Ti ricordiamo che questo materiale
è di proprietà dell'Autore.
Come partecipante al
XXVIII CONGRESSO NAZIONALE SIMRI
questo materiale ti è fornito da SIMRI
per esclusivo uso personale
concesso dall'Autore

Società Italiana per le Malattie Respiratorie Infantili **SIMRI**

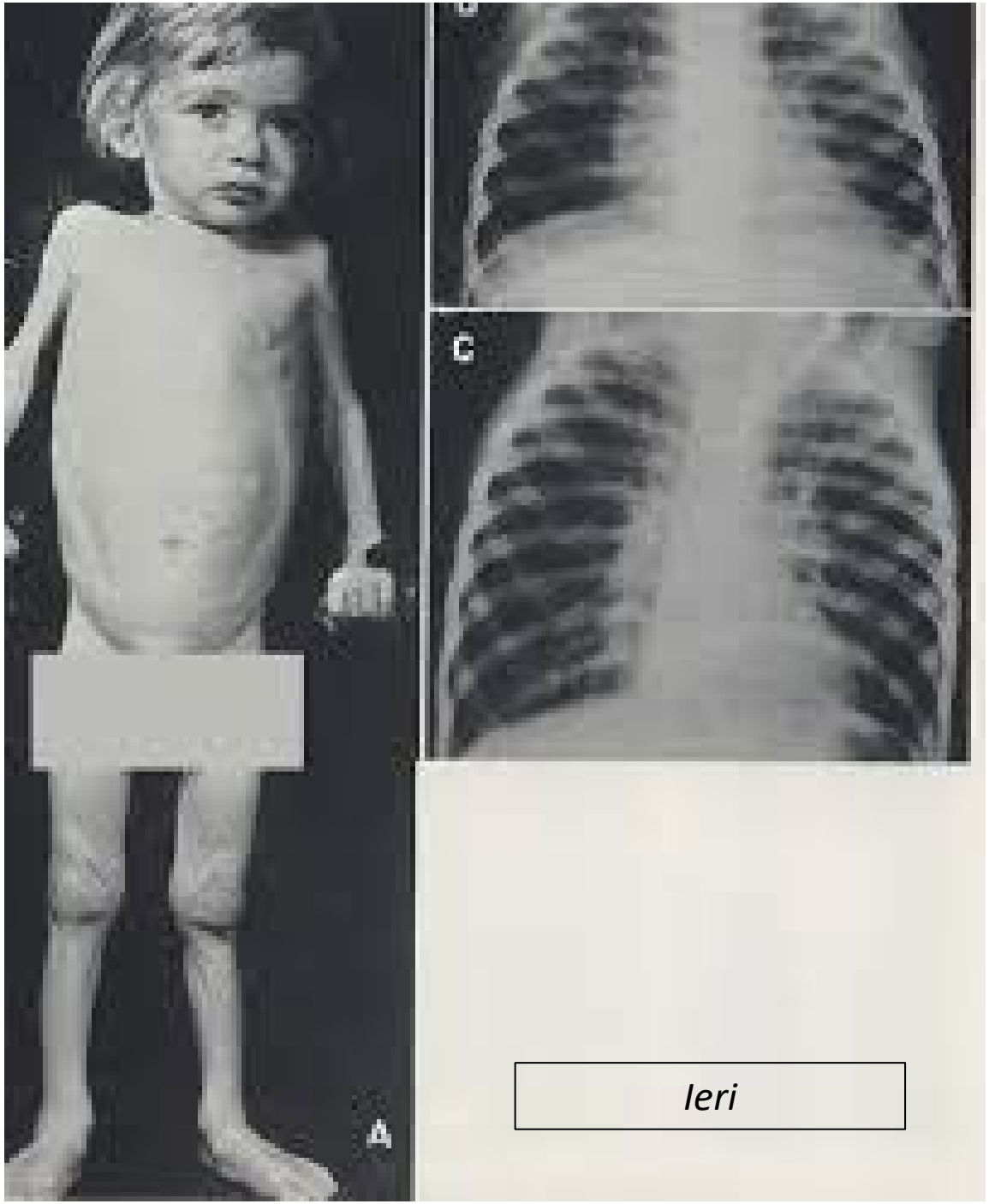
La Fibrosi Cistica

«Oggi»

Giuseppe F. Parisi

Pediatra

UOC Broncopneumologia Pediatrica e Fibrosi Cistica
AOU Policlinico – San Marco – Catania
Direttore: Prof. S. Leonardi



Ieri

Oggi

*Cystic fibrosis (CF) was first recognized as a separate disease entity in **1938** when autopsy studies of malnourished infants distinguished a disease of mucus plugging of the glandular ducts, termed "cystic fibrosis of the pancreas," from others with celiac syndrome. This disease was characterized by malabsorption of fat and protein, steatorrhea, growth failure, and pulmonary infection.*

«LA MALATTIA DAL BACIO SALATO»

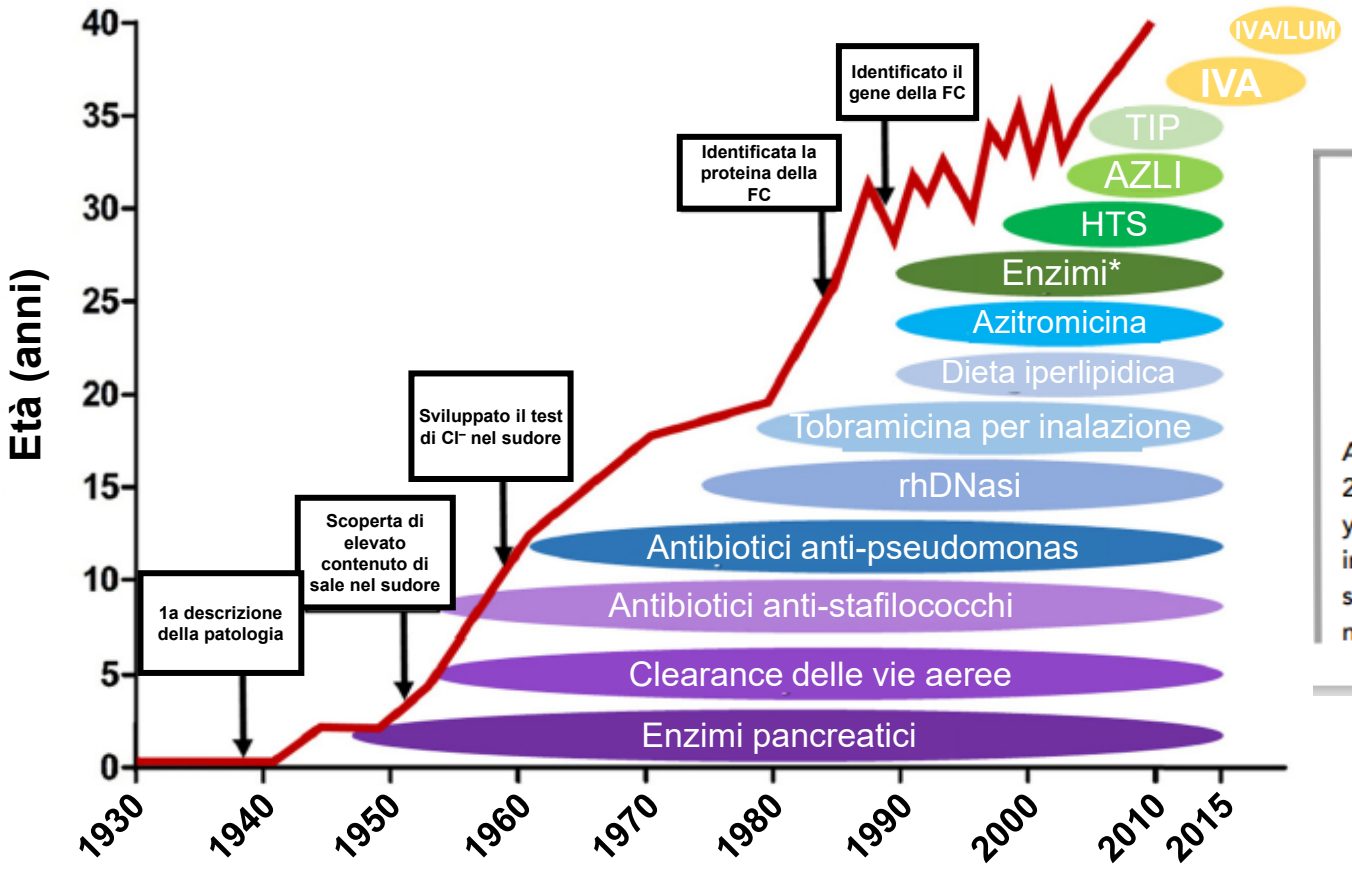
Già le mamme romane, due millenni fa, riconoscevano il bambino malato per il sapore di mare nel baciargli la fronte.

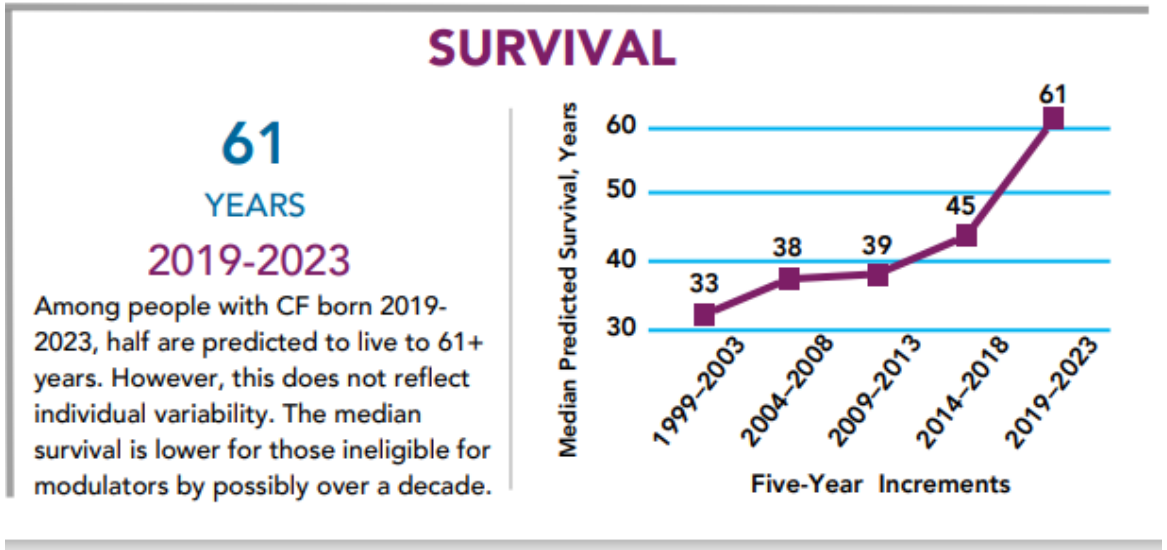
Nel XVIII secolo in uno scritto veniva riportato:

“Guai per il bambino che sapora di salato da un bacio sulla fronte, perché è maledetto e presto deve morire”

Progressione della FC

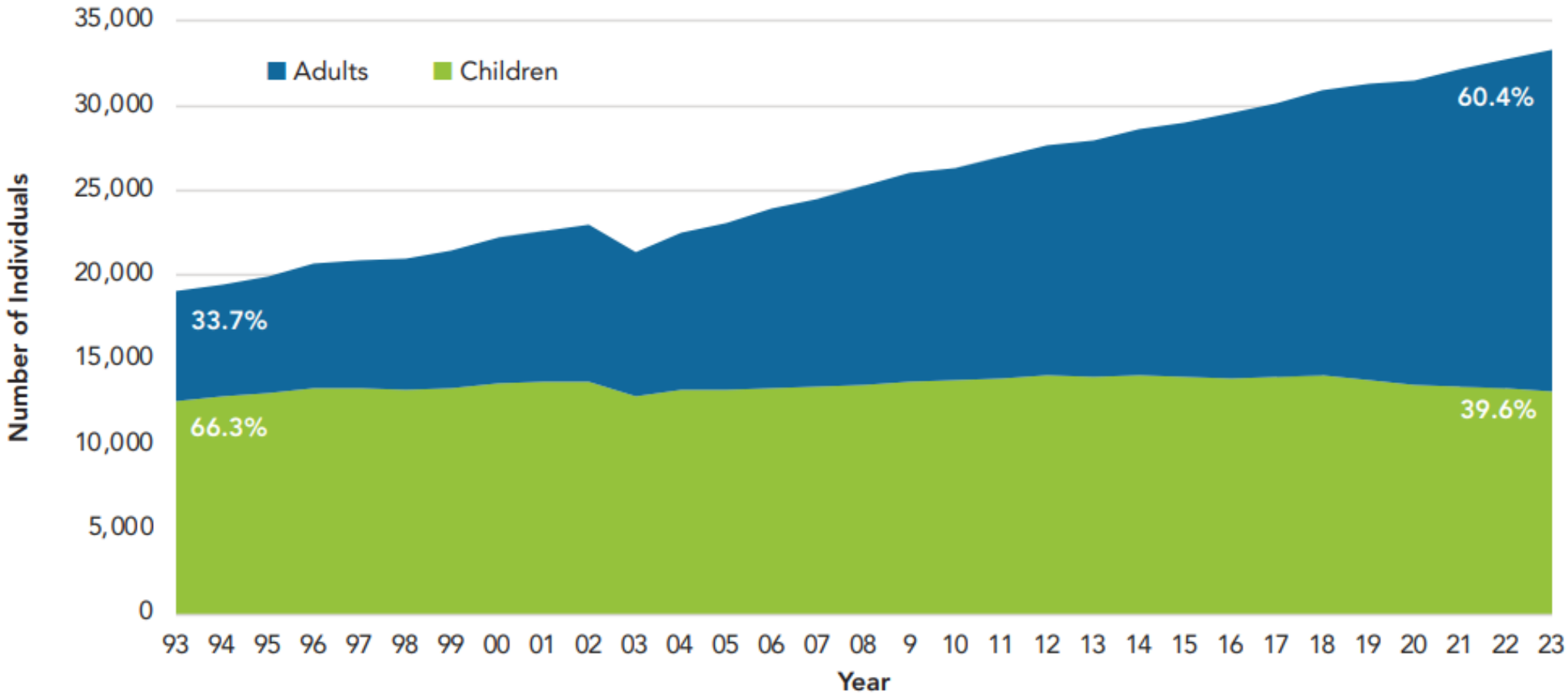
Effetto delle terapie sull'aspettativa di vita dei pazienti con FC





AZLI, aztreonam; HTS, screening ad alta capacità; IVA, ivacaftor; LUM, lumacaftor; rhDNAsi, desossiribonucleasi umana ricombinante; TIP, tobramicina. Riprodotto e adattato col permesso di European Respiratory Society©: *The European Lung White Book Respiratory Health and Disease in Europe*, 2nd Ed. © 2013 European Respiratory Society, Sheffield, UK. Lopes-Pacheco M. *Front Pharmacol.* 2016;7:275.

Number of Children and Adults With CF, 1993–2023



The decrease in the number of individuals reported in 2003 is due to a delay in obtaining informed consent forms before the close of the calendar year at some CF Care Centers.

Serie "Medicina di transizione in Pneumologia"
a cura Elisabetta Bignamini

Transizione del paziente con fibrosi cistica

Transition in cystic fibrosis

Giuseppe Fabio Parisi[1], Salvatore Leonardi[1], Manuela Goia[2], Elisabetta Bignamini[2]

[1] UOC Broncopneumologia Pediatrica e Fibrosi Cistica, Presidio Ospedaliero San Marco, Azienda Ospedaliera Universitaria Policlinico di Catania, Catania; [2] SC Pneumologica Pediatrica, Centro Regionale di Riferimento: Fibrosi Cistica Piemonte-Valle d'Aosta, Insufficienza respiratoria cronica in età evolutiva, OIRM Città della Salute e della Scienza di Torino, Torino

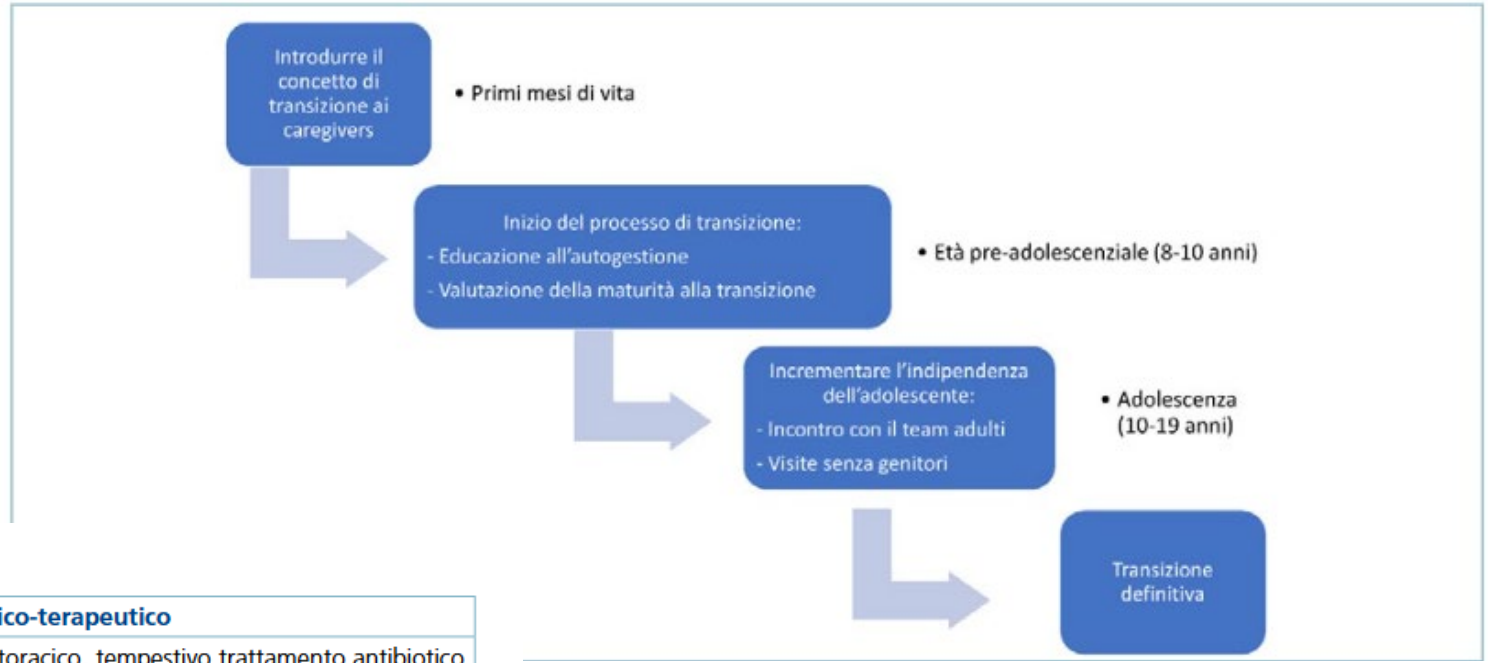


Tabella I. Caratteristiche cliniche del paziente in fase di transizione.

Presentazione clinica	*Work-up* diagnostico-terapeutico
Riacutizzazione respiratoria	Valutazione clinica, laboratoristica e di *imaging* toracico, tempestivo trattamento antibiotico con implementazione di quello mucolitico e fisioterapico
Emottisi	Valutazione se moderata, grave o recidivante, eventuale indicazione a embolizzazione delle arterie bronchiali
Pneumotorace	Eventuale posizionamento di drenaggio pleurico in base all'entità
Insufficienza respiratoria cronica	Prescrizione di O_2 terapia cronica ed eventuale utilizzo di NIV notturna in presenza di insufficienza respiratoria ipercapnica
Poliposi nasale/sinusite	Controlli periodici ORL/*imaging* cranio-sinusale per eventuale intervento di chirurgia endoscopica nasale (FESS)
Epatopatia/pancreatiti ricorrenti/DIOS	Controlli gastroenterologici periodici e monitoraggio ecografico/doppler epatico e degli esami ematologici di funzionalità epatica
Malassorbimento	Controllo digestivo feci, vitamine liposolubili e visite nutrizionali
Diabete	*Screening* periodico con curva da carico di glucosio e, se alterata, valutazione diabetologica per impostazione di eventuale terapia insulinica
Osteoporosi	Controllo periodico delle vitamine liposolubili, MOC e valutazione endocrinologica per terapia con bifosfonati oltre a supplementazione
Infertilità maschile	*Counselling* pre-concepimento per impostazione di eventuali tecniche di fecondazione assistita
Stato ansioso depressivo	Valutazione psichiatrica per terapia specifica antidepressiva

***Rassegna di Patologia dell'Apparato Respiratorio* 2023**;38:166-173
doi: 10.36166/2531-4920-712

cancers

MDPI

Review

Cystic Fibrosis and Cancer: Unraveling the Complex Role of CFTR Gene in Cancer Susceptibility

Giuseppe Fabio Parisi [1,*], Maria Papale [1], Giulia Pecora [1], Novella Rotolo [1], Sara Manti [2], Giovanna Russo [3] and Salvatore Leonardi [1]

Pancreatic cancer	• Chronic inflammation • Altered bile flow • Oxidative stress	5–10
Liver cancer	• Chronic inflammation • Altered bile flow • Impaired liver regeneration • Genetic variations in modifier genes, such as the Solute Carrier Organic Anion Transporter (SLCO) family	1.5–2
Intestinal cancers	• Chronic inflammation • Oxidative stress • Altered composition of intestinal microbiota • Genetic polymorphisms • Implications of tumor suppressor genes	6
Breast cancer	• Hormonal imbalances, such as increased estrogen levels	not well-established
Lung cancer	• Chronic inflammation • Altered mucociliary clearance	not well-established

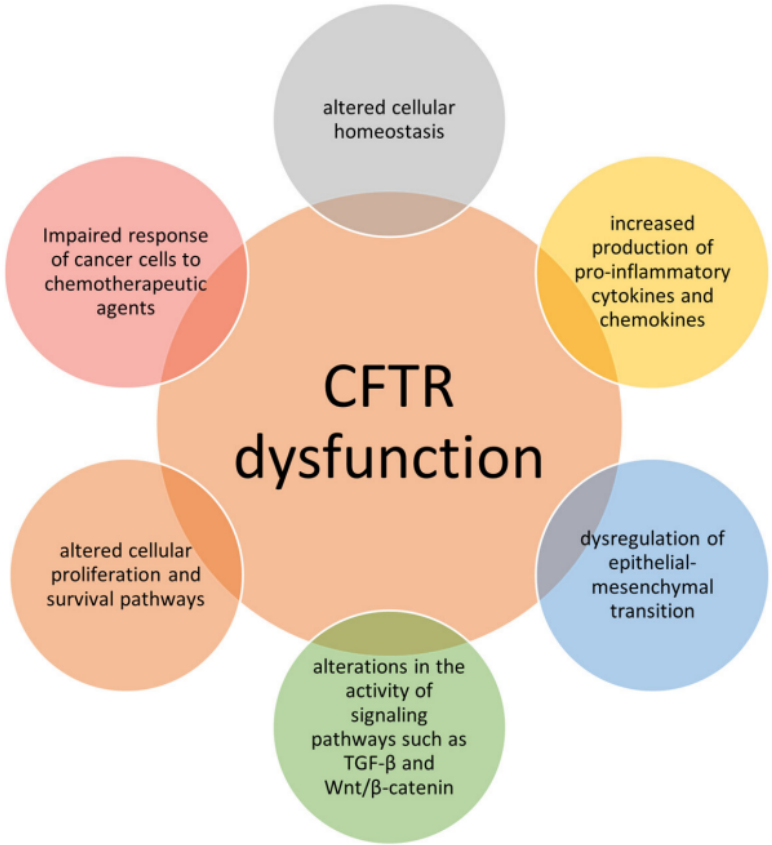
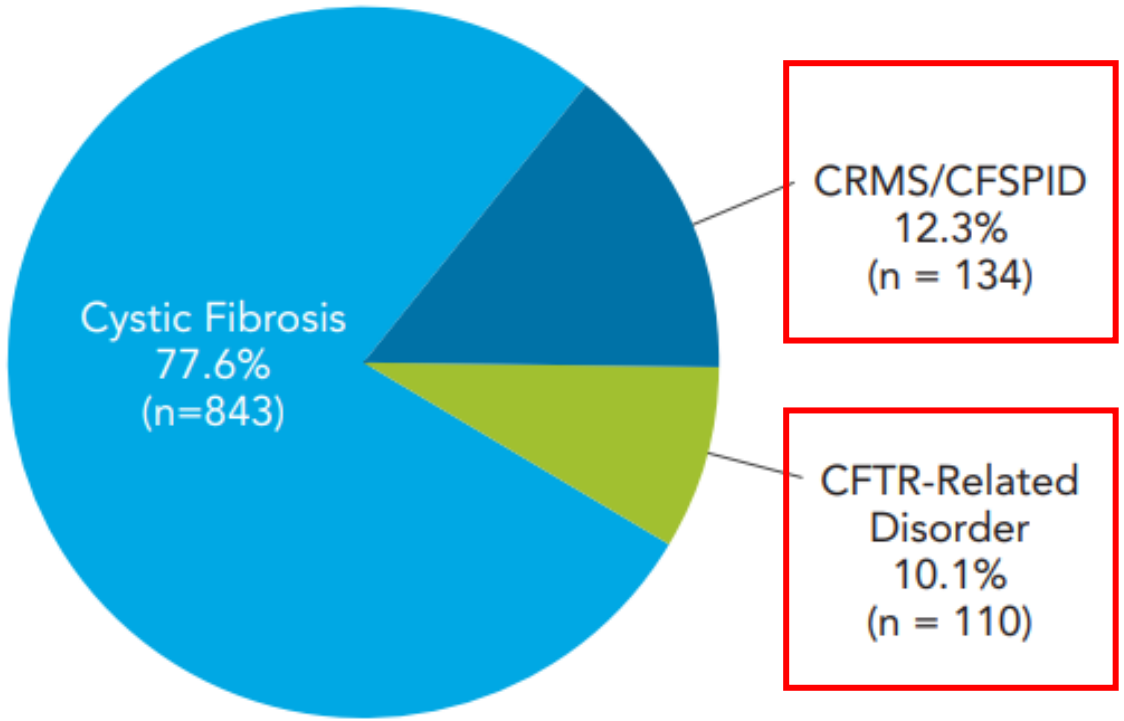


Figure 1. CFTR dysfunction and mechanisms related to predisposition to cancers. CFTR dysfunction in CF triggers chronic inflammation, impaired DNA repair, and hormonal imbalances. These mechanisms collectively predispose individuals to various cancers, highlighting the intricate interplay between CF and cancer susceptibility.

CF, CRMS/CFSPID, and CFTR-Related Disorder New Diagnoses in 2023



CFSPID

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis

Screening Neonatale Positivo

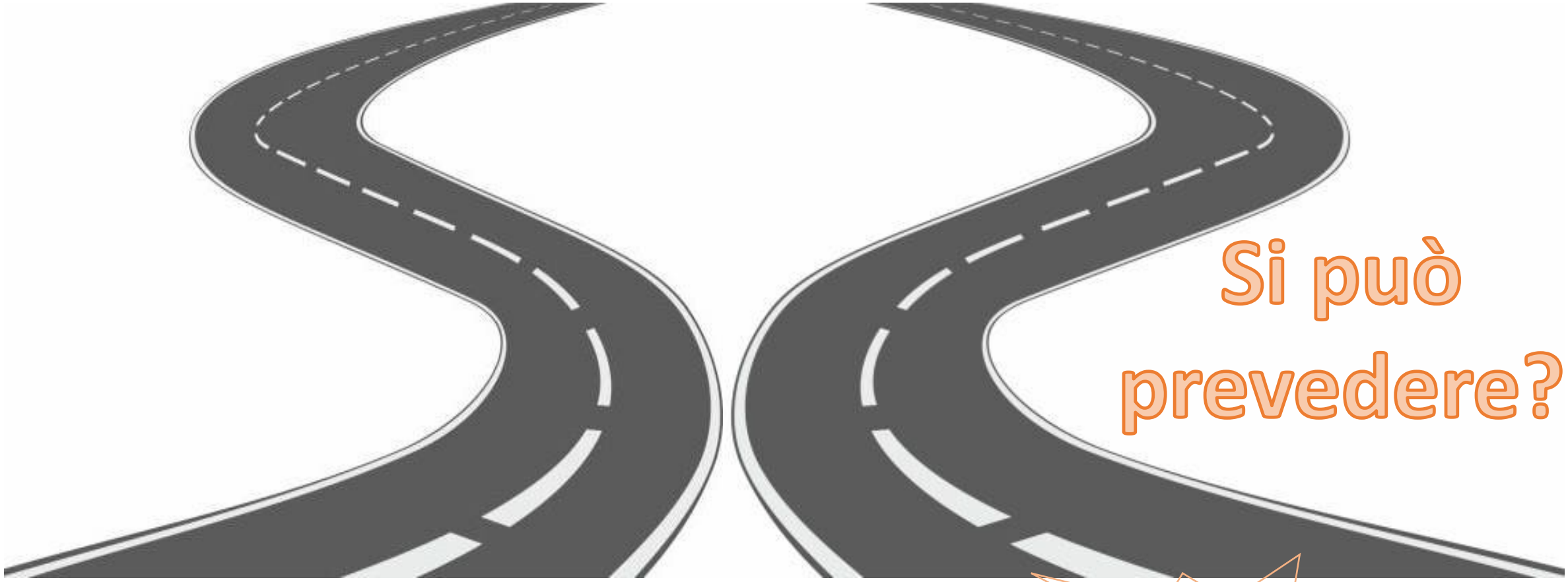
Test del sudore negativo
(Cloro < 30 mmol/L)

2 mutazioni del CFTR,
di cui almeno una di significato patogenetico incerto

Test del sudore dubbio
(Cloro 30 – 59 mmol/L)

1 o nessuna mutazione del CFTR

CFSPID



Si può prevedere?

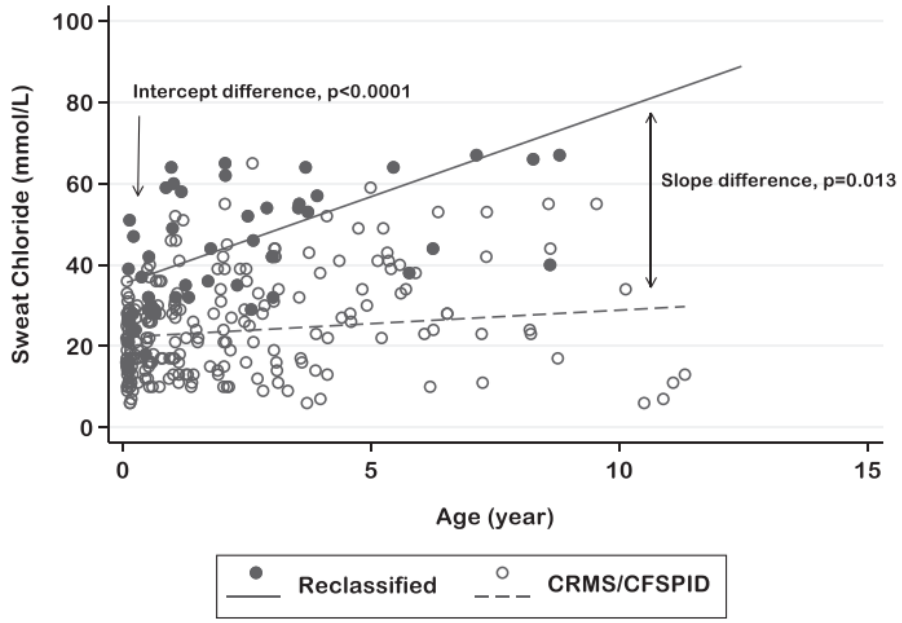
CF

CFSPID

› Pediatr Pulmonol. 2023 Apr;58(4):1074-1084. doi: 10.1002/ppul.26296. Epub 2023 Jan 6.

Gradual increase in sweat chloride concentration is associated with a higher risk of CRMS/CFSPID to CF reclassification

Danieli B Salinas [1], Daniella K Ginsburg [1], Choo Phei Wee [2], Muhammed M Saeed [3], John J Brewington [4]



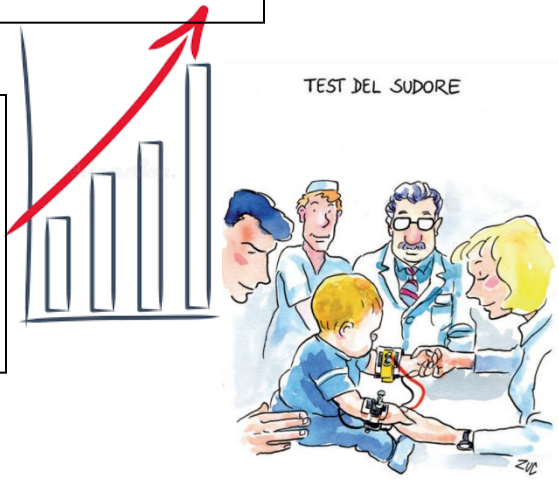
Linear median quantile mixed model of sweat chloride over time	n	Intercept(SE)	Slope (SE)	95% CI (p)	Increase per year
Reclassified from CRMS/CFSPID to CF	12	32.40 (2.31)	4.71 (1.03)	2.45 – 6.97 (0.001)	4.71 mmol/L/y
CRMS/CFSPID	59	22.07 (0.89)	1.21 (0.40)	0.41 – 2.02 (0.004)	1.21 mmol/L/y

112 bambini con screening positivo → CF = 53 (12 ex CFSPID)

112 bambini con screening positivo → CFSPID = 59

i **valori iniziali di sw[Cl]** erano significativamente **differenti tra i gruppi** (P **<0,0001**).

Tra i bambini che hanno **mantenuto** la designazione **CRMS/CFSPID rispetto** a quelli che sono stati **riclassificati in CF** si sono evidenziate **traiettorie distinte** (valore **p** per differenza di inclinazione= **0,013**)



I bambini con **CRMS/CFSPID** che avevano una **coltura** respiratoria **positiva per PSA** avevano **maggiori probabilità di riclassificarsi in FC** (odds ratio aggiustato [OR] [IC 95%] = 6,43 [1,15–36,07], p = 0,034)

CONCLUSIONI

L'aumento di sw[Cl] e una **storia di colonizzazione** con **PSA** sono associati al **rischio di riclassificazione da CFSPID a CF**

Paediatric Respiratory Reviews 51 (2024) 46–55

Contents lists available at ScienceDirect

Paediatric Respiratory Reviews

journal homepage: www.sciencedirect.com/journal/paediatric-respiratory-reviews

Review

Biochemical and genetic tools to predict the progression to Cystic Fibrosis in CRMS/CFSPID subjects: A systematic review

Vito Terlizzi [a], Sara Manti [b,*], Federica D'Amico [b], Giuseppe F. Parisi [c], Elena Chiappini [d,e], Rita Padoan [f]

[a] Department of Pediatric Medicine, Meyer Children's Hospital IRCCS, Cystic Fibrosis Regional Reference Center, Florence, Italy
[b] Department of Human Pathology of Adult and Evolutive Age "Gaetano Barresi", University of Messina, Messina, Italy
[c] Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[d] Infectious Diseases Unit, Meyer Children's Hospital IRCCS, Florence, Italy
[e] Department of Health Sciences, University of Florence, Florence, Italy
[f] Italian Cystic Fibrosis Registry, Scientific Board, Rome, Italy

Table 2
Percentage of CFSPID > CF/CFSPID in the different populations.

Authors	Year	CFSPID > CF/CFSPID	%	Ref.
Terlizzi V et al.	2021	18/336	5.3 %	[16]
Tosco A et al.	2022	6/58	10.3 %	[35]
Ooi CY et al.	2015	11/82	11.0 %	[25]
Ooi CY et al.[§]	2019	14/98	14.3 %	[26]
Gunnett MA et al.	2023	11/63	17.5 %	[34]
Salinas DB et al.	2022	12/59	20.3 %	[37]
Gonska T et al.	2021	24/115	21.0 %	[28]
Munck A et al.	2020	28/63	44.0 %	[30]
Groves T et al.	2015	14/29	48.0 %	[54]

[§] also includes patients from the same authors' 2015 paper.

EDUCATIONAL AIMS

The reader will come to appreciate:

- An analysis of the characteristics of CFSPID individuals who evolve into CF.
- That the presence of one CF-causing CFTR variant, an initial sweat chloride (SC) ≥ 40 mmol/L or an increase of SC > 2.5 mmol/L/year could allow identification of subjects at risk of progression to CF.
- That CFSPID individuals with a CF causing variant/VVCC genotype and first SC in the higher borderline range may require more frequent and prolonged clinical follow-up.

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Journal of Cystic Fibrosis 20 (2021) 810–819

Original Article

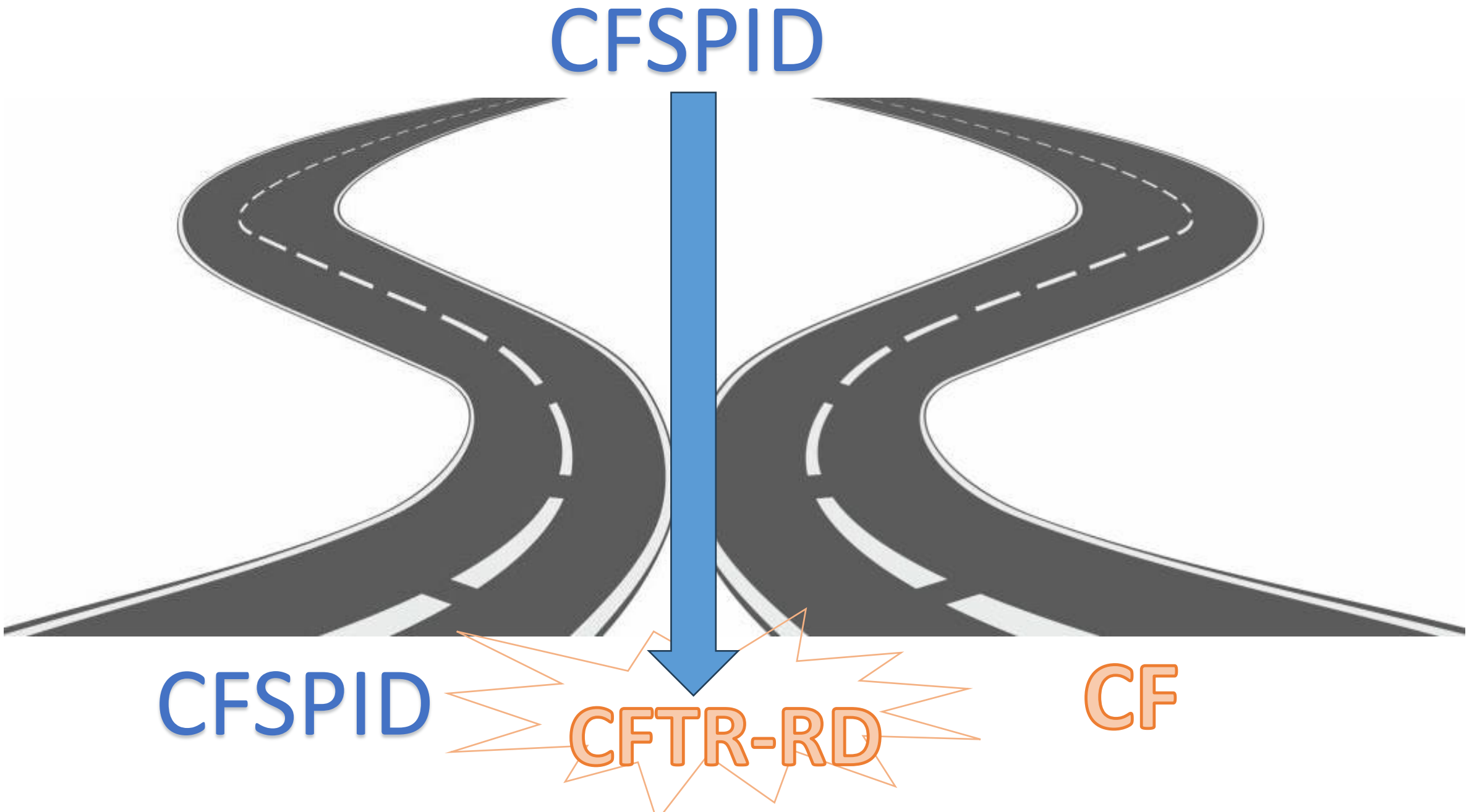
Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID)

Jürg Barben[a,*], Carlo Castellani[b], Anne Munck[c], Jane C. Davies[d,e], Karin M. de Winter–de Groot[f], Silvia Gartner[g], Nataliya Kashirskaya[h], Barry Linnane[i], Sarah J Mayell[j], Susanna McColley[k], Chee Y. Ooi[l,m], Marijke Proesmans[n], Clement L. Ren[o], Danieli Salinas[p], Dorota Sands[q], Isabelle Sermet-Gaudelus[r], Olaf Sommerburg[s], Kevin W Southern[t], For the European CF Society Neonatal Screening Working Group (ECFS NSWG)

CRMS/CFSPID.

	Initial assessment	6 months of age	12 months of age	2 years of age	3 years of age	4 years of age	5 years of age	6 years of age **
Diagnostic testing *								
Sweat chloride concentration	X	X	C	X	C	C	C	X
Extended *CFTR* analysis	X							C
Check for updates in clinical relevance of *cftr* variants at www.cftr2.org	X	X	X	X	X	X	X	X
Fecal elastase-1 measurement (stool assessment)	X	C	X	C	C	C	C	C
Care Management								
Inform GP/Paediatrician about CRMS/CFSPID (or change of diagnosis)	X	X	X	C	C	C	C	X
Provide explanations to parents on the follow-up (discuss the potential outcomes)	X	X	X	X	X	X	X	X
Genetic counselling	X							C
Respiratory assessment: history (cough, infections), including auscultation, RR	X	X	X	X	X	X	X	X
Abdominal assessment: history and examination	X	X	X	X	X	X	X	X
Nutritional assessment: weight, length/height, BMI centiles	X	X	X	X	X	X	X	X
Respiratory culture	C	C	C	C	C	C	C	C
Chest Imaging	C	C	C	C	C	C	C	X
MBW/LCI measurement								X
Spirometry								X
Educate about tobacco exposure avoidance	X	C	C	C	C	C	C	C

X = Do at this visit
C = Consider if clinically indicated
* = At each meeting with family, consider whether the CRMS/CFSPID designation is still appropriate (is there evidence to transfer to a CF diagnosis?).
** = Review evidence from Year 6 assessment and discuss future care plans with the family.


CFSPID
CFSPID
CFTR-RD
CF

CFTR-RD Diagnosi

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Original Article

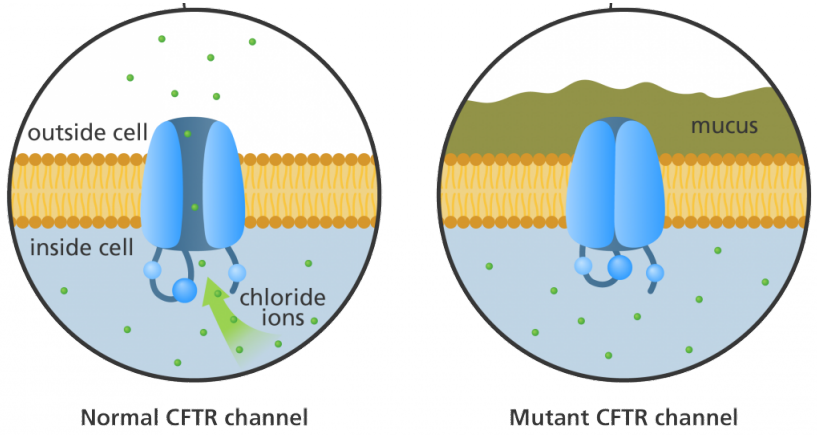
ECFS standards of care on CFTR-related disorders: Updated diagnostic criteria

C Castellani[a,*], K De Boeck[b], E De Wachter[c], I Sermet-Gaudelus[d], NJ Simmonds[e], KW Southern[f], on behalf of the ECFS Diagnostic Network Working Group

Journal of Cystic Fibrosis 21 (2022) 908–921

Table 3
CFTR-RD diagnostic criteria.

CRITERIA	SPECIFICS
Distinctive phenotypes isolated or in combination	CBAVD; acute recurrent or chronic pancreatitis; bilateral bronchiectasis Allergic Bronchopulmonary Aspergillosis; Chronic rhinosinusitis; Primary Sclerosing Cholangitis; Aquagenic Wrinkling currently under examination Usually mono-organ, but can be polyorgan (see text)
CFTR dysfunction	*In vivo* or *ex vivo* CFTR dysfunction in the CFTR-RD range in at least 2 different CFTR functional tests (sweat test, NPD, ICM) OR one *CFTR* variant and evidence of in vivo or *ex vivo* dysfunction in at least two functional tests OR two *CFTR* variants shown to reduce CFTR function, with at most one CF-causing variant
CF excluded	Criteria to be excluded: CF clinical manifestations and/or positive newborn screening and/or a CF sibling AND sweat chloride > 59 mmol/L/L and/or two CF-causing mutations and/or CF consistent electrophysiology test results [4,119]



Normal CFTR channel Mutant CFTR channel

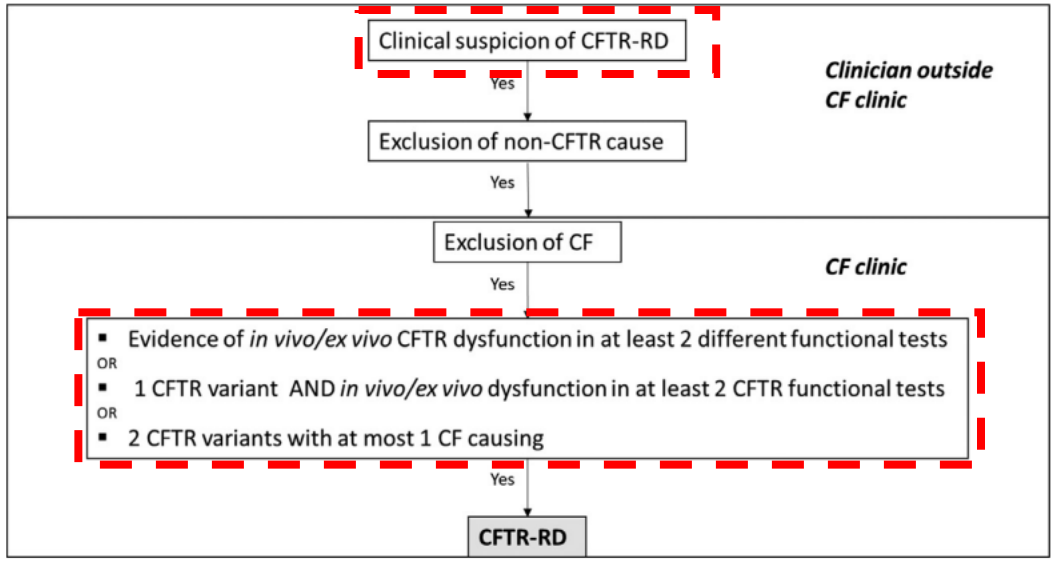


Fig. 2. The path to CFTR-RD diagnosis.

); Published: 8 August 2020

CFSPID può diventare CFTR-RD

Neonati diagnosticati come CF o CF-SPID da
NBS dal 2008 al 2019 nella Regione Campania

diagnostics

MDPI

Article

Cystic Fibrosis-Screening Positive Inconclusive Diagnosis: Newborn Screening and Long-Term Follow-Up Permits to Early Identify Patients with CFTR-Related Disorders

Alice Castaldo [1,*], Chiara Cimbalo [1], Raimondo J. Castaldo [1], Marcella D'Antonio [2], Manuela Scorza [2], Laura Salvadori [1], Angela Sepe [1], Valeria Raia [1] and Antonella Tosco [1]

- 47 pazienti con CF
- 99 pazienti con CF-SPID

→ monitorati negli ultimi 11 anni →

8 si sono evoluti in disturbi correlati a CFTR (CFTR-RD) tra 1-8 anni

Table 5. Data of newborn screening of 8 subjects with CF-SPID evolved to CF (cases 1 and 2) or to CFTR-RD (cases 3 to 10).

#	Sex	Current Age	Final Diagnosis	I IRT	II IRT	SC at Birth	SC at Final Diagnosis	*CFTR* Genotype
		years	and age (years)	ng/mL	ng/mL	mmol/L	mmol/L	
1	F	3	CF, 2	115	47.0	56	87, 84	Y849X//[5T;TG12]
2	M	2	CF, 2	82.1	44.0	7	61, 76	D1152H//[5T;TG12]
3	M	11	CFTR-RD, 8	70.7	16.7	21	28	F508del/Q1476X
4	M	11	CFTR-RD, 8	71.8	13.2	26	27	1717-1G>A/[5T;TG12]
5	M	11	CFTR-RD, 7	61.6	24.1	16	11	F508del/L997F
6	F	7	CFTR-RD, 2	50.8	25	25	35	R334Q/L997F
7	M	6	CFTR-RD, 4	72.9	56.8	14	26	F508del/D1152H
8	F	5	CFTR-RD, 3	63.5	58.4	10	12	S1426F/D1152H
9	M	7	CFTR-RD, 2	108	59.4	21	27	L732X/D1152H
10	M	4	CFTR-RD, 1	116.4	92.8	12	28	F508del/D1152H

CF-SPID—CF-screening positive inconclusive diagnosis; CFTR-RD—CFTR-related disorders; IRT—immunoreactive trypsinogen; SC—sweat chloride.

Molto si è discusso se le CFTR-patie possano avere radici negli CFSPID, senza univoca risposta da parte della letteratura →

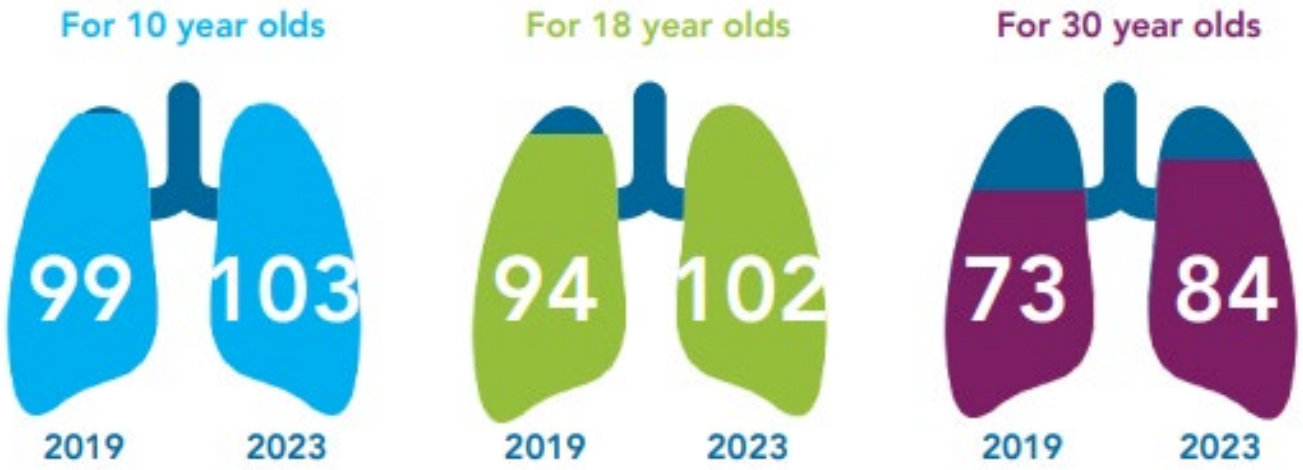
Il rischio per un bambino con CFSPID di sviluppare CFTR-RD non può ancora essere determinato con i dati attuali a disposizione. →

Ancora breve durata del periodo di osservazione!

2023 CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY HIGHLIGHTS

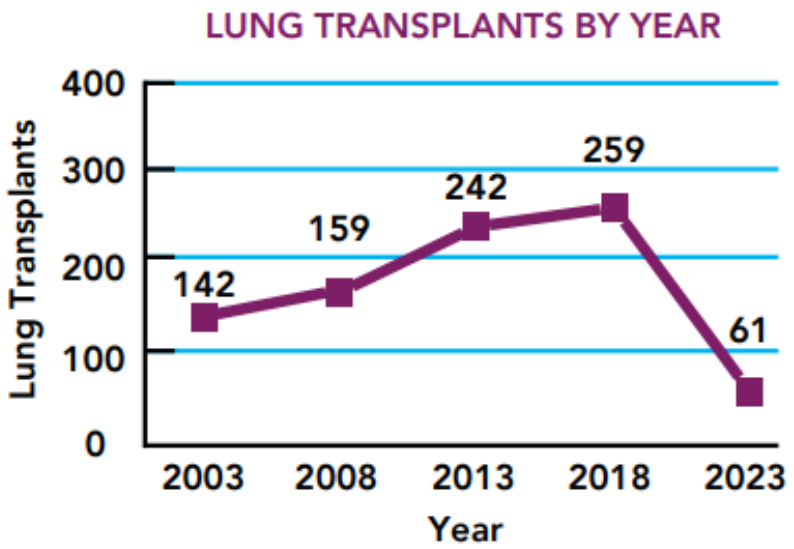
CYSTIC FIBROSIS FOUNDATION

Median FEV_1 Percent Predicted



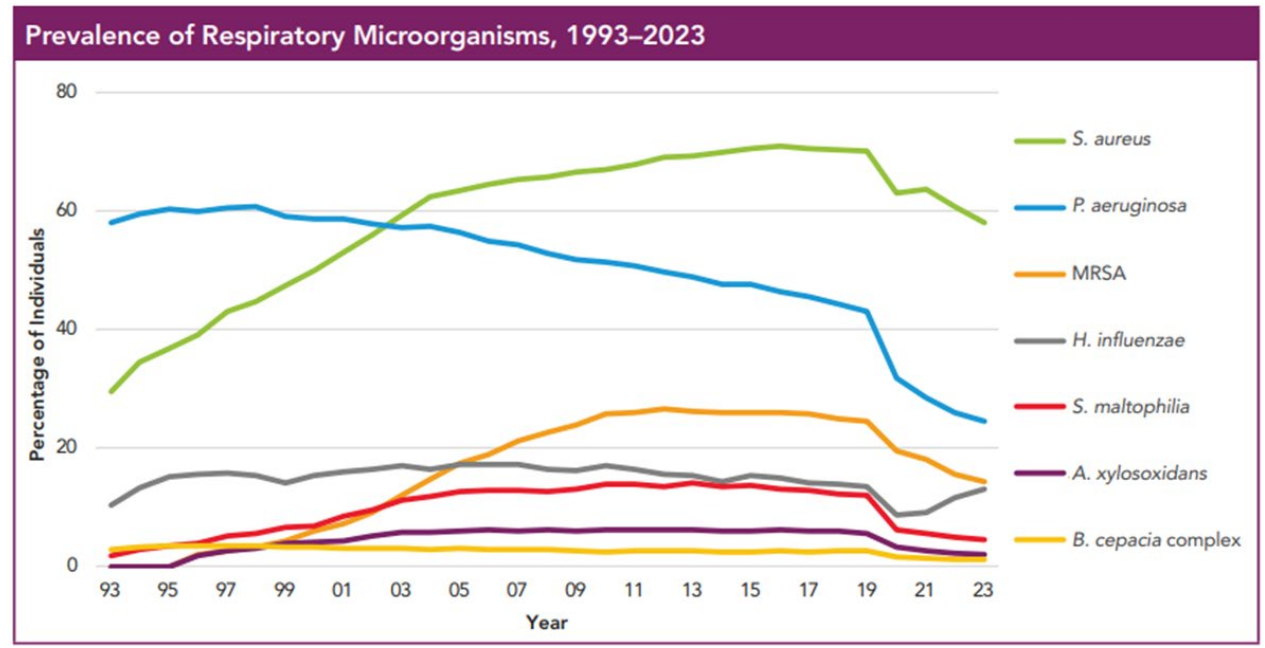
TRANSPLANTATION

In the Registry, there has been a dramatic decrease in the number of lung transplants reported compared to the numbers prior to the adoption of elexacaftor/tezacaftor/ivacaftor. In 2023, there were 61 lung transplants reported.

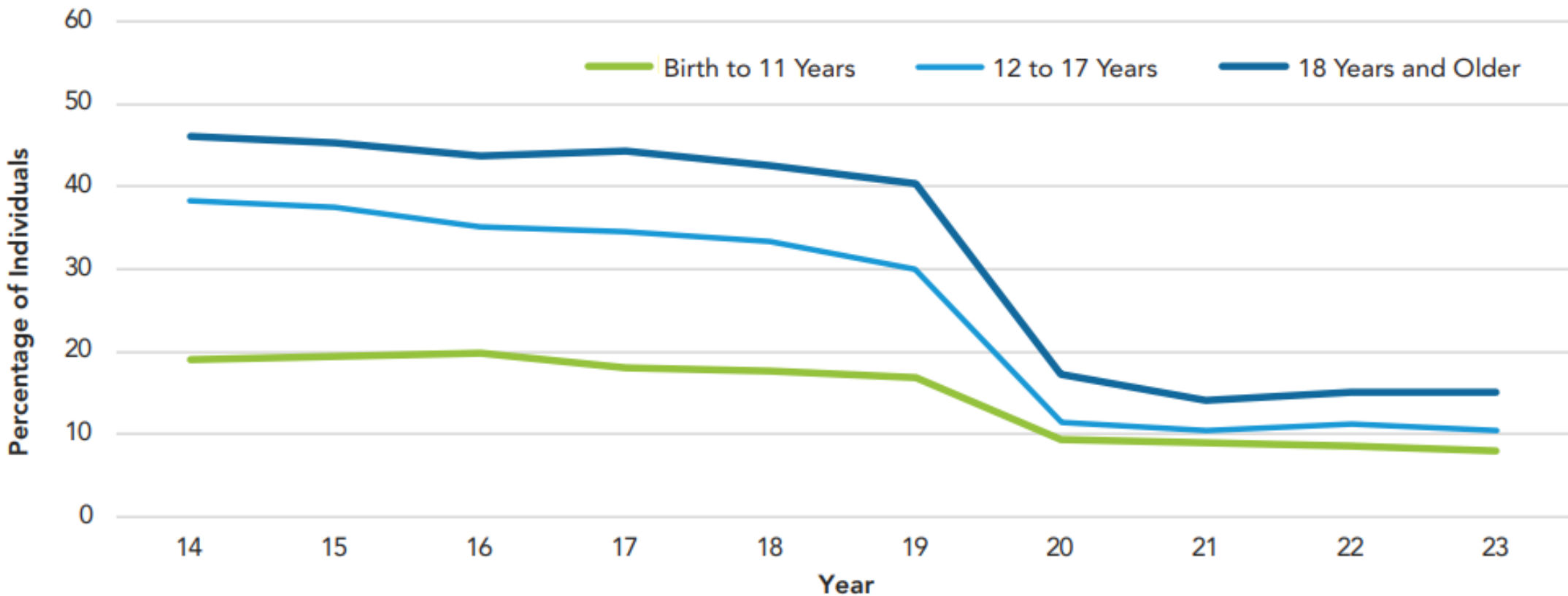


MICROBIOLOGY

Bacteria	Percent With Infection	Median Age in Years at First Infection
Pseudomonas aeruginosa	25%	5
Stenotrophomonas maltophilia	5%	9
Methicilin-resistant Staphylococcus aureus	14%	10
Achromobacter xylosoxidans	2%	14
Burkholderia cepacia complex	1%	20
Nontuberculous mycobacteria	10%	25



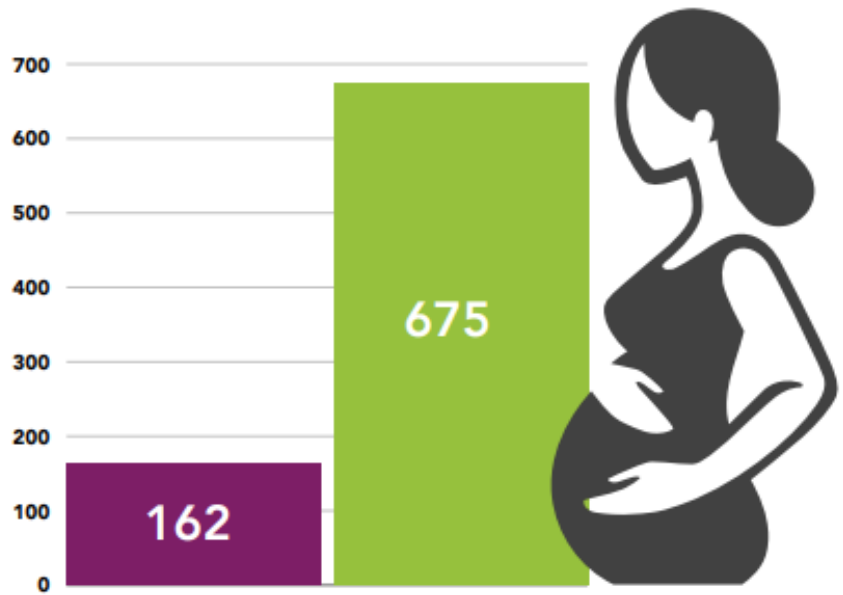
Individuals Treated With IV Antibiotics for a Pulmonary Exacerbation, 2014–2023



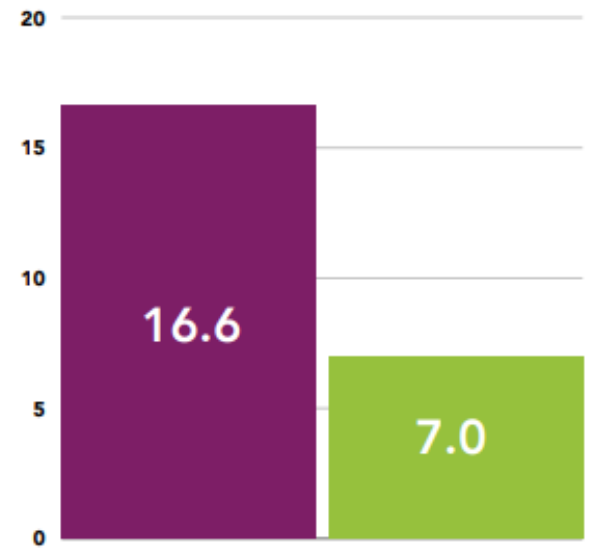
20 YEARS OF PROGRESS

2003 2023

18 Years or Older
2003: 8,518 2023: 20,107



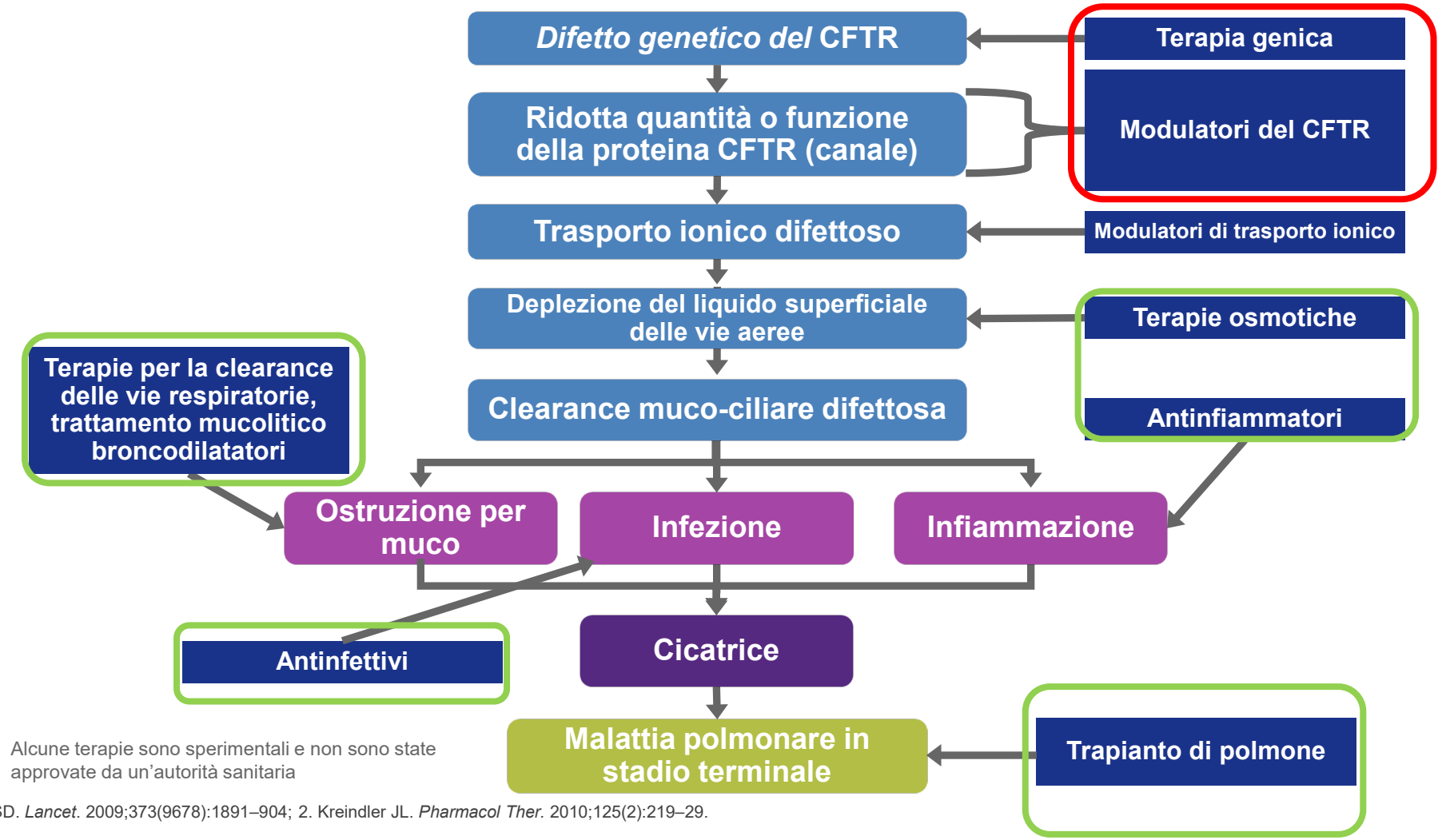
Pregnancies



Annual Mortality Rate
(Per 1,000 People)

Le terapie che mirano ai difetti sottostanti sono potenzialmente in grado di ritardare o prevenire i sintomi[1,2]

Cascata patofisiologica della malattia polmonare nella FC[1,2]



Alcune terapie sono sperimentali e non sono state approvate da un'autorità sanitaria

1. O'Sullivan BP & Freedman SD. *Lancet*. 2009;373(9678):1891–904; 2. Kreindler JL. *Pharmacol Ther.* 2010;125(2):219–29.

Promesse e sfide della terapia genica in FC

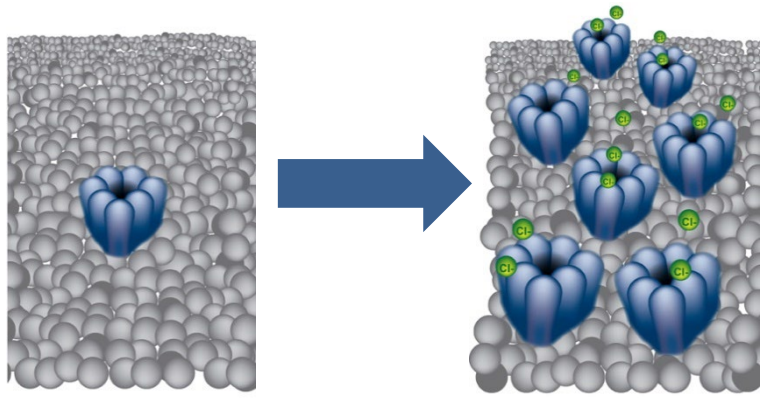
- **La terapia genica ha la potenzialità di correggere tutte le mutazioni CFTR, indipendentemente dalla classe di mutazione[1]**
- La clonazione del gene CFTR nel 1989 aveva fatto sperare che la terapia di sostituzione genica potesse essere usata nella cura di FC[2]

Vantaggi teorici della terapia genica[3]
Indipendente dalla classe di mutazione e potenzialmente idonea per tutti i pazienti
Agisce sul difetto genetico di FC - potenziale prevenzione di malattie polmonari, con un intervento precoce
Mutazione-agnostica, è quindi possibile che il genotipo non debba essere confermato

- Tuttavia, l'identificazione di un vettore idoneo di trasferimento genico si è rivelata un problema[1]
  - Vanno superati dei solidi meccanismi fisici e immunologici di difesa delle vie aeree[1]

1.Colemeadow J, et al. *Expert Rev Precis Med Drug Dev*. 2016;1(2):169–80; 2. Quon BS & Rowe SM. *BMJ*. 2016;352:i959; 3. Griesenbach U, et al. *Hum Gene Ther*. 2015;26(5):266–75.

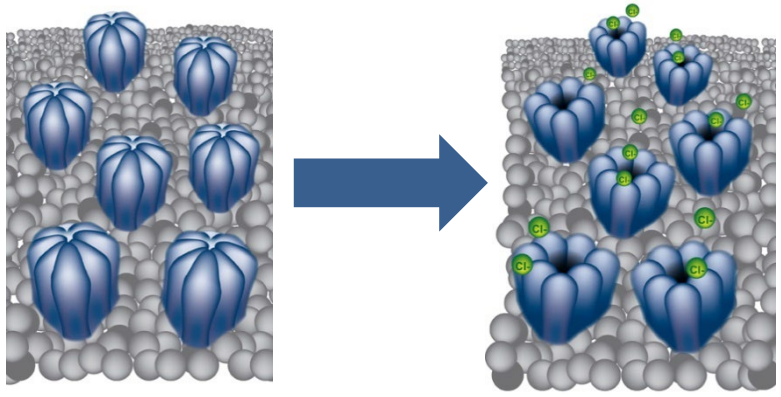
I modulatori di CFTR influenzano l'attività di CFTR e aumentano il trasporto di Cl^{-}[1,2]



Correttori di CFTR

Facilitano un aumentato trasporto di Cl^{-}, aumentando la quantità di CFTR trasportata verso la superficie cellulare

per es. lumacaftor; tezacaftor; FDL169; GLPG2222; VX-152; VX-440,VX-445; VX-659; PTI-801



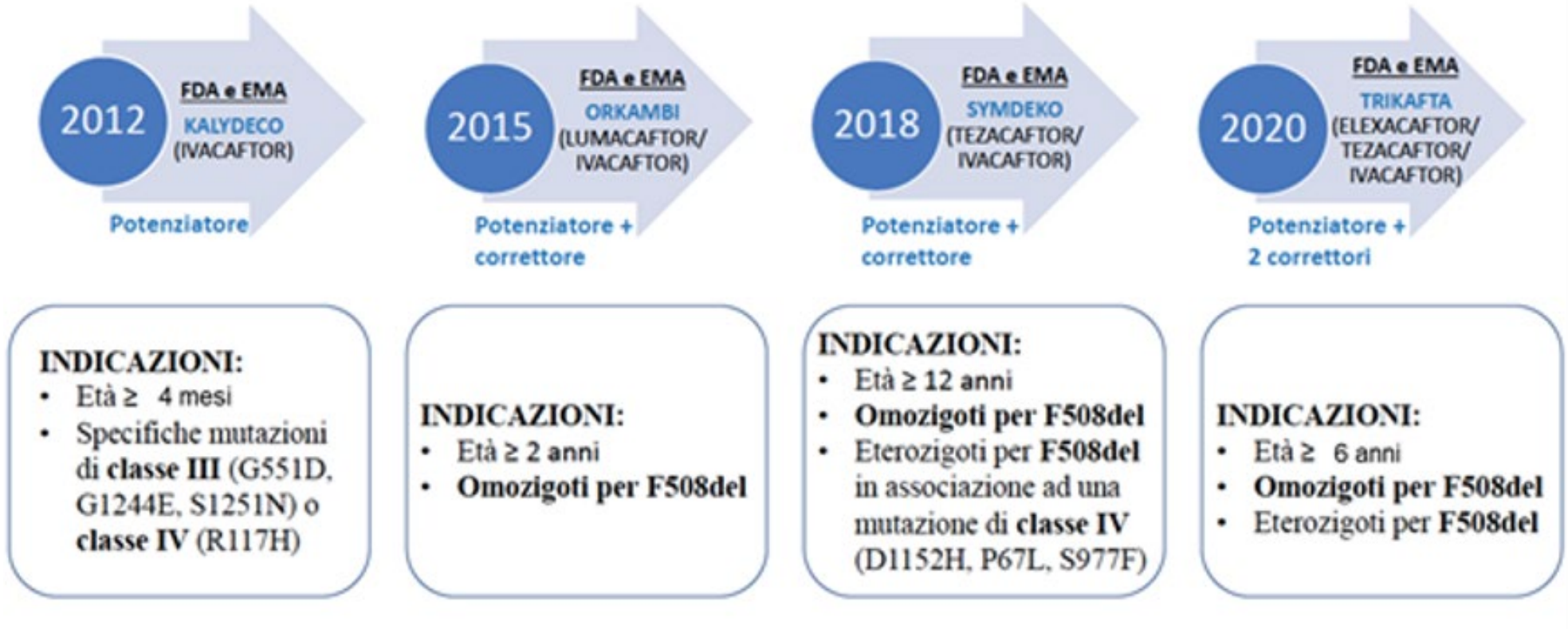
Potenziatori di CFTR

Facilitano un aumentato trasporto di Cl^{-}, incrementando la probabilità di apertura del canale della proteina CFTR sulla superficie cellulare

per es. ivacaftor; VX-561; QBW251; PTI-808

1. Van Goor F, et al. *Proc Natl Acad Sci USA*. 2011;108(46):18843–8; 2. Van Goor F, et al. presentato presso ECFS, Lisbona, Portugal, 15-17 giugno 2013;
3. CFF: Drug development pipeline. Disponibile all'indirizzo: www.cff.org/Trials/pipeline (ultima consultazione: aprile 2018).

NUOVE TERAPIE VOLTE A MODULARE LA FUNZIONE/QUANTITÀ DELLA PROTEINA CFTR ALTERATA

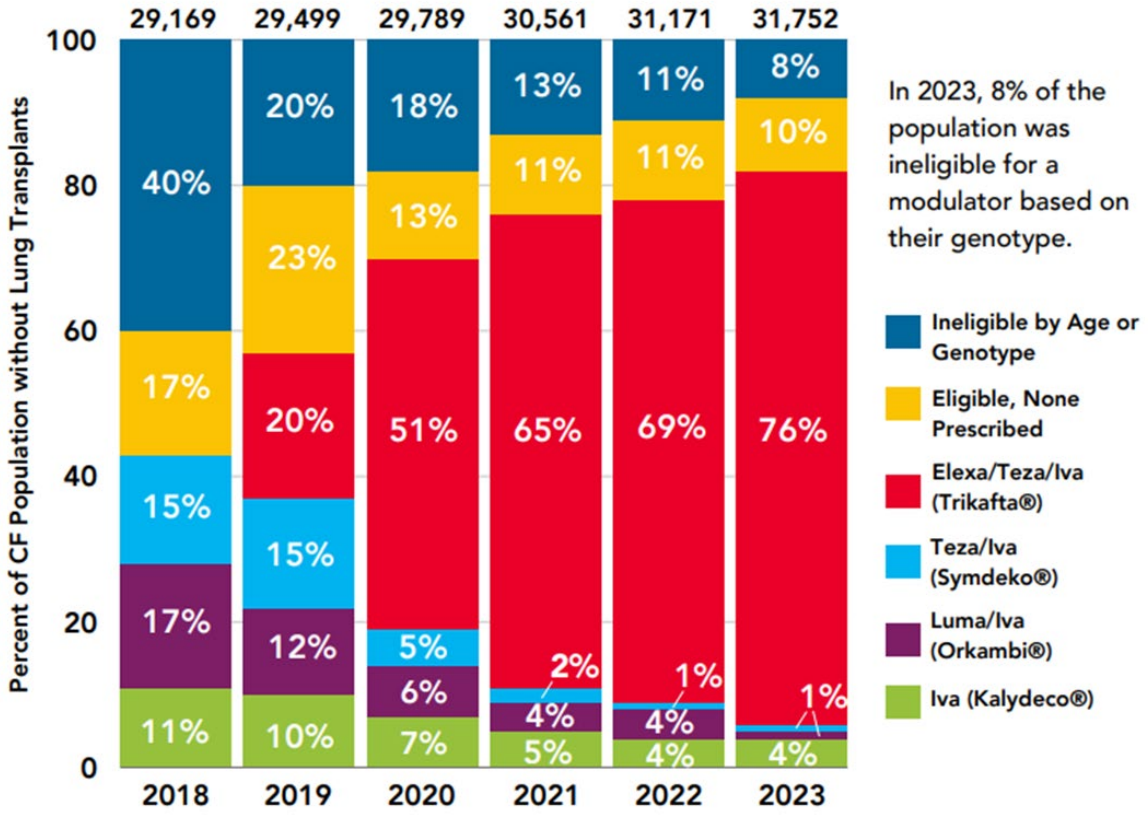


Sepe et al. Pneumologia Pediatrica n. 23

2023 CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY HIGHLIGHTS

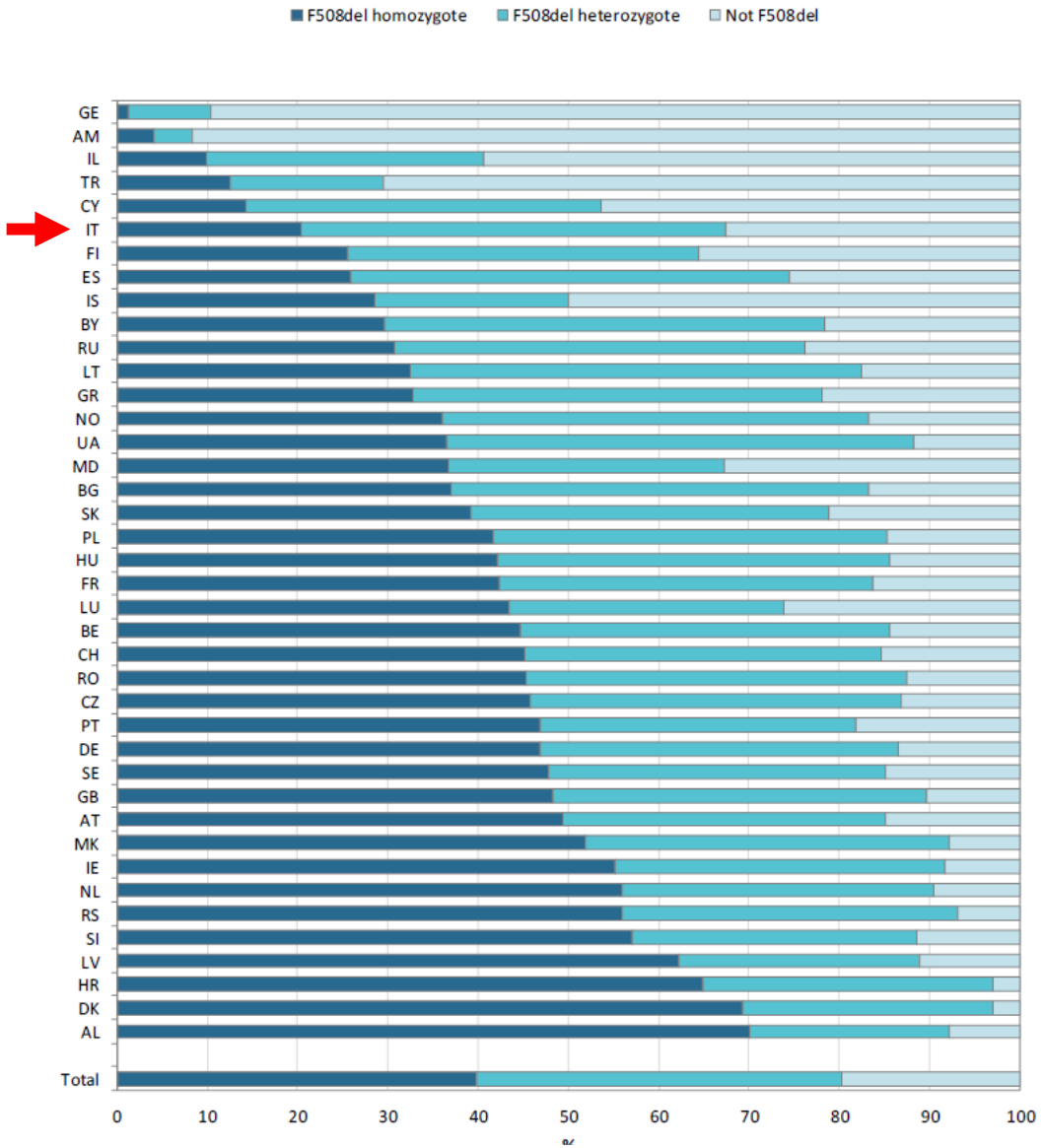
CYSTIC FIBROSIS FOUNDATION

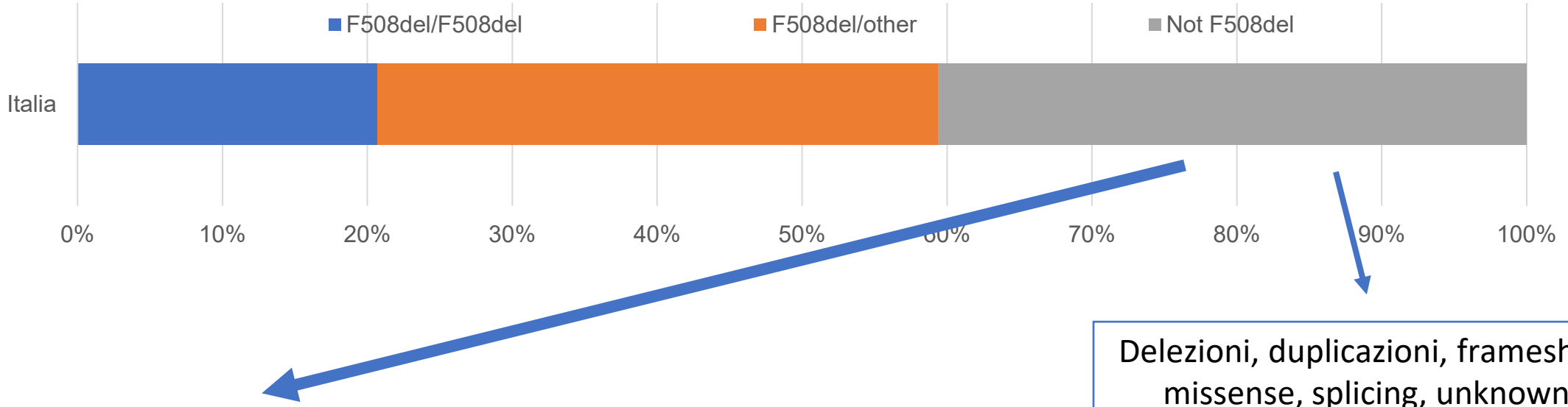
CFTR MODULATORS



In 2023, 8% of the population was ineligible for a modulator based on their genotype.

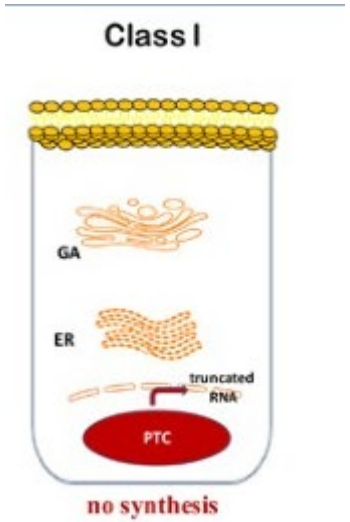
- Ineligible by Age or Genotype
- Eligible, None Prescribed
- Elexa/Teza/Iva (Trikafta®)
- Teza/Iva (Symdeko®)
- Luma/Iva (Orkambi®)
- Iva (Kalydeco®)





Delezioni, duplicazioni, frameshift, missense, splicing, unknown

Mutazioni non-sense (stop, classe I):
Arresto prematuro della produzione di CFTR



MUTAZIONE TIPO "STOP"	2022	
	n.	%
G542X	528	8,7
W1282X	222	3,7
R553X	138	2,3
R1162X	129	2,1
E585X	54	0,9
R1158X	52	0,9
E831X	29	0,5
S1455X	22	0,4
Q1476X	13	0,2
R709X	11	0,2
L732X	10	0,2
Y849X	9	0,1
R785X	9	0,1
Q220X	8	0,1

NOTA: Omozigosi (mutazione stop/mutazione stop): 61

Tabella 9. Numero di pazienti portatori di almeno una delle mutazioni "non senso" (*stop codon*) (n. 1.234; 20,3%) con frequenza allelica ≥0,1% (n. 6.076). Anno 2022.
Table 9. Number of patients with at least one "non-sense" mutation (stop codon) (No. 1,234; 20.3%) with allelic frequency ≥0.1% (No. 6,076). Year 2022.

GENOTIPO	2022	
	n.	%
F508del / Altro*	2.329	38,3
Altri genotipi	1.389	22,9
F508del / F508del	1.249	20,6
F508del / Funzione residua	548	9,0
Funzione residua/Altro*	502	8,3
Funzione residua/Funzione residua	59	1,0
F508del / Funzione Minima	1.545	25,4
Funzione Minima/ Funzione Minima	654	10,8
Funzione Minima / Altro**	2.490	41,0
Funzione Residua / Altro**	1.050	17,3
F508del / Gating	110	1,8
Gating / Altro**	198	3,3
F508del / Unknown	50	0,8

*Include tutte le mutazioni non *F508del* e non funzione residua
**Incluse tutte le altre mutazioni non *F508del* né funzione residua né funzione minima

Tabella 8. Prevalenza dei pazienti con mutazione *F508del* e funzione residua in omozigosi ed eterozigosi composta (n. 6.076). Anno 2022.
Table 8. Prevalence of homozygous and compound heterozygous patients *F508del* carriers and residual function carriers (No. 6,076). Year 2022.

Dati Registro Italiano 2021-22, pubblicati nel 2024

2018 Priorities	2023 Priorities
1.What are the effective ways of simplifying the treatment burden of people with CF?	1.What options are available for those not able to take current CFTR modulators (including rarer mutations, not eligible and unable to tolerate)?
2.How can we relieve gastro-intestinal symptoms, such as stomach pain, bloating and nausea?	2.What is the best way to diagnose lung infection when there is no sputum e.g. children and those on modulators?
3.What is the best treatment for non-tuberculous mycobacterium (including when to start and what medication)?	**3.How can we relieve gastro-intestinal symptoms, such as stomach pain, bloating and nausea?**
4.Which therapies are effective in delaying or preventing progression of lung disease in early life?	4.How do we manage an ageing population with CF?
5.Is there a way of preventing CF related diabetes?	**5.Is there a way of reducing the negative effects of antibiotics e.g. resistance risk and adverse symptoms in people with CF?**
6.What effective ways of motivation, support and technologies help people with CF improve and sustain adherence to treatment?	6.What are the long-term effects of medications (including CFTR modulators) in CF?
7.Can exercise replace chest physiotherapy?	7.What are the effects of modulators on systems outside the lungs such as pancreatic function, liver disease, gastro-intestinal, bone density etc.?
8.Which antibiotic combinations and dosing plans should be used for CF exacerbations and should antibiotic combinations be rotated?	**8.What are the effective ways of simplifying the treatment burden of people with CF?**
9.Is there a way of reducing the negative effects of antibiotics e.g. resistance risk and adverse symptoms in people with CF?	9.Can genetic therapies (such as gene editing, stem cell and mRNA technology) be used as a treatment for CF?
10.What is the best way of eradicating *Pseudomonas aeruginosa*?	**10. Is there a way of preventing CF related diabetes (CFRD) in people with CF?**

Figure 2 The top 10 questions for research in cystic fibrosis in 2018 and 2023. Those marked in bold feature in both.

THERATYPING

Sperimentazione, a livello cellulare, di farmaci già in uso clinico per la FC, su genotipi non precedentemente valutati e per i quali non erano progettati.

ORIGINAL ARTICLE
CYSTIC FIBROSIS AND BASIC SCIENCE

Correction of CFTR function in intestinal organoids to guide treatment of cystic fibrosis

Anabela S. Ramalho[1], Eva Fürstová[2], Annelotte M. Vonk[3,4], Marc Ferrante[5,6], Catherine Verfaillie[7], Lieven Dupont[8,9], Mieke Boon[1,10], Marijke Proesmans[1,10], Jeffrey M. Beekman[3,4], Ifat Sarouk[11], Carlos Vazquez Cordero[12], Francois Vermeulen[1,10] and Kris De Boeck[1,10] on behalf of the Belgian Organoid Project[13]

children MDPI

Review

Organoid Technology and Its Role for Theratyping Applications in Cystic Fibrosis

Jessica Conti [1], Claudio Sorio [1,*] and Paola Melotti [2,*]

[1] Department of Medicine, Division of General Pathology, University of Verona, 37134 Verona, Italy
[2] Cystic Fibrosis Centre, Azienda Ospedaliera Universitaria Integrata Verona, 37126 Verona, Italy
* Correspondence: claudio.sorio@univr.it (C.S.); paola.melotti@aovr.veneto.it (P.M.)

J Physiol. 2022 Mar;600(6):1285-1286. doi: 10.1113/JP282586. Epub 2022 Jan 31.

Nasal epithelial cells as a gold-standard predictive model for personalized medicine in cystic fibrosis

Nicoletta Pedemonte [1]

Affiliations + expand

PMID: 35038767 DOI: 10.1113/JP282586

Free article

FDA Approves Expansion of Modulators for People With Certain Rare Mutations

The U.S. Food and Drug Administration (FDA) today expanded its approval of three CFTR modulators to include additional people with CF who have certain rare mutations. The approval enables more than 600 individuals with CF who were not previously eligible for modulators to access drugs that treat the underlying cause of their disease for the first time.

Dec. 21, 2020 | 3 min read

Table 6: List of *CFTR* Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO

546insCTA	*E92K*	*G576A*	*L346P*	*R117G*	*S589N*
711+3A→G *	*E116K*	*G576A;R668C*†	*L967S*	*R117H*	*S737F*
2789+5G→A *	*E193K*	*G622D*	*L997F*	*R117L*	*S912L*
3272-26A→G *	*E403D*	*G970D*	*L1324P*	*R117P*	*S945L**
*3849+10kbC→T**	*E588V*	*G1069R*	*L1335P*	*R170H*	*S977F**
A120T	*E822K*	*G1244E*	*L1480P*	*R258G*	*S1159F*
A234D	*E831X*	*G1249R*	*M152V*	*R334L*	*S1159P*
A349V	*F191V*	*G1349D*	*M265R*	*R334Q*	*S1251N*
*A455E**	*F311del*	*H939R*	*M952I*	*R347H**	*S1255P*
A554E	*F311L*	*H1054D*	*M952T*	*R347L*	*T338I*
A1006E	*F508C*	*H1375P*	*P5L*	*R347P*	*T1036N*
A1067T	*F508C;S1251N*†	*I148T*	*P67L**	*R352Q**	*T1053I*
D110E	*F508del* ^	*I175V*	*P205S*	*R352W*	*V201M*
*D110H**	*F575Y*	*I336K*	*Q98R*	*R553Q*	*V232D*
D192G	*F1016S*	*I601F*	*Q237E*	*R668C*	*V562I*
D443Y	*F1052V*	*I618T*	*Q237H*	*R751L*	*V754M*
D443Y;G576A;R668C†	*F1074L*	*I807M*	*Q359R*	*R792G*	*V1153E*
*D579G**	*F1099L*	*I980K*	*Q1291R*	*R933G*	*V1240G*
D614G	*G126D*	*I1027T*	*R31L*	*R1066H*	*V1293G*
D836Y	*G178E*	*I1139V*	*R74Q*	*R1070Q*	*W1282R*
D924N	*G178R*	*I1269N*	*R74W*	*R1070W**	*Y109N*
D979V	*G194R*	*I1366N*	*R74W;D1270N*†	*R1162L*	*Y161S*
*D1152H**	*G194V*	*K1060T*	*R74W;V201M*†	*R1283M*	*Y1014C*
D1270N	*G314E*	*L15P*	*R74W;V201M;D1270N*†	*R1283S*	*Y1032C*
E56K	*G551D*	*L206W**	*R75Q*	*S549N*	
E60K	*G551S*	*L320V*	*R117C**	*S549R*	

* Clinical data for these mutations in Clinical Studies *[see Clinical Studies (14.1 and 14.2)]*.
^ A patient must have two copies of the *F508del* mutation or at least one copy of a responsive mutation presented in Table 6 to be indicated.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Table 5: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA

3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N*†	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del**	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C†	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N*†	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M*†	*S364P*	*Y161S*
E116K	*G576A;R668C*†	*L165S*	*R74W;V201M;D1270N*†	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (14)]*.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

The FDA decision expands the labels for **Trikafta®** (elexacaftor/tezacaftor/ivacaftor), Symdeko® (tezacaftor/ivacaftor), and Kalydeco® (ivacaftor) to include additional rare mutations that were previously not approved for CFTR modulators. Trikafta is now approved for individuals who are 12 years and older with at least one of 177 newly-approved mutations; Symdeko is now approved for individuals who are 6 years and older with one of 127 additional mutations; and Kalydeco is now approved for individuals who are 4 months and older with one of 59 additional mutations.

The French Compassionate Program of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del *CFTR* variant

Pierre-Régis Burgel, Isabelle Sermet-Gaudelus, Isabelle Durieu, Reem Kanaan, Julie Macey, Dominique Grenet, Michele Porzio, Nathalie Coolen-Allou, Raphael Chiron, Christophe Marguet, Benoit Douvry, Nadine Dufeu, Isabelle Danner-Boucher, Pierre Foucaud, Lydie Lemonnier, Emmanuelle Girodon, Jennifer Da Silva, Clémence Martin, on Behalf of the French CF Reference Network study group

Results:

- Tra gli 84 pazienti con FC arruolati, ETI era efficace in 45 di essi.
- Tra i responders, 22/45 (49%) erano portatori di mutazioni non approvate dalla FDA.

Metodi:

- Studio osservazionale sugli effetti di ETI su una popolazione di pazienti FC con patologia polmonare avanzata (FEV1<40%), non eleggibili a ETI.
- Efficacia valutata da una commissione a 4-6 settimane in termini di manifestazioni cliniche, cloro sudorale, FEV1%.

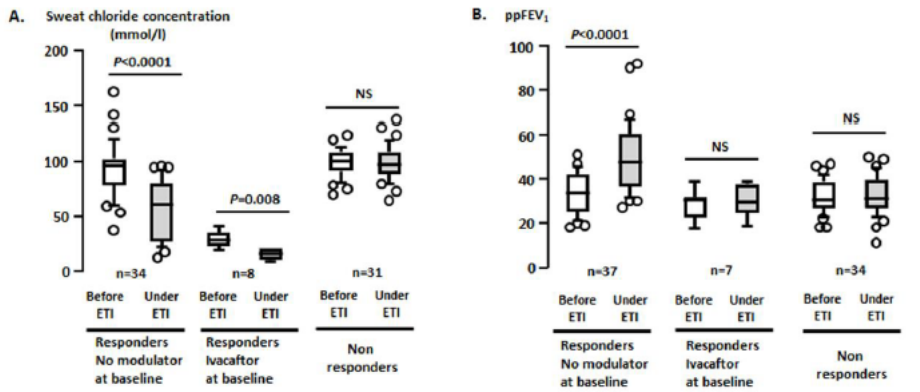


Figure 1. Comparison of sweat chloride concentration and ppFEV1 before ETI and under ETI according to responder status and ivacaftor at baseline. A. Sweat chloride concentration B. ppFEV1. Box plots: median [IQR] (error bars, 10-90 percentile) with outliers. Data were analyzed using the nonparametric Wilcoxon's test.

Eur Respir J 2023

Les médicaments et moi
Qui sommes-nous ?
Actualités
Bulletin officiel des actes, décisions et avis
Disponibilité des produits de santé
Vos démarches
Documents de référence
Informations de sécurité
Dossiers thématiques
Espace presse
Contactez-nous

Retour
ACTUALITÉS > INNOVATION > ACCÈS COMPASSIONNEL > MUCOVISCIDOSE : DE NOUVEAUX PATIENTS VONT POUVOIR ...

PUBLIÉ LE 19/05/2022 - MIS À JOUR LE 01/06/2023

Mucoviscidose : de nouveaux patients vont pouvoir bénéficier de l'association des comprimés pelliculés Kaftrio et Kalydeco

A+ A-

Actualisation du 1er juin 2023

Depuis le 1er juin 2023, le cadre de prescription compassionnelle (CPC) associant les médicaments Kaftrio et Kalydeco s'étend aux patients atteints de mucoviscidose non porteurs d'une mutation F508del, dès l'âge de 6 ans et quel que soit le degré de sévérité de la maladie. Le traitement n'est pas indiqué chez les patients qui présentent 2 gènes mutés prédictifs de l'absence de synthèse de la protéine CFTR.
L'élargissement du CPC prend en compte l'évolution des connaissances scientifiques.

Il est toujours recommandé que la prescription du traitement soit soumise à l'avis du centre coordinateur du centre de référence maladie rare (CRMR) mucoviscidose et affections liées à une anomalie de CFTR, selon la pratique clinique actuelle, et que les patients traités dans le cadre de ce CPC soient inscrits dans le registre français de la mucoviscidose.

Accédez au protocole d'utilisation thérapeutique et de suivi des patients (PUT-SP), qui détaille les modalités d'emploi de Kaftrio 75 mg/50 mg/100 mg comprimé pelliculé, Kaftrio 37,5 mg/25 mg/50 mg comprimé pelliculé, associés respectivement à Kalydeco 150 mg comprimé pelliculé et Kalydeco 75 mg comprimé pelliculé dans les conditions de ce CPC.

The expanded French compassionate programme for elexacaftor–tezacaftor–ivacaftor use in people with cystic fibrosis without a F508del *CFTR* variant: a real-world study

*Pierre-Régis Burgel, Isabelle Sermet-Gaudelus, Emmanuelle Girodon, Isabelle Durieu, Véronique Houdouin, Camille Audousset, Julie Macey, Dominique Grenet, Michele Porzio, Marlène Murris-Espin, Philippe Reix, Mélisande Baravalle, Chantal Belleguic, Laurent Mely, Juliette Verhille, Laurence Weiss, Martine Reynaud-Gaubert, Marie Mittaine, Rebecca Hamidfar, Sophie Ramel, Laure Cosson, Benoit Douvry, Isabelle Danner-Boucher, Pierre Foucaud, Charlotte Roy, Espérie Burnet, Caroline Raynal, Marie-Pierre Audrezet, Jennifer Da Silva, Clémence Martin, on behalf of the French Cystic Fibrosis Reference Network study group**

Interpretation In France, over half of the population with cystic fibrosis without a F508del variant responded to elexacaftor–tezacaftor–ivacaftor, with most responders having no FDA-approved variant. The treatment period was relatively short and further research is warranted to describe the long-term safety and effectiveness of elexacaftor–tezacaftor–ivacaftor in this population.

37 variants were unequivocally non-responsive (always non-responsive in at least three non-responders), including I507del, L227R, E1104X, E585X, G542X, Q220X, R1162X, R553X, S466X, W1098X, W1282X, W846X, Y122X, 1078delT, 1677delTA, 2183AA>G, 3659delC, 394delTT, 1717-1G>A, 2622+1G>A, 3120+1G>A, 621+1G>T, 711+1G>T, CFTRdele17a-18, CFTRdele2-3, 1811+1.6kbA>G, and c.3469-1304C>G. In addition, 96 variants (two FDA-approved [I175V and M152V] and and 94 non-FDA-approved) were probably non-responsive (always non-responsive in one or two non-responders).

Another 64 variants were present only in trans of known responsive variants and could therefore not be categorised.

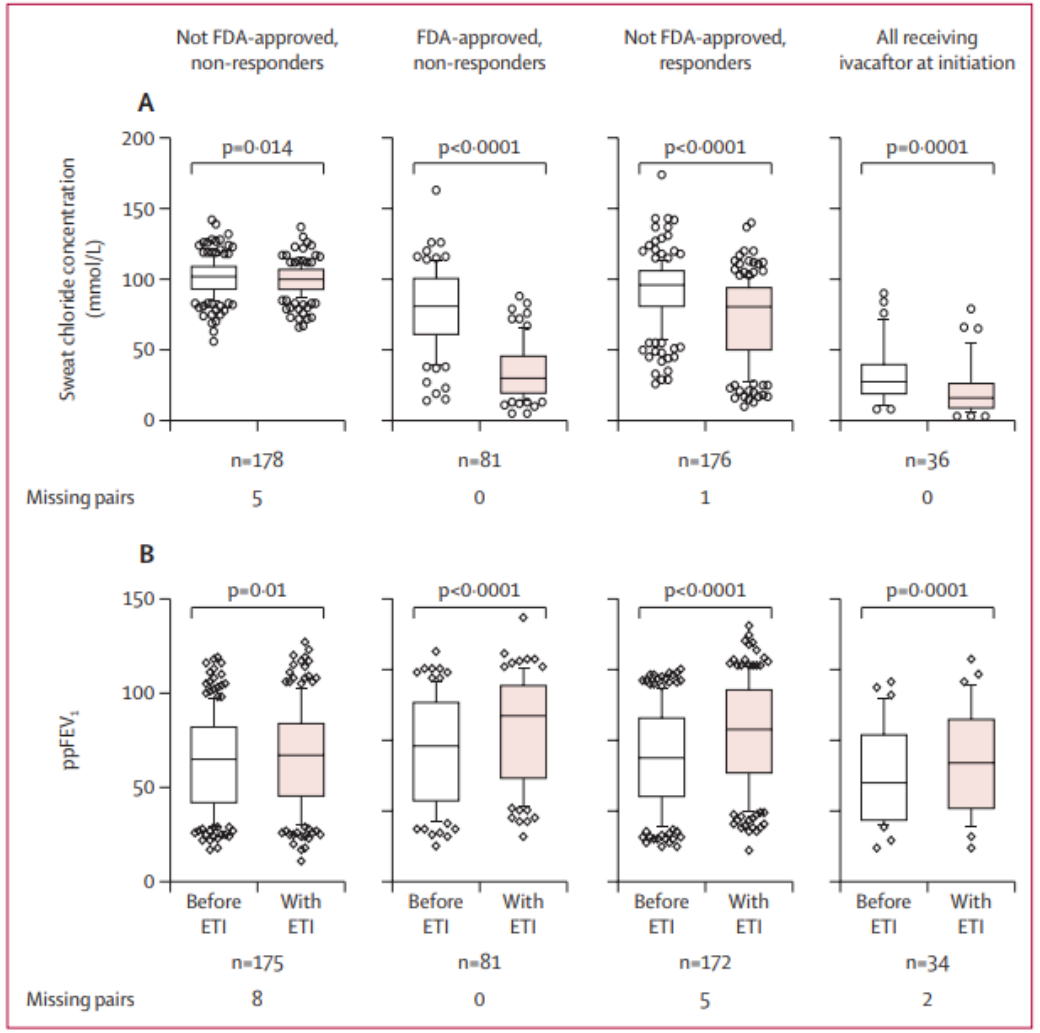


Figure 2: **Comparison of (A) sweat chloride concentration and (B) ppFEV$_1$ before ETI initiation and with ETI treatment**

Vertex Announces European Medicines Agency Validation for Marketing Authorization Application Extension for KAFTRIO® in Combination With Ivacaftor to Include People With Cystic Fibrosis and Responsive Rare Mutations

November 24, 2023

-Application to add ~200 non-F508del CFTR mutations to the KAFTRIO® license-

-If approved, ~2,800 people with cystic fibrosis in the European Union ages 2 and above could receive a medicine that treats the underlying cause of their disease for the first time-

LONDON--(BUSINESS WIRE)--Nov. 24, 2023-- Vertex Pharmaceuticals (Nasdaq: VRTX) today announced that the European Medicines Agency (EMA) has validated a Type II variation application to the Marketing Authorization for KAFTRIO® (ivacaftor/tezacaftor/elexacaftor) in combination with ivacaftor. The application is for expansion of the approved indication for KAFTRIO® in a combination regimen with ivacaftor for the treatment of people with cystic fibrosis (CF) ages 2 and above who have a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive based on clinical and/or *in vitro* data, including the *N1303K* mutation. The application will now be reviewed by the Committee for Medicinal Products for Human Use (CHMP), which will issue an opinion to the European Commission regarding the potential approval of this license expansion.

Data to support this submission includes the results of a Phase 3, randomized, placebo-controlled clinical study in people with rare non-*F508del* KAFTRIO®-responsive *CFTR* mutations. This study met its primary endpoint and showed that KAFTRIO® in combination with ivacaftor resulted in rapid, statistically significant, and clinically meaningful improvements in lung function compared to placebo (9.2 percentage point increase in $ppFEV_1$; $P<0.0001$; 95% CI [7.2, 11.3]). The medicine was generally well tolerated, with safety data generally consistent with the established safety profile of KAFTRIO® in combination with ivacaftor.

The Marketing Authorization Application submission package also includes real-world evidence data from the U.S. Cystic Fibrosis Foundation Patient Registry with respect to people with CF with non-*F508del* KAFTRIO®-responsive *CFTR* mutations who are receiving commercially available TRIKAFTA® (which is the name for KAFTRIO® in the U.S.). In addition, the submission includes *in vitro* data using a well-established laboratory model that has been the basis of approval of the rare mutations indication in the U.S.

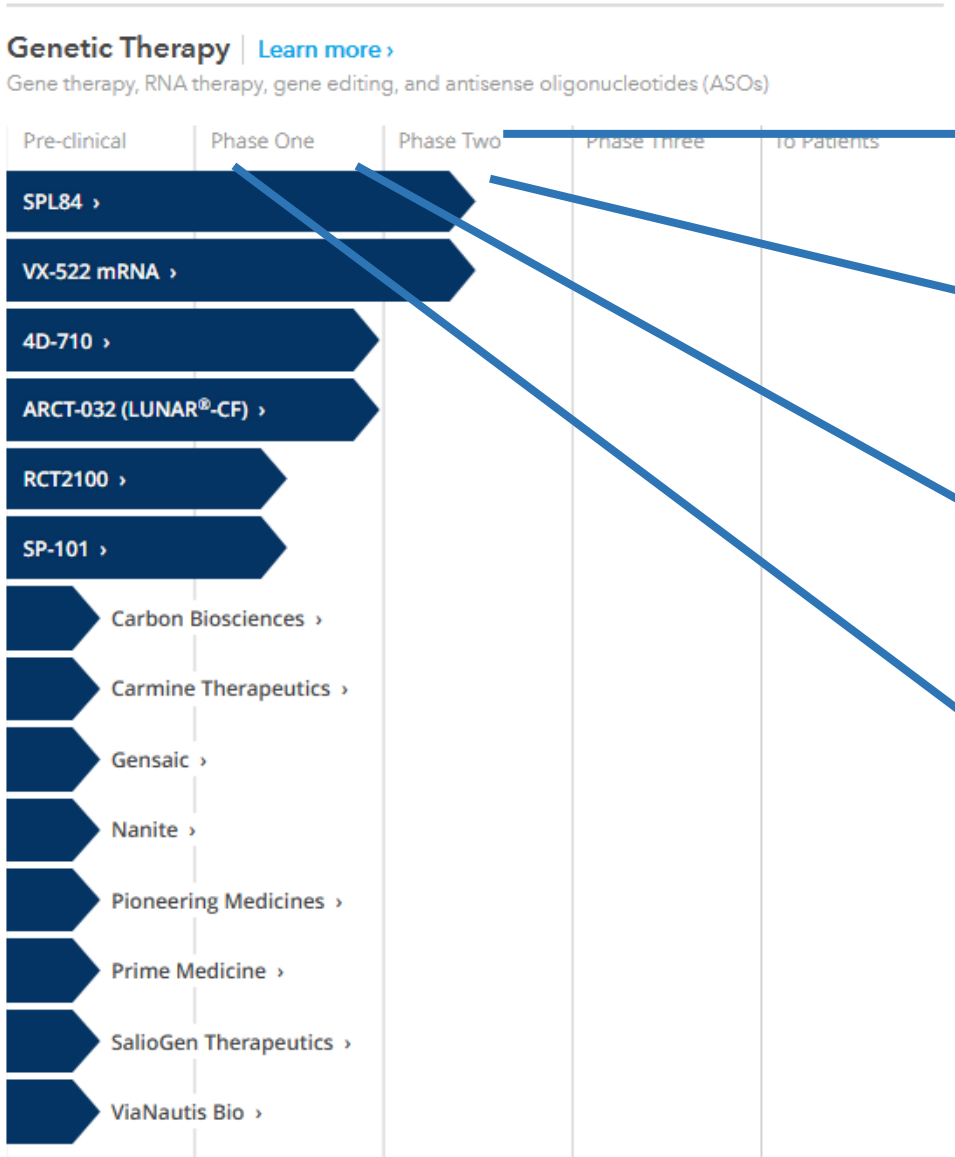
"It is encouraging to see such positive clinical trial results for KAFTRIO in people with CF with these rare types of mutations, which are non- *F508del*," said Professor Isabelle Fajac, Professor of Physiology, Cochin Hospital, Assistance Publique-Hôpitaux de Paris, Université Paris Cité, Paris, France. "The majority of these people currently have no treatment option to address the underlying cause of their CF, so this submission is an extremely important step towards a medicine becoming available for these people with high unmet medical needs."

"We are committed to going the distance in cystic fibrosis and dedicated to bringing treatments to all people with CF," said Nia Tatsis, Ph.D., Executive Vice President, Chief Regulatory and Quality Officer at Vertex. "We look forward to working with the EMA on this important submission for people with CF who have non-*F508del* KAFTRIO-responsive rare mutations, who currently cannot access KAFTRIO for the underlying cause of their disease."

Vertex plans to submit regulatory filings for the same mutations in Australia, Brazil, Canada, New Zealand and Switzerland. The company also plans to submit a subset of these mutations, including *N1303K* and non-canonical splice mutations, not currently included in the U.S. TRIKAFTA® label to the U.S. FDA.

About Cystic Fibrosis

CYSTIC FIBROSIS FOUNDATION



Terapia genica

fornisce all'organismo una copia corretta di un gene difettoso o un altro gene che possa compensarne il malfunzionamento

mRNA

fornisce alla cellula le informazioni corrette per sintetizzare la proteina CFTR normale

Editing genomico

manipolazione genetica in cui si procede alla delezione, all'inserimento, alla sostituzione o alla modifica del DNA genomico di un organismo vivente

Oligonucleotidi antisenso

piccoli pezzi di DNA o RNA che si legano alla molecola di RNA e correggono queste istruzioni in modo da poter produrre una proteina CFTR a lunghezza intera

CFF, Ottobre 2024

← Back to the Drug Development Pipeline

VX-522 mRNA

Email | Print

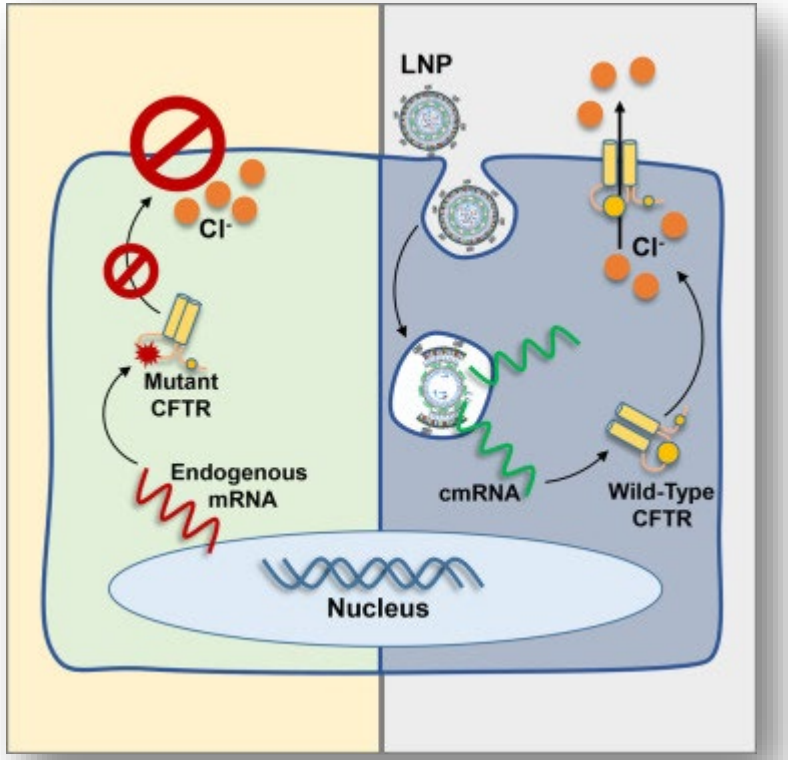
STATUS
Phase One

THERAPEUTIC APPROACH
Genetic Therapy

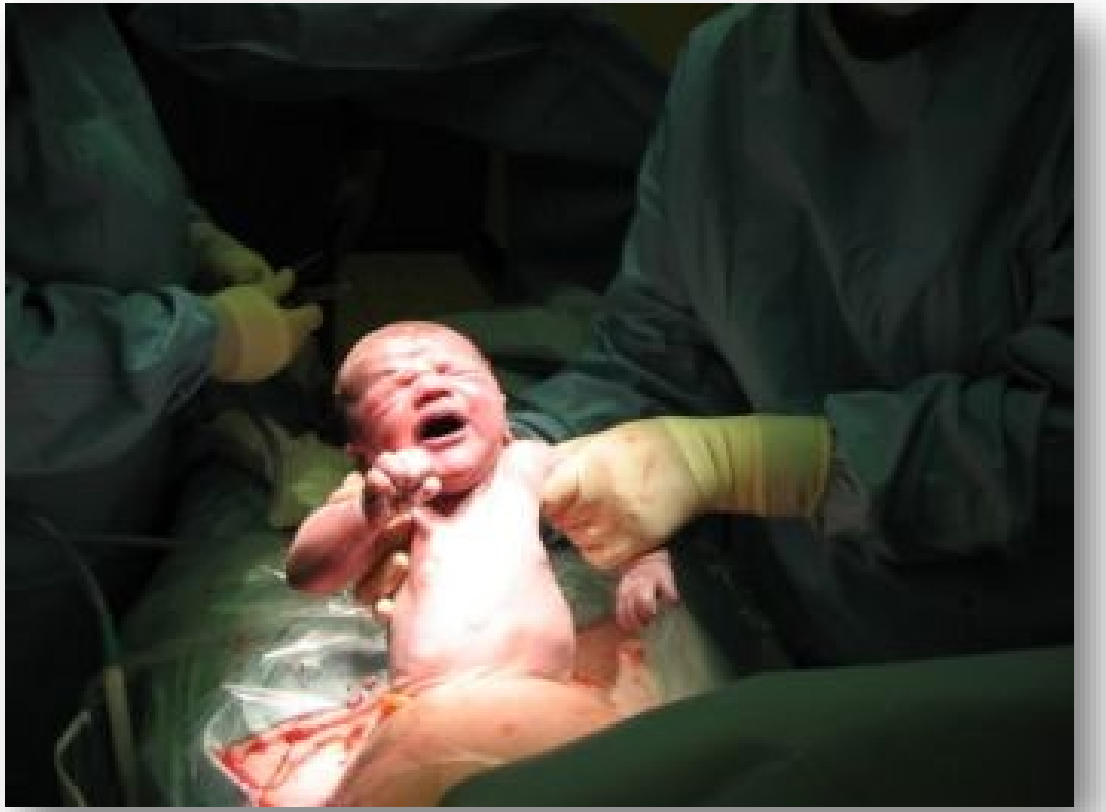
VX-522 is an inhaled messenger RNA (mRNA) therapy. It aims to deliver a full-length copy of CFTR mRNA to lung cells using a lipid nanoparticle. Lung cells would then use the instructions in the mRNA to create functional CFTR protein. This type of therapy could work for any person with CF, regardless of their CFTR mutations.

Status

A phase 1 study to test the safety and tolerability of VX-522 is underway. The study is for adults with CF who have CFTR mutations that are not responsive to CFTR modulator therapy.



- L'obiettivo è fornire una copia a lunghezza intera del CFTR mRNA alle cellule polmonari utilizzando come vettore una nanoparticella lipidica.
- Le cellule polmonari userebbero quindi le istruzioni contenute nel mRNA per creare la proteina CFTR funzionale.
- Questa terapia potrebbe funzionare per qualsiasi persona con FC, indipendentemente dalle sue mutazioni CFTR.



Università di Catania

U.O.C. Broncopneumologia Pediatrica

Ospedale San Marco – AOU Policlinico - Catania

Direttore:
Prof. Salvatore Leonardi

Dirigenti Medici:
Dr. Maria Papale
Dr. Giuseppe F. Parisi
Dr. Giulia Pecora
Dr. Santiago Presti
Dr. Novella Rotolo
Dr Pietro Sciacca
Dr. Massimo Spina

Medici in formazione specialistica:

Dott.ssa Desirée Balconara
Dott.ssa Giusi Caltabiano
Dott.ssa Ersilia Campo
Dott. Salvatore Carnazzo
Dott. Claudio Coppola
Dott.ssa Laura Sciuto
Dott.ssa Monica Tosto

gf.parisi@policlinico.unict.it