Cystic Fibrosis: diagnosis and recent therapeutic advances

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Conflict of interest disclosure

- ❑ I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation: **Vertex**
- ❑ Other conflicts of interest

Affiliation / financial interest	Nature of conflict / commercial company name
Tobacco-industry and tobacco corporate affiliate related conflict of interest	None
Grants/research support (to myself, my institution or department):	GSK, Vertex
Honoraria or consultation fees:	Astra-Zeneca, Boerhinger Ingelheim, Chiesi, GSK, Insmed, Novartis, Pfizer, Vertex, Zambon
Participation in a company sponsored bureau:	None
Stock shareholder:	None
Spouse/partner – conflict of interest (as above):	None
Other support or other potential conflict of interest:	None

Agenda

- Cystic fibrosis
- Diagnosis
- Therapeutic revolution

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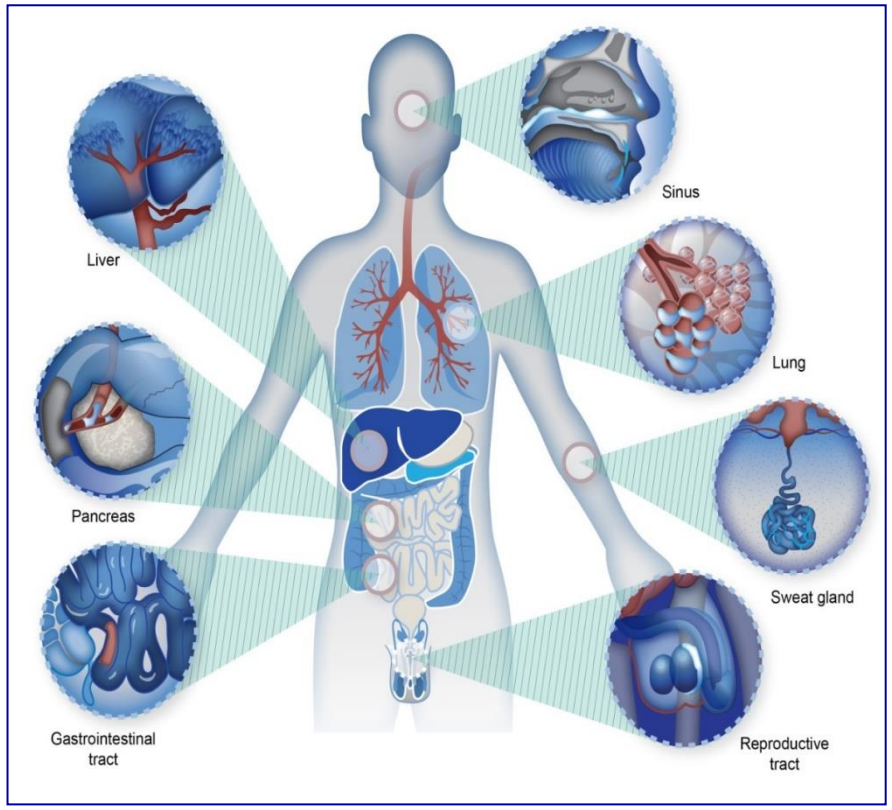
- Cystic fibrosis
- Diagnosis
- Therapeutic revolution

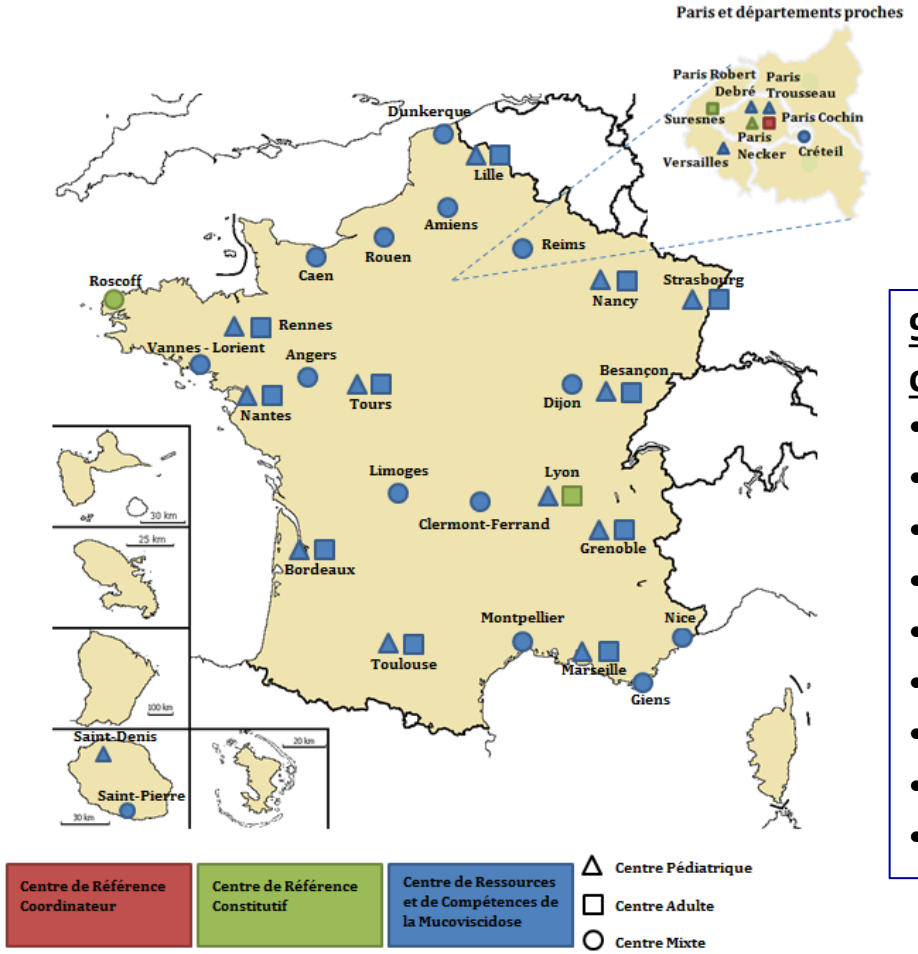
Cystic fibrosis

Autosomal recessive
Mutations in the *CFTR* gene >2000 mutations
7500 patients in France; 32000 in the US
Over 100,000 patients worldwide



Diabetes

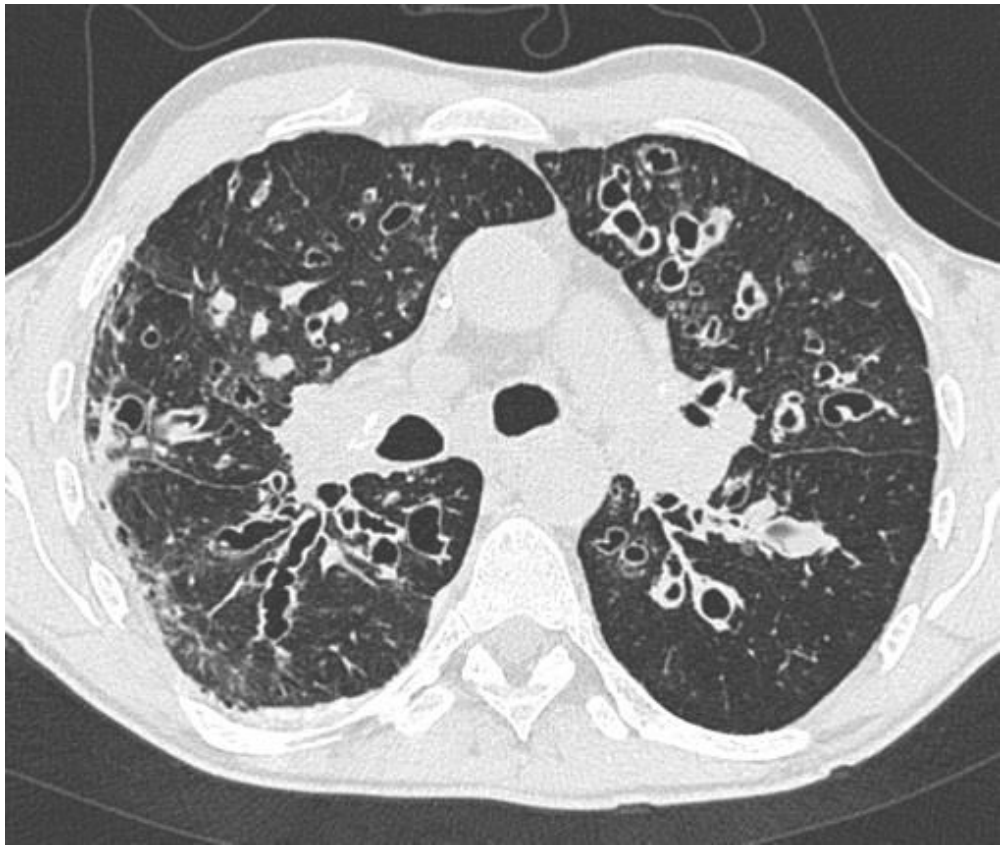
CF centres in France



9 transplant centers

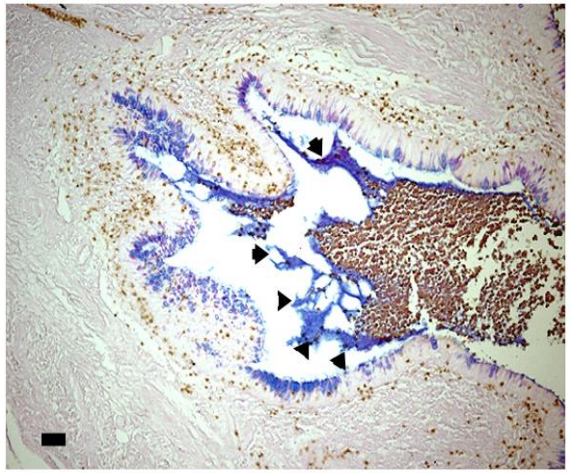
- **Foch**
- **Bichat**
- **Toulouse**
- **Bordeaux**
- **Nantes**
- **Lyon**
- **Grenoble**
- **Marseille**
- **Strasbourg**

Cystic fibrosis: diffuse bronchiectasis

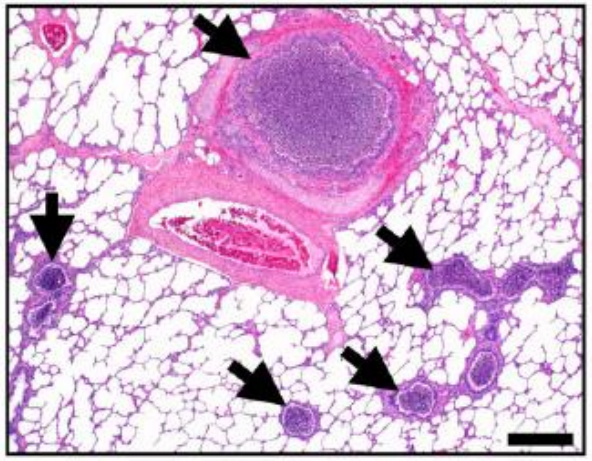


Cystic fibrosis and the lung: mucus and airway infection

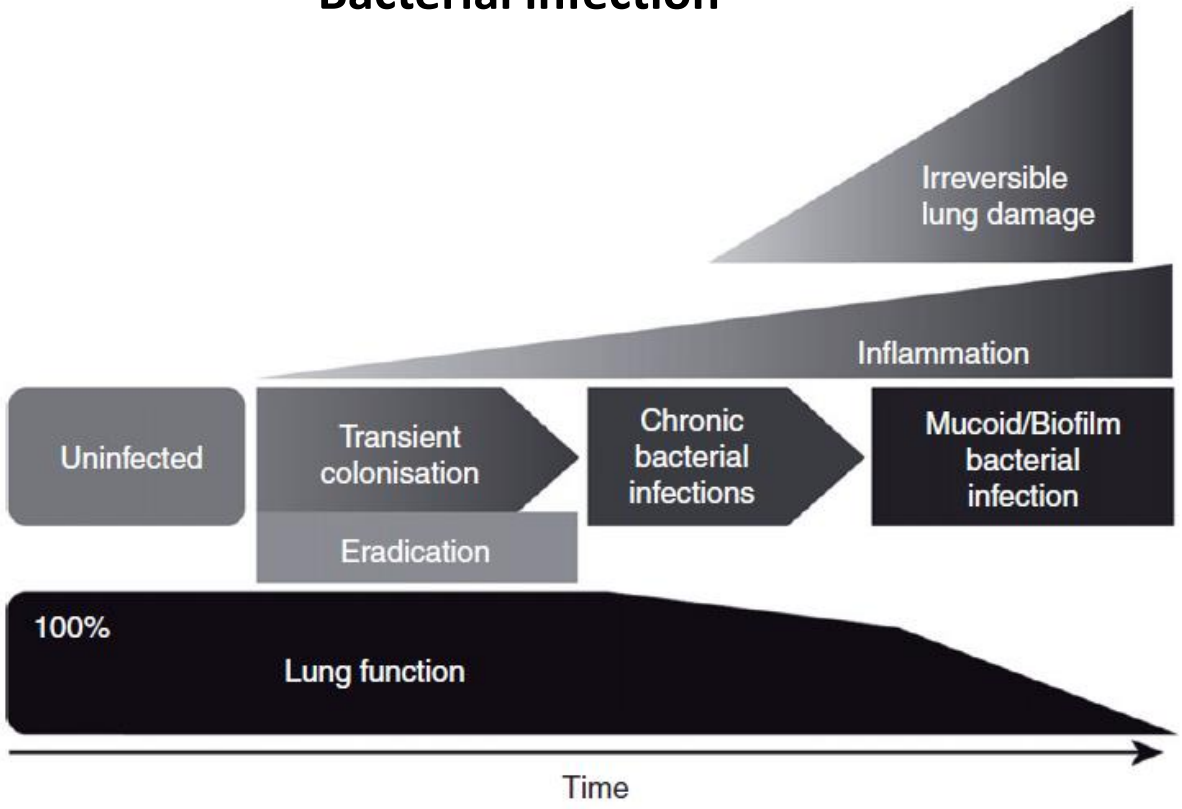
Mucus
Human



Minipig
CFTR -/-



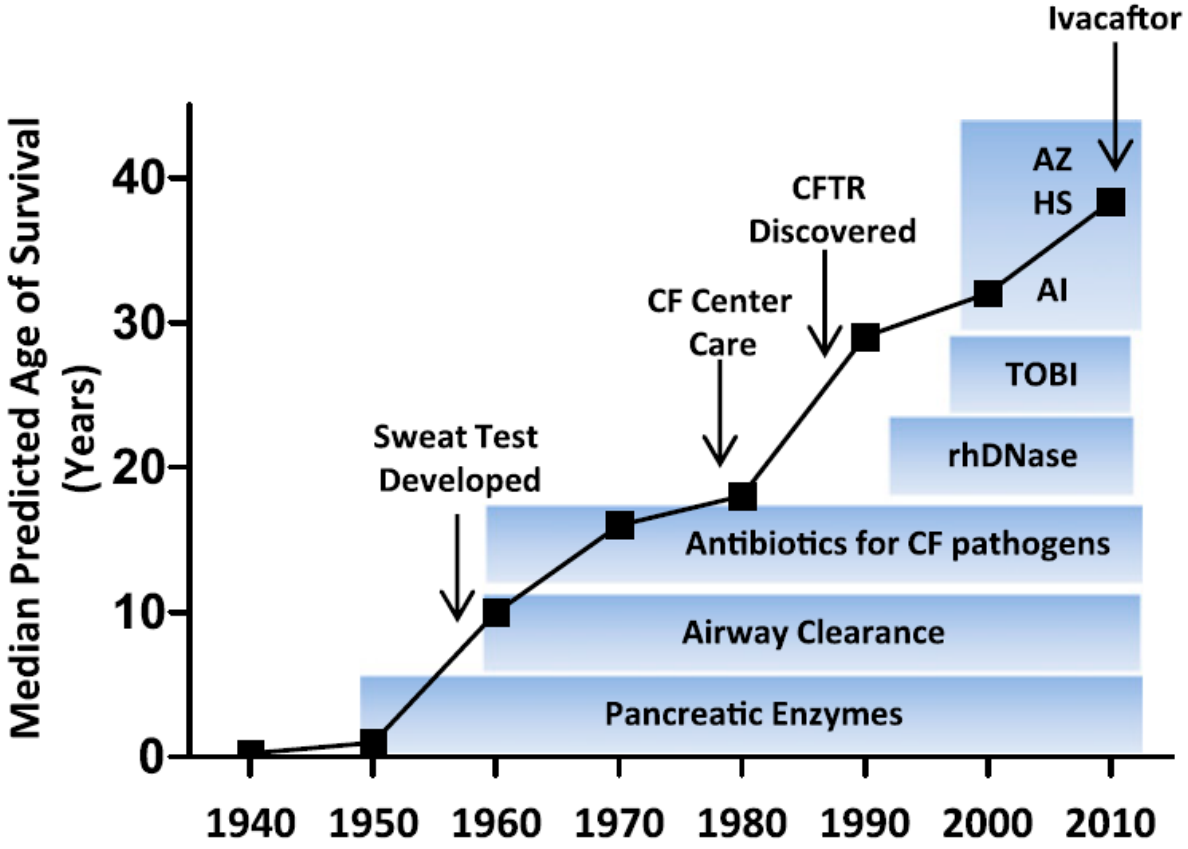
Bacterial infection



Burgel PR et al *Thorax* 2007; 62: 153-161
Greally et al *CMRO* 2012; 28: 1059–1067
Stoltz DA; Sci Transl Med. 2010; 2(29): 29-31

Cystic fibrosis: median age of survival vs. treatment

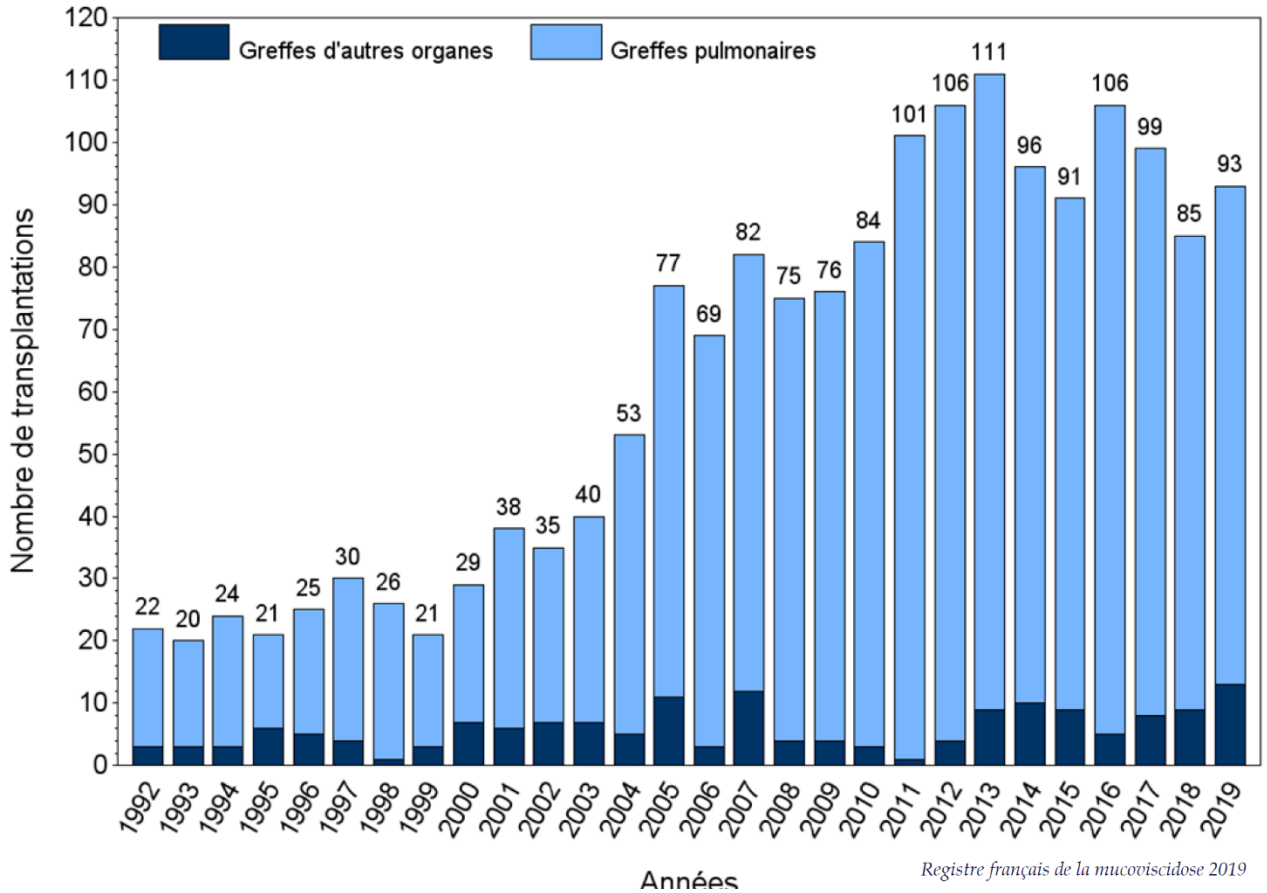
- *Clancy & Jain, AJRCCM 2012;186:593-7*



Transplantation for cystic fibrosis in France

Approximately 30% of all lung transplantations until 2019

1st or 2nd cause of lung transplantation

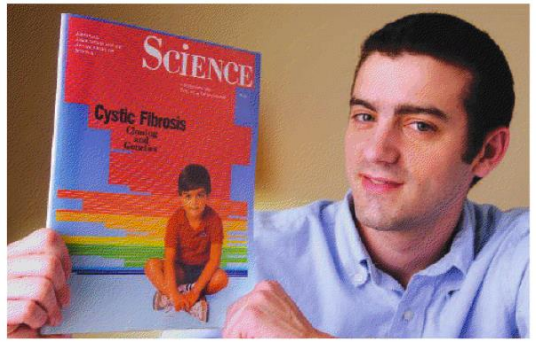


CF demography has changed over the past 30 years

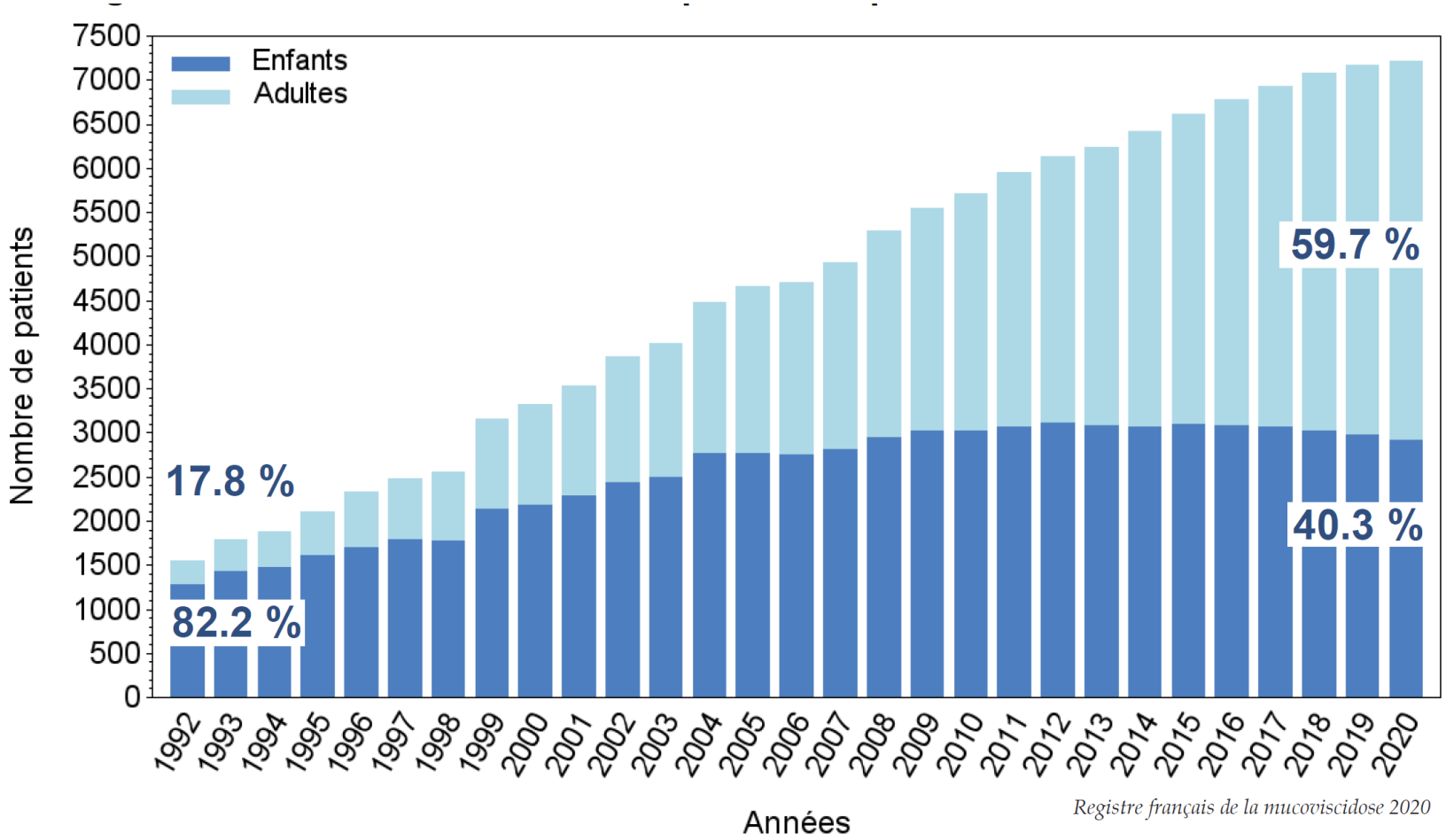
From a pediatric to a pediatric and adult disease

1989

2009



French CF population from 1992 to 2020



Registre français de la mucoviscidose 2020

Agenda

Cystic fibrosis

Diagnosis

Therapeutic revolution

Criteria for a diagnosis of cystic fibrosis

Criteria for a diagnosis of CF.

(1) One or more characteristic phenotypic features
- chronic sinopulmonary disease
- gastrointestinal and nutritional abnormalities
- salt depletion syndrome
- male urogenital abnormalities

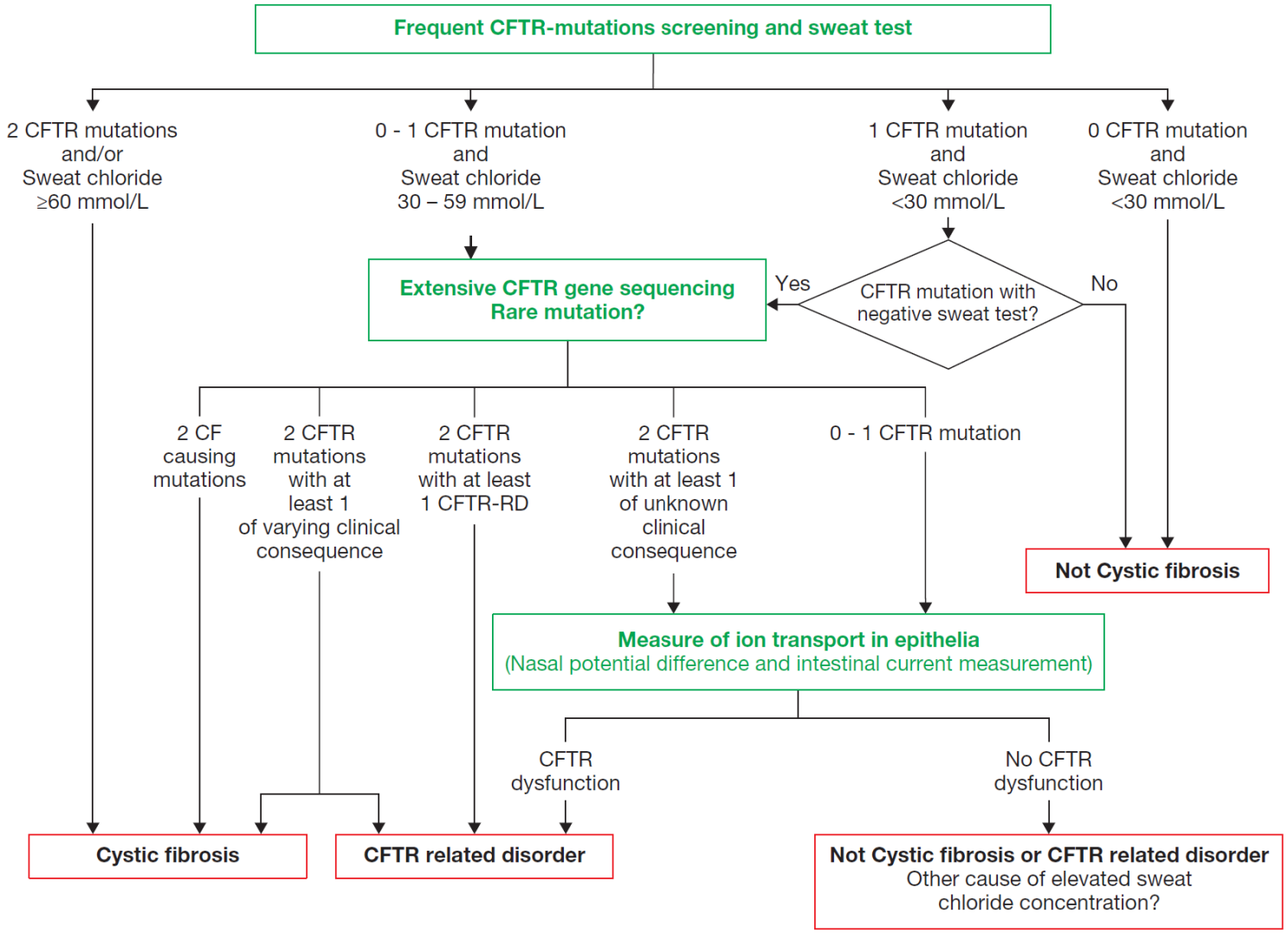
Or a history of CF in a sibling
Or a positive newborn screening test
(2) with laboratory evidence of a CFTR abnormality
- elevated sweat chloride concentration > 60 mmol/L
- and/or identification of mutations in each gene known to cause CF

(3) and/or in vivo demonstration of characteristic ion transport abnormalities by ancillary tests (nasal potential difference; intestinal current measurement) *

* ancillary tests are recommended in patients with intermediate sweat chloride values (30-59 mmol/L), and fewer than two CF-causing mutations.

Archives de Pédiatrie 27 (2020) eS25–eS29

Sweat test and *CFTR* mutations



Archives de Pédiatrie 27 (2020) eS25–eS29

Agenda

Cystic fibrosis

CFTR modulators

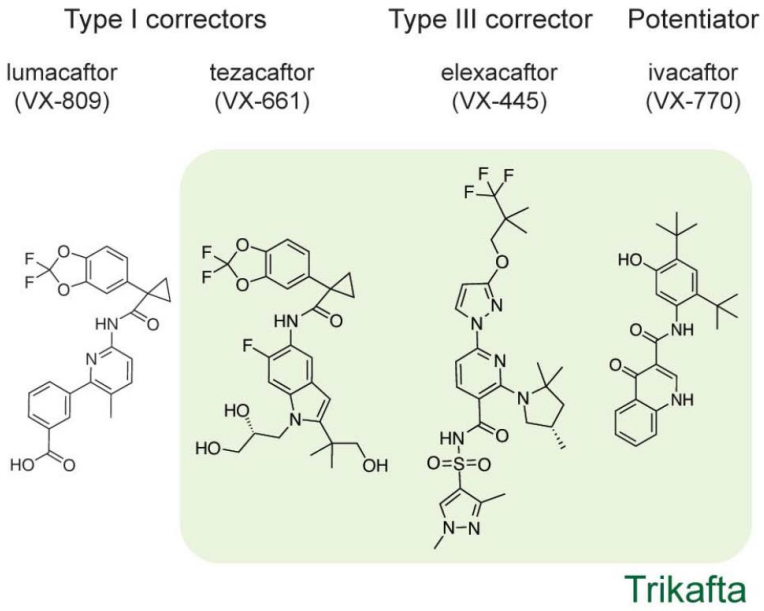
What’s next?

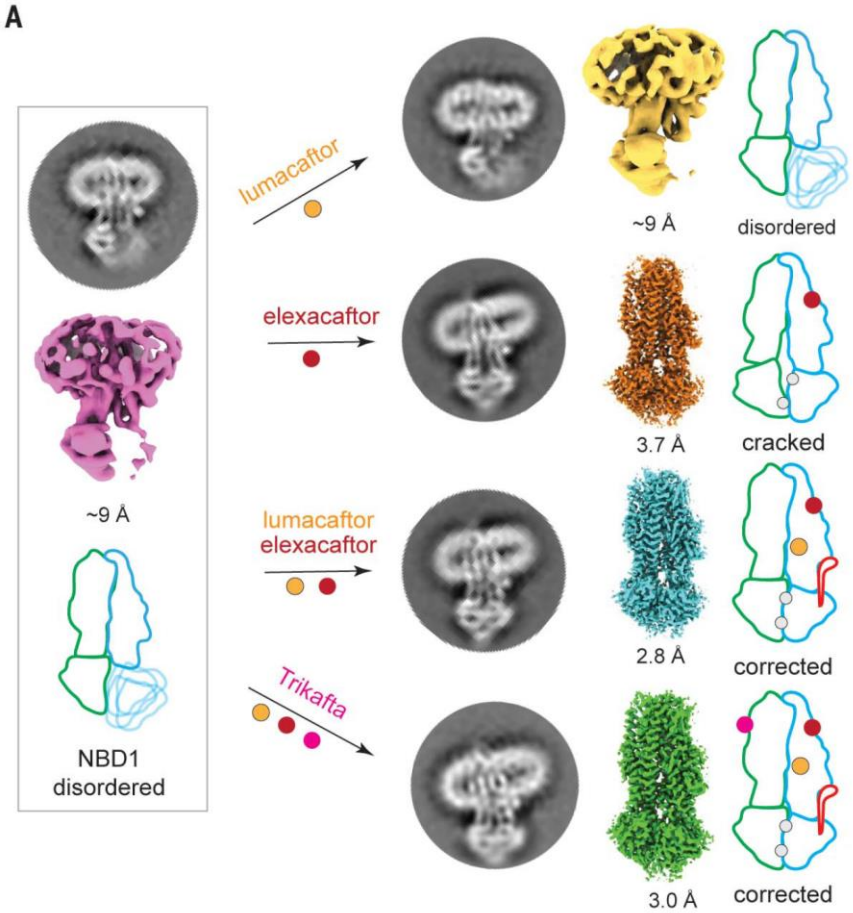
CFTR modulators

CYSTIC FIBROSIS

Molecular structures reveal synergistic rescue of Δ508 CFTR by Trikafta modulators

Karol Fiedorczuk[1] and Jue Chen[1,2]*

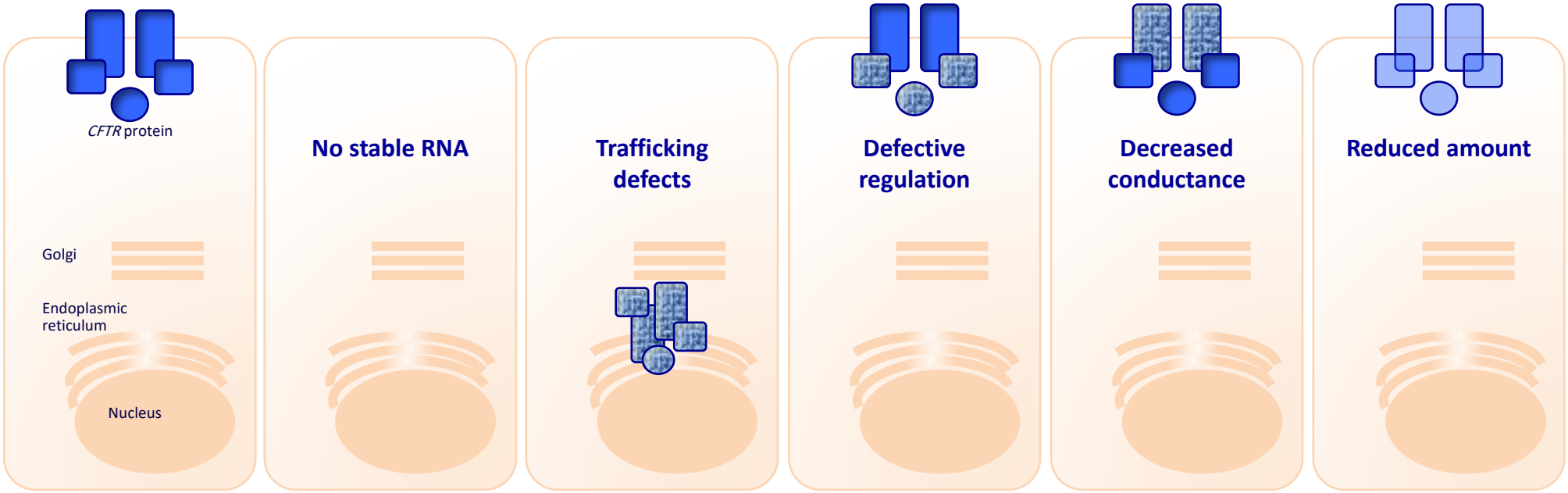




Fiedorczuk et al., Science 378, 284–290 (2022)

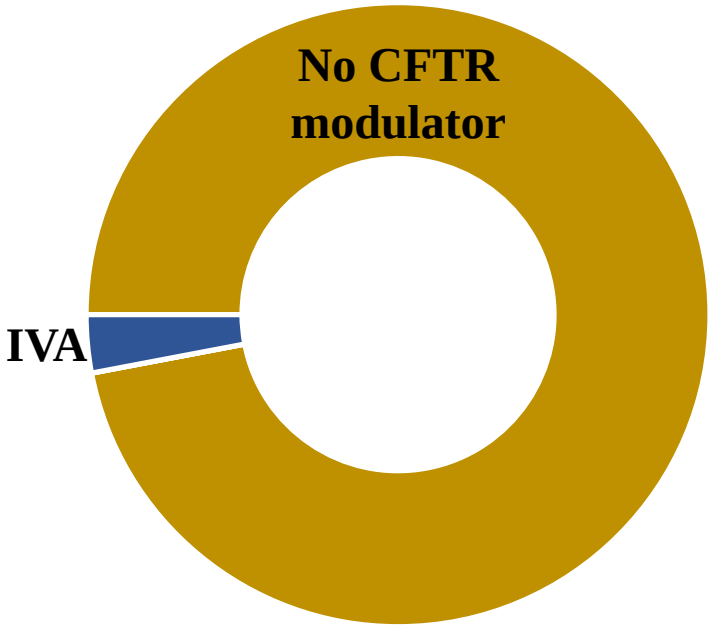
CFTR Mutations: classification and effects on CFTR protein localization and function

% of people with CF who have at least one mutation in that class



Normal	Class I	Class II	Class III	Class IV	Class V
	G542X W1282X dele2,3(21 kb)	**F508del** N1303K	**G551D** **G178R** **S549N** **S549R** **G551S** **G1244E** **G1349D** **S1251N** **S1255P**	**R117H** R334W R347P	3849+10kbC→T 2789+5G→A A455E

Proportion of the French CF population aged 12 years and older eligible to CFTR modulator therapy between 2011 and 2023



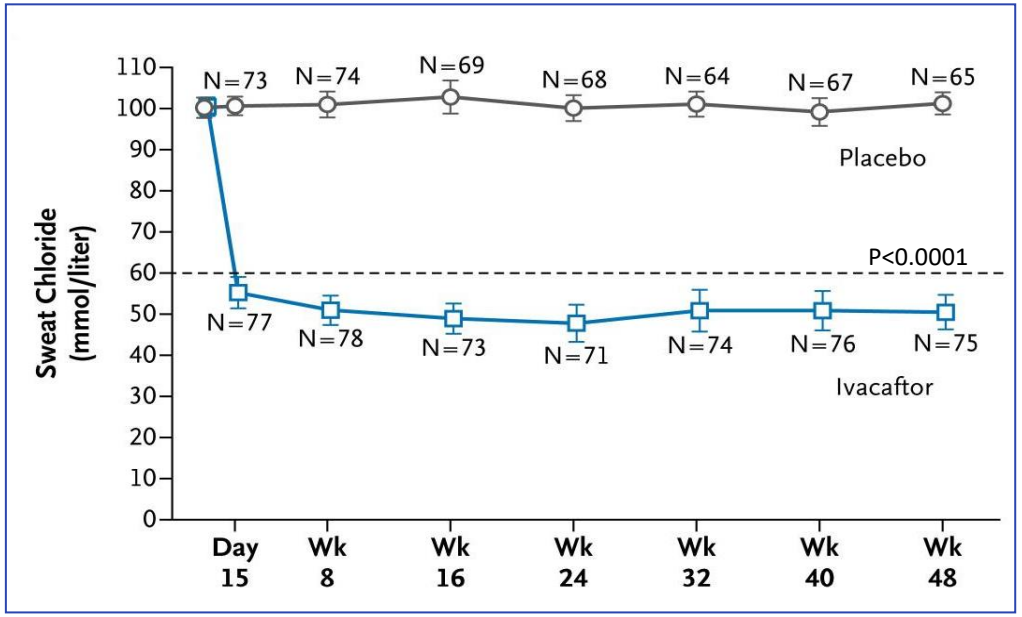
2011

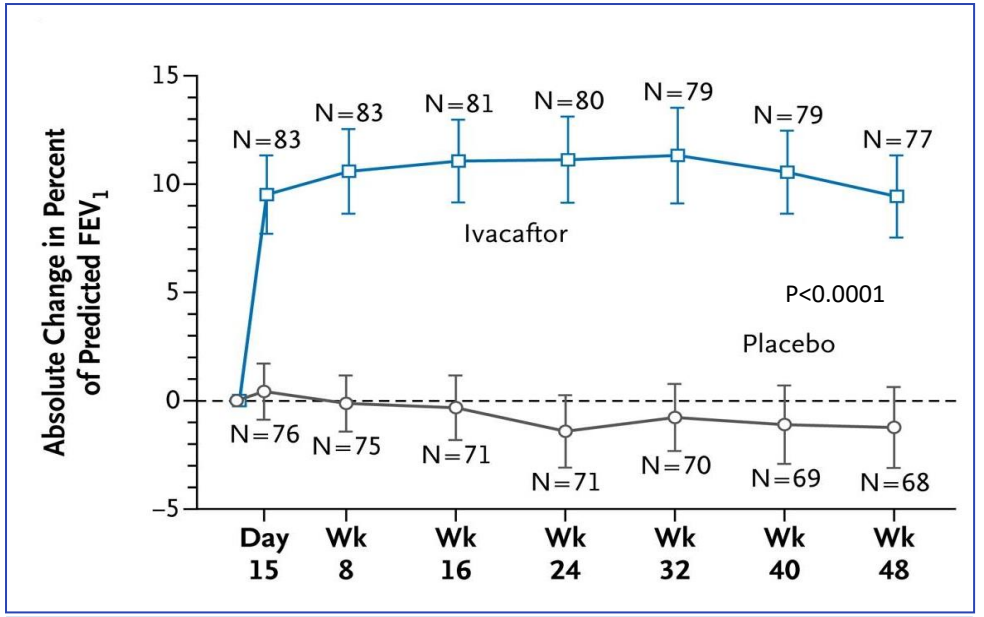
G551D

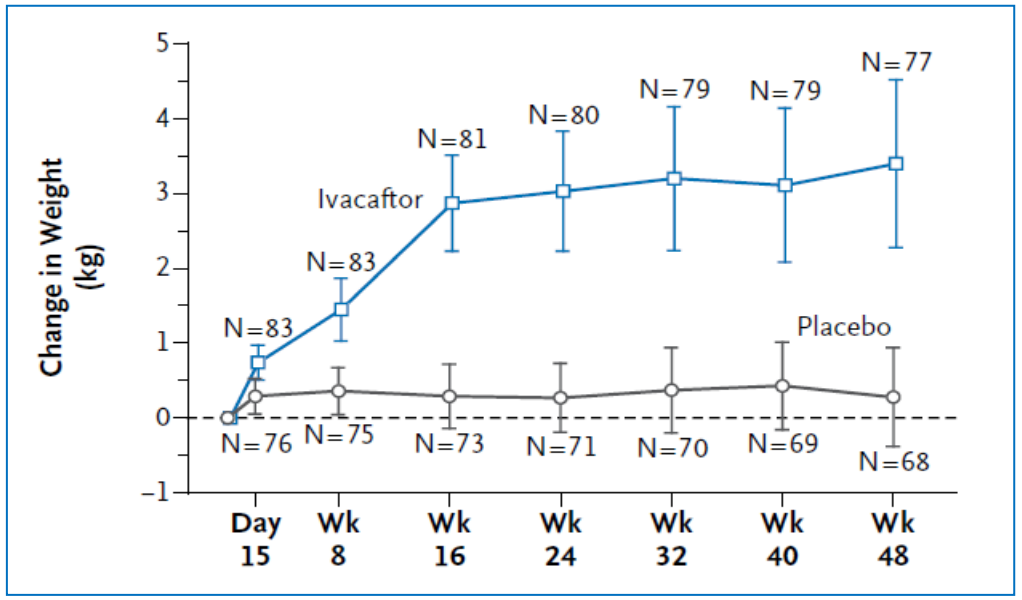
Gating mutations

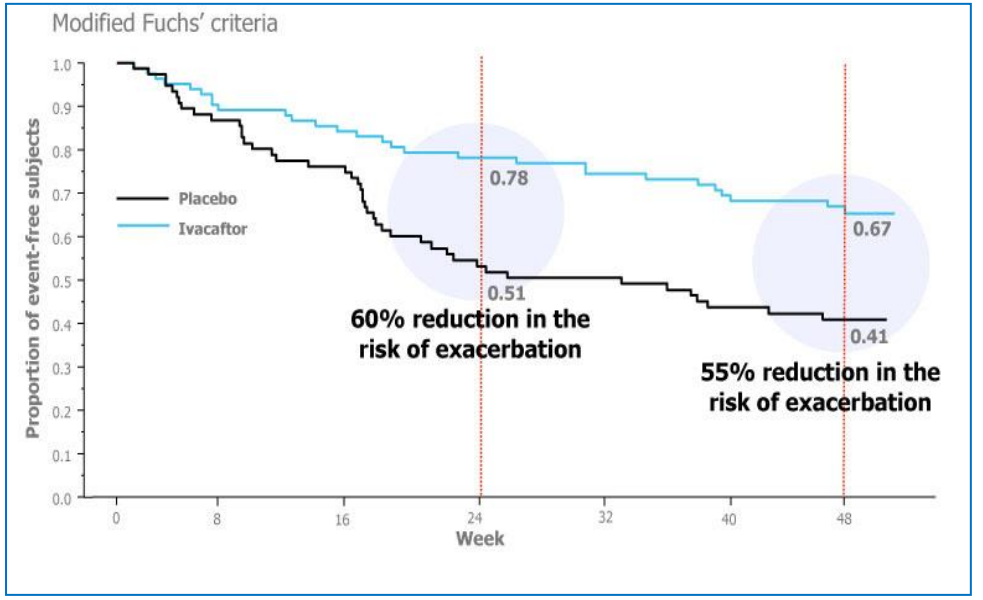
Regard L et al. Cells **2022**, 11, 1769

Effects of ivacaftor in CF adolescents and adults with a G551D *CFTR* mutation



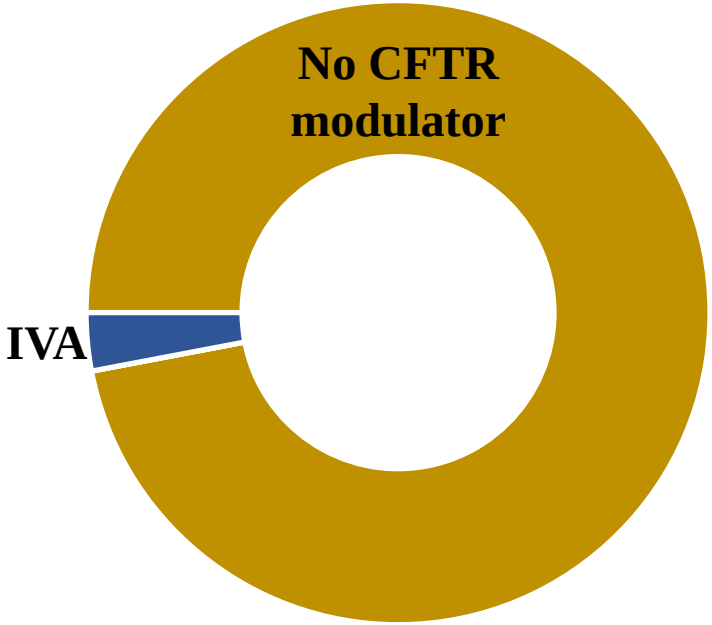






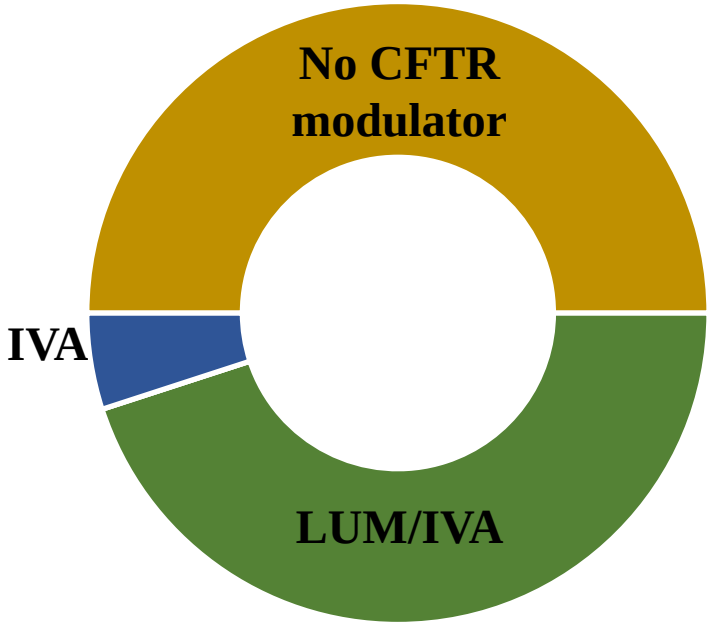
Ramsey & al, N Engl J Med 2011;365:1663-72, Davies et al, AJRCCM 2013; 187:1217-25

Proportion of the French CF population aged 12 years and older eligible to CFTR modulator therapy between 2011 and 2023



2011

G551D
Gating mutations

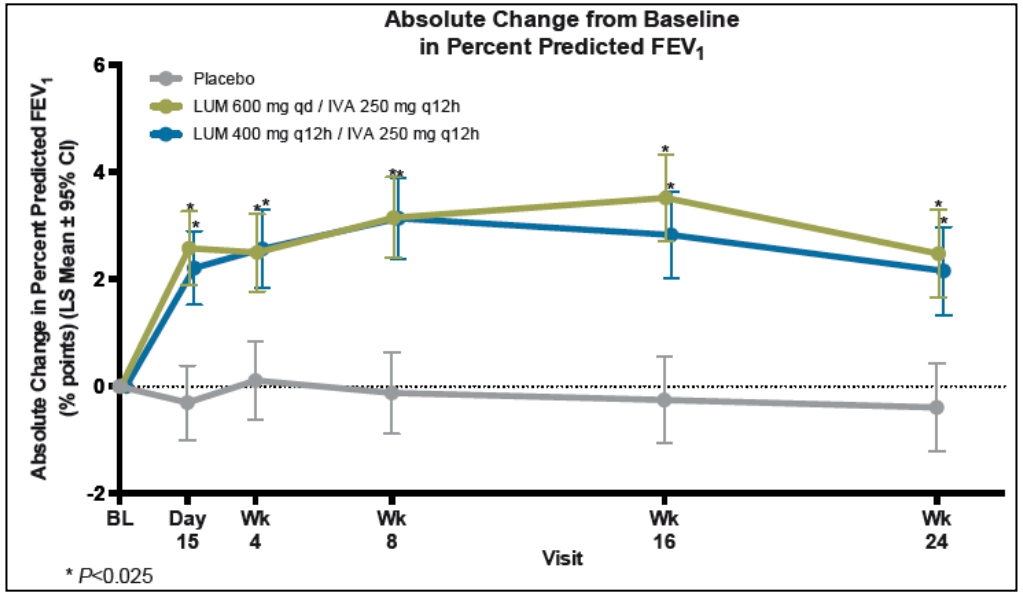


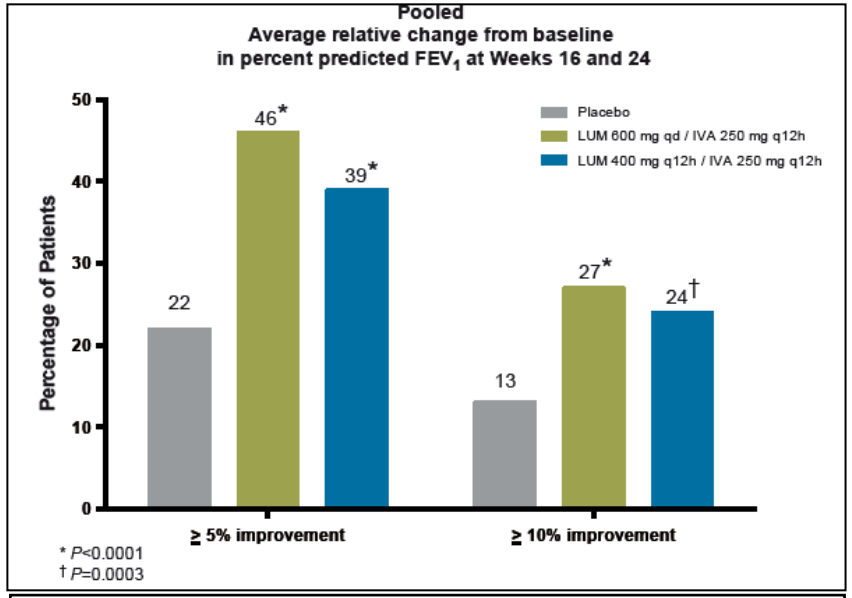
2015

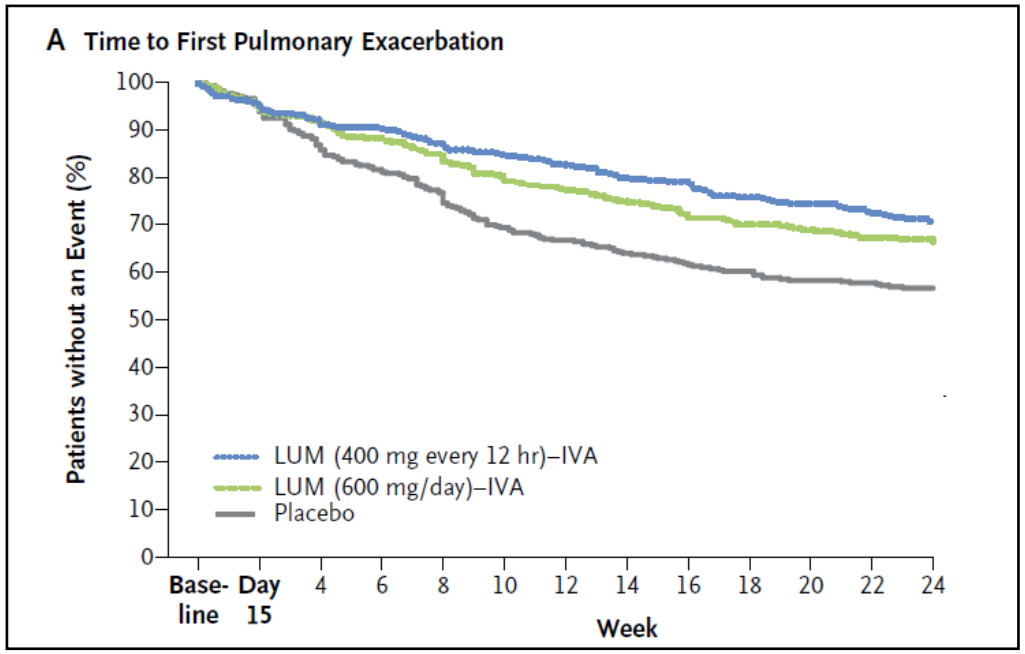
G551D
Gating mutations
F508del/F508del

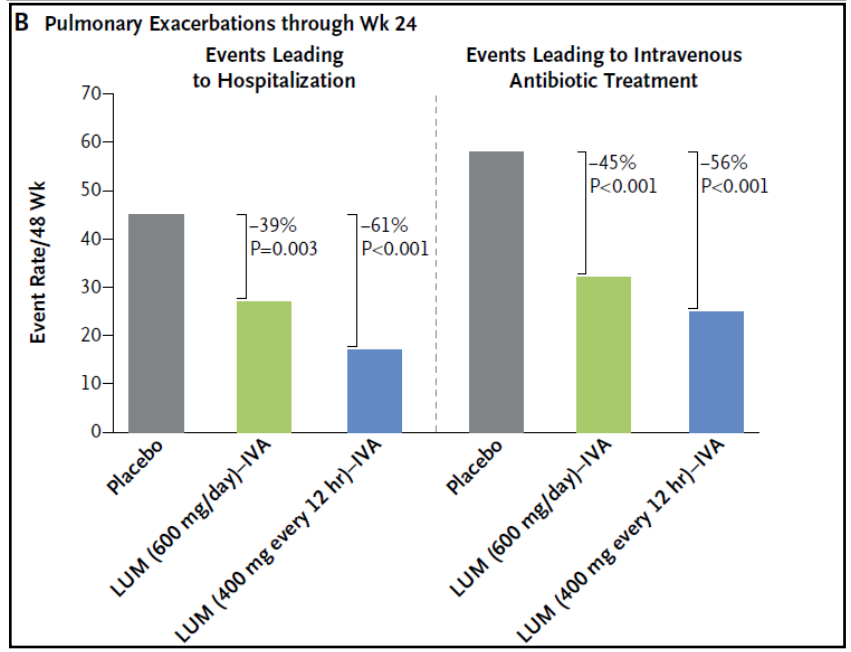
Regard L et al. Cells **2022**, 11, 1769

Effects of Lumacaftor-Ivacaftor in adolescents and adults homozygous for F508del



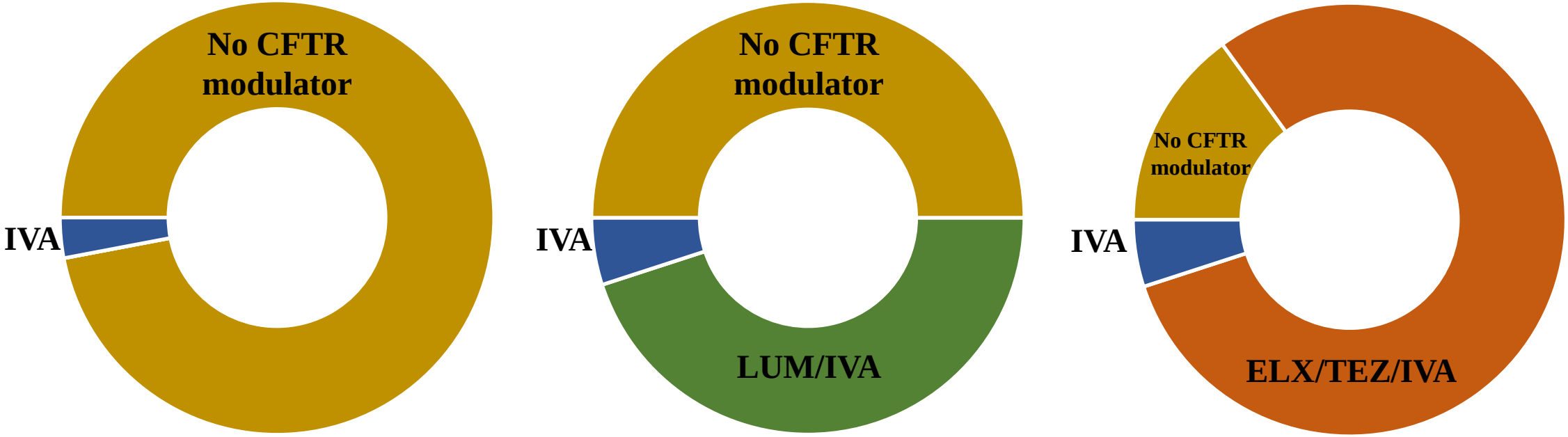






July 2015: FDA approval and Nov 2015: EMA approval of **Orkambi™** to treat F508del/F508del CF patients aged 12 and older

Proportion of the French CF population aged 12 years and older eligible to CFTR modulator therapy between 2011 and 2023



2011

G551D
Gating mutations

2015

G551D
Gating mutations
F508del/F508del

2021

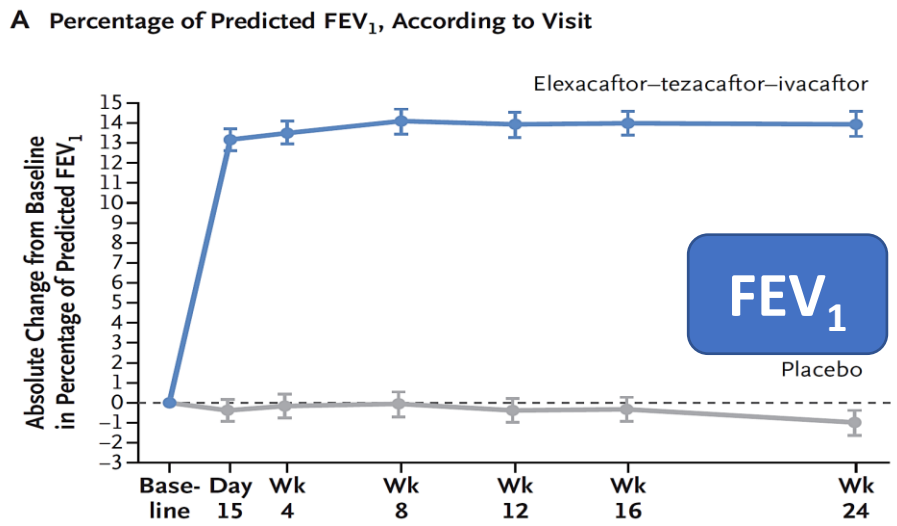
G551D
Gating mutations
F508del/any

Regard L et al. Cells **2022**, 11, 1769. https://doi.org/10.3390/cells11111769

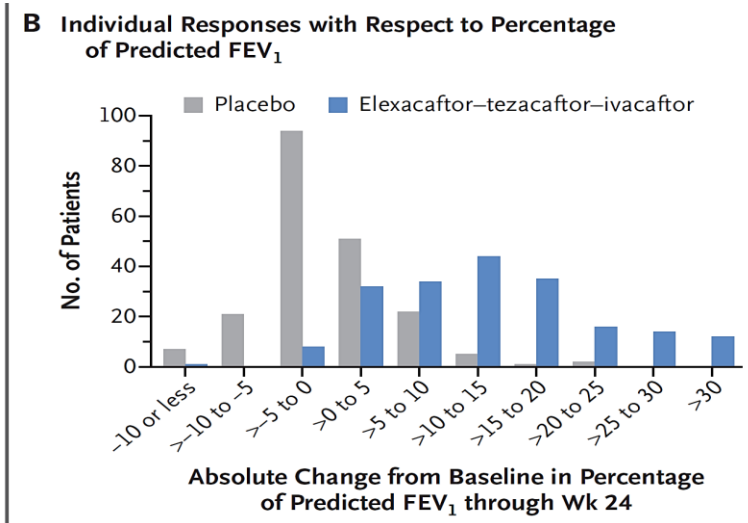
Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele

12 years and older
ppFEV$_1$ 40-90%

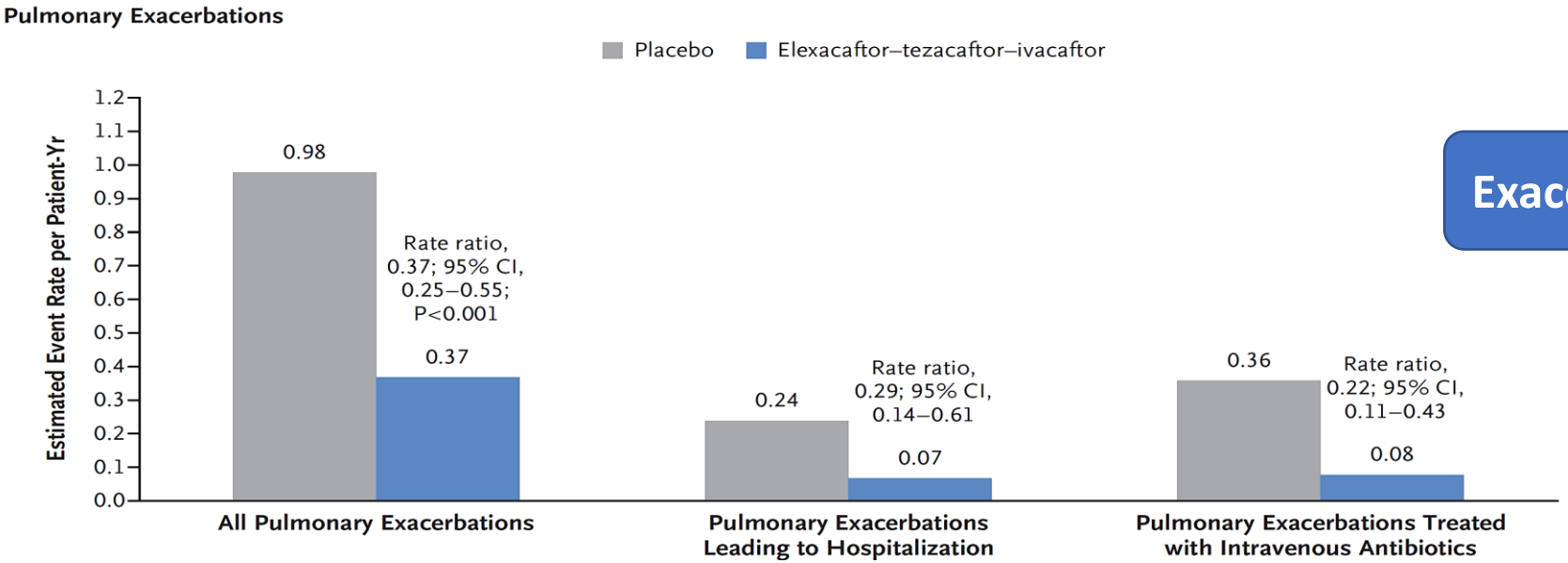
6 months



FEV$_1$



FEV$_1$



Exacerbations

N Engl J Med 2019;381:1809-19.

American Journal of Respiratory and Critical Care Medicine

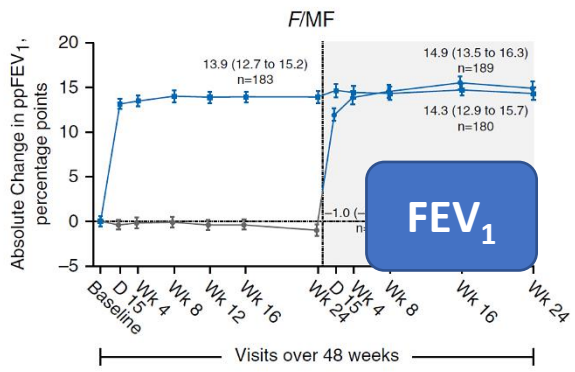
Volume 203 Number 3 | February 1 2021

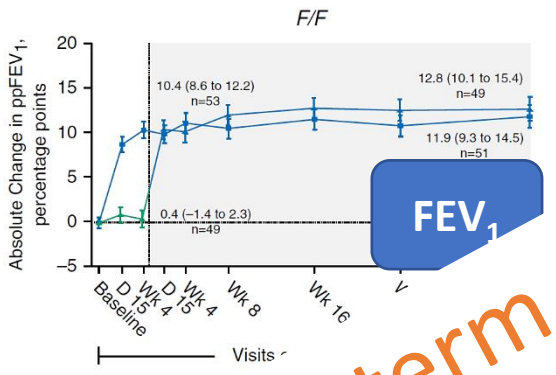
Check for updates

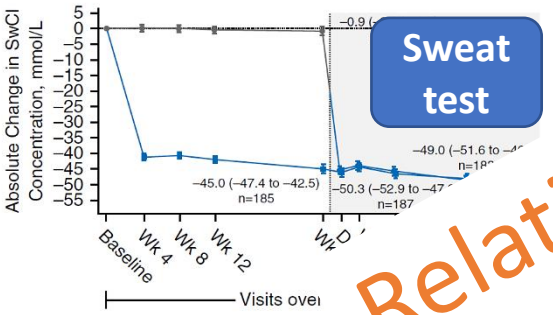
Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor for 24 Weeks or Longer in People with Cystic Fibrosis and One or More *F508del* Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial

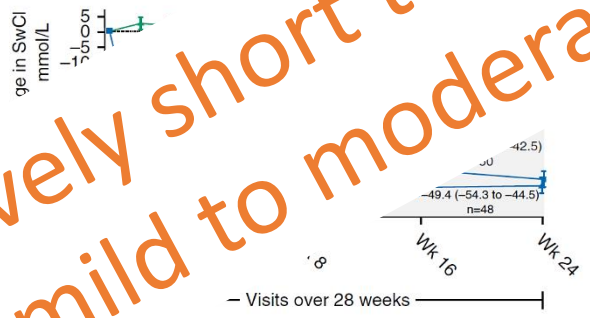
12 years and older, ppFEV
24 to 36 weeks

Relatively short term studies, stable patients, mild to moderate disease, no death

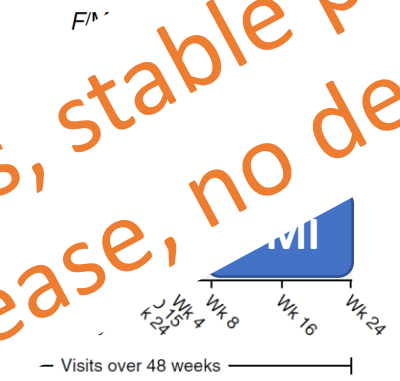


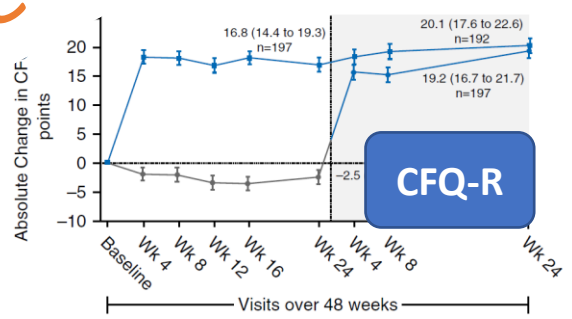




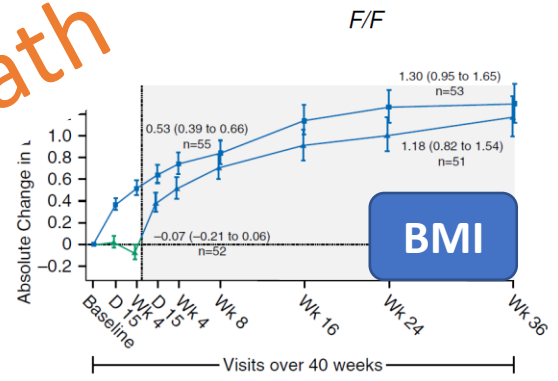


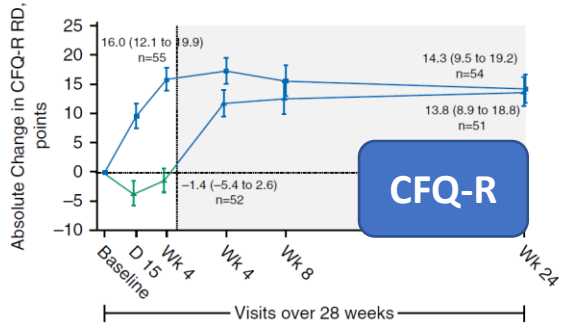
PBO→ELX/TEZ/IVA ■
The white shaded portion of the graph corresp
pivotal study and the gray shaded portion of the
to the OLE.





PBO→ELX/TEZ/IVA ■ ELX/TEZ/IVA
The white shaded portion of the graph corresponds to the *F/MF*
pivotal study and the gray shaded portion of the graph corresponds
to the OLE.





TEZ/IVA →ELX/TEZ/IVA ■ ELX/TEZ/IVA
The white shaded portion of the graph corresponds to the *F/F*
pivotal study and the gray shaded portion of the graph corresponds
to the OLE.

Rapid Improvement after Starting Elexacaftor–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease

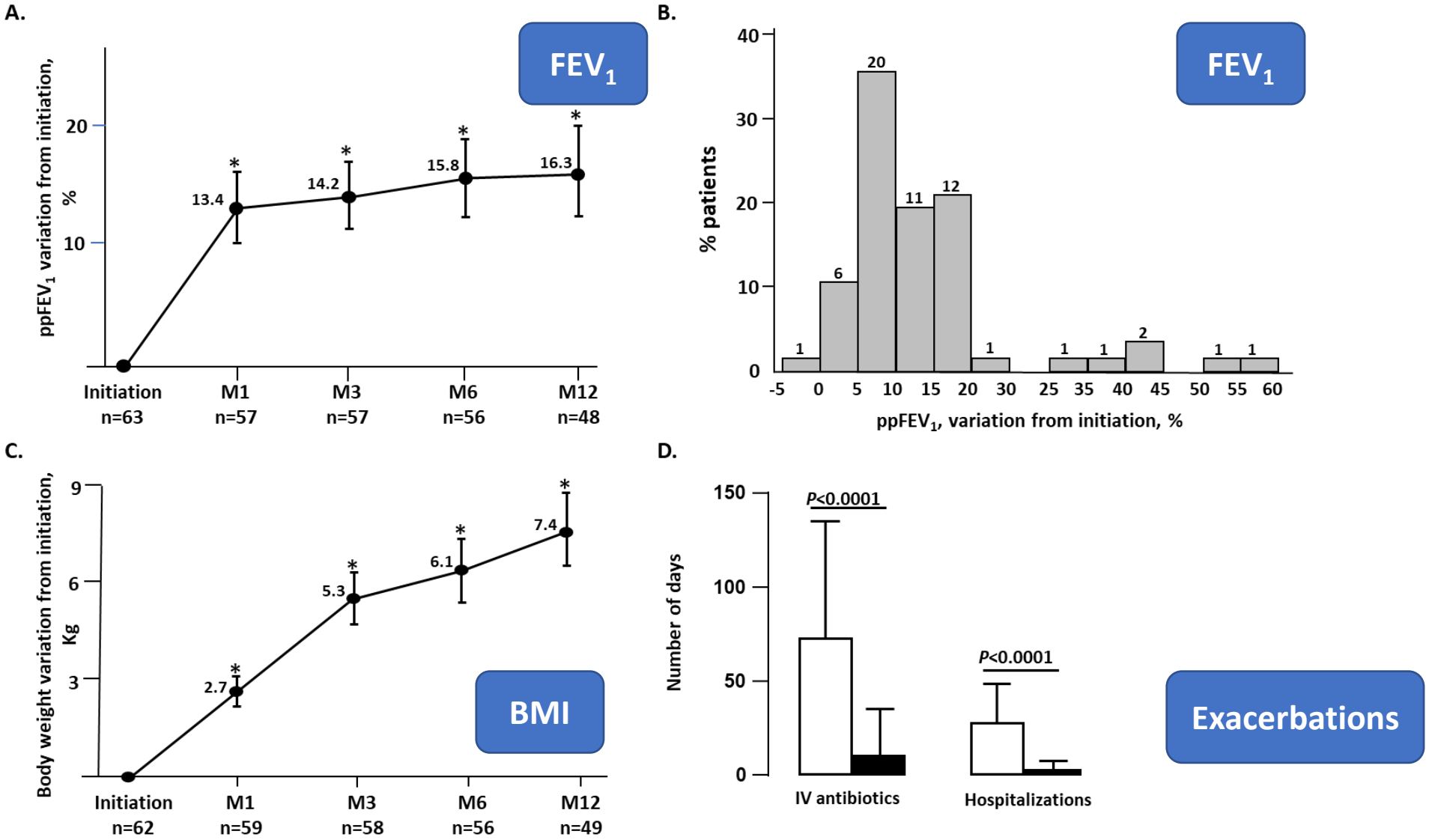
Pierre-Régis Burgel[1,2,3], Isabelle Durieu[3,4,5], Raphaël Chiron[6], Sophie Ramel[7], Isabelle Danner-Boucher[8], Anne Prevotat[9], Dominique Grenet[10], Christophe Marguet[11], Martine Reynaud-Gaubert[12], Julie Macey[13], Laurent Mely[14], Annlyse Fanton[15], Sébastien Quetant[16], Lydie Lemonnier[17], Jean-Louis Paillasseur[18], Jennifer Da Silva[1,3,19], and Clémence Martin[1,2,3]; for the French Cystic Fibrosis Reference Network Study Group

12 years and older
ppFEV$_1$<40

	Not Treated with a CFTR Modulator (*n* = 179)		Treated with a CFTR Modulator (*n* = 57)		*P* Value
ppFEV$_1$					
At initiation	Missing, *n* = 1	29 (24–35)	Missing, *n* = 0	28 (24–33)	0.42
After 1 mo	Missing, *n* = 35	41 (34–50)	Missing, *n* = 6	41 (34–51)	0.87
After 3 mo	Missing, *n* = 33	43 (36–53)	Missing, *n* = 19	42 (35–50)	0.69
Absolute change from initiation, ppFEV$_1$					
After 1 mo	Missing, *n* = 35	+11 (7–17)	Missing, *n* = 6	+11 (8–17)	0.43
After 3 mo	Missing, *n* = 34	+12 (8–20)	Missing, *n* = 19	+13 (7–19)	0.77
After 1 and 3 mo (pooled)*	Missing, *n* = 4	+13 (8–20)	Missing, *n* = 0	+14 (8–20)	0.90
Weight					
At initiation	Missing, *n* = 0	52 (46–60)	Missing, *n* = 0	53 (47–60)	0.89
After 1 mo	Missing, *n* = 28	54 (49–62)	Missing, *n* = 6	56 (49–62)	0.87
After 3 mo	Missing, *n* = 32	58 (52–66)	Missing, *n* = 18	56 (49–63)	0.43
Absolute change from initiation, weight (kg)					
After 1 mo	Missing, *n* = 28	+2.0 (1.0–3.9)	Missing, *n* = 6	+2.0 (0.5–3.5)	0.62
After 3 mo	Missing, *n* = 32	+4.4 (2.7–6.5)	Missing, *n* = 18	+4.0 (2.5–6.0)	0.43
After 1 and 3 mo (pooled)	Missing, *n* = 0	+4.0 (2.0–6.0)	Missing, *n* = 0	+3.0 (2.0–5.0)	0.02

Am J Respir Crit Care Med Vol 204, Iss 1, pp 64–73, Jul 1, 2021

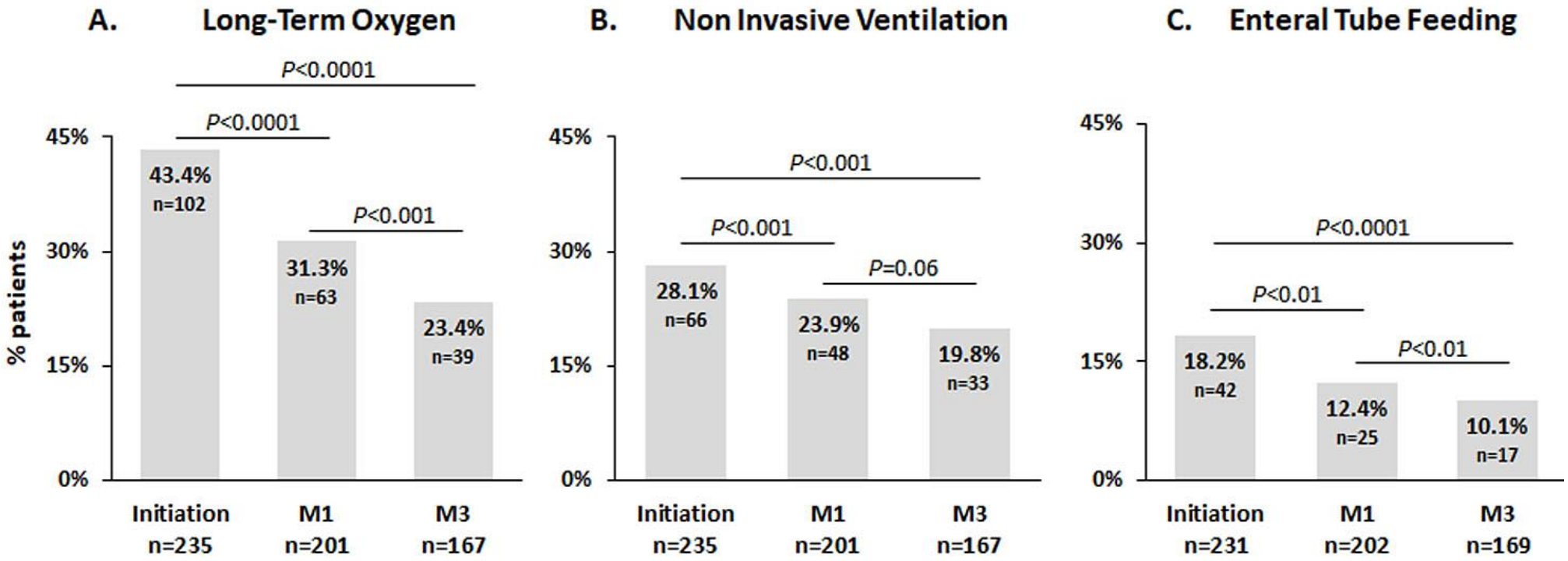
Effects of 12 months of ELX-TEZ-IVA in lung transplant candidates



Martin et al. *J Cyst Fibrosis* 2022; 21(3):489-496

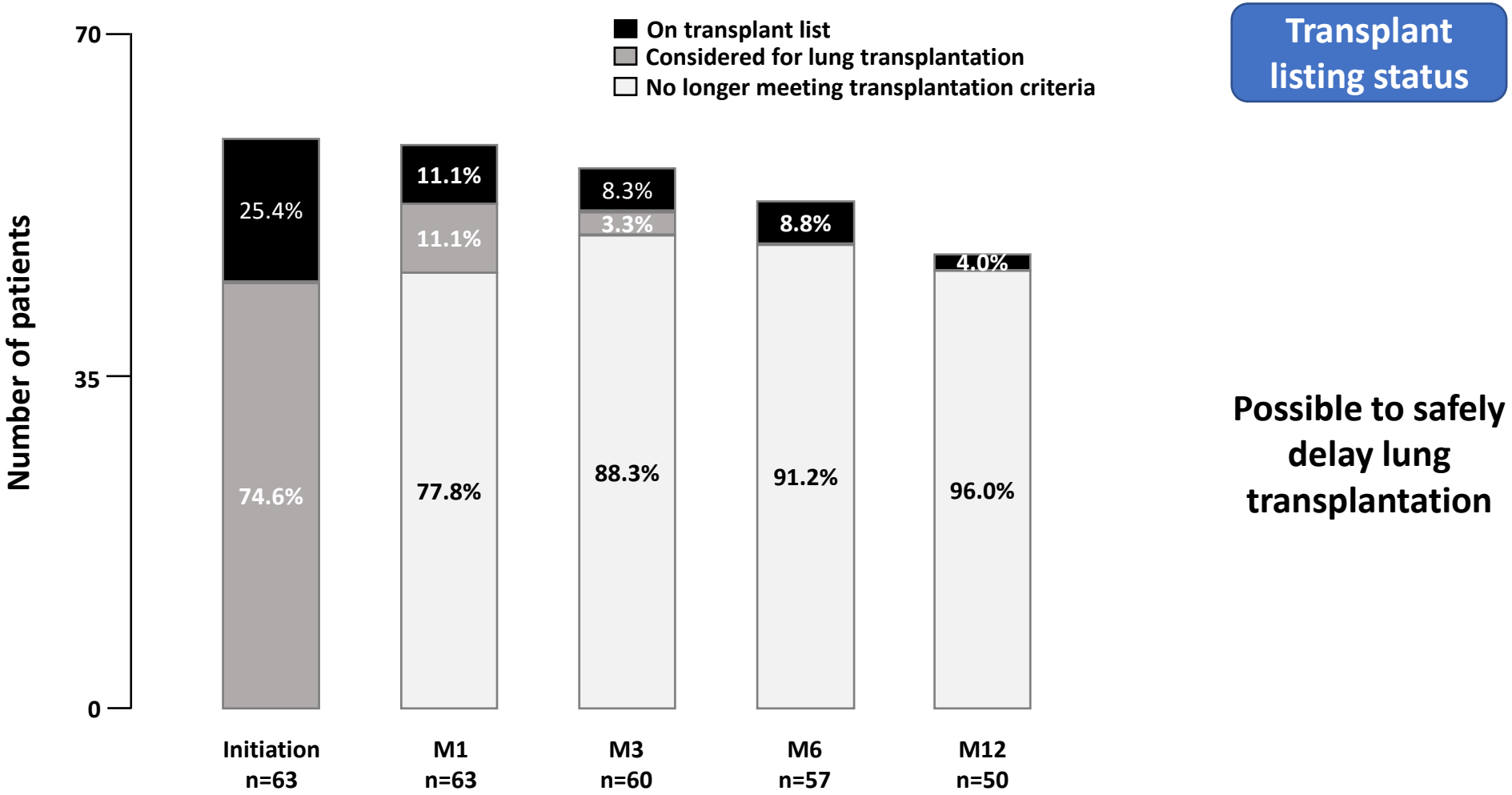
Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease

Discontinuation of selected therapies



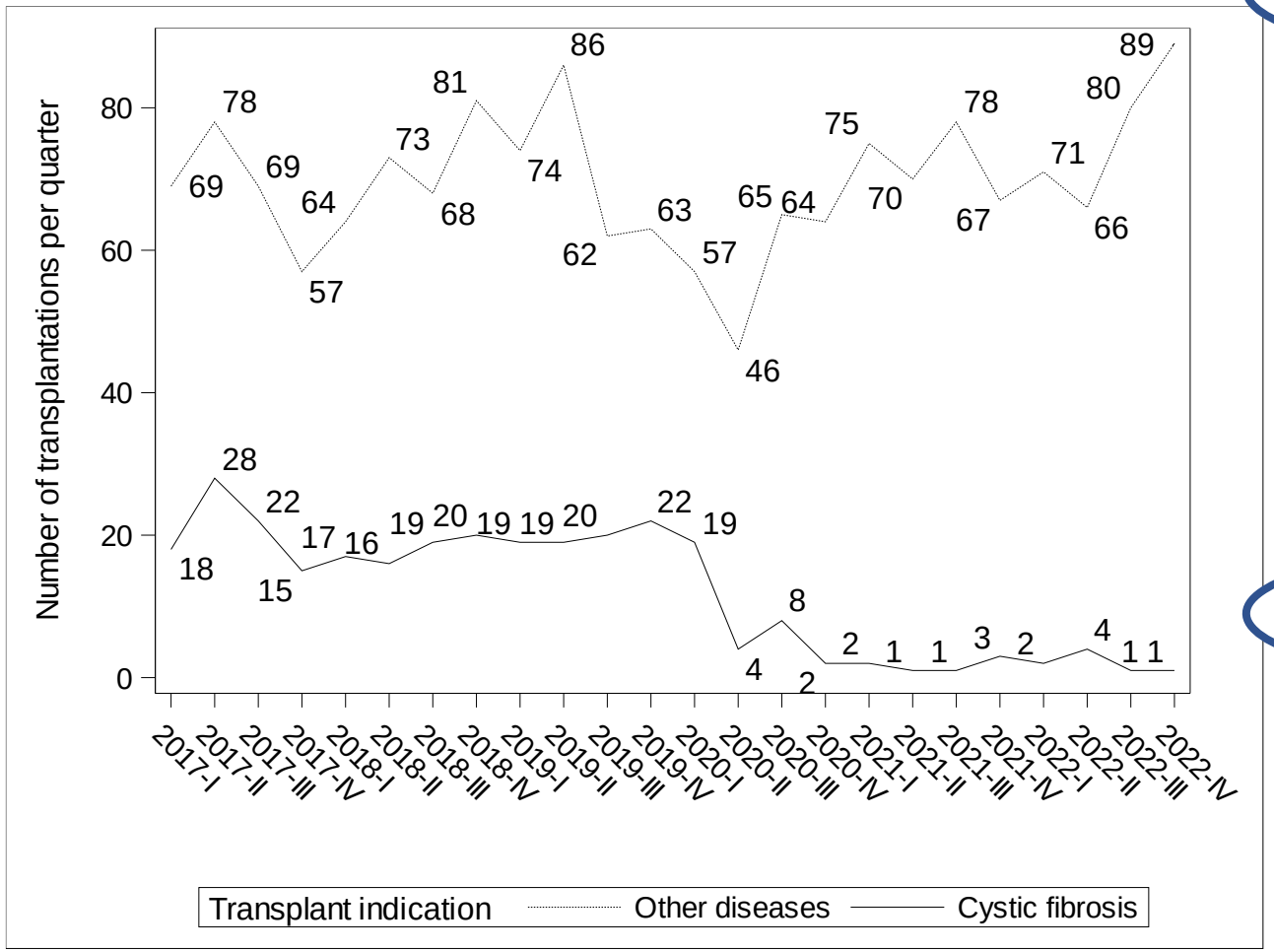
Burgel et al. AJRCCM 2021; doi: 10.1164/rccm.202011-4153OC

Effects of 12 months of ELX-TEZ-IVA in lung transplant candidates



Martin et al. *J Cyst Fibrosis* 2022; 21(3):489-496

Major decrease in lung transplantation in patients with CF in France



Other diseases

Cystic fibrosis

Martin C et al. *Am J Respir Crit Care Med* 2022; 205(5):584-586

EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
P-R. BURGEL ET AL.

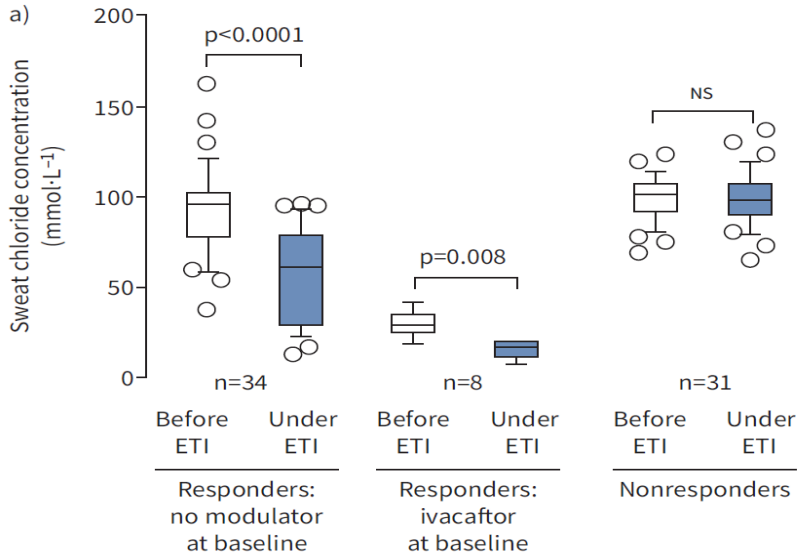
The French compassionate programme of elexacaftor–tezacaftor–ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del *CFTR* variant

Burgel et al. *Eur Respir J* 2023; in press (https://doi.org/10.1183/13993003.02437-2022).

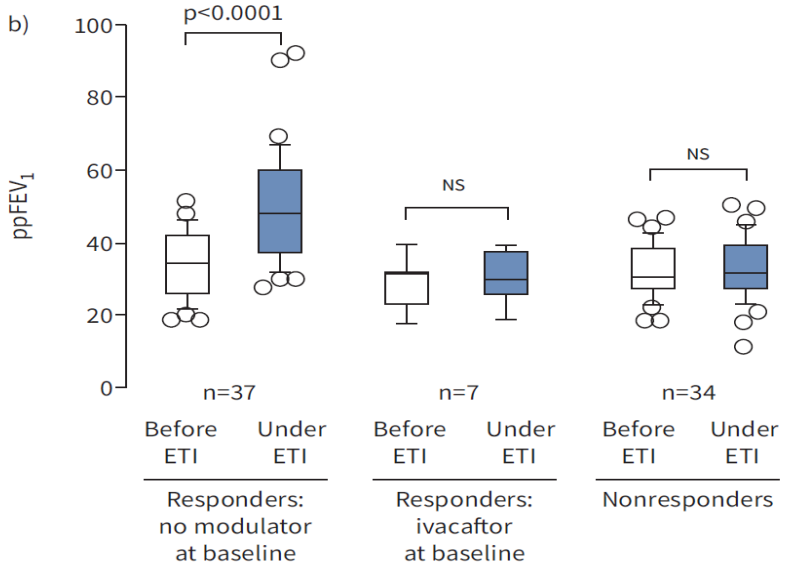
15% of patients with Cystic fibrosis have no F508del mutation
84 patients tested: 55% have positive response to ELX-TEZ-IVA

After
4-6 weeks

Sweat test



FEV1



Shareable abstract (@ERSpublications)
A large subset of people with cystic fibrosis and advanced lung disease but no F508del variant may respond to elexacaftor–tezacaftor–ivacaftor. The observed clinical benefits seem comparable to those described in patients with the F508del variant. https://bit.ly/3YATRfQ

Conclusion

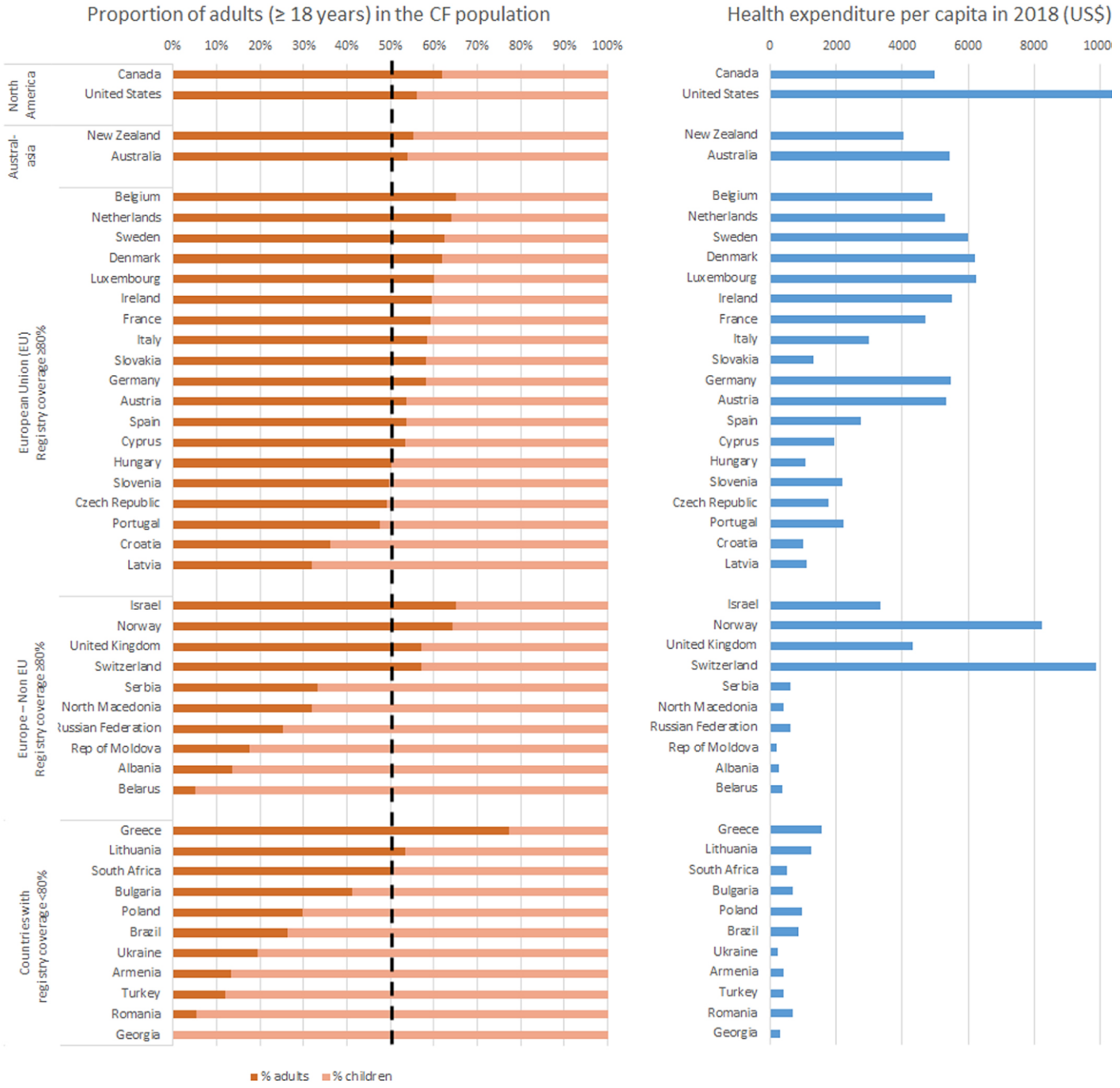
- CF has changed over the past 50 years due to better care
- In the past 3 years: elexacaftor-tezacaftor-ivacaftor
  - Rapid improvement in symptoms/lung function/weight gain/lung transplantation
  - Elexacaftor-tezacaftor-ivacaftor:
    - ~85 % of pwCF with at least one F508del mutation
    - 15 % not eligible no F508del mutation:
      - Half respond to elexacaftor-tezacaftor-ivacaftor
      - Half will need newer therapeutic advance
    - High (unjustified!) cost: 150,000 $ /patient/year
    - Manufacturing cost: 5,000$/patient/year

What patients say

following initiation of elexacaftor- tezacaftor-ivacaftor

Martin C, Burnet E et al. *Respir Med Res* 2021 https://doi.org/10.1016/j.resmer.2021.100829

Proportion of adults in the CF population: relation with health expenditure per capita



Burgel et al. Chest 2022,
https://doi.org/10.1016/j.chest.2022.07.004