Cross Canada Rounds: Long Case

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September 21, 2017

Case

- 14 yo M with persistent cough, occasional wheeze
- Half Japanese / half Scottish descent

- **Cough** began 6 yo, after coming to Canada 2008
- **Dx asthma** (family physician) based on audible wheeze: ICS and Ventolin PRN, with only mild benefit
- *Japan 2009*: PFT normal

- *Scotland 2011*: "asthma attacks" with viruses
- *2013*: camping, grass pollen and campfire smoke, required Ventolin in ED overnight
- *Canada 2013*: more frequent exacerbations, 3/year

Photo consent obtained

Case

- *March 2016*: persistent wet cough x 2-3 weeks, presumed pneumonia resolved with Amox
- *2016–present*: wet cough when well

- Cough **not** exacerbated by exercise, pets (1 dog in home); although ?grass pollen trigger

ROS:

- +Rhinorrhea since toddler, worse outdoors
- +Otitis media 1/year, perforated left TM 2014
- +Fatigue and decreased energy 2-3 years
- +Poor weight gain: weight 50th %ile age 2 yrs → below 10th %ile age 11 → now 2nd %ile
- Height always ~50th %ile
- Otherwise unremarkable

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Photo consent obtained

Case

Birth History:

- Born Scotland SVD term, Apgars normal, BW 50th %ile, no neonatal distress

Medications:

- Advair diskus 100 mcg 2 puffs BID (Community Resp)
- Ventolin MDI PRN (rarely used)

Allergies: NKDA

- Rhinitis outside- ?grass pollen
- Possible sensitivity to family dog- rhinitis

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Photo consent obtained

Case

Environmental:



FmHx:

- Healthy 9 yo brother
- Mother (**Japanese**) – accounting, healthy
  Father (**Scottish**) – desk job, pectus, Hx pneumonias and rhinitis; 3 aunts with asthma/eczema

O/E:

- Thin, left TM perforated, good AE with mild intermittent wheeze RUL, mild pectus carinatum, joint flexibility

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Case One

Differential diagnosis?

Top 3 possibilities in this case?

Approach to Cough

Chronic: **ACCP– ≤14 yo: daily cough ≥4 weeks**
BTS – cough lasting ≥8 weeks

History	Possible etiology
Chronic wet, productive	Suppurative lung diseases (PBB, CF, PCD, other bronchiectasis, aspiration)
Hemoptysis	Infection (ie. TB), ILD, bronchiectasis, autoimmune
Wheeze	Asthma (if no other specific cough pointers), bronchiectasis, eosinophilic disorders
Recurrent pneumonias	Immunodeficiency, obstructed airways, bronchiectasis
Symptoms neonatal	Congenital, immune function, PCD
Onset after choking	Foreign body
Worsens with anxiety, suppressible	Tic or habit cough

Chang (ACCP), Chest, 2006
Shield (BTS), Thorax, 2008

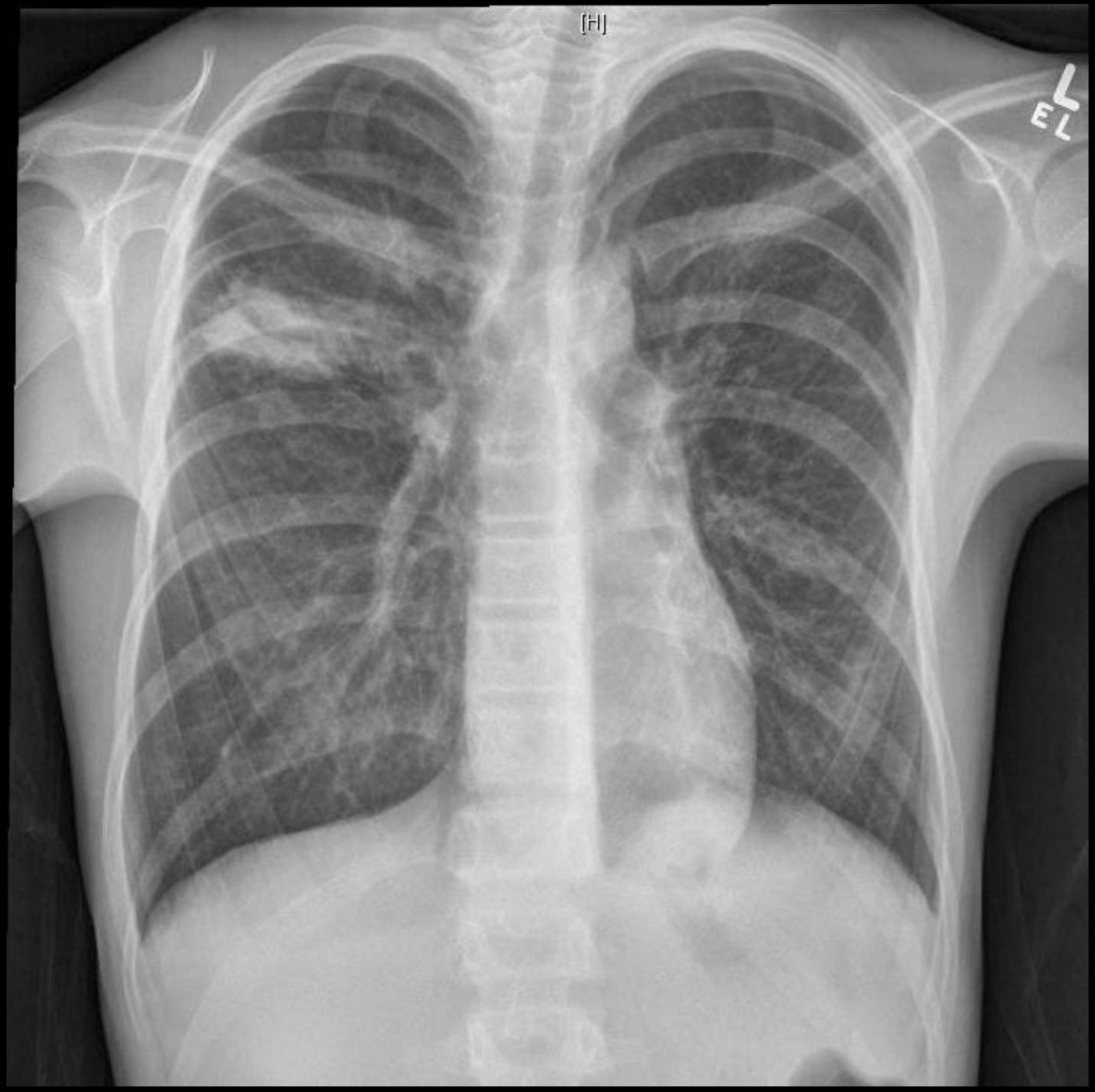
Approach to Cough

Classical characteristic	Possible etiology
Barking, brassy, honking	Tracheomalacia, tic/habit, psychogenic
Paroxysmal cough (violent attack)	Pertussis, parapertussis
Staccato	Chlamydia in infants
Productive with casts	Plastic bronchitis, severe mucous plugs
Chronic wet or AM productive	Suppurative lung disease (bronchiectasis, CF)

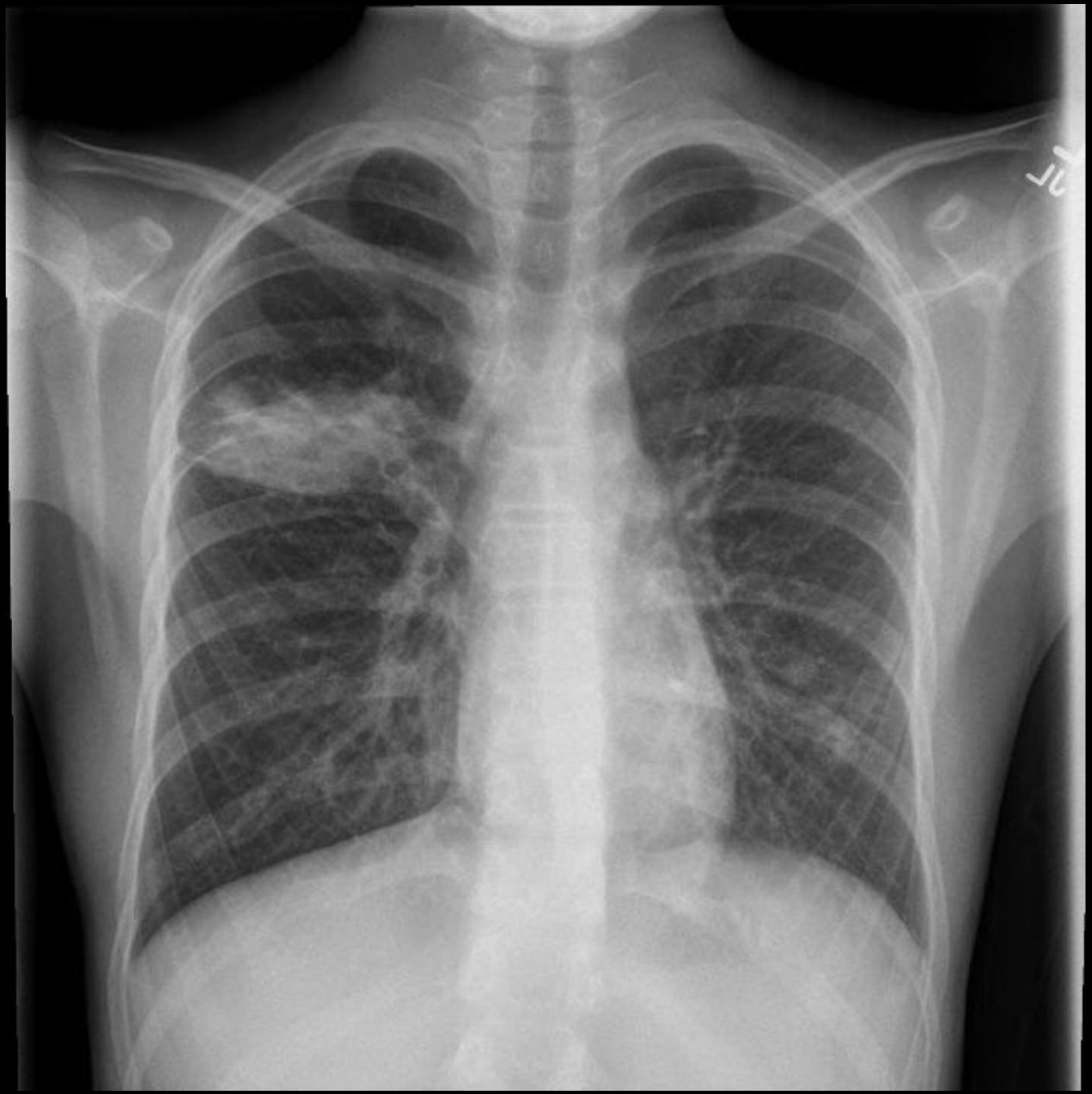
Chang (ACCP), Chest, 2006
Shield (BTS), Thorax, 2008

Case

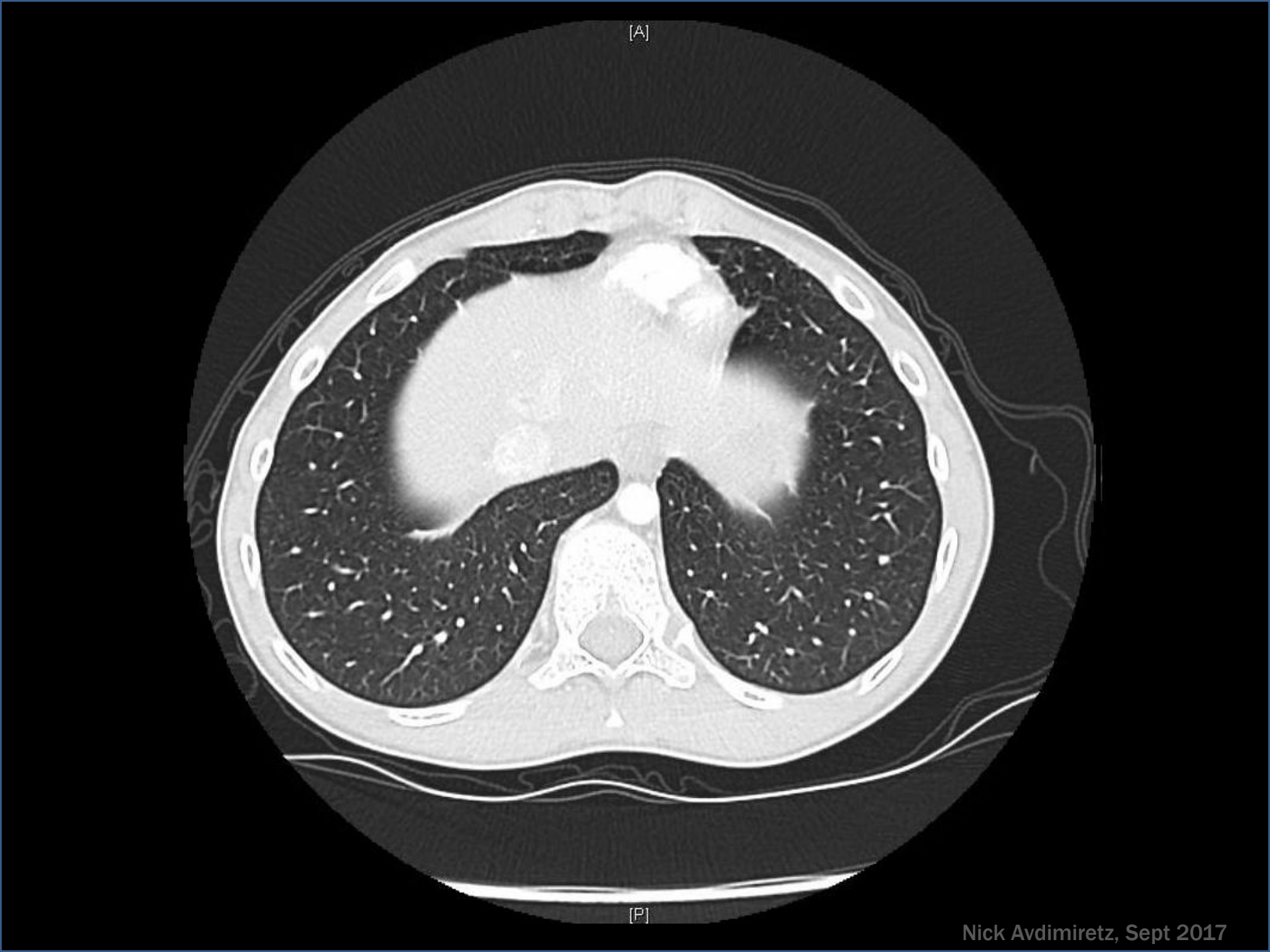
Five investigations at this point?



Nick Avdimiretz, Sept 2017



Nick Avdimiretz, Sept 2017



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Approach to Cough

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Onset after choking	Foreign body
Worsens with anxiety, suppressible	Tic or habit cough
Productive especially in AM	Suppurative lung disease (bronchiectasis, CF)

Chang (ACCP), Chest, 2006
Shield (BTS), Thorax, 2008

Case

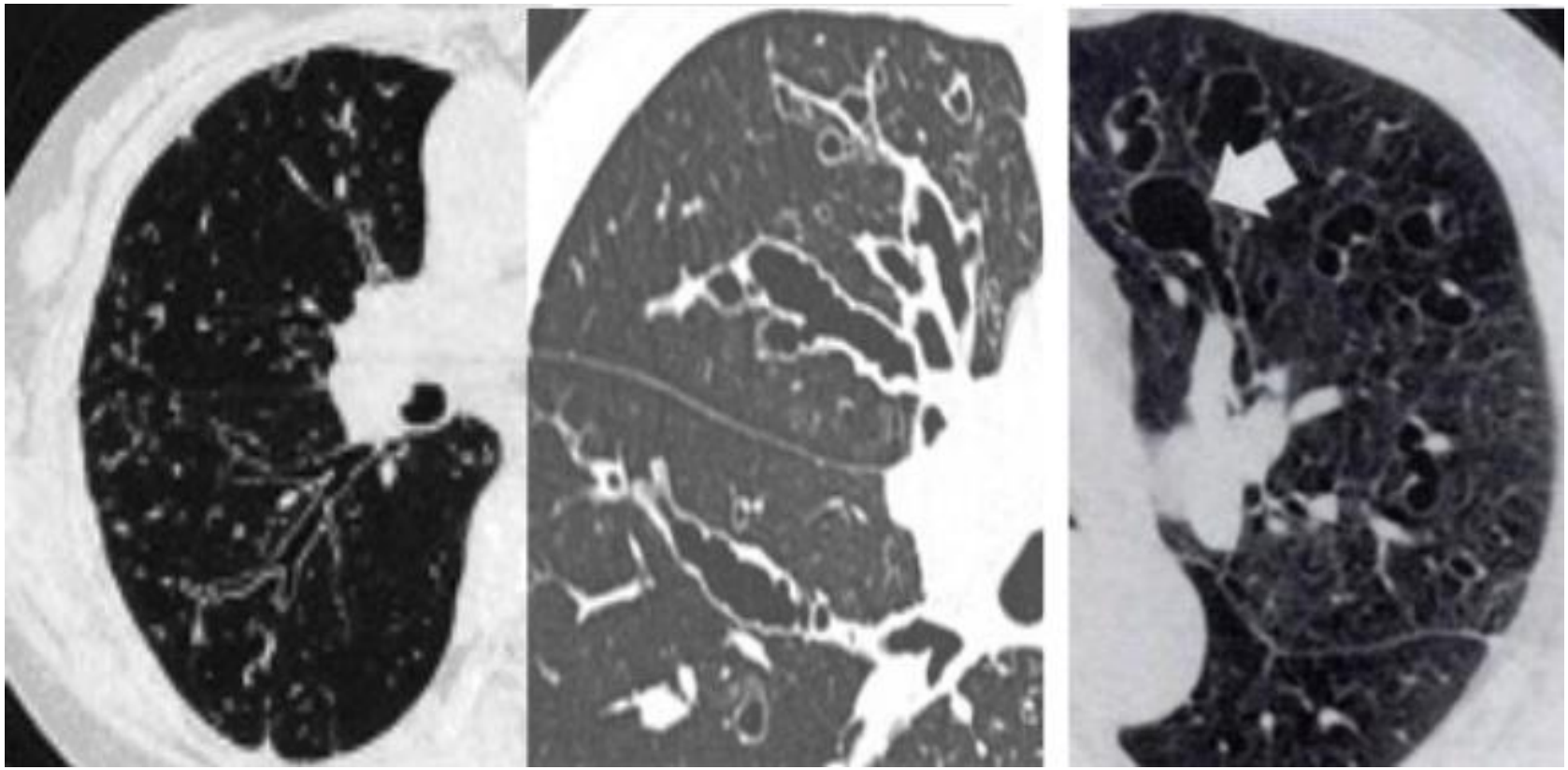
Differential diagnosis?

Any further key investigations?

Bronchiectasis

Reid classification:

Cylindrical/tubular/fusiform → Varicose → Cystic/saccular



Donnely, Fundamentals of pediatric radiology, 2001
Koo et al, Tuberc Resp Dis, 2013

Approach to Bronchiectasis

CF most common cause – resource-rich countries

Non-CF: **no underlying cause** in up to 40%

- Systematic review 12 studies (N=989) – etiology found in 63% cases
- Previous pneumonia / infection: 19%
- PID: 17%
- Recurrent aspiration / foreign body: 10%
- PCD: 7%
- PBB (persistent bacterial bronchitis) ???

Brower et al, Pediatr, 2014
Boren et al, Clin Rev Allergy Immunol, 2008

Approach to Bronchiectasis

#1

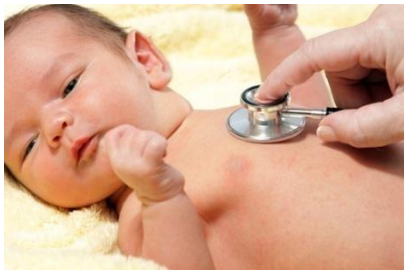
Infections
Bacterial (*Bordatella pertussis*, *Mycoplasma pneumoniae*, *Haemophilus influenza*, *Pseudomonas aerugenosa*, *Klebsiella pneumoniae*, *Stapholococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*)
Viral (RSV, measles, influenza, varicella, HIV)
Mycobacterial (tuberculosis, MAC)
Fungal (*Aspergillus* spp.)

#2

Immune deficiency/immunologic
Primary: hypogammaglobulinemia, IgG subclass deficiency, IgA or IgM deficiency, CVID, X-linked agammaglobulinemia
Secondary/acquired: AIDS, medication-induced immunosuppression, malignancy
Allergic bronchopulmonary aspergillosis (ABPA) /allergic bronchopulmonary mycoses (APBM)

Boren et al, Clin Rev Allergy Immunol, 2008

Approach to Bronchiectasis



#3

Congenital
- Cystic fibrosis
- Primary ciliary dyskinesia
- Pulmonary sequestration
- Alpha-1 antitrypsin deficiency
- Williams–Campbell syndrome (cartilage deficiency)
- Mounier–Kuhn syndrome (tracheobronchomegaly)
- Swyer–James syndrome (unilateral hyperlucent lung)
- Yellow nail syndrome (yellow nails and lymphedema)
- Marfan's syndrome
- Right middle lobe/lingula syndrome (abnormal angle of lobar bronchus at takeoff)

Boren et al, Clin Rev Allergy Immunol, 2008

Approach to Bronchiectasis

#4

Aspiration/bronchial obstruction/inhalation
- Foreign body aspiration
- Gastric contents/gastroesophagel reflux with aspiration
- Endobronchial mass/tumor
- Extrinsic airway narrowing (vascular ring, adenopathy, compressive mass)
- Toxic inhalation (chlorine, ammonia)

#5

Other
- Rheumatic and autoimmune disease (rare): rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus,
- Arsenic exposure
- Idiopathic

Boren et al, Clin Rev Allergy Immunol, 2008

Case

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Photo consent obtained

Referred to HSC from Community Resp:

- CXR reports:
  Migratory opacities (mainly RUL) >6 mo
- CT as before
- Echo: normal anatomy, good biventricular fxn
- C3, C4, CH50 normal
- Alpha-1 antitrypsin normal
- TST negative

- **Eosinophils high** **1.10 x 10^9/L** (0.00–0.50)
- **IgE high** **15,500** µg/L (0–480)
- Anti-*Aspergillus* Ab – indeterminate (inconclusive)

- Sweat chloride **36 mmol/L**

Case

Photo removed for confidentiality

Photo consent obtained

- Repeat sweat **30 mmol/L**
- Sputum: heavy **MSSA**, ***Aspergillus fumigatus***
- **Vitamin D low** 54; **vitamin A low** 0.7; vitamin E normal
- Fecal elastase >500 (sufficient)

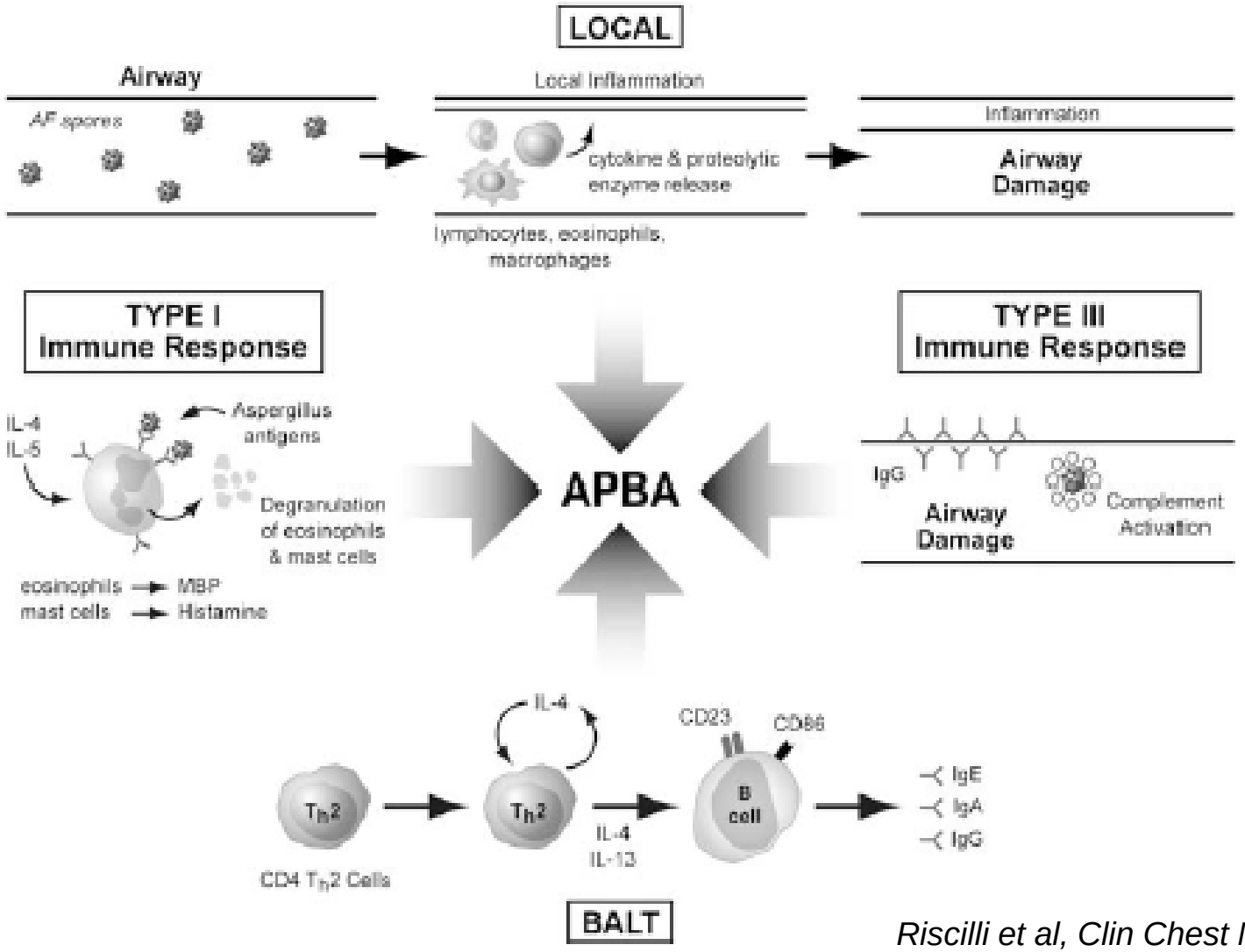
- PFT: **FEV1 76%**, FEV1/FVC 85%, Negative BD response
  TLC 82%, RV/TLC 22%, DLCO 82%
- **Exhaled NO high** 48 ppb
- Nasal NO 1055 ppb

- SPT:
  Markedly positive to *Aspergillus*
  Positive to grass, dust mites, cat, feathers, hormodendrum
  Borderline to dog

Case

Next steps?

ABPA



Riscilli et al, Clin Chest Med, 2009

ABPA

- In 1–2% of **asthmatics**
- In 2–10% of **CF patients**

Am. J. Hum. Genet. 59:45–51, 1996

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Gene Mutations in Allergic Bronchopulmonary Aspergillosis

Patrice Weiner Miller,[1,2] Ada Hamosh,[1] Milan Macek, Jr.,[1] Paul A. Greenberger,[5] James MacLean,[4] Sandra M. Walden,[2] Raymond G. Slavin,[3] and Garry R. Cutting[1]

- One early study 11 patients with ABPA
- Patients also had normal sweat Cl (<40 mmol/L)
- **6/11** → at least one CFTR mutation (4 with single delta F508)

Miller et al, Clin Chest Med, 2009

ABPA

TABLE 3. CLUES TO THE PRESENCE OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

	Asthma	Cystic Fibrosis
Mucus production	New, brown-black	Increased, Brown-Black
Total IgE > 1,000 IU/mL	+	+
Bronchiectasis	Central	Predominantly central, extensive
Fleeting pulmonary opacities	+	+
High attenuation mucus plugs on chest CT	+	+

Patterson et al, Am Thorac Soc, 2010

ABPA Diagnosis

International Society for Human & Animal Mycology (ISHAM):

- Predisposing conditions (need 1):
  - **Asthma**
  - **CF**
- Obligatory criteria (need both):
  - ***Aspergillus* SPT positive** or **elevated IgE against *Aspergillus fumigatus***
  - **Elevated total IgE** >1000 IU/mL*
- Other criteria (at least 2):
  - **Serum Ab to *A. fumigatus*** or **elevated serum Aspergillus IgG**
  - **Radiographic opacities** consistent with ABPA
  - **Eosinophils** >500 cells/uL in steroid-naïve (can be historical)

* If meets other criteria, total IgE <1000 can be acceptable

** Supporting (but not Dx): sputum +*Aspergillus*, +Galactomannan

Agarwal, Clin Exp Allergy, 2013

ABPA Diagnosis in CF

CF Foundation Consensus Guidelines– 2003

- **Classic criteria**:
  - Acute or subacute clinical deterioration
  - Total IgE >1000, unless on steroids
  - SPT *Aspergillus* +ve or IgE *Aspergillus* +ve
  - Precipitating Ab to *A. fumigatus* or IgG to *A. fumigatus*
  - New/recent abnormality CXR/CT
- **Minimal criteria**:
  - Acute or subacute clinical deterioration
  - Total IgE >500
  - SPT *Aspergillus* +ve or IgE *Aspergillus* +ve
  - One of: (1) precipitins, (2) CXR/CT

CYSTIC FIBROSIS FOUNDATION

Stevens et al, Clin Inf Dis, 2003

ABPA Treatment

- **Corticorticosteroids**
  - **Prednisone 0.5–2.0 mg/kg/day** x 2 wks, then tapered over 2–3 mo
  - Treatment plan based on clinical + IgE response
  - Increase IgE by 100% baseline requires treatment

- **Anti-fungals**
  - Adjunct x 3–6 months → *IDSA: itraconazole as part of initial Tx*
  - Indications: poor response to steroids, steroid toxicity
  - Improves lung function, # exacerbations, steroid use
  - **Itraconazole** most studied (less S/E than vori, broader than keto)
  - *Take full stomach; <u>needs acid</u> (no PPI!), baseline LFTs, levels*

Stevens et al, Clin Inf Dis, 2003
Patterson et al, Am Thorac Soc, 2010

ABPA Treatment

Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis (Review)

Elphick HE, Southern KW

- No completed RCTs included
- Trials in patients without CF – clinical and serological improvement, reduced steroid use, no increase in adverse effects

Elphick, Cochrane Database Syst Rev, 2012

ABPA Treatment

Anti-IgE therapy for allergic bronchopulmonary aspergillosis in people with cystic fibrosis (Review)

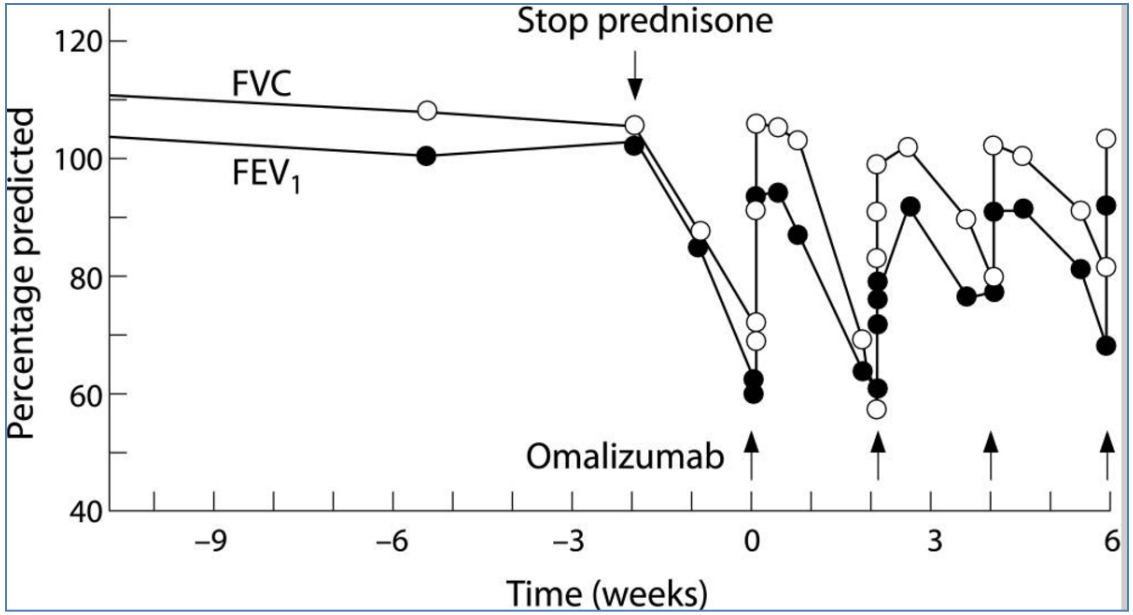
Jat KR, Walia DK, Khairwa A

- Only one trial N=14 eligible, terminated early (unable to recruit)
- Lack of evidence for efficacy and safety of anti-IgE (Omalizumab) in CF patients with ABPA

Jat et al, Cochrane Database Syst Rev, 2013

ABPA Treatment

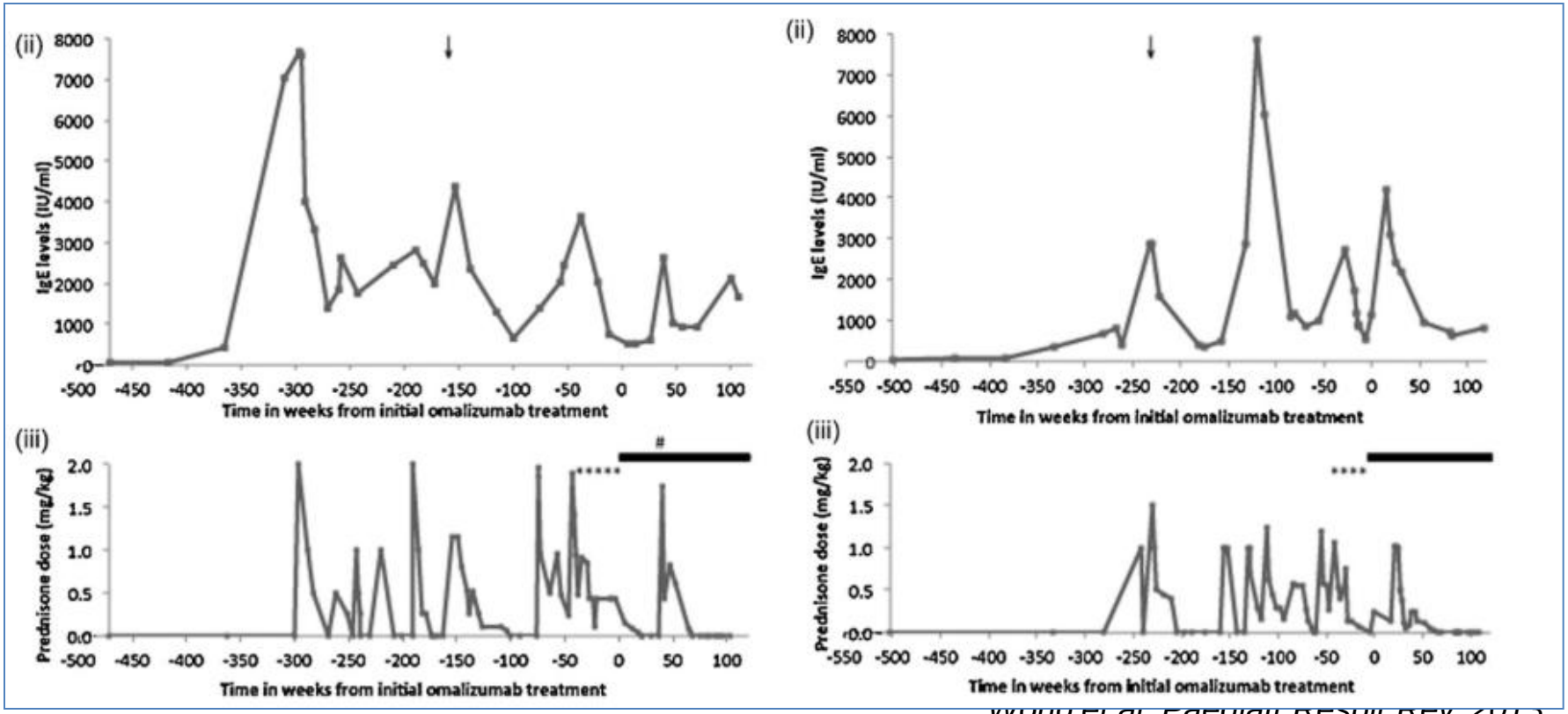
- Case report 2007 with Omalizumab:
  - 12 yo F, CF and ABPA, IgE 5200
  - Prednisone 50 mg/day → symptoms resolved but could not wean



Van der Ent et al, Thorax, 2007

ABPA Treatment

- **Two cases 2013 with Omalizumab:**
  - **14 and 15 yo, CF and ABPA**



Wong et al, Paediatr Respir Rev, 2013

Voskamp et al, J Allergy Clin Immunol Pract, 2015

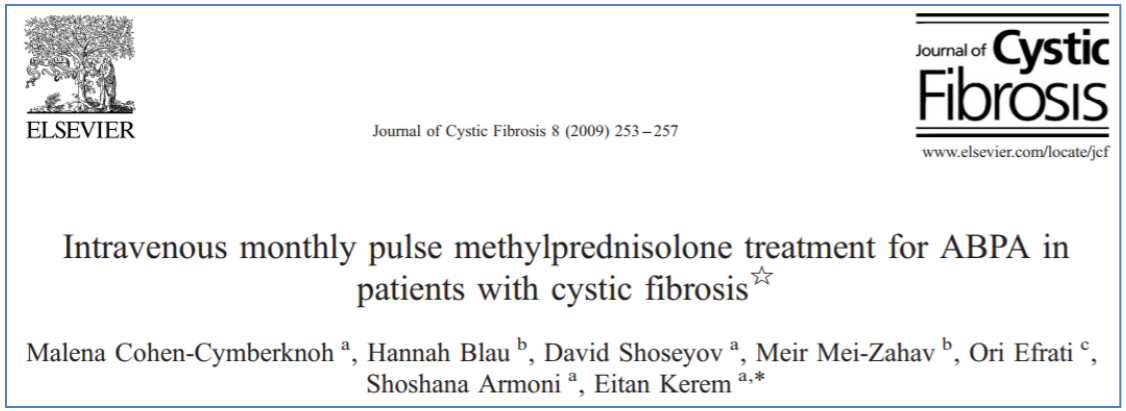
ABPA Treatment

- Two cases 2013 with Omalizumab:
  - 14 and 15 yo, CF and ABPA

- Voskamp et al (2015):
  - First RCT 13 *asthmatics* with ABPA
  - Omalizumab 750 mg monthly x 4 mo vs. placebo
  - **Significant reduction in exacerbations** (2 vs. 12 events, *p*=0.048)

Wong et al, Paediatr Respir Rev, 2013
Voskamp et al, J Allergy Clin Immunol Pract, 2015

ABPA Treatment



ELSEVIER

Journal of Cystic Fibrosis 8 (2009) 253–257

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Intravenous monthly pulse methylprednisolone treatment for ABPA in patients with cystic fibrosis☆

Malena Cohen-Cymberknoh [a], Hannah Blau [b], David Shoseyov [a], Meir Mei-Zahav [b], Ori Efrati [c], Shoshana Armoni [a], Eitan Kerem [a,*]

- CF patients N=9 (mean age 17 yrs):
  - **Pulses high-dose IV methylpred** (10–15 mg/kg/d) x 3 days per month plus itraconazole
  - Compared to standard PO Prednisone
  - ***All had clinical and lab improvement*** (↑FEV1, ↓IgE), Tx stopped after 6–10 pulses

  (PO Pred group: 4/5 deteriorated with tapering)

Cohen-Cymberknoh et al, J Cyst Fibros, 2009

Case

Before Tx – BAL:

- Purulent secretions, especially RUL
- Neuts 2%, Lymphs 16%
- Micro: **+MSSA** and ***+Aspergillus fumigatus***
- Negative for AFB/mycobacterial, PJP, atypicals, etc.
- Galactomannan negative

Treatment:

- **Cloxacillin** x 2 weeks for MSSA
- **Prednisone** 60 mg daily (~1.6mg/kg/dose) x 1 mo
- Physiotherapy via PEP

Follow-up:

- FEV1 improved 76% → **89%**
- IgE 15,500 → **3,390**
- Repeat sweat **27 normal**
  → ***"Unlikely CF" <30 for all ages – recent change***

Photo removed for confidentiality

Photo consent obtained

Case

Genetics:

(1) **delta F508**

(2) **c.4045G>A** (p.Gly1349Ser) – *likely pathogenic.*

Reported in 1 Japanese patient with CBAVD (but not CF)

Photo removed for confidentiality

Photo consent obtained

CF/CBAVD in Japan

- CF rare in Asian populations – only 130 typical CF cases in Japan
- Incidence 1 in 100,000–350,000
- **CBAVD** not uncommon in Japan: 1% male infertile patients (>US)
- Analysis for CF in Japan: novel, rare CFTR mutations

- In CBAVD, **58%** have at least 1 mutated allele (vs 5% in controls)
- High prevalence **5T allele** in CFTR in Japanese CBAVD

Anzai et al, J Cyst Fibros, 2003

Case

Question for fellows–

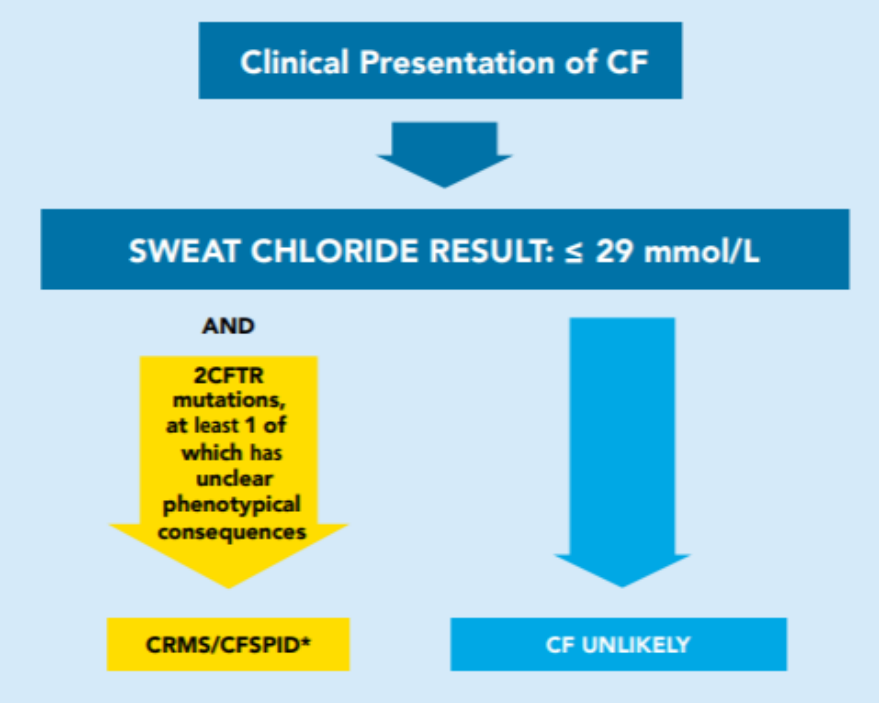
Would you diagnose him with CF?

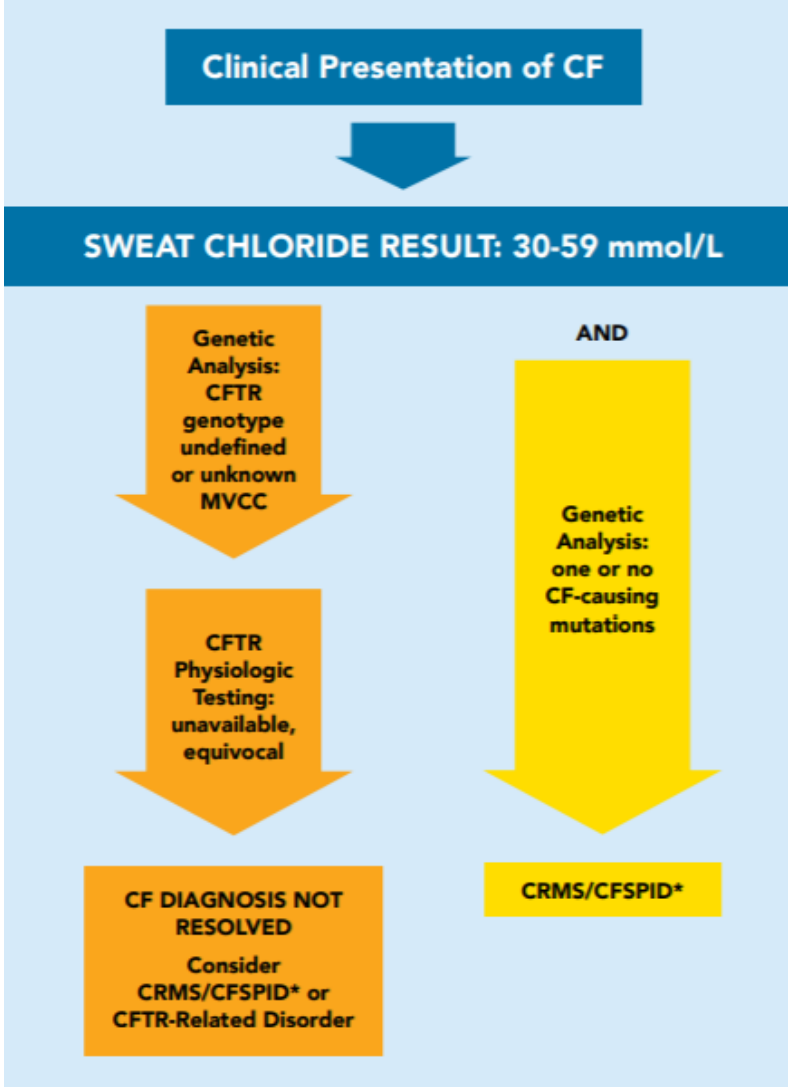
Sweats: 27, 36, 30

Genetics: dF508 / 4045G>A

CRMS/CFSPID?

Sweats: 27, 36, 30

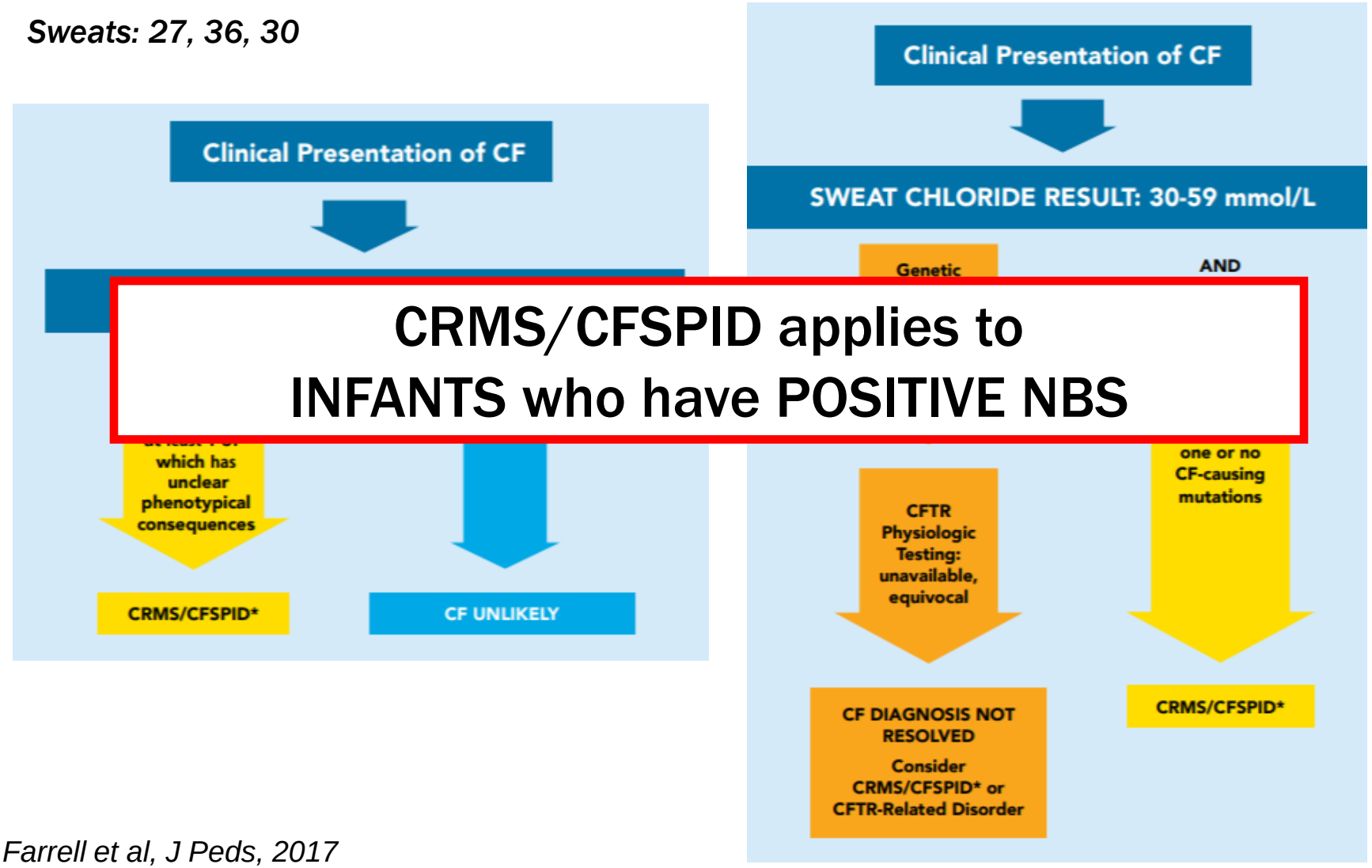




Farrell et al, J Peds, 2017

CRMS/CFSPID?

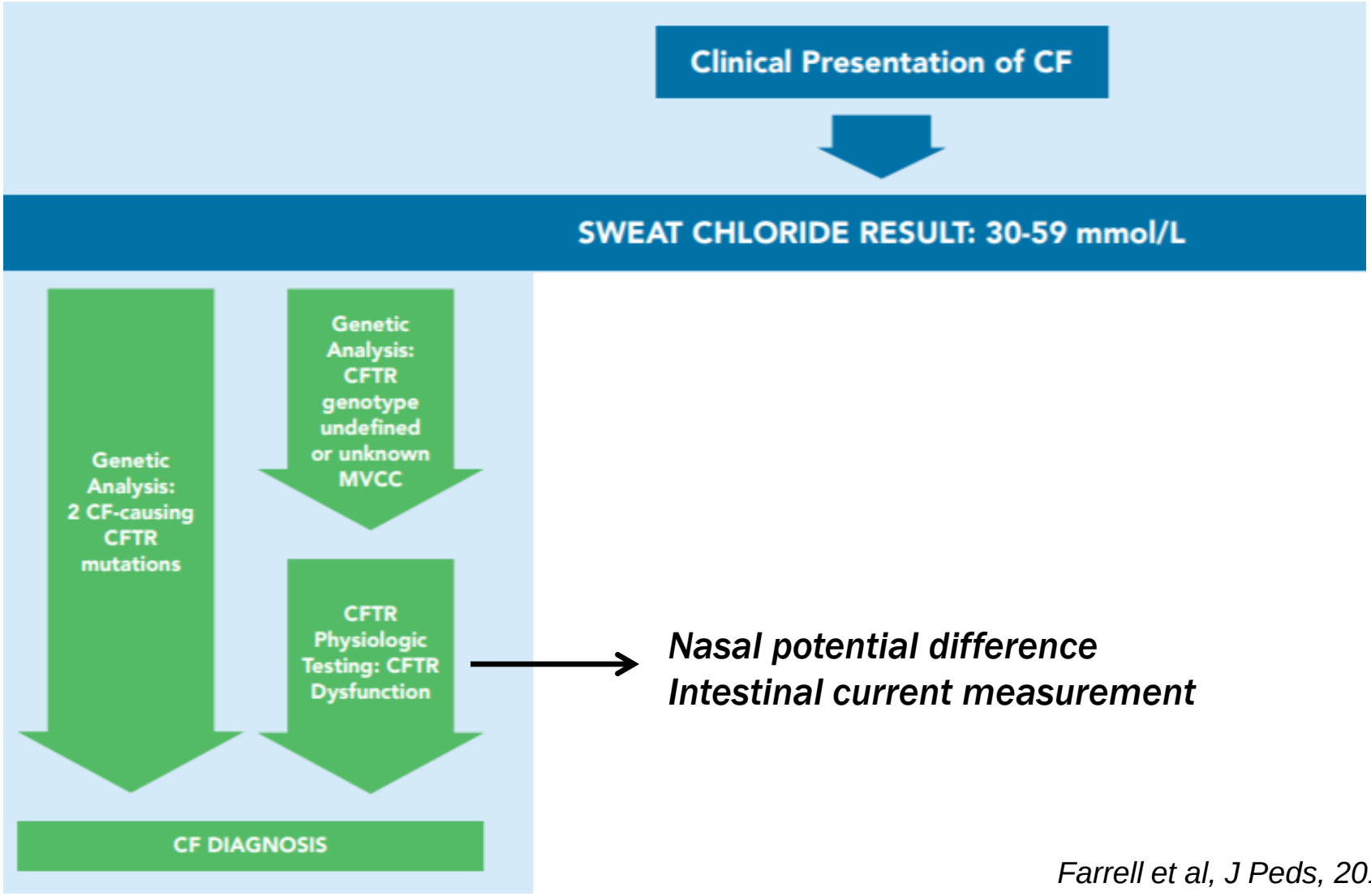
Sweats: 27, 36, 30



CRMS/CFSPID applies to INFANTS who have POSITIVE NBS

Farrell et al, J Peds, 2017

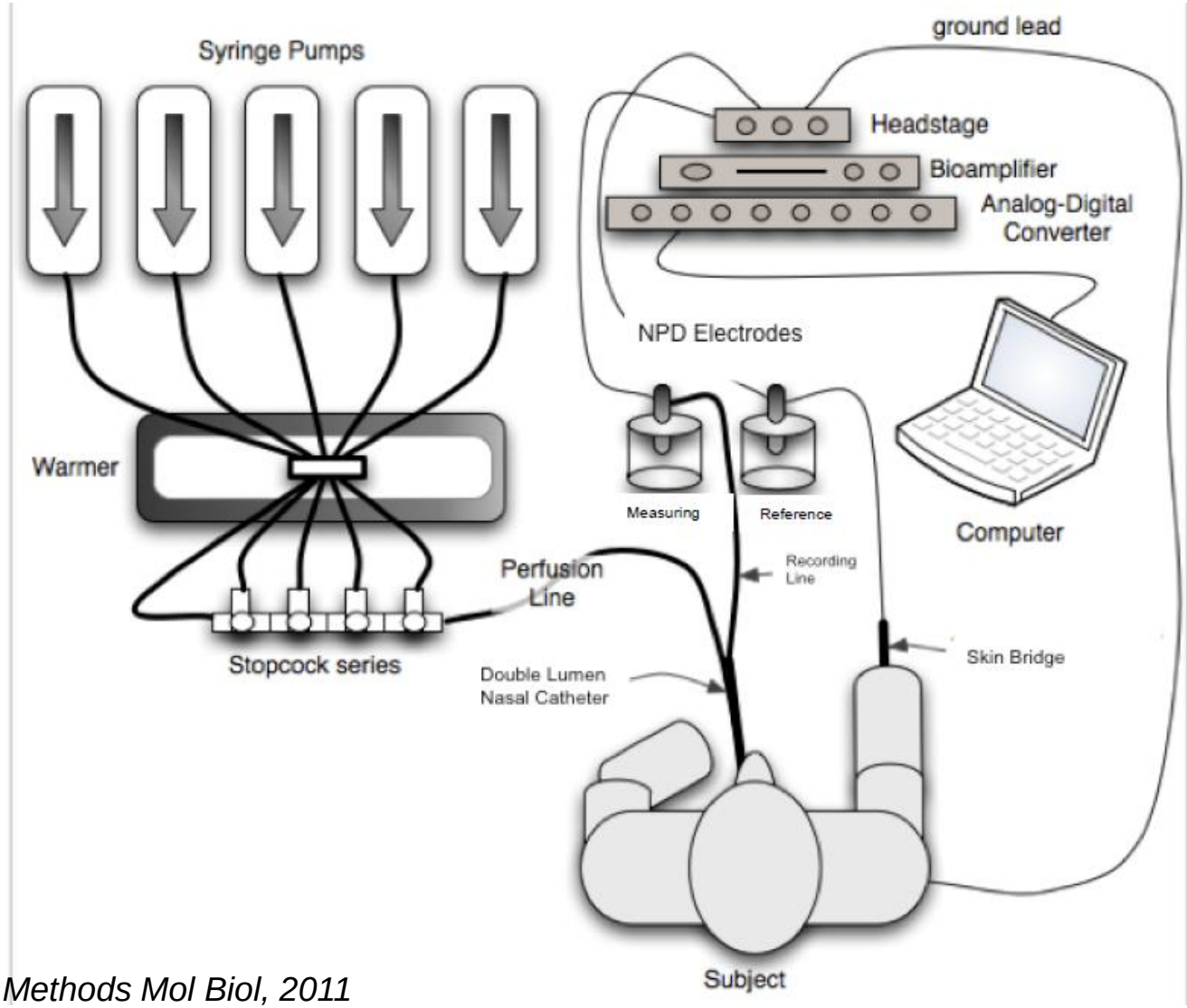
CFTR Function?



Nasal potential difference
Intestinal current measurement

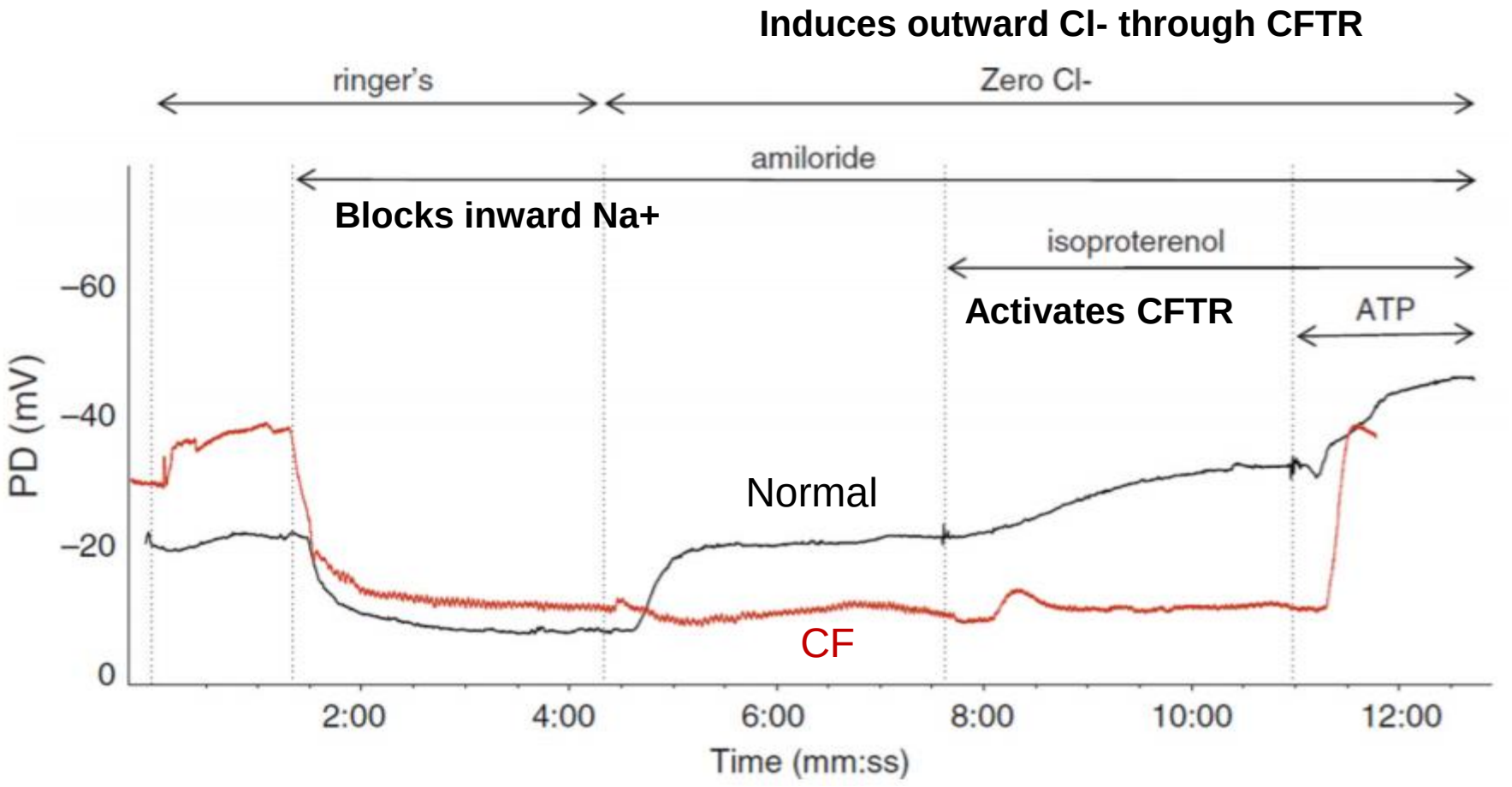
Farrell et al, J Peds, 2017

Nasal Potential Difference (NPD)



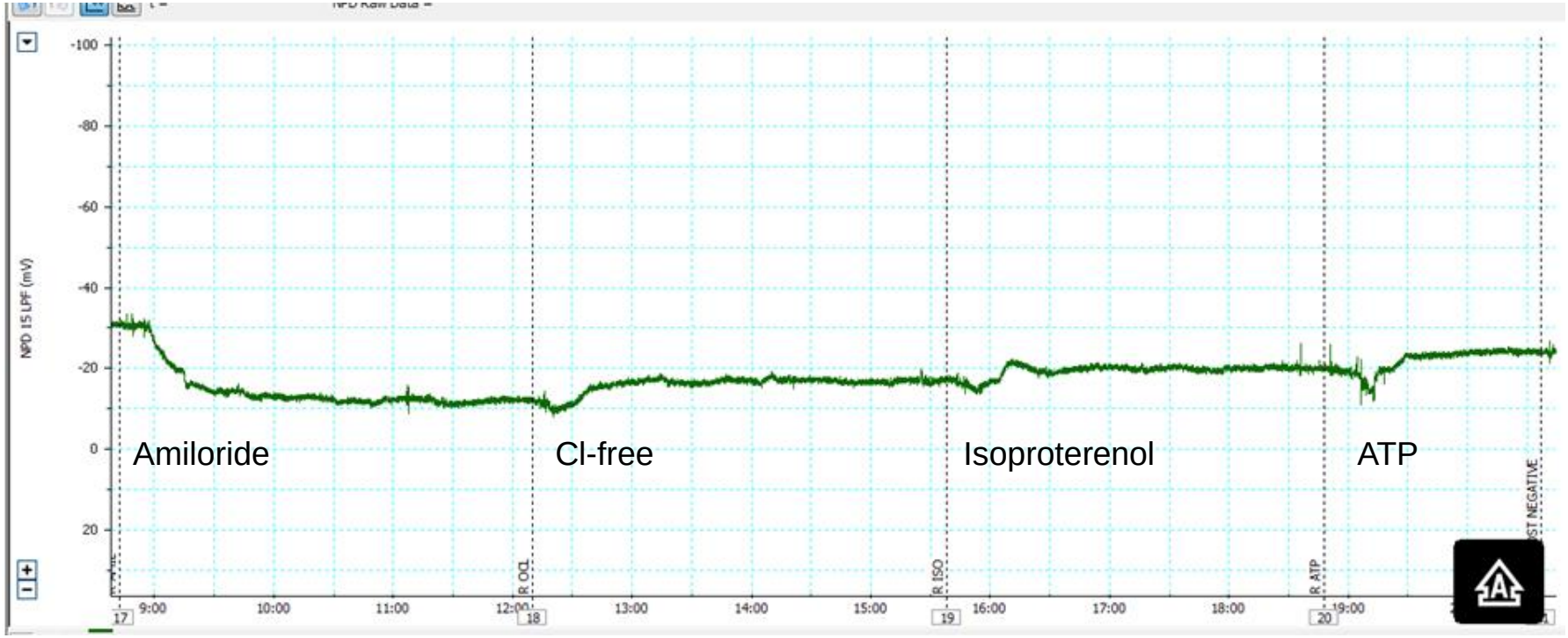
Rowe et al, Methods Mol Biol, 2011

Nasal Potential Difference (NPD)



Rowe et al, Methods Mol Biol, 2011

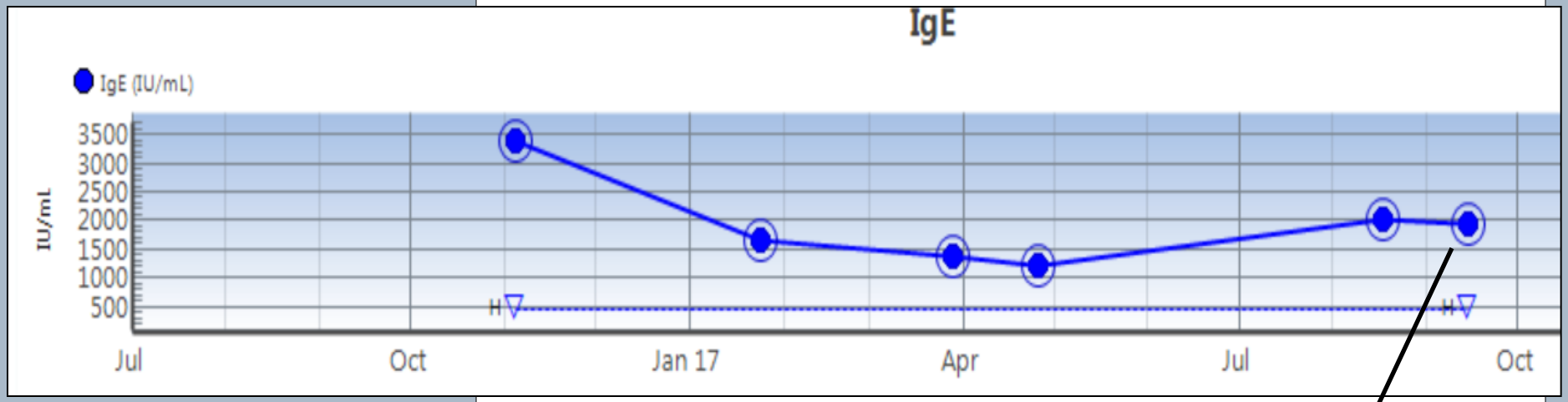
Case – NPD



- If classic CF, expect more negative start (–40mV) – ?appropriate for mutations
- Minimal response to Cl-free solution: **sign of CFTR dysfunction**
- Poor response to Isoproterenol (<7.7mV change from Amil): **CFTR dysfunction**
- Poor response to ATP: poor test?

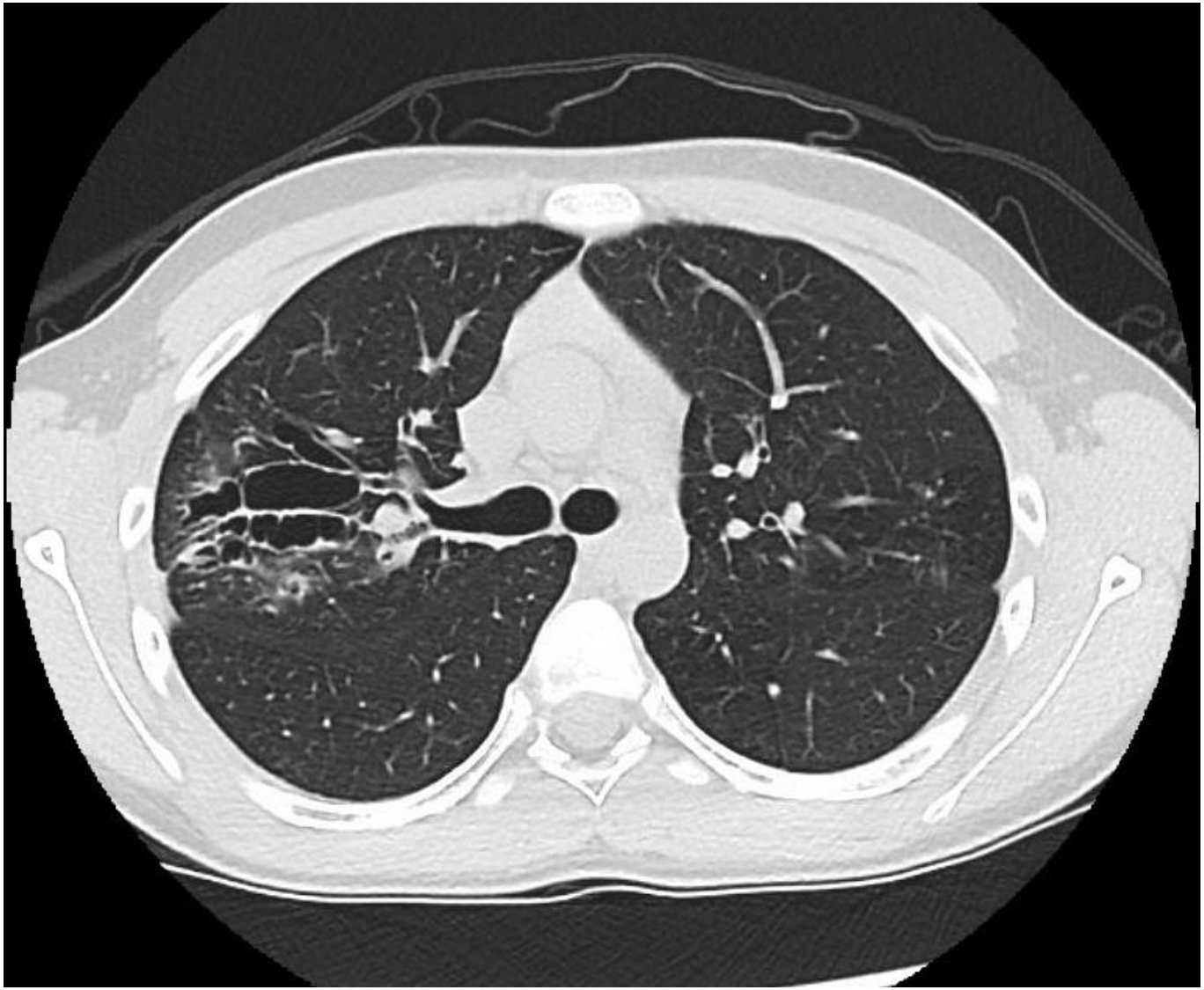
Case

- Diagnosed as CF (vs. CFTR-Related Disorder)
- Prednisone tapered over course of 10 months



Itraconazole started

Case



Case – Complicating Factors

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Photo consent obtained

PCD? – yearly OM, perforated TM, chronic rhinorrhea

Nasal ciliary scraping PCD:

- Possible central complex defect in **15-20% cilia**

Genetics for PCD:

- Variant of uncertain significance in **DNAH11** (heterozygous)

Marfan syndrome?

- Pectus carinatum, tall & thin, joint flexibilty
- Classic association pneumo, emphysema (10–15%), blebs
- *Bronchiectasis* in adults ~20% (single lobe)

Take Home Messages

1. Bronchiectasis – recall diagnostic categories
2. ABPA – aim to reduce IgE and symptoms
3. ABPA – recall azoles, ?omalizumab as adjuncts
4. CFSPID/CRMS applies to infants with positive NBS
5. If available, consider CFTR function tests in “possible” CF

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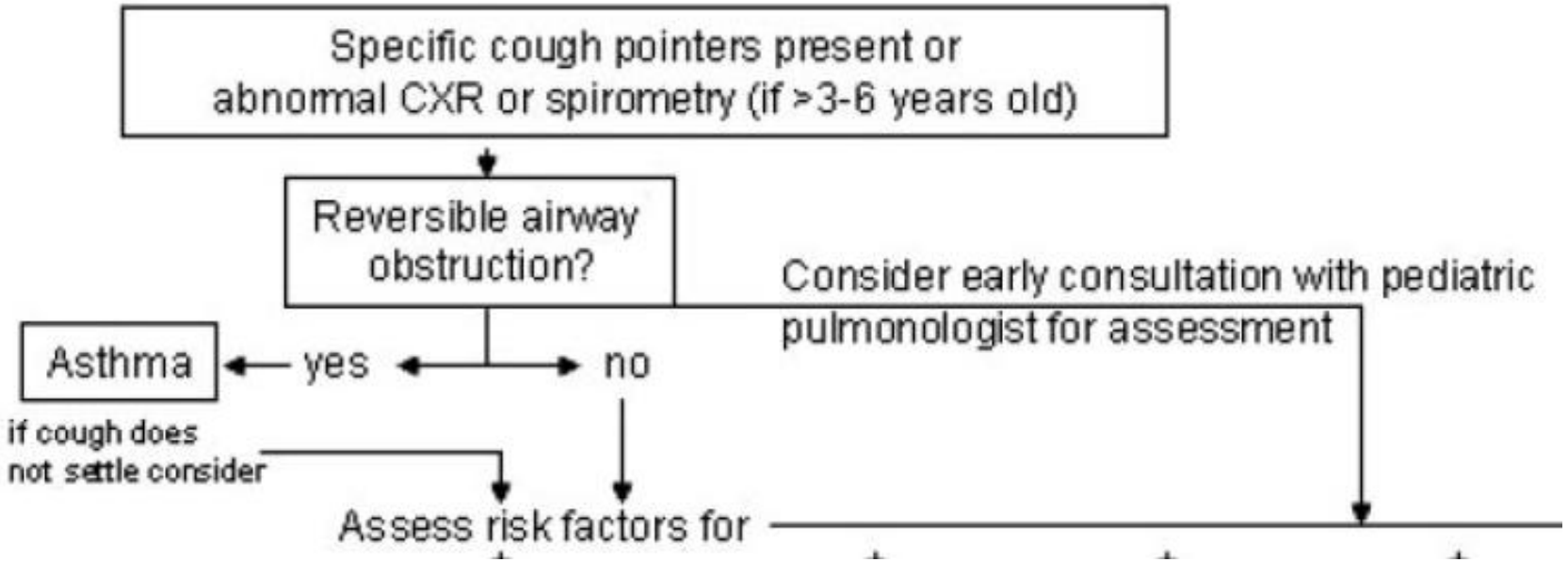
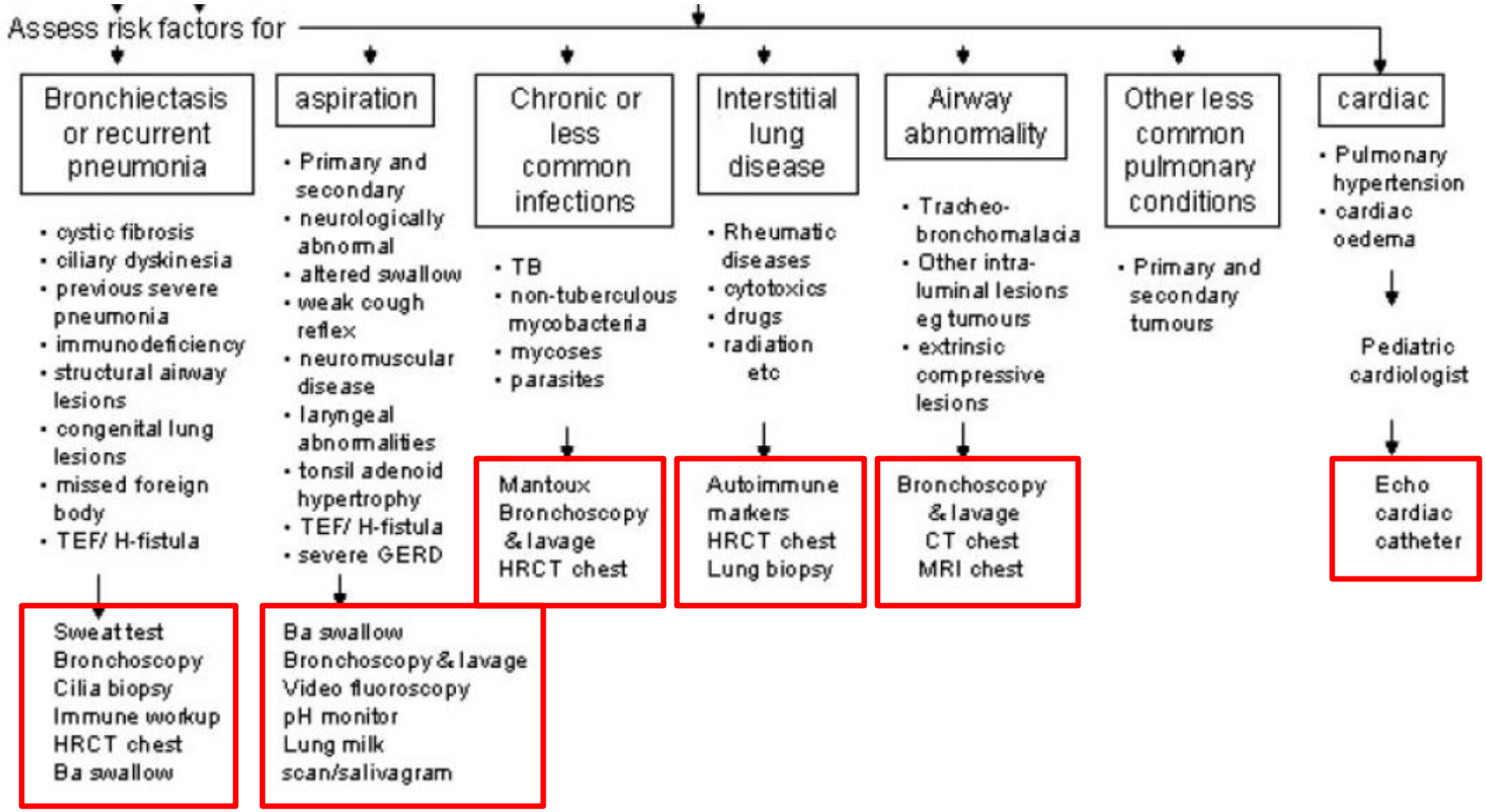
Thank You!

Extra Slides: Approach to Cough



Chang (ACCP), Chest, 2006

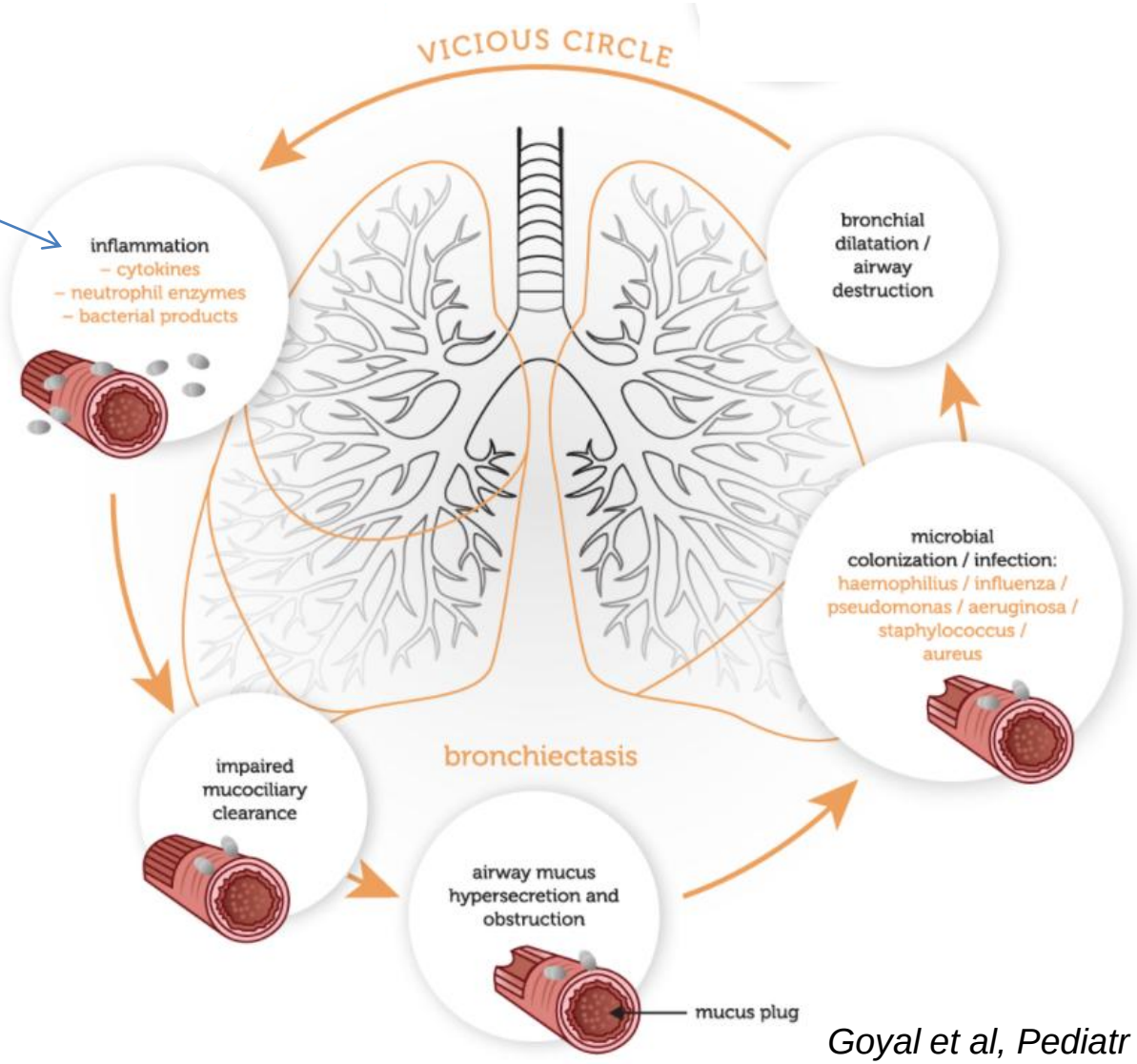
Extra Slides: Approach to Cough



Chang (ACCP), Chest, 2006

Extra Slides: Bronchiectasis

TNF-alpha
IL-1B, IL-8



Goyal et al, Pediatr Pulmonol, 2016

Extra Slides: Bronchiectasis

Clinical manifestations:

- Persistent wet cough (80–90%)
- Purulent sputum (57–74%) → *Absence does not exclude bronchiectasis*
- Episodic exacerbations of infection (fever, pleurisy, cough, sputum)
- Hemoptysis only 4–7% children
- Dyspnea, exercise intolerance uncommon
- If severe: cyanosis → *If hypoxemia due to V/Q mismatch*

- Crackles and rhonchi common
- Wheezing less common (still 7–11%)
- Digital clubbing (44–51%)
- Findings pointing to underlying etiology: FTT, sinusitis, congenital anomalies, etc

Karakoc et al, Pediatr Pulmonol, 2001

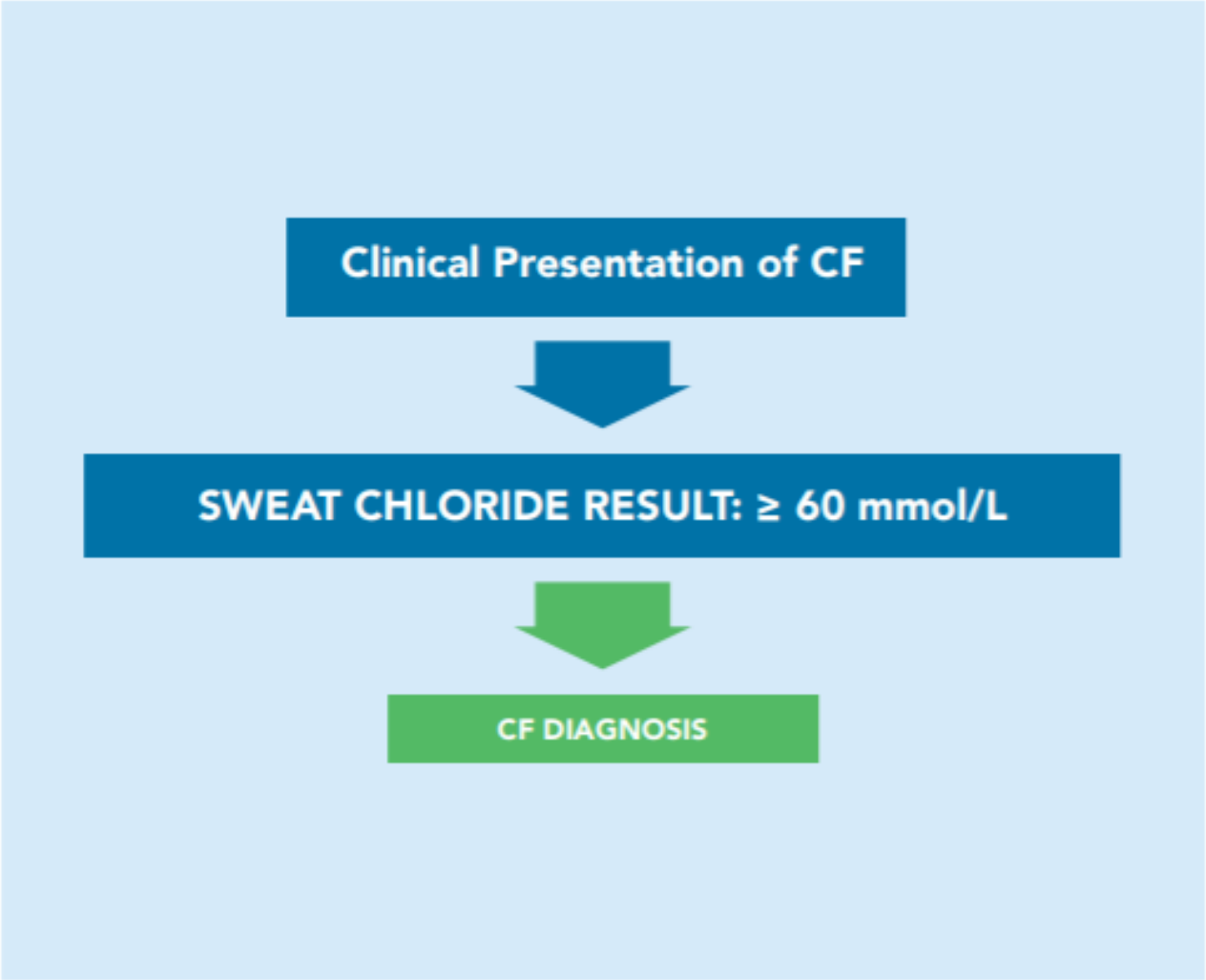
Extra Slides: Approach to Bronchiectasis

Evaluation:

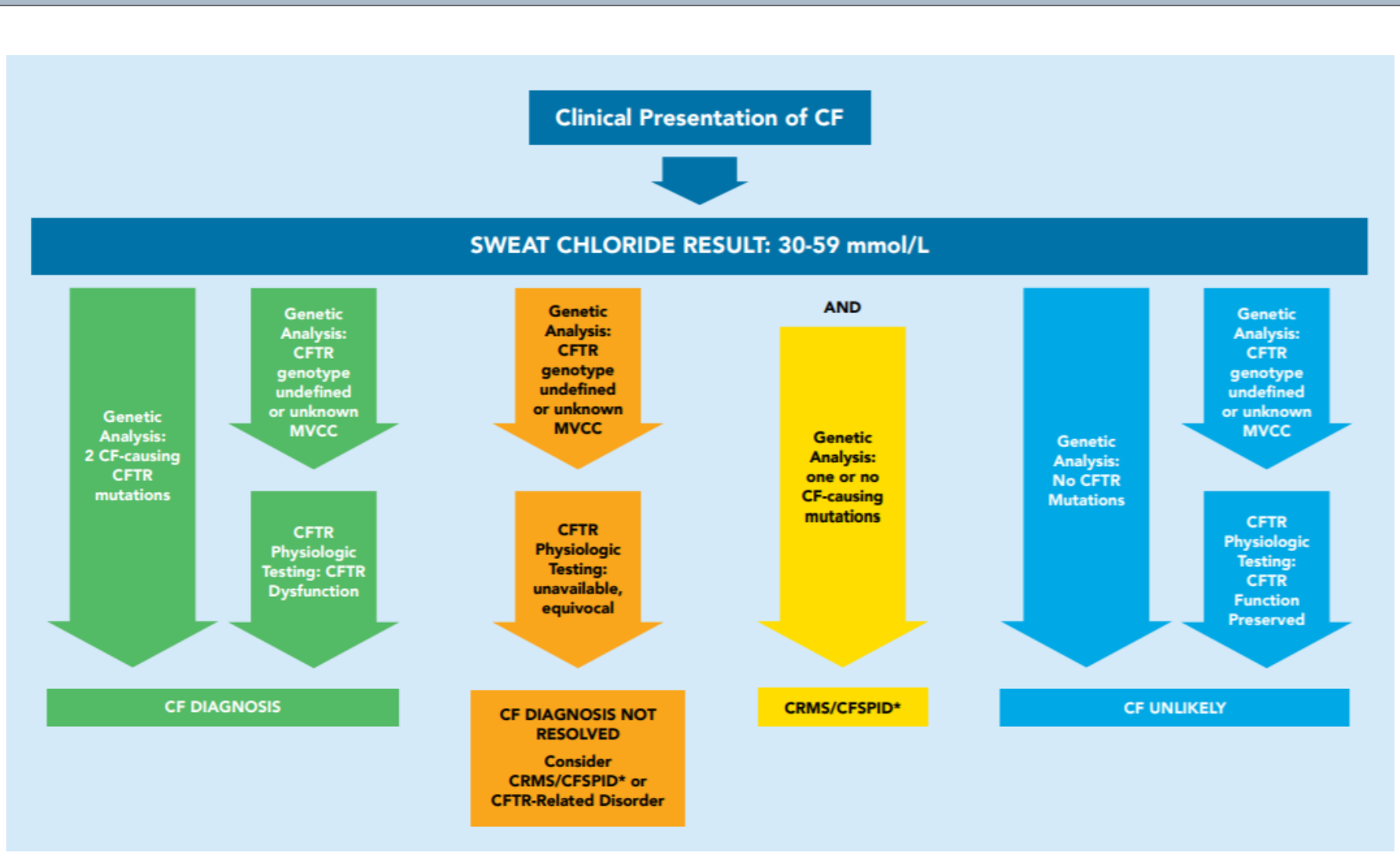
- **Radiographic** – HRCT "gold standard"
- **Bloodwork** – CBC-diff, serum Ig's, +/- pre/post-vaccination titers, NOBI, lymphocyte enumeration, mitogen stimulation, C3/C4/CH50, +/- HIV testing
- **Other Labs** – sweat Cl, sputum culture, nasal scraping for EM, alpha-1 antitrypsin
- **If ABPA suspected** – total IgE, IgE to Aspergillus, *Aspergillus precipitans*, SPT
- **If autoimmune suspected** – ESR, RF, auto-antibodies
- **Procedures** – BAL (?FB, culture)
- **If aspiration suspected** – barium swallow, pH probe, etc.
- **If TB suspected** – Mantoux
- **Functional Evaluation** – PFT including bronchodilator

Boren et al, Clin Rev Allergy Immunol, 2008

Extra Slides: Diagnosing CF



Extra Slides: Diagnosing CF



Nick Avdimiretz, Sept 2017

Extra Slides: Diagnosing CF