Asthma Biologicals: How to Choose/ for which Patients/ for How Long?

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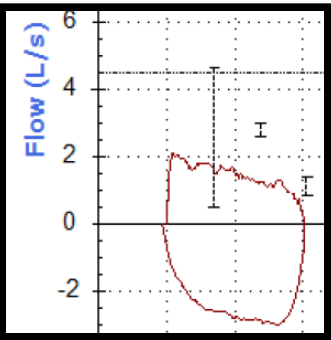
Problematic Respiratory Symptoms not Responding to Asthma Therapy

Diagnostic Work-up

Evidence of asthma? Not asthma at all?



PSA: MDT Evaluation

These three may have overlap features

Asthma plus

Difficult asthma (DA)

Severe, therapy resistant asthma

MDT Intervenes

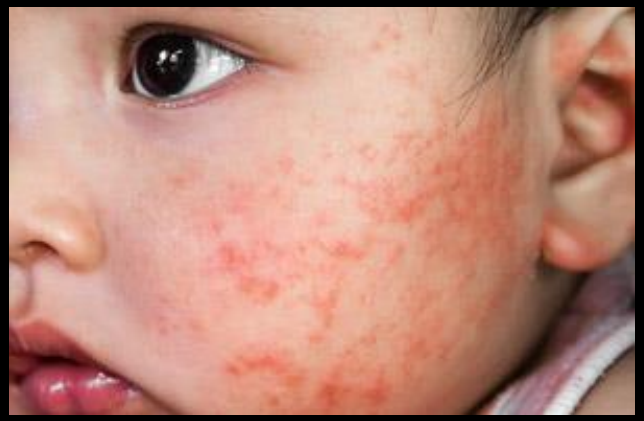
Refractory DA (adherence)

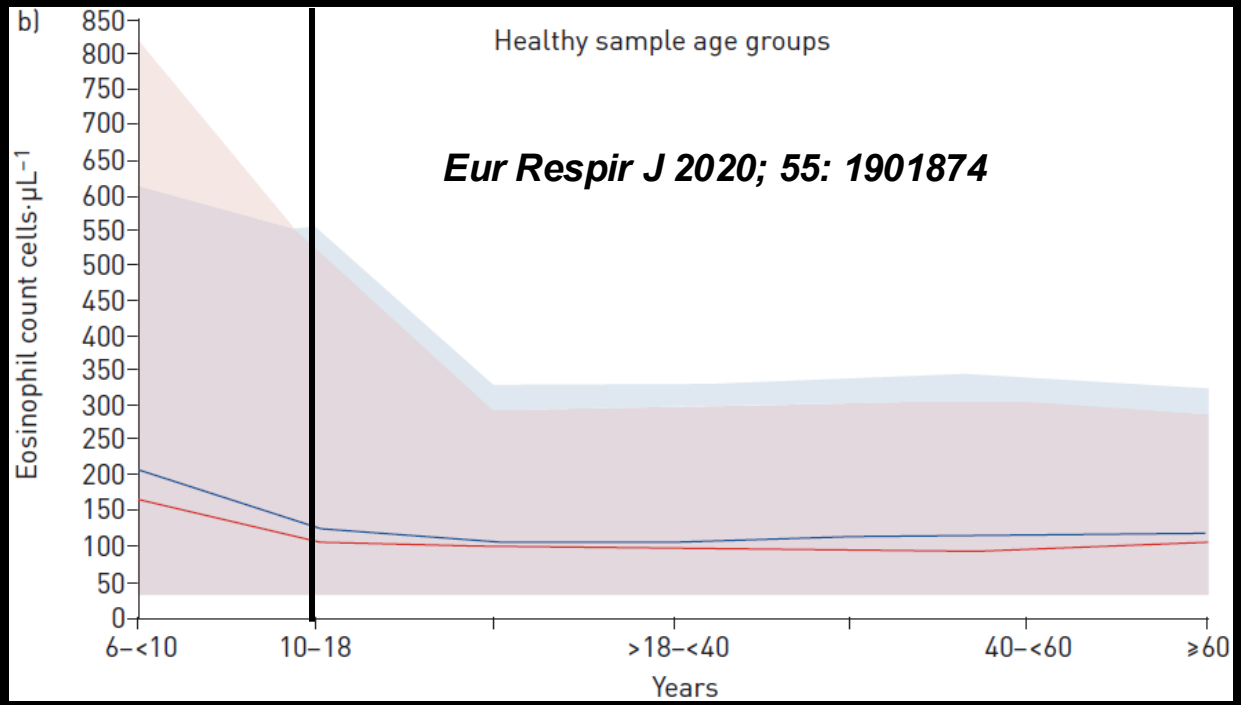
Refractory asthma plus (obesity, failed weight loss)

No longer problematic

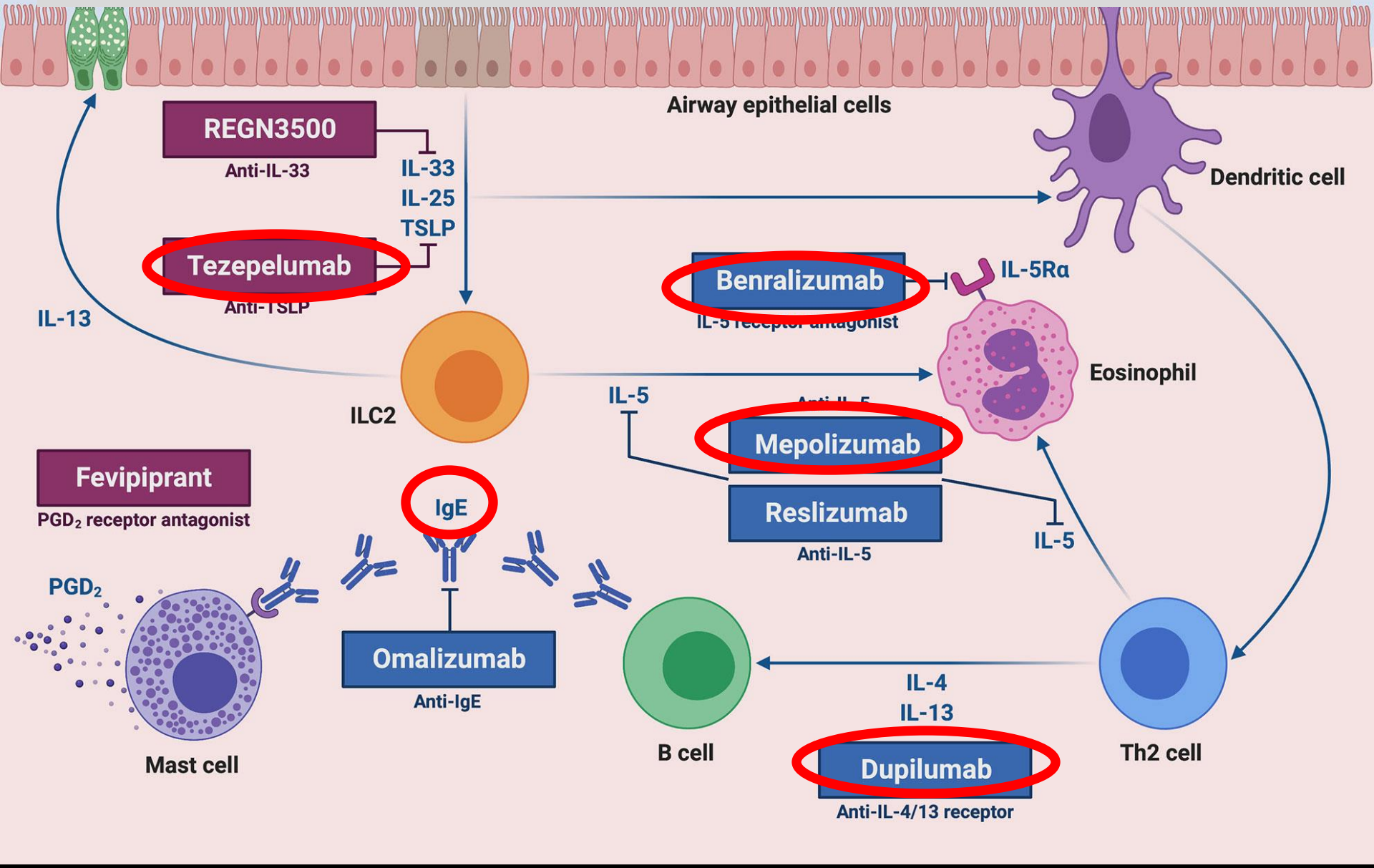
Blood, IS, BAL & Airway disease

- IS is a good marker of BAL cytology in school age and adult patients, but largely a research technique
- No blood eosinophilia likely = none in BAL
- Blood eosinophilia may be driven by other atopic disease

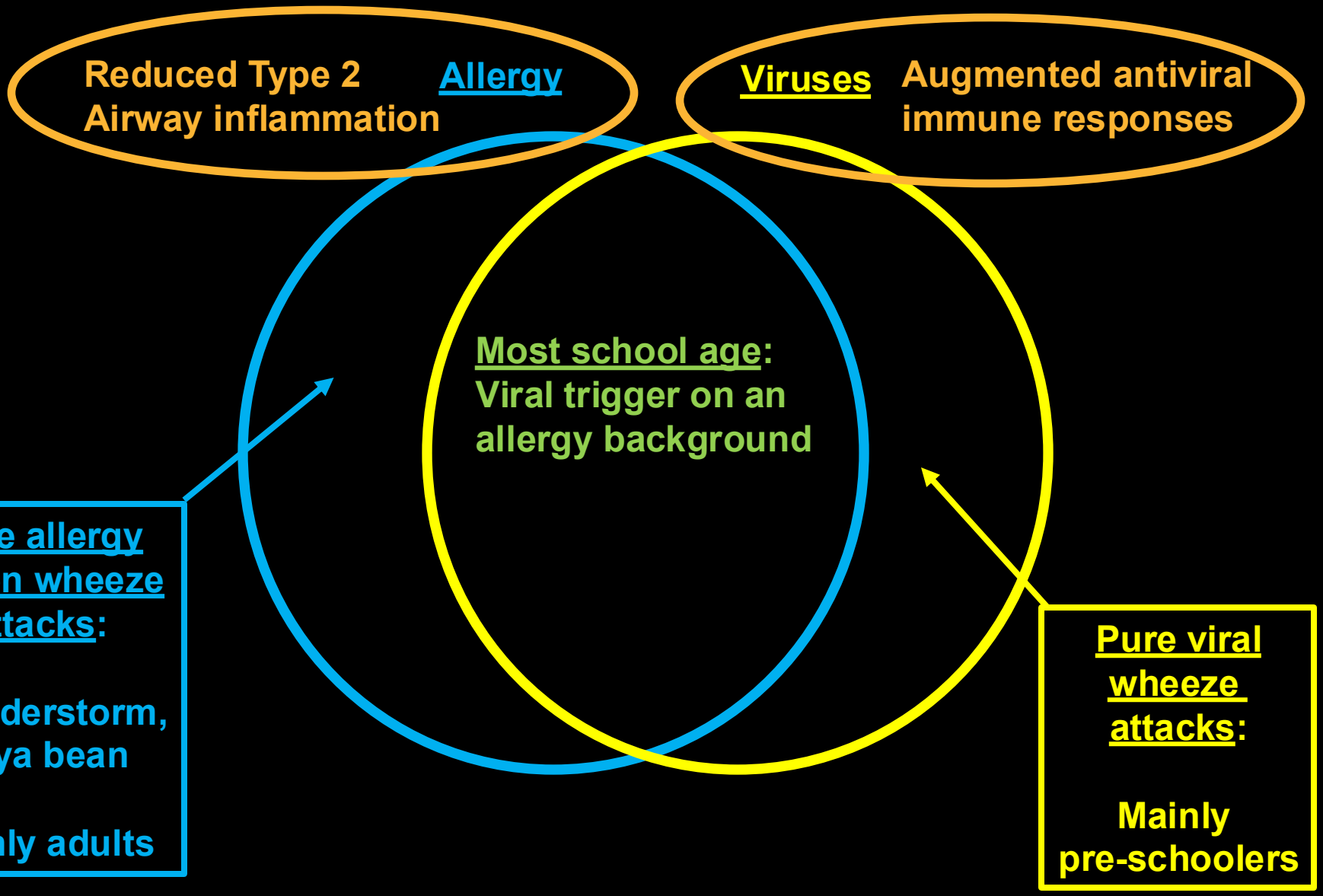




Children age ≥6 (>12 for Tezepelumab)



Omalizumab and Asthma attacks



Where are we with monoclonals?

- Shameful lack of paediatric efficacy and safety studies, we rely too much on adult data including predictive biomarkers
- Little or no data in LMIC settings, and cost prohibitive
- Potentially useful monoclonals not available to us (e.g. reslizumab), and others which do not work in adults are assumed not to work in children
- We cannot assume that all eosinophils are the bad guys, and it is clear that too dramatic ablation may bring problems

THE LANCET Global Health

COMMISSION ON MEDICAL OXYGEN SECURITY

Increasing medical oxygen access for newborns, children, and adolescents:

The Lancet Global Health Commission on Medical Oxygen Security

3rd INSPiRED Congress, Barcelona, 27 June 2025

Global medical oxygen need

Who needs oxygen?

374 million people

306 million (82%) live in LMICs

- 30% in South Asia
- 29% in East Asia & Pacific
- 24% in Sub-Saharan Africa
- 8% in Latin America & Caribbean
- 5% in Middle East & North Africa
- 4% in Europe & Central Asia

4.6 billion cubic meters (Nm3)

- 1·2 billion Nm3 for acute medical and surgical
- 3.2 billion Nm3 for COPD

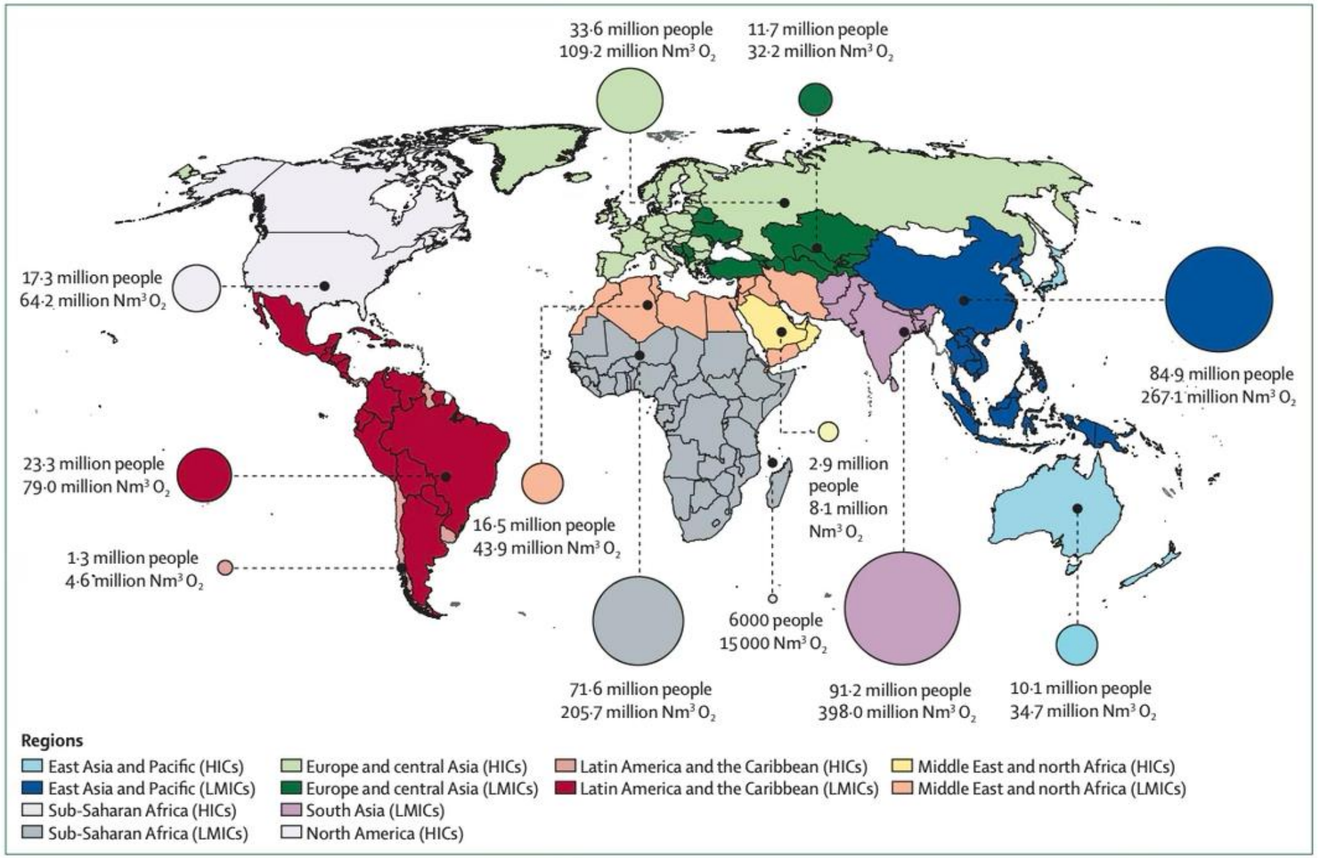


Figure 1: **Location of people with acute medical and surgical oxygen needs in 2021, and minimum volume of oxygen required to meet need, by World Bank region**
Note that this figure excludes oxygen requirements related to COVID-19. Oxygen need is represented by the circles, the sizes of which are proportional to the number of people in that region who need medical oxygen therapy. Minimum volume of oxygen required to meet need was calculated using data for recommended and usual flow rates and duration for various conditions and assumes no inefficiencies in oxygen use and no wastage or inefficiencies in upstream oxygen production, supply, and distribution. HICs=high-income countries. LMICs=low-income and middle-income countries. Nm^3=normal cubic metres.

THE *LANCET GLOBAL HEALTH* COMMISSION
MEDICAL OXYGEN SECURITY

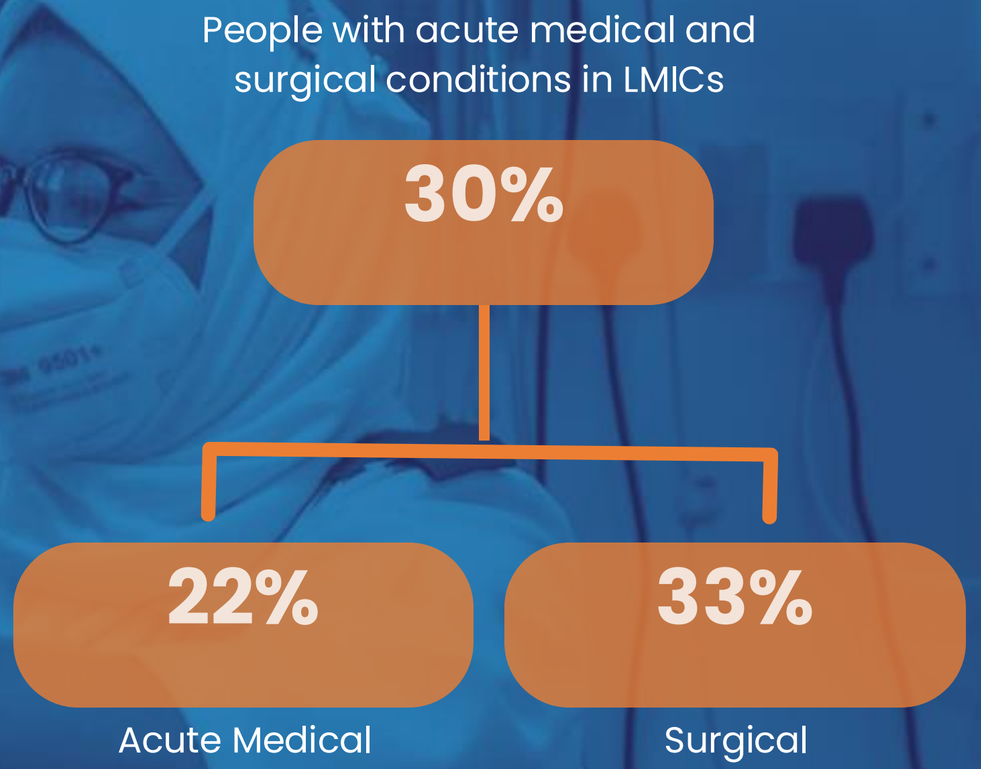
Oxygen coverage gaps

Who receives oxygen in LMICs?

In LMICs, less than 1 in 3 people who need oxygen receive it

- 30% coverage for people with acute medical and surgical conditions (89 of 299 million)
- 22% coverage for people with acute medical conditions (20 of 87 million)
- 33% coverage for people with surgical conditions (70 of 212 million)
- Long-term oxygen therapy not included

In contrast, more than 3 in 4 people with HIV/AIDS or TB in LMICs get treated [1,2]



1) Global tuberculosis report 2024, WHO 2024
2) AIDS at a crossroads: 2024 global AIDS update, UNAIDS 2024.

THE *LANCET GLOBAL HEALTH* COMMISSION
MEDICAL OXYGEN SECURITY

Oxygen coverage gaps

Facility level inequities in LMIC health facilities

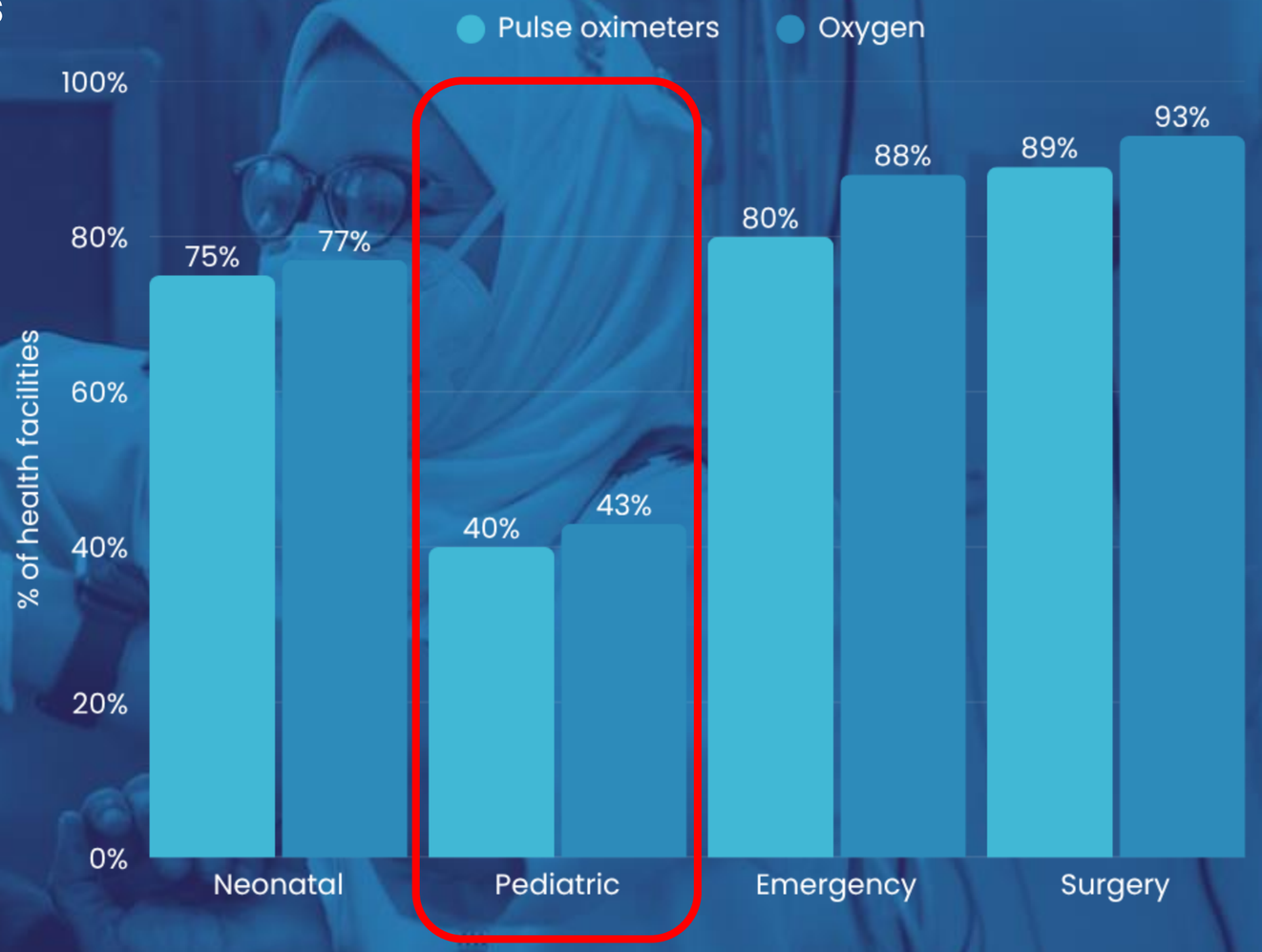
Pulse oximeters and oxygen available in:

- 10% and 12% of primary health facilities
- 54% and 58% of general hospitals
- 83% and 86% of tertiary hospitals

Ward level inequities in LMIC health facilities

Pulse oximeters and oxygen are available in:

- 75% and 77% of neonatal wards
- 40% and 43% of pediatric wards
- 80% and 88% of emergency departments
- 89% and 93% of surgical wards



The greatest inequities in pulse oximetry and oxygen service delivery are for people—particularly children—attending small health facilities in rural areas, especially in sub-Saharan Africa and south Asia.

Lancet Global Health Oxygen Commission

THE *LANCET GLOBAL HEALTH* COMMISSION
MEDICAL OXYGEN SECURITY

Costing the oxygen coverage gap

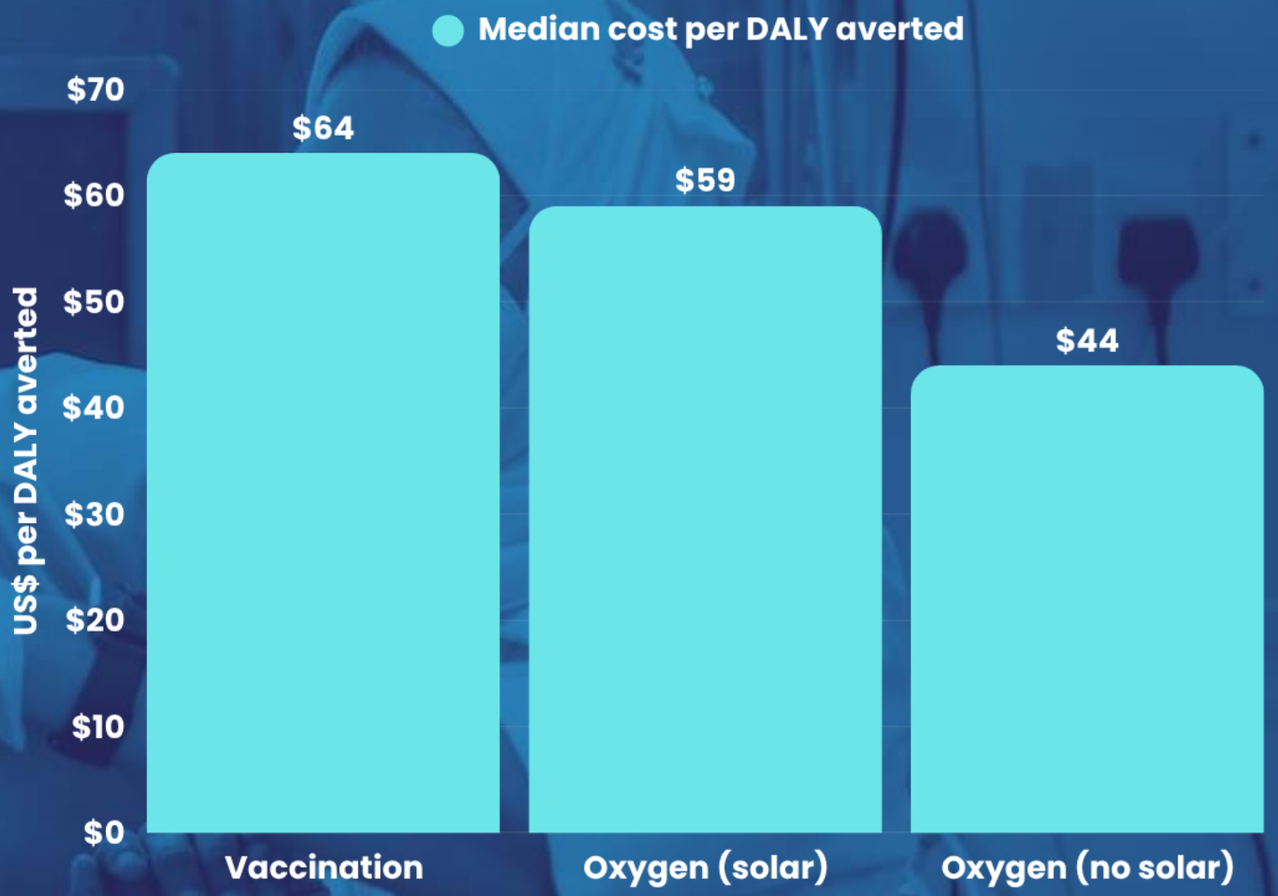
US$6.8 billion a year is needed to close the coverage gap - US$34 billion from 2025-2030

Highly cost-effective:

- US$44-59 per DALY averted (based on child pneumonia)
- Simlar to the most cost-effective child survival interventions (e.g, vaccination)

Each dollar invested could deliver estimated returns of US$21, and additional funding can cost approximately US$168 per DALY averted, and as little as US$23 in countries with very high burdens.

Global Oxygen Strategic Framework and Investment Case 2025-30, 2024



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Oxygen solutions: the total picture

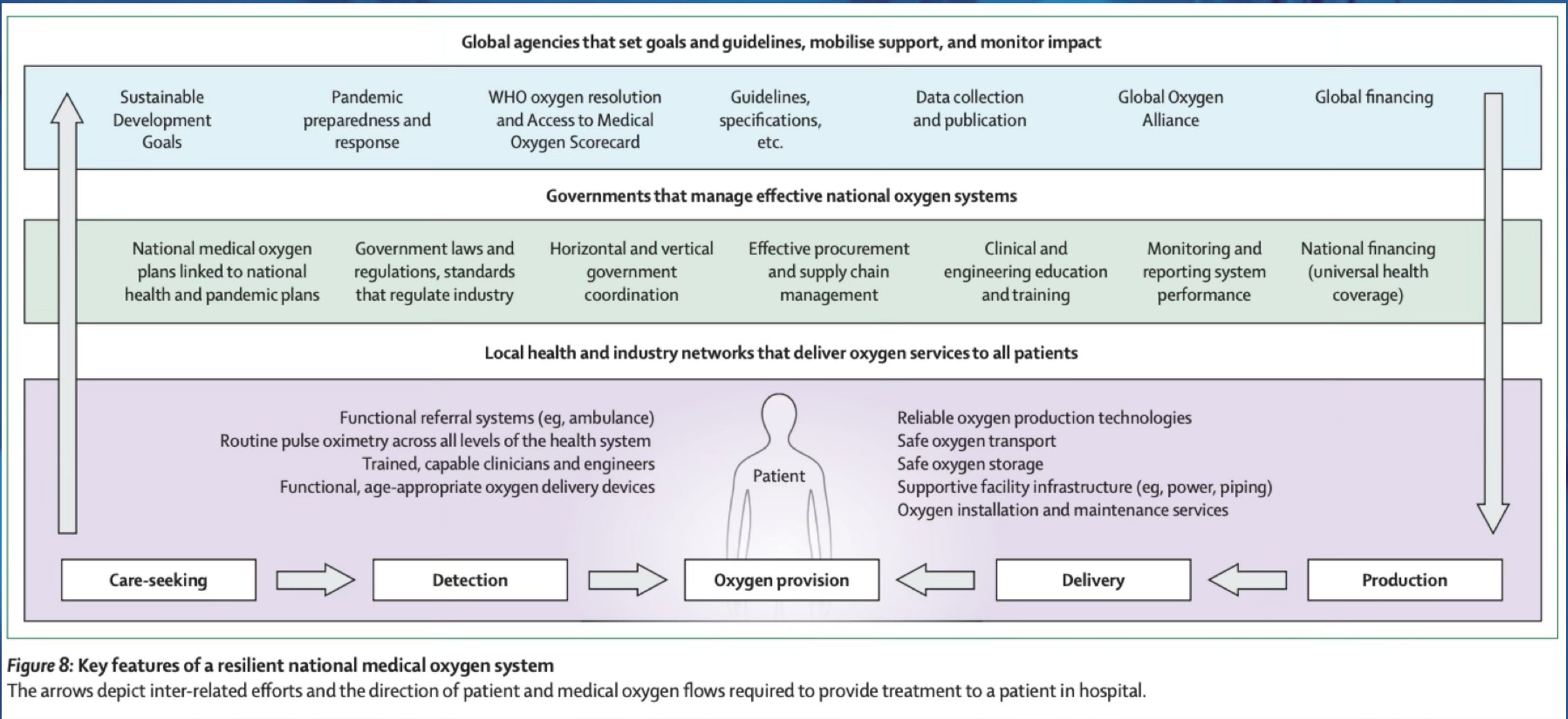

Figure 8: **Key features of a resilient national medical oxygen system**
The arrows depict inter-related efforts and the direction of patient and medical oxygen flows required to provide treatment to a patient in hospital.

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MEDICAL OXYGEN SECURITY

Find out more...

The full Commission package is available at www.stoppneumonia/lancetoxygencommission.org

- Report with Comments
- Media Statement
- Policy Brief (English, French, Spanish, Arabic, Chinese, and Russian)
- Spotlight Brief: Access to Medical Oxygen Scorecard ($ATMO_2S$)
- Spotlight Brief: Patient and Caregiver Testimonies
- Spotlight Brief: 10 Oxygen Coverage Indicators
- Spotlight Brief: 20 Priority Areas for Oxygen Innovation
- Country Case Studies (Bangladesh, India, Malawi, Nigeria, Sweden, Uganda)

THE *LANCET GLOBAL HEALTH* COMMISSION
MEDICAL OXYGEN SECURITY

Artificial Intelligence and Respiratory Technology for Sleep Disordered Breathing: Are we there yet?

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The 3rd Congress of
INSPiRED
INternational Society of Pediatric REspiratory Diseases
The Only Global Congress Focused on Pediatric Respiratory Diseases
26-29 June 2025 | Barcelona, Spain

What is Artificial Intelligence?

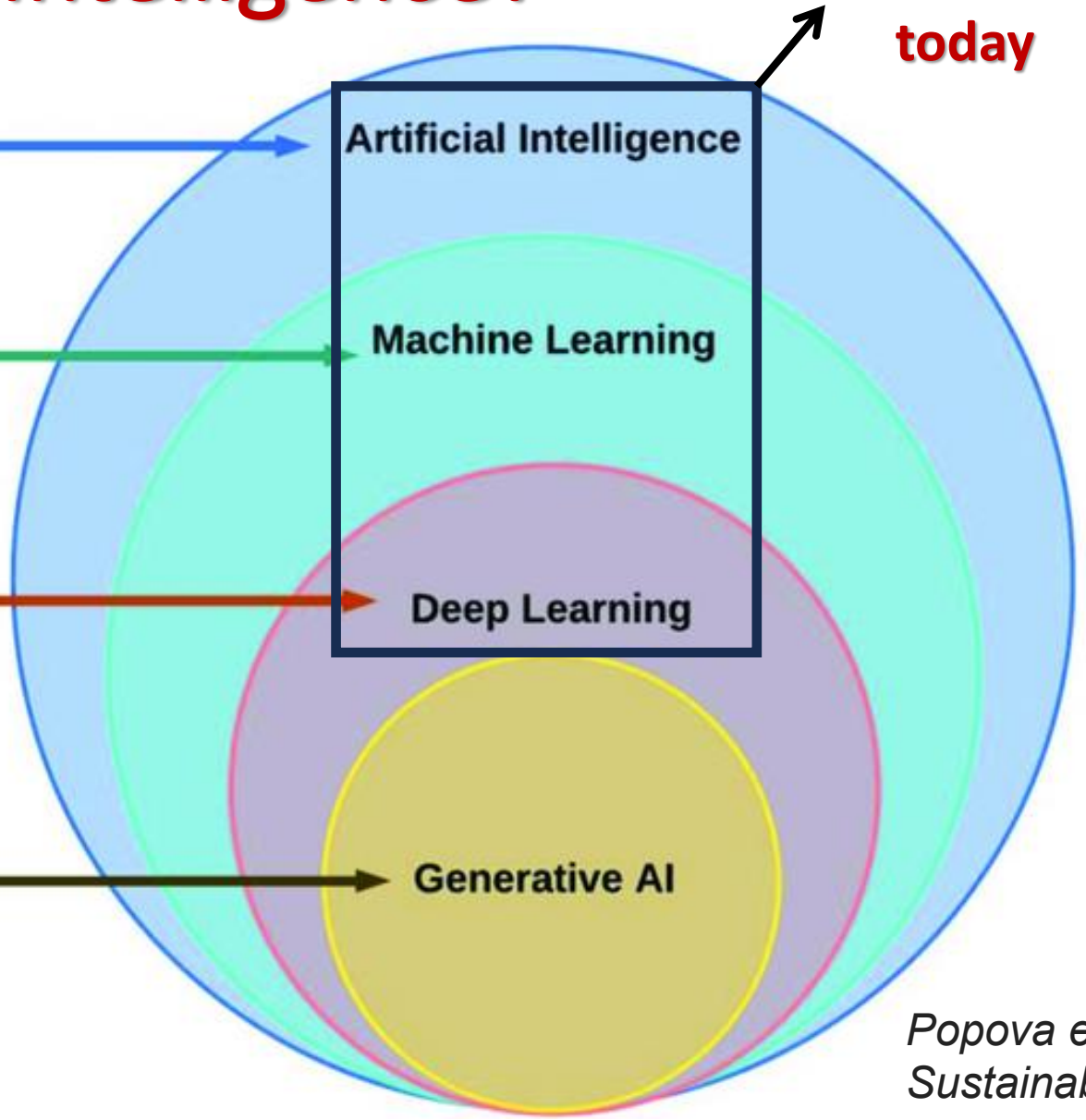
Our focus today

Artificial Intelligence
AI involves techniques that equip computers to emulate human behavior, enabling them to learn, make decisions, recognize patterns, and solve complex problems in a manner akin to human intelligence.

Machine Learning
ML is a subset of AI, uses advanced algorithms to detect patterns in large data sets, allowing machines to learn and adapt. ML algorithms use supervised or unsupervised learning methods.

Deep Learning
DL is a subset of ML which uses neural networks for in-depth data processing and analytical tasks. DL leverages multiple layers of artificial neural networks to extract high-level features from raw input data, simulating the way human brains perceive and understand the world.

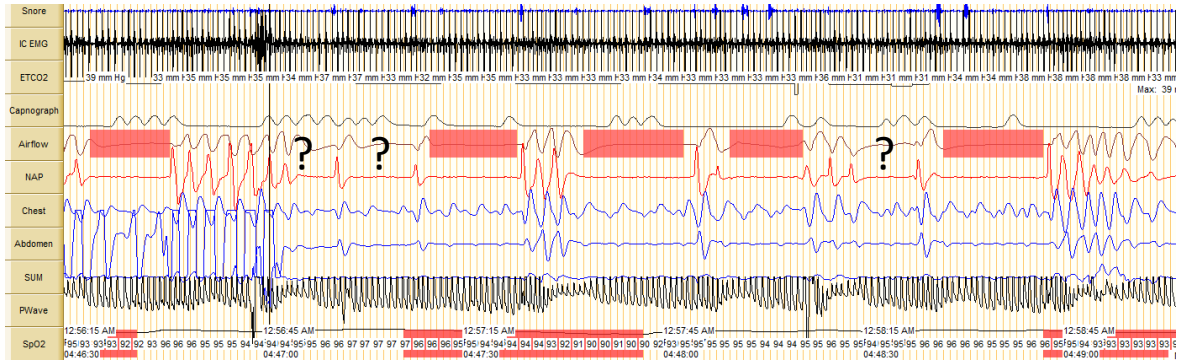
Generative AI
Generative AI is a subset of DL models that generates content like text, images, or code based on provided input. Trained on vast data sets, these models detect patterns and create outputs without explicit instruction, using a mix of supervised and unsupervised learning.



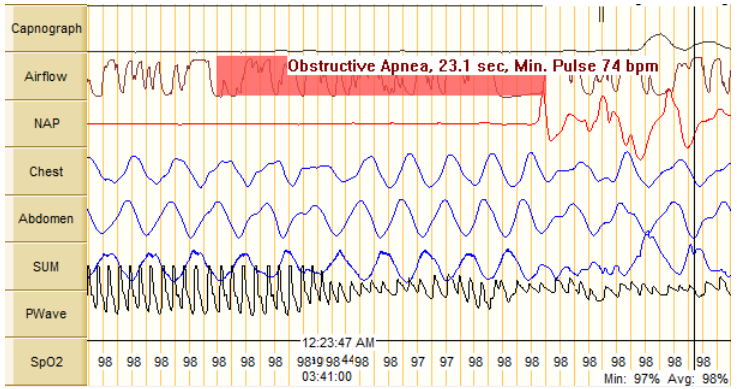
Popova et al. Sustainability **2023**

Real case study #1: AI-assisted PSG analyses

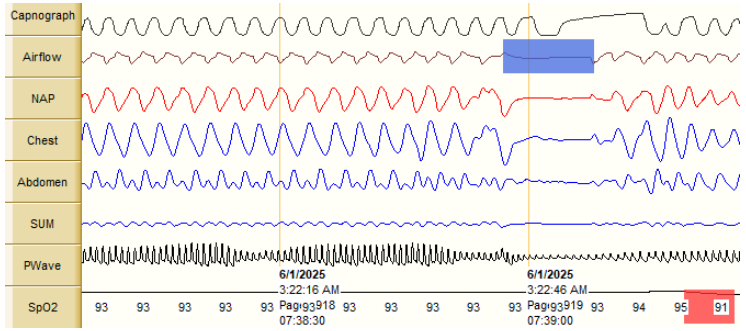
Is OSA diagnosis really black and white?



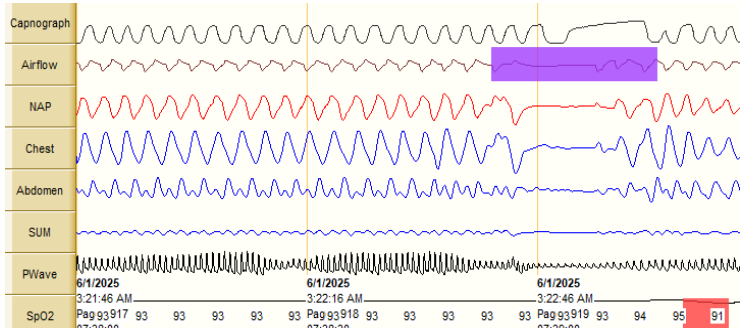
Artifact marked as apnea (AI)



Central apnea (AI)



Mixed apnea (Human)

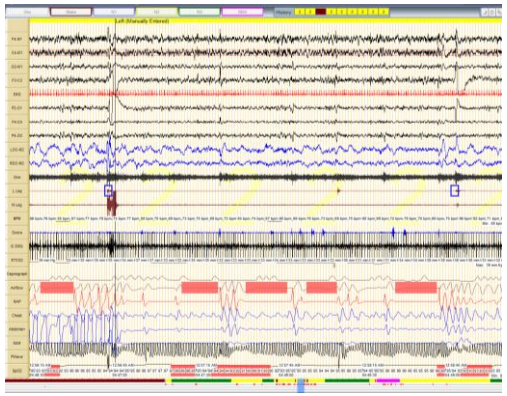


Real case study #1: AI-assisted PSG analyses

Computer best — **Human best**

- Basic measurements (flow, Spo2)
- Complex measurements (EEG)
- Basic integration (Flow, effort)
- Basic rule classifier (>10 sec)
- Complex rule classifier (REM)
- Higher integration (snoring, video)
- Basic context (artifacts, feeding, movement)
- Higher context (physiology, clinical risk)

AI-assisting human

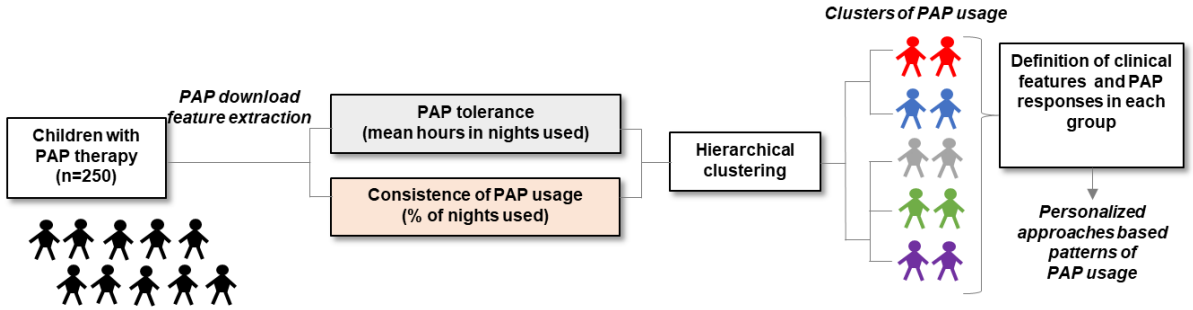


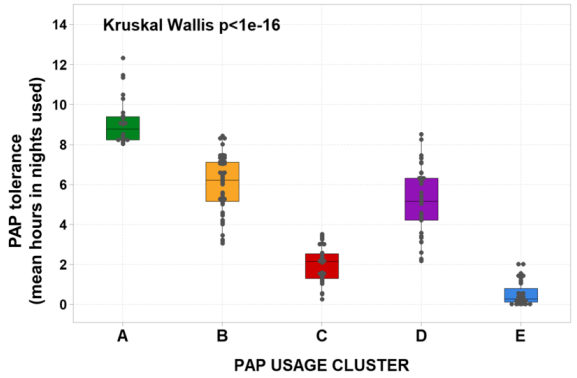
The path from PSG to OSA diagnosis and treatment

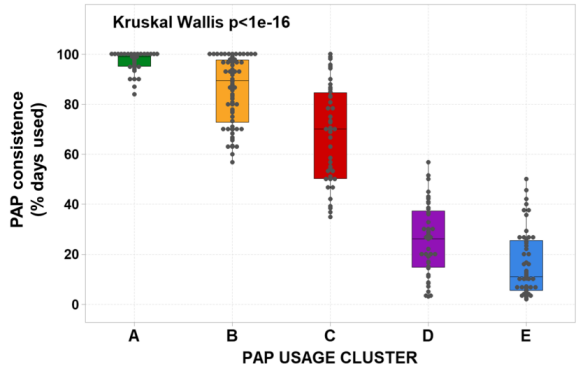
Human medical decision making cannot be replaced but it can be AI-assisted

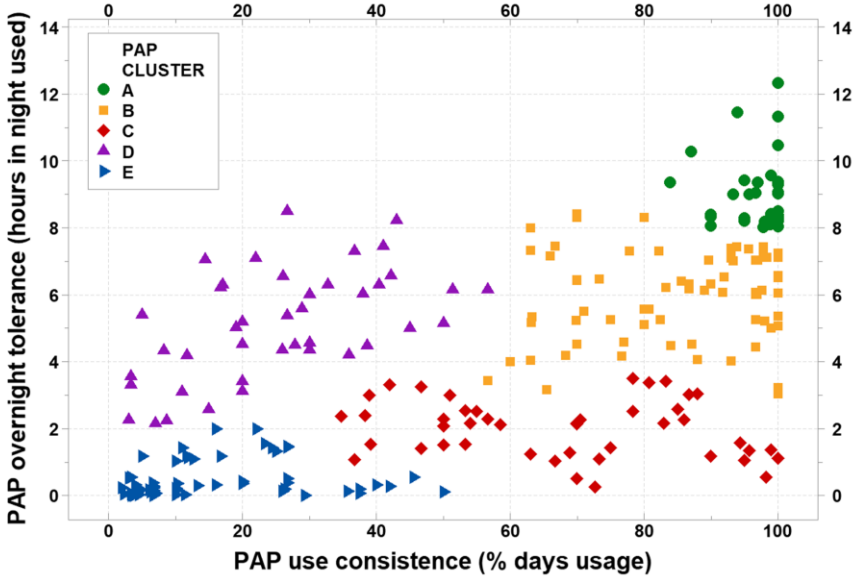
Real case study #2: AI and PAP optimization

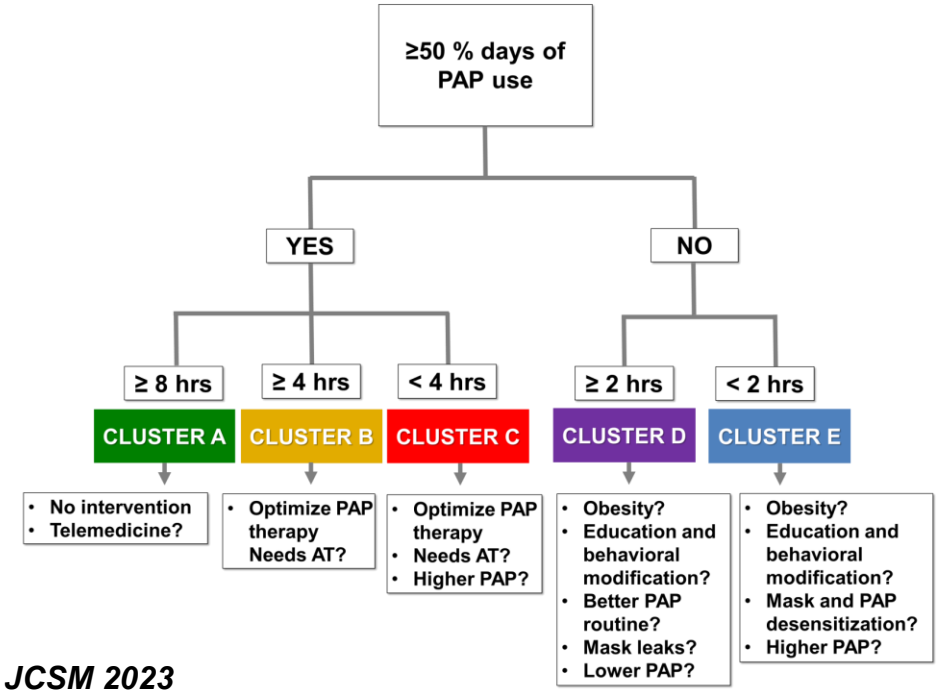
AI- Real time use analyses to improve adherence





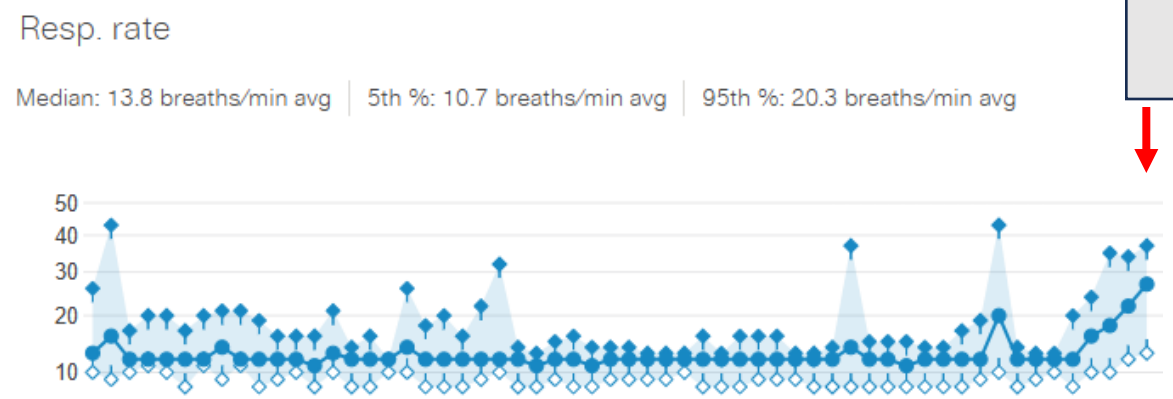


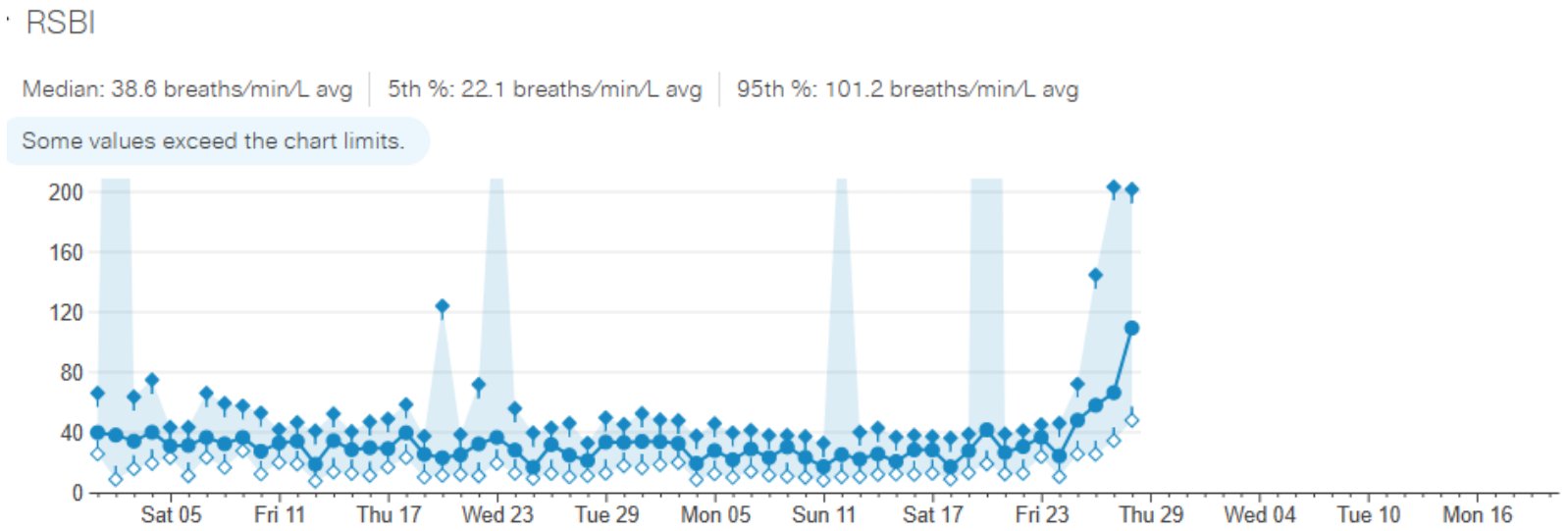




Weiss M. et al JCSM 2021 and
Aguilar H, Kahanowitch R . et al JCSM 2023

Real case study #3: Real time AI to treat respiratory failure





Data review via telemedicine with family: Impending respiratory failure (RSBI increase)

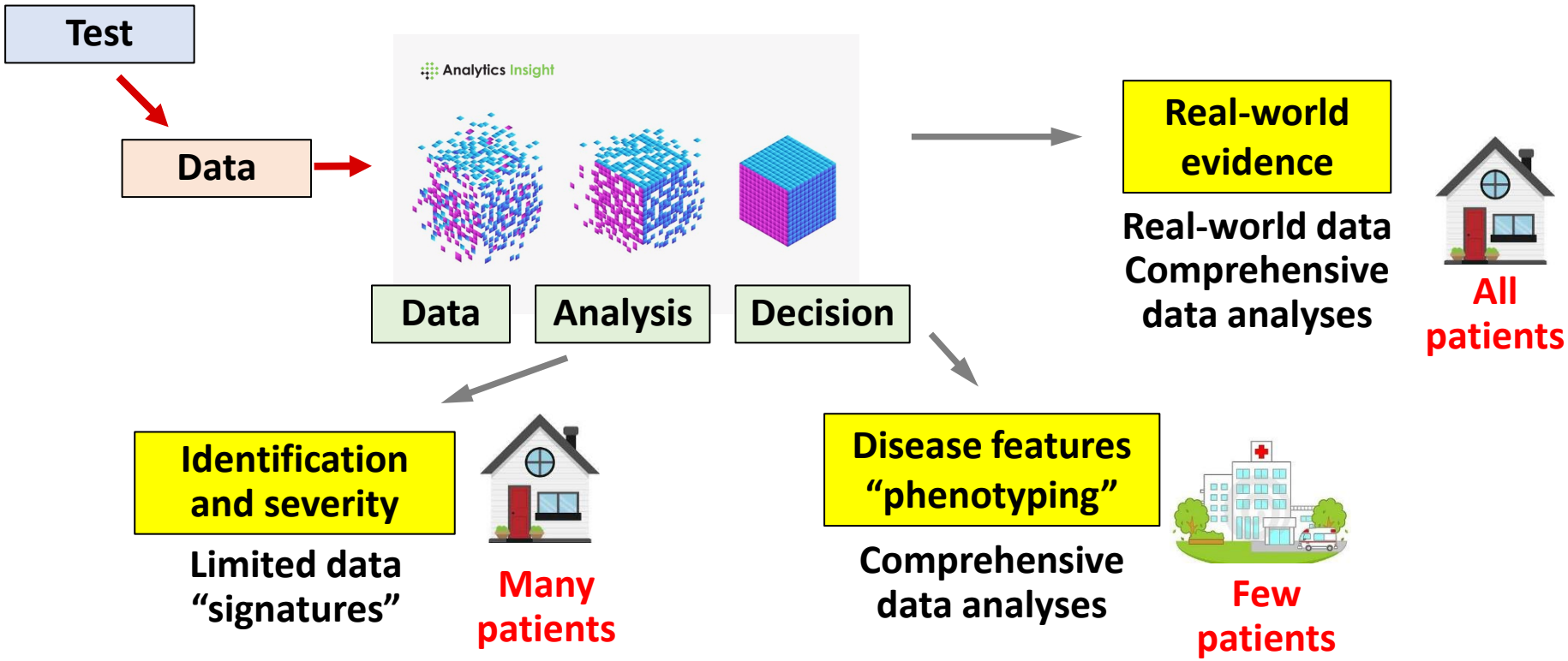
"sick plan" started on Friday 23

No response thus hospitalized on Thursday 29

ICU stabilization with higher PAP, IV antibiotics, increase airway clearance. **NOT intubated**

Discharged Tuesday 03 – stable on O2 – will take weeks to recover

Artificial Intelligence and the Future of Respiratory Technology for Sleep Disordered Breathing



האוניברסיטה העברית בירושלים
THE HEBREW UNIVERSITY OF JERUSALEM

Highlights from

"The Journey of CFTR- from Cloning to Drug Development"

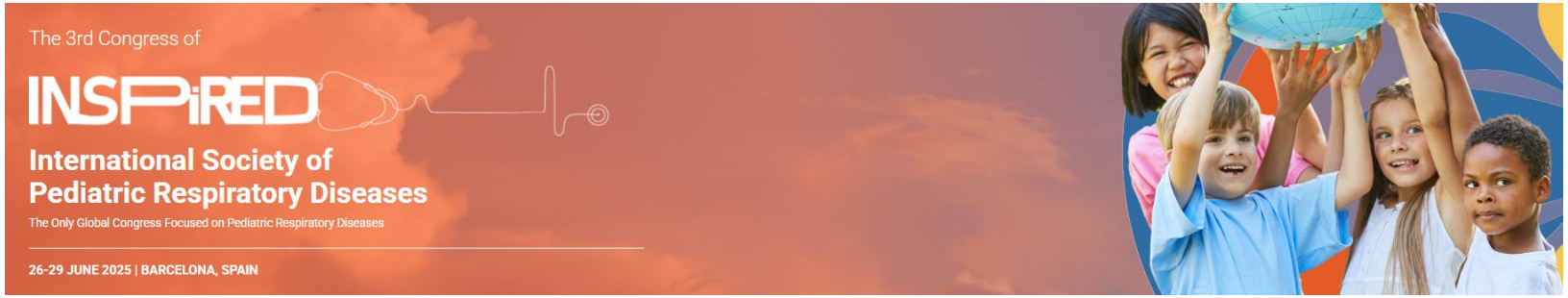
Prof. Malena Cohen-Cymberknoh, M.D.

Head, Pediatric Pulmonology Unit and Cystic fibrosis Center

Hadassah-Hebrew University Medical Center

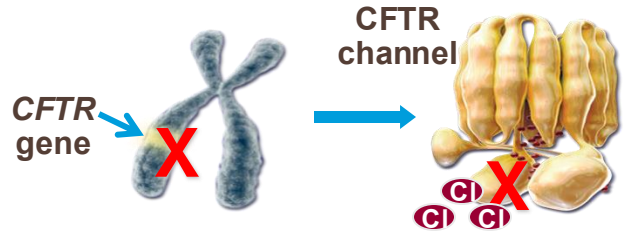
Jerusalem, Israel

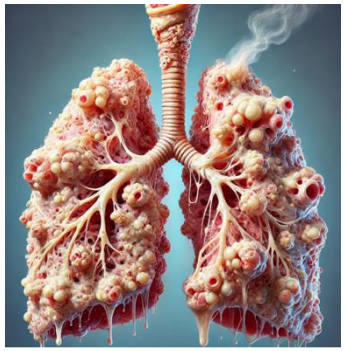
Barcelona, June 27th, 2025



CFTR Mutations, Milestones & Future Therapies

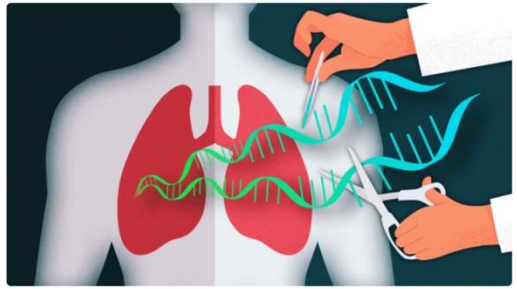
- CFTR gene mutations disrupt chloride transport → thick mucus, multi-organ disease





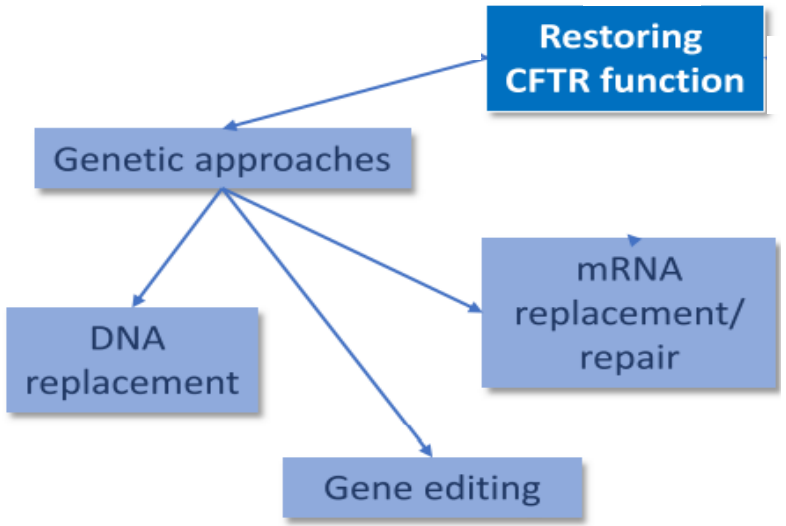
- Key milestones since CF was first described (1938): Sweat test, CFTR gene discovery (1989), and the breakthrough development of CFTR modulators

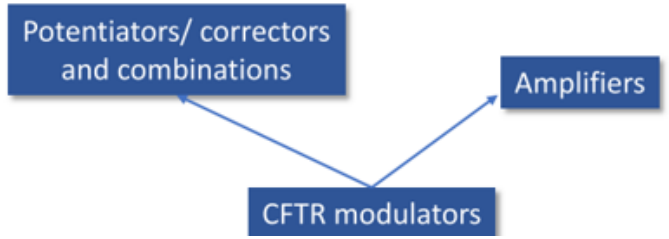
- New genetic therapies are in development mainly for non-responders



New CF Therapies in Development

- **mRNA-based therapies** (e.g. VX-522, ARCT-032, RCT2100): deliver functional CFTR message to lung cells- *Phase 2*
- **RNA Repair** (SPL84): corrects splicing mutations- *Phase 2*
- **Gene Editing**: experimental but promising (CRISPR/Cas9)
- **PTC Readthrough agents** (e.g. Ataluren): limited success in CF
- **New CFTR correctors** (e.g. SION-109, SION-451, SION-719)- target specific protein sites (*Phase 1)*





Allen et al, Nat Commun. 2023; CFF- Drug Development Pipeline

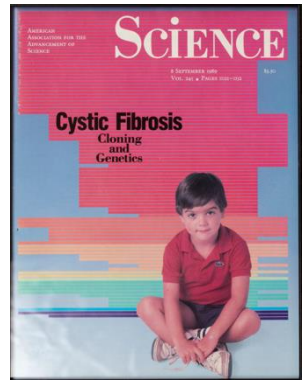
Pulmonary and Extrapulmonary Impact of CFTR Modulators

- Improvement in FEV_1, reduce PEx, hospitalizations, mortality
- Reduces chronic infection and inflammation
- Improves BMI, pancreatic function, GI, liver disease and fertility
- Emerging evidence: apparently safe in pregnancy
- VANZ/TEZ/DEU: once-daily, comparable efficacy to ETI, potential broader reach

O'Sullivan BP & Freedman SD. Lancet 2009;Davis Am J Respir Crit Care Med 2006; Tiddens Proc Am Thorac Soc 2007; Walkowiak. Eur J Gastroenterol Hepatol 2008; Colombo Pediatr Gastroenterol Nutr 2006; Keating et al, www.thelancet.com/respiratory 2025; CFF- Drug Development Pipeline

"Science is not finished until it's communicated—and it makes a difference"

Sir Mark Walport 2013



The science behind CFTR wasn't finished when the gene was discovered—it was finished when that discovery was transformed into treatments that changed the lives of people with CF

Future Directions

Theratypes & Theranostics

- **Theratypes**: CFTR variants grouped by their effect on protein function
- **Theranostics**: Personalized testing of drug response on patient-derived tissue (e.g., rectal organoids)

Need for

- Next-gen modulators
- Gene therapies for non-responders
- Universal access and long-term outcome data

Post Infectious Bronchiolitis Obliterans: Risk Factors, Diagnostic Challenges, and Biomarkers

Post Infectious Bronchiolitis Obliterans Workshop
June 30, 2025. Barcelona, Spain

IDRC · CRDI
International Development Research Centre
Centre de recherches pour le développement international

Canada

Alejandro Teper, MD
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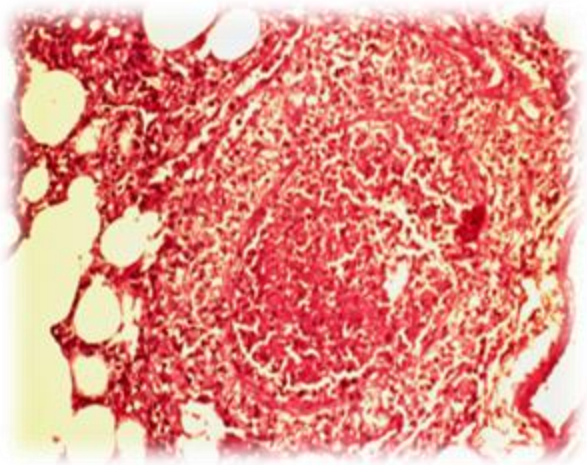
ateper@gmail.com

150 años
H N R G
HOSPITAL DE NIÑOS
RICARDO GUTIÉRREZ

Bronchiolitis Obliterans Etiology



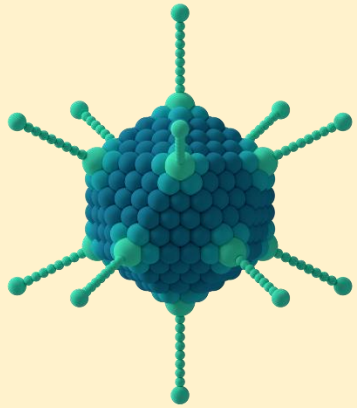
Viral infection	**Adenovirus** Influenza Measles
Bacterial infection	Bordetella Pertussis **Mycoplasma Pneumoniae**
Transplants	Bone marrow Lung
Gastroesophageal reflux	
Connective tissue disease	JRA Eschlerodermia
Fumes inhalation	
Idiopathic	

PIBO

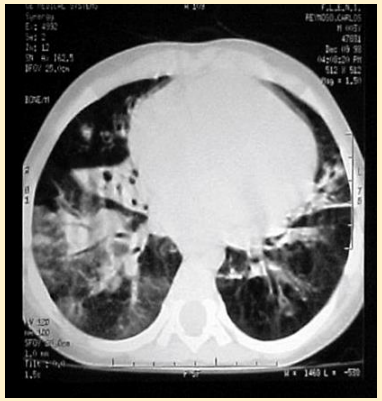
Kurland G, Michelson P. Pediatr Pulmonol. 2005;39:193-208

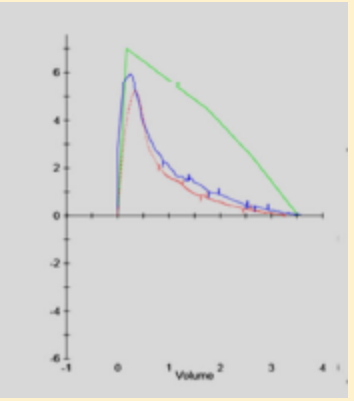
Identification of the Genetic Basis of PIBO

HYPOTHESIS



Genetic predisposed patient





OBJECTIVE

- To identify genetic variation/s associated with PIBO

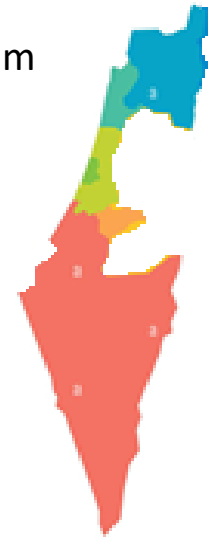
Identification of the Genetic Basis of PIBO

Latin America

A Teper
A Colom
C Castaños
J Maggiolo
JA Castro Rodríguez
ME Aráuz
G Fischer
LV Ferreira Filho
L de Freitas
S Ucrós

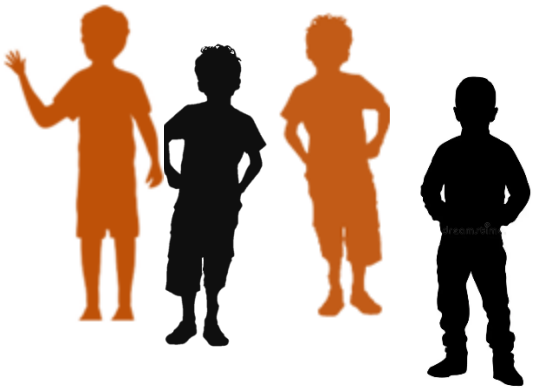
Israel

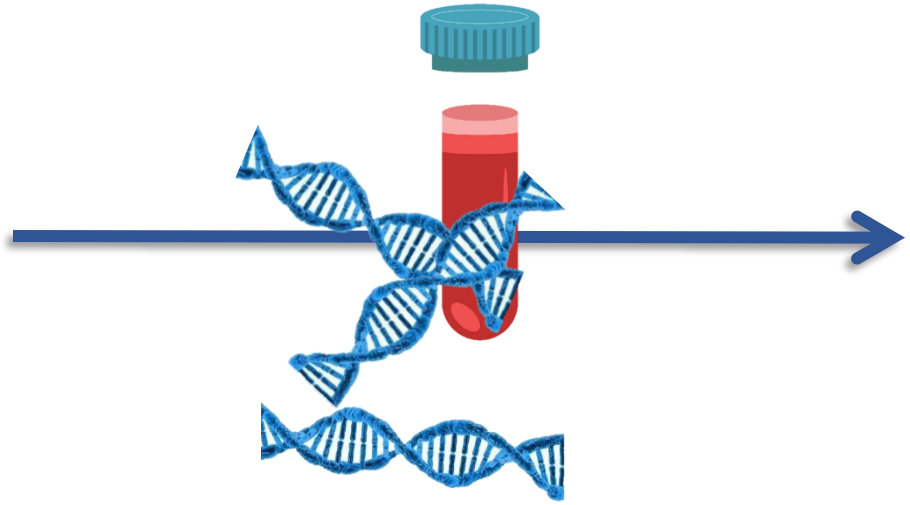
E Kerem



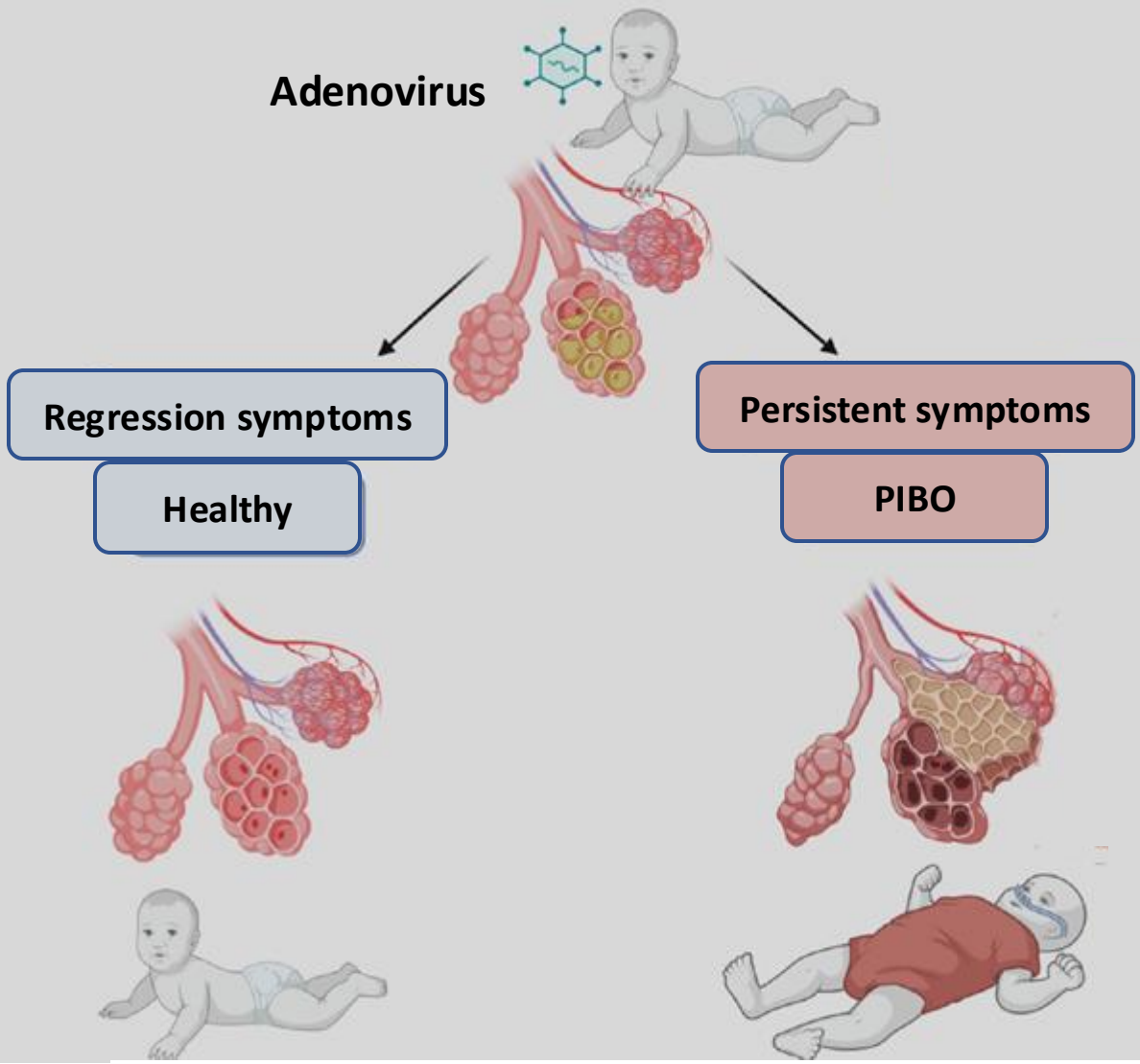
Canada

F Ratjen
L Strug





Risk Factors and Diagnosis Criteria for PIBO



Risk Factors

- During initial infection:
  - Mechanical ventilation
  - Duration of fever
  - Length of hospitalization
  - Severe and prolonged hypoxemia
- Male
- Genetic predisposition

Criteria Diagnosis

- Positive PIBO Clinical Score (> 7 points)
  - Severe lower airways acute infectious event in a previously healthy child (4 points)
  - Adenovirus (3 points)
  - HRCT: mosaic pattern (4 points)
- Persistent, severe and fixed airflow obstruction
- Exclusion of differential diagnosis

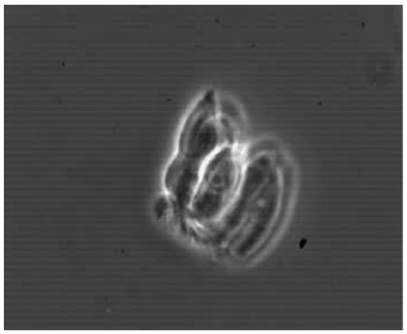
Modified from Mazenq J et al. Paediatr Respir Rev. 2024;52:58-65

Post Infectious Bronchiolitis Obliterans: Risk Factors, Diagnostic Challenges, and Biomarkers

Rare in developed countries, but not THAT rare in South America
Chronic respiratory insufficiency: severe and fixed bronchial obstruction, and severe alterations of the elastic properties of the lung
Strongly associated with Adenovirus (young) and Mycoplasma (older)
Immune host responses are involved in its pathological injuries
A genetic predisposition may explain the susceptibility in certain populations and its geographical distribution
Previously healthy, severe lower respiratory infection, chronic respiratory symptoms, pulmonary images and Function Tests compatible

Recent advances in PCD genetics and overlap syndromes

European Reference Network | Respiratory Diseases (ERN-LUNG)



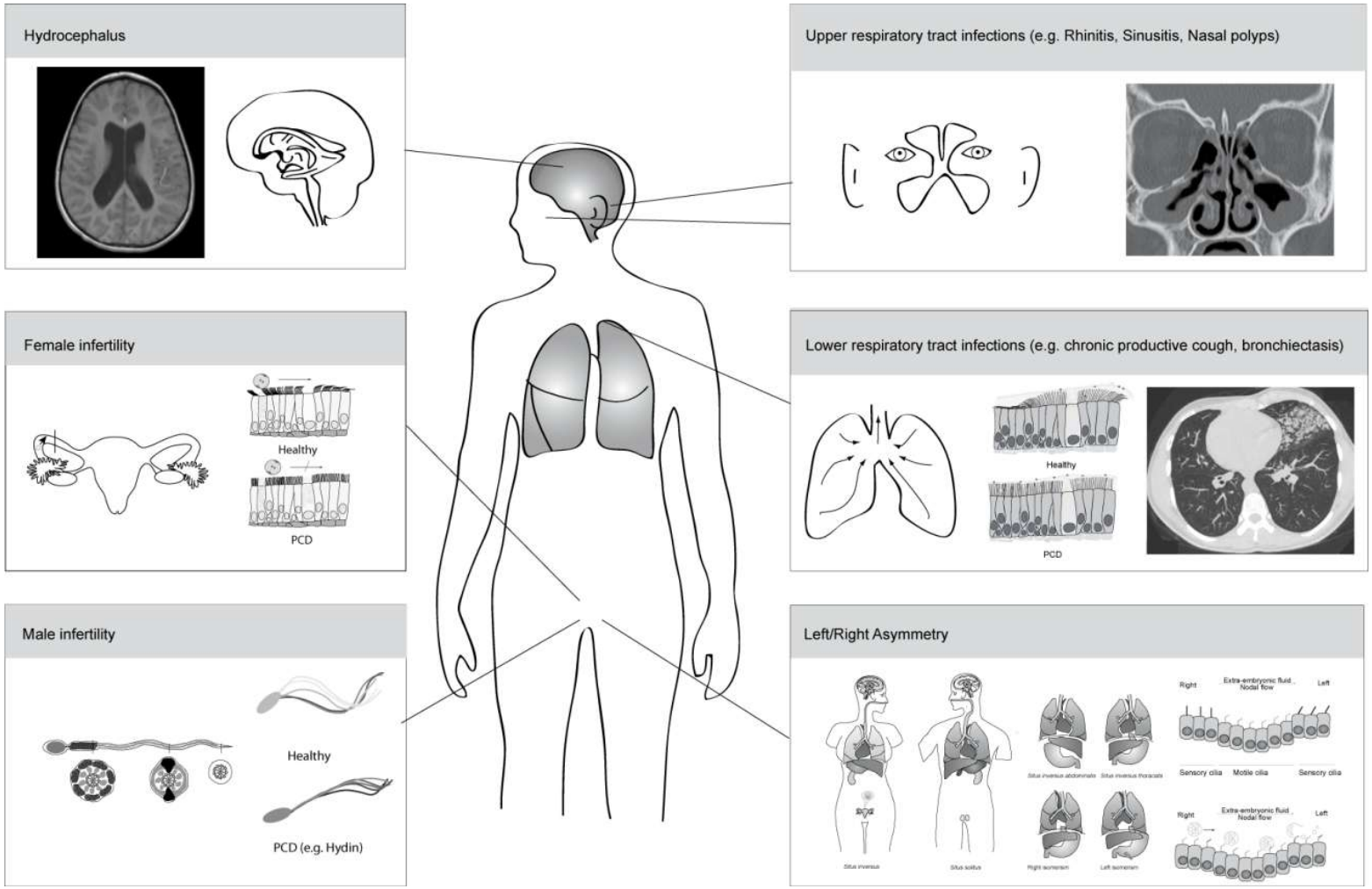
Heymut Omran

ERN LUNG PCD Core Coordinator

Westfälische Wilhelms-Universität Münster

UKM Universitätsklinikum Münster

Motile ciliopathies



Motile ciliopathies. Nat Rev Dis Primers 6, 77 (2020)

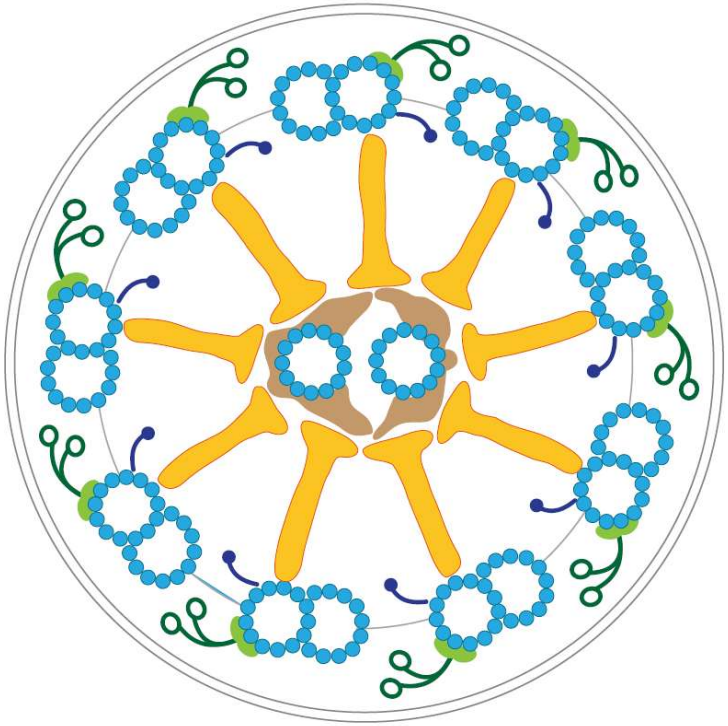
PCD is not a single genetic disorder but a term that summarizes a clinically and genetically heterogeneous group of diseases

ODA:
DNAH5, DNAH11, (DNAH9), DNAI1, DNAI2, DNAL1, NME8, CCDC103, LRRC56

ODA docking:
CCDC114, ARMC4, CCDC151, TTC25, CLXN, DAW1, LRRC56

Preassembly Factor:
DNAAF1, DNAAF2, DNAAF3, DNAAF4, DNAAF5, DNAAF6, DNAAF7, DNAAF11, SPAG1, CFAP298, CFAP300, TTC12

96nm Axonemal Ruler:
CCDC39, CCDC40



Radial Spoke:
RSPH1, RSPH4A, RSPH9, RSPH3, DNAJB13, RSPH23, NME5

N-DRC:
DRC1, DRC2, DRC4

CP:
HYDIN, SPEF2, STK36, CFAP46, CFAP54, CFAP74,CFAP221

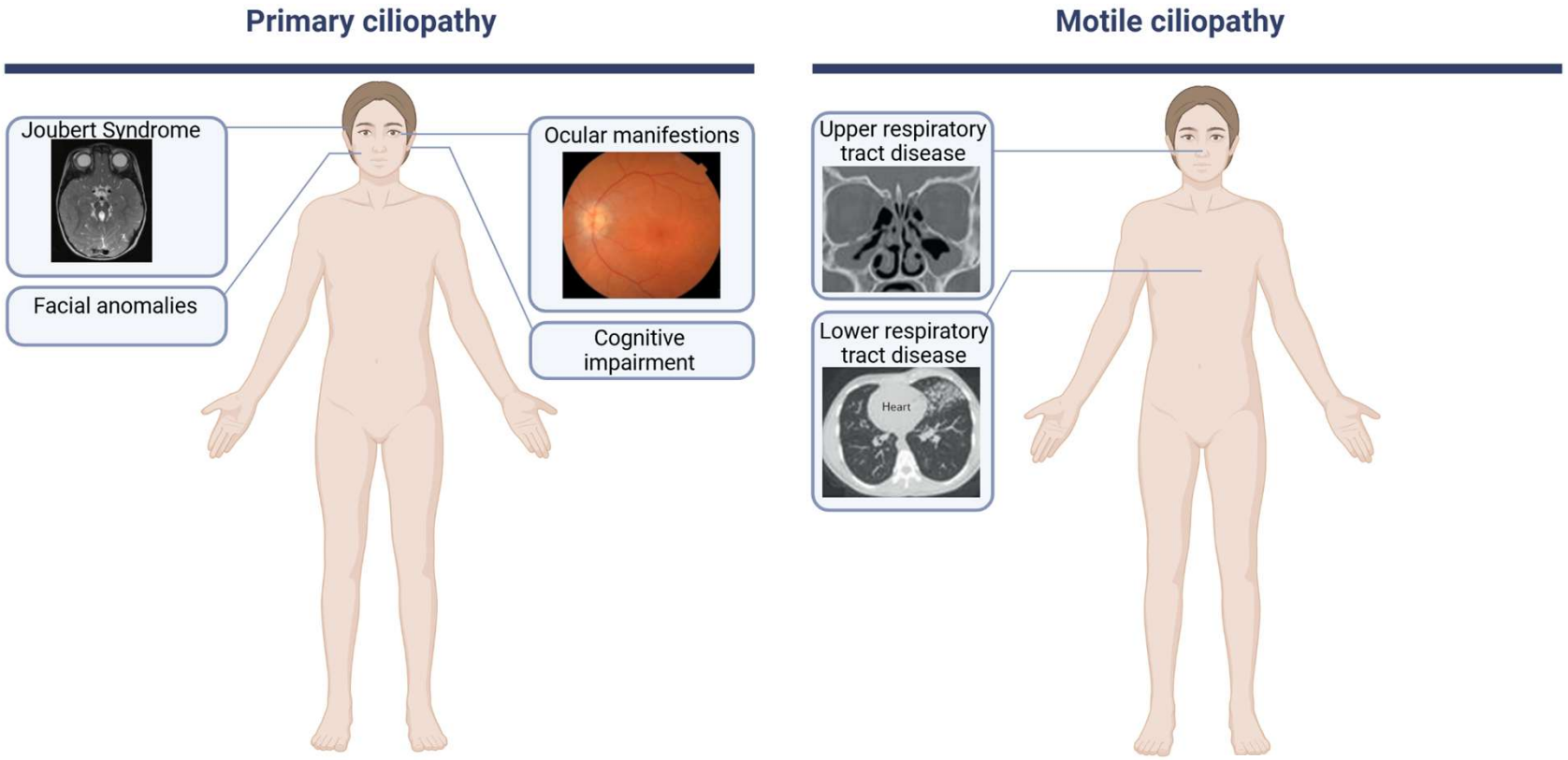
MIPs:
CCDC11 (CFAP53), ENKUR, WDR16 (CFAP52), MNS1,

Ciliogenesis defects:
CCNO, MCIDAS, OFD1, NEK10, DYNC2H1, TP73, IFT74, TUBB4B, FOXJ1, TALPID3

Other:
CBY1, RPGR, GAS2L2, CFAP57

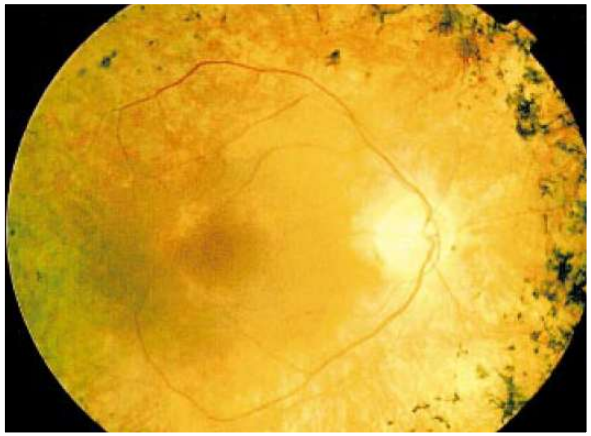
Most PCD variants are inherited as autosomal recessive disease traits. However, we recently reported X-chromosomal recessive and autosomal dominant de novo disease mechanisms

KIAA0586/TALPID3-mutations result in a novel combined ciliopathy (primary and motile ciliopathy)

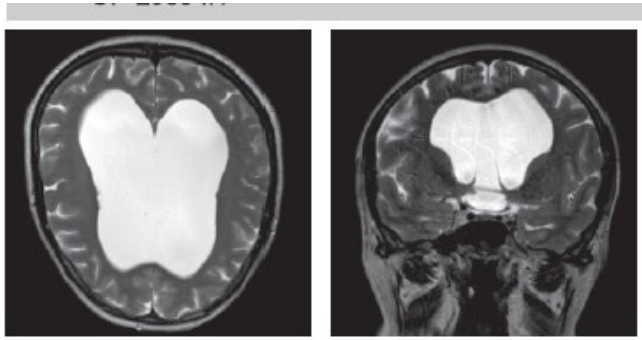


Taudien et al., 2025, iScience *28*, 111670
February 21, 2025 © 2024 The Author(s). Published by Elsevier Inc.
https://doi.org/10.1016/j.isci.2024.111670

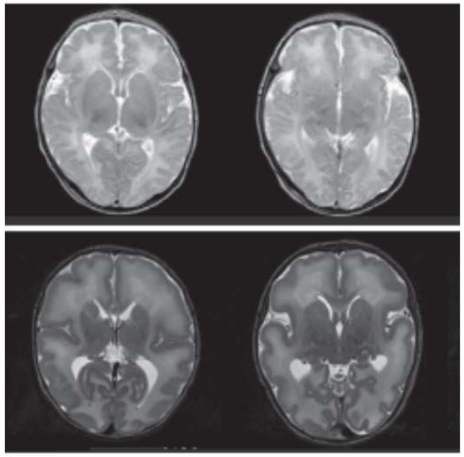
Syndromic PCD variants also have defects of non-motile cilia



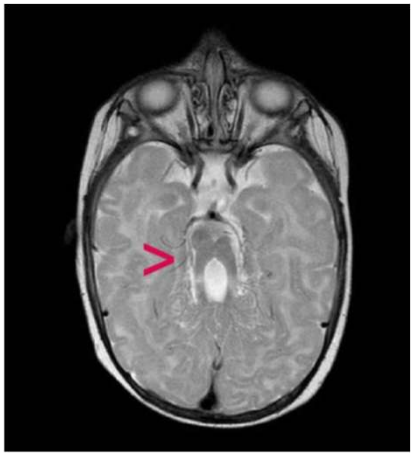
Retinitis pigmentosa (*RPGR*)



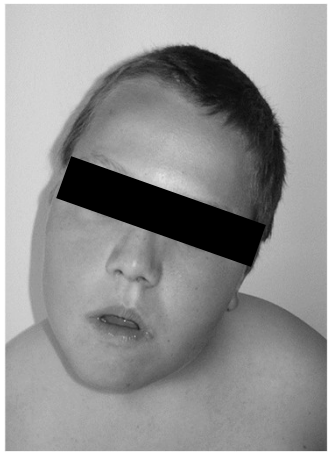
FOXJ1 (dominant de novo),
TUBB4B (dominant de novo),
MCIDAS, CCNO



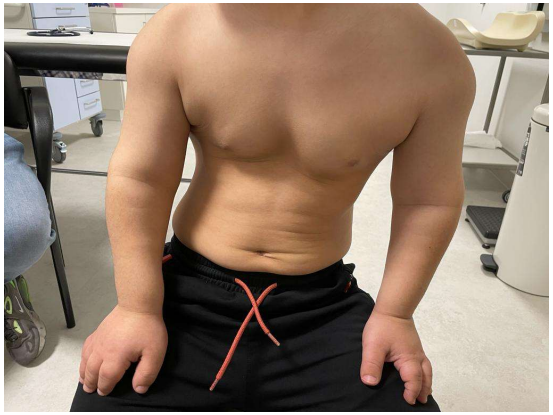
Lissencephaly (*TP73*)



Joubert syndrome
(*CBY1*, *TALPID3*)

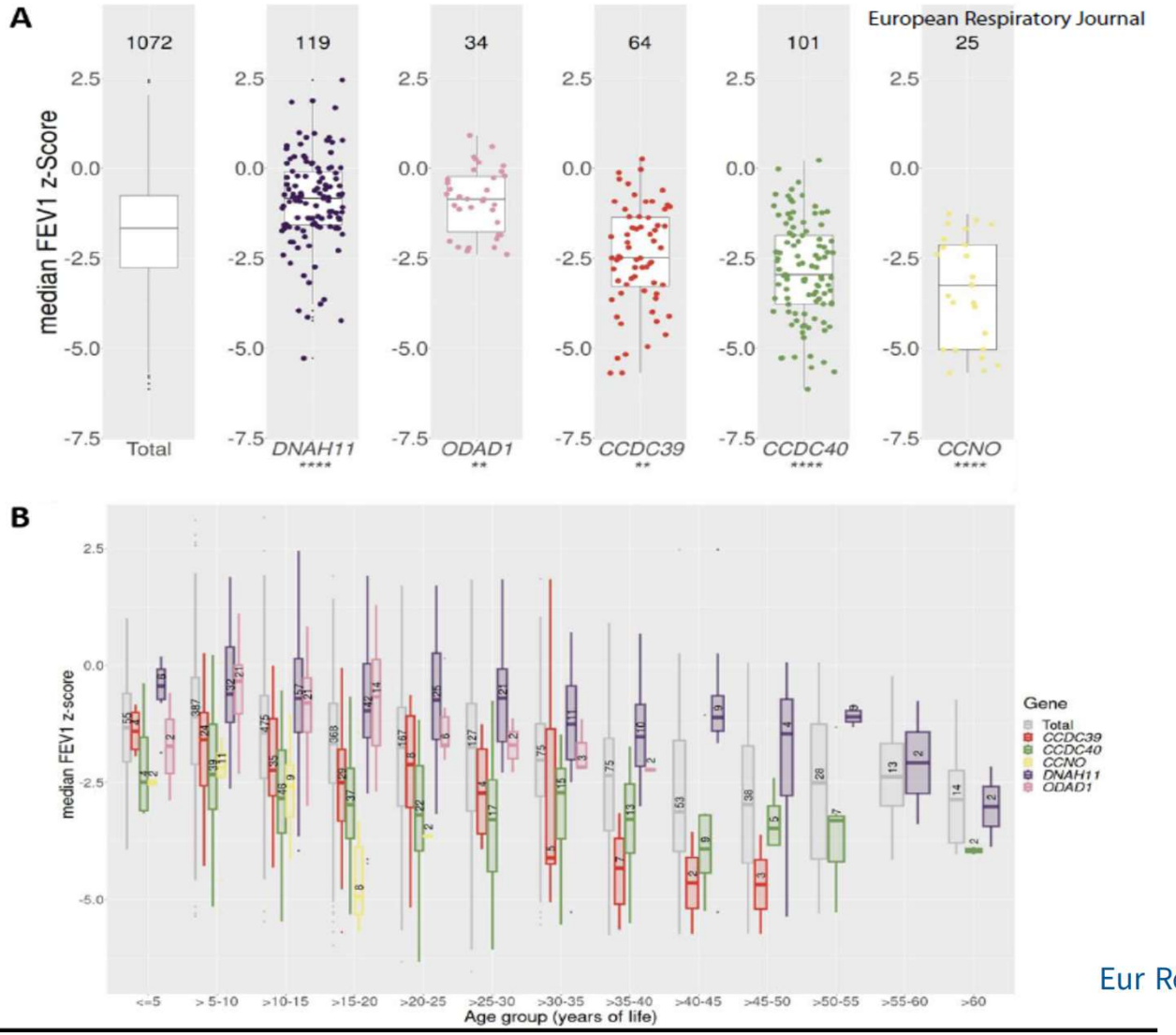


Cognitive Dysfunction
(*OFD1*)



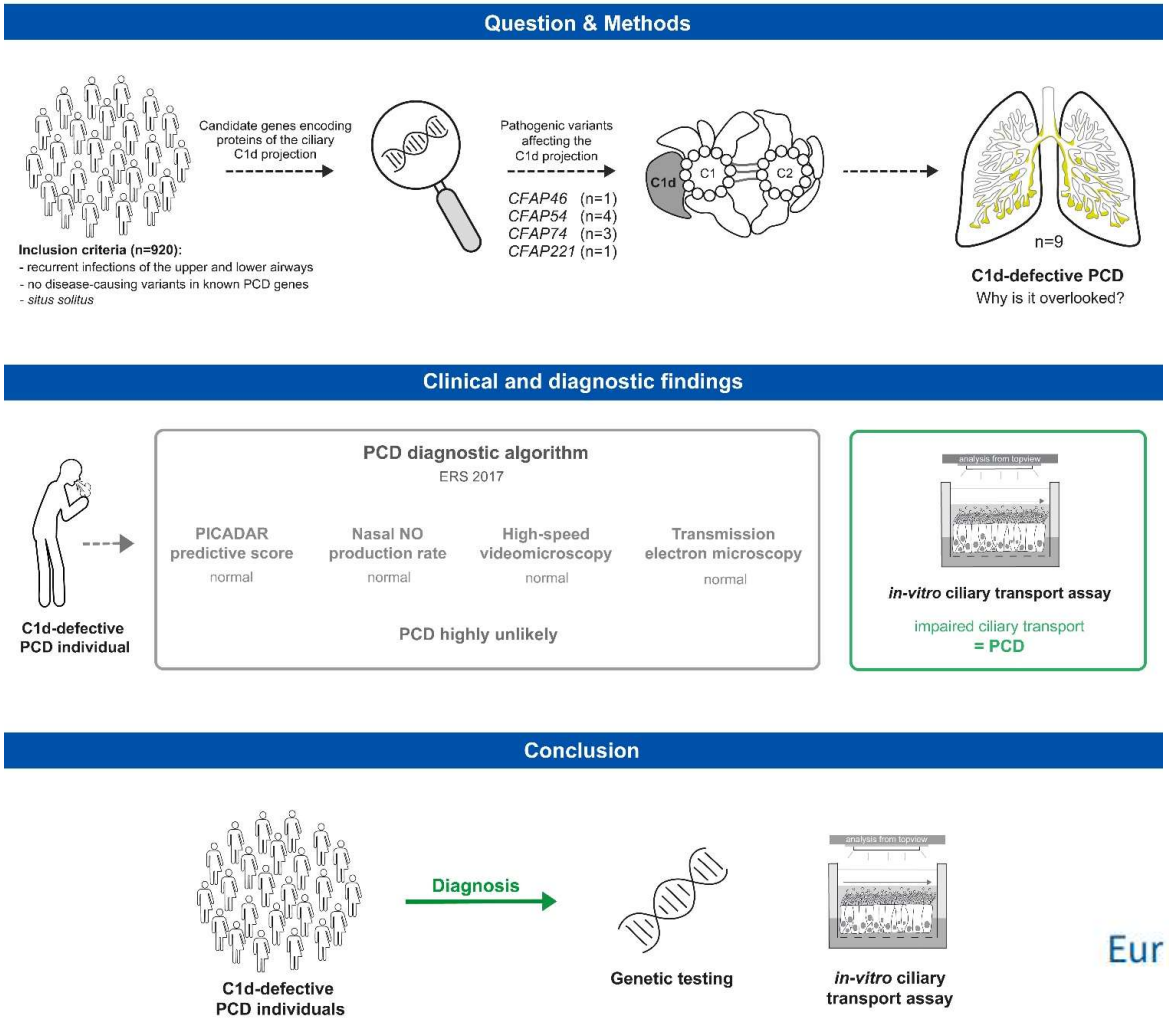
Jeune thoracic dystrophy
(*DYNC2H1, IFT74*)

Genotype-Phenotype-correlations



Eur Respir J 2024; 64: 2301769

In vitro ciliary transport assay a novel tool to establish PCD diagnosis

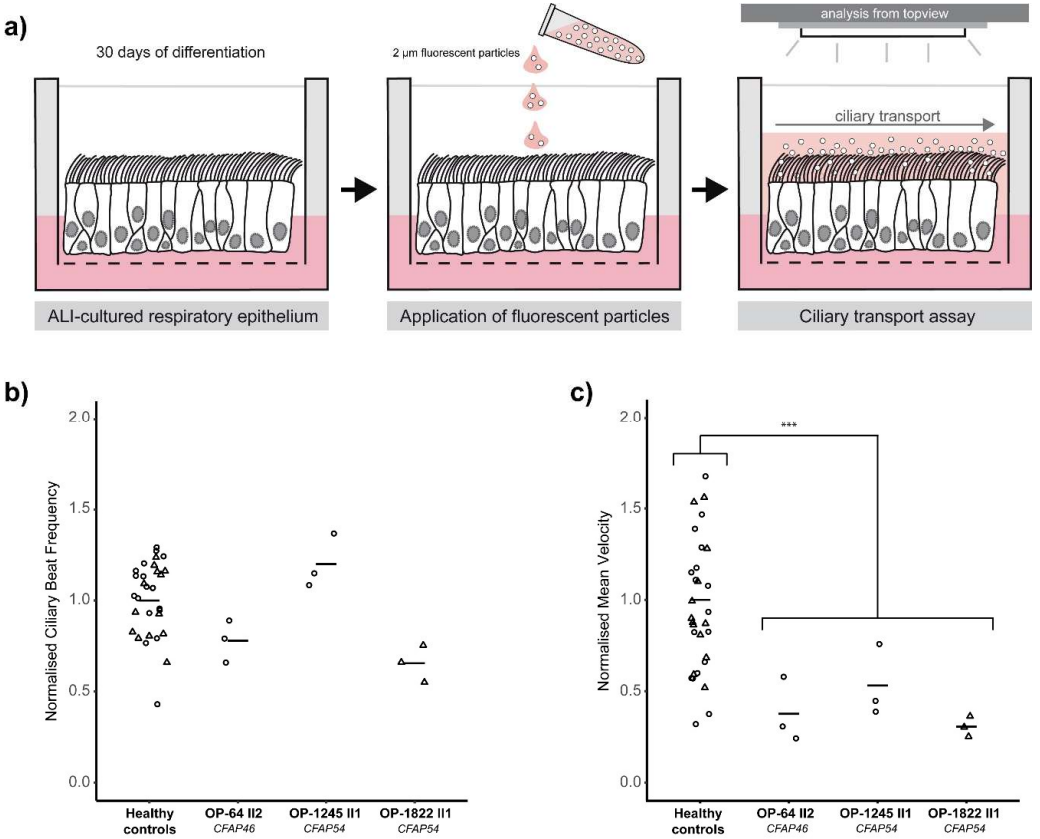


Eur Respir J 2024; 64: 2400790

Pathogenic variants in *CFAP46, CFAP54, CFAP74*, and *CFAP221* cause Primary Ciliary Dyskinesia with a defective C1d projection of the central apparatus

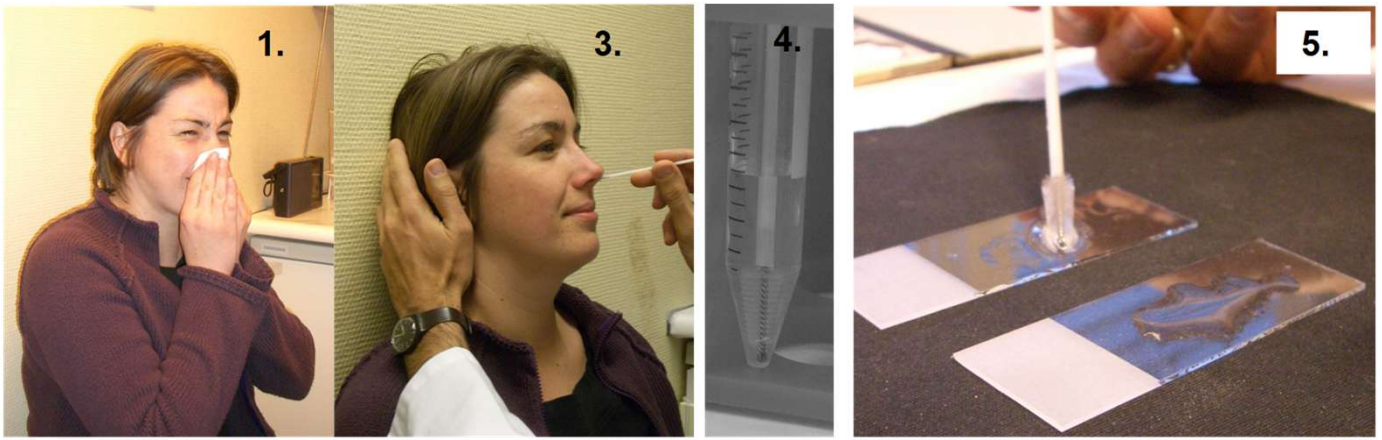
Mean Ciliary Beat Frequency (CBF) in *CFAP46*- and *CFAP54*-variant individuals do not differ significantly from healthy controls

Mean velocities of fluorescent particles are significantly reduced in ALI-inserts from *CFAP46*- and *CFAP54*-variant individuals



Eur Respir J 2024; 64: 2400790

Take home message for PCD diagnostics



1) Nasal NO-Measurement (Screening); Cave in ca. 15% normal
2) High-speed videomicroscopy for evaluation of beating pattern (needs expert, frequently false abnormal, can be normal)
3) Immunfluorescence microscopy is better than transmission electron microscopy
4) *in vitro* Ciliogenesis (including particle tracking) new gold standard
5) Gene Panel: **Best Test, but not all PCD genes are discovered**

Eur Resp. J 121:616-622, 2009

Many thanks

If you need support for PCD diagnostics,

ERN LUNG PCD Core will try to help!

Heymut.Omran@ukmuenster.de

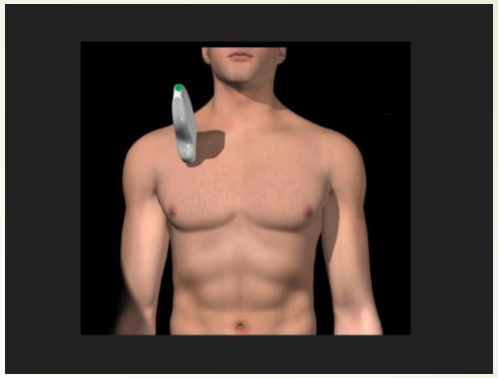
Lung and Diaphragm Point-of-Care Ultrasound (POCUS)

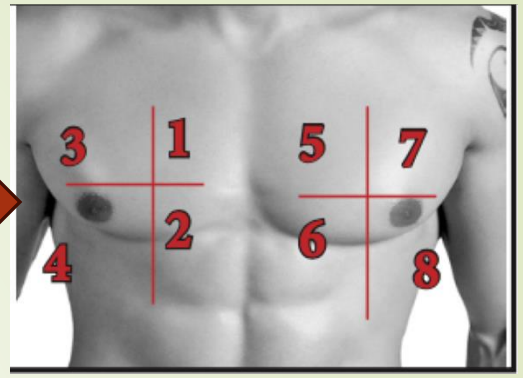
Sigmund Kharasch, MD

Director, Pediatric Emergency Ultrasound

Massachusetts General Hospital, Havard Medical School

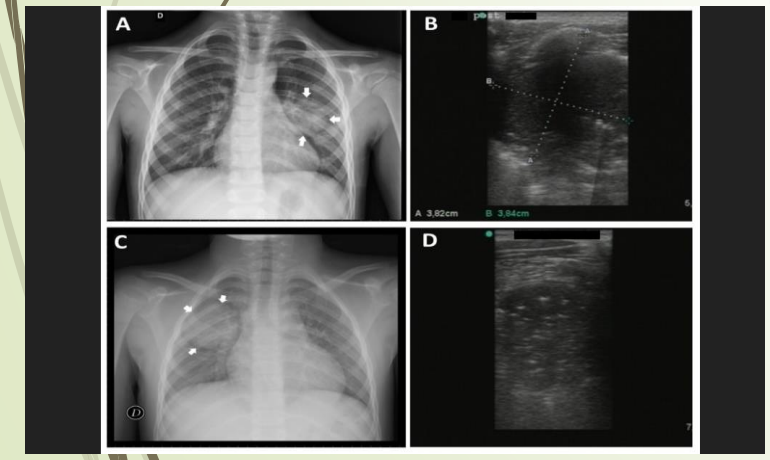
Lung Ultrasound



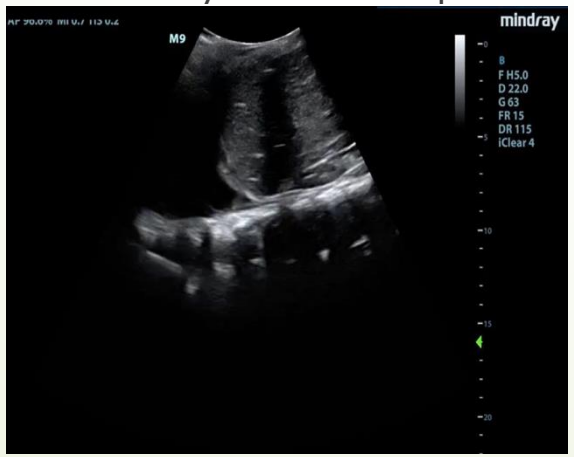


Scanning Zones

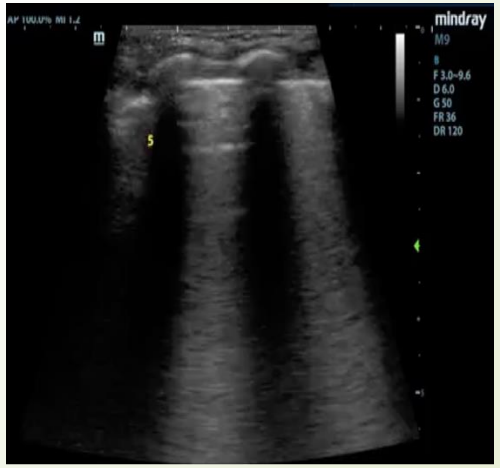
- Discussion of lung artifacts-A-lines, B-lines, scanning zones
- Applications: pneumothorax, pneumonia, pleural effusions, pulmonary edema, bronchiolitis
- Lung ultrasound can safely substitute for CXR for pneumonia
- Lung ultrasound is more sensitive than CXR for the diagnosis of PTX, pleural effusions, pulmonary edema, pulmonary contusion

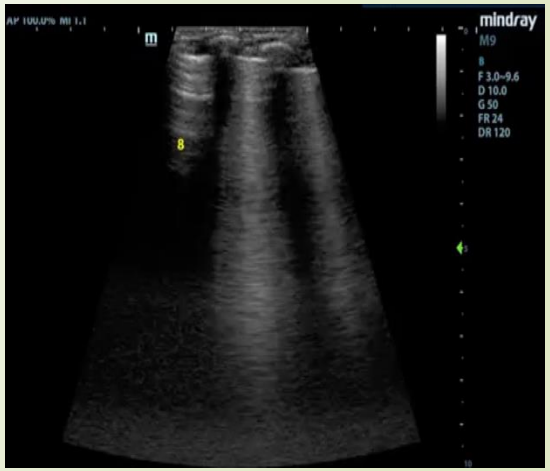


Pneumonia



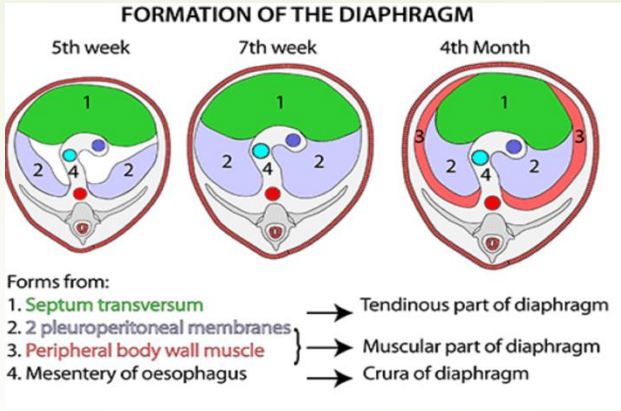
Pleural effusion

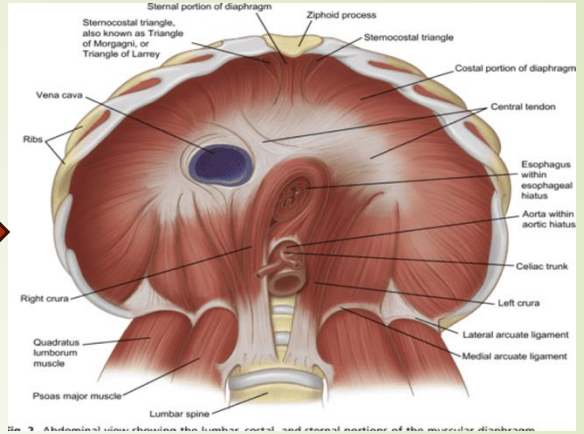




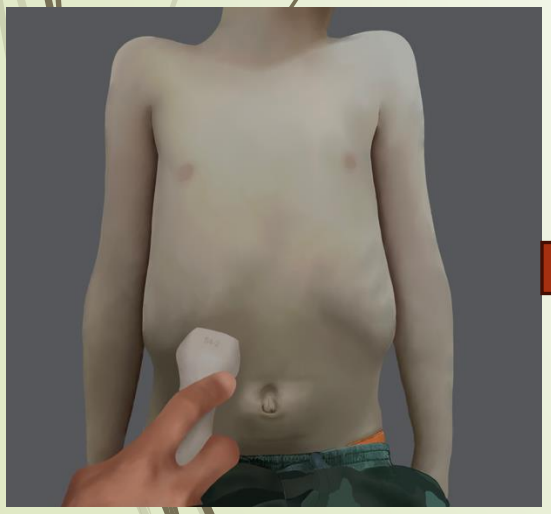
Bilateral B-lines-Pulmonary edema

Diaphragm Ultrasound

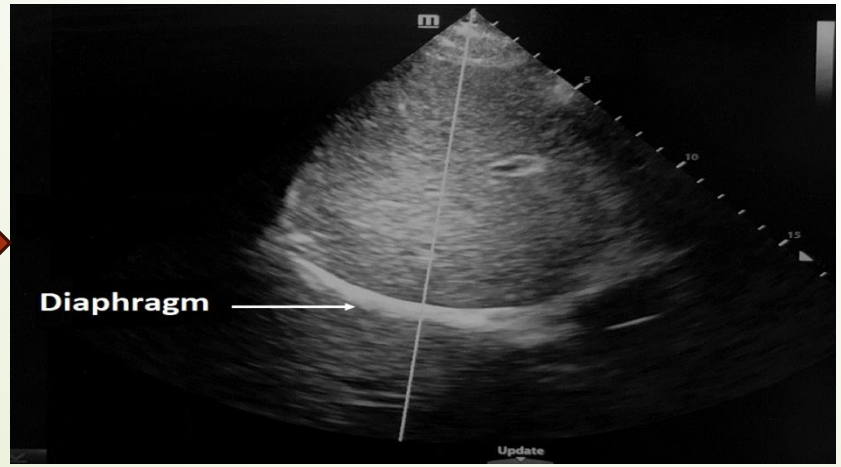




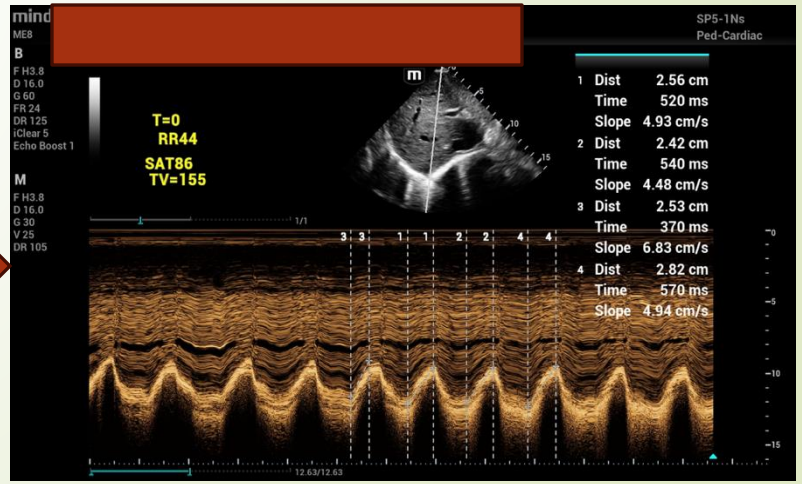
- Discussion of diaphragm development-central tendon and costal diaphragm at the zone of apposition
- Applications of diaphragm ultrasound: Asthma, ventilator-induced diaphragm dysfunction, COPD, trauma, bronchiolitis, acute dyspnea
- 2 US approaches-1.Anterior subcostal approach, evaluates diaphragm excursion in M-Mode



Subcostal Approach

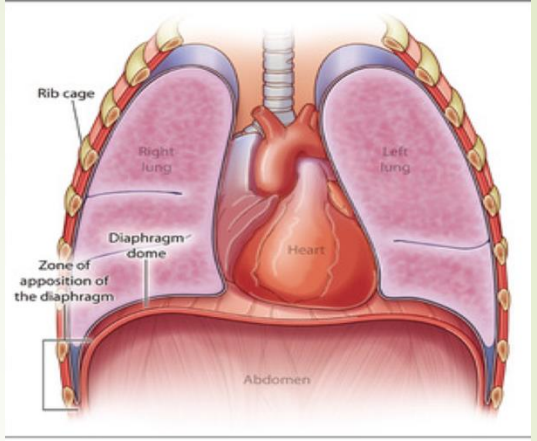


Diaphragm with M-mode line

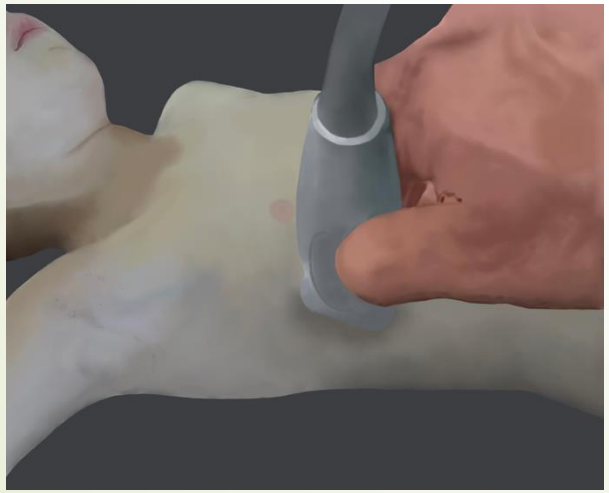


M-Mode measurements

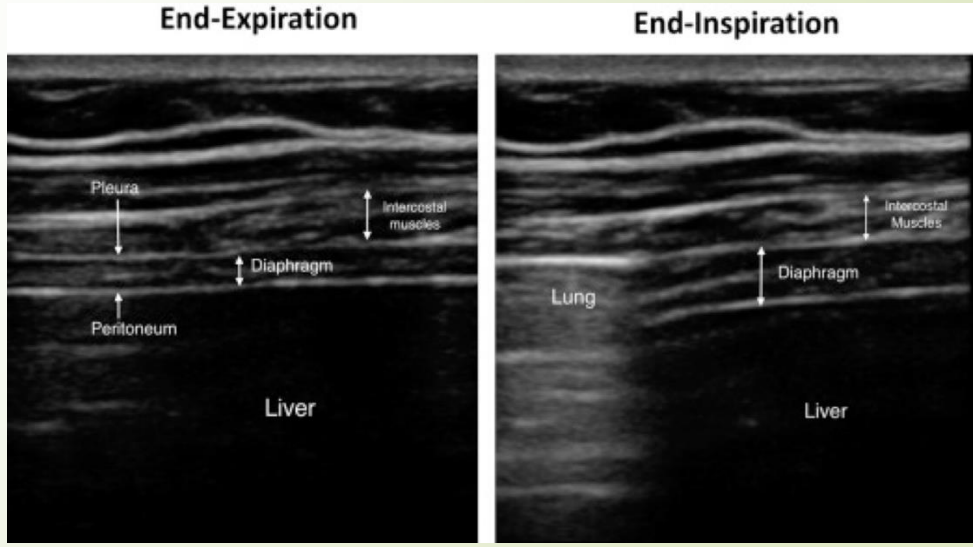
Zone of Apposition Approach



- The region of the diaphragm that abuts the lower rib cage (lower 6 ribs) constitutes the ZOA
- As the central tendon does not extend to the ZOA, allows direct assessment of diaphragm contraction with POCUS. The diaphragm on POCUS appears as a 3 layered structure, bordered by plural and peritoneal membranes.
- When the diaphragm contracts, it shortens and thickens



ZOA Approach



At FRC

At TLC

Measurements of Diaphragm Thickening and Thickening Fraction

CME Review Article

Review of Point-of-Care Diaphragmatic Ultrasound in Emergency Medicine

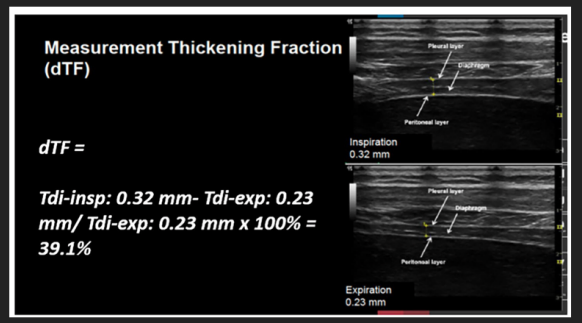
Background, Techniques, Achieving Competency, Research, and Recommendations

Sigmund J. Kharasch, MD,†‡ Sonja Salandy, MD,§ Paloma Hoover, RA,|| and Virginia Kharasch, MD¶*

Pediatric Emergency Care. 2025;41 (1), 68-74

DTF=TDI-INSPIRATION - TDI-EXPIRATION /TDI-EXPIRATION X 100

DTF: NORMAL AND ABNORMAL VALUES



The DTF is an index of muscle shortening during contraction. Calculated as the percentage increase in thickness during inspiration.

	0-6 mos	7mos-1yr	2-4 yrs	5-8 yrs
	Age group 1 $n=28$	Age group 2 $n=25$	Age group 3 $n=25$	Age group 4 $n=44$
Tdi-insp (mm)	2.07 (0.40)	2.09 (SD 0.40)	1.69 (0.30)	1.72 (0.30)
Tdi-exp (mm)	1.64 (0.30)	1.67 (0.30)	1.38 (0.20)	1.42 (0.20)
dTF (%)	25.4 (10.40)	25.2 (8.30)	22.8 (10.90)	21.3 (7.10)

Duyndam A. Reference values of diaphragmatic dimensions in healthy children. EJP-2023

Adult Values

Diaphragmatic area	Parameter and test	Mean normal values ± SD	Pathologic values	Reference
Zone of apposition	diaphragmatic thickness	2.7±0.5 mm	<2 mm	Gottesman et al. [26], 1997
	thickening fraction[a]	37±9%	<20%	

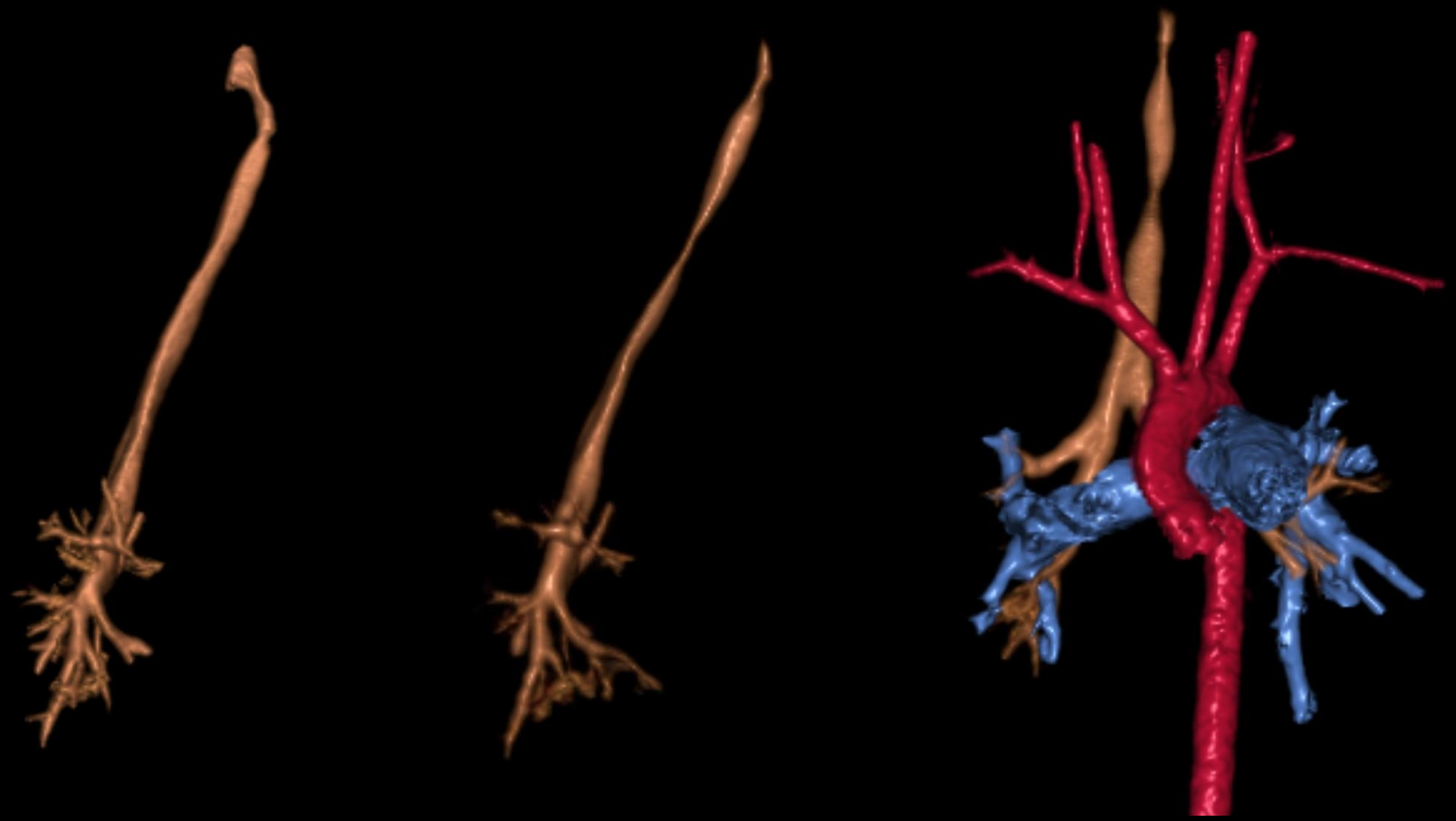
CONGRESS HIGHLIGHTS – THORACIC IMAGING

R. Paul Guillerman, MD
Professor of Radiology, Chief of Thoracic Imaging
Department of Radiology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio USA

Dynamic Airway CT

- Simultaneous imaging of the airways, lungs and blood vessels throughout the respiratory cycle achievable with the latest CT scanners
- Acceptable radiation dose
- No sedation or intubation required
- Guides management and reduces need for potentially risky diagnostic bronchoscopy

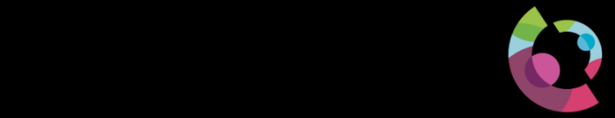
Multifocal expiratory central airway collapse revealed by dynamic airway CT in a 21-month-old



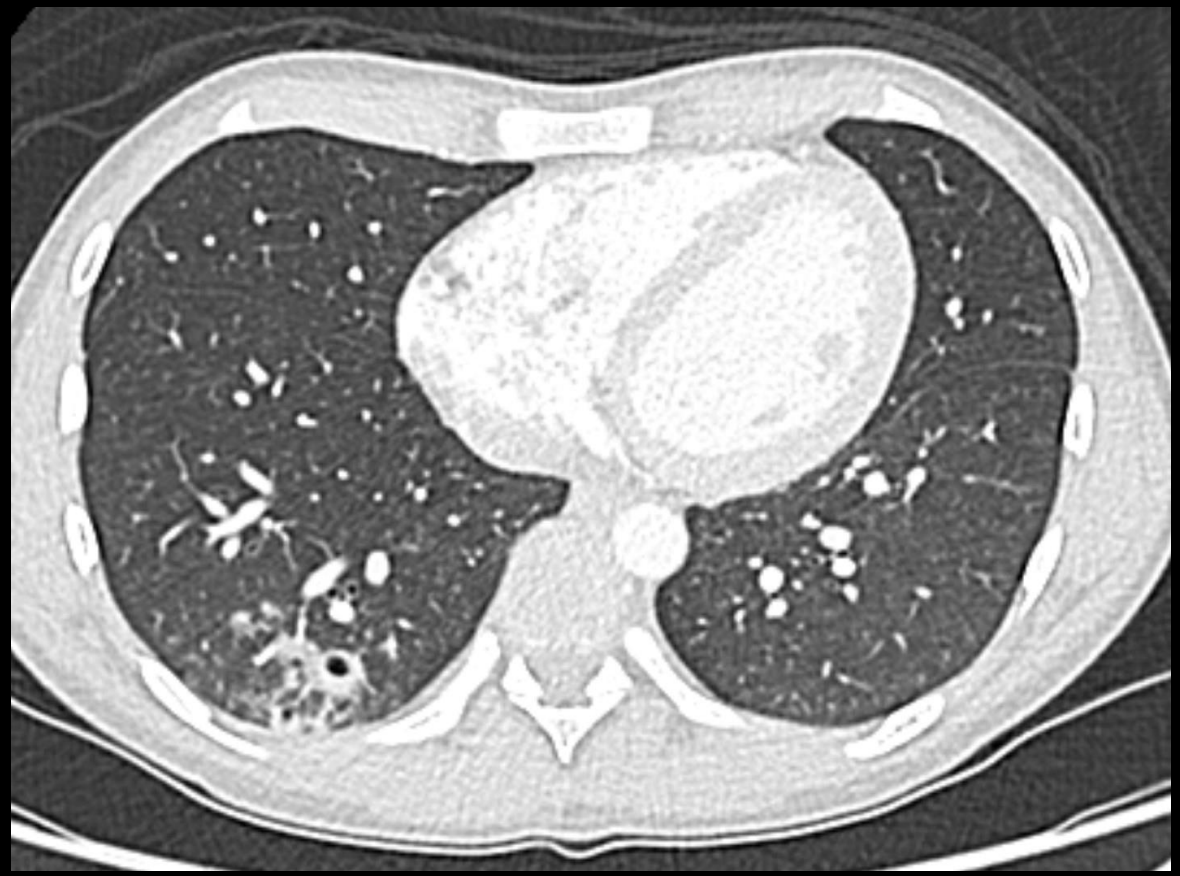
Inspiration Expiration

Emerging Thoracic MRI Techniques

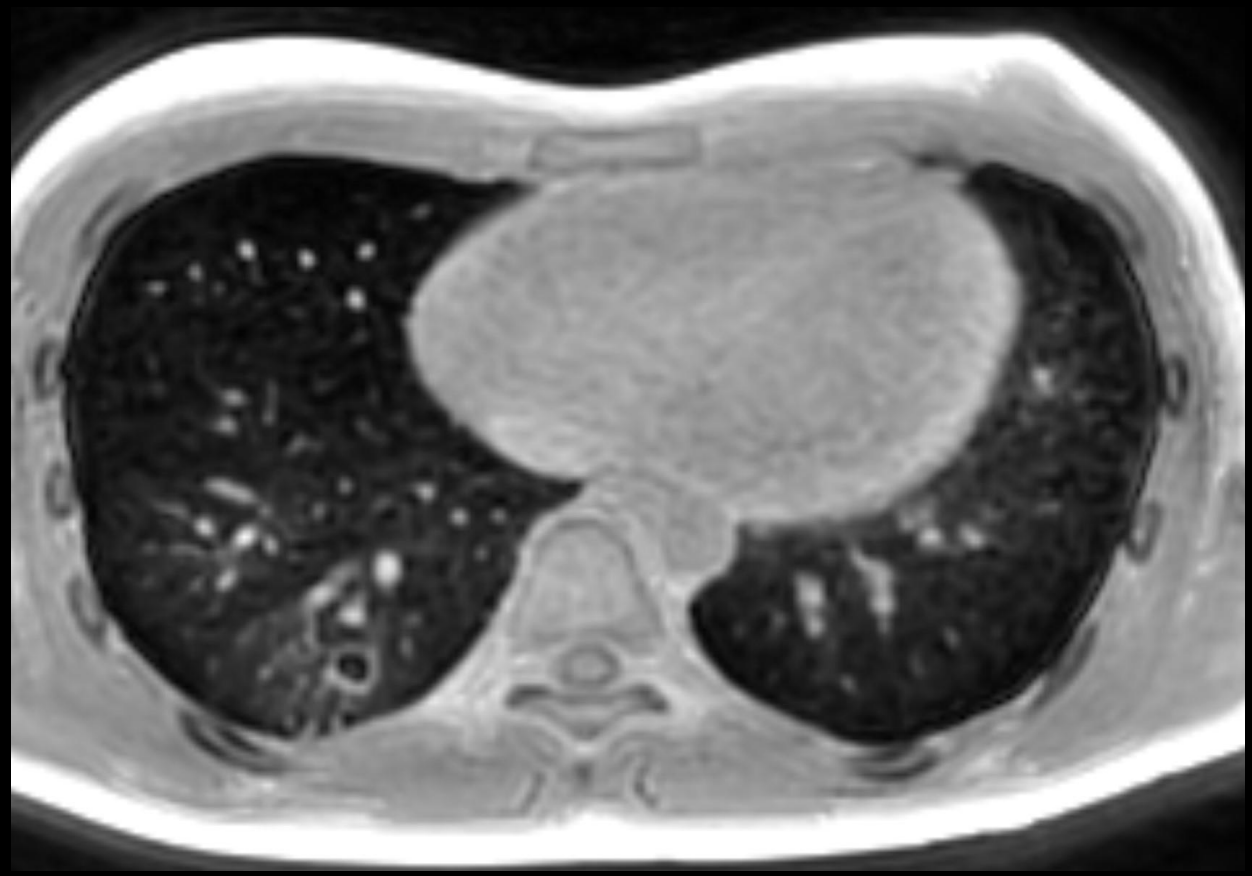
- Ultrashort echo time (UTE) MRI
  - Much better depiction of lung detail compared to conventional MRI
- Hyperpolarized gas MRI
  - Can provide quantitative information on regional lung ventilation and gas-exchange
- Dynamic MR lymphangiography
  - Allows direct visualization of the central conducting lymphatics and lymphatic flow



16-year-old with acute myelogenous leukemias on induction therapy with invasive pulmonary aspergillosis

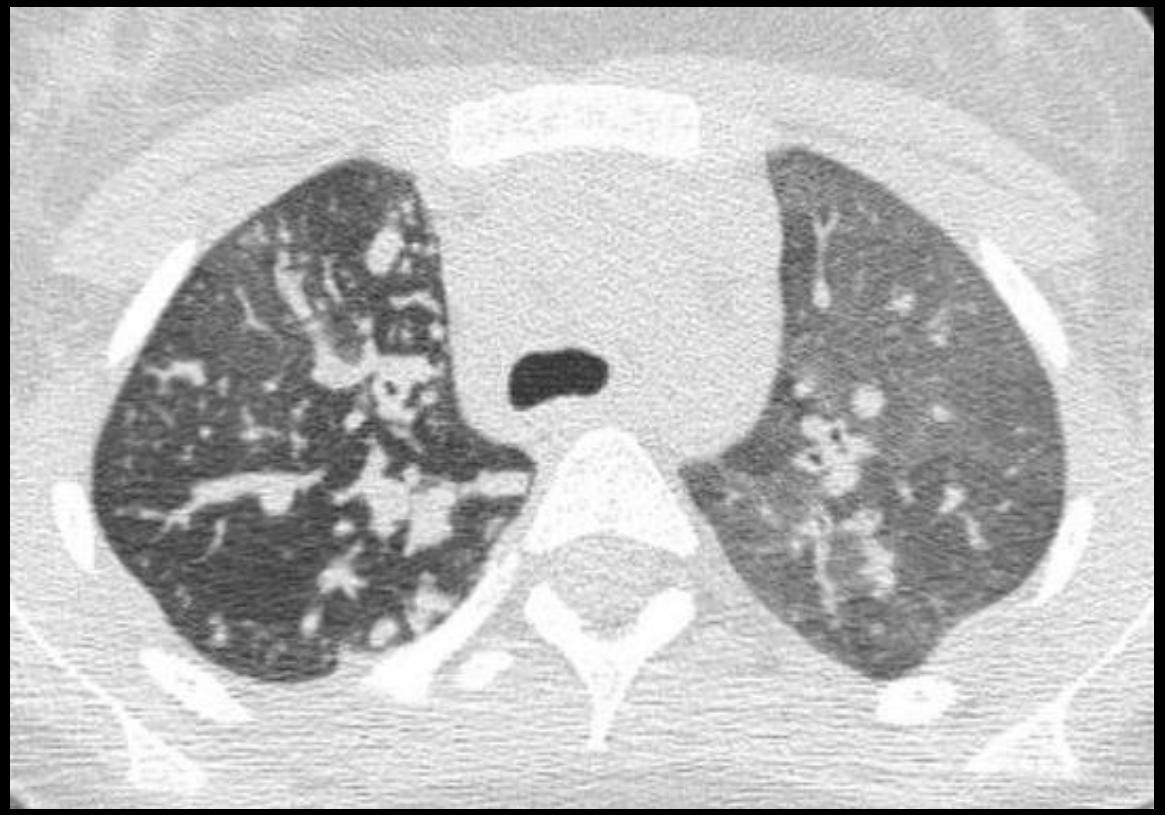


CT

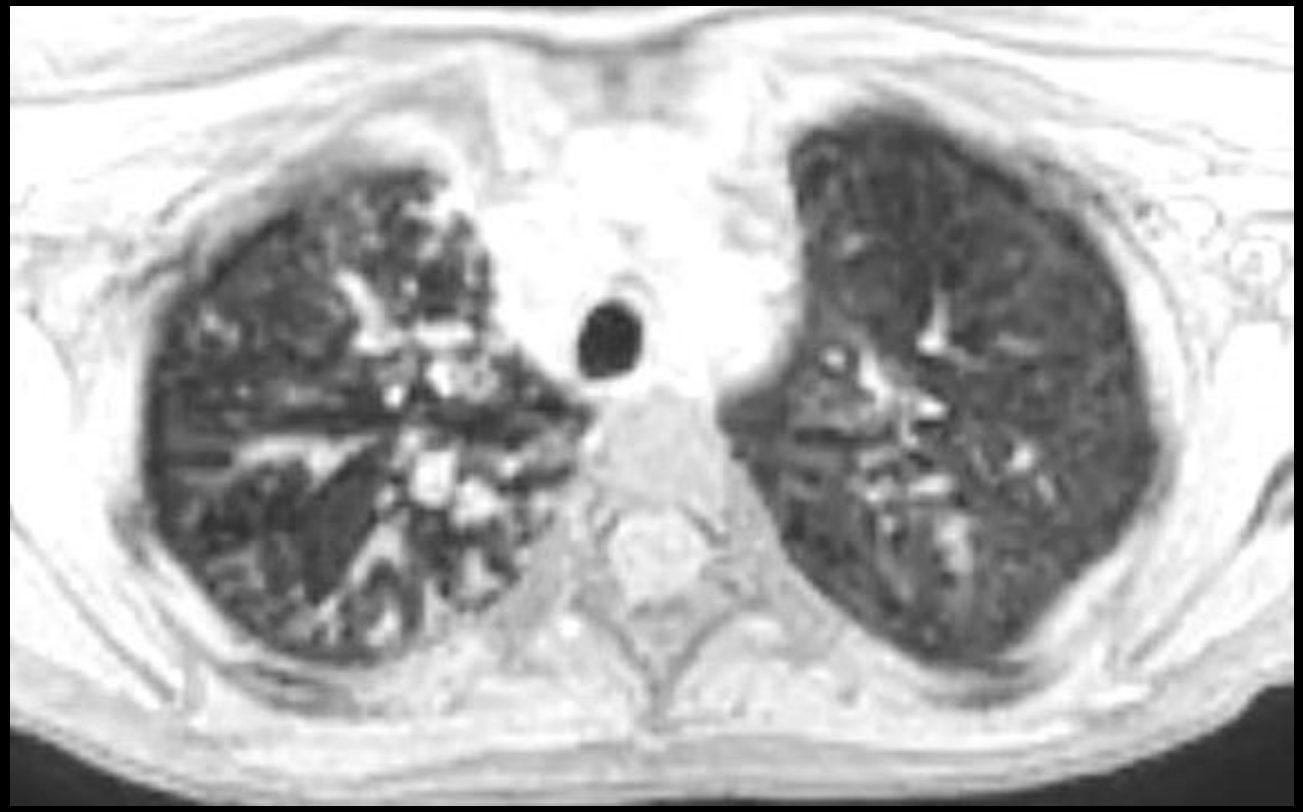


UTE MRI

11-year-old girl with cystic fibrosis

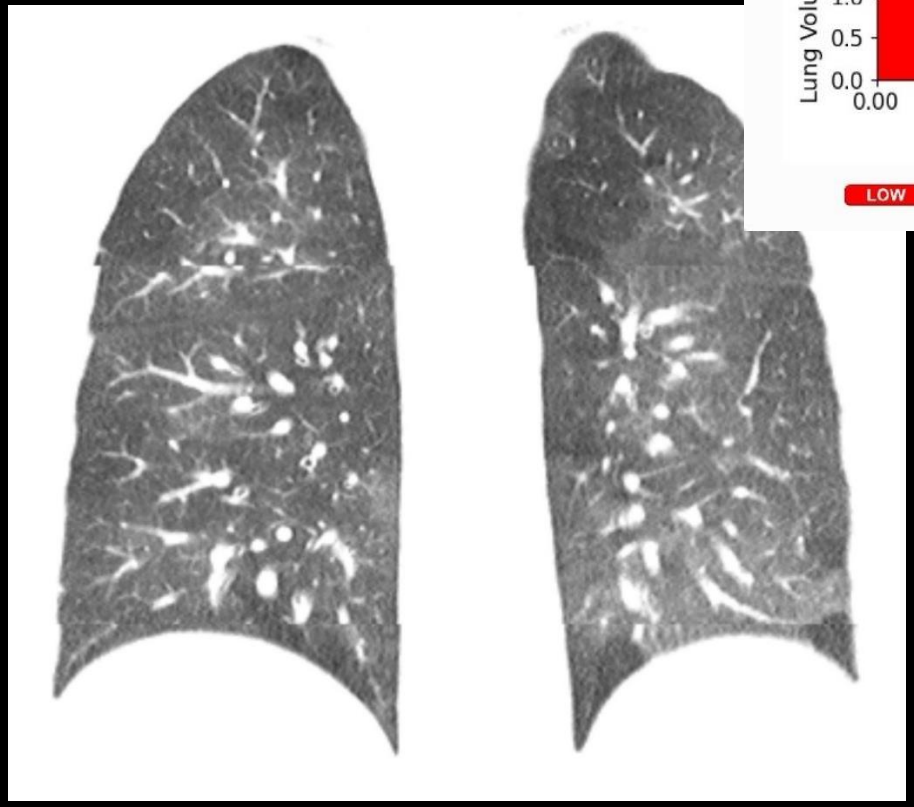


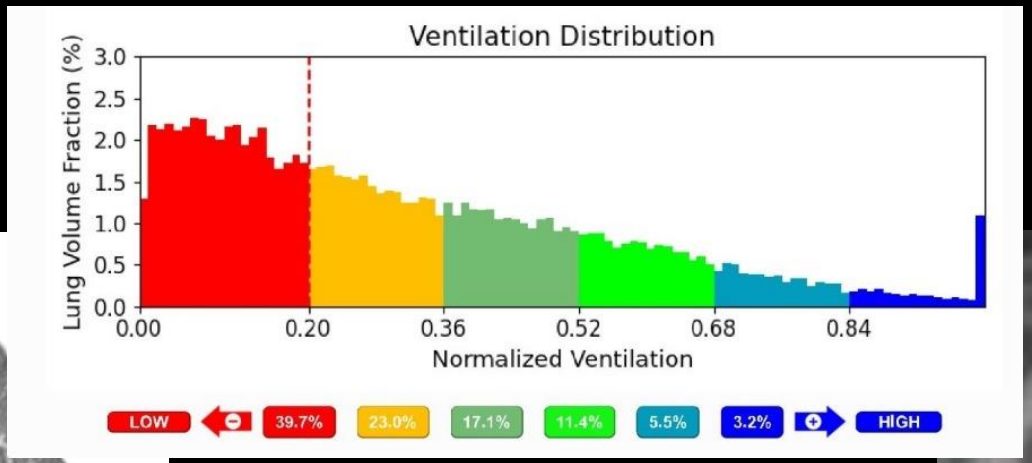
CT

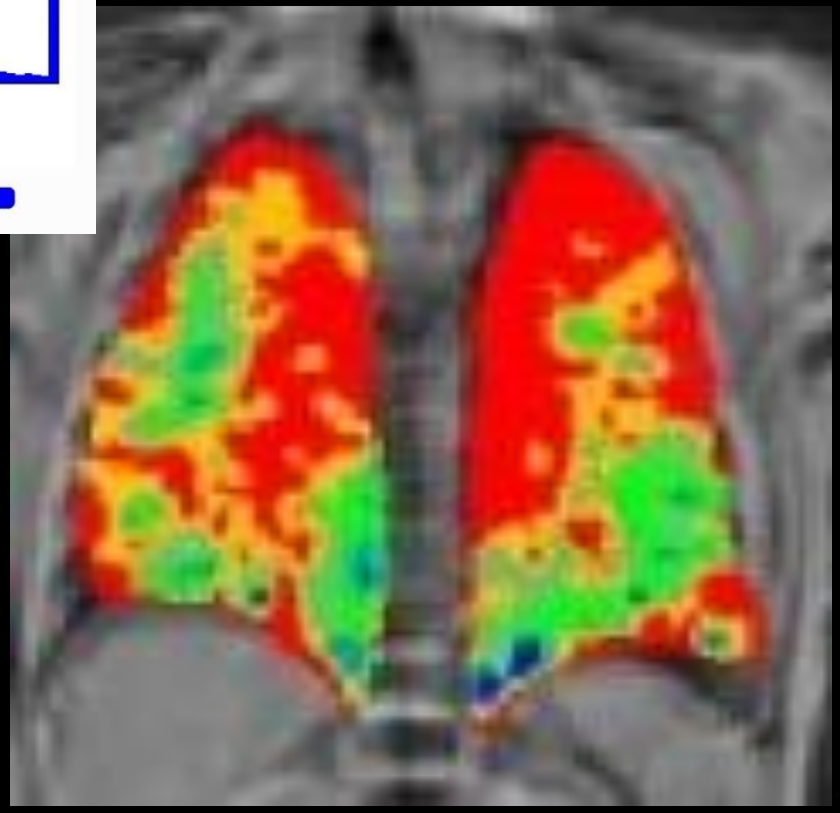


UTE MRI

^{129}Xenon MRI of 12-year-old with acute myelogenous leukemia revealing extensive ventilation defects due to post-transplant bronchiolitis obliterans







Dynamic MR lymphangiography revealing upper thoracic duct occlusion and peribronchial chylolymphatic reflux in 11-year-old post-Fontan procedure with plastic bronchitis