Aggiornamenti dagli ultimi Congressi scientifici internazionali

Giuseppe F. Parisi
Pediatra
UOC Broncopneumologia Pediatrica e Fibrosi Cistica
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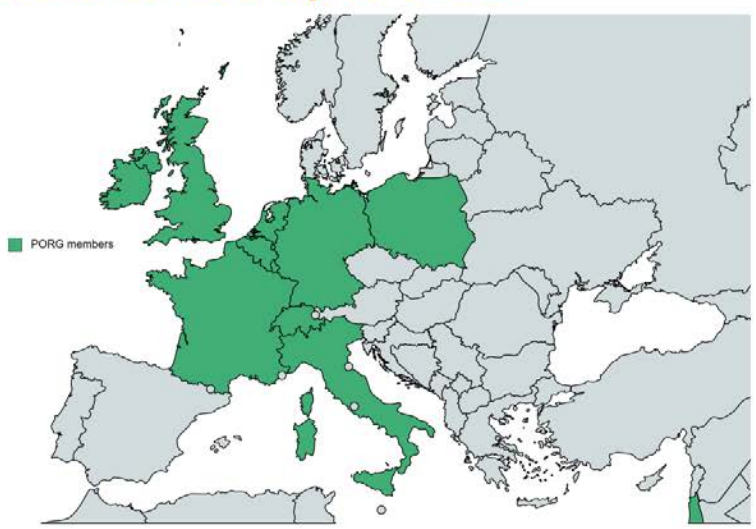
Direttore: Prof. S. Leonardi

Patient Organisations Research Group (PORG)



- L'obiettivo del PORG è quello di migliorare le partnership tra le organizzazioni europee associate, al fine di espandere la rete europea di ricerca sulla FC e accelerare l'accesso a nuovi farmaci per le persone con FC attraverso la ricerca.
- Il PORG conta attualmente 11 membri, tra cui Belgio, Francia, Germania, Irlanda, Israele, Italia, Lussemburgo, Paesi Bassi, Polonia, Svizzera e Regno Unito.

Patient Organisations Research Group (PORG)

- Priorità di ricerca secondo i pazienti
- Collaborazione con ECFS Patient Registry
- Collaborazione con ECFS Clinical Trials Network
- Organizzazione dell'European CF Young Investigators Meeting (EYIM)
- Organizzazione dell'incontro pre-conferenza prima della ECFS Basic
- Science Conference
- Supporto finanziario (insieme a ECFS) di ricercatori postdoc

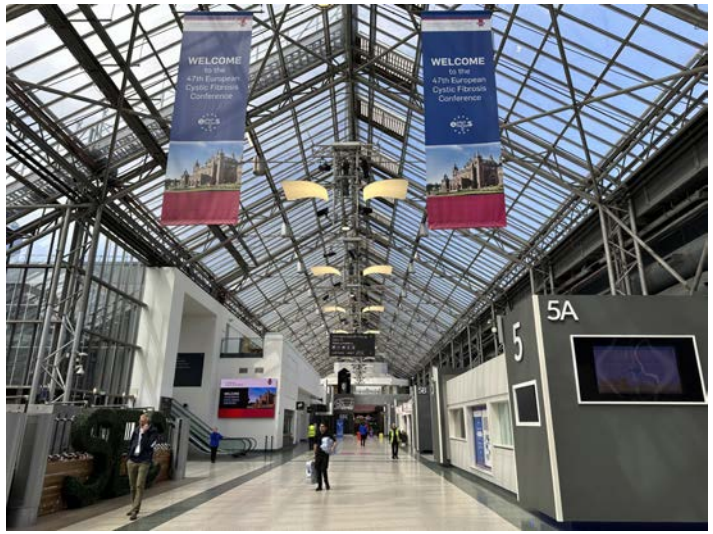
forum 2024

LIFC Lega Italiana Fibrosi Cistica

ecfs

47th EUROPEAN CYSTIC FIBROSIS CONFERENCE

5 – 8 JUNE 2024 | GLASGOW, UNITED KINGDOM



2023 CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY HIGHLIGHTS

CYSTIC FIBROSIS FOUNDATION®

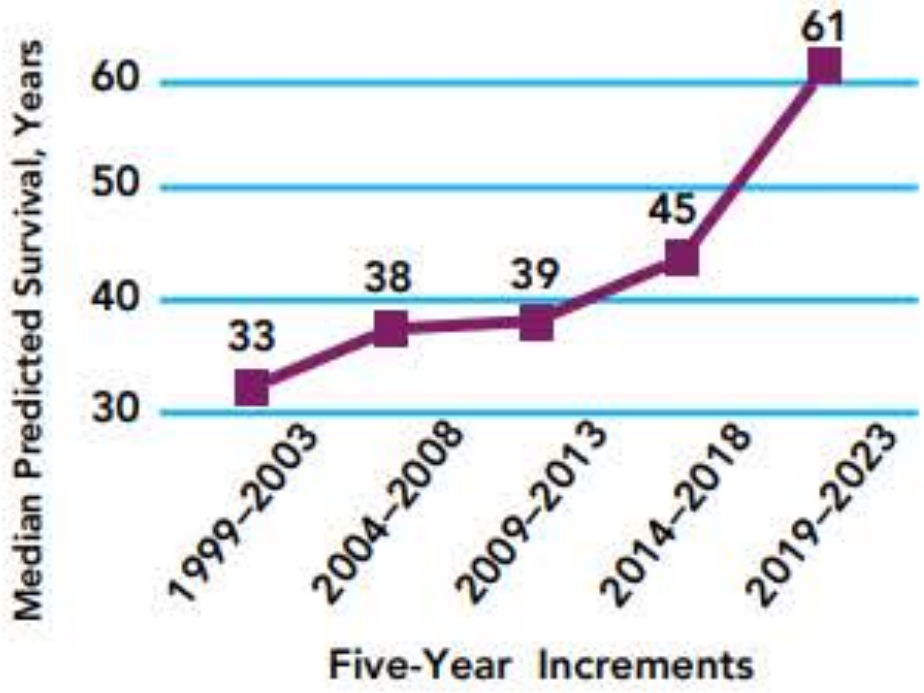
SURVIVAL

61

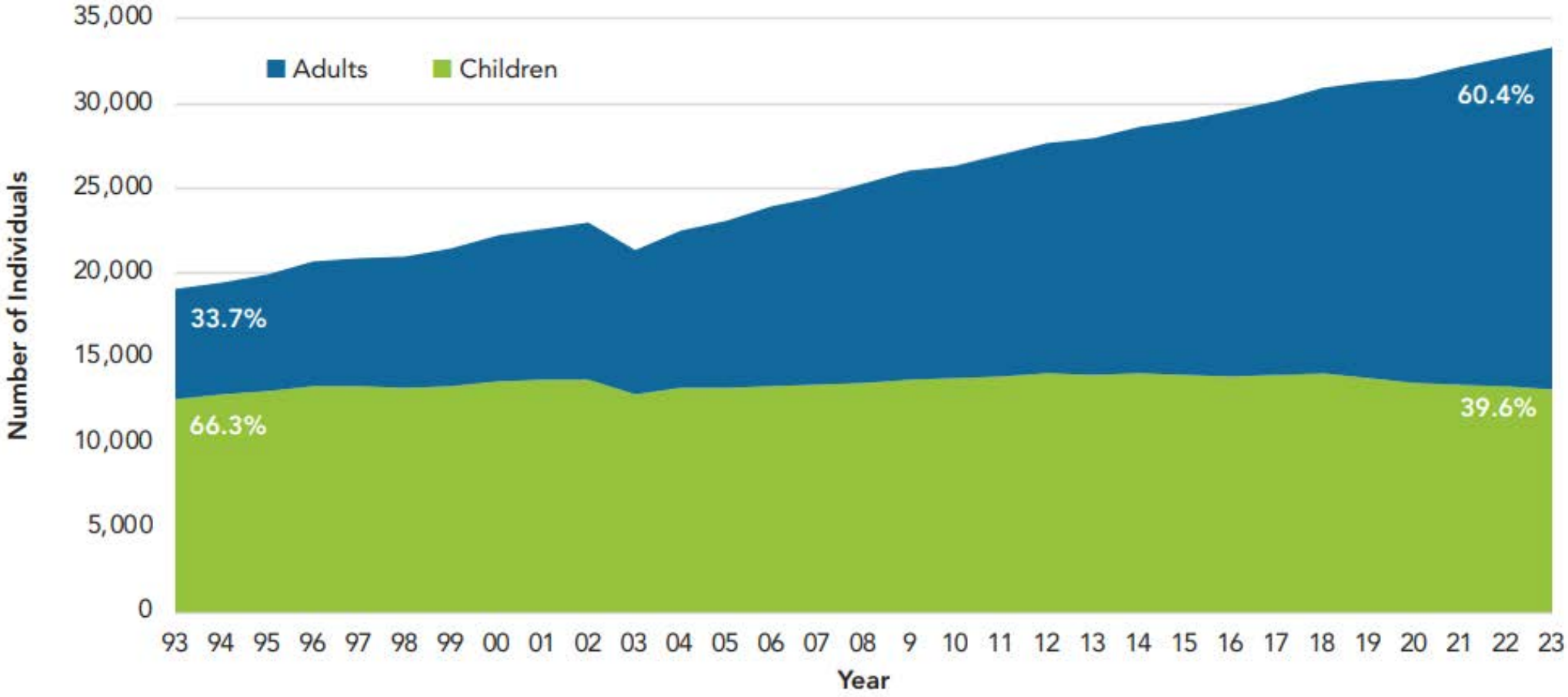
YEARS

2019-2023

Among people with CF born 2019-2023, half are predicted to live to 61+ years. However, this does not reflect individual variability. The median survival is lower for those ineligible for modulators by possibly over a decade.



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

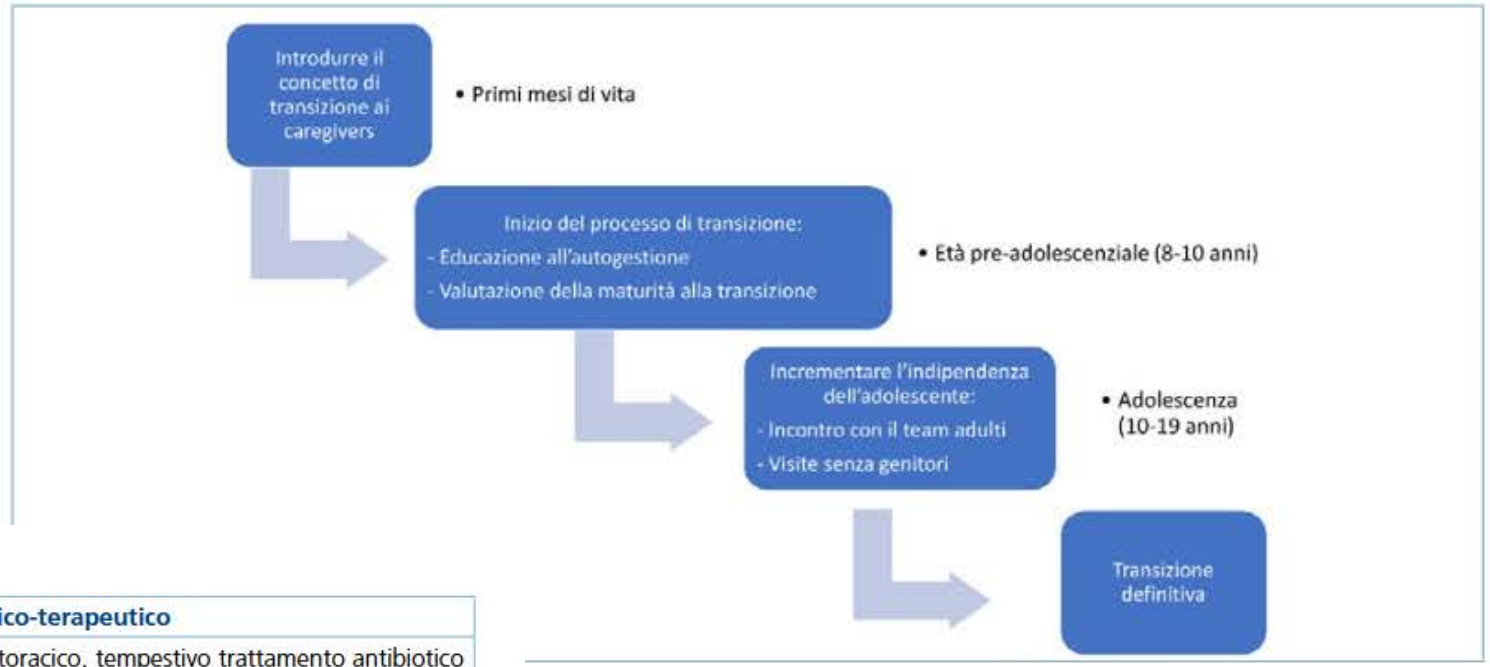


Tabella I. Caratteristiche cliniche del paziente in fase di transizione.

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

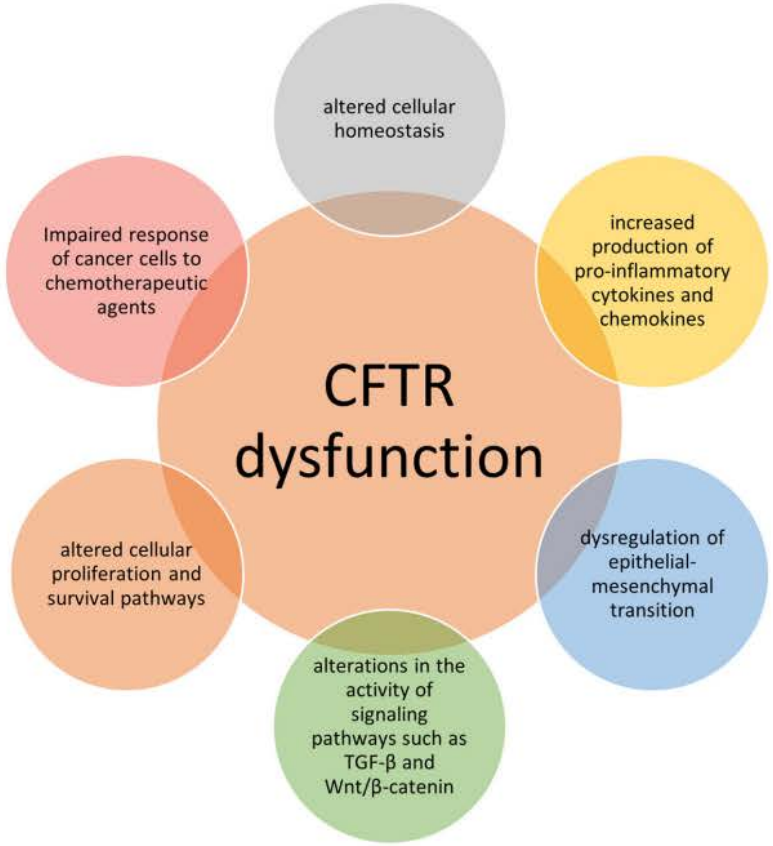
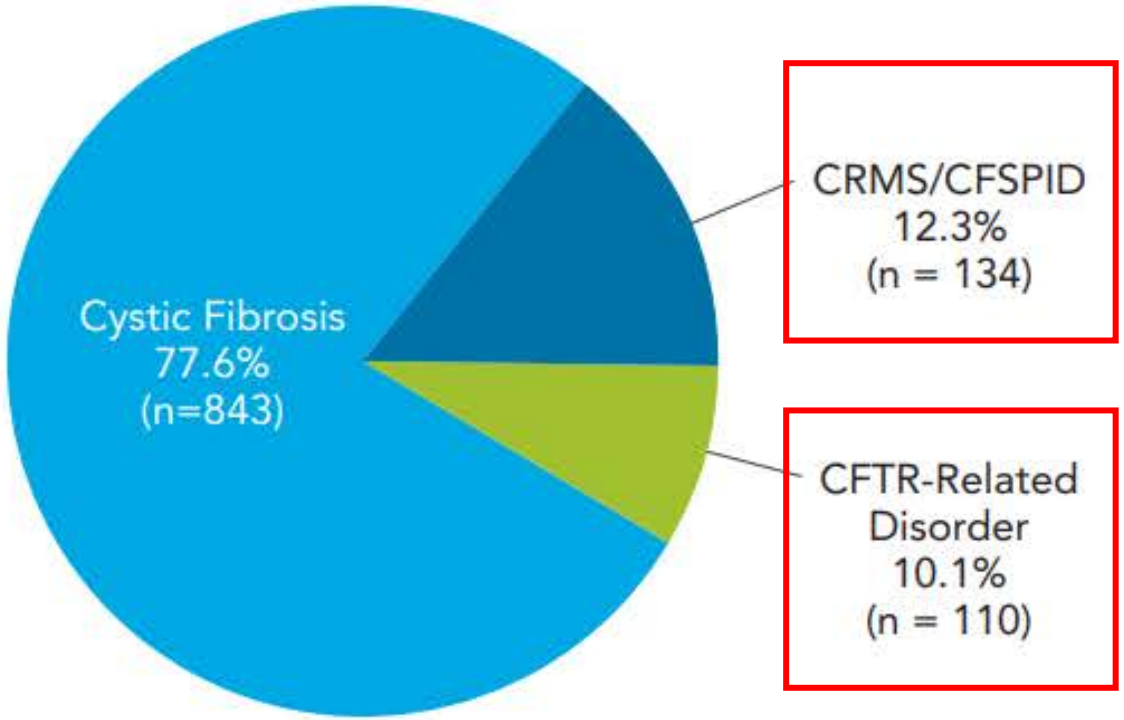


Figure 1. CFTR dysfunction and mechanisms related to predisposition to cancers. CFTR dysfunction in CF triggers chronic inflammation, impaired DNA repair, and hormonal imbalances. These mechanisms collectively predispose individuals to various cancers, highlighting the intricate interplay between CF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

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



CFSPID

Cystic Fibrosis Screen Positive, Inconclusive Diagnosis

Screening Neonatale Positivo

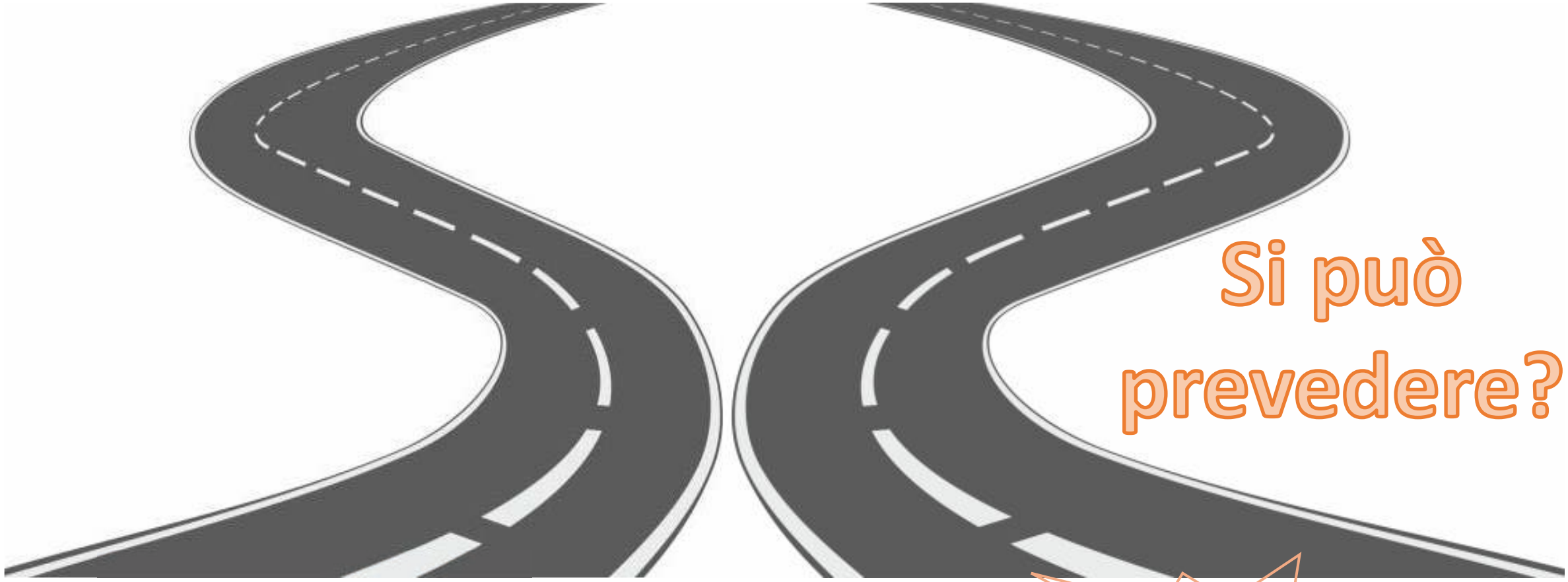
Test del sudore negativo
(Cloro < 30 mmol/L)

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

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

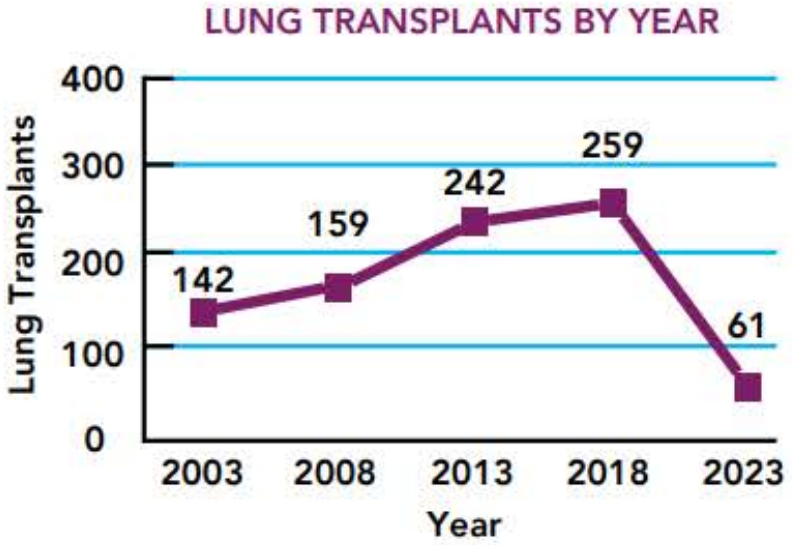
The reader will come to appreciate:

- 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) $\geq$ 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.

Median FEV_1 Percent Predicted

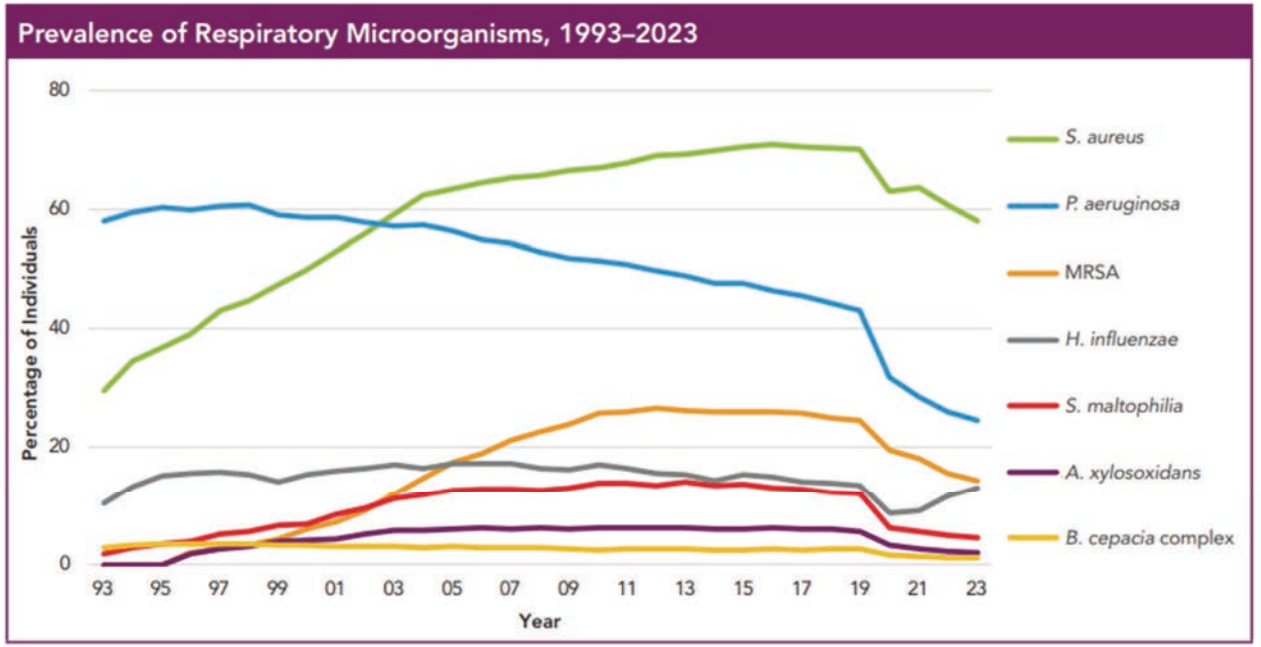
TRANSPLANTATION

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.

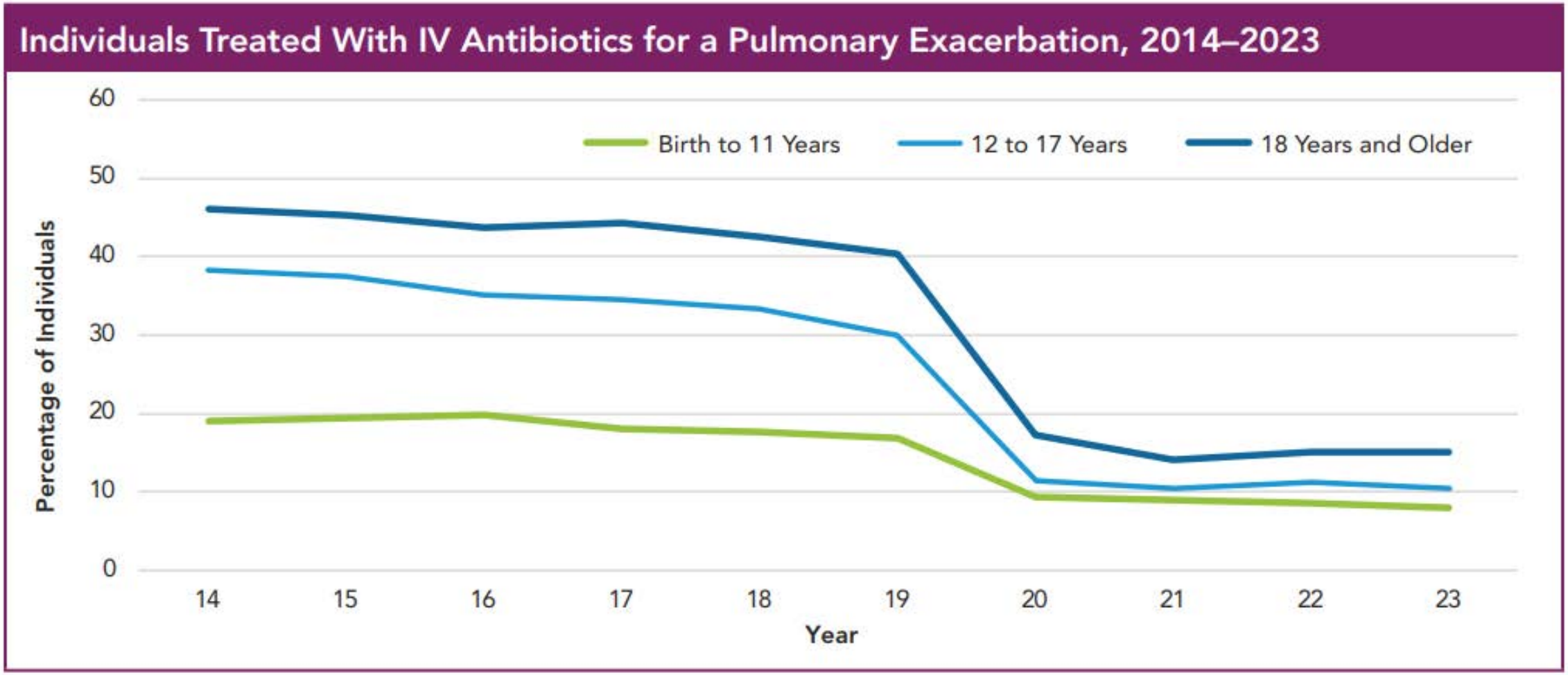


MICROBIOLOGY

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



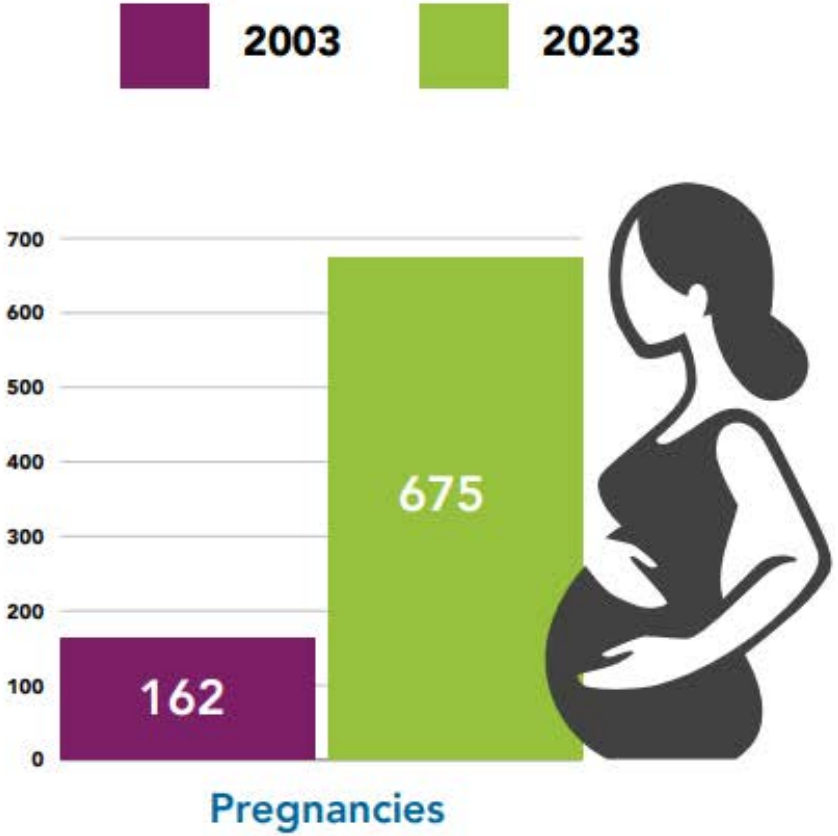
CYSTIC FIBROSIS FOUNDATION

2023 PATIENT REGISTRY

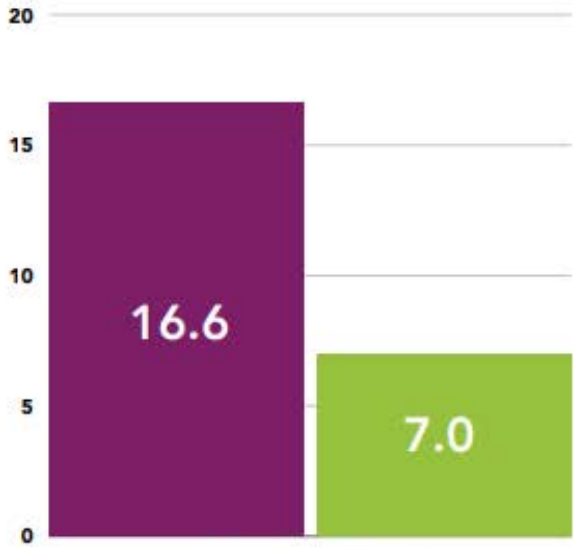
20 YEARS OF PROGRESS

18 Years or Older

2003: 8,518 2023: 20,107



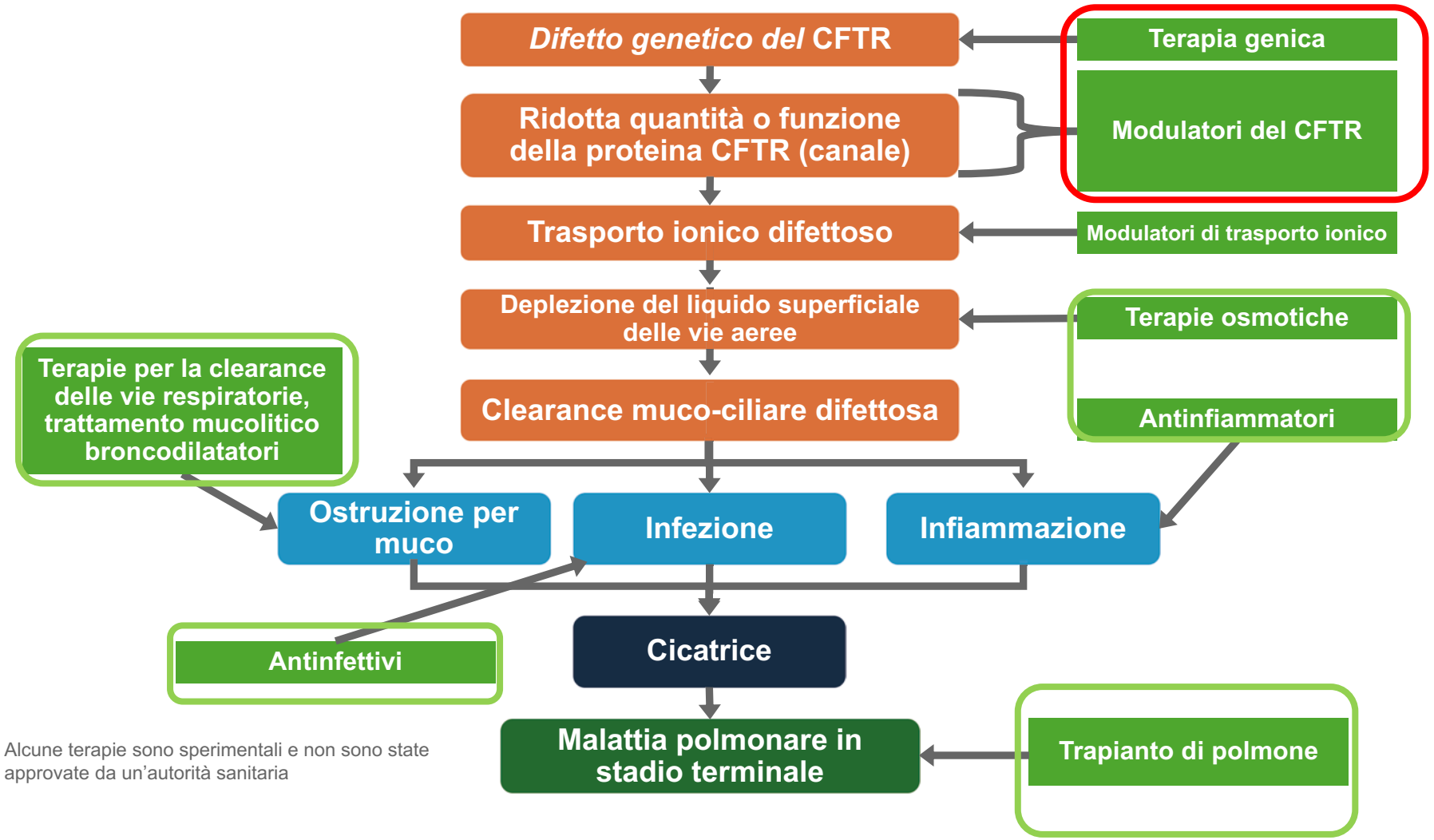
Pregnancies



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.

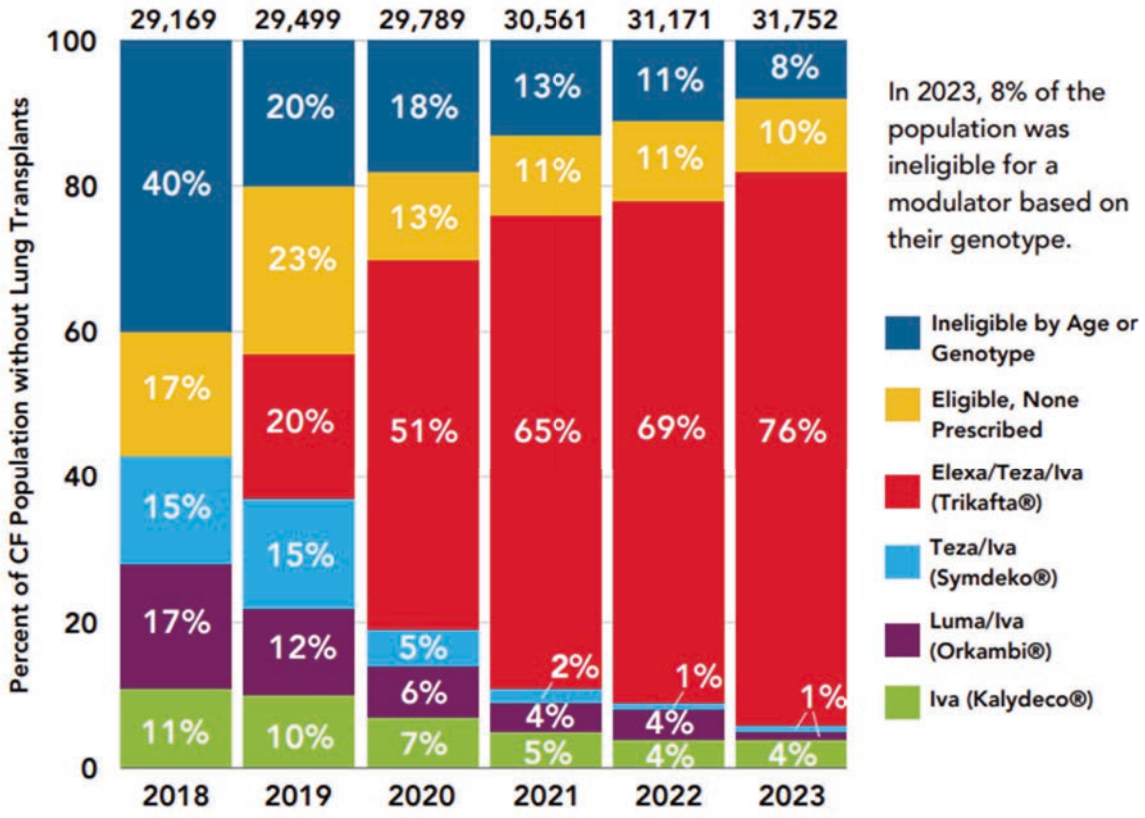
2023 CYSTIC FIBROSIS FOUNDATION PATIENT REGISTRY HIGHLIGHTS

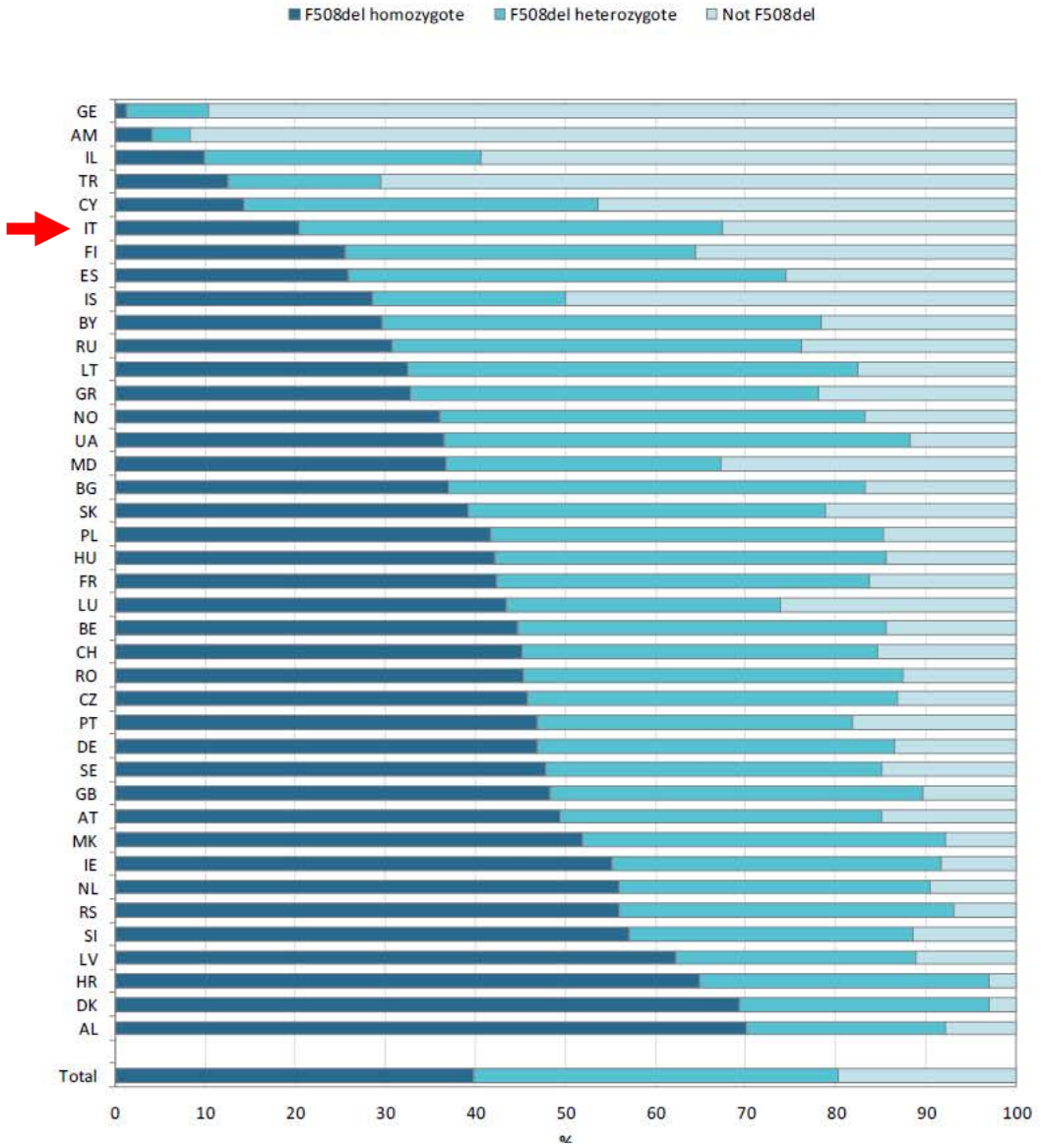
CYSTIC FIBROSIS FOUNDATION

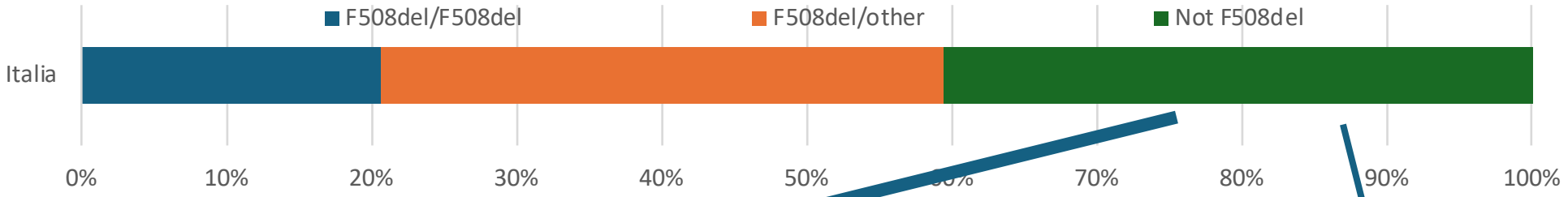
forum 2024

LIFC Lega Italiana Fibrosi Cistica

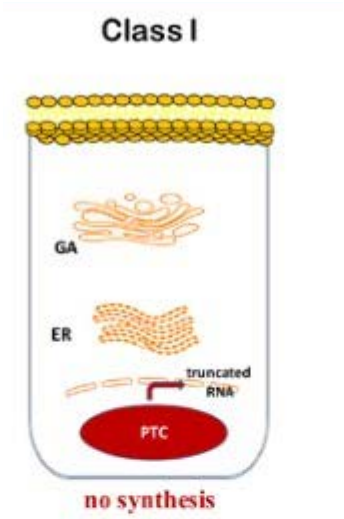
CFTR MODULATORS







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.

Delezioni, duplicazioni, frameshift, missense, splicing, unknown

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?**

Quali opzioni sono disponibili per coloro i quali non sono eleggibili al trattamento con modulatori CFTR?

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

Rowbotham NJ, *et al*. *Thorax* 2023;**78**:840–843. doi:10.1136/thorax-2023-220100

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

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%.

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.

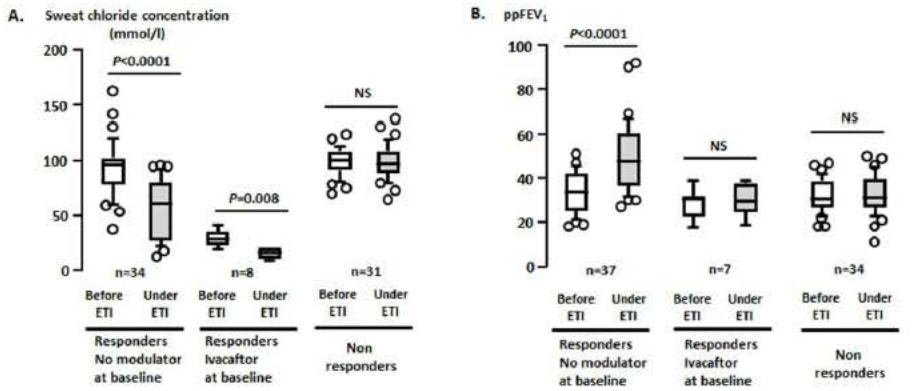


Figure 1. Comparison of sweat chloride concentration and ppFEV1 before ETI and under ETI according to responder status and ivacaftor at baseline. A. Sweat chloride concentration B. ppFEV1. Box plots: median [IQR] (error bars, 10-90 percentile) with outliers. Data were analyzed using the nonparametric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

Eur Respir J 2023

Les médicaments et moi
Qui sommes-nous ?
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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.

ansm
Agence nationale de sécurité du médicament et des produits de santé

DÉCISIONS (MÉDICAMENTS) - ACCÈS DÉROGATOIRE

PUBLIÉ LE 05/02/2024

Décision du 02/02/2024 - Modification du CPC Kaftrio (ivacaftor, tezacaftor, élexacaftor) et Kalydeco (ivacaftor)

La directrice générale de l'ANSM,

Vu le code de la santé publique, notamment les articles L. 5121-12-1 III, L. 5121-14-3 et R. 5121-76-9 ;

Vu le cadre de prescription compassionnelle (CPC) établi le 19/05/2022 et modifié le 01/06/2023 ;

Vu l'autorisation d'accès précoce (AAP) octroyée par la Haute autorité de santé le 07/09/2023 dans l'indication « en association dans le traitement des patients atteints de mucoviscidose âgés de 6 ans et plus, non porteurs d'une mutation F508del du gène CFTR (cystic fibrosis trans-membrane conductance regulator) et porteurs d'une mutation répondeuse à ivacaftor/tezacaftor/elexacaftor sur base de la données in vitro disponibles (voir rubrique 5.1 du RCP) ;

Vu les échanges intervenus entre l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) et l'exploitant des autorisations de mise sur le marché (AMM) des spécialités concernées ;

Considérant que suite à l'octroi de l'AAP précitée, l'indication thérapeutique mentionnée dans le CPC doit être modifiée ;

Considérant que, dans l'intérêt des patients, il est nécessaire de maintenir un encadrement sécurisé de l'utilisation de Kaftrio et Kalydeco dans les autres indications couvertes par le CPC ;

Considérant que la modification apportée au CPC n'emporte pas de conséquence sur la durée de validité de celui-ci ;

Décide :

Article 1er :
Le CPC précité est modifié comme suit en ce qui concerne le libellé de l'indication thérapeutique :
« Traitement de la mucoviscidose chez les patients âgés de 6 ans et plus non porteurs de la mutation F508del, hormis ceux présentant 2 gènes mutés prédictifs de l'absence de synthèse de protéine CFTR et ceux porteurs d'une mutation répondeuse à ivacaftor/tezacaftor/elexacaftor sur la base de données in vitro disponibles telles que définies dans le cadre de l'autorisation d'accès précoce ».

Article 2 :
Le protocole d'utilisation thérapeutique et de suivi des patients joint à la présente décision remplace le protocole en vigueur.

"Trattamento della fibrosi cistica in pazienti di età pari o superiore a 6 anni non portatori della mutazione F508del, ad eccezione di quelli con 2 geni mutati per cui è documentata la non responsività alla terapia, come definito nell'autorizzazione all'accesso anticipato".

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.

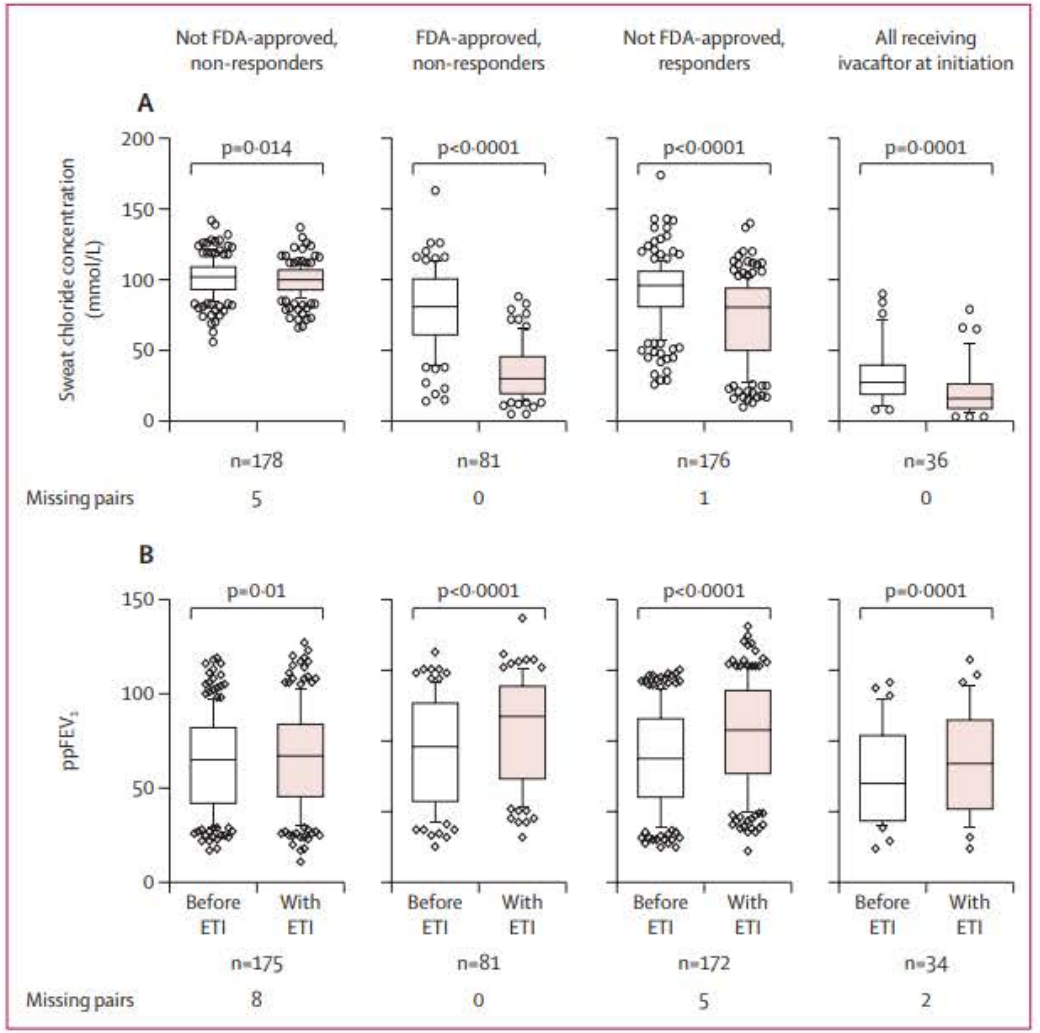


Figure 2: **Comparison of (A) sweat chloride concentration and (B) ppFEV$_1$ before ETI initiation and with ETI treatment**

Newsletter HIT-CF Europe

September 2018

HIT-CF Europe aims to evaluate the efficacy and safety of three drug candidates in patients with CF and rare mutations, pre-selected by their mini-intestines in the laboratory.

We take some tissue from the intestine | This tissue is cultured in the lab | The result is an organoid | On this organoid we test medicines | And we bring the correct medicines to the patients

Organoid screening study

The first part of the HIT-CF project aims at enrolling 500 people with CF with two rare CFTR-mutations from across Europe. A biopsy from these people will be taken and organoids will be generated.
In each European participating country separately, approval has to be obtained from the local Ethical Committee before the biopsy can be taken.

This month, recruiting will start in several countries!

- We have received approval for the study in: Czech Republic, Portugal, Spain, Belgium, Israel and the Netherlands!
- In the following countries we hope to get approval very soon: Poland, Sweden, Germany, France and Austria
- The other countries that are initializing the study are the following: United Kingdom, Italy and Denmark

More detailed information on the countries and hospitals that are participating can be found on www.hitcf.org

Testing organoids in different laboratories

All biopsies will be sent to HUB located in Utrecht, the Netherlands. HUB will generate organoids from biopsies and send the organoids to the organoid screening laboratories of University Medical Centre Utrecht, KU Leuven and Lisbon University.

Utrecht, Leuven, Lisbon and HUB have been working hard on preparing for the organoid screening phase, and we are confident we can start screening the first organoids in the months to come.

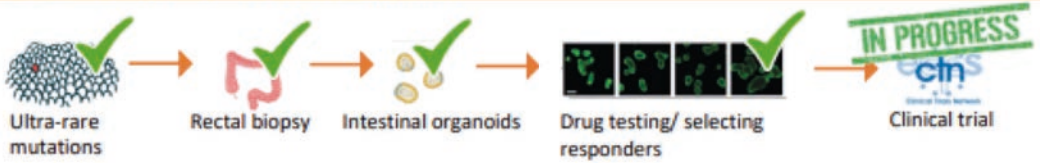
Do you want to participate, or do you want more info about the HIT-CF project?
Visit the website of HIT-CF or send an e-mail to HITCF@umcutrecht.nl

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 755021

Newsletter HIT-CF Europe

September 2024

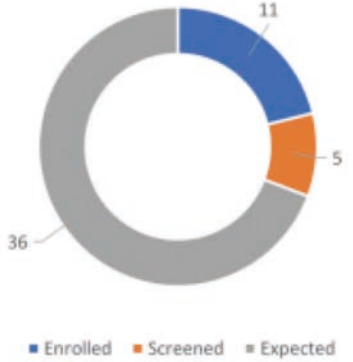
The HIT-CF Europe project aims to provide new treatment options to people with cystic fibrosis (CF) and ultra-rare genetic profiles. The project will evaluate the efficacy and safety of drug candidates provided by collaborating pharmaceutical companies in patients selected through preliminary tests in the laboratory on their mini-intestines – also called organoids.

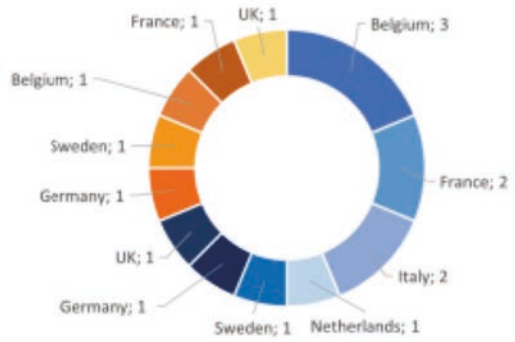


Ultra-rare mutations → Rectal biopsy → Intestinal organoids → Drug testing/ selecting responders → Clinical trial

Enrollment in the CHOICES trial is in full swing

We hope you all enjoyed a relaxing summer and were able to spend time with your loved ones. During the summer months, the CHOICES study team and the staff at the local study sites have been hard at work. At this moment, 11 people have been enrolled in CHOICES. Enrolled means that they are taking the active drug or placebo. An additional 5 have been screened. Screened means that all necessary exams have been done and participants are ready to start the trial. The left graph, or "pie" represents al 52 people that need to be enrolled in CHOICES. In blue you see the ones that are already enrolled, in orange the ones that are screened to be enrolled, and in grey the participants that are expected, but not yet screened. CHOICES is currently running in 10 study sites in 7 countries: Belgium, France, Italy, the Netherlands, Germany, Sweden and the UK. On the right "pie" you see how many participants are enrolled (shades of blue) and screened (shades of orange) per country.





CYSTIC FIBROSIS FOUNDATION

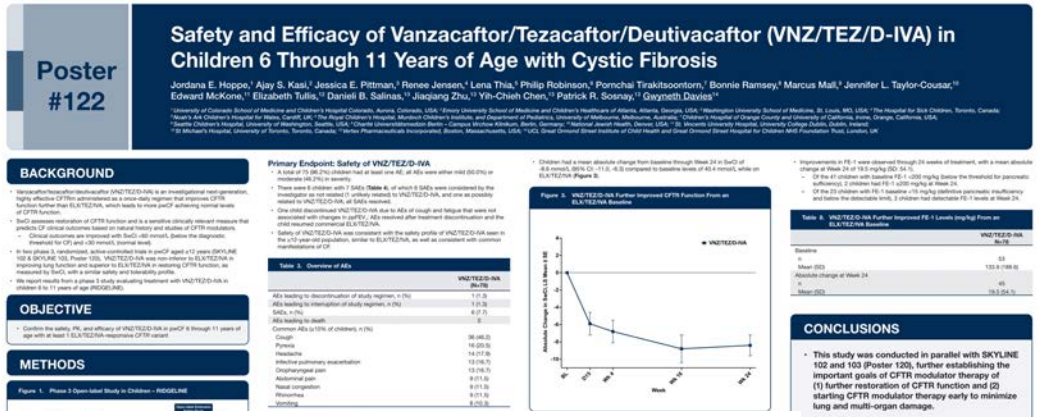
forum 2024

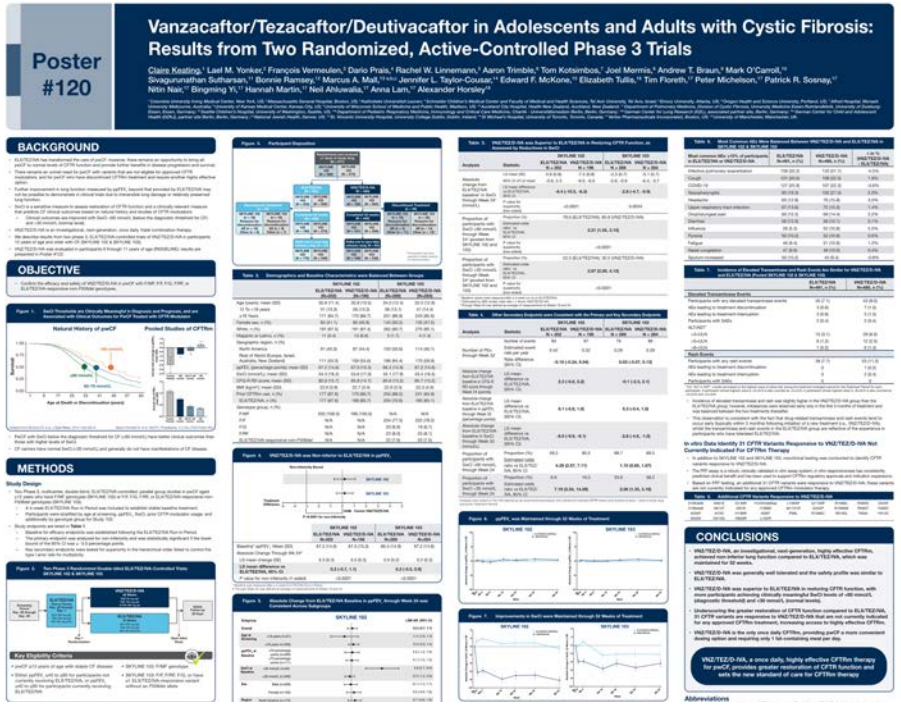
LIFC Lega Italiana Fibrosi Cistica

Restore CFTR Protein | Learn more ›

Modulators and nonsense readthrough therapies

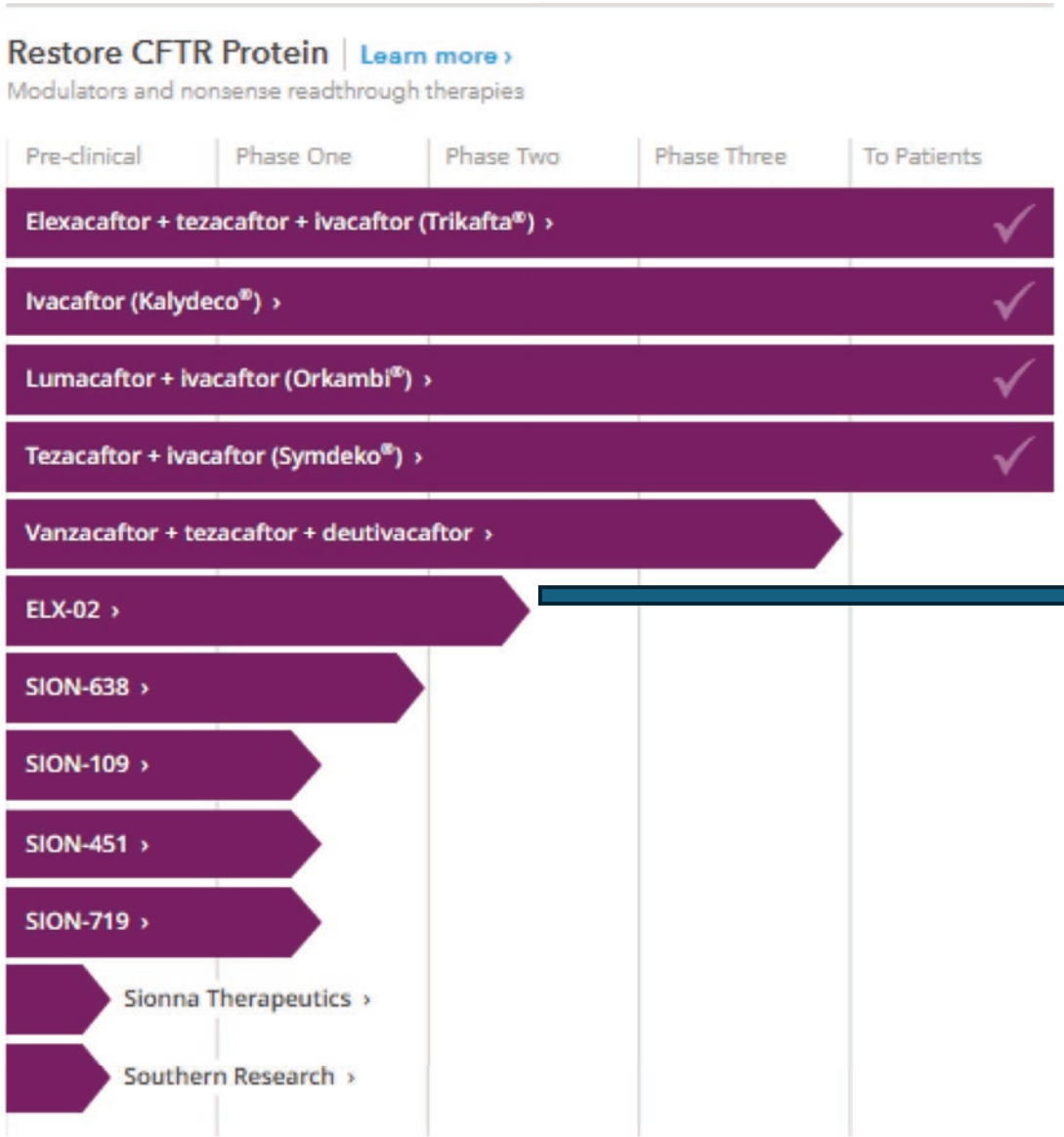
Pre-clinical	Phase One	Phase Two	Phase Three	To Patients
Elexacaftor + tezacaftor + ivacaftor (Trikafta®) ›				✓
Ivacaftor (Kalydeco®) ›				✓
Lumacaftor + ivacaftor (Orkambi®) ›				✓
Tezacaftor + ivacaftor (Symdeko®) ›				✓
Vanzacaftor + tezacaftor + deutivacaftor ›				
ELX-02 ›				
SION-638 ›				
SION-109 ›				
SION-451 ›				
SION-719 ›				
Sionna Therapeutics ›				
Southern Research ›				





CFF, Novembre 2024

CYSTIC FIBROSIS FOUNDATION



Eloxx Pharmaceuticals, Inc. annuncia la valutazione dei dati finali dello studio clinico di Fase 2 di combinazione di ELX-02 nei pazienti di Fibrosi Cistica (FC) di Classe 1

14 giugno 2023 alle 22:53

Condividi

Eloxx Pharmaceuticals, Inc. ha annunciato la valutazione finale dei dati dello studio clinico di Fase 2 di ELX-02 in combinazione con ivacaftor in pazienti FC di Classe 1 con almeno una mutazione nonsense. Nella valutazione finale, ELX-02 ha dimostrato un miglioramento clinicamente rilevante del ppFEV1. La valutazione finale dei dati include una rianalisi che utilizza la variazione di ppFEV1 dal Giorno 1 anziché dal basale, poiché diversi pazienti hanno avuto una progressione della malattia tra lo screening e il trattamento.

I risultati iniziali di questo studio sono stati comunicati nel settembre 2022.
Valutazione finale dello studio di combinazione di fase 2 di ELX-02 in pazienti con FC di classe 1: Lo studio clinico di combinazione di Fase 2 di ELX-02 è stato progettato per valutare la sicurezza e l'attività biologica in pazienti con FC di Classe 1 con mutazione nonsenso G542X, come monoterapia e in combinazione con ivacaftor dopo 5 settimane di trattamento. I risultati dell'analisi finale di 13 pazienti valutabili, rispetto agli 11 al momento della valutazione iniziale, sono riassunti di seguito: 6 dei 13 pazienti sono entrati nello studio dal braccio di monoterapia (dopo una media di 463 giorni) e hanno avuto una diminuzione della funzione polmonare (riduzione annualizzata del -4,26% del ppFEV1) a causa della progressione della malattia.

Il trattamento con ELX-02 ha stabilizzato la malattia nel complesso e ha determinato un aumento clinicamente rilevante del ppFEV1 in sei dei tredici pazienti, in base alla variazione del ppFEV1 alla fine del trattamento, al Giorno 35, rispetto all'inizio del trattamento, al Giorno 1. I dati topline precedenti hanno confermato l'attività biologica.

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

← Back to the Drug Development Pipeline

SPL84

Email | Print

STATUS
Phase Two

THERAPEUTIC APPROACH
Genetic Therapy

This program is working to develop a potential therapy for people with CF who have splicing mutations. Splicing is an essential process in which RNA is cut into pieces and then stitched back together in a specific way. Splicing mutations in the CFTR gene cause the RNA to be cut or stitched incorrectly, leading to a mutated CFTR protein. SPL84 is a short nucleotide, or a small piece of genetic material, that is designed to bind to RNA and change its properties in specific ways. In the case of a splicing mutation, the short nucleotide is designed to ensure that the RNA is cut and stitched correctly, allowing functional CFTR protein to be made.

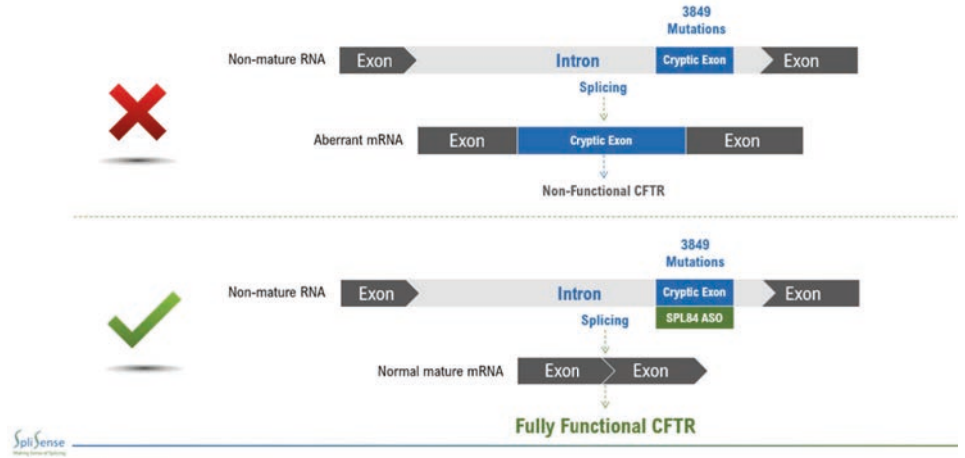
Recent SPL84 Studies

ENROLLING

Study to evaluate SPL84 in adults with cystic fibrosis carrying the 3849 + 10 Kb C->T mutation (SpliSense SPL84-002)

View all SPL84 studies ›

SPL84 Produces Mature and Functioning WT CFTR



- Mutazioni splicing.
- Lo splicing è un processo essenziale in cui l'RNA viene tagliato in pezzi e poi ricucito insieme in un modo specifico.
- Le mutazioni di splicing nel gene CFTR causano un taglio o una ricucitura errata dell'RNA, che porta a una proteina CFTR mutata.
- SPL84 è un breve nucleotide, o un piccolo pezzo di materiale genetico, progettato per legarsi all'RNA e modificarne le proprietà in modi specifici. Nel caso di una mutazione di splicing, il nucleotide è progettato per garantire che l'RNA venga tagliato e ricucito correttamente, consentendo la produzione di una proteina CFTR funzionale.

VX-522 mRNA

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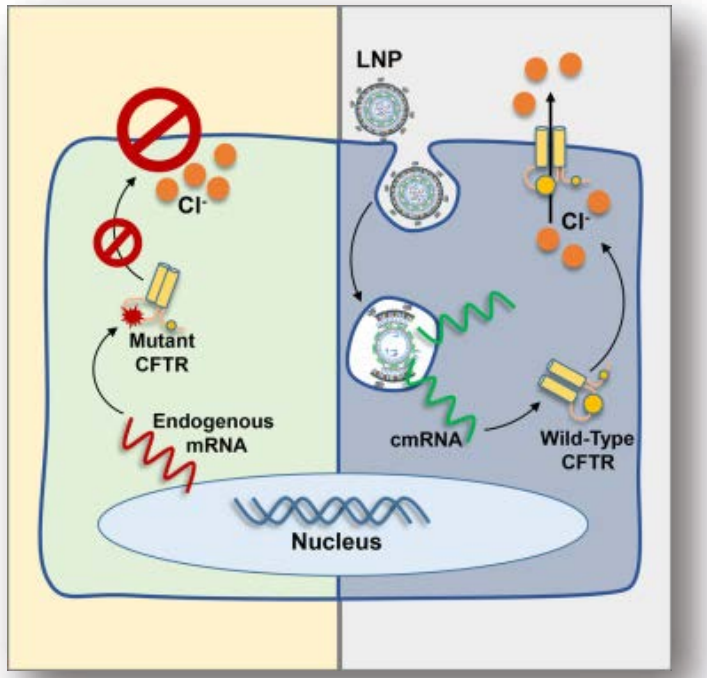
STATUS
Phase Two

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, including those with nonsense (also known as "x" or "stop") and other rare mutations that do not respond to CFTR modulators.



- 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.

← Back to the Drug Development Pipeline

LUNAR®-CF

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STATUS
Phase One

THERAPEUTIC APPROACH
Genetic Therapy

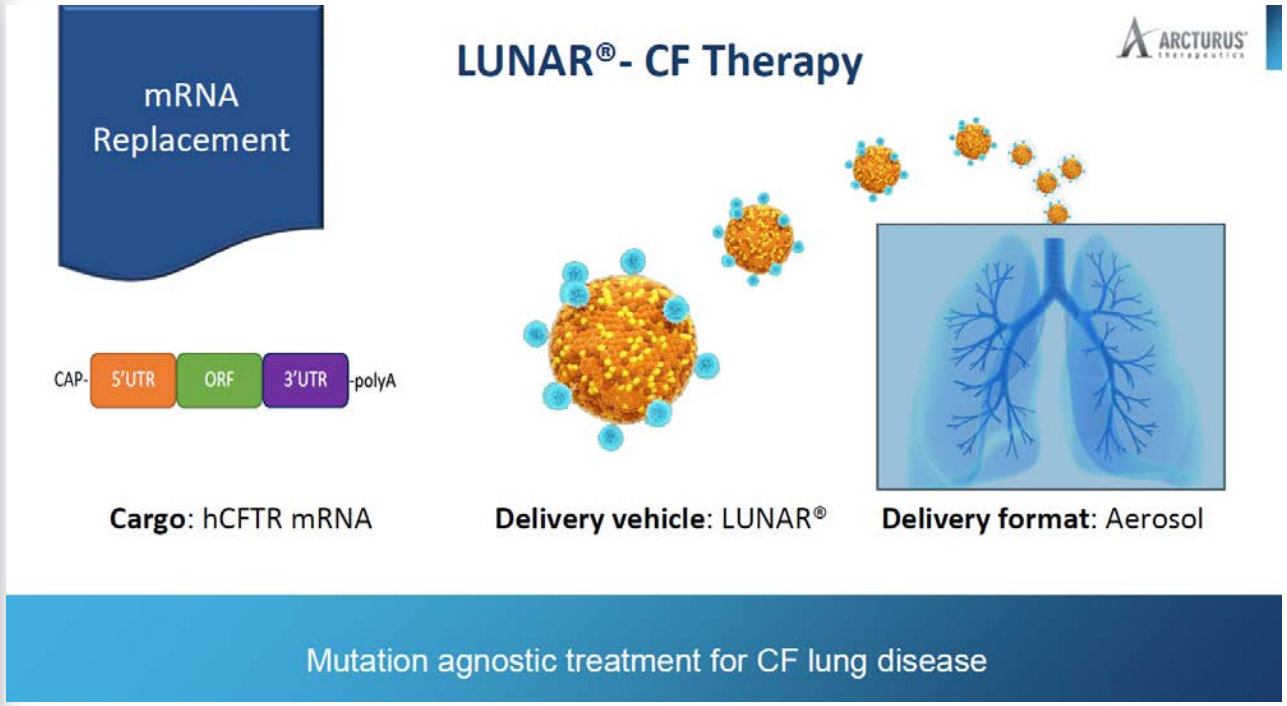
This program is developing a potential inhaled therapy to deliver normal CFTR messenger RNA (mRNA) to the lungs. Lung cells would then use the instructions in the mRNA to create functional CFTR protein. This type of therapy could work for any person with CF, regardless of their CFTR mutations.

Status

A Phase 1 study to test the safety and tolerability of this potential therapy is currently underway in New Zealand. The study initially enrolled healthy volunteers and is planned to expand to adults with CF later this year.

Sponsor

This program is sponsored by Arcturus Therapeutics and is partially funded by the Cystic Fibrosis Foundation.



- LUNAR®-CF è una terapia sostitutiva dell'mRNA, per aerosol per il trattamento della malattia polmonare nella fibrosi cistica ed è indipendente dal genotipo.
- un mRNA CFTR umano incapsulato in LUNAR®, una nanoparticella lipidica, è stato sviluppato per fornire l'mRNA nell'epitelio delle vie aeree. Le proprietà fisicochimiche di LUNAR® erano stabili dopo l'aerosol.

← Back to the Drug Development Pipeline

4D-710

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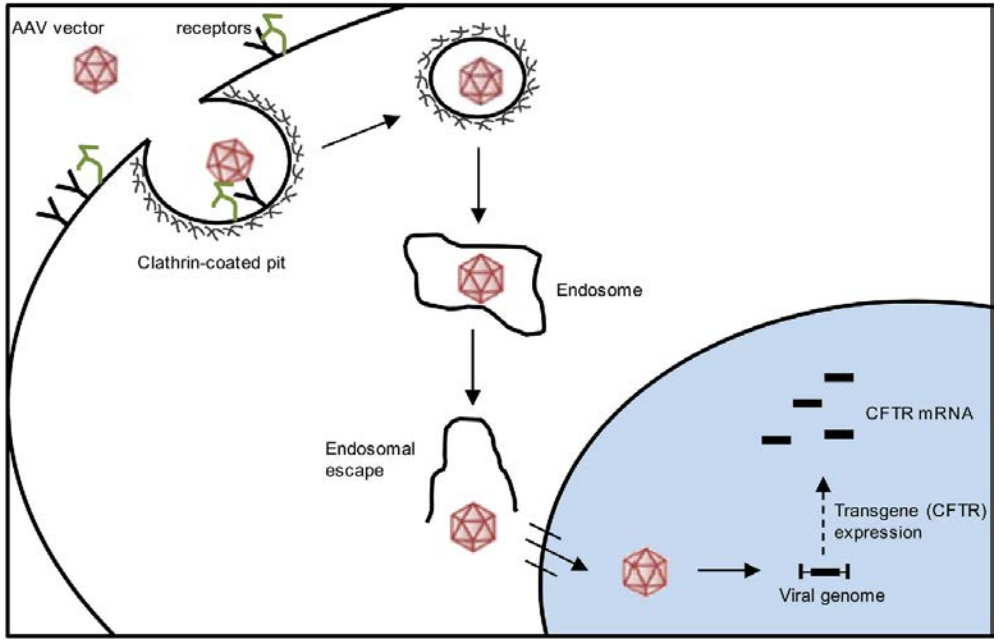
STATUS
Phase One

THERAPEUTIC APPROACH
Genetic Therapy

This program is working to advance a gene delivery vehicle that targets cells in the lung. 4D-710 is a customized adeno-associated virus (AAV) vector designed to deliver a healthy CFTR gene specifically to cells in the lungs of people with CF. This would allow the lung cells to create normally functioning CFTR protein, regardless of an individual's specific CFTR gene mutation.

Status

A Phase 1 study to test the safety of 4D-710 in adults with CF is underway.



- Terapia genica con vettore adenovirus associato
- Ridotta immunogenicità rispetto ai vettori adenovirali «classici»

TERAPIA GENICA

NUOVI VETTORI VIRALI

- Vettori Adenovirus Associati (AAV) – 4DMT / SPIROVANT
- Herpes Simplex (HSV) – KRYSTAL BIO
- Bocavirus – CARBON BIOSCIENCE
- Lentivirus – BOEHRINGER INGELHEIM


Mutazioni rare


Grazie per l'attenzione!