Primary Ciliary Dyskinesia

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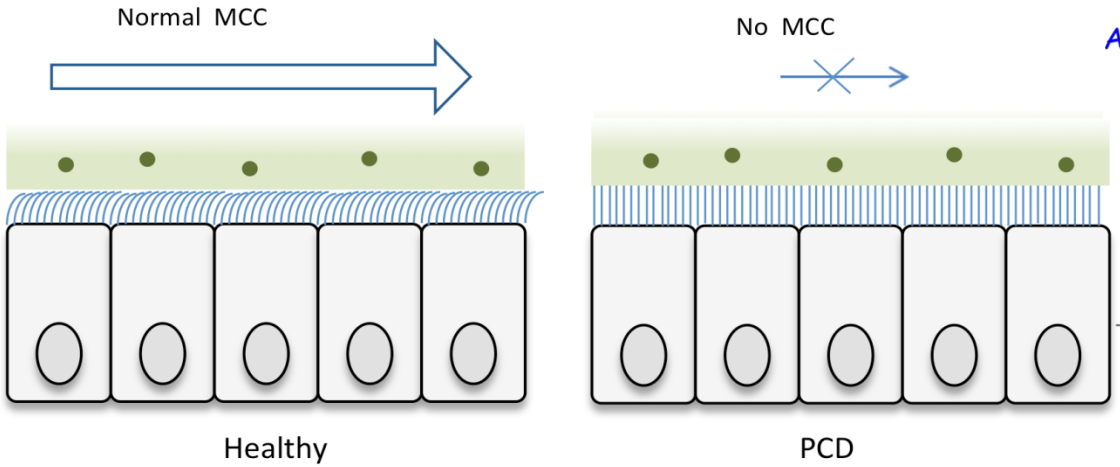
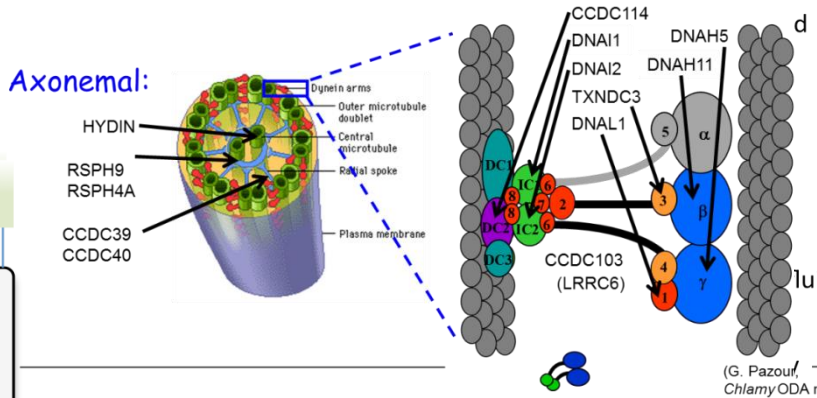
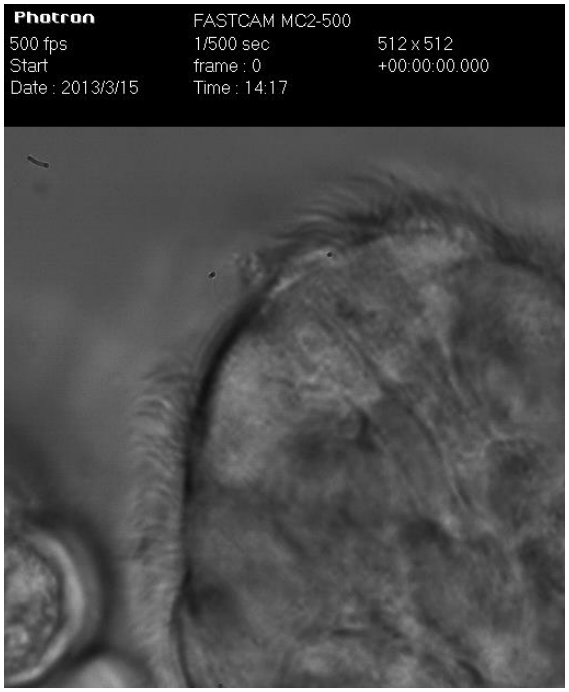
Clinical research in Southampton is a partnership between University Hospital Southampton NHS Foundation Trust and the University of Southampton, combining clinical and scientific excellence. It is enabled by funding from the National Institute for Health Research, Cancer Research UK, Medical Research Council and many others.


Normal MCC
No MCC
Healthy
PCD


Axonemal:
HYDIN
RSPH9
RSPH4A
CCDC39
CCDC40
Dynein arms
Outer microtubule doublet
Central microtubule
Radial spoke
Plasma membrane
CCDC114
DNAI1
DNAI2
TXNDC3
DNAL1
DNAH5
DNAH11
CCDC103
(LRRC6)
DC1
DC2
DC3
IC1
IC2
α
β
γ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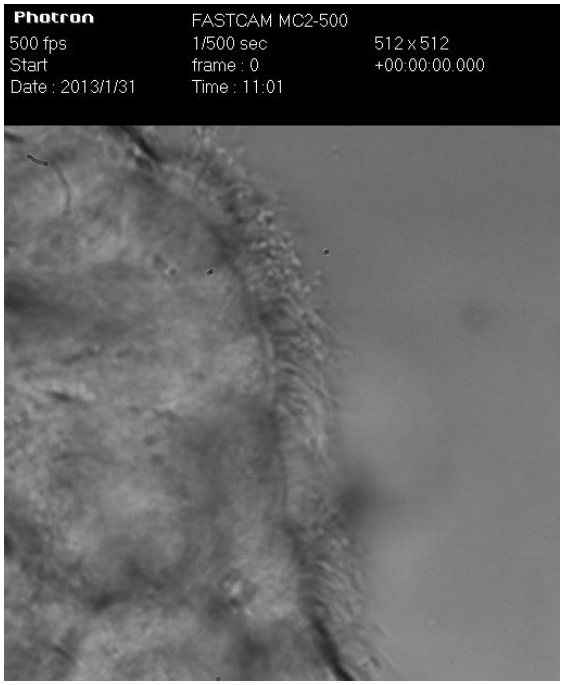
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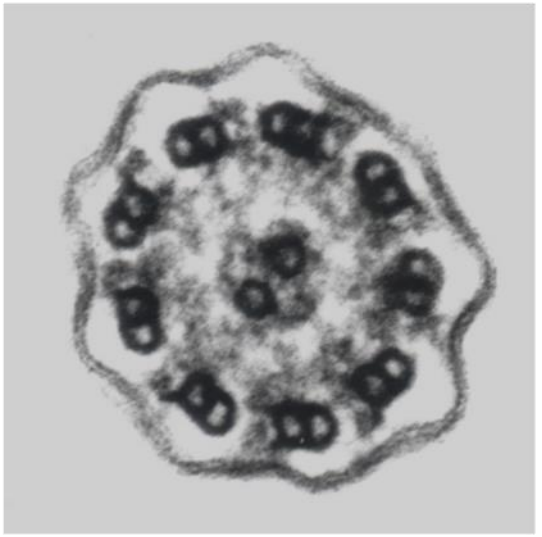
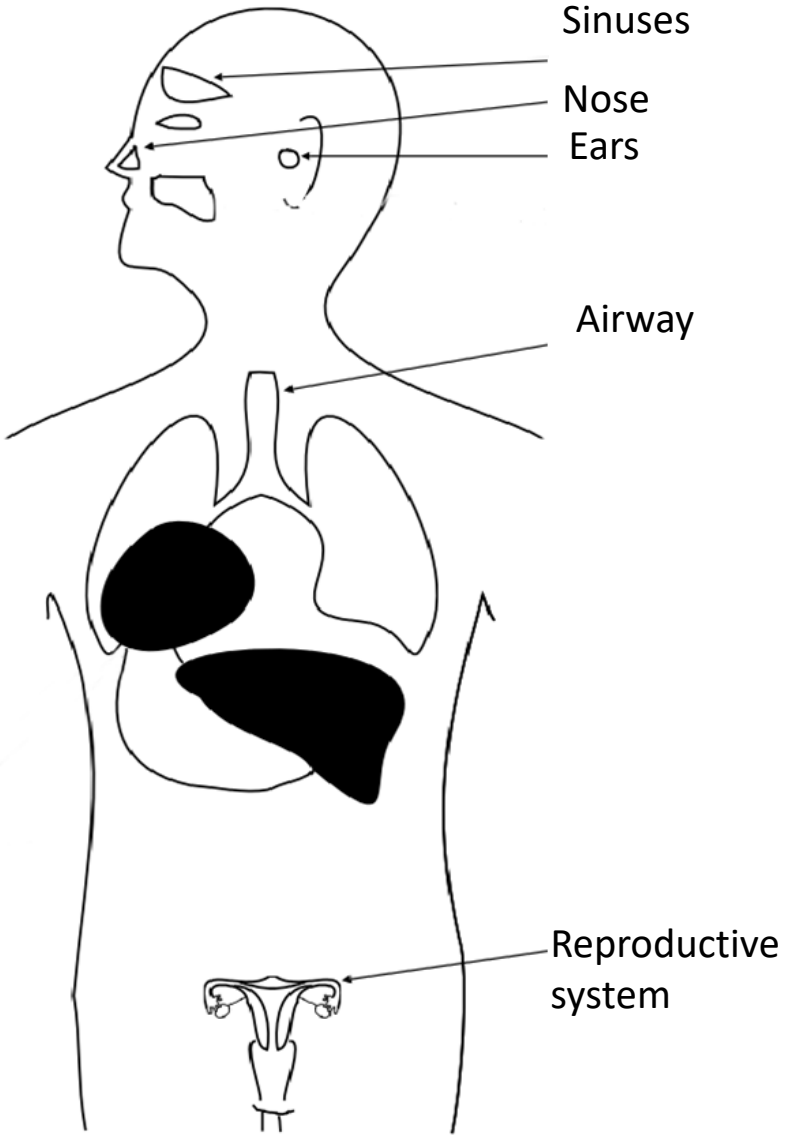
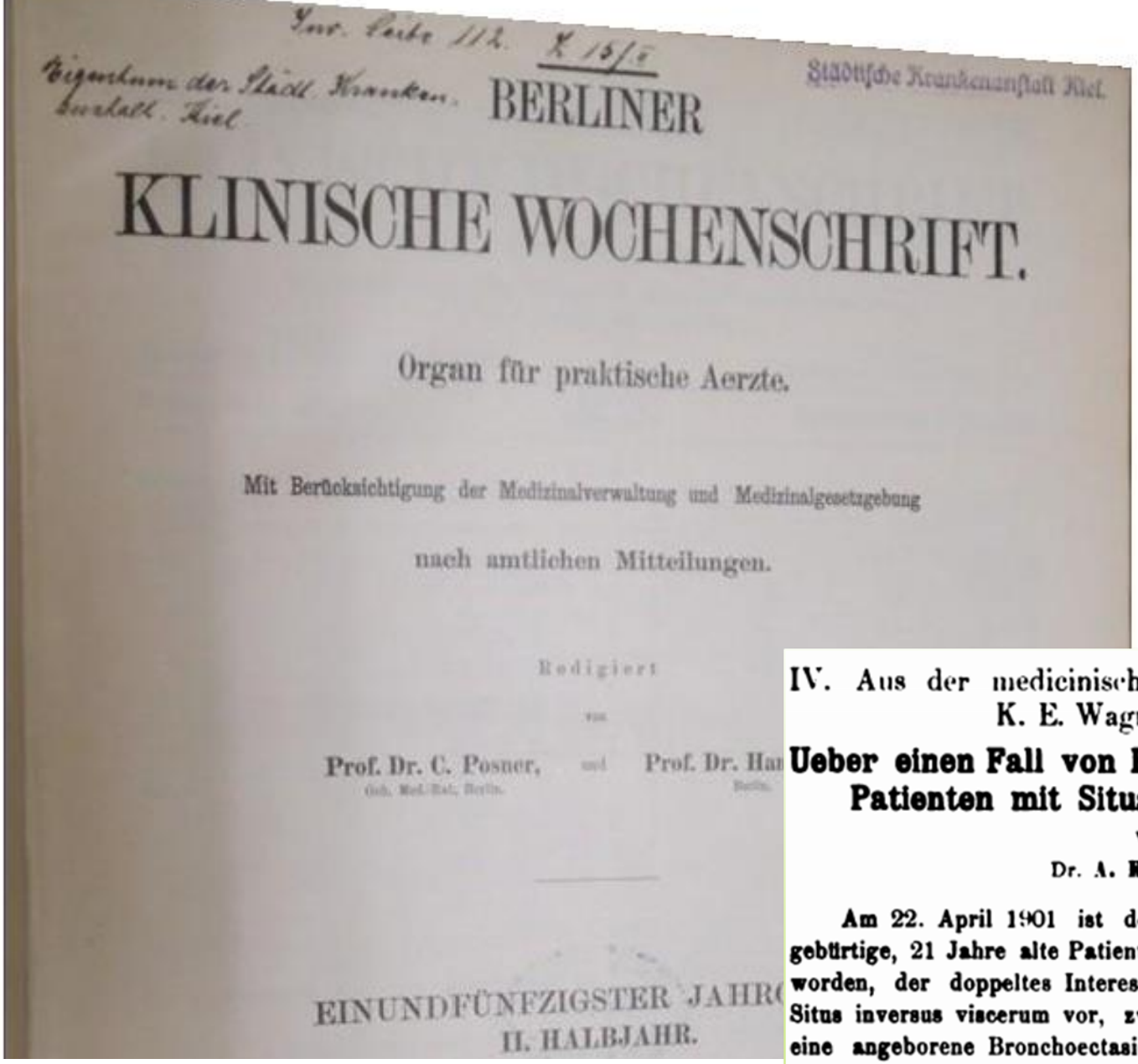




- Lung disease
  - Infections
  - Wet cough
  - Progressive loss of lung function
- Sinusitis
- Constant blocked nose and postnasal drip
- Hearing problems
- Fertility problems
- Half of patients have heart and lungs ‘in the wrong place’



Eigenthum der Städt. Kranken. Invalid. Kiel

Städtische Krankenanstalt Kiel.

BERLINER

KLINISCHE WOCHENSCHRIFT.

Organ für praktische Aerzte.

Mit Berücksichtigung der Medizinalverwaltung und Medizinalgesetzgebung

nach amtlichen Mitteilungen.

Redigiert

von

Prof. Dr. C. Posner, Geh. Med.-Rat, Berlin. und Prof. Dr. Han Berlin.

EINUNDFÜNFZIGSTER JAHRG

II. HALBJAHR.

IV. Aus der medicinischen Klinik des Herrn Prof. K. E. Wagner zu Kiew.

Ueber einen Fall von Bronchiectasie bei einem Patienten mit Situs inversus viscerum.

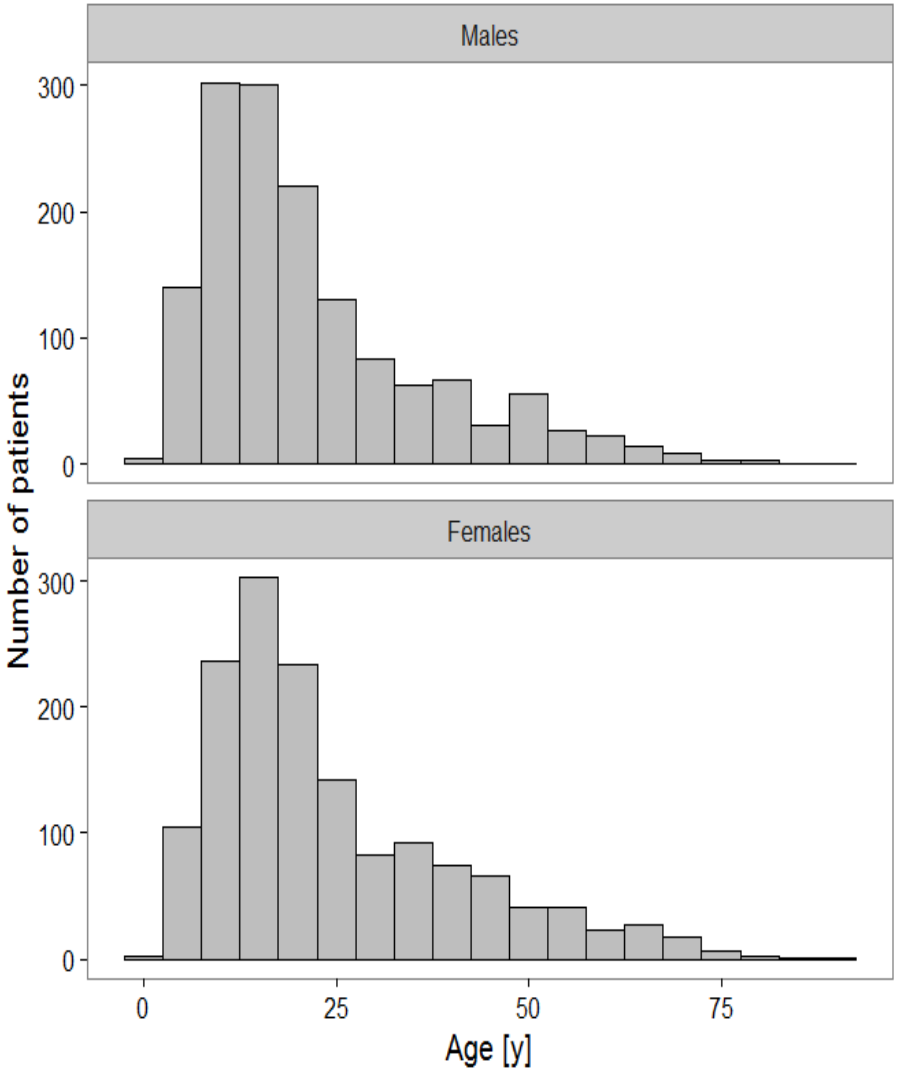
Von

Dr. A. K. Siewert.

Am 22. April 1901 ist der aus dem Gouvernement Kiew gebürtige, 21 Jahre alte Patient A. W. in die Klinik aufgenommen worden, der doppeltes Interesse darbot: erstens lag bei ihm Situs inversus viscerum vor, zweitens, was noch wichtiger ist, eine angeborene Bronchoectasie, die bekanntlich eine äusserst seltene, fast exclusive Erkrankung ist. Auf Anregung des Herrn Prof. K. E. Wagner erlaube ich mir, diesen Fall zu beschreiben.

Siewert AK (1904). "Über einen Fall von Bronchiectasie bei einem Patienten mit situs inversus viscerum". *Berliner klinische Wochenschrift*. **41**: 139–141.

International (iPCD) Cohort



- 2016:
  - (N=3013)
  - 55% <20 yrs

Goutaki. Eur Resp J 2017

Eur Respir J 2016; 48: 1096–1107 | DOI: 10.1183/13993003.02018-2015

ORIGINAL ARTICLE
PRIMARY CILIARY DYSKINESIA

Diagnosing primary ciliary dyskinesia: an international patient perspective

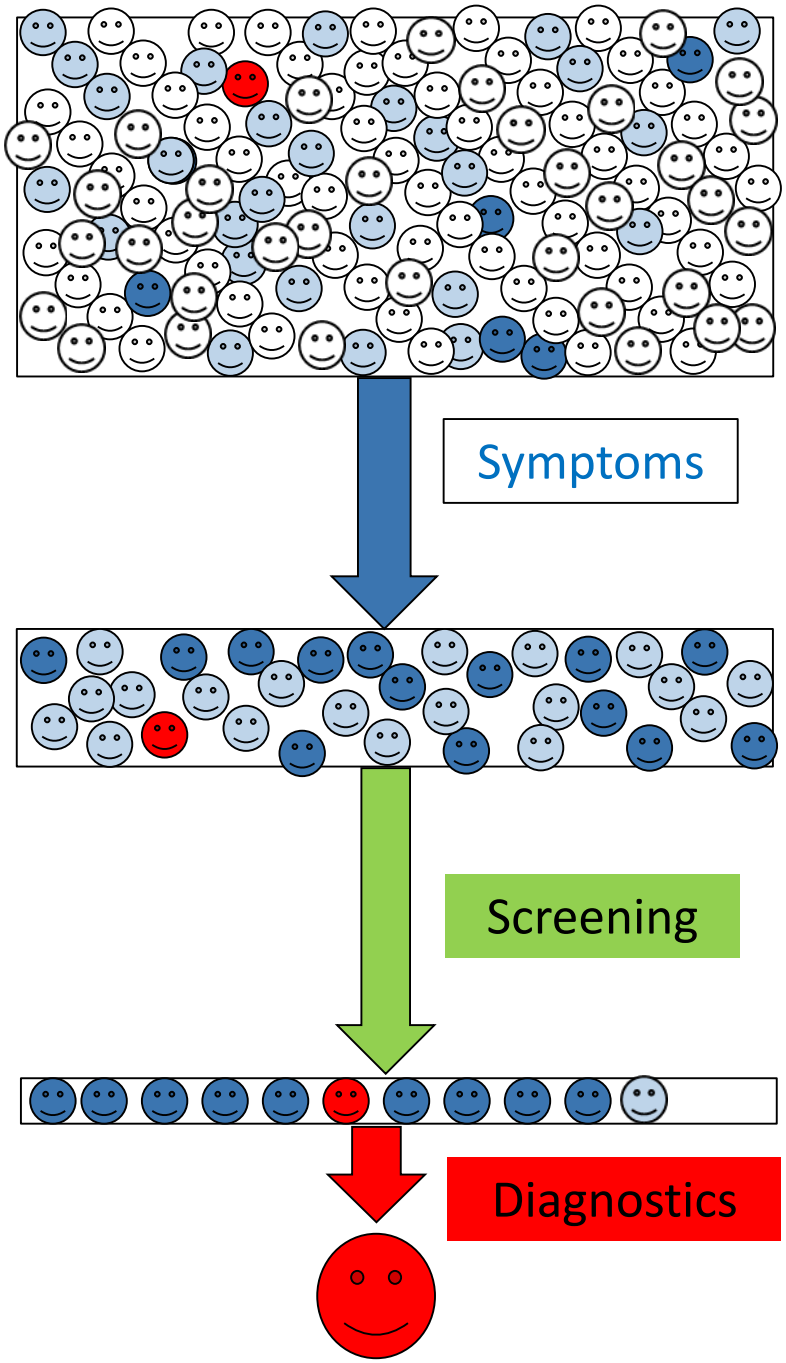
Laura Behan[1,2,3], Audrey Dunn Galvin[3], Bruna Rubbo[1,2], Sarah Masefield[4], Fiona Copeland[5], Michele Manion[6], Bernhard Rindlisbacher[7], Beatrice Redfern[5] and Jane S. Lucas[1,2]

- 35% visited a doctor >40 times before diagnostic referral
- Lack of knowledge about PCD by general physicians
- Failure to take previous history into account

Why is PCD 'missed'?

- Rare disease (1:10,000)
- No gold standard diagnostic test
- Combination of tests necessary, all
  - expensive
  - need up-to date equipment
  - highly skilled team
- Single symptoms non-specific,
  - but combination typical

Kuehni & Lucas. Ann Am Thorac Soc, 2016; 13:1249-43.



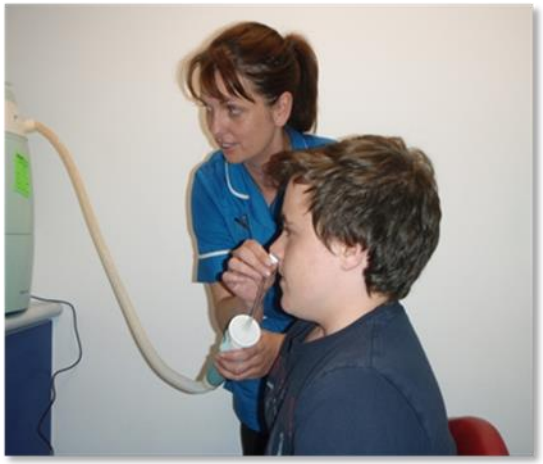
General Population	1:10,000
Pulmonologist	1:1,000
Non-CF bronchiectasis	3:100
Children with wet cough	5:100
PCD reference centre	1:10

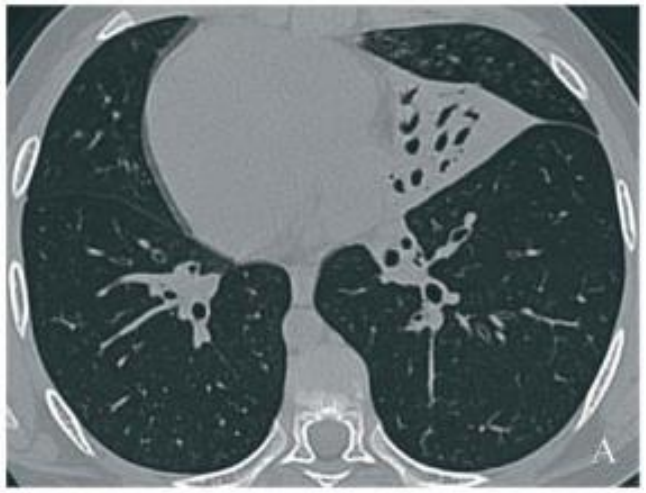
correct tests, technique & interpretation

Adapted from Kuehni, ERS Congress 2016

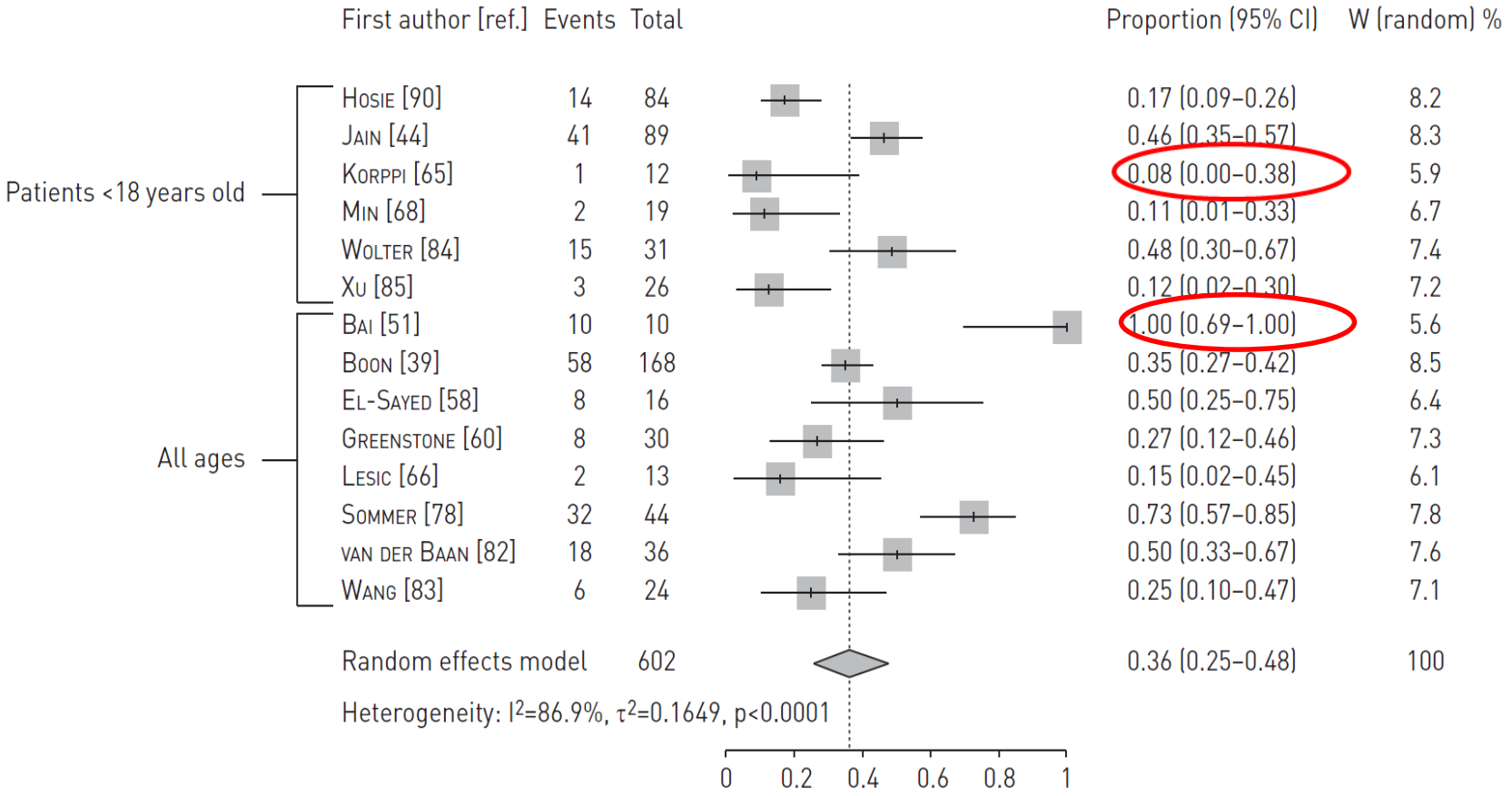
Screening for PCD

- Symptoms and history
- Nasal Nitric Oxide





How frequent are PCD symptoms eg. hearing?



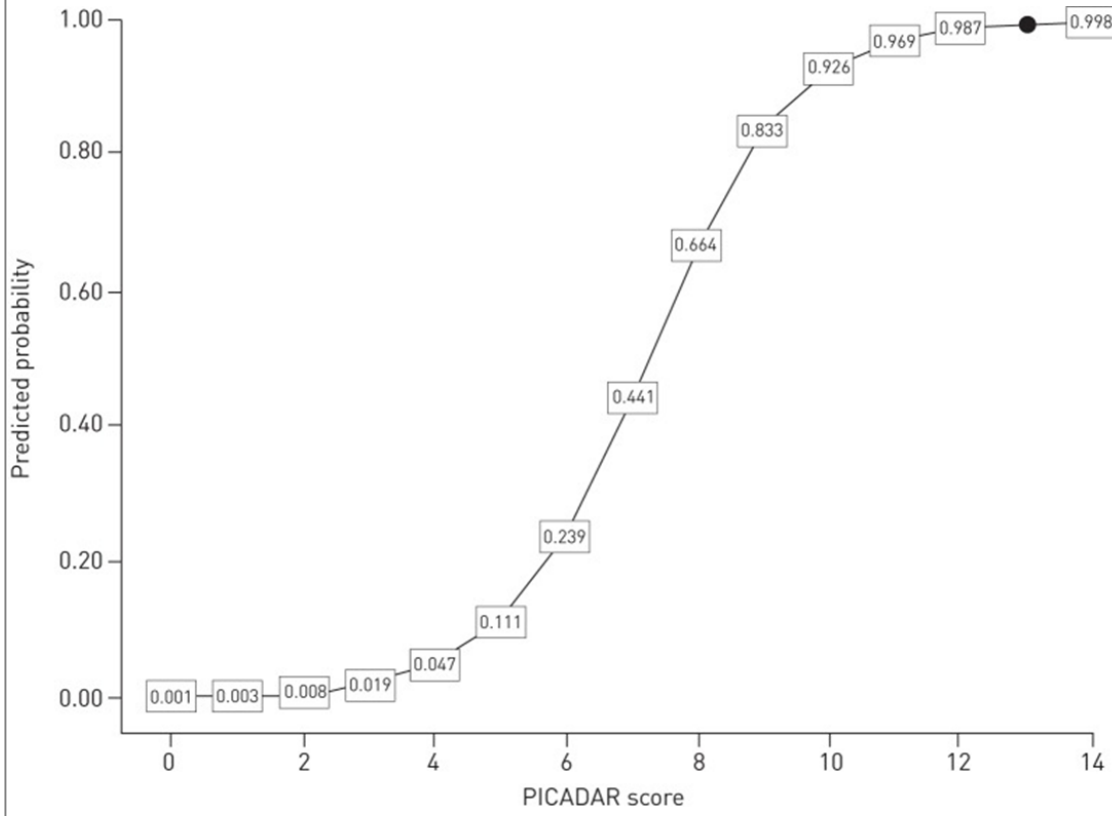
Goutaki M et al 2016, ERJ

Clinical Manifestation	Sensitivity	Specificity
Neonatal manifestations		
Neonatal chest symptoms	**0.75**	**0.83**
Neonatal rhinitis	0.27	**0.94**
Neonatal respiratory support	0.41	**0.93**
Neonatal unit admission	0.61	**0.86**
Upper respiratory manifestations after the postnatal period		
Chronic rhinitis	**0.81**	0.43
Chronic serous otitis media	0.57	0.81
Hearing loss	0.49	0.84
Chronic ear perforation	0.12	**0.91**
Chronic sinusitis	0.28	0.76

Clinical Manifestation	Sensitivity (95% C.I.)	Specificity (95% C.I.)
Lower respiratory manifestations after the postnatal period		
Chronic wet cough	**0.93**	0.15
Recurrent wheeze	0.48	0.62
Previous pneumonia	0.41	0.65
Bronchiectasis	0.29	0.68
Other manifestations (various ages)		
Situs anomalies**	0.51	**0.94**
Congenital heart disease	0.08	**0.98**
Developmental delay	0.11	0.94
Hydrocephalus	0.01	0.99
Subfertility*	0.91	0.82
Of otitis media	0.07	0.89

PICARDAR: a predictive tool for PCD

PICADAR		
Does the patient have a daily wet cough that started in early childhood?	Yes- complete PICADAR No- STOP. PICADAR is not designed for patients without a wet cough	
1. Was the patient born preterm or full term?	Term	2
2. Did the patient experience chest symptoms in the neonatal period (eg. tachypnoea, cough, pneumonia)?	Yes	2
3. Was the patient admitted to a neonatal unit?	Yes	2
4. Does the patient have a situs abnormality (situs inversus or heterotaxy)?	Yes	2
5. Does the patient have a congenital heart defect?	Yes	4
6. Does the patient have persistent perennial rhinitis	Yes	1
7. Does the patient experience chronic ear or hearing symptoms (e.g. glue ear, serous otitis media, hearing loss, ear perforation)	Yes	1
	Total Score =	



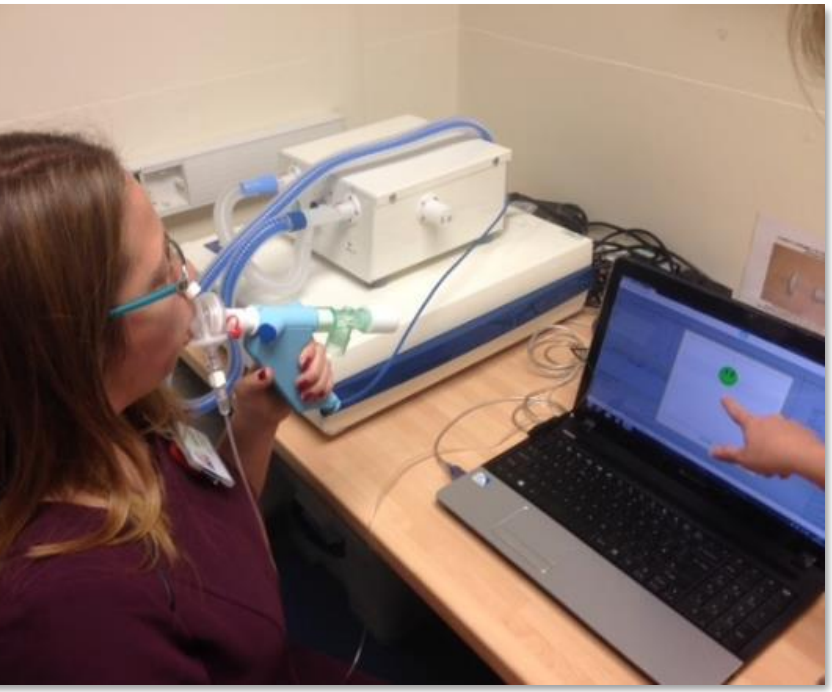
Behan Eur Resp J 2016

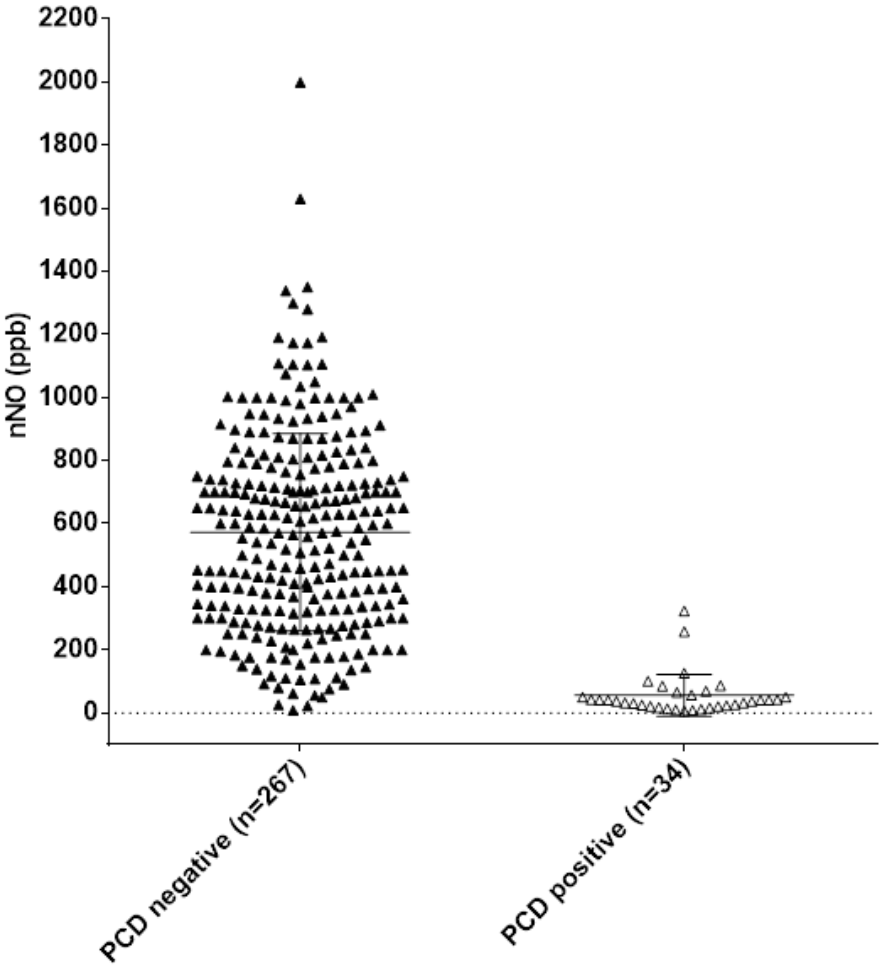
ERS Task Force recommendations

1. **Patients should be tested for PCD if they have several of**: persistent wet cough; situs anomalies; congenital cardiac defects; persistent rhinitis; chronic middle ear disease +/-hearing loss; history of neonatal upper and lower respiratory symptoms or NICU admittance in term infants
2. **Patients with normal situs** with symptoms suggestive of PCD
3. **Siblings**, particularly if symptoms suggestive of PCD
4. **Use combinations of distinctive PCD symptoms and predictive tools** (e.g. PICADAR)

Lucas et al European Task Force Guidelines, Eur Resp J 2017

Nasal Nitric Oxide



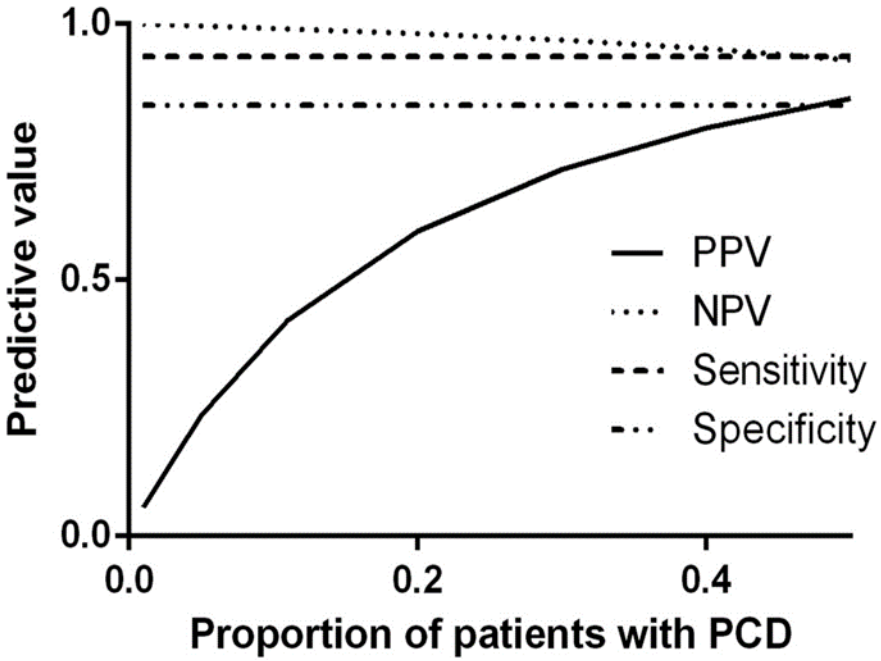


- 282 consecutive referrals
- 31 (11%) PCD positive
- Cut-off 77 nL/min)

  - Sensitivity 94%,
  - Specificity 84%,
  - PPV 44%

Jackson, Behan et al ERJ 2015

BUT…….. Predictive value depends on prevalence



Collins S. Thorax 2016;71:560-1

Setting	Prevalence	PPV
Community	0.01%	0.06%
Pulmologist	0.1%	0.6%
PCD centre	11%	44%

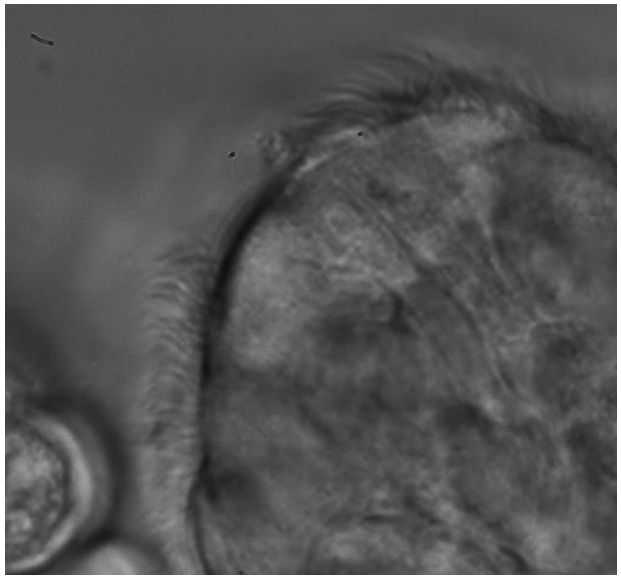
Recommendations: Nasal nitric oxide

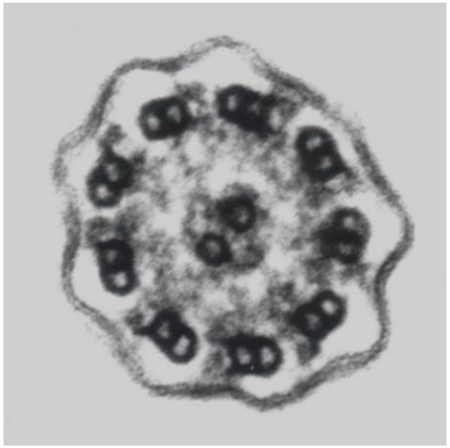
- **≥6y** using a chemiluminescence analyser with velum closure (*portable analyser/ tidal breathing acceptable*)

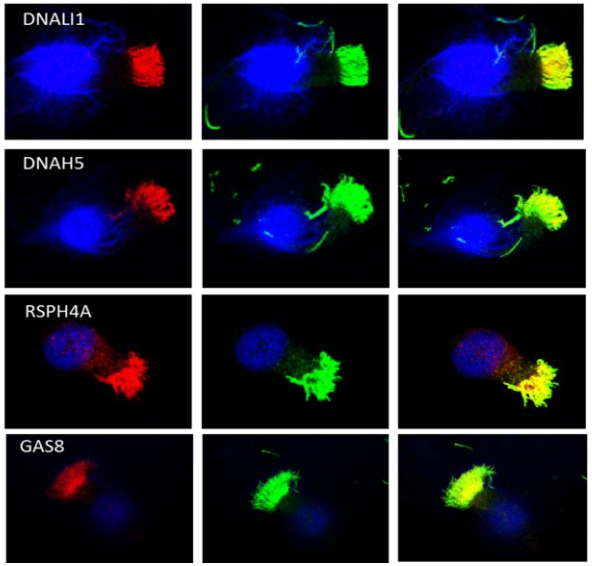
- **<6y** using tidal breathing (*poor discrimination in infants*)

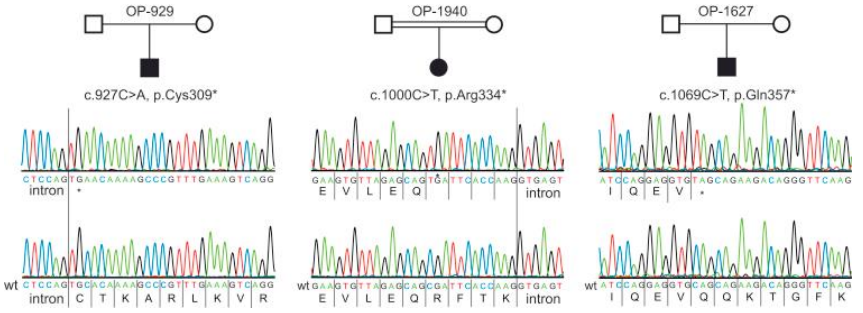
- Patients with a strong clinical history should undergo further testing, even if nNO is normal

Lucas et al European Task Force Guidelines, Eur Resp J 2017






DNALI1
DNAH5
RSPH4A
GAS8

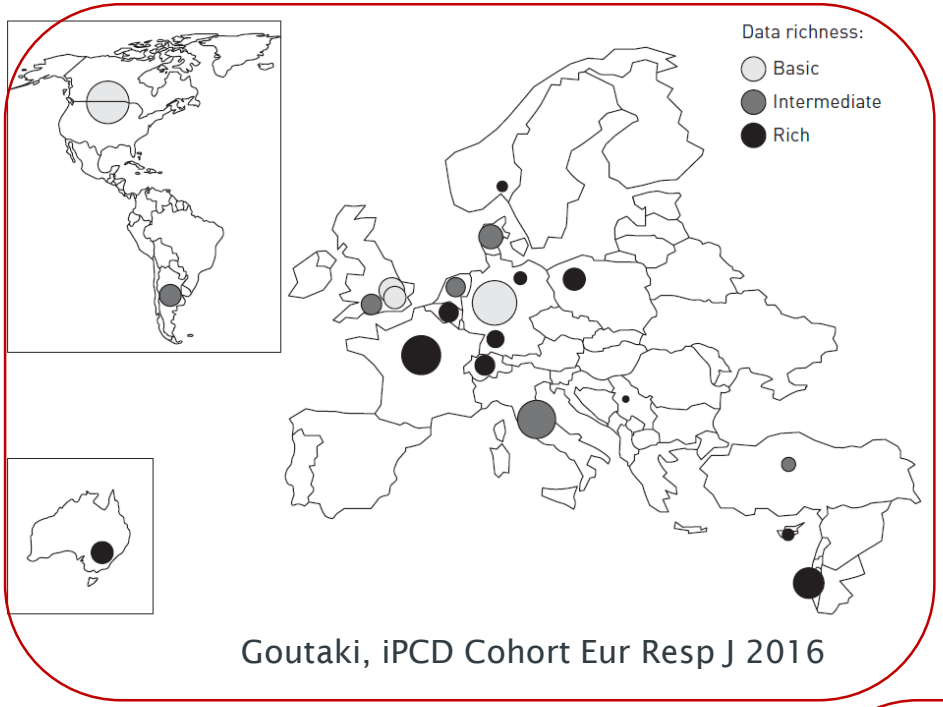

OP-929
c.927C>A, p.Cys309*
intron
wt
intron C T K A R L K V R
OP-1940
c.1000C>T, p.Arg334*
E V L E Q
intron
wt
E V L E Q R F T K intron
OP-1627
c.1069C>T, p.Gln357*
I Q E V *
wt
I Q E V Q Q K T G F K

No Perfect Diagnostic Test

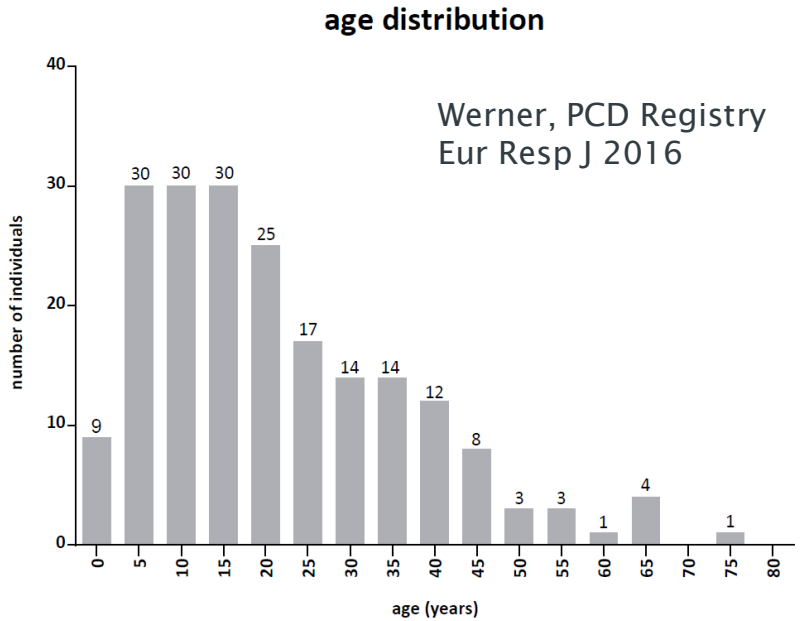
- High speed video-
  - only reliable in expert labs
  - Secondary defects are common
- Electron microscopy
  - Normal in 16% of PCD patients
- Genetics
  - No suitable studies to evaluate use as a diagnostic tool
  - Several studies suggest it identifies ≈65%
- Immunofluorescence
  - No suitable studies to evaluate use as a diagnostic tool

Lucas et al European Task Force Guidelines, ERJ 2017

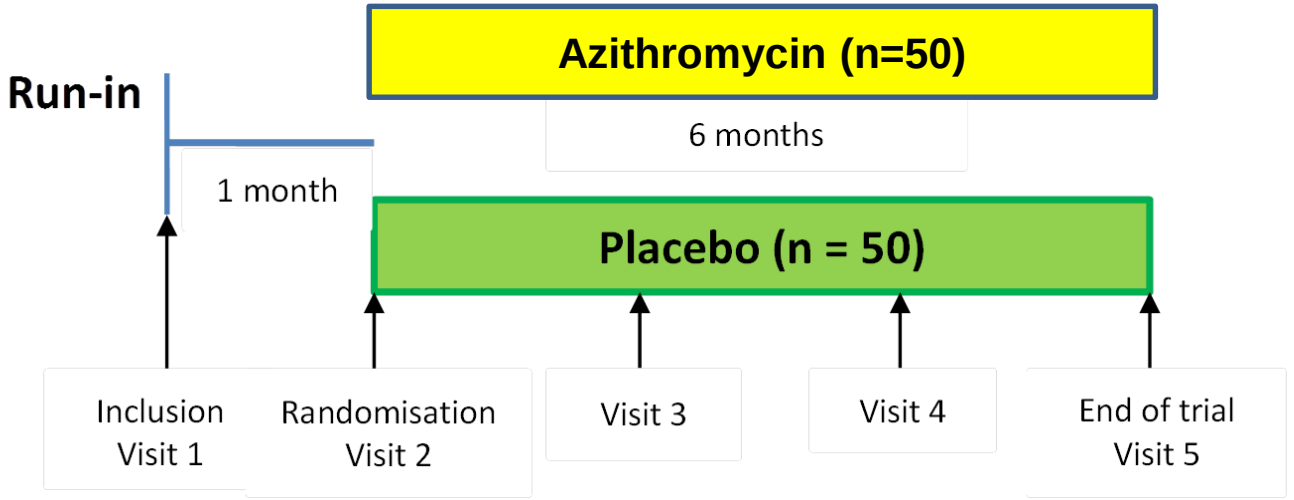
PCD Cohorts



Goutaki, iPCD Cohort Eur Resp J 2016



BESTCILIA



PARION SCIENCES

CLEAN-PCD
Clearing Lungs with ENaC Inhibition in Primary Ciliary Dyskinesia

Vero Nasal Mode n=50 PCD n=100 HC

BEAT-PCD

- COST Action project
- Europe-led network of clinicians & scientists
- To promote research from basic science to clinical care
- Ultimate goal:

  - develop treatments
  - lead to measurable improvements
  - Improve long-term outcomes

BEAT-PCD
BETTER EXPERIMENTAL APPROACHES TO TREAT PCD

BEAT-PCD

BETTER EXPERIMENTAL APPROACHES TO TREAT PCD

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Kerry Gove

Amanda Harris & Amanda Friend

Liz Adam & Claire Jackson

Anton Page & Patricia Goggin

Janice Coles & James Thompson

Peter Lackie

Samantha Packham

Lynn Reeves

Samuel Collins

Laura Behan

Bruna Rubbo

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