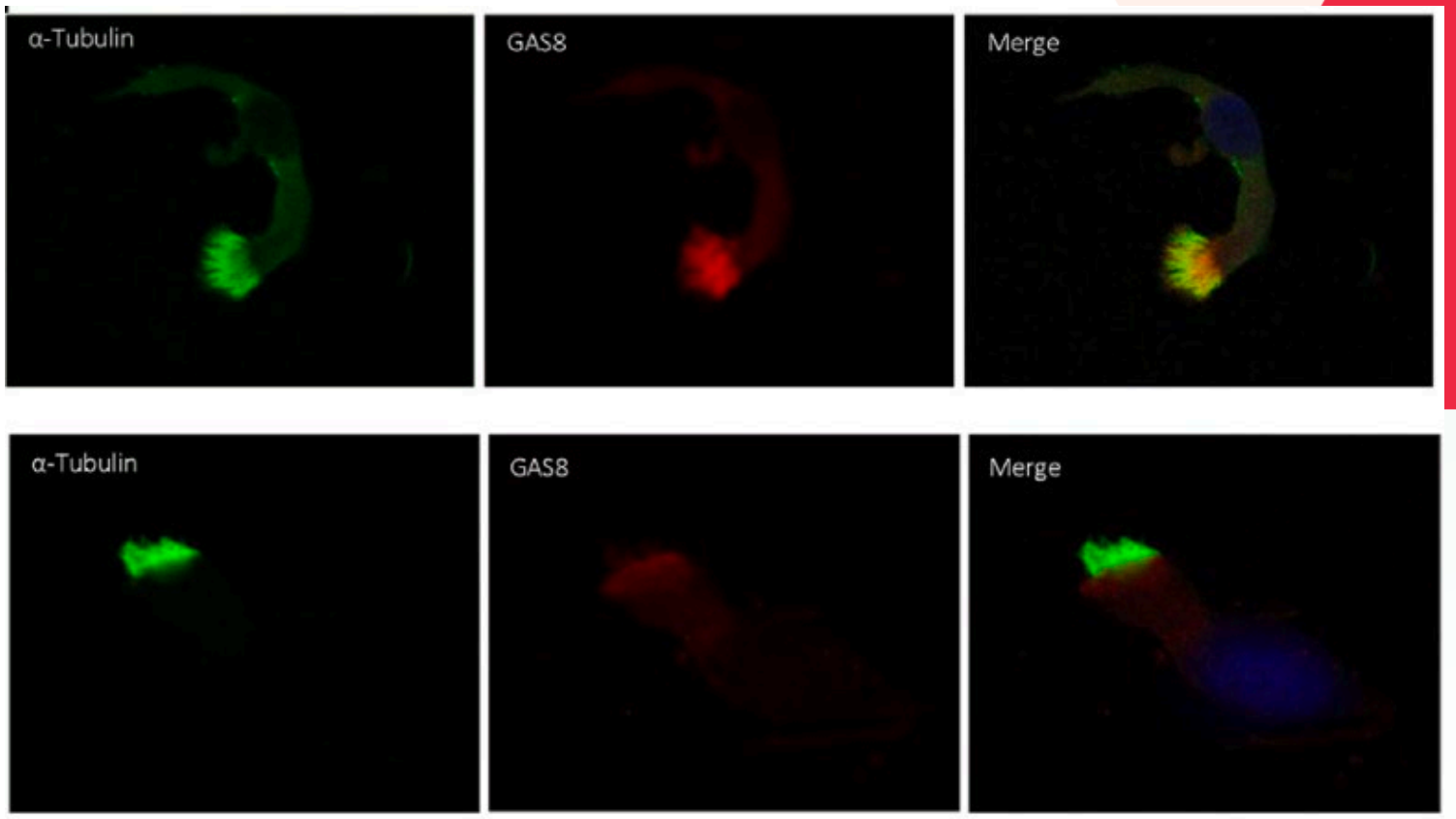
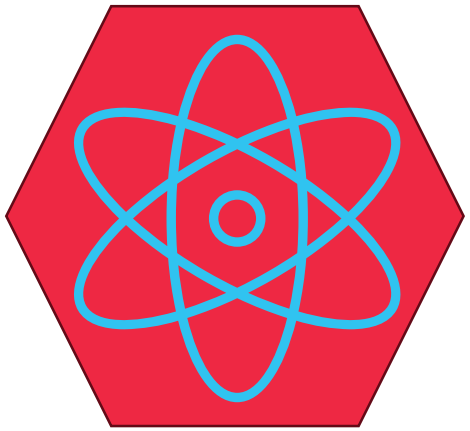
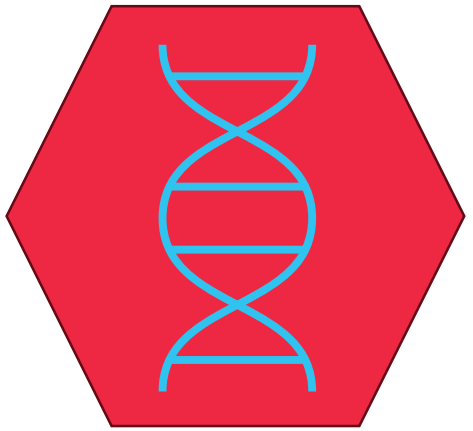


Goutaki & Shoemark 2022

Diagnostic Tools



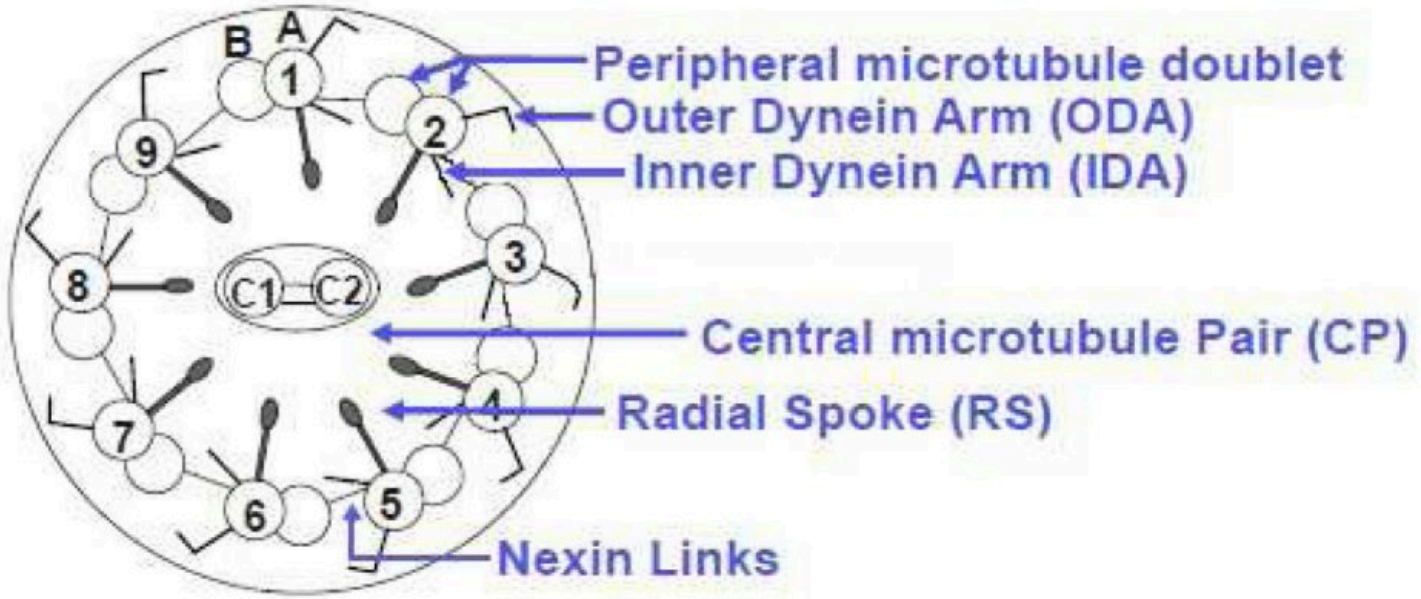
Transmission Electron Microscopy



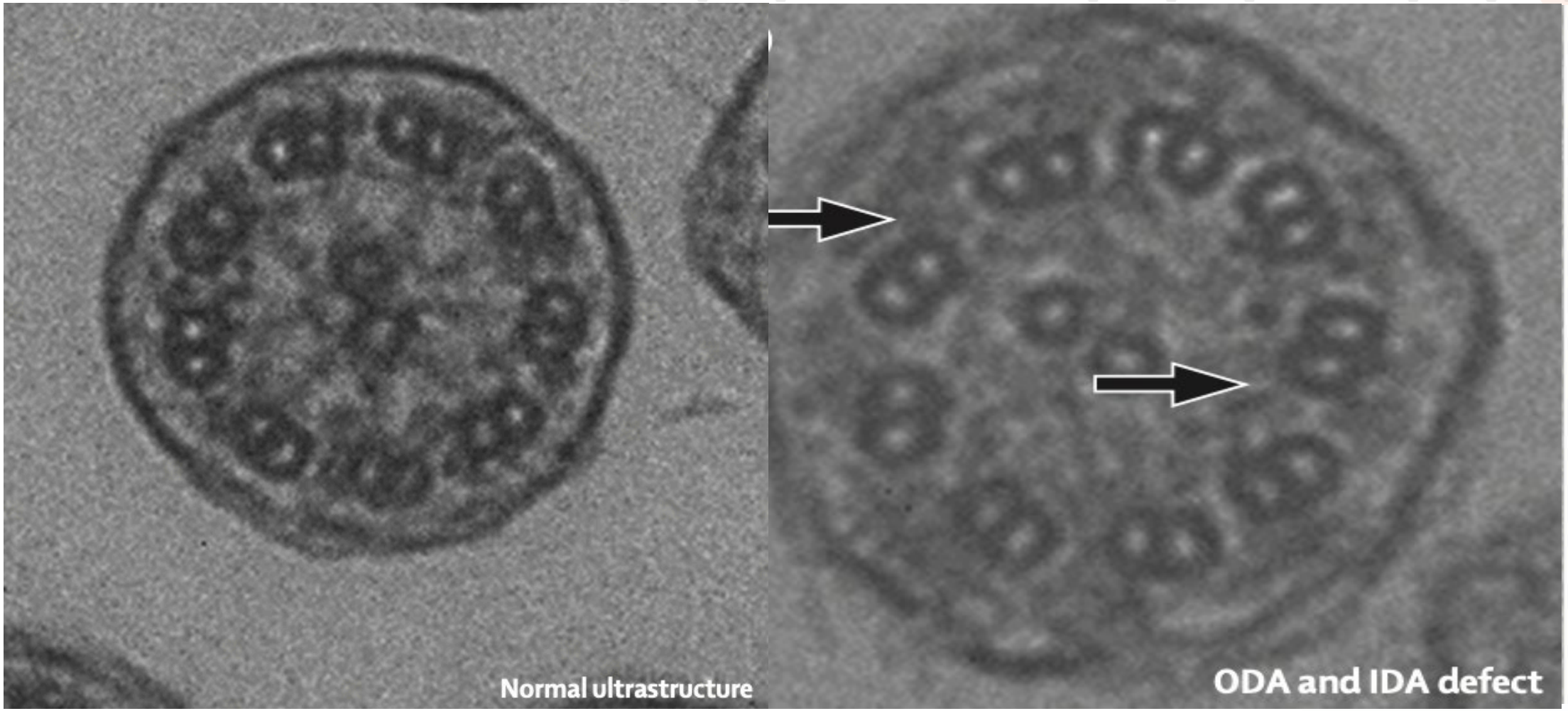
Genetic Testing

Diagnostic Tools

Transmission Electron Microscopy

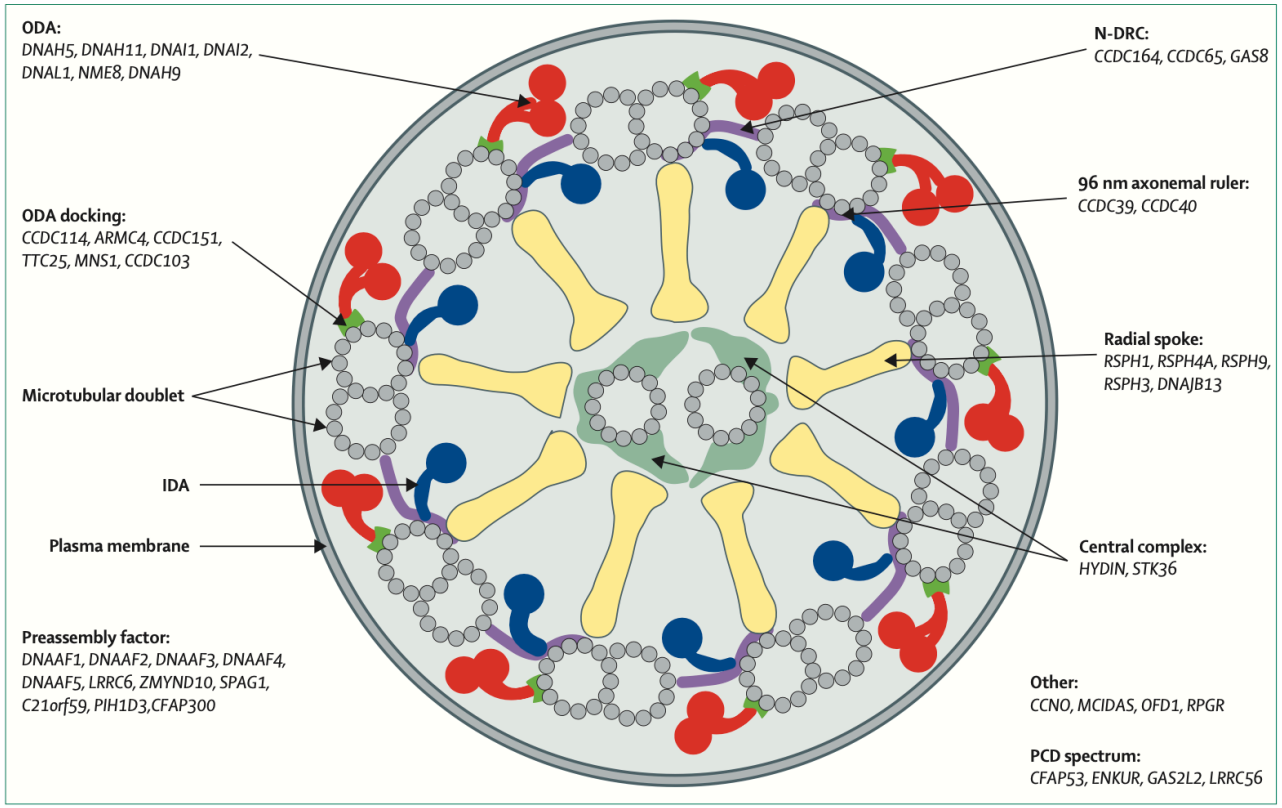


Knowles et al 2016



Lucas et al 2020

Diagnostic Tools



Lucas et al 2020

Genetic Testing

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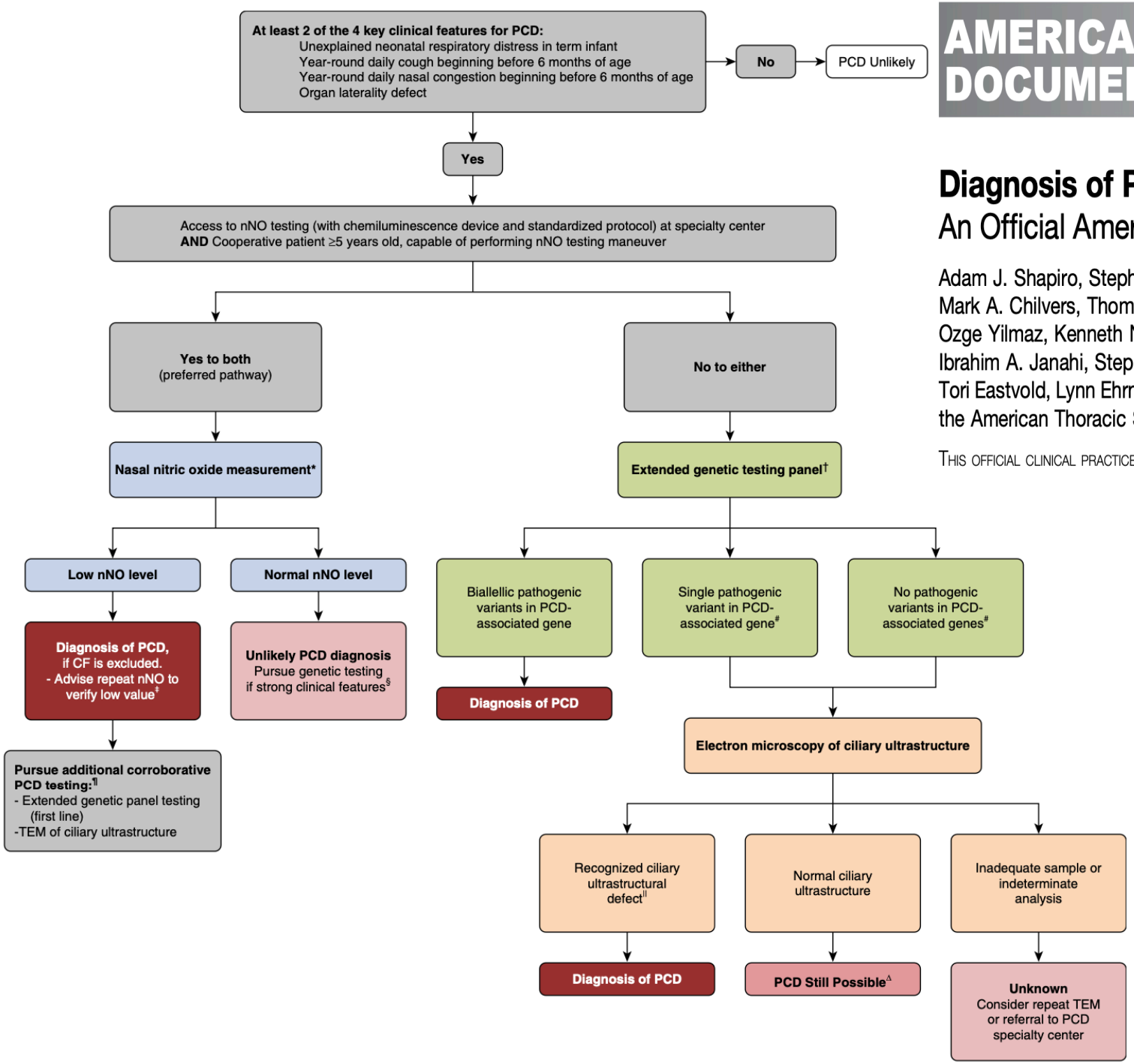

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Primary Ciliary Dyskinesia

An Official American Thoracic Society Clinical Practice Guideline

Adam J. Shapiro, Stephanie D. Davis, Deepika Polineni, Michele Manion, Margaret Rosenfeld, Sharon D. Dell, Mark A. Chilvers, Thomas W. Ferkol, Maimoona A. Zariwala, Scott D. Sagel, Maureen Josephson, Lucy Morgan, Ozge Yilmaz, Kenneth N. Olivier, Carlos Milla, Jessica E. Pittman, M. Leigh Anne Daniels, Marcus Herbert Jones, Ibrahim A. Janahi, Stephanie M. Ware, Sam J. Daniel, Matthew L. Cooper, Lawrence M. Nogee, Billy Anton, Tori Eastvold, Lynn Ehrne, Elena Guadagno, Michael R. Knowles, Margaret W. Leigh, and Valery Lavergne; on behalf of the American Thoracic Society Assembly on Pediatrics

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED MAY 2018

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What is CPC?

Diagnosis:

Primary Ciliary Dyskinesia

Confirmatory Test:

Extended Genetic Panel

Please take a moment at the end of the session to complete your evaluation.

Thank you!

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