

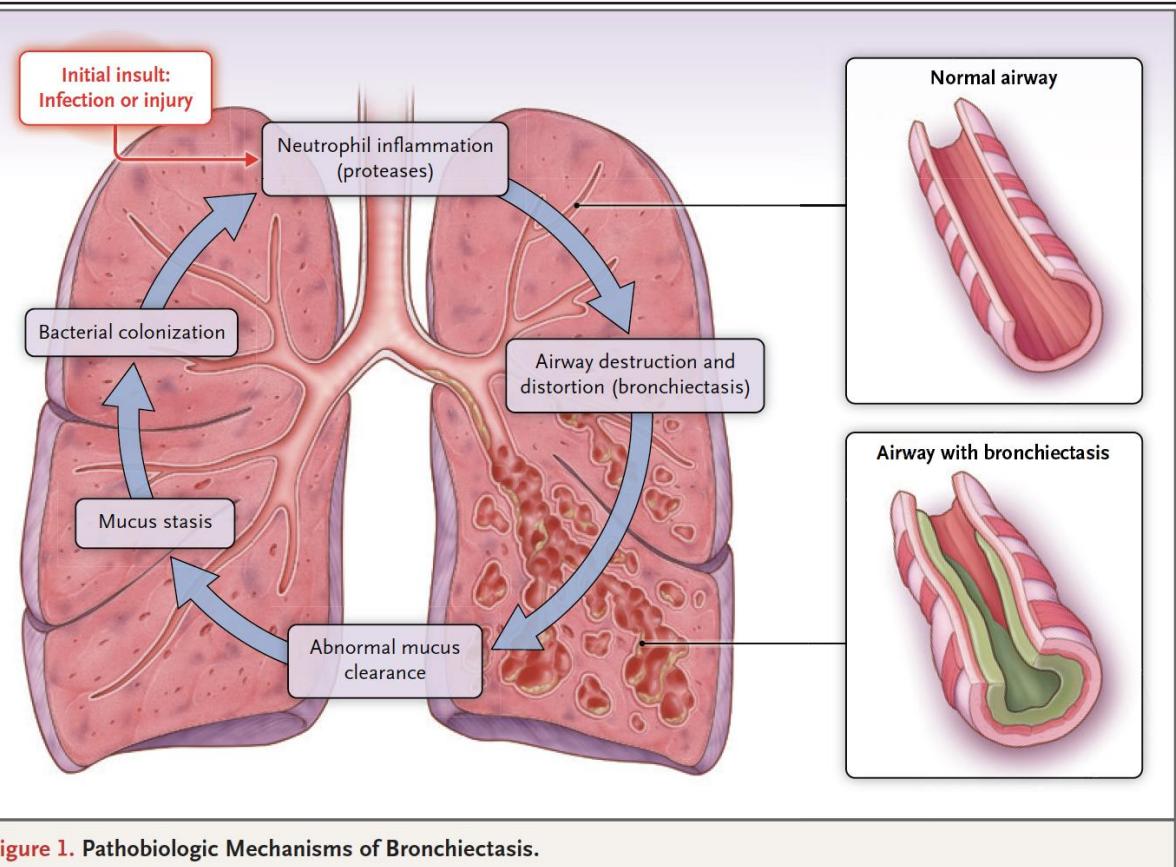
# Les bronchectasies diffuses hors mucoviscidose, des thérapeutiques spécifiques?

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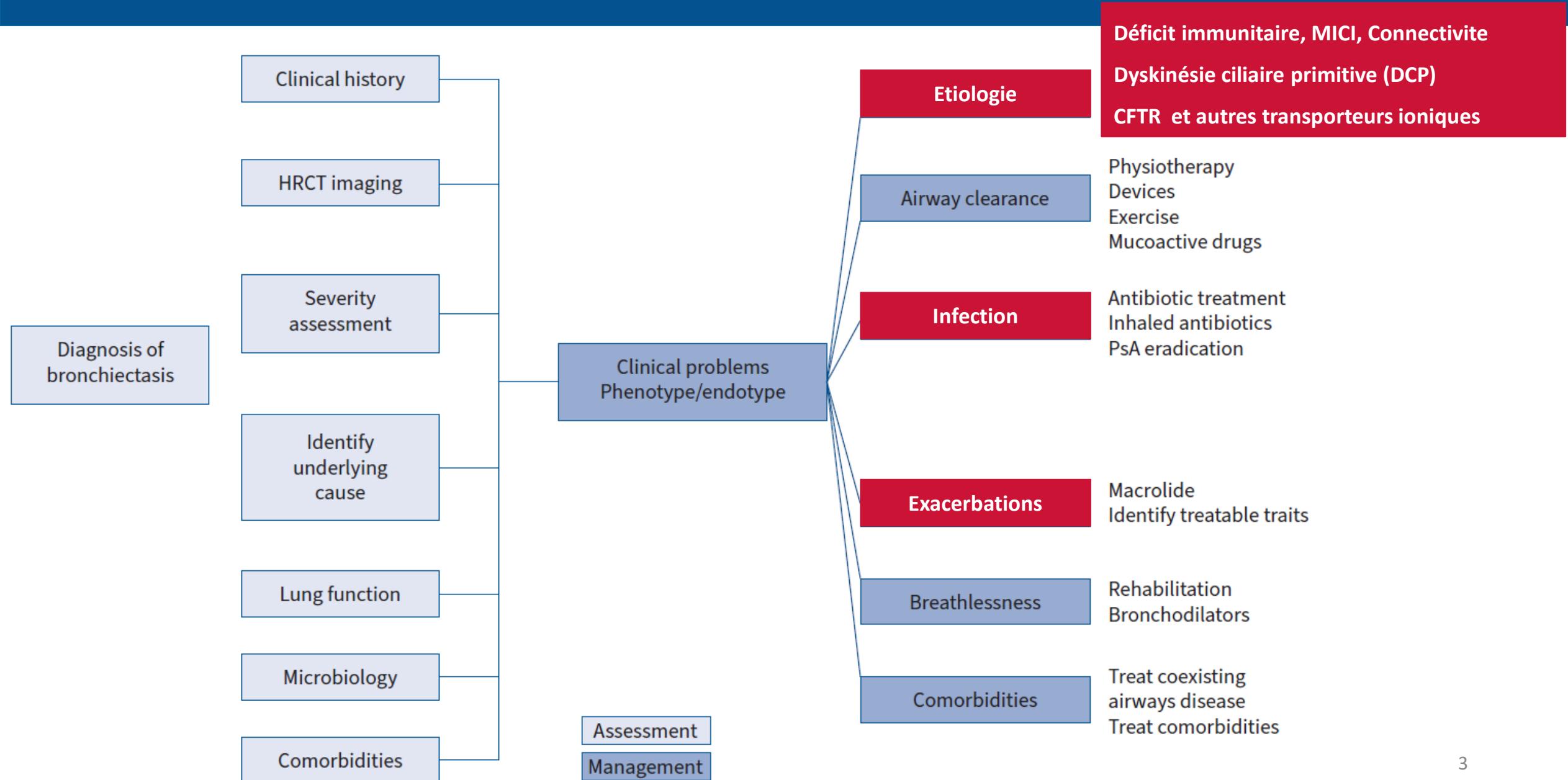
# Bronchiectasies diffuses



**Table 1. Prognosis Scoring in Patients with Bronchiectasis, According to Two Scales.**

Factor	Bronchiectasis Severity Index*		FACED Scale†	
	Value	Score	Value	Score
Forced expiratory velocity in 1 sec	>80%	0	≥50%	0
	50–80%	1	<50%	2
	30–49%	2		
	<30%	3		
Age	<50 yr	0	<70 yr	0
	50–69 yr	2	≥70 yr	2
	70–79 yr	4		
	≥80 yr	6		
Chronic <i>Pseudomonas aeruginosa</i> infection	No	0	No	0
	Yes	3	Yes	1
No. of involved lobes	<3	0	1 or 2	0
	≥3	1	>2	1
Dyspnea scale‡	0	0	0, I, or II	0
	2	2	III or IV	1
	3	3		
Hospital admission	No	0	—	—
	Yes	5		
Annual exacerbations	None	0	—	—
	1 or 2	0		
	≥3	2		
Colonization with other organisms	No	0	—	—
	Yes	1		
Body-mass index§	<18.5	2	—	—
	18.5–25	0		
	26–29	0		
	≥30	0		
Total score range		0–26	0–7	

# Bronchiectasies diffuses « Treatable Traits »



# Bronchectasies diffuses : Diagnostic étiologique

## Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity

40 to 60% of idiopathic bronchiectasis

Table 2. Etiology of bronchiectasis among the entire population and according to severity of disease

	Entire Study Population	Mild Disease	Moderate Disease	Severe Disease	P Value*
Postinfective	1,258 (100)	394 (100)	506 (100)	358 (100)	
	257 (20)	88 (22)	104 (21)	65 (18)	0.364
COPD	129 (15)	11 (2.8)	41 (8.1)	77 (22)	<0.001
Connective tissue disease	128 (10)	35 (8.9)	62 (12)	31 (8.7)	0.131
Immunodeficiency	73 (5.8)	26 (6.6)	32 (6.3)	15 (4.2)	0.299
Asthma	41 (3.3)	12 (3)	22 (4.3)	7 (2)	0.143
ABPA	56 (4.5)	13 (3.3)	23 (4.5)	20 (5.6)	0.313
Ciliary dysfunction	21 (1.7)	11 (2.8)	8 (1.6)	2 (0.6)	0.567
Inflammatory bowel disease	24 (1.9)	14 (3.6)	5 (1)	5 (1.4)	0.014
Aspiration/esophageal reflux	8 (0.6)	1 (0.3)	1 (0.2)	6 (1.7)	0.014
Congenital malformation	7 (0.6)	2 (0.5)	3 (0.6)	2 (0.6)	0.986
$\alpha_1$ -Antitrypsin deficiency	8 (0.6)	3 (0.8)	3 (0.6)	2 (0.6)	0.929
Obstructive	2 (0.2)	1 (0.3)	1 (0.2)	0 (0)	0.657
Pink disease	1 (0.1)	0 (0)	1 (0.2)	0 (0)	0.475
Yellow nail syndrome	1 (0.1)	0 (0)	0 (0)	1 (0.3)	0.284
Idiopathic	502 (40)	176 (45)	200 (40)	126 (35)	0.029

Definition of abbreviations: ABPA = allergic bronchopulmonary aspergillosis; BSI = Bronchiectasis Severity Index; COPD = chronic obstructive pulmonary disease.

\*Among groups: mild = BSI score 0–4; moderate = BSI score 5–8; severe = BSI score ≥9.

## Adult Patients With Bronchiectasis

### A First Look at the US Bronchiectasis Research Registry

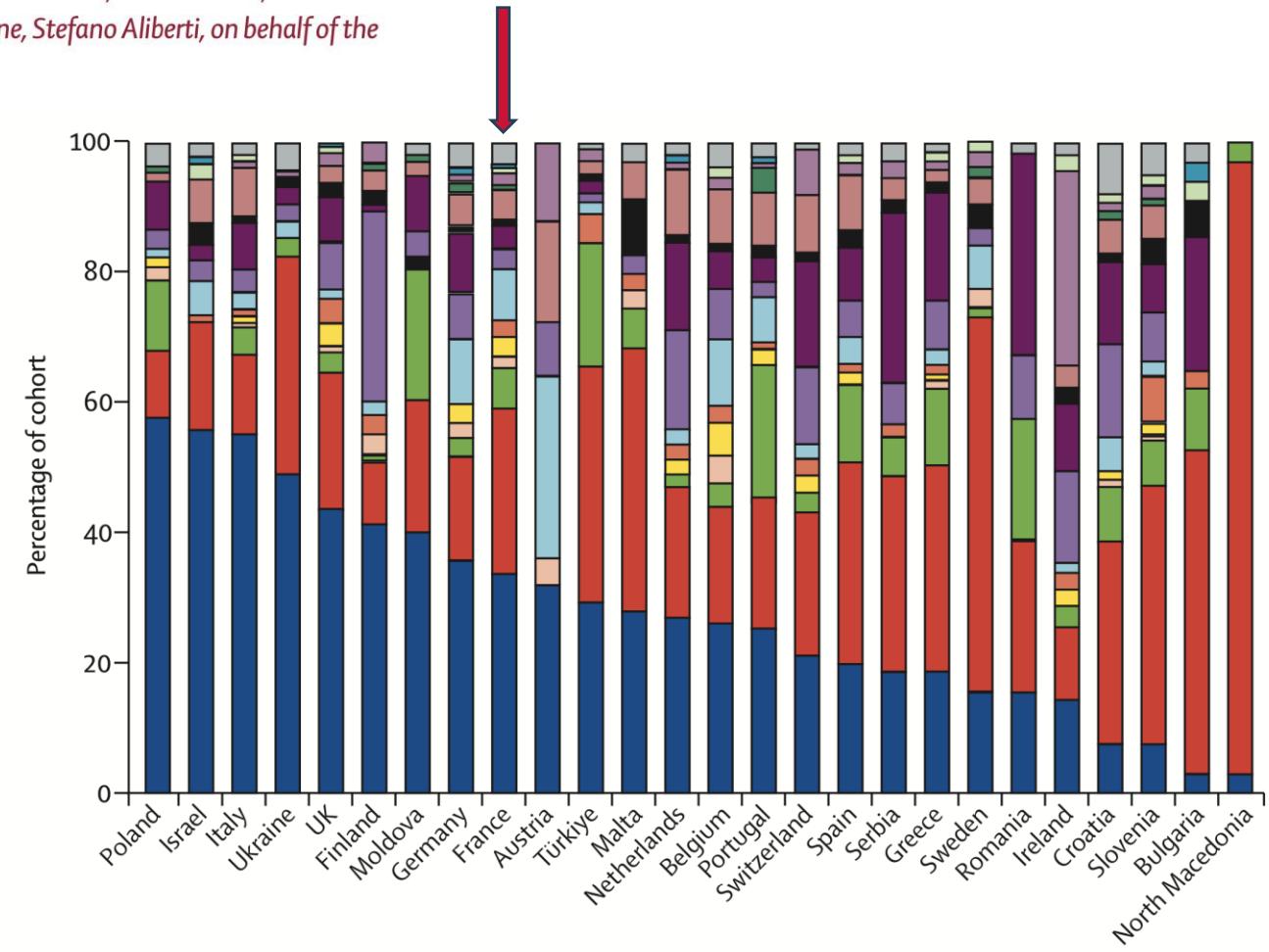
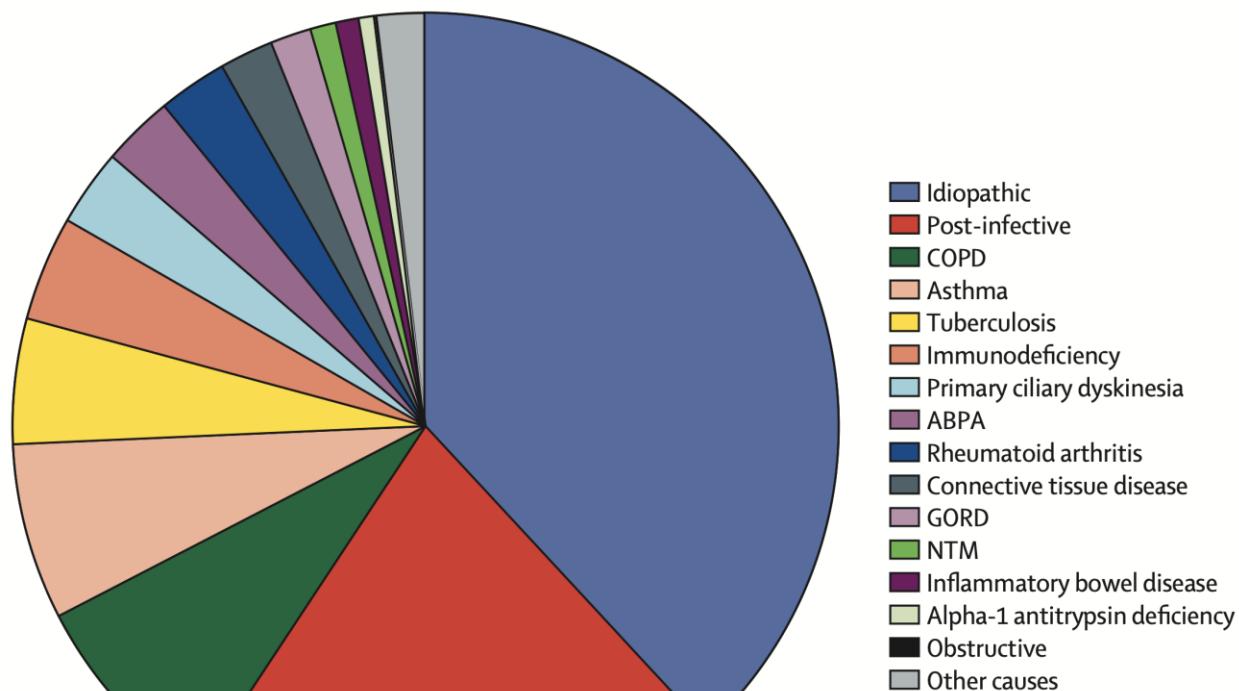
Around 68% of « idiopathic » bronchiectasis

Comorbidities, No. (%)	Data Available (No.)	Overall (N = 1,826)	NTM (n = 1,158)	No NTM (n = 668)	P Value <sup>b</sup>
History of pneumonia	1,745	1,187 (68)	758 (69)	429 (67)	.45
COPD	1,778	350 (20)	217 (19)	133 (20)	.60
Asthma	1,783	515 (29)	298 (26)	217 (33)	< .01
GERD	1,789	841 (47)	577 (51)	264 (40)	< .01
Rheumatologic disease	1,775	142 (8)	87 (8)	55 (8)	.60
Chronic ulcerative colitis or Crohn's disease	1,795	47 (3)	26 (2)	21 (3)	.25
Primary immunodeficiency	1,776	89 (5)	44 (4)	45 (7)	< .01
Primary ciliary dyskinesia	1,791	52 (3)	20 (2)	32 (5)	< .01

# Bronchectasies diffuses : Diagnostic étiologique

## Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC)

James D Chalmers, Eva Polverino, Megan L Crichton, Felix C Ringshausen, Anthony De Soyza, Montserrat Vendrell, Pierre Régis Burgel, Charles S Haworth, Michael R Loebinger, Katerina Dimakou, Marlene Murris, Robert Wilson, Adam T Hill, Rosario Menendez, Antoni Torres, Tobias Welte, Francesco Blasi, Josje Altenburg, Michal Shtenberg, Wim Boersma, J Stuart Elborn, Pieter C Goeminne, Stefano Aliberti, on behalf of the EMBARC Registry Investigators



# Dyskinésies ciliaires primitives : Sous diagnostic?

## Genome sequencing reveals underdiagnosis of primary ciliary dyskinesia in bronchiectasis

Etude observationnelle (UK 100,000 Genomes Project) – Bronchectasies idiopathiques (exclusion des suspicions cliniques de DCP) – Whole genome sequencing

17 patients parmi 142 (12%) étaient porteurs de variants de gènes impliqués ou potentiellement impliqués dans la motilité ciliaire.

British Thoracic Society audit

Parmi 4898 patients porteurs de bronchectasies audités :

<2% avaient été testés pour la DCP

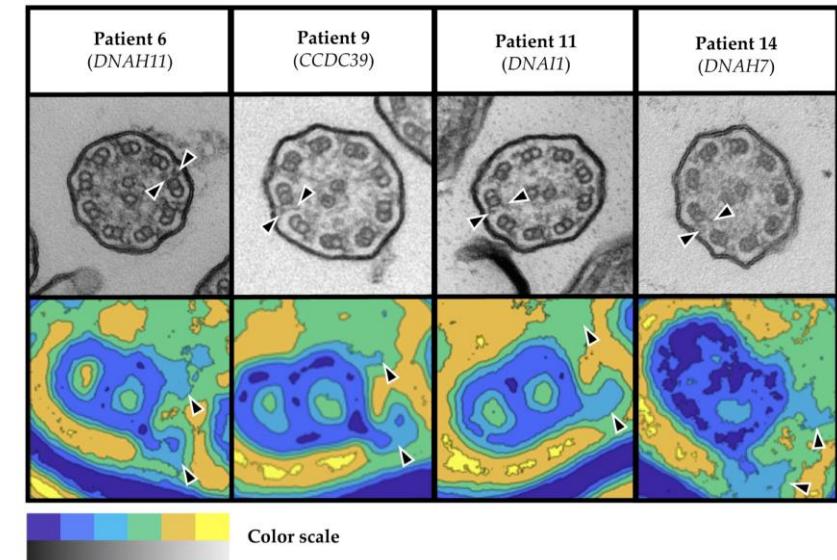
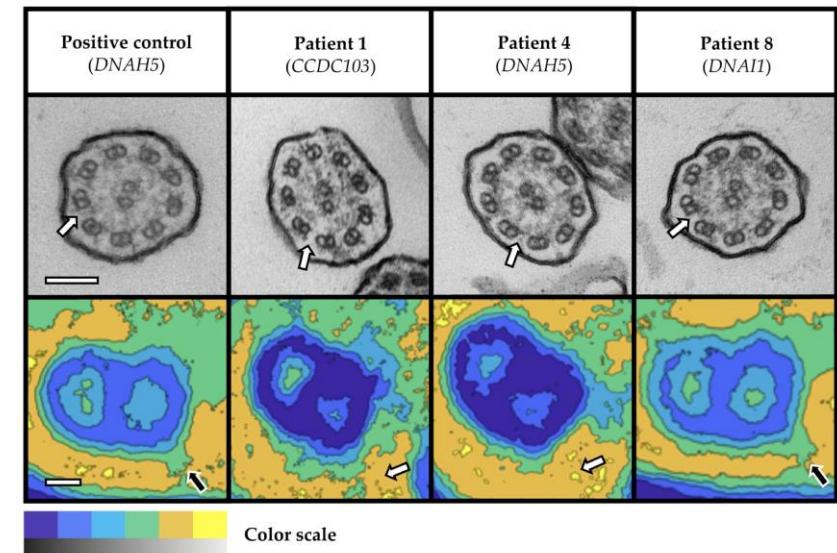
<1% avaient bénéficié de tests génétiques

# Dyskinésies ciliaires primitives : Sous diagnostic?

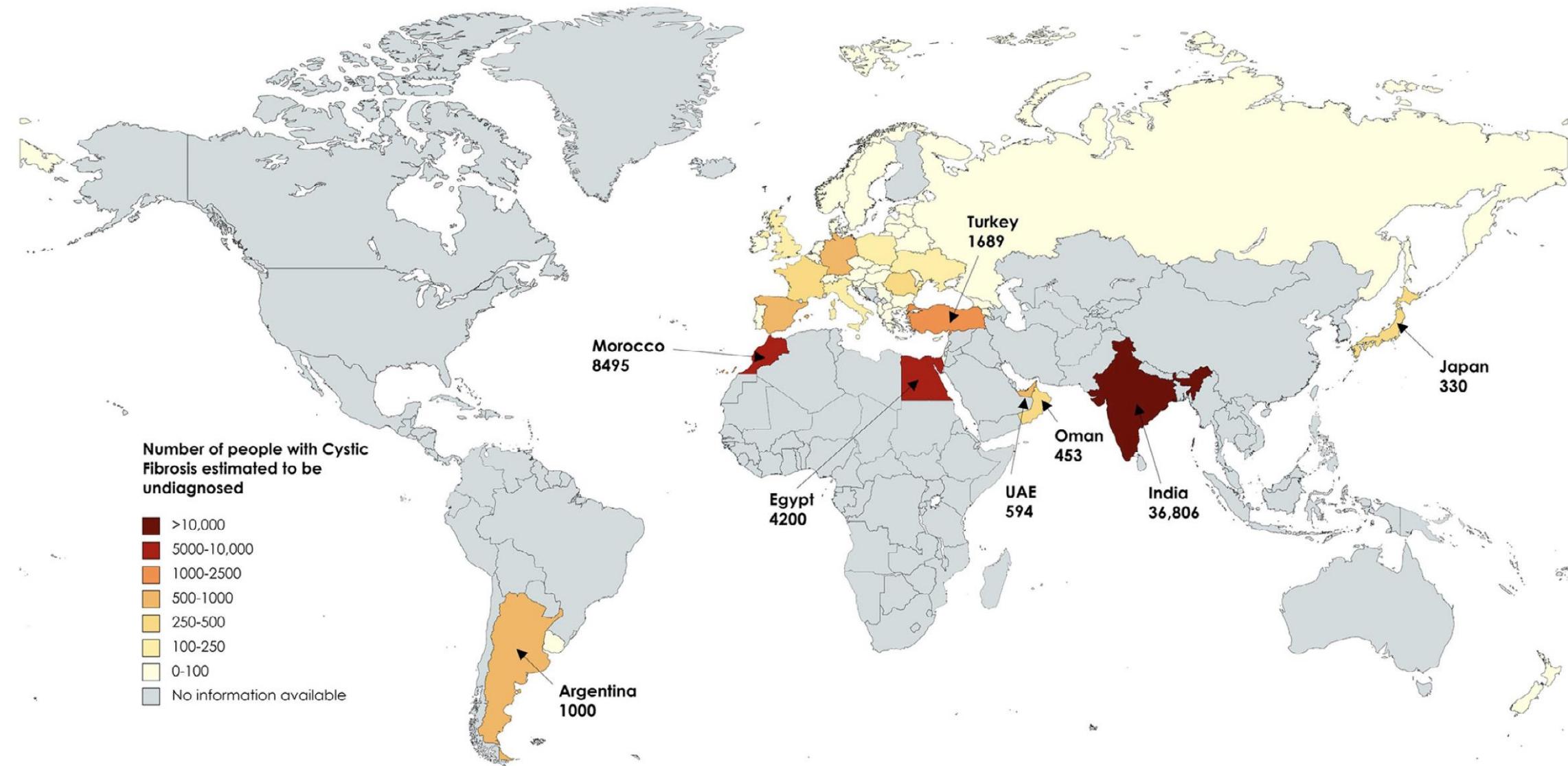
## Ciliary Ultrastructure Assessed by Transmission Electron Microscopy in Adults with Bronchiectasis and Suspected Primary Ciliary Dyskinesia but Inconclusive Genotype

Ben O. Staar <sup>1,2,3</sup>, Jan Hegermann <sup>2,4</sup>, Bernd Auber <sup>5</sup> , Raphael Ewen <sup>1,2,3</sup>, Sandra von Hardenberg <sup>5</sup>, Ruth Olmer <sup>2,6,7</sup>, Isabell Pink <sup>1,2,3</sup>, Jessica Rademacher <sup>1,2,3</sup>, Martin Wetzke <sup>2,8</sup> and Felix C. Ringshausen <sup>1,2,3,\*</sup>

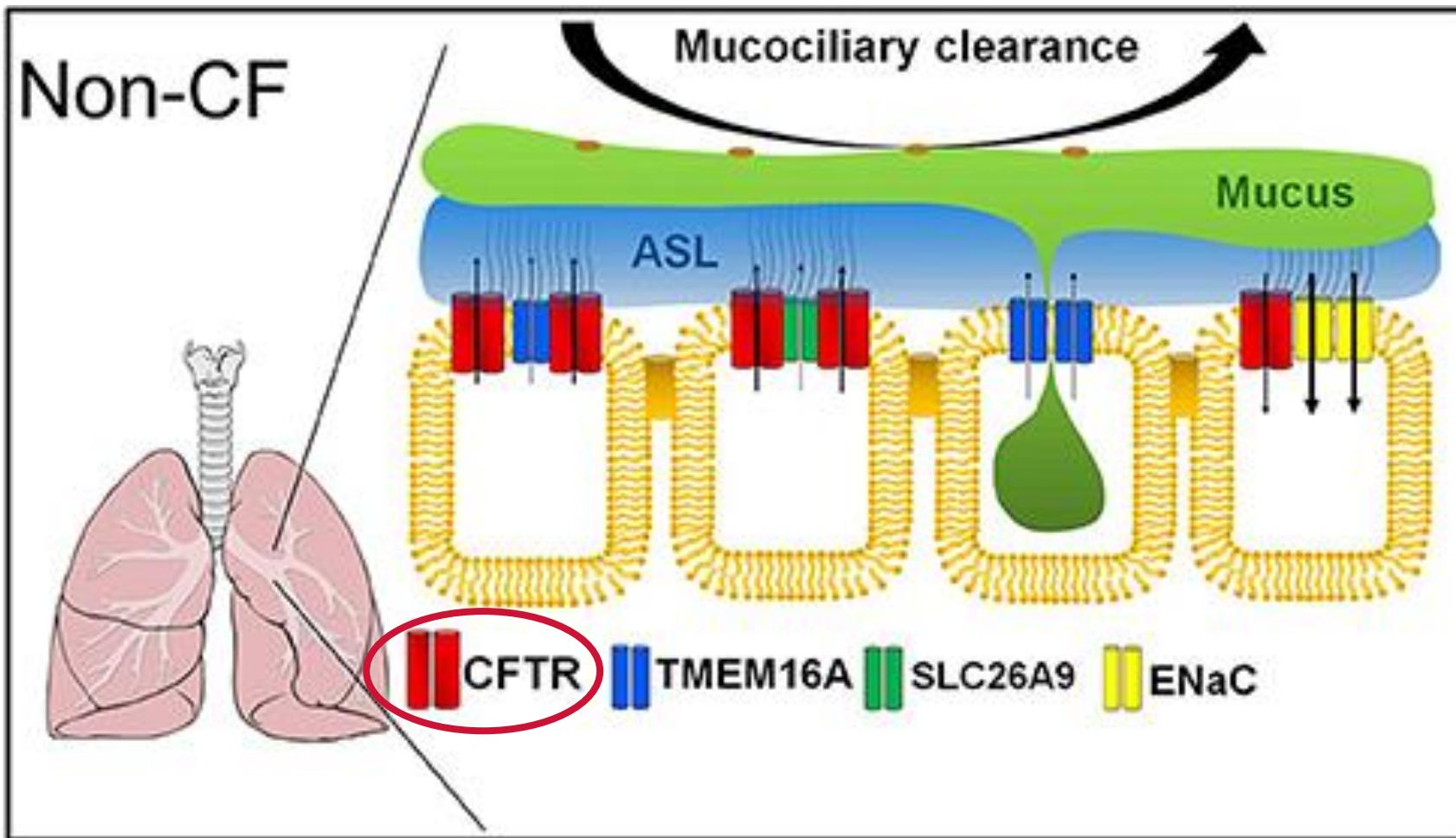
Subject	Age	Sex	Origin	Initial Etiology	Etiology after TEM	Nasal NO (nL/min)	ppFEV <sub>1</sub>	Patient History (Signs, Symptoms, and Findings) <sup>a</sup>	Gene <sup>b</sup>	cDNA Change	Protein Change	ACMG Class	TEM Results
1	29	F	Turkey	Probable PCD	Definite PCD	11	69	NRD, early onset of chronic wet cough and CRSwNP; repeat sinus surgery, chronic otitis media, and history of grommet insertions	CCDC103	c.548T>C c.548T>C	p.(Leu183Pro) p.(Leu183Pro)	3 3	ODA
2	61	F	Russia	Idiopathic bronchiectasis	Idiopathic bronchiectasis	251	37	School-age onset of chronic wet cough, and <i>P. aeruginosa</i> infection	DNAH1	c.5639C>T c.6925C>A	p.(Thr1880Met) p.(Pro2309Thr)	3 3	Normal
3	63	M	Germany	Possible PCD	Possible PCD	170	33	Pre-school onset of chronic wet cough and CRSwNP; positive family history, history of infertility, and <i>P. aeruginosa</i> infection	DNAH1	c.2995C>T c.7633A>G	p.(Arg999Cys) p.(Ile2545Val)	3 3	Normal
4	38	F	Germany	Probable PCD	Definite PCD	27	109	NRD, early onset of chronic wet cough, CRSwNP; repeat sinus surgery, chronic otitis media, history of grommet insertions, <i>P. aeruginosa</i> infection, and abnormal HSVM (immotile cilia)	DNAH5	c.10815delT c.11212-4>G (intronic)	p.(Pro3606Hisfs*23)	5 3	ODA
5	58	F	Kenya	Probable PCD	Probable PCD	46	77	Young-adult onset of chronic wet cough, CRSwNP; repeat sinus surgery, and <i>P. aeruginosa</i> infection	DNAH8	c.3215G>A c.1169T>C c.12401T>C c.2943T>C c.1043+5G>C	p.(Arg1072Gln) p.(Leu3723Leu) p.(Leu4134Pro) p.(Asp981=) p.?	3 3 3 3 3	Normal
6	18	M	Germany	Asthma	Asthma	240	59	Adolescent onset of chronic wet cough, and <i>P. aeruginosa</i> infection	DNAH11	c.5924+12G>A c.6226G>A	p.? p.(Val2076Met)	3 3	Normal
7	47	M	Germany	Probable PCD	Probable PCD	37	69	NRD, early onset of chronic wet cough and CRSwNP; repeat sinus surgery, history of infertility, and abnormal HSVM (static stroke)	DNAH11	c.7456A>G c.9815>G	p.(Thr2486Ala) p.(Asn3272Ser)	3 3	Normal
8	46	F	Turkey	Probable KS	Definite KS	-	30	Situs inversus, early onset of chronic wet cough and CRSwNP; repeat sinus surgery, history of lower lobe resection, middle lobe atelectasis, and <i>M. abscessus</i> infection	DNAI1	c.1168G>A c.1168G>A	p.(Asp390Asn) p.(Asp390Asn)	3 3	ODA
9	23	M	Tunisia	Possible PCD	Possible PCD	290	36	NRD, early onset chronic wet cough and CRSwNP	CCDC39	c.1363-3delC c.1781C>T	p.? p.(Thr594Ile)	3 3	Normal
10	53	M	Germany	Probable PCD	Definite PCD	8	56	NRD, early onset of chronic wet cough and CRSwNP; repeat sinus surgery, chronic otitis media, hearing loss and aid, history of middle lobe resection, and atrial septal defect	CCDC40	c.3129delC c.354C>A	p.(Phe1004Serfs*35) p.(Tyr1118*)	5 3	MTD + IDA
11	19	M	Germany	Idiopathic bronchiectasis	Idiopathic bronchiectasis	236	82	Adolescent onset of chronic wet cough	DNAI1	c.1055A>G c.1207C>T	p.(Tyr352Cys) p.(His403Tyr)	3 3	Normal
12	44	F	Germany	Probable PCD	Definite PCD	21	40	Early onset chronic wet cough and CRSwNP; repeat sinus surgery, history of infertility, and <i>P. aeruginosa</i> infection	CCDC40	c.1345C>T c.2597A>G	p.(Arg449*) p.(Asn866Ser)	5 3	MTD + IDA
13	24	M	Turkey	Probable KS	Definite KS	17	51	Situs inversus, NRD, early onset of chronic wet cough and CRSwNP; repeat sinus surgery, chronic otitis media, <i>P. aeruginosa</i> infection, and abnormal HSVM (reduced amplitude, rigid stroke)	DNAH5 CCDC40	c.358G>A c.3656G>A c.615G>C c.615G>C	p.(Asp120Asn) p.(Arg1219His) p.= p.=	3 3 3 3	MTD + IDA
14	51	M	Turkey	Possible PCD	Possible PCD	112	32	Early onset of chronic wet cough and CRSwNP; parental consanguinity, and <i>P. aeruginosa</i> infection	DNAH7	c.12056_12060delTATGT c.12056_12060delTATGT	p.(Leu4019Serfs*3) p.(Leu4019Serfs*3)	3 3	Normal
15	23	F	Turkey	Probable PCD	Probable PCD	4	70	Early onset of chronic wet cough and CRSwNP; repeat sinus surgery, history of middle and lower lobe resection, parental consanguinity, positive familial segregation analysis, <i>P. aeruginosa</i> infection, and abnormal HSVM (uncordinated and circular beating)	NME5	c.415delA c.415delA	p.(Ile139Tyrfs*8) p.(Ile139Tyrfs*8)	4 4	CC
16	27	M	Syria	Probable PCD	Probable PCD	238	42	NRD, early onset of chronic wet cough and CRSwNP; chronic otitis media, lower lobe stenosis, sibling / positive familial segregation analysis, parental consanguinity, and <i>P. aeruginosa</i> infection	NEK10	c.1389C>A c.1389C>A	p.(Tyr463*) p.(Tyr463*)	4 4	N/A



# Mucoviscidose : Sous diagnostiquée aussi...



# CFTR et autres transporteurs ioniques : De nouvelles cibles thérapeutiques?



# Hétérozygotie CFTR parmi les patients porteurs de bronchectasies

## 50 bronchiectasis and/or pulmonary NTM infection

24 patients presented at least one CFTR mutation (50%), 10 were CF  
CFTR mutation-frequency increased vs general population: 12% vs 3% for phe508del

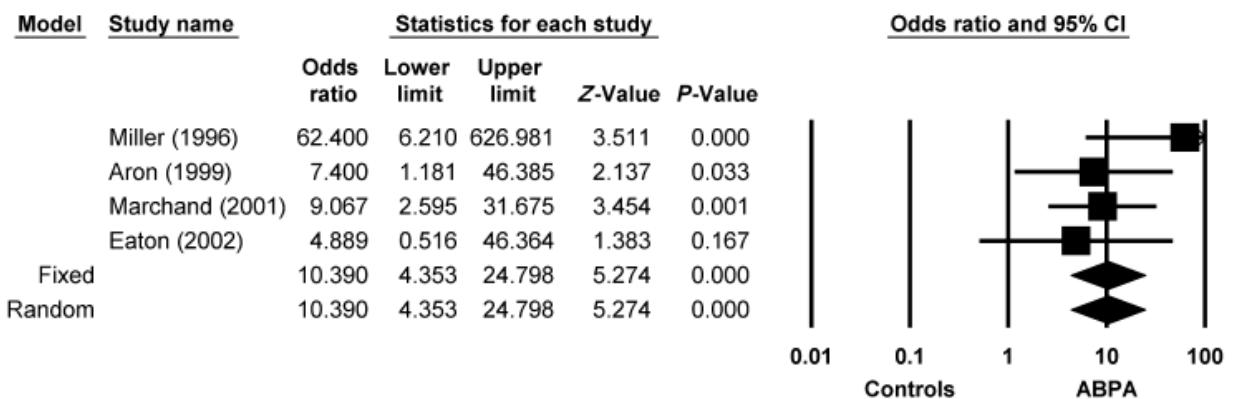
Ziedalski TM et al. 2006, Chest 130; 995-1002

## 122 idiopathic bronchiectasis

Group	n
DB-0	85
DB-1	22 30.33%
DB-2	15 CF

Bienvenu T et al., Am J Respir Crit Care Med Vol 181. pp 1078-84, 2010

## Higher risk of encountering CFTR mutation among ABPA cohorts



Agarwal et al. Mycoses, 2012, 55, 357–365

## CFTR variants commonly detected in patients with bronchiectasis unrelated to CF

CFTR variant	Legacy name	Gene location	Consequence
c.1521_1523delCTT	F508del	Exon 11	p.Phe508del
c.224G>A	R75Q	Exon 3	p.Arg75Gln
c.1727G>C	G576A	Exon 13	p.Gly576Ala
c.2002C>T	R668C	Exon 14	p.Arg668Cys
c.2991G>C	L997F	Exon 19	p.Leu997Phe
c.1210-12T [5]	IVS8-5T	Intron 8	affects intron 8 splicing
c.1408A>G	M470V	Exon 11	p.Met470Val
c.1584G>A	1716G/A	Exon 10	no change (Glu at 528)

Nokolic A. Lung (2018) 196:383-392

# Hétérozygotie CFTR : Un facteur de risque ?

## Innate CFTR impairment in CF Carrier

### Chloride transport

Higher sweat chloride concentrations in infant CF carriers

Significant difference in NPD index in CF carriers with bronchiectasis

### Pancreatic function

Increased blood immunoreactive trypsinogen in newborn CF carriers

### Innate immune response

Delayed neutrophil apoptosis in CF carriers

## Life-style conditions of acquired CFTR impairment

### Cigarette smoke

### Infectious diseases

*Influenzae* virus

*Pseudomonas aeruginosa*

Neutrophil products

### Genetics

Association with ENaC mutation / Epigenetic CpG island hypermethylation

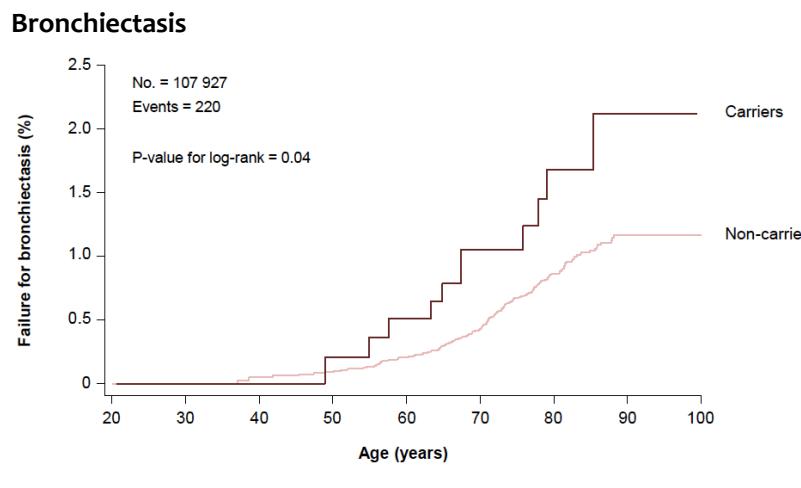
- Farrell PM et al. Pediatrics 1996;97(4):524-8  
Bienvenu T et al. Am J Respir Crit Care Med 2010;181(10):1078-84  
Castellani C et al. J Med Genetics 2005;135A(2):142-4  
Lecoq I et al. Acta Paediatr. 1999;88(3):338-41  
Moriceau S et al. J Innate Immun. 2010;2(3):260-6

- Cantin AM et al. Am J Respir Crit Care Med 2006;173(10):1139-44  
Raju SV et al. Am J Respir Crit Care Med 2013;188(11):1321-30  
Brand JD et al. JCI insight 2018;3(20)  
Saint-Criq V et al. Thorax 2018;73(1):49-61  
Le Gars M et al. Am J Respir Crit Care Med 2013;187(2):170-9  
Shin Y et al. J Clin Med 2020;9(3)

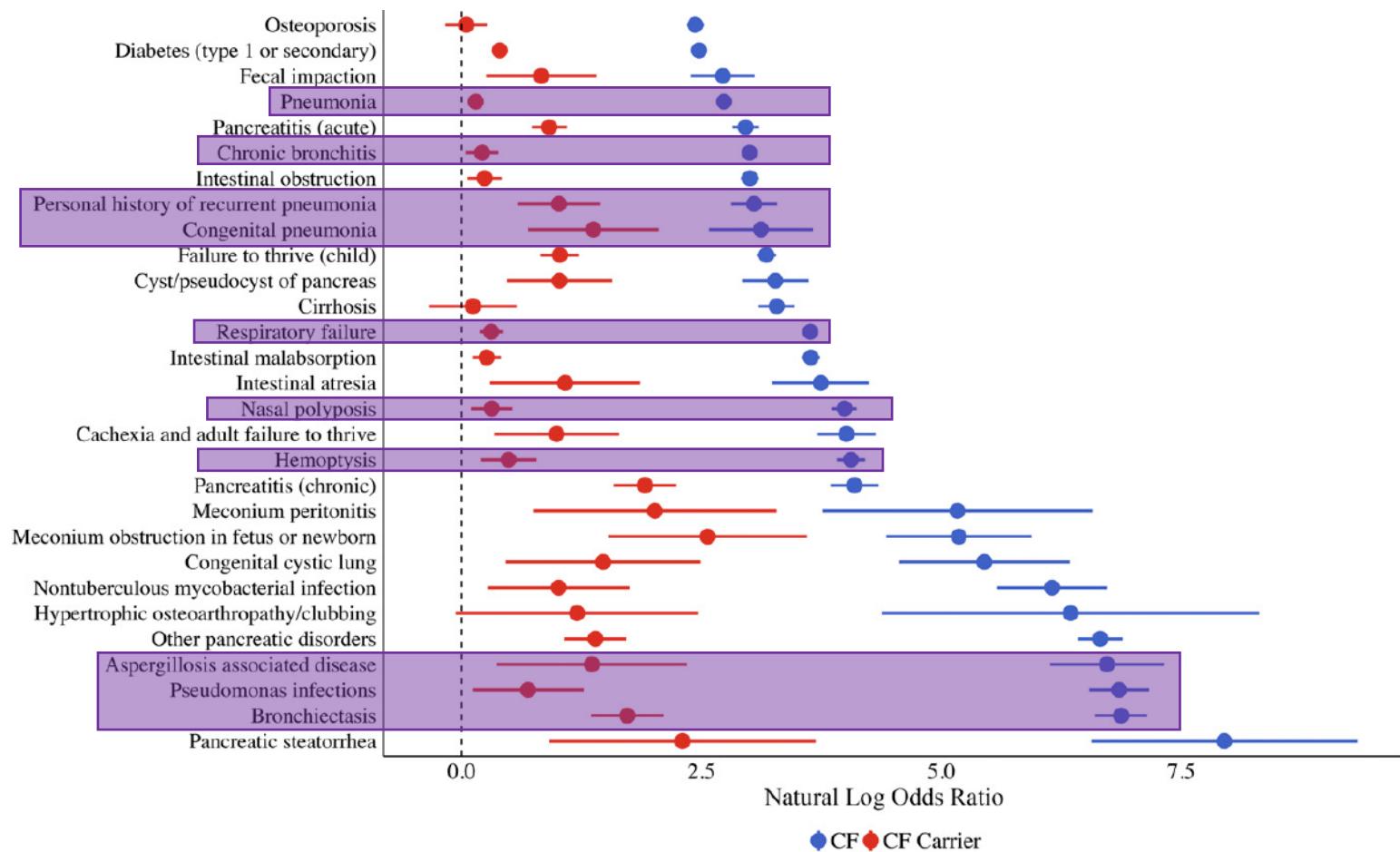
# Hétérozygotie CFTR : Un facteur de risque ?

Genotyping of 108 035 randomly selected white Danish individuals for phe50del mutation:  
1 carrier out of 38 individuals (2858)

Higher risk of ....



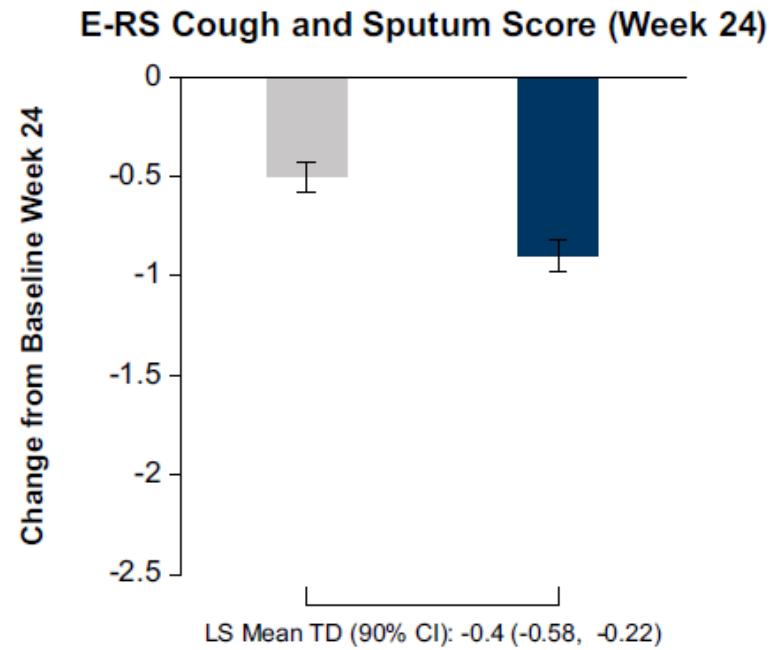
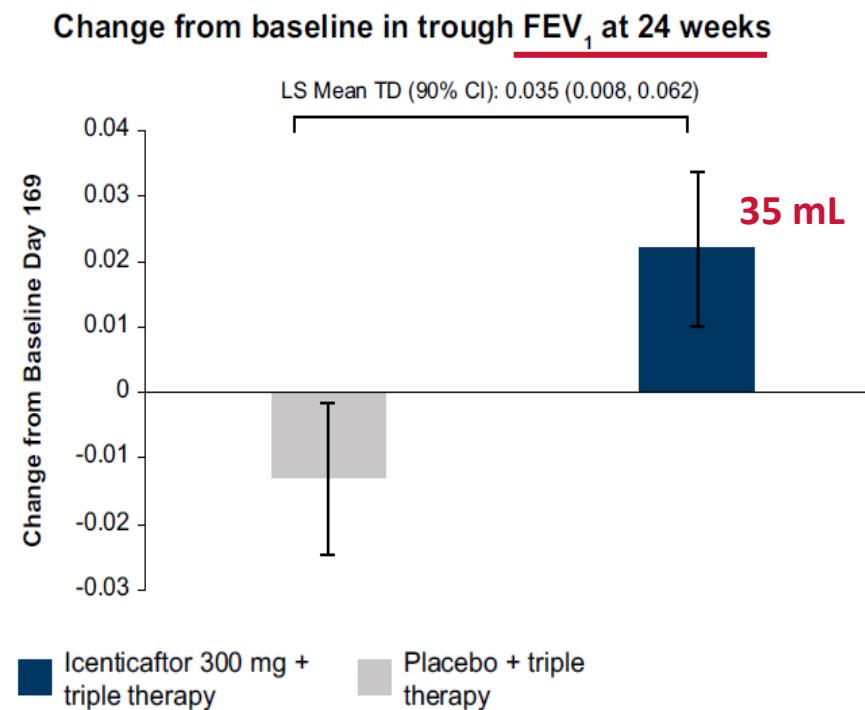
19 802 CF carriers in an US administrative data base (1 carrier / 5 controls)



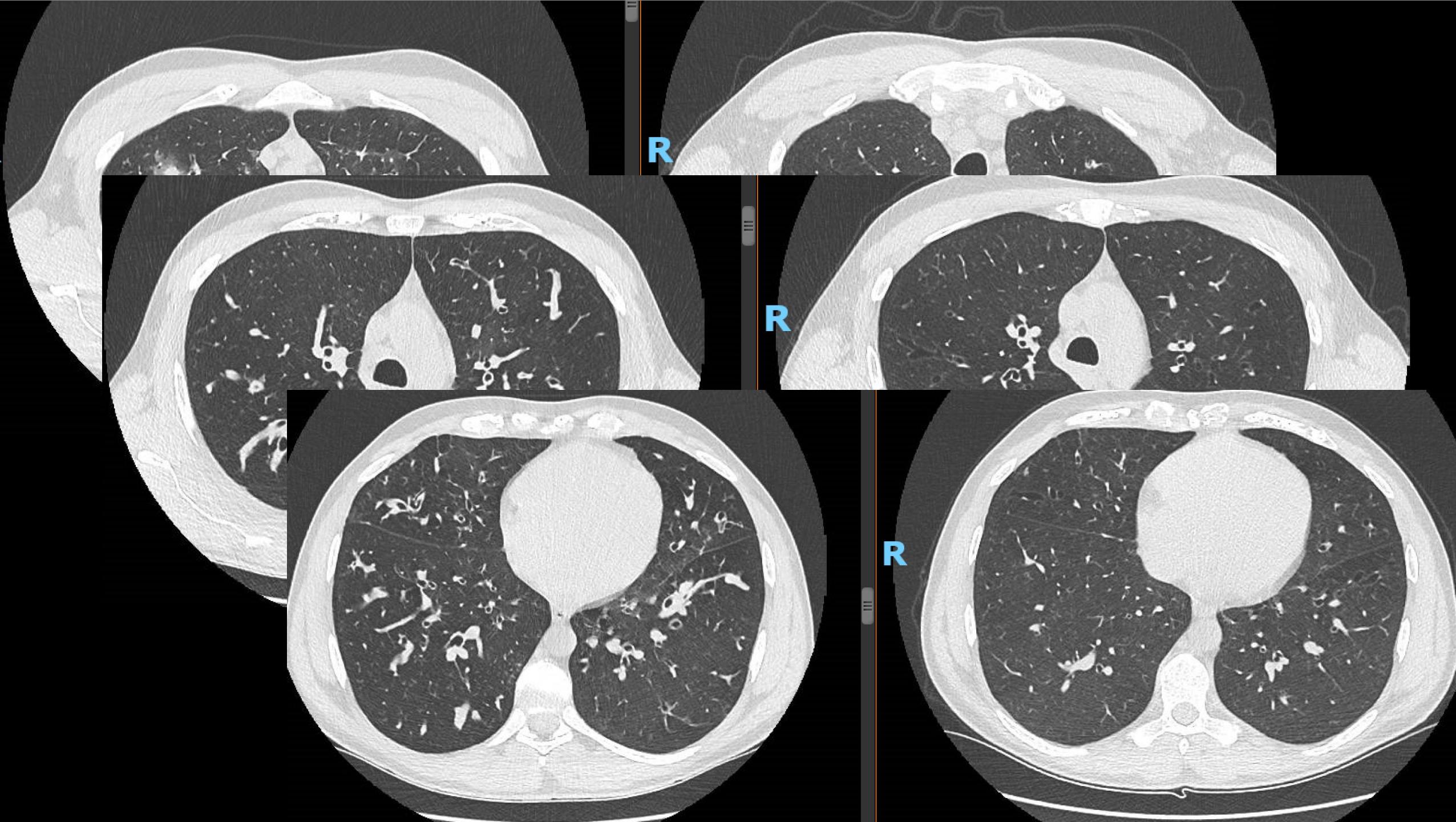
Increased risk for 57 CF-related conditions

# La protéine CFTR au de-là de la mucoviscidose

## Icenticaftor, a CFTR Potentiator, in COPD: A Multicenter, Parallel-Group, Double-Blind Clinical Trial



COPD patients with chronic bronchitis  
Encouraging but not life-changing results  
Sweat chloride?



**To be continued....**

## **Trikafta for Patients With Non-cystic Fibrosis Bronchiectasis**

**Elexacaftor–Tezacaftor–Ivacaftor**

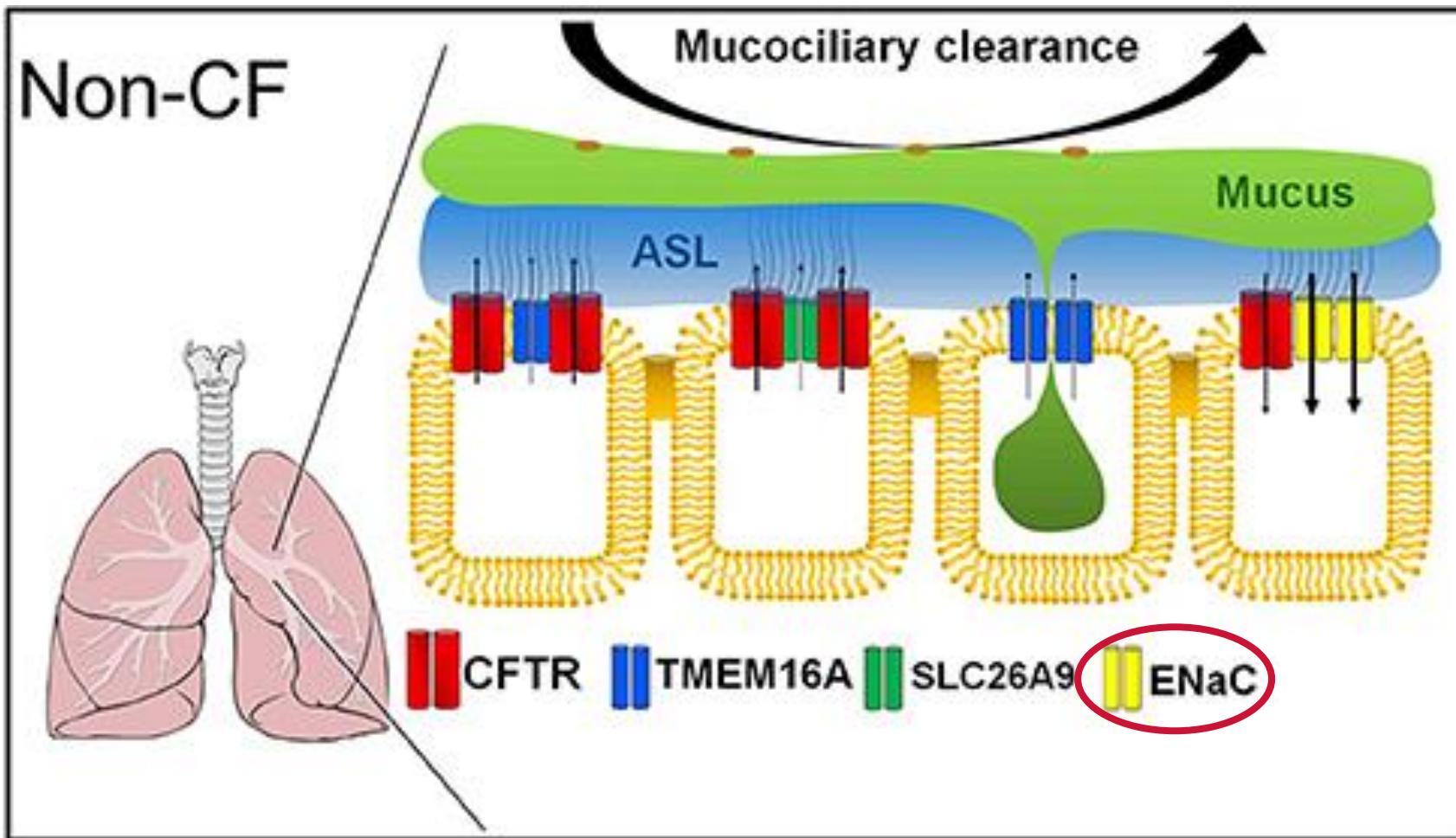
ClinicalTrials.gov Identifier: NCT05743946

Recruitment Status  : Recruiting

First Posted  : February 24, 2023

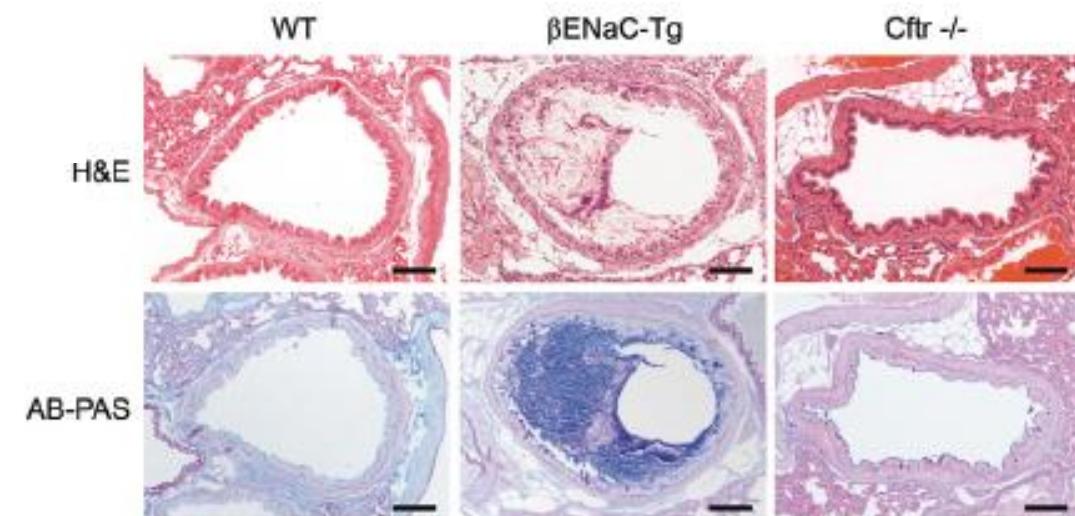
Last Update Posted  : February 24, 2023

# CFTR et autres transporteurs ioniques : De nouvelles cibles thérapeutiques?



# Le canal ENaC impliqué dans la pathogénie des bronchectasies?

The  $\beta$ ENaC-overexpressing mouse as a model of cystic fibrosis lung disease



Zhou et al. *J of Cystic Fibrosis* Vol. 10 suppl 2(2011) S172-S182.

Could a defective epithelial sodium channel lead to Bronchiectasis?

Among 55 idiopathic bronchiectasis

Table 2: Main characteristics of the 5 patients with idiopathic bronchiectasis bearing a missense mutation in ENaC $\beta$  gene

	Age (years)	Sex	BMI (Kg.m <sup>-2</sup> )	FEV1 (%pred.)	CFTR mutation	ENaC $\beta$ mutation	Sweat Cl <sup>-</sup> (mmol/L)	Basal PD (mV)
Group 1	66	F	22	77	IVS8-5T	p.Ser82Cys	44	- 13
	62	F	19	89	F508del	p.Ser82Cys	38	- 8
	35	F	23	86	none	p.Pro369Thr	22	- 43
	60	F	21	93	none	p.Asn288Ser	57	- 10
Group 2	67	M	20	80	IVS8-5T	p.Ser82Cys	28	- 22

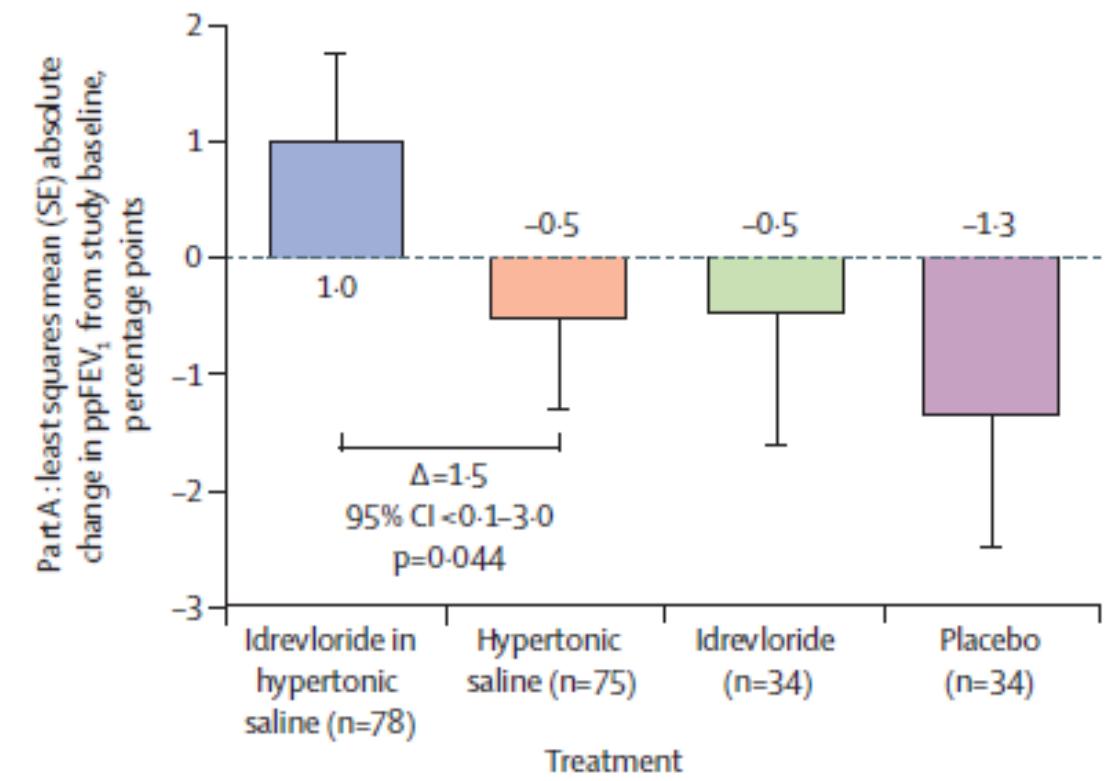
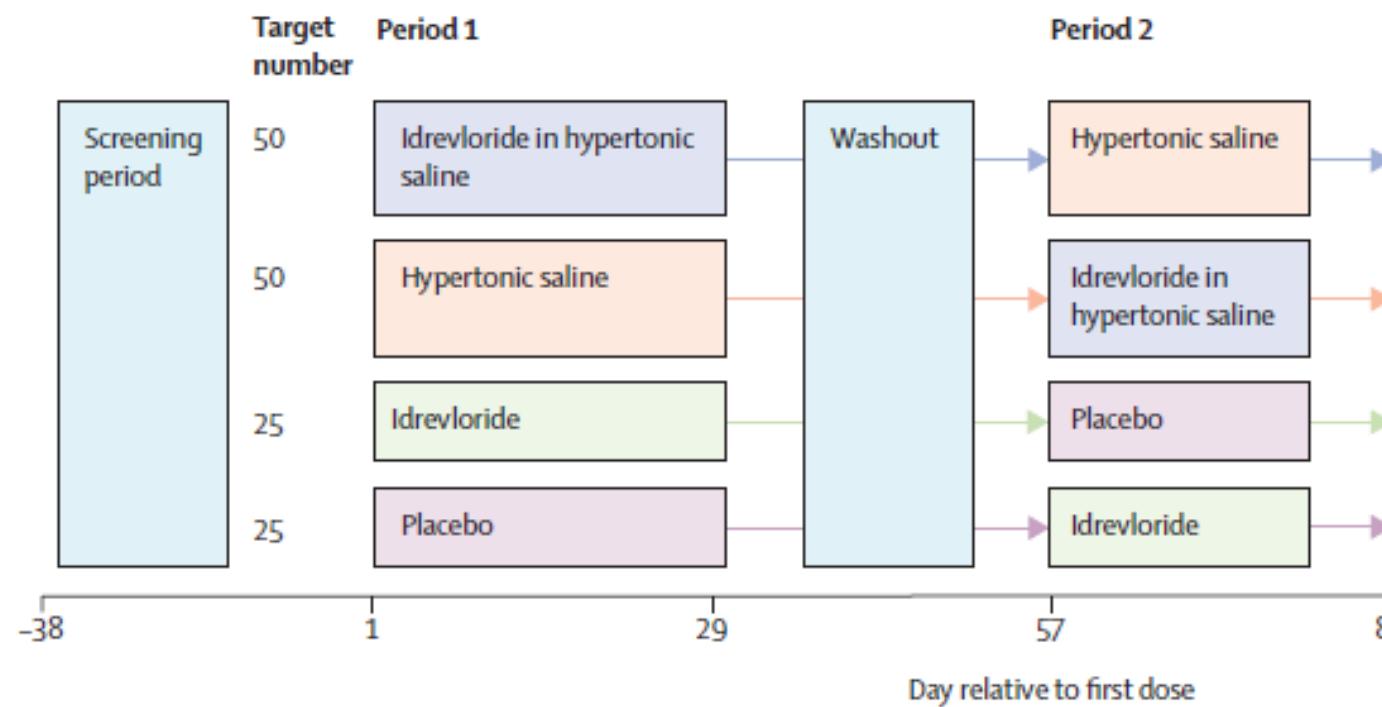
F : female, M : male, BMI : body mass index, FEV1 : forced expiratory volume in 1 second, pred : predicted, PD : nasal potential difference.

Fajac I, et al. *Respiratory Research* 2008, 9:46; Fajac I, Viel M et al, *Eur Respir J* 2009 34: 772-773.

## ENaC une cible thérapeutique?

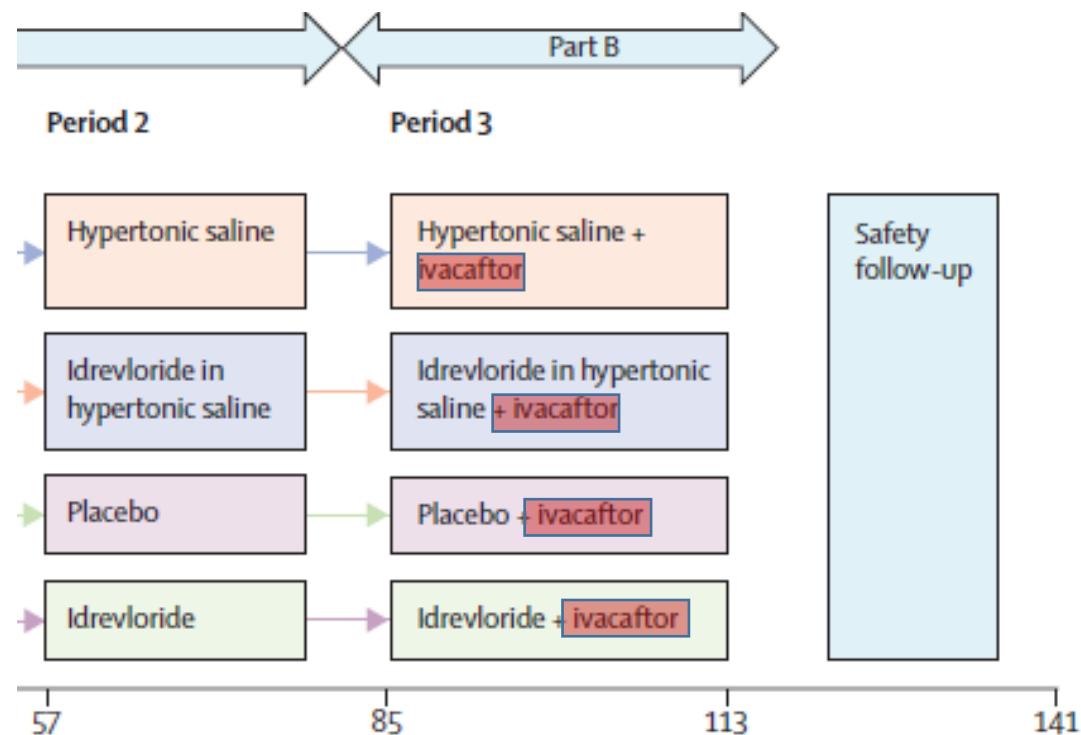
# ENaC : une cible thérapeutique?

Safety and efficacy of the epithelial sodium channel blocker idrevloride in people with primary ciliary dyskinesia (CLEAN-PCD): a multinational, phase 2, randomised, double-blind, placebo-controlled crossover trial

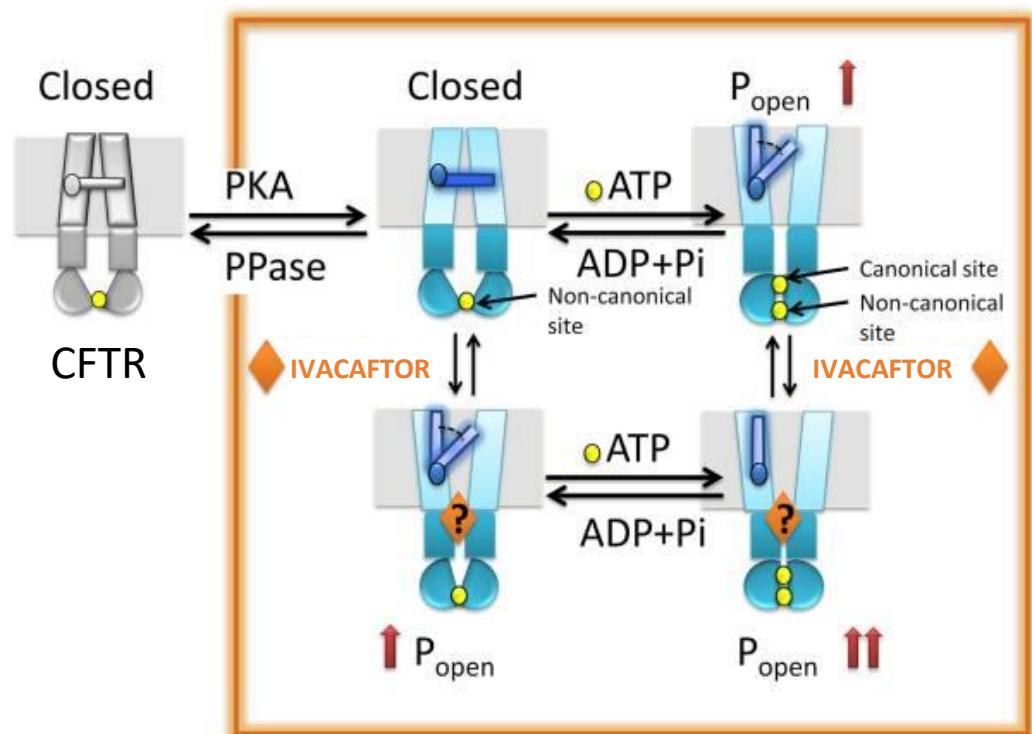


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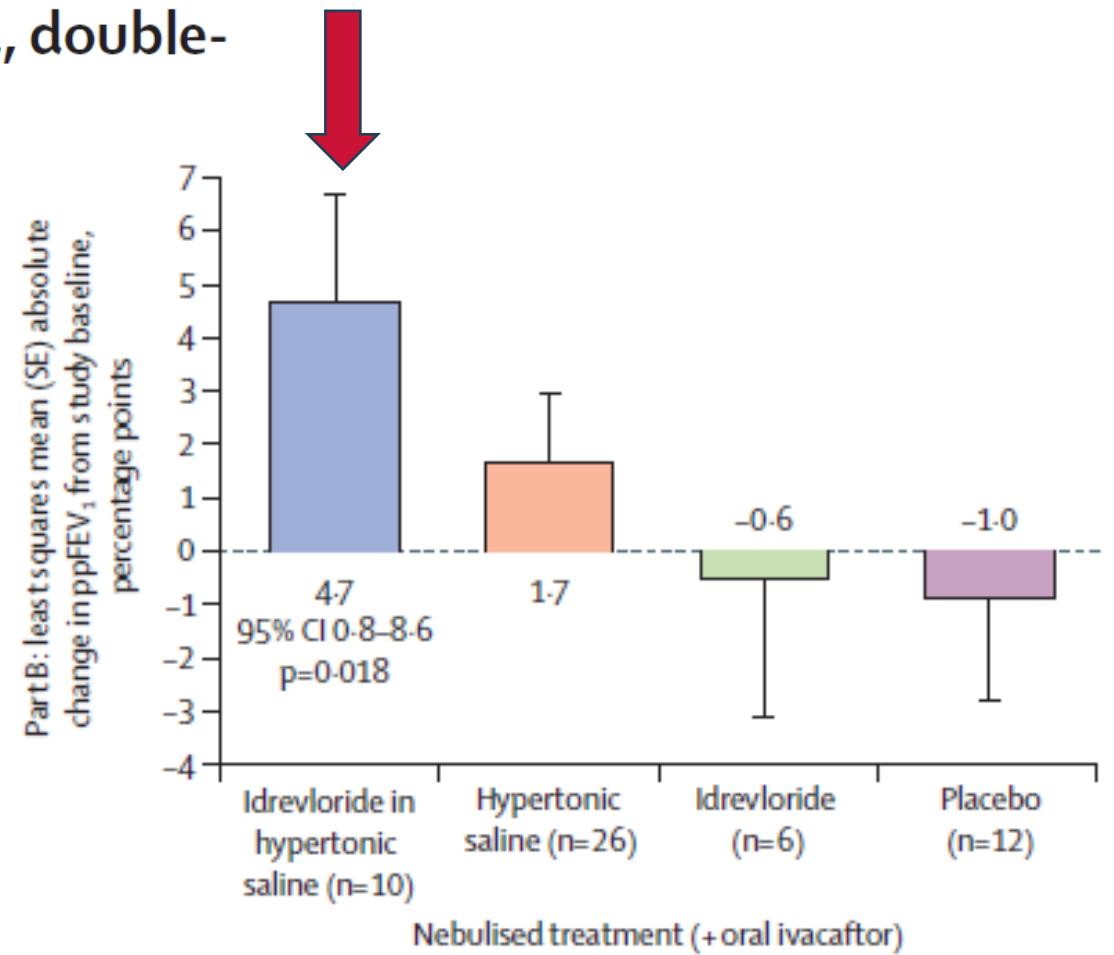
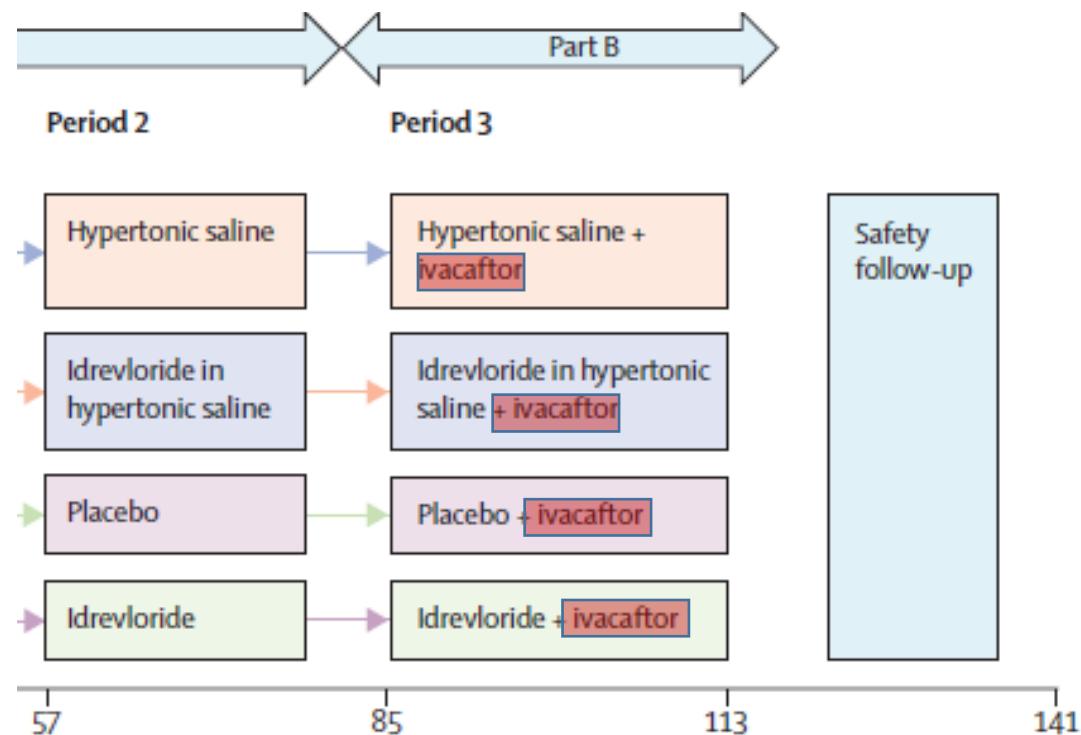
- Identification par screening à haut rendement
- Potentiateur de CFTR, Fixation directe à CFTR
- Stabilise CFTR en état canal-ouvert



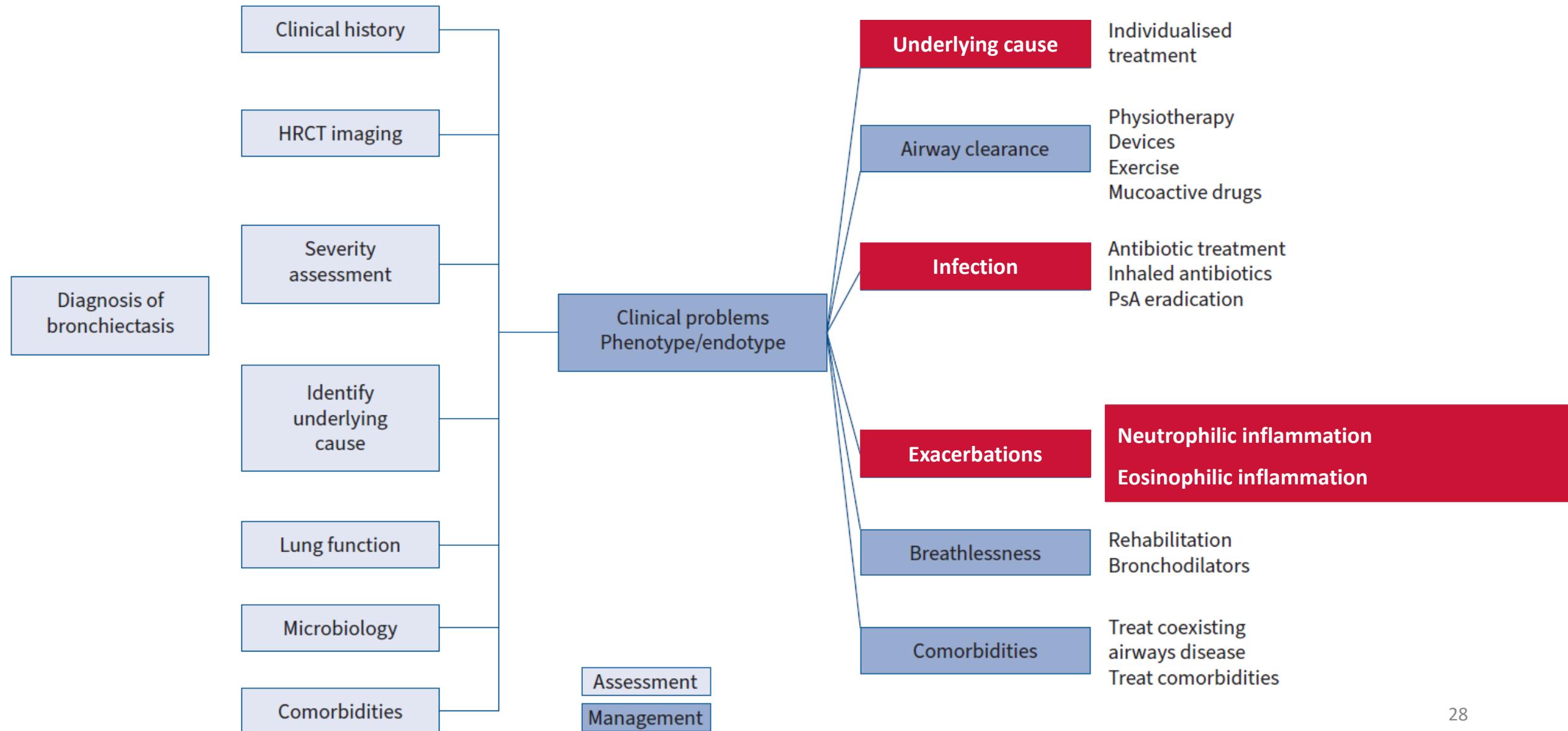
Van Goor et al, PNAS 2009; 106: 18825-30  
Eckford et al, JBC 2012; 287:36639-49  
Jih & Hwang, PNAS 2013; 110: 4404-09

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# Bronchiectasies diffuses « Treatable Traits »



# L'inflammation neutrophilique: une cible thérapeutique

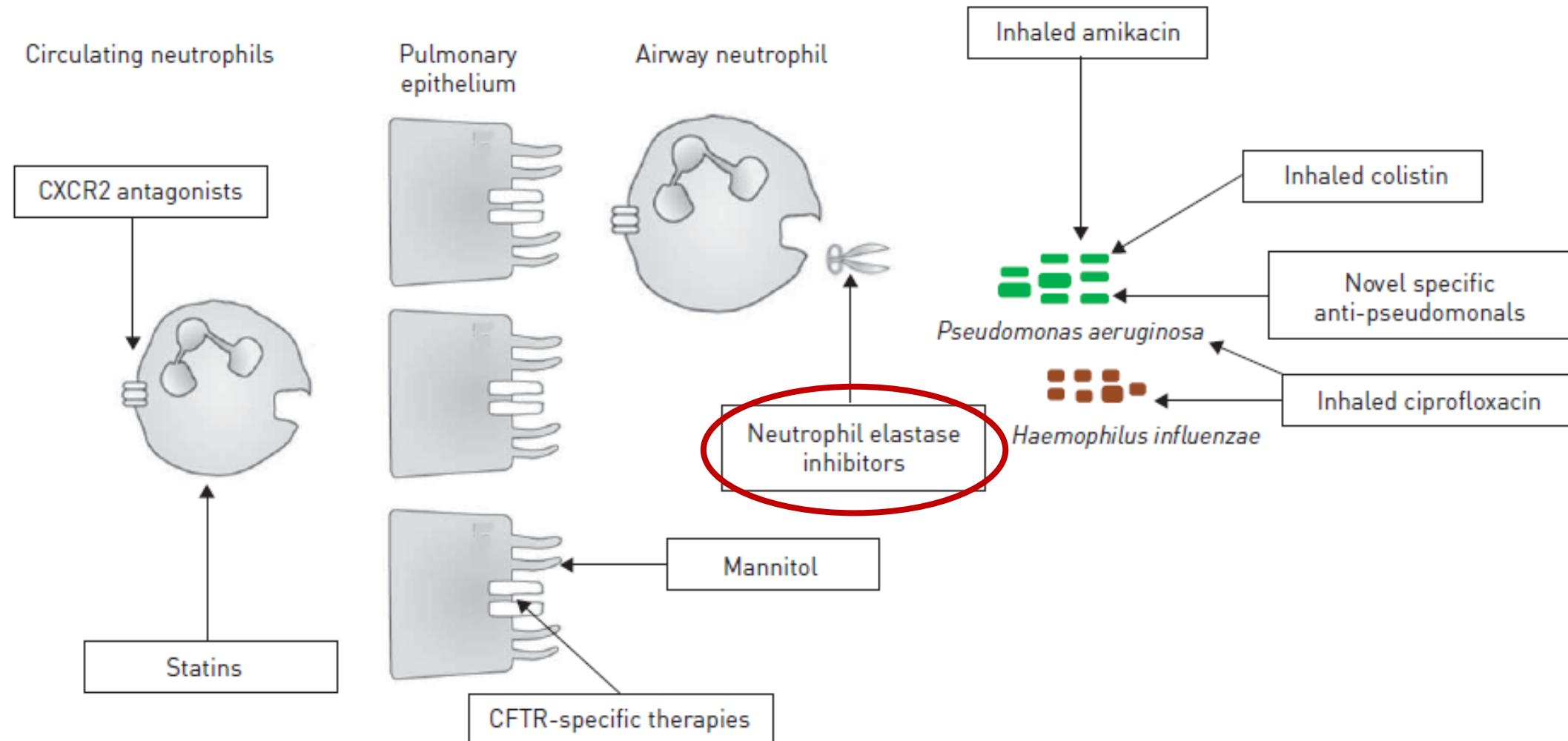
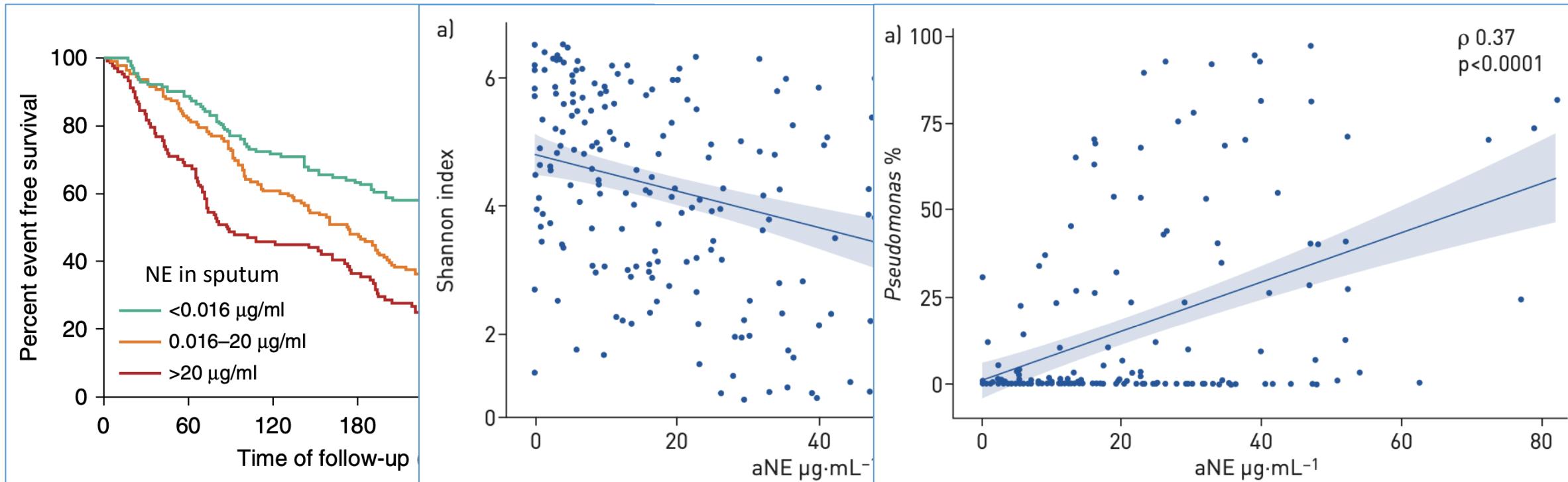


FIGURE 3 New therapies in development for bronchiectasis and their possible role. CFTR: cystic fibrosis transmembrane conductance regular.

# L'inflammation neutrophilique: une cible thérapeutique

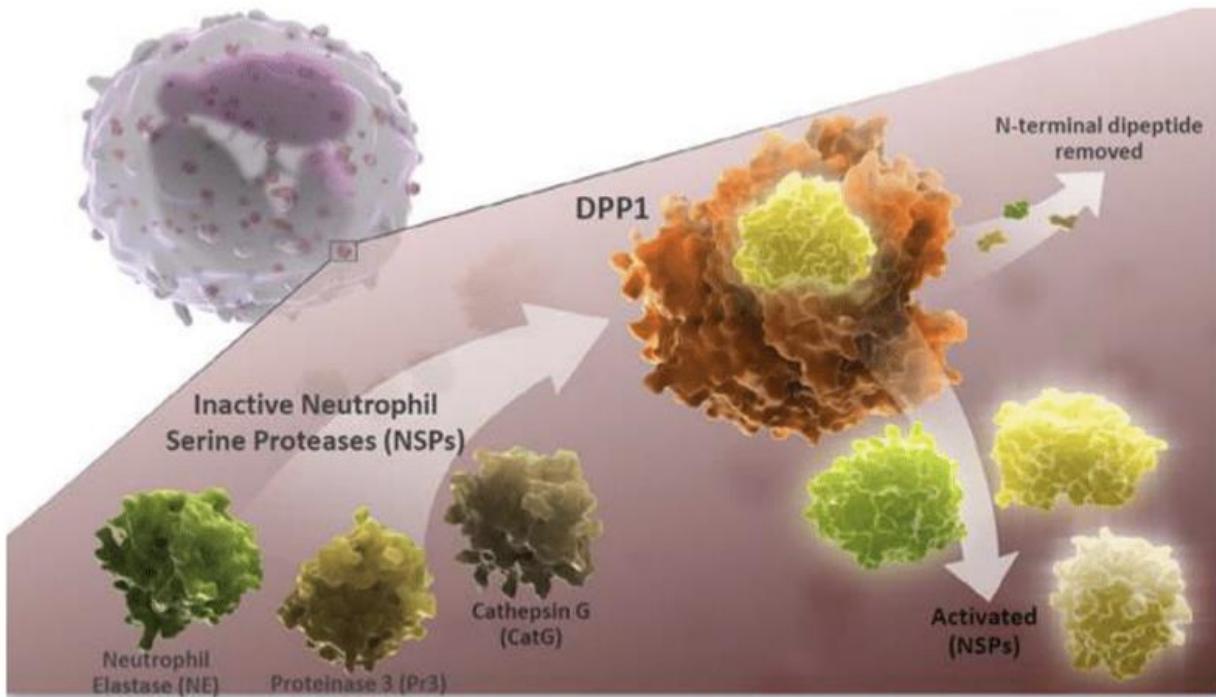


Neutrophilic exacerbations in bronchiectasis

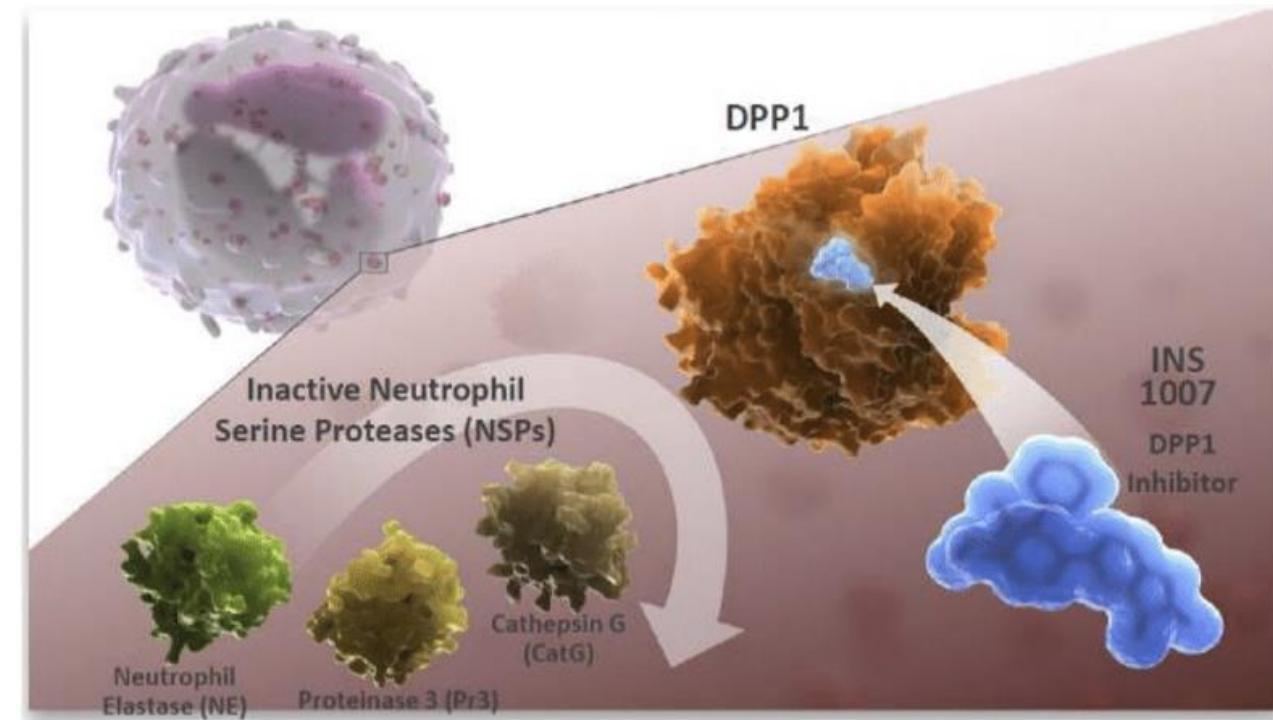
Sputum concentrations of NE correlates with worse prognosis

Neutrophil Elastase activity rate correlates with microbiota dysbiosis and *P. aeruginosa* load

# L'inflammation neutrophilique: une cible thérapeutique



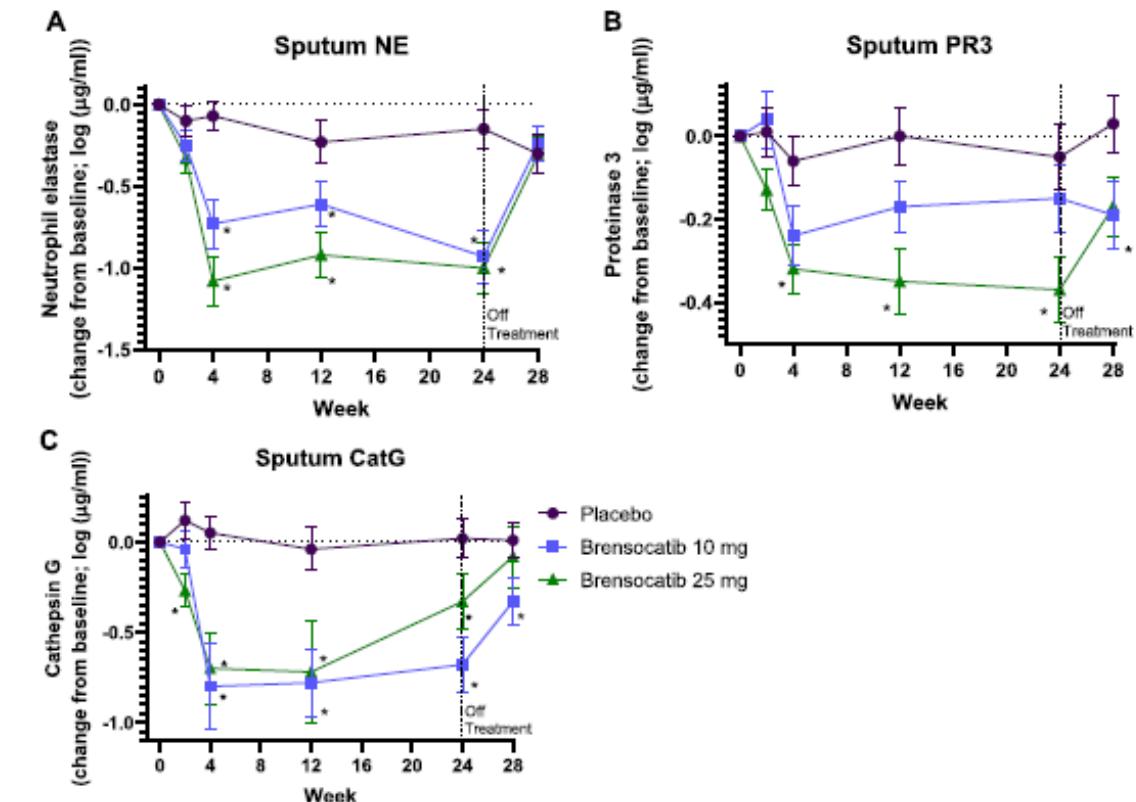
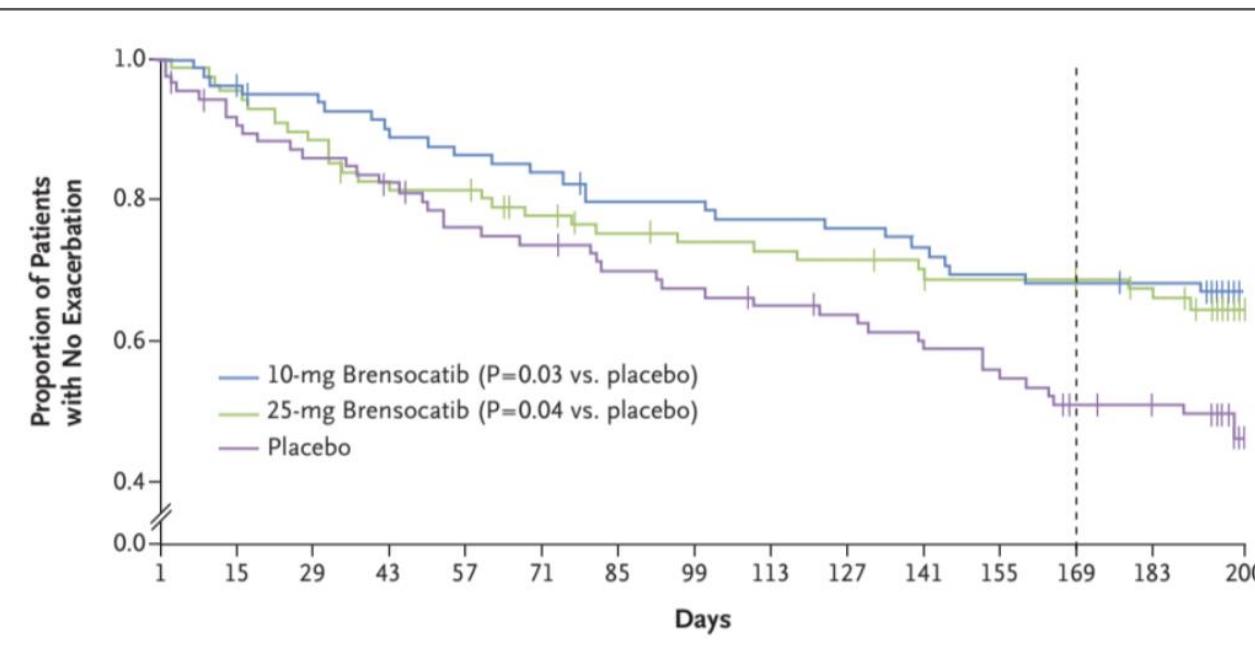
Cathepsine C (DPP1) est une protéase lysosomale qui active les séries protéases du neutrophile



Brensocatib (INS 1007) est un inhibiteur de la cathepsine C

# L'inflammation neutrophilique: une cible thérapeutique

## Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis



Phase 3 study (ASPEN) with Brensocatib (recruitment completed, 1600 patients)

Phase 2 study (BI Trial 1397-0012 - Airleaf) with new drug BI 1291583 (oral cathepsin C inhibitor)

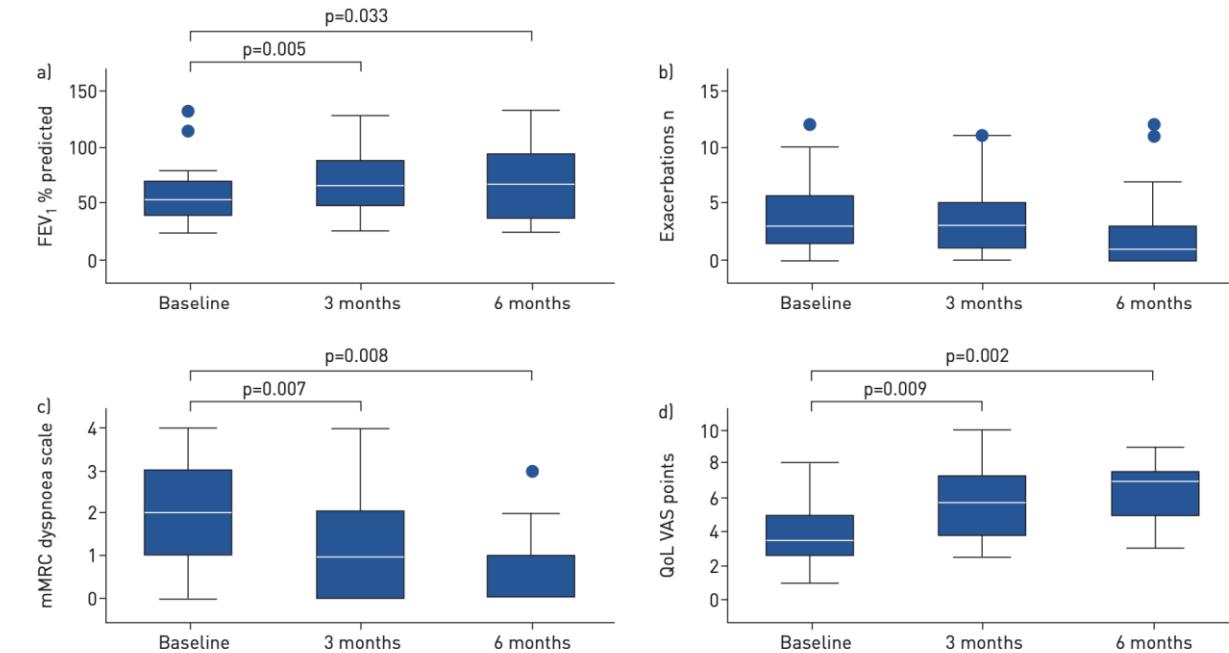
# L'inflammation éosinophilique: une cible thérapeutique?

## Anti-IL5 and anti-IL5R $\alpha$ therapy for clinically significant bronchiectasis with eosinophilic endotype: a case series

Research letter

Refractory disease despite optimised maintenance therapy and blood eosinophils  $\geq 300$  cells· $\mu\text{L}^{-1}$

21 patients :  
Mepolizumab (12)  
Benralizumab (9)



Rademacher J, Konwert S, Fuge J, et al. Eur Respir J 2020; 55: 1901333

Asthmes éosinophiliques sévères + Bronchectasies diffuses...

97 patients :  
Mepolizumab, Benralizumab et Reslizumab

Etude rétrospective ?, suivi d'au moins 12 mois

Real-World Effectiveness of IL-5/5Ra Targeted Biologics in Severe Eosinophilic Asthma With Comorbid Bronchiectasis

# Conclusions

## Le diagnostic étiologique et caractérisation du profil inflammatoire des patients:

- mieux adapter les traitements des patients (Inhibiteurs de la cathepsin C, Anti-IL5, futures biothérapies...)
- améliorer leur recrutement dans les essais thérapeutiques en développement.

## CFTR et les autres transporteurs ioniques sont de potentielles cibles thérapeutiques

### Mémo : Ne pas oublier les bases!

- Traitement étiologique (mucoviscidose à révélation tardive, déficit immunitaire...)
- *Pseudomonas aeruginosa et compagnies. Même si les antibiothérapies inhalées n'ont pas l'AMM... Colistine et Tobramycine inhalées font partie de l'arsenal thérapeutique...*
- *Eviter les CSI dans la mesure du possible*
- *Dépister et traiter les comorbidités*
- *Drainage bronchique et traitement de l'obstruction*