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SAPIENZA
UNIVERSITÀ DI ROMA



Nuovi Orizzonti in Pneumologia Pediatrica

Bronchiectasie / Discinesia Ciliare Primaria

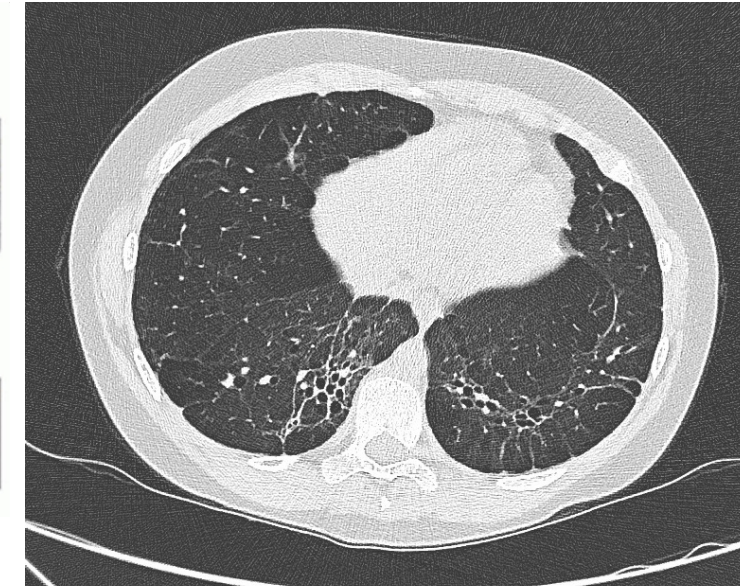
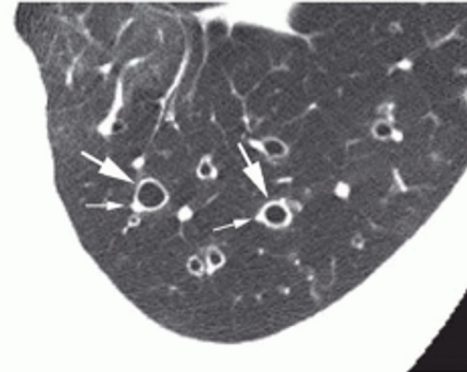
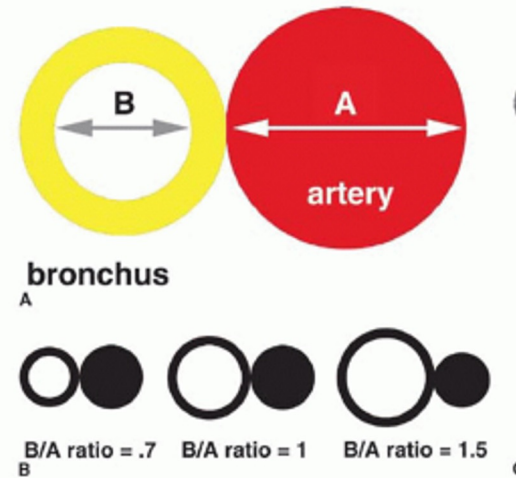
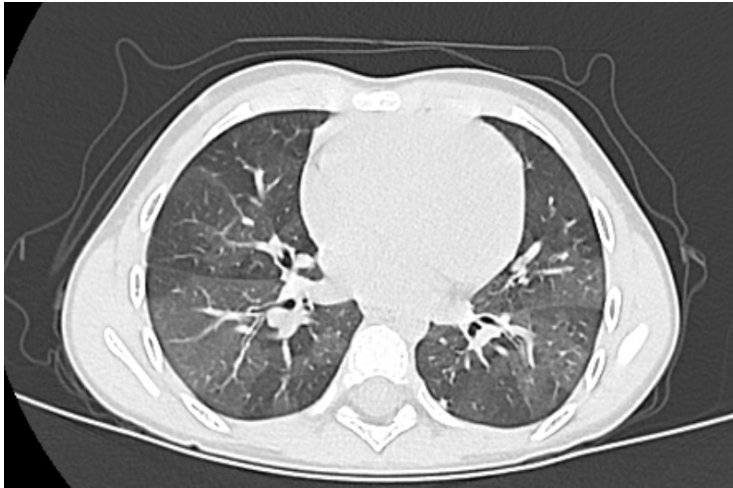
10 ottobre 2024

Laura Petrarca

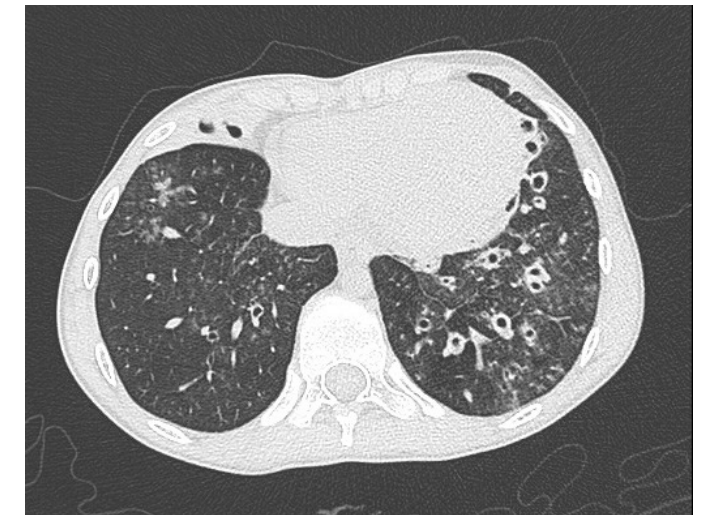
Dipartimento Materno Infantile e Scienze Urologiche

laura.petrarca@uniroma1.it

Bronchiectasie

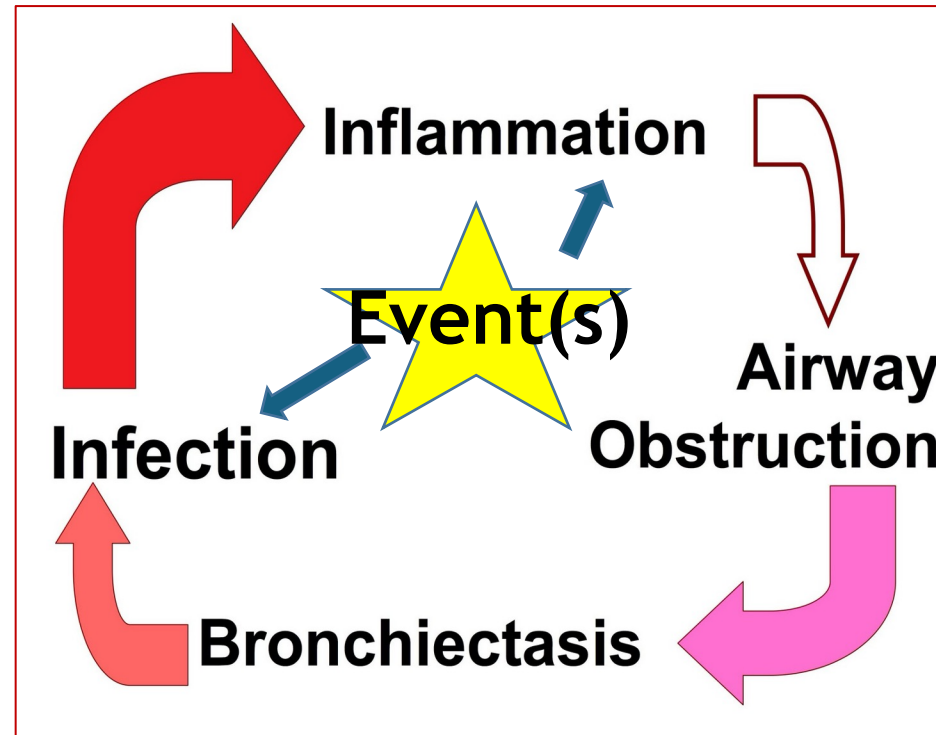
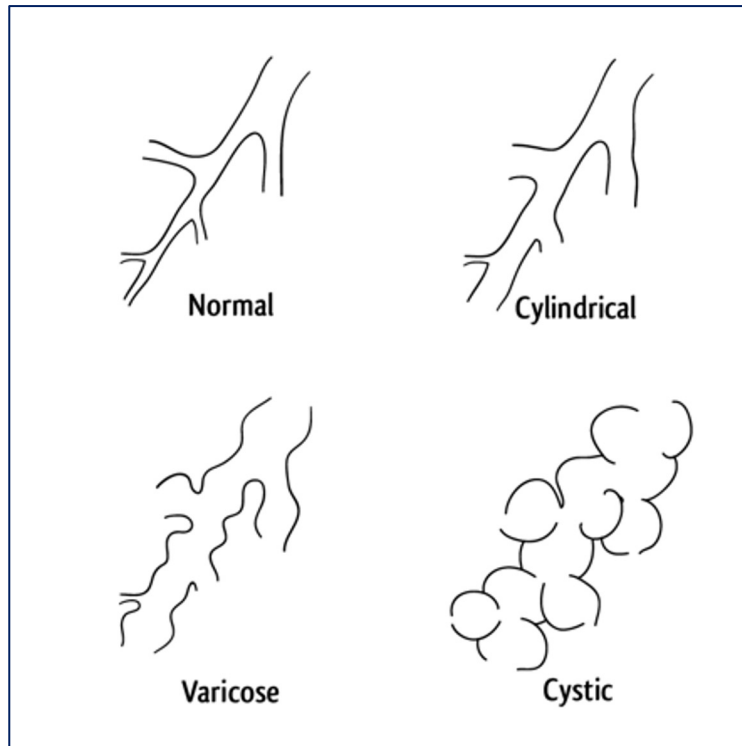


- Dilatazione dei bronchi alla TC torace BAR (bronchoarteriolar Ratio) >0.8
- Sintomi clinici: tosse produttiva, frequenti infezioni delle basse vie aeree/ riacutizzazioni

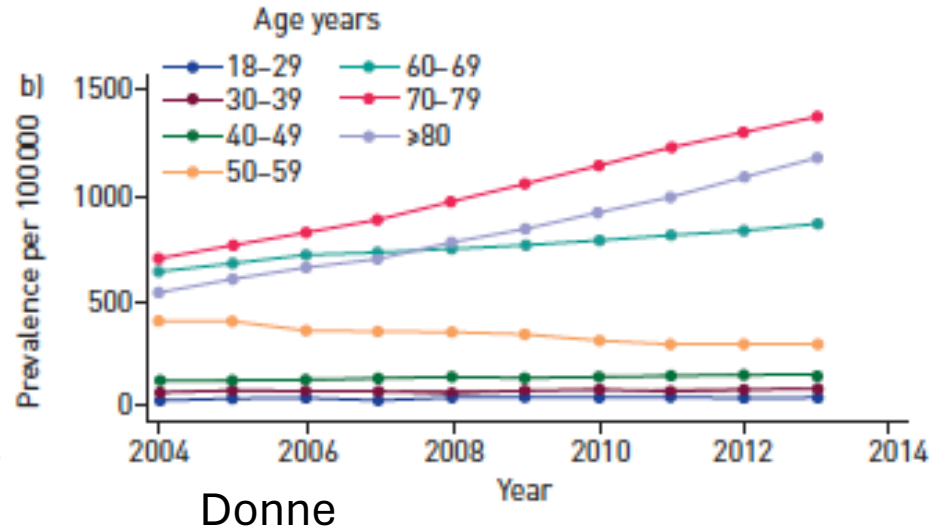
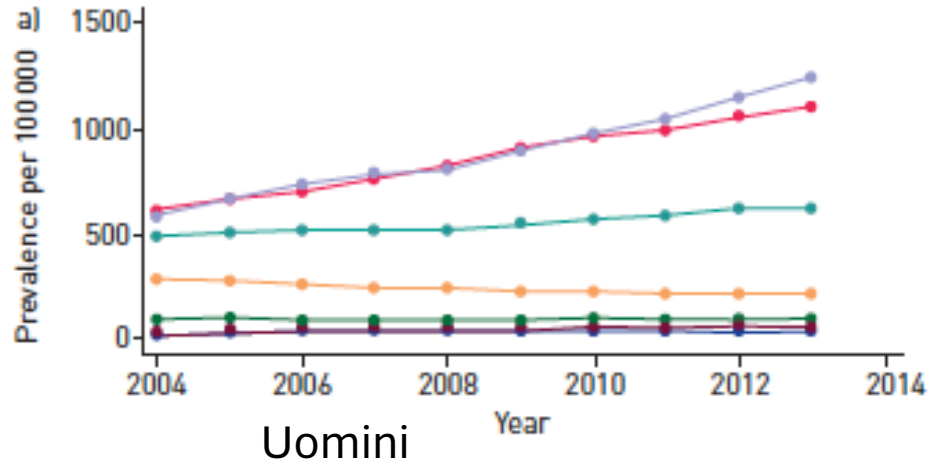




Bronchiectasie: fisiopatologia



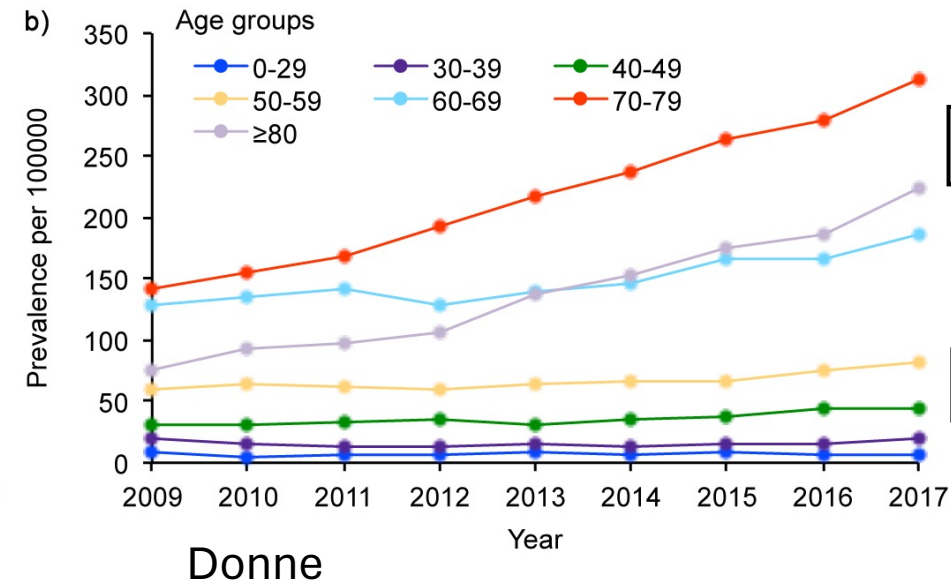
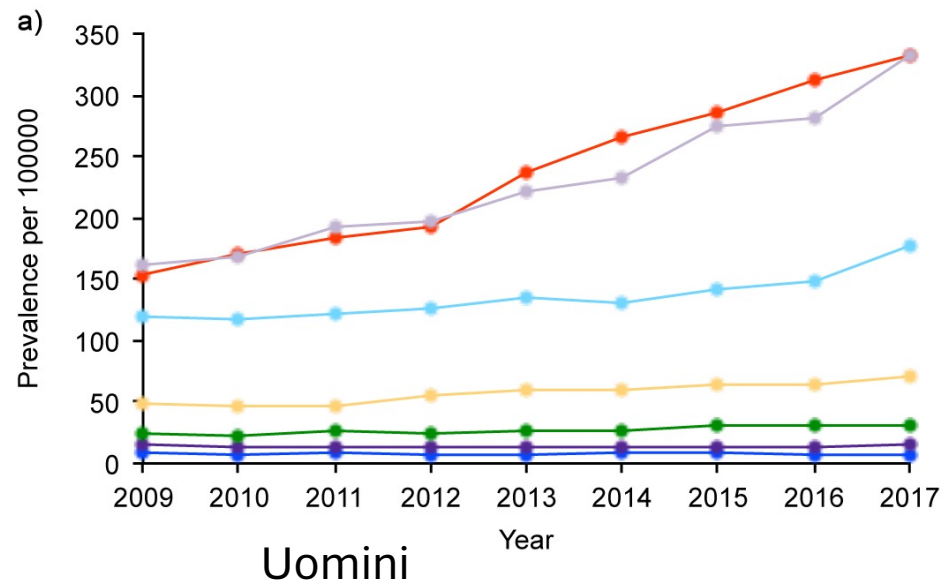
Incidenza/prevalenza bronchiectasie non FC



Incidenza 35,2 per 100000
persone/anno nel 2013
(adulti)

UK 2004-2013

Quint et al., ERJ 2016



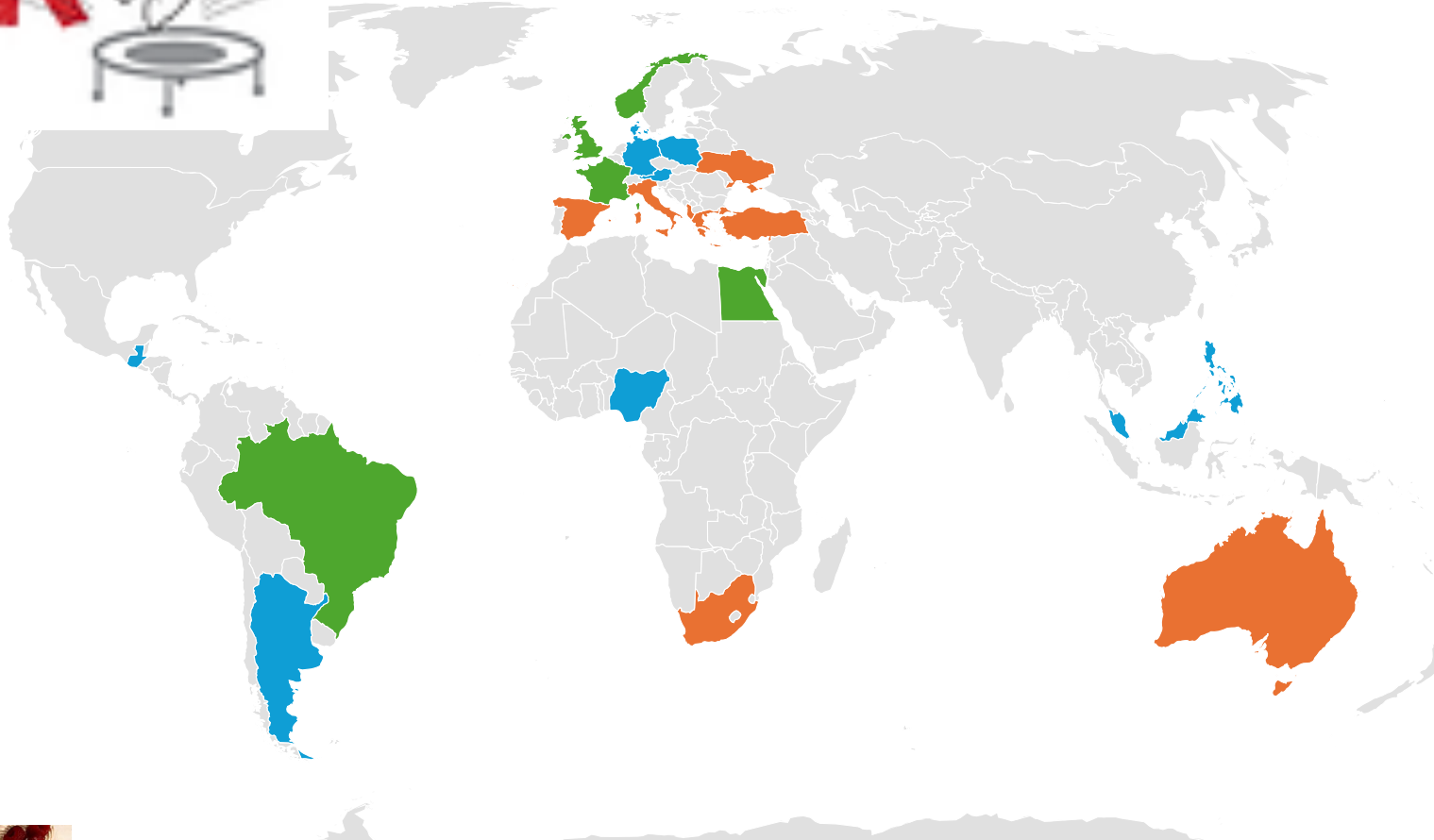
Germania 2009-2017

Ringshausen et al, ERJ 2019



Registry

- Collecting data
- Ethics and approval
- Discussions



CRC is an international collaboration with a goal to improve the care and clinical outcomes of children with bronchiectasis, formed under the auspices of the European Respiratory Society in 2021.

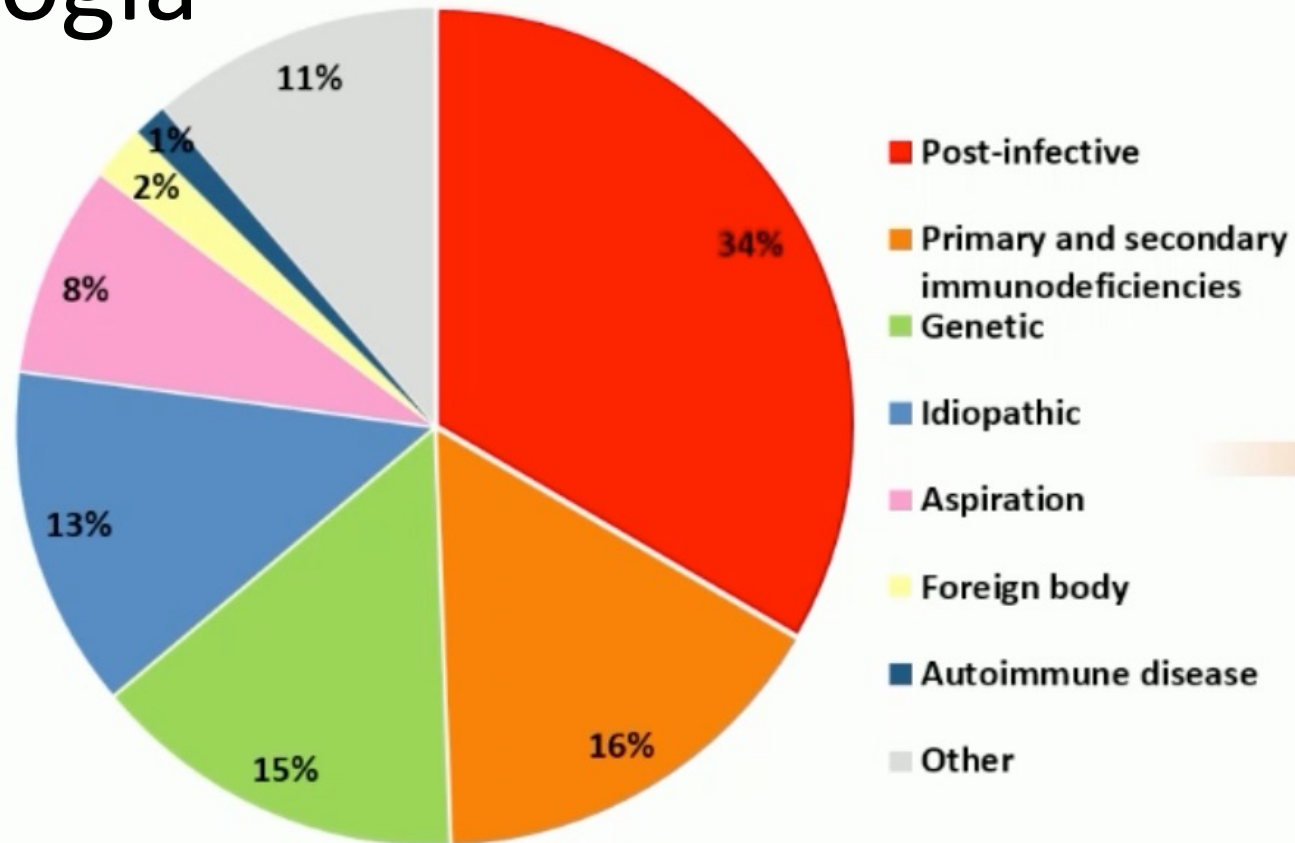
<https://www.improvebe.org/>



Total Cohort= 408

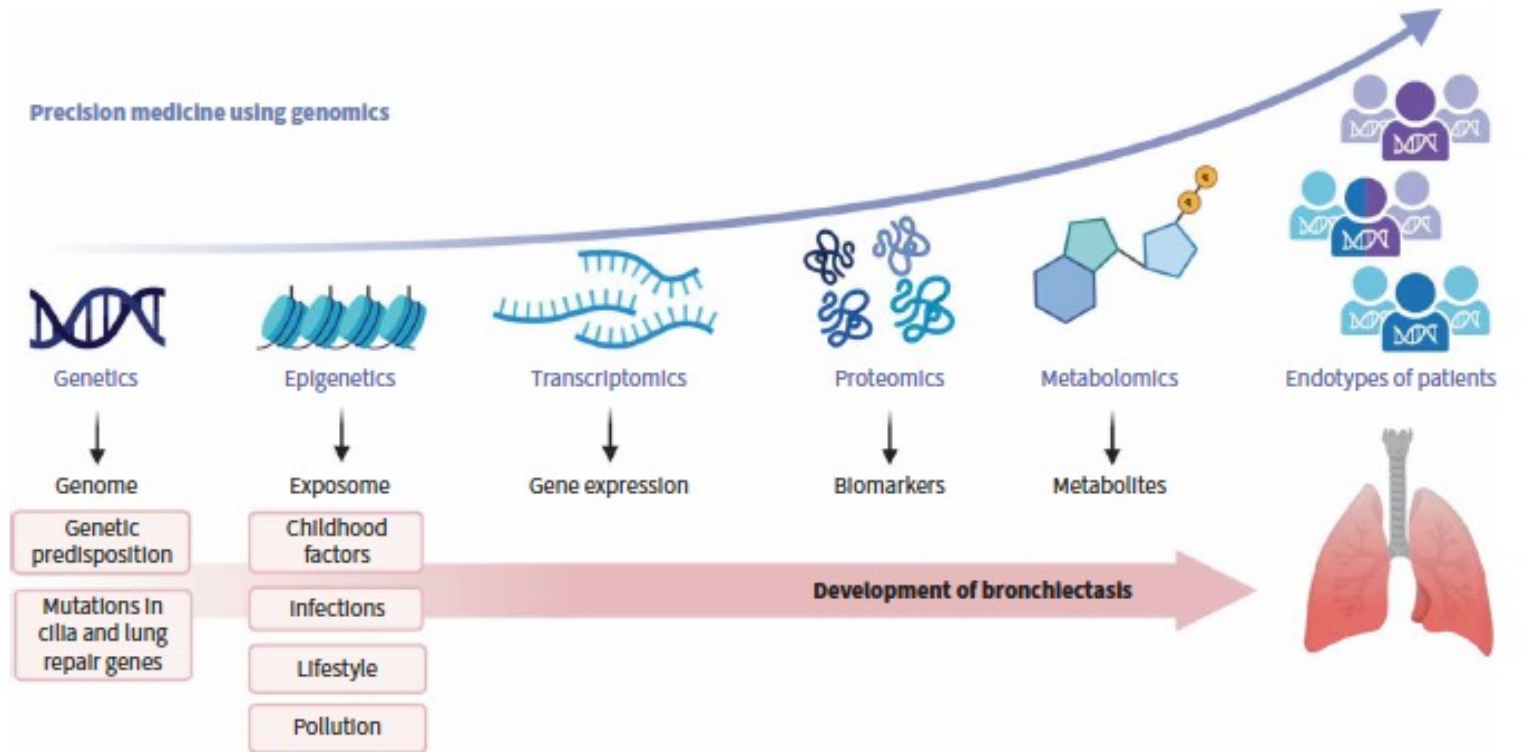
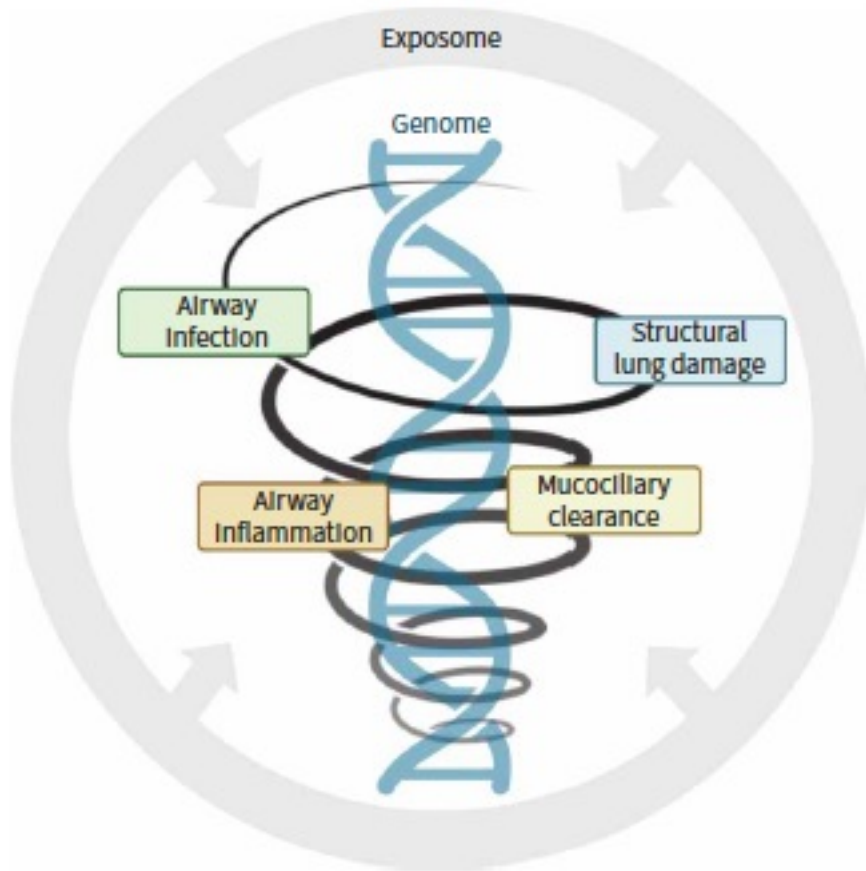
**South Africa
Albania/Turkey/Ukraine
Greece/Italy/Spain
Australia**

Eziologia



*Under review

Circolo vizioso di Cole modificato



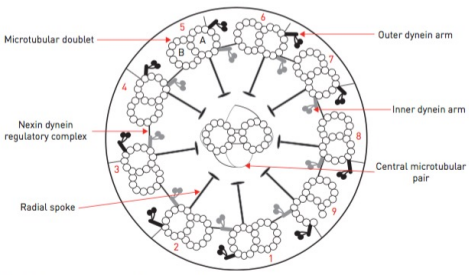
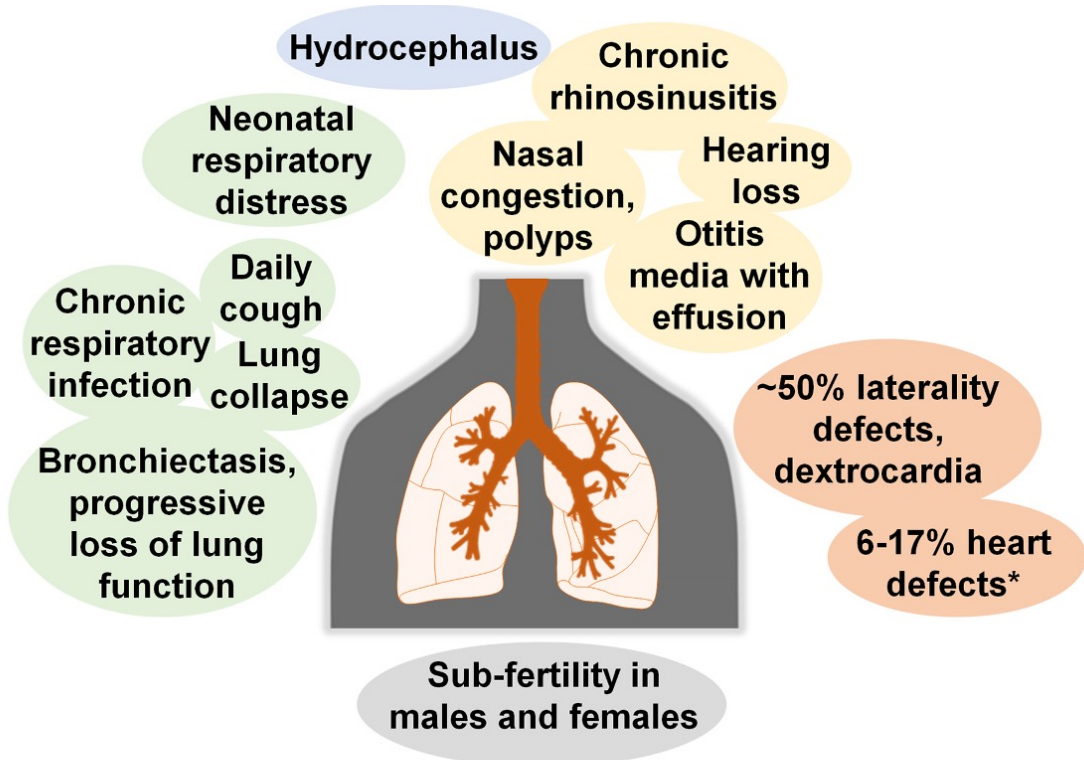
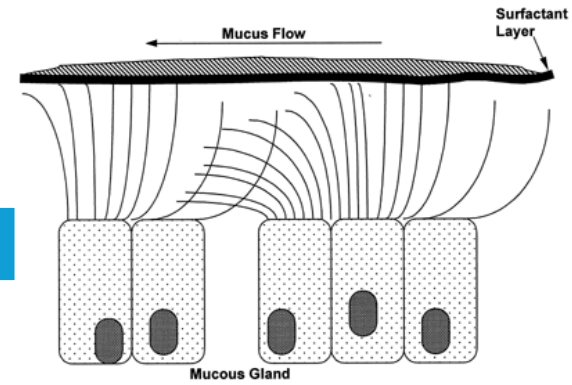


FIGURE 1 Diagram of normal ultrastructure of the ciliary axoneme in transverse section.

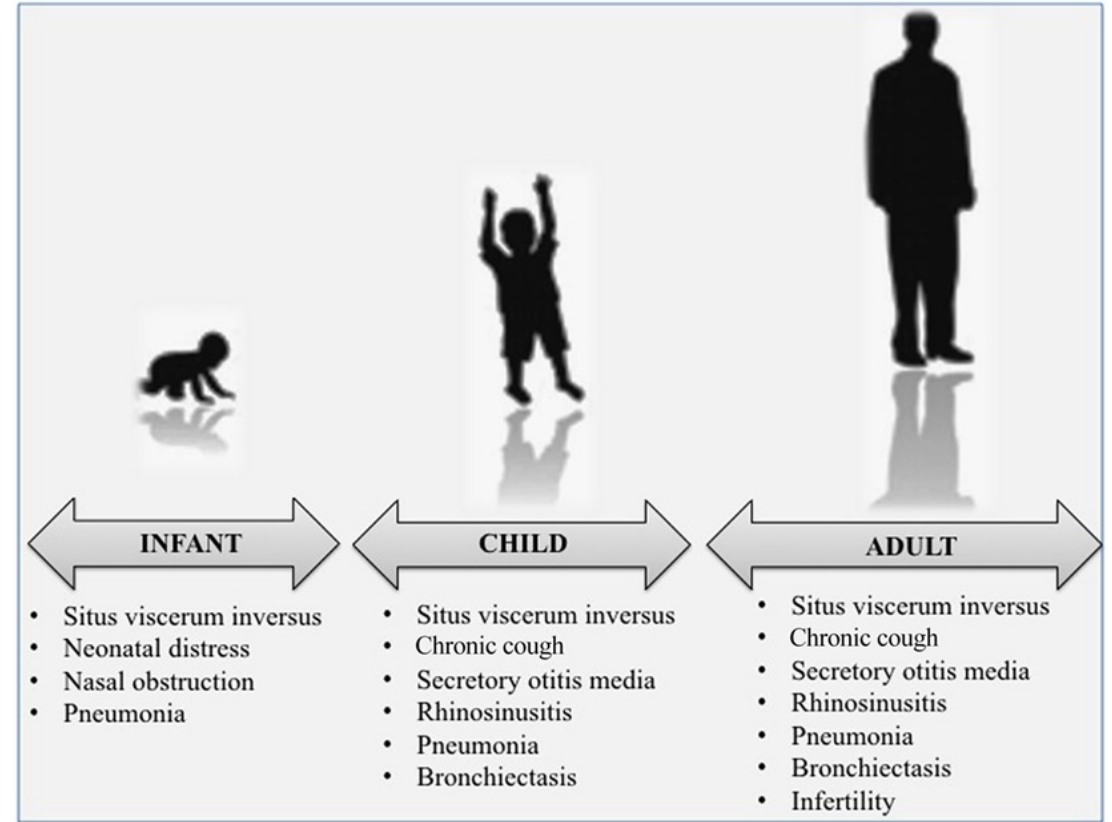
DISCINESIA CILIARE PRIMARIA

AR, AD, X-linked

Prevalenza 1:7500 nati vivi

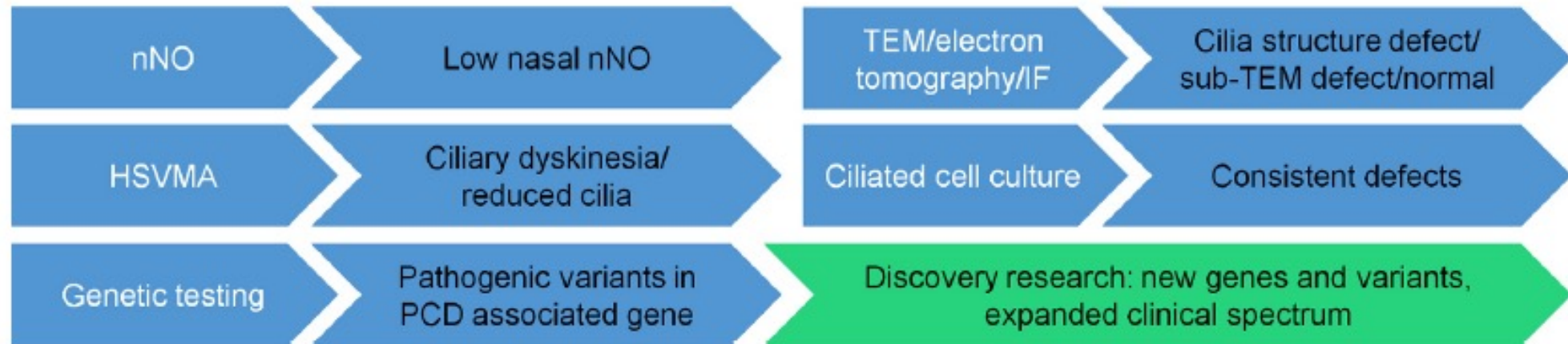


Legendre et al. Semin Cell Dev Biol. 2021

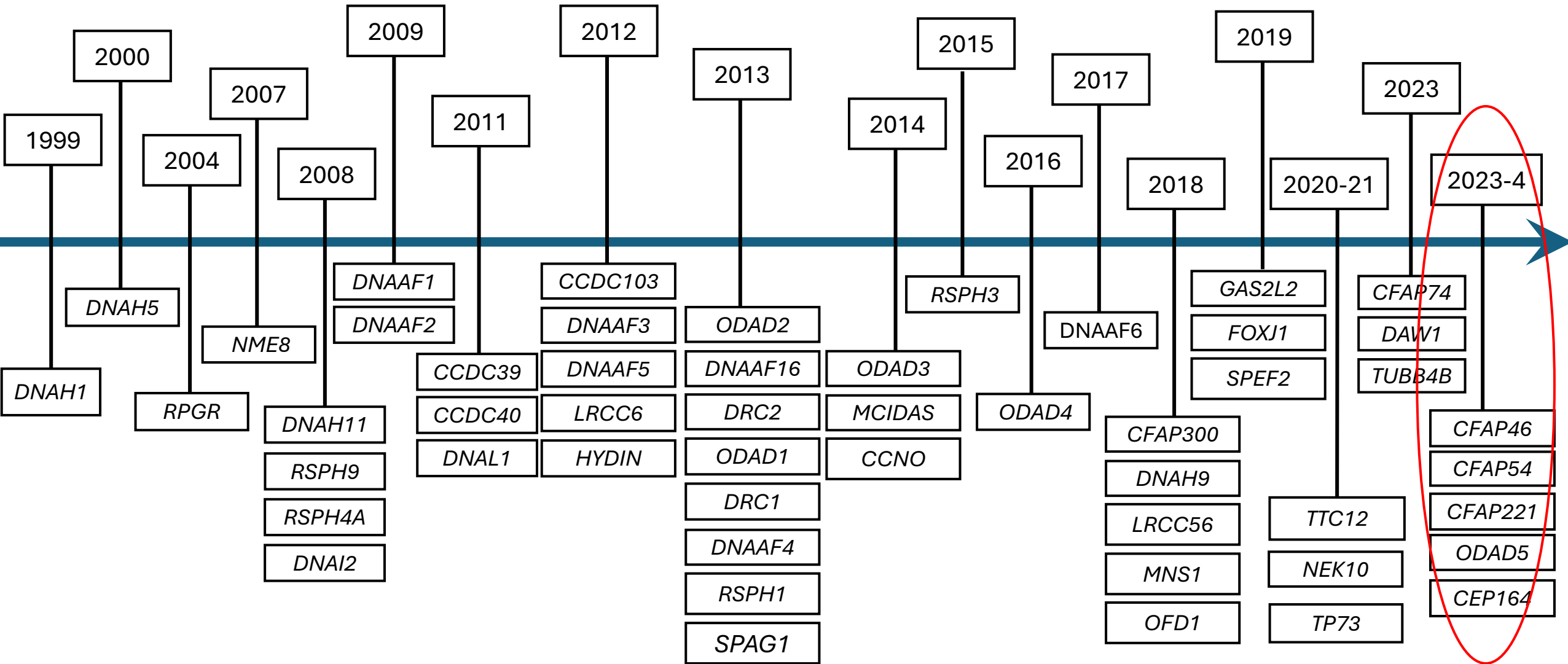


Mirra et al. Front. Pediatr 2017

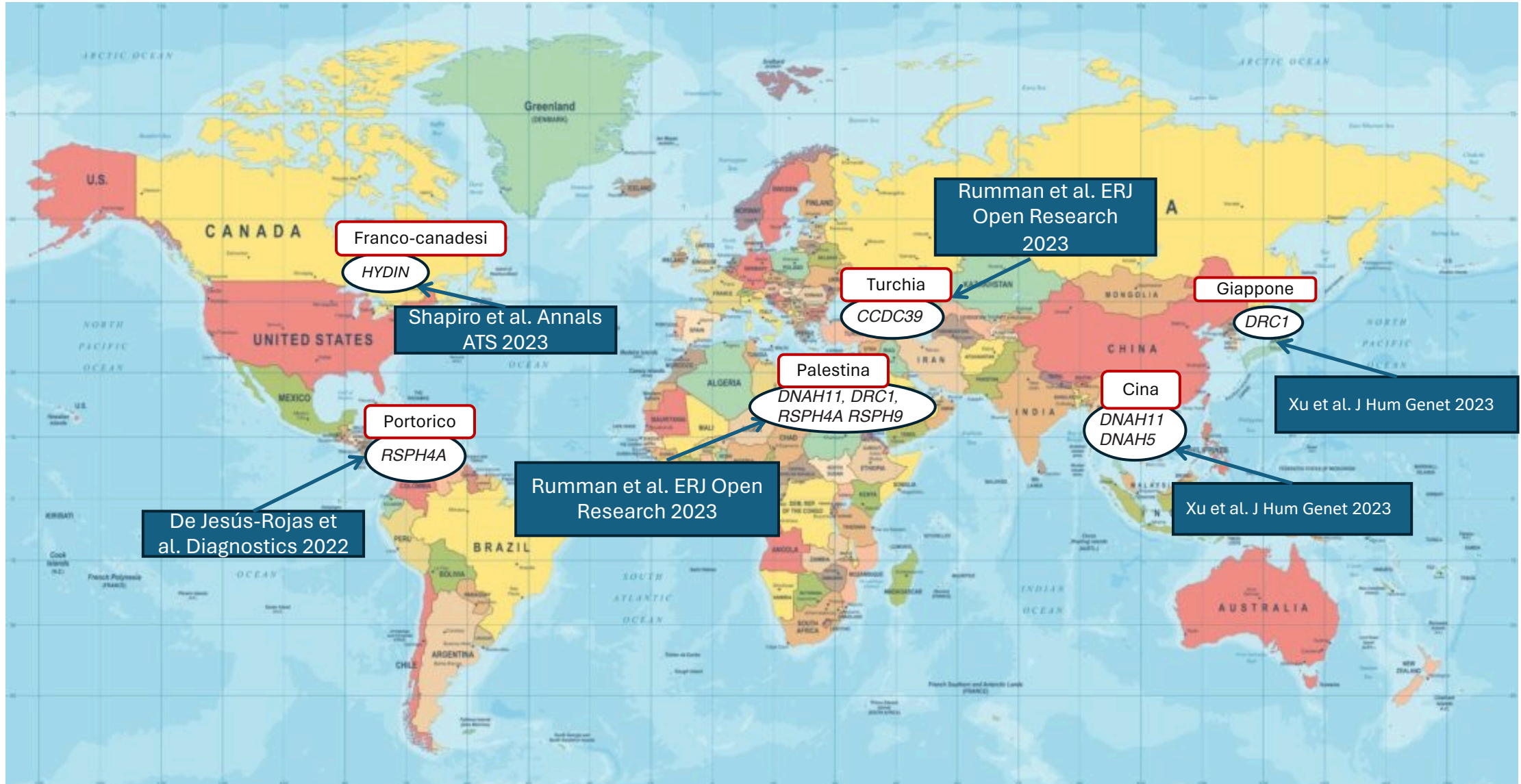
Strumenti diagnostici



Linea temporale dei geni identificati associati a DCP



Distribuzione mondiale dei geni responsabili di DCP



Distribuzione europea dei geni responsabili di DCP

1236 pz con DCP

Raidt et al ERJ 2024.

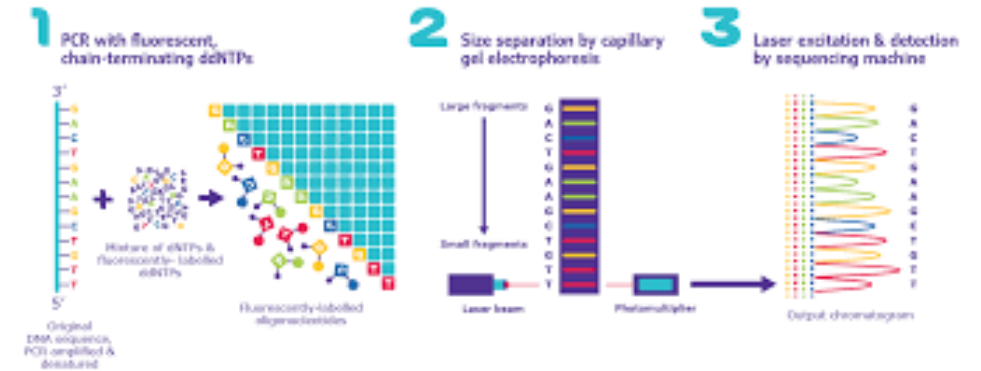


Variants

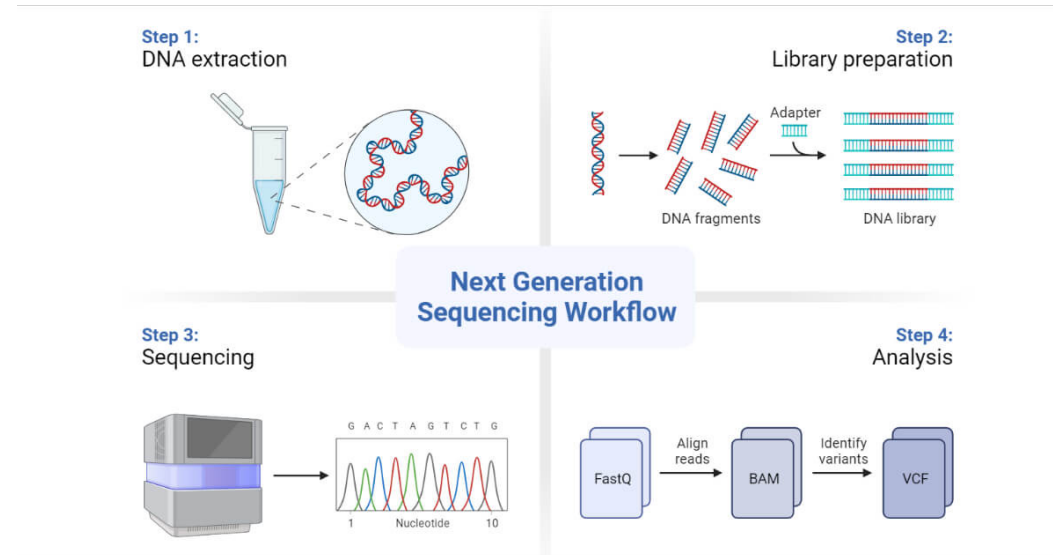
- No patient
- No single most frequent variant
- CCDC103:c.461A>C (22/306 variants, 0.0719)
- CCDC39:c.1871_1872del (6/24 variants, 0.25)
- CCDC40:c.248del (31/326 variants, 0.0951)
- CCDC40:c.552+6T>A (10/282 variants, 0.0355)
- CCNO:c.248_252dup (8/94 variants, 0.0851)
- DNAAF11:c.436G>C (18/186 variants, 0.0968)
- DNAI1:c.48+2dup (24/642 variants, 0.0374)
- ODAD1:c.742G>A (40/70 variants, 0.5714)
- RSPH1:c.85G>T (7/46 variants, 0.1522)
- RSPH9:c.670+2T>C (12/62 variants, 0.1935)
- SPAG1:c.2014C>T (46/330 variants, 0.1394)
- ZMYND10:c.47T>G (5/38 variants, 0.1316)

Genetica nella DCP

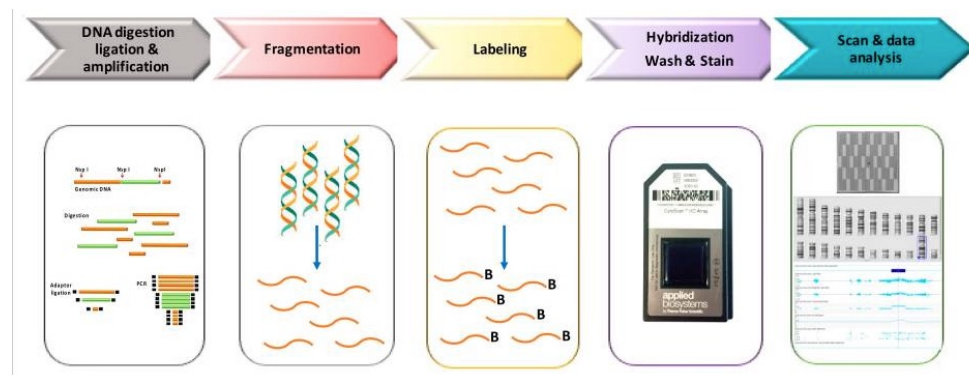
- Sanger



- NGS (WES; WGS)



- CNV (array)



Classificazione delle varianti (ACGM/AMP*)

Class 1	Pathogenic	} Diagnostici
Class 2	Likely pathogenic	
Class 3	Variant of uncertain significance (VUS)	????
Class 4	Likely benign	
Class 5	Benign	

*American college of medical genetics and genomics /association of medical pathology

La nostra casistica

39 diagnosi di DCP confermata

(21 maschi, età mediana 25,5 anni, Range 2,5- 54,3 anni)

Policlinico Umberto I di Roma e Spedali Civili di Brescia*

Caratteristiche cliniche	N (%)
Situs inversus viscerum	22/39 (56,4)
Rinite cronica	31/39 (79,5)
Sinusite	26/37 (70,3)
Distress respiratorio neonatale	18/39 (46,2)
Tosse cronica produttiva	32/39 (82,1)
Ipoacusia:	19/34 (55,9)
- Neurosensoriale	2
- Trasmissiva	11
- mista	6
Bronchiectasie	32/38 (84,2)
Difetto genetico noto	29/39 (74,4)

Ped Pulmonol
In press

* In collaborazione con IRCCS Casa Sollievo della Sofferenza – Mendel

CNV: CytoScan Xon array

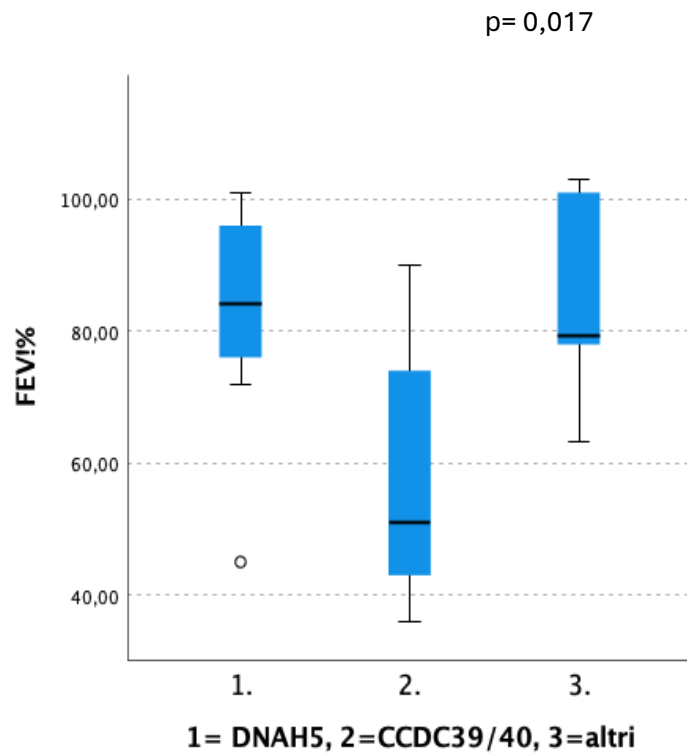
s e s s o	Data di nascita	Gene	NM	nucleotide	protein	dbSNP	tipo eredità	eredità	significato	genotipo conclusivo/non conclusivo	difetto TEM
M	23/05/80	DNAH5	NM_001369.2	c.5146C>T;	p.Arg1716Trp	rs368644722	het	mat	verosimilmente patogenetica	non conclusivo	ODA
F	11/01/92	DNAAF2	NM_018139	c.775C>T	p.Gln259*	r1293060723	het	mat	patogenetica	non conclusivo	IDA + ODA
		DNAAF3	NM178837.4	c.308A>T	p.Asp103Val	/	het	de novo	significato incerto		
M	16/12/01	NME8	NM_016616.5	c.454C>T	p.Gln152*	r199901385	het	?	significato incerto	non conclusivo	IDA + ODA
M	02/05/98	DNAH11	NM_001277115	c.5778+1G>A	/	r72657333	het	pat	patogenetica	non conclusivo	IDA + ODA
		DNAAF5	NM_017802	c.835C>T	p.Arg279Cys	r755305361	het	mat	significato incerto VUS		
		DNAH5	NM_001369	c.1206T>A	p.Asn402Lys	r140782270	het	pat	probabile variante benigna (LB su Varsome/US su intervar/US su Clinvar)		
M	23/10/68	DNAH5	NM_001369.3	c.4510G>C	p.(Gly1504Arg)	/	het	?	significato incerto	Non conclusivo	IDA + ODA

Duplicazione di 57 Kb che interessa gli esoni 57-75 [ISCN 2020]: arr[GRCh37] 5p15.2 (13712877-13769775)x3

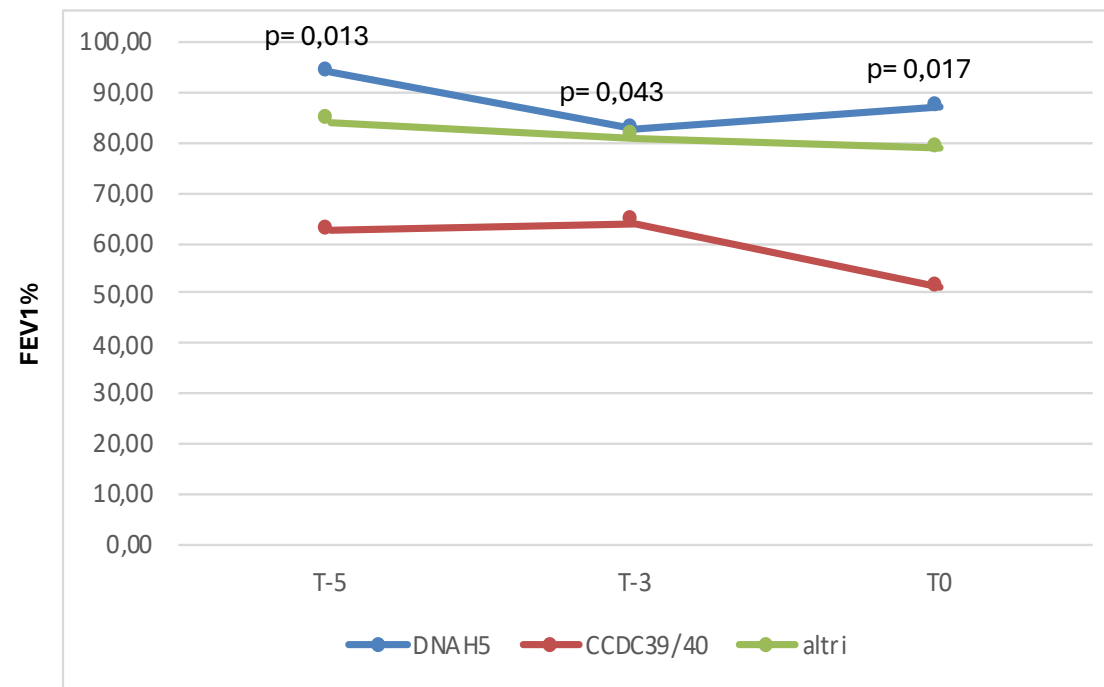
Correlazione genotipo-fenotipo

Caratteristiche cliniche	DNAH5 (8) N (%)	CCDC39/40 (9) N (%)	Altri (12) N (%)	p value
Situs inversus viscerum	5 (62,5)	5 (55,6)	5 (41,7)	0,634
Sinusite	7 (87,5)	7/8 (87,5)	6/11 (54,5)	0,158
Rinite cronica	8 (100)	8 (88,9)	9 (75,0)	0,272
Distress respiratorio neonatale	2 (25,0)	7 (77,8)	5 (41,7)	0,079
Ipoacusia	6/8 (75,0)	6/8 (75,0)	3/8 (37,5)	0,202
Deficit ventilatorio alla spirometria	2/8 (25,0)	8/9 (88,9)	5/9 (55,6)	0,029
Bronchiectasie	8 (100)	9 (100)	8/11 (72,7)	0,075
Pseudomonas aeruginosa	4 (50,0)	5 (55,6)	4/11 (39,3)	0,674

Variazione della funzionalità respiratoria nel tempo



a



b

DCP come causa non diagnosticata di bronchiectasie negli adulti?



EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
A. SHOEMARK ET AL.

Genome sequencing reveals underdiagnosis of primary ciliary dyskinesia in bronchiectasis

Amelia Shoemark ^{1,2,12}, Helen Griffin ^{3,12}, Gabrielle Wheway ⁴, Claire Hogg ², Jane S. Lucas ^{5,6}, Genomics England Research Consortium ^{7,14}, Carme Camps ^{8,9}, Jenny Taylor ^{8,9}, Mary Carroll ⁵, Michael R. Loebinger ², James D. Chalmers ¹, Deborah Morris-Rosendahl ¹⁰, Hannah M. Mitchison ^{11,13} and Anthony De Soyza ^{12,13}

Eur Respir J 2022; 60: 2200176

UK 100,000 Genomes Project

In 17/142 (12%) pazienti con bronchiectasie tramite WGS sono state trovate mutazioni patogenetiche o verosimilmente patogenetiche in geni responsabili di DCP.

Criteria di inclusione:

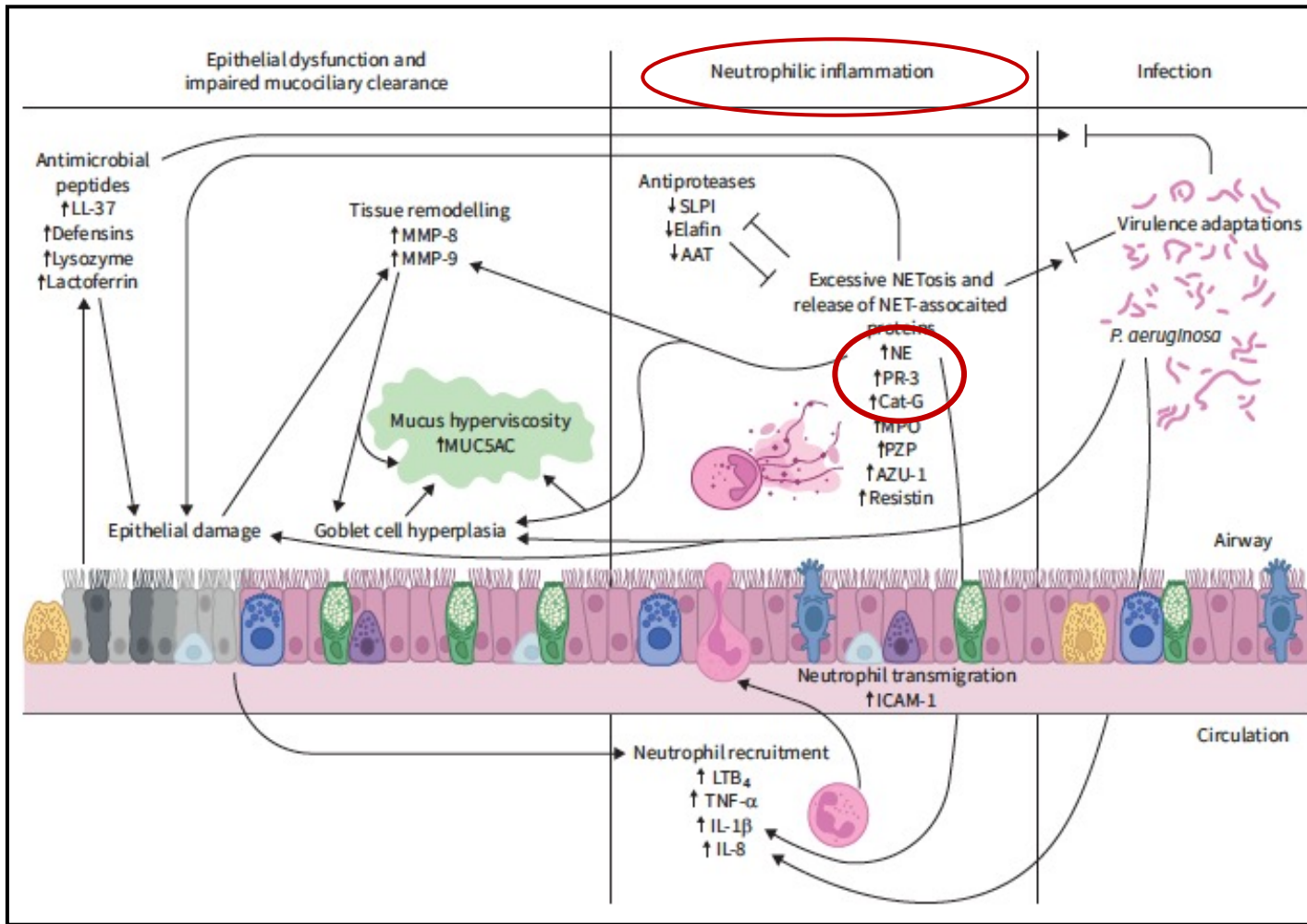
Pz con bronchiectasie non-FC + almeno uno dei seguenti:

- Malattia grave (FEV1 <30% del predetto),
- Età <50 anni
- Coinvolgimento di più lobi polmonari
- 2 o più membri della famiglia affetti
- Sospetta anomalia genetica

Nuove terapie BE/DCP

- Inibitori della inibitori della DPP1 (BE)
- Idrevloride (CLEAN-PCD)
- ETH42 (PCD)

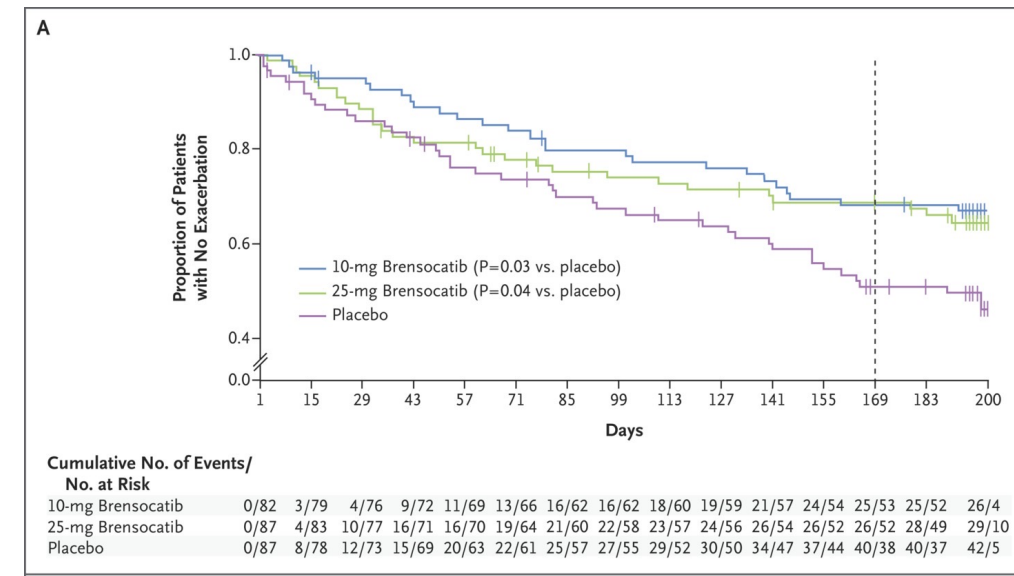
Inibitori della Catepsina/DPP1



Johnson et al Eur Resp Rev 2024; 33: 230234

Brensocatib Orale, selettivo, reversibile

WILLOW study (studio di fase 2)
solo adulti



Chalmers et al. NEJM 2020; 383: 2127-2137

ASPEN trial (studio di fase 3) ha
incluso adolescenti, in press

Idrevloride (CLEAN-PCD)

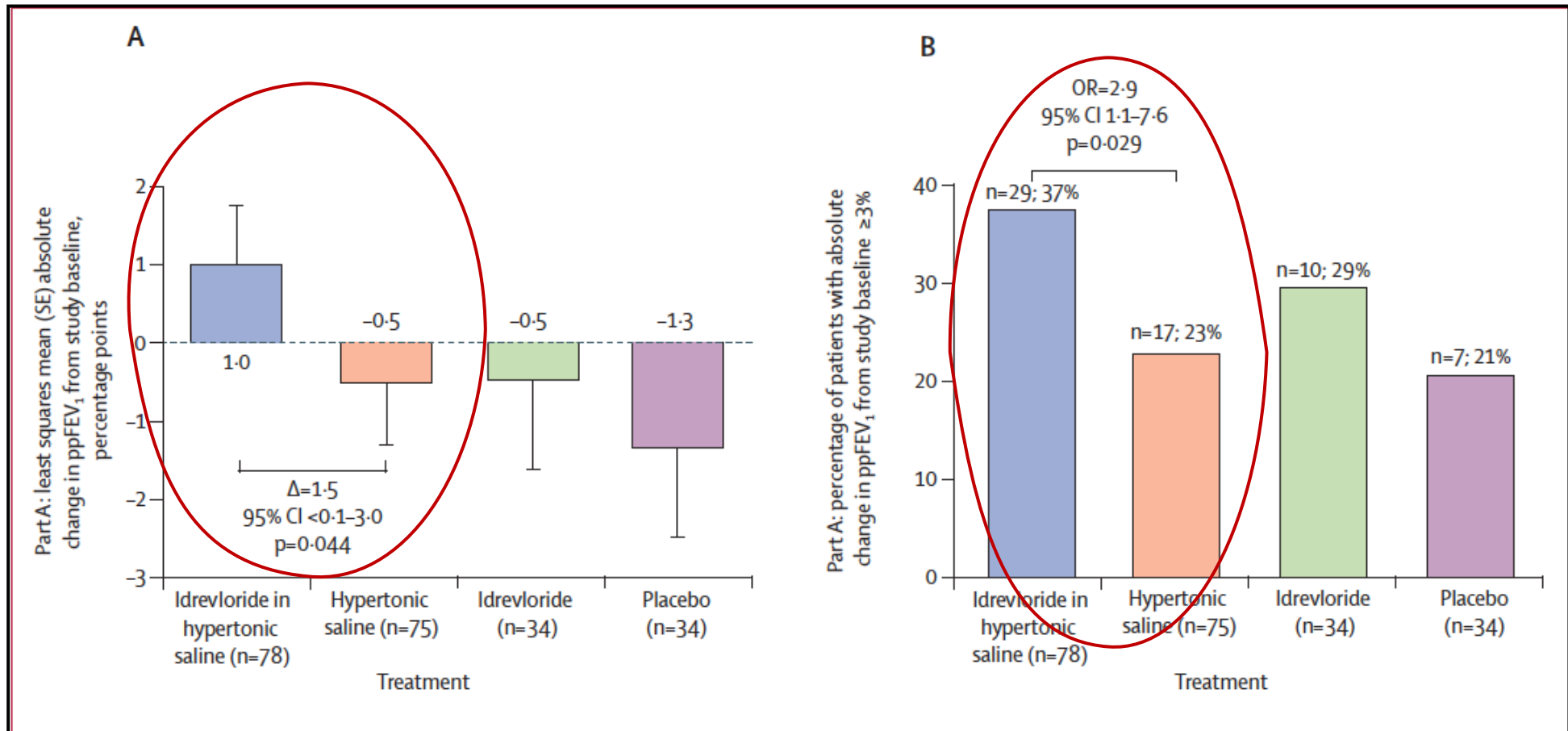
- Phase 2, randomised, double-blind, placebo-controlled crossover trial
- Inalatorio
- blocca il canale del sodio epiteliale (ENaC) → «idrata» il liquido sulla superficie delle cellule epiteliali in vitro (> con soluzione ipertonica).

	Idrevloride in hypertonic saline (N=43)	Hypertonic saline (N=41)	Idrevloride (N=21)	Placebo (N=18)	Overall (N=123)
Age at screening visit, years	29.2 (10.9)	28.0 (13.1)	27.6 (16.6)	24.3 (12.9)	27.8 (12.9)
Aged younger than 18 years	8 (19%)	14 (34%)	8 (38%)	6 (33%)	36 (29%)
Aged younger than 18 years with bronchiectasis	5 (63%)	12 (86%)	7 (88%)	3 (50%)	27 (75%)
Sex					
Male	14 (33%)	17 (41%)	6 (29%)	8 (44%)	45 (37%)
Female	29 (67%)	24 (59%)	15 (71%)	10 (56%)	78 (63%)
Race					
White	39 (91%)	36 (88%)	17 (81%)	14 (78%)	106 (86%)
Black	2 (5%)	1 (2%)	1 (5%)	1 (6%)	5 (4%)
Asian	1 (2%)	3 (7%)	1 (5%)	3 (17%)	8 (7%)
Other	1 (2%)	1 (2%)	2 (10%)	0	4 (3%)
Height, cm	169 (10.2)	166 (11.2)	166 (11.7)	166 (11.1)	167 (10.9)
BMI, kg/m ²	22.5 (3.2)	23.0 (5.7)	21.8 (3.0)	21.6 (3.7)	22.4 (4.2)
Percentage of predicted FEV ₁	65.2 (13.6)	67.7 (13.9)	63.3 (13.3)	68.0 (13.7)	66.1 (13.6)
Percentage of predicted forced vital capacity	83.6 (11.6)	84.1 (12.2)	82.7 (14.2)	84.3 (13.4)	83.7 (12.5)
Percentage of predicted mid-maximal expiratory flow rates	39.3 (18.2)	39.4 (18.2)	38.5 (15.2)	38.5 (15.5)	39.1 (17.3)
Mean historical nasal nitric oxide, nL/min	20 (25); n=32	19 (14); n=25	17 (10); n=15	24 (43); n=12	20 (23); n=84
Median historical nasal nitric oxide, nL/min	14 (9–21)	14 (11–32)	15 (10–25)	9 (3–36)	14 (8–24)
Laterality defect	17 (40%)	18 (44%)	5 (24%)	8 (44%)	48 (39%)

Data shown as mean (SD) or n (%). The number of participants who had historical nasal nitric oxide values is noted and median (IQR) is reported for nasal nitric oxide only, because the distribution is skewed.

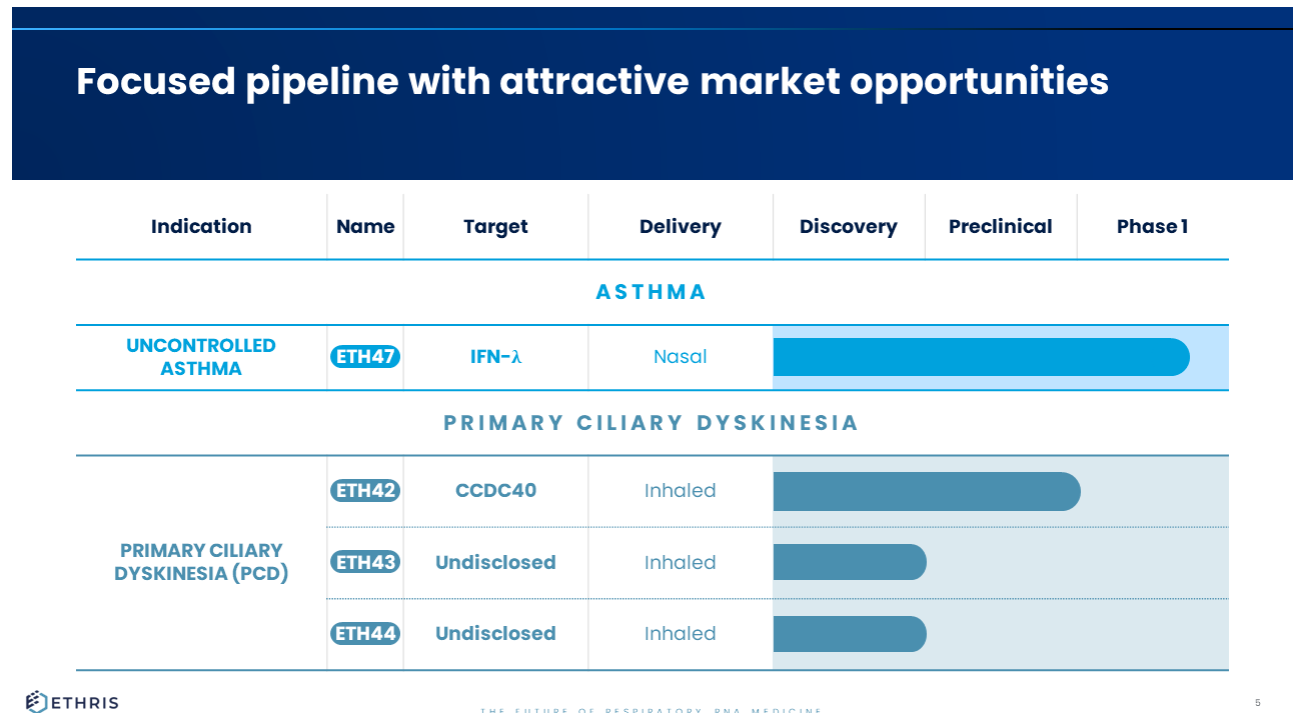
Table 1: Demographic and baseline characteristics of participants, overall and segregated by period 1 treatment

CLEAN- PCD



ETH 42: mRNA inalatorio per pazienti con mutazioni in CCDC40

- **ETH42 Stabilized Non-Immunogenic mRNA (SNIM® RNA) platform** includes a toolbox of technologies to generate mRNA molecules that have low immunogenicity, maximum potency and superior production yields.



Conclusioni

- ✓ L'eziologia delle bronchiectasie non legate alla fibrosi cistica è in continua evoluzione (interazione tra ambiente e genetica)
- ✓ Una delle cause frequenti delle bronchiectasie non FC è la discinesia ciliare primaria (DCP), in cui nessun test diagnostico da solo rappresenta attualmente il gold standard per la diagnosi
- ✓ La combinazione di più test genetici (NGS+CNV) permette di migliorare la capacità diagnostica nella DCP (AR)
- ✓ Nuove terapie promettenti in fase di studio



Grazie!!!

CHILDREN'S BEAR NETWORK

Children's **B**ronchiectasis **E**ducation
Advocacy and **R**esearch Network



Visit our website (improvebe.org) for more information, frequently asked questions, information on our registry and links to resources.



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Email: childbearnnet@qut.edu.au