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forum 2023

Cambiamento nelle prospettive di vita e di cura in relazione all'assunzione/non assunzione dei modulatori

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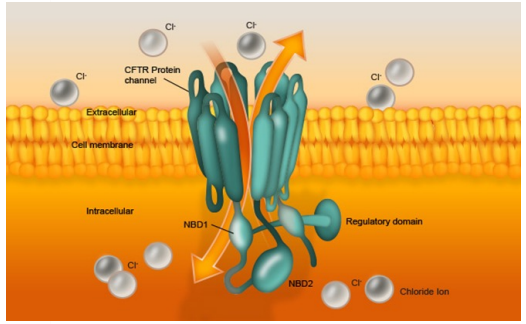
Fibrosi Cistica: Dalla ‘malattia del bacio’ alla scoperta del gene

8 settembre 1989

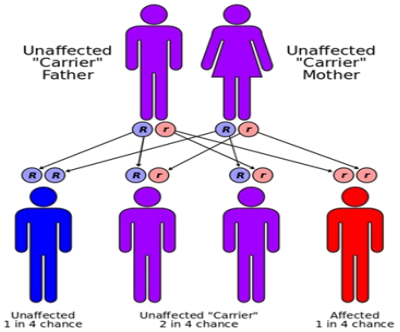
Tsui – Collins & Riordan



CFTR protein

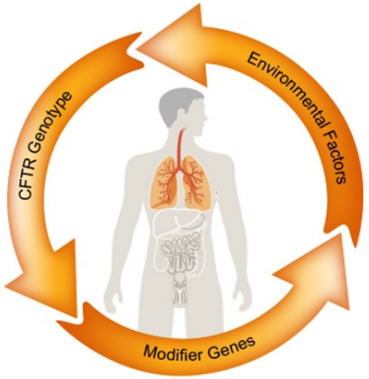
Ad oggi note ca 2000 mutazioni

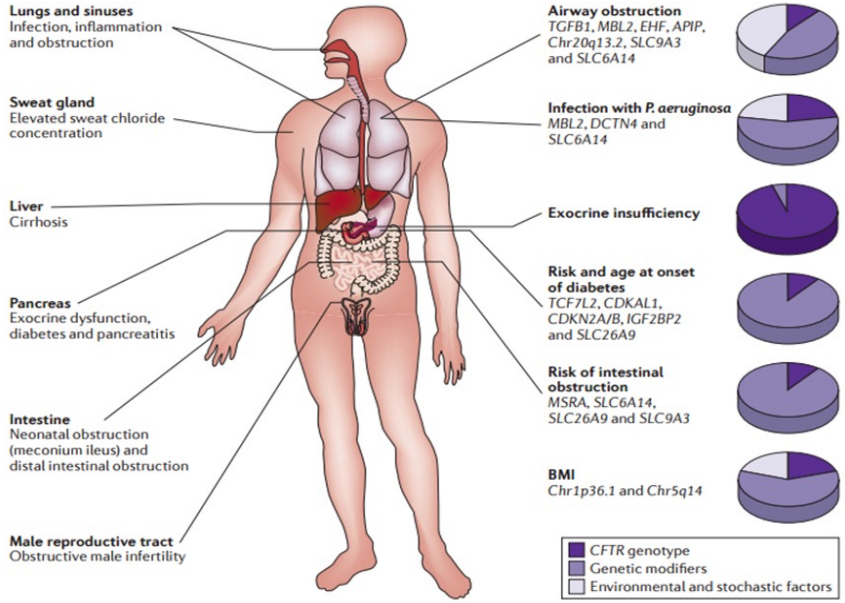
La FC è l' esempio di come la scoperta del meccanismo patogenetico causante la malattia abbia avuto come ricaduta la modifica della sua storia naturale.



Centro FC

3 | FROM DIAGNOSIS VIA SYMPTOMS TO CF NEWBORN SCREENING





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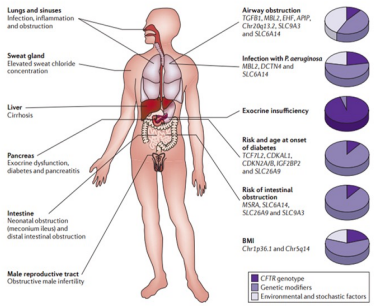
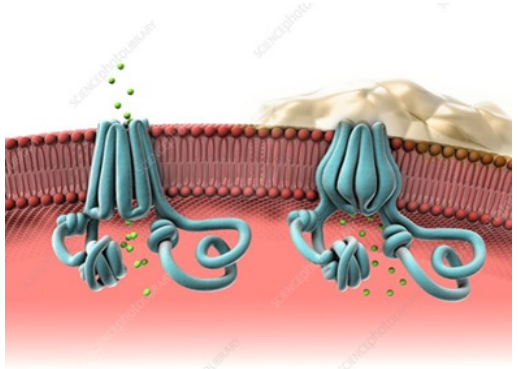
La disfunzione della proteina CFTR causa una malattia multiorgano
<u>Prognosi</u> legata >> alla compromissione respiratoria
Lo sviluppo delle terapie 'di supporto' si concentra in particolare su questo aspetto (mucoattivi e antimicrobici)
- 1993 rhDNase approvata in CF
- 1997 Tobramycin IH
- 2000 HTS
- 2010 AZLI





Ad ogni decade un passo avanti

<u>Il 'passato'</u>

FIGURE 1 Over the six decades, symptomatic treatments have greatly improved the survival of patients with cystic fibrosis. Reproduced with permission of the ERS© 2019. Elborn[57]

La profonda conoscenza dei meccanismi patogenetici ha portato ai trials clinici finalizzati allo sviluppo di farmaci utili al 'recupero' della funzione di CFTR:
Modulatori: -Potenziatori
-Correttori

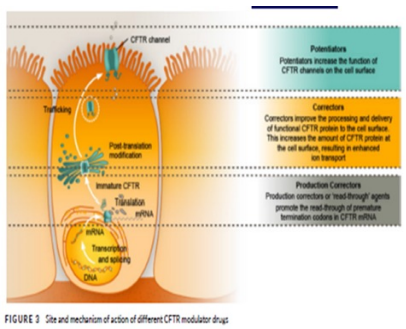


FIGURE 3 Site and mechanism of action of different CFTR modulator drugs

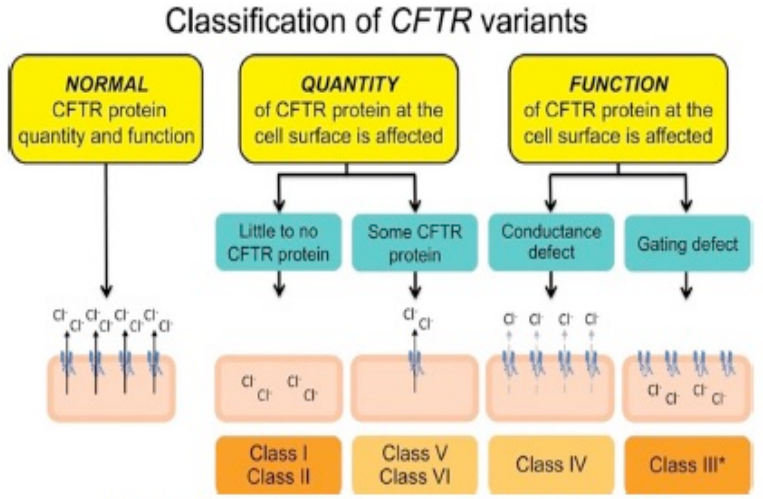
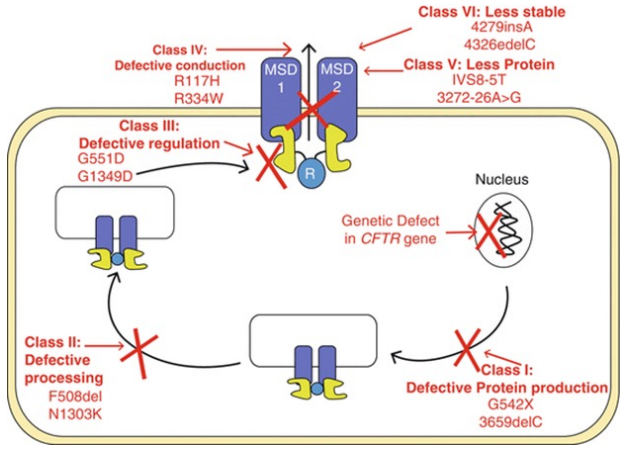
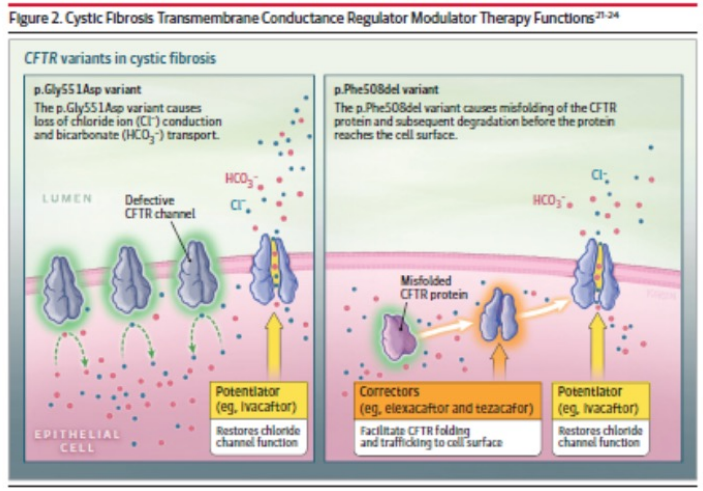


Fig. 1. A functional classification of CFTR gene variants (Adapted from Foil et al. [24]).



-I potenziatori > probabilità di apertura del canale CFTR: IVA
-I correttori correggono la carenza di proteina sulla membrana: LUM-TEZ-ELX



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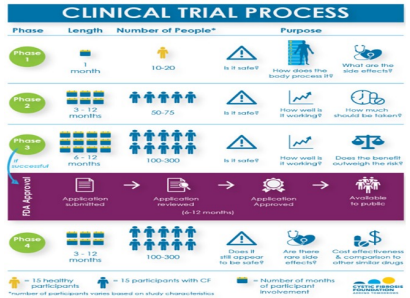
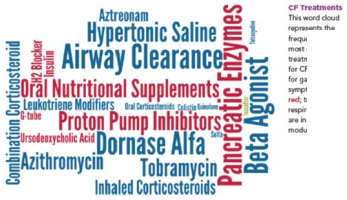
La prima linea di terapie polmonari in persone con FC consiste nelle terapie di 'supporto' ma attualmente il 90% ca può beneficiare anche di una combinazione di modulatori disponibili:

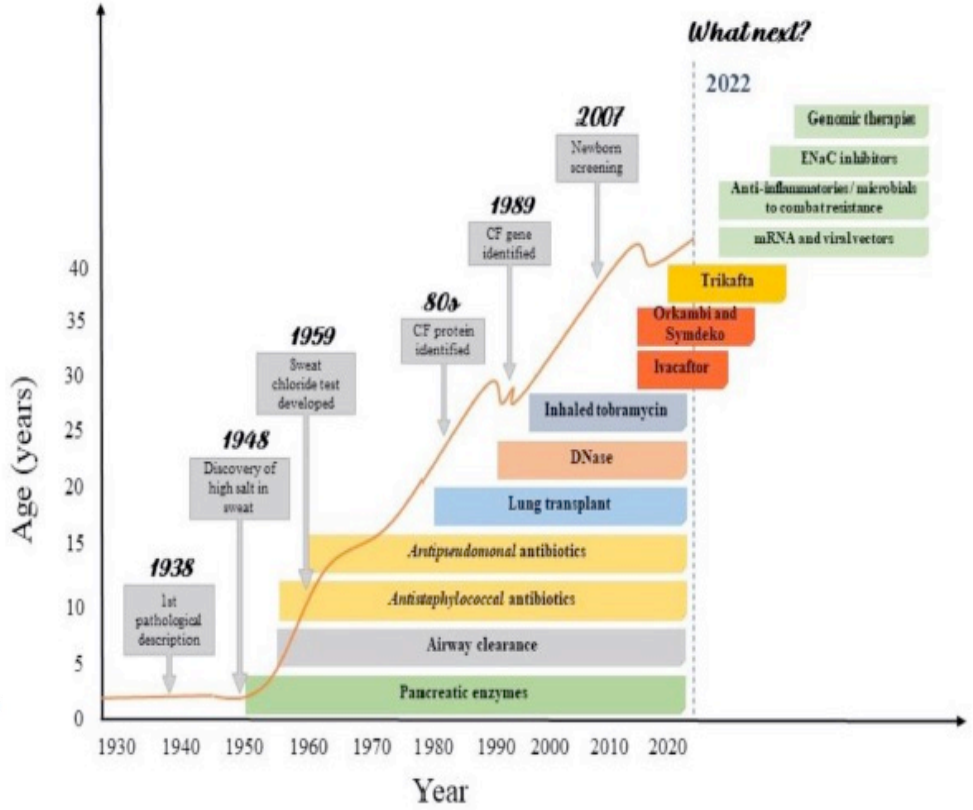
-IVA (Gating -Classe III) (EMA 2012)
-LUM-IVA (f508del/f508del)
-TEZ-IVA (f508del/f508del- f508del/RF
-ELX-TEZ-IVA (f508del/any)



Ad ogni decade una conquista

Il futuro

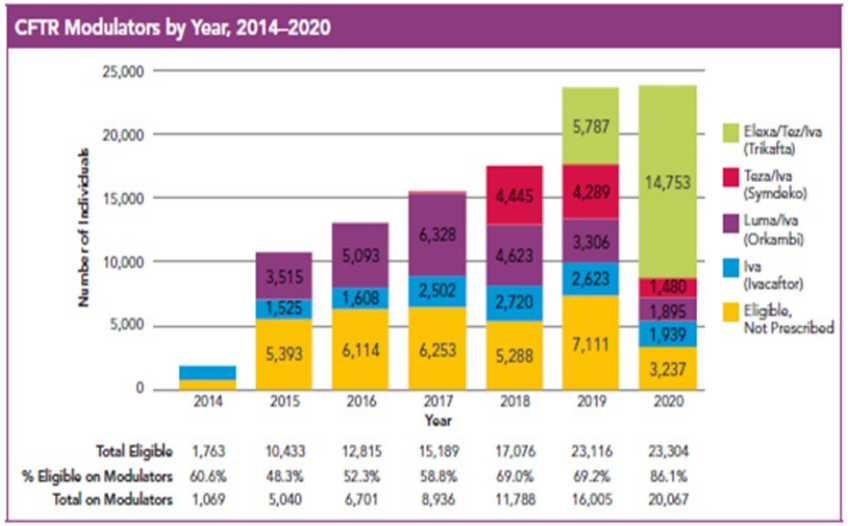


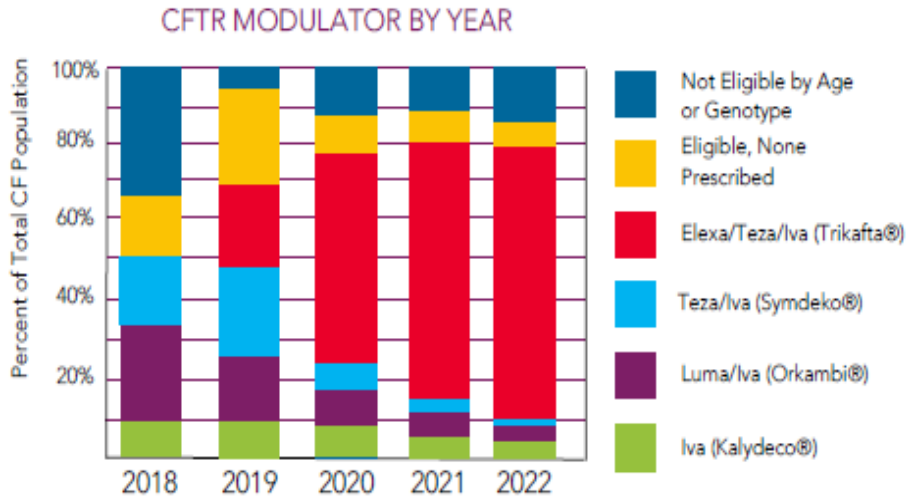


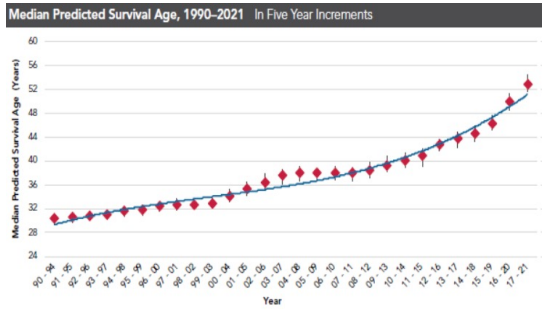
Actions of cystic fibrosis transmembrane conductance regulator (*CFTR*) modulators as correctors and potentiators.[21,24] People with at least 1 copy of the F508del variant or 177 other variants are responsive to elexacaftor-tezacaftor-ivacaftor combination therapy.[23,78] Adapted from Cutting.[24]

p.Gly551Asp indicates glycine at residue 551 replaced by aspartic acid; and p.Phe508del, phenylalanine deleted at position 508.

Accesso alle terapie correttive (HEMT) nella popolazione FC







La possibilità di accesso si amplia per disponibilità di HEMT, genotipo ed età

CYSTIC FIBROSIS FOUNDATION

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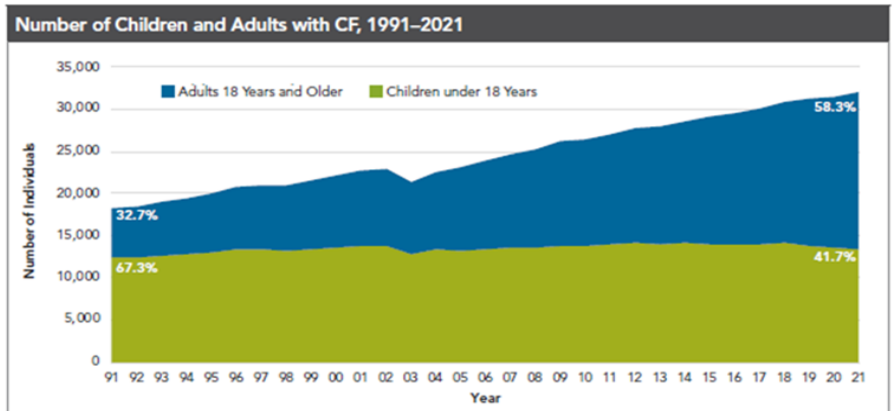
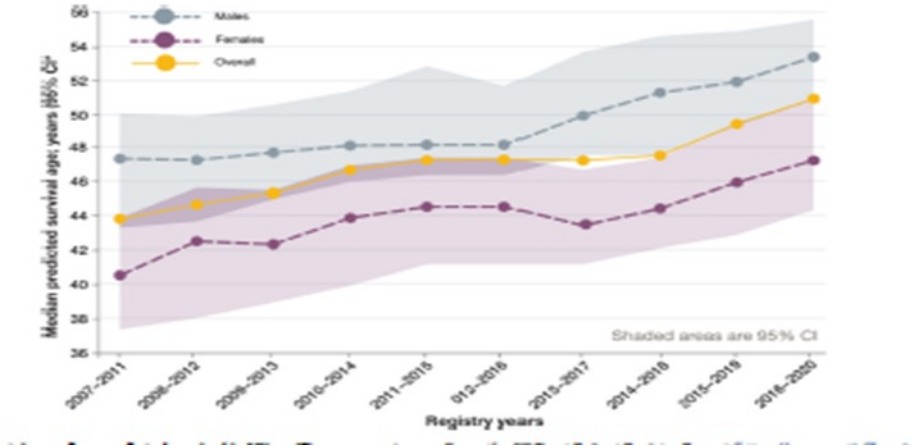
La popolazione FC cambia negli anni in US come in EU: Sempre più adulti

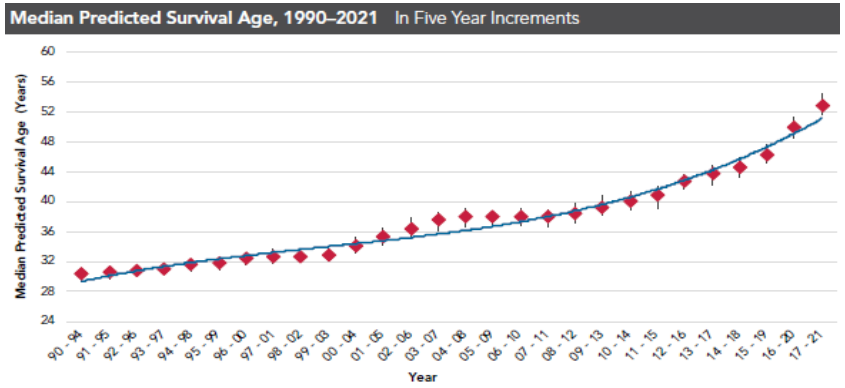




Nel 2021 in US, 32100 pts
58,3% adulti
Età mediana 23,8 aa(range 0-91,7)

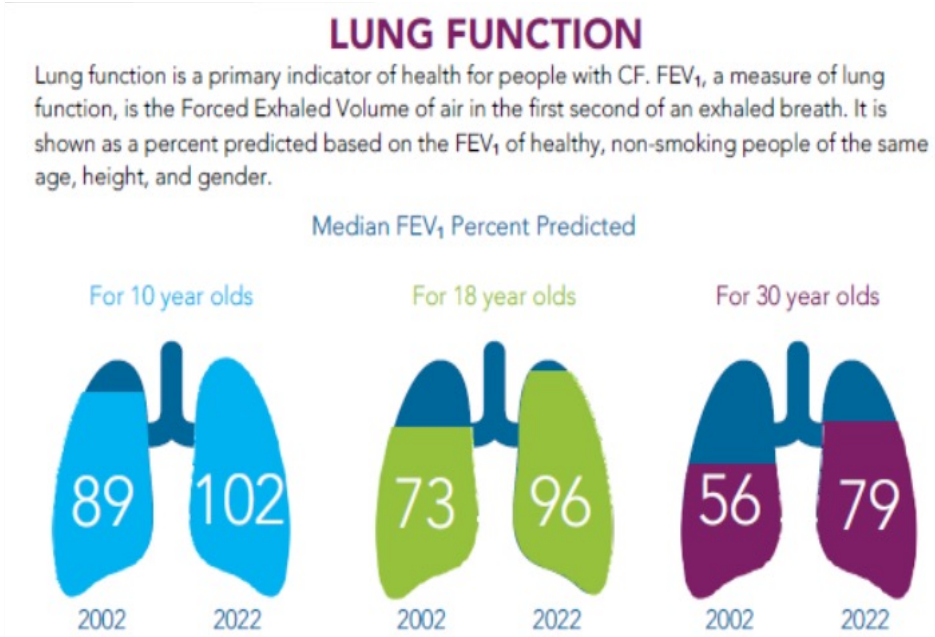
CYSTIC FIBROSIS FOUNDATION

- Most patients with cystic fibrosis (CF) now survive to adulthood, and many countries have instituted CF newborn screening because early diagnosis improves outcome.
- The discovery of the CF transmembrane conductance regulator (CFTR) gene has transformed the lives of patients with CF, by leading to treatment that may prevent major complications if started early in childhood.

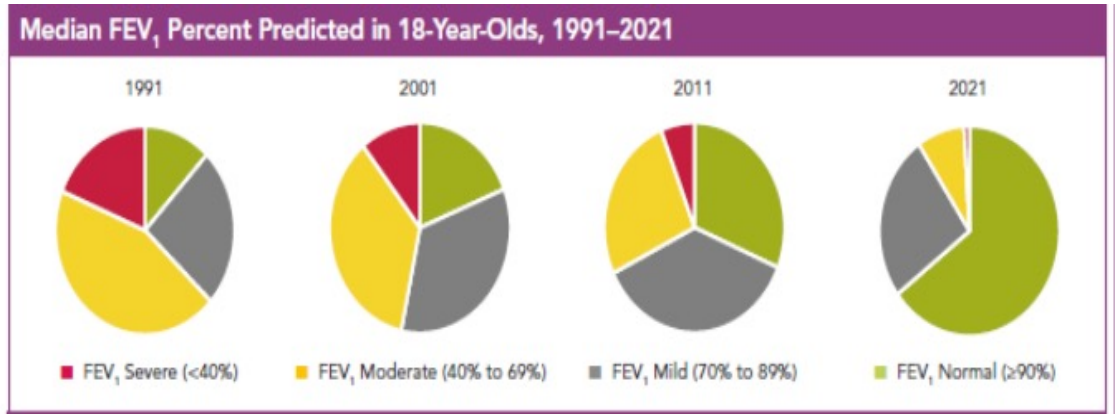


Nel 2020 in Italia,
5801 pts
Età mediana 22,4 aa

Non solo una popolazione con sempre più adulti: FEV1 indicatore principale di efficacia



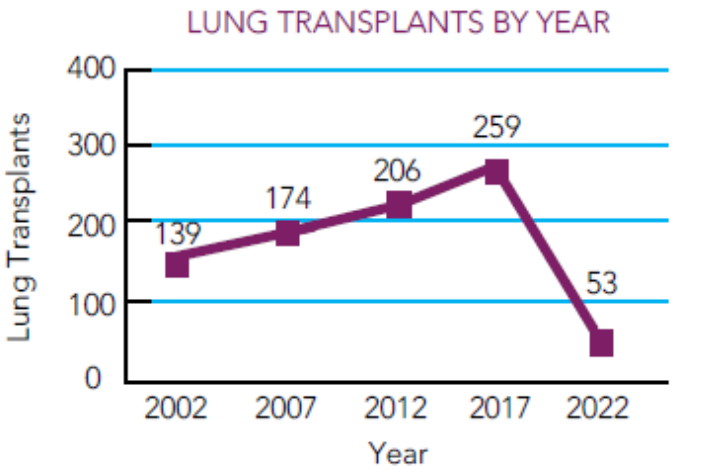
+23% pt

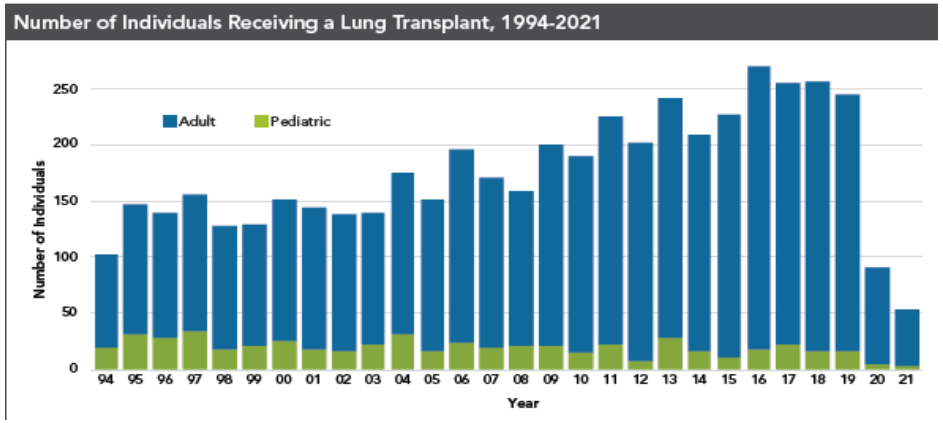


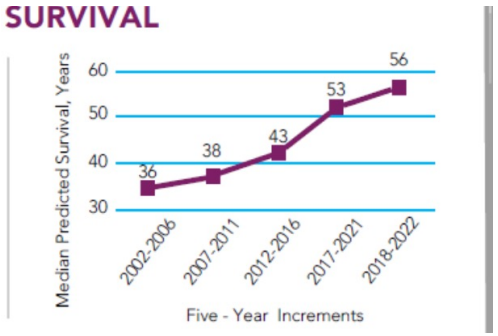
Popolazione FC 18 aa con FEV1 > 90% pred raddoppiata in 10 aa

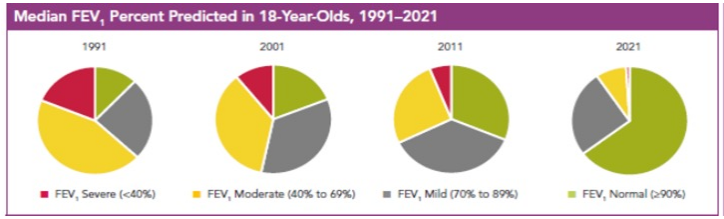
CYSTIC FIBROSIS FOUNDATION

In US Numero di trapianti: 53 tx nel 2022 (14 ritrapianti)
Netto calo dal 2019
Corrispettivo del miglioramento della funzione polmonare





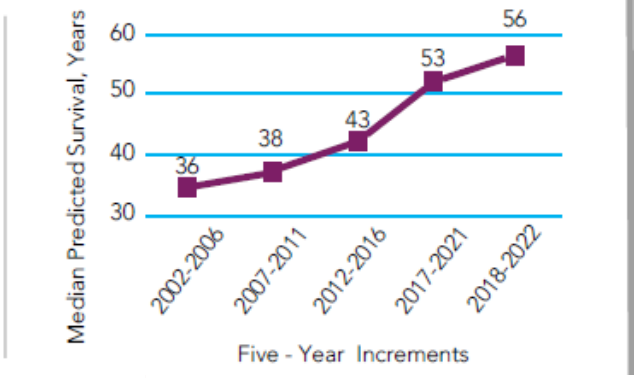




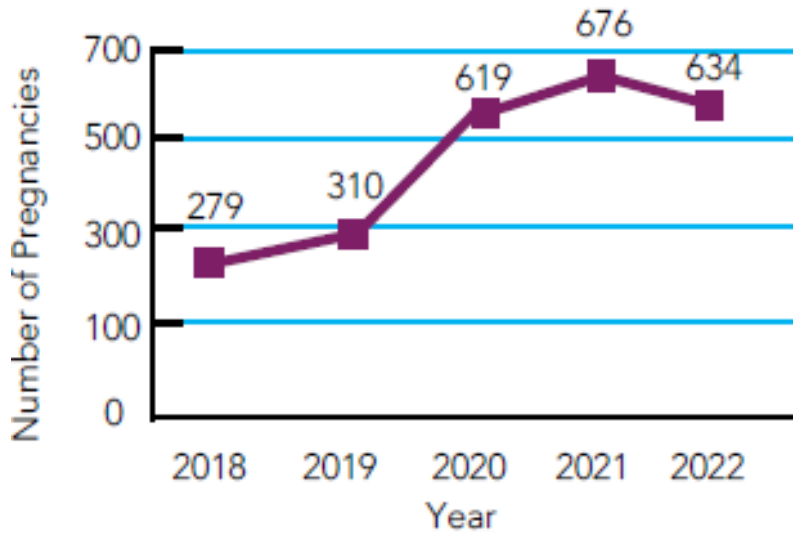
CYSTIC FIBROSIS FOUNDATION

Ricaduta pratica e nella real life della popolazione FC

SURVIVAL



PREGNANCIES



MILESTONES

EMPLOYMENT

57%

of adults with CF have full-time or part-time jobs.

EDUCATION

41%

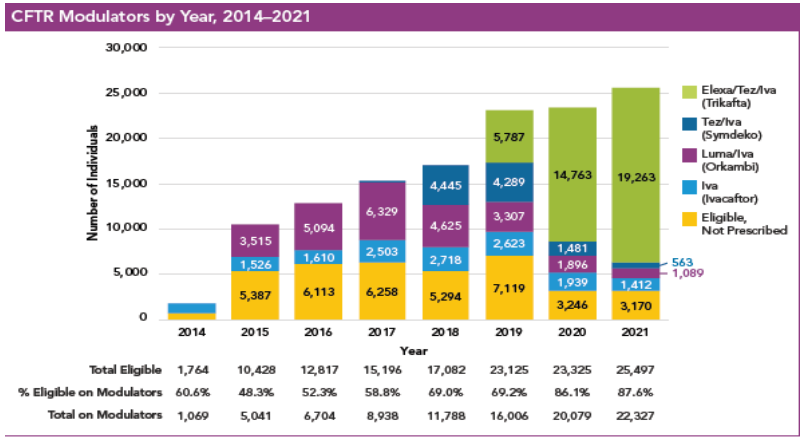
of adults with CF have a college degree.

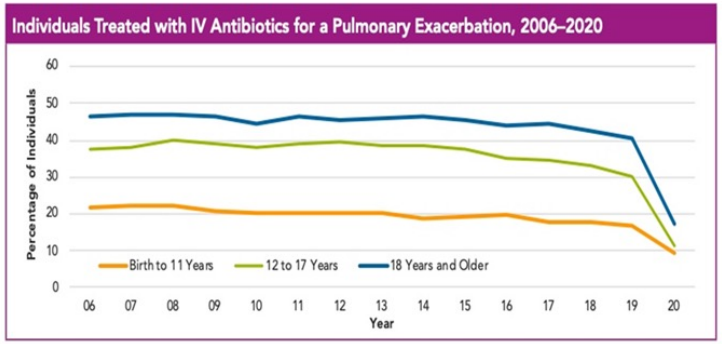
CYSTIC FIBROSIS FOUNDATION

Popolazione FC sempre più dinamica e con progetti di vita: carriera , famiglia, viaggi …..

Accesso precoce a modulatori HEMT

Nel giugno 2021 FDA approva ETI per bambini con FC >6 aa





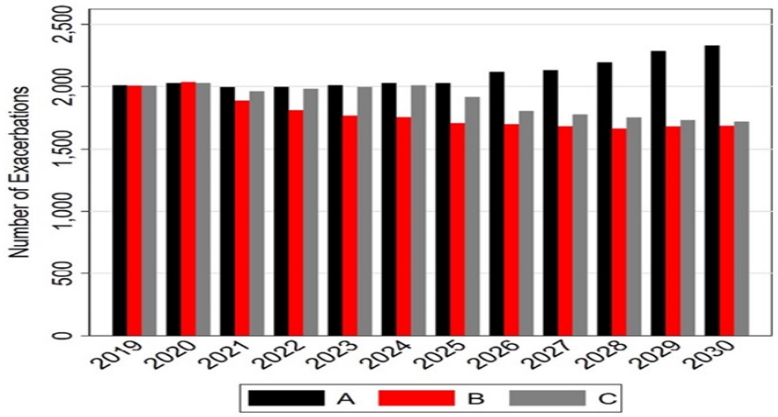
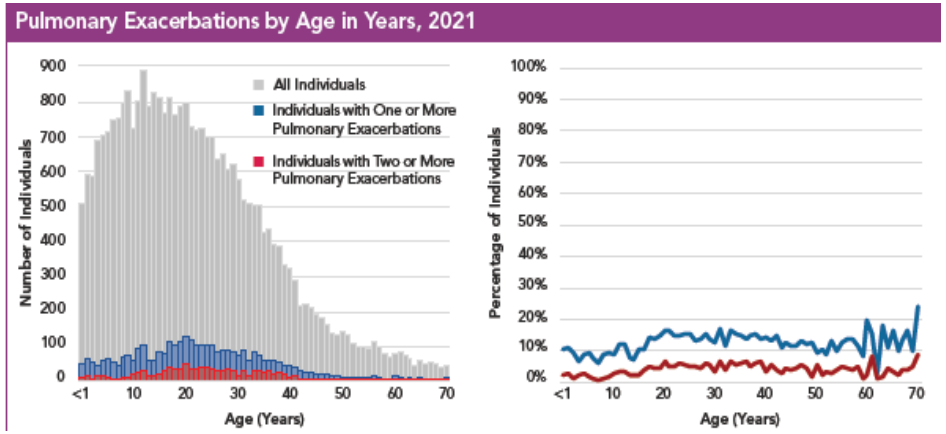


Fig. 3. Number of pulmonary exacerbations per year from a single simulation under the three scenarios: baseline (A), elexacaftor/tezacaftor/ivacaftor introduction in 2021 (B) and delayed introduction of elexacaftor/tezacaftor/ivacaftor in 2025 (C).



Cambiano le prospettive della popolazione FC: ‘un mondo tutto nuovo’ – ‘ respiro senza pensarci’- ‘di notte invece di tossire dormo’- ‘a nascondino adesso vinco anche io qualche volta’

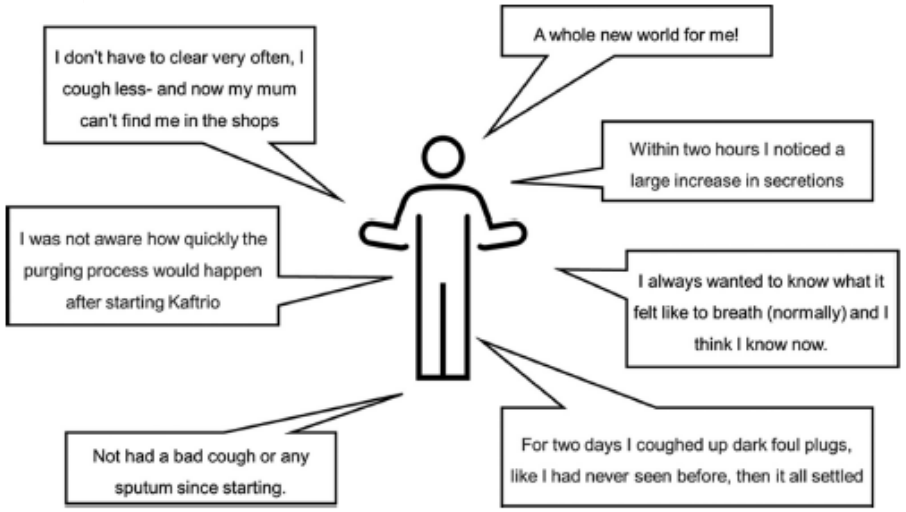


Fig. 2. Comments from pwCF upon starting VST.

K.W. Southern, C. Castellani, E. Lammertyn et al.
Journal of Cystic Fibrosis 22 (2023) 17–30

Follow-up regolari e mantenere alta l'attenzione su alcuni aspetti (oltre a quelli noti di safety)

-Percentuale di soggetti colonizzati ridotta ma.....

-PEXs ridotte numericamente ma……

Role of inhaled antibiotics in the era of highly effective CFTR modulators

Role of antibiotics amid CFTR modulators

CFTR modulator therapy is highly effective and is now part of standards of care for the majority of people with CF [61, 63]. Access to these drugs remains limited in several countries owing to their high cost. Furthermore, pulmonary exacerbations still occur in patients receiving CFTR modulator therapy, and there is a wide range of response observed in real-world evidence data and possibly a change in the symptom profile associated with exacerbations. Studies suggest that early initiation of modulator therapy (*i.e.* initiated at a younger age) might reduce the risk of lung infections [39]. However, there is no evidence so far that people with CF can stop or alter their current standard of care (antibiotics, physiotherapy, mucolytic agents, macrolides, *etc.*) while on CFTR modulators, especially since chronic infections are common in CF and may not disappear with current CFTR modulators.

Points for clinical practice

- Inhaled antibiotics continue to be prescribed for cystic fibrosis patients who receive cystic fibrosis transmembrane conductance regulator (CFTR) modulators to treat chronic respiratory infections.
- Patients are recommended to continue their existing treatment regimen while receiving CFTR modulators.
- Clinicians are encouraged to balance the simplification of treatment with the risk of clinical deterioration due to microbial infections when making treatment decisions.

J. Stuart Elborn[1], Francesco Blasi[2,3], Pierre-Régis Burgel[4,5] and Daniel Peckham[6]

La microbiologia della popolazione FC ha ancora un ruolo cruciale

Segregazione, sorveglianza e terapia mirata

Bacteria	2018 Percent With Infection	2022 Percent With Infection
Pseudomonas aeruginosa	44%	26%
Stenotrophomonas maltophilia	12%	5%
Methicilin-resistant Staphylococcus aureus	25%	16%
Achromobacter xylosoxidans	6%	2%
Burkholderia cepacia complex	3%	1%
Nontuberculous mycobacteria	14%	10%

MICROBIOLOGY

People with CF are vulnerable to airway infections. To help prevent the spread of germs, infection prevention and control guidelines were created for clinics hospitals, homes, schools, and workplaces. Compared to 2018, the collection of respiratory cultures decreased in 2022, likely due to a continued decrease of in-person clinic attendance and inability to produce sputum for some. This may influence detection rates.

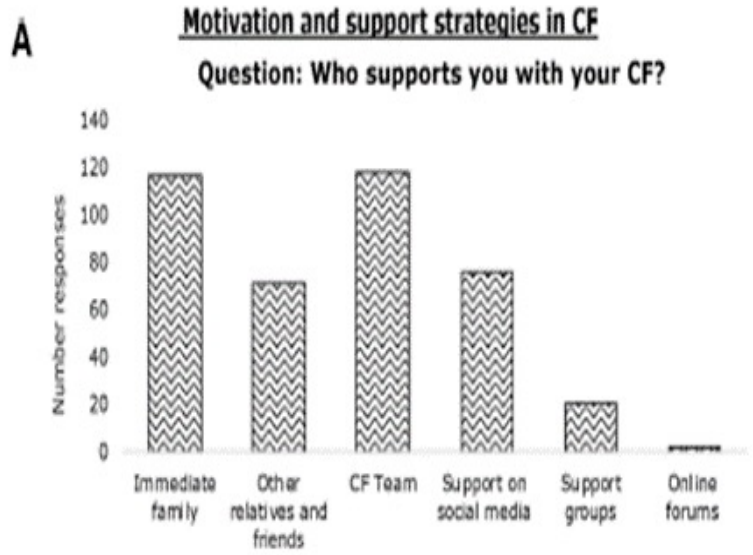
CYSTIC FIBROSIS FOUNDATION

ETI e Aderenza alle terapie

Il pesante carico terapeutico in FC contribuisce a percentuali di aderenza <50% per le terapie standard of care; i dati peggiorano ulteriormente in terapia con ETI
Dati della letteratura non sufficienti per dare linee guida

Importante motivare ed incoraggiare le persone con FC promuovendo con loro alleanza e adottando strategie di equilibrio sulle scelte possibili

What effective ways of motivation, support and technologies help people with cystic fibrosis improve and sustain



Calthorpe RJ, *et al. BMJ Open Resp Res* 2020;**7**:e000601. doi:10.1136/bmjresp-2020-000601

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Le terapie di base nelle persone FC in modulatori CFTR: calo di aderenza

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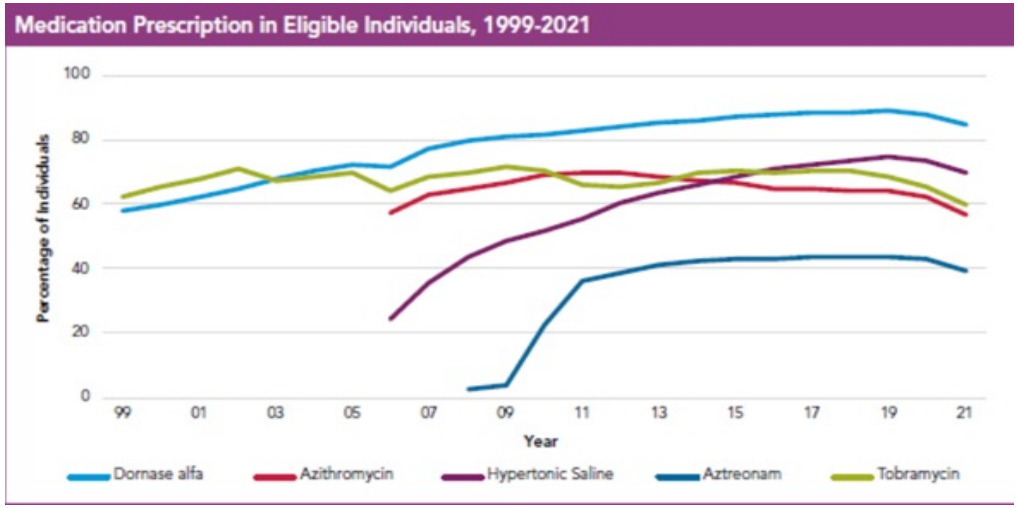
Maintenance of lung health with daily airway clearance and the addition of mucolytics, such as hypertonic saline and dornase alfa, are standard of care and have been shown to decrease exacerbations and improve lung function.[5,6] Unfortunately, the burden of treatment is high in patients with cystic fibrosis and adherence to daily mucolytics is typically low. One study based on medication possession ratios has shown that adherence to mucolytics was 45% before patients started ETI, decreasing to 21% for dornase alfa and 14% for hypertonic saline.[7]



Necessaria una modulazione condivisa con il team di cura

SIMPLIFYing cystic fibrosis treatment in a post-modulator era

Discontinuation versus continuation of hypertonic saline or dornase alfa in modulator treated people with cystic fibrosis (SIMPLIFY): results from two parallel, multicentre, open-label, randomised, controlled, non-inferiority trials

www.thelancet.com/respiratory Vol 11 April 2023

Role of inhaled antibiotics in the era of highly effective CFTR modulators

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FC in ETI e rischio di iperlipidemia e ipertensione

-Aumento età media e CFRD
-Alimentazione ricca di grassi
-Integrazione salina
-Aumento BMI (>23 F >24 M)
-Aumentato rischio di patologie cerebrovascolari e cardiovascolari

Cosa fare

-Supporto nutrizionale regolare
-Monitoraggio della PA
-Monitoraggio profilo lipidico
-Monitoraggio CFRD

ETI ha probabilmente accelerato un trend

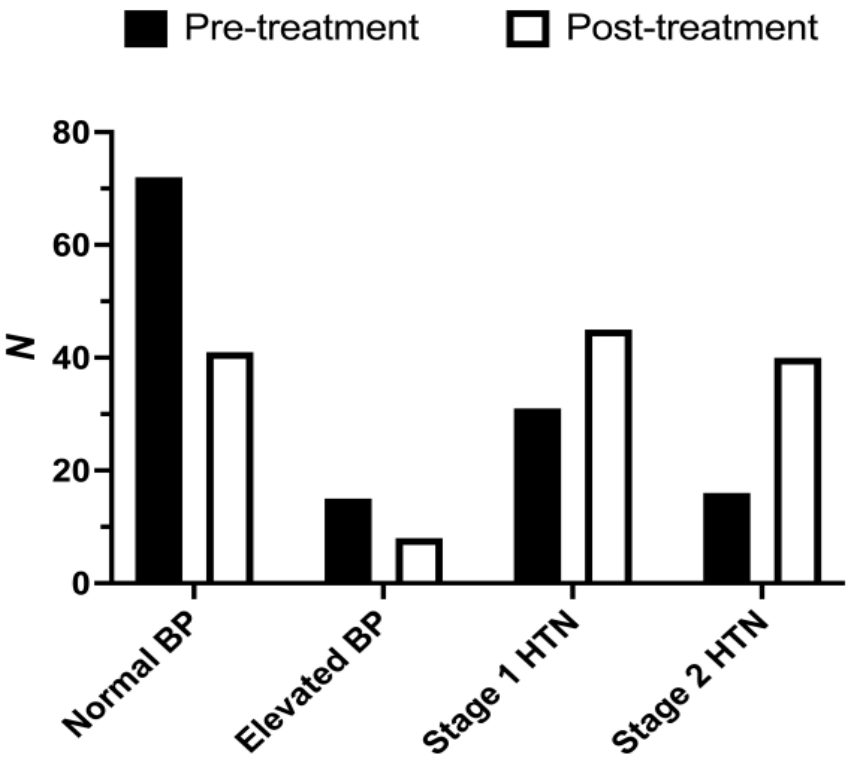

Figure 2.
Effect of elexacaftor-tezacaftor-ivacaftor on rates of normal blood pressure (SBP < 120 mmHg and DBP < 80 mmHg), elevated blood pressure (SBP 120–129 mmHg and DBP < 80 mmHg), stage 1 hypertension (HTN) (SBP 130–139 mmHg or DBP 80–89 mmHg), and stage 2 hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg). $P < 0.0001$ for difference in blood pressure category distribution.

J Cyst Fibros. 2022 March ; 21(2): 265–271. doi:10.1016/j.jcf.2021.11.012.

EFFECT OF ELEXACAFTOR-TEZACAFTOR-IVACAFTOR ON BODY WEIGHT AND METABOLIC PARAMETERS IN ADULTS WITH CYSTIC FIBROSIS

Max C. Petersen[a], Lauren Begnel[b], Michael Wallendorf[c], Marina Litvin[a,*]

ETI e CFRD (Diabete FC relato)

Dati ancora non sufficienti ma apparente miglioramento in termini di ridotta necessità di Unità di Insulina (U/kg/die), >BMI e miglior controllo omeostasi glucidica (<HbA1c)

Utili studi con CGM (monitoraggio più realistico dell'andamento glucidico)

Combined CFTR modulator therapies are linked with anabolic benefits and insulin-sparing in cystic fibrosis-related diabetes

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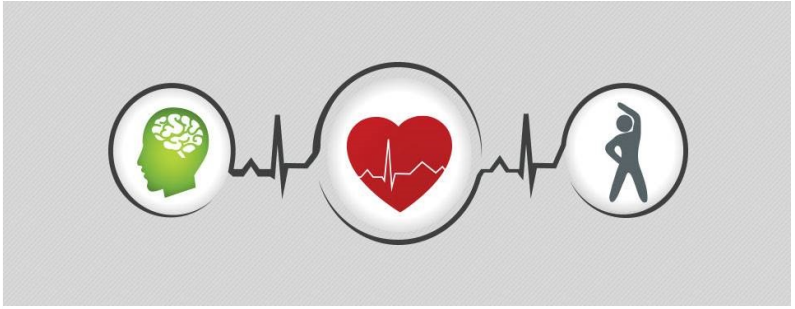
Table 1
Clinical and biological changes after CFTR modulator therapy in CFRD patients.

	Baseline, modulator-naïve population (n = 17)	On-treatment (n = 17)*	p
Weight (kg)	60 (18.05)	64 (20.25)	*0.001*
BMI (kg/m^2)	20.9 (1.90)	22.1 (3.70)	*0.014*
Insulin requirements (U/kg/day)	0.85±0.3	0.71±0.3	*0.001*
Total daily insulin dose (U/day)	50±16	44±20	*0.017*
FEV_1 (% predicted value)	67.9±19.5	79.3±20.3	*<0.001*
HbA1c (%)	7.7±1.6	7.3±1.1	*0.072*

Le persone con FC sono state sempre 'incoraggiate' a seguire una dieta ipercalorica e iperlipidica
Con ETI e possibili complicanze metaboliche è necessario rivedere e monitorare l'assetto calorico/nutrizionale individualizzandolo

Essenziale promuovere attività fisica

Sport in FC comprensibilmente pre ETI non facile se tosse, PEXs e <FEV1 ma ora….iscriviamoci in palestra!!



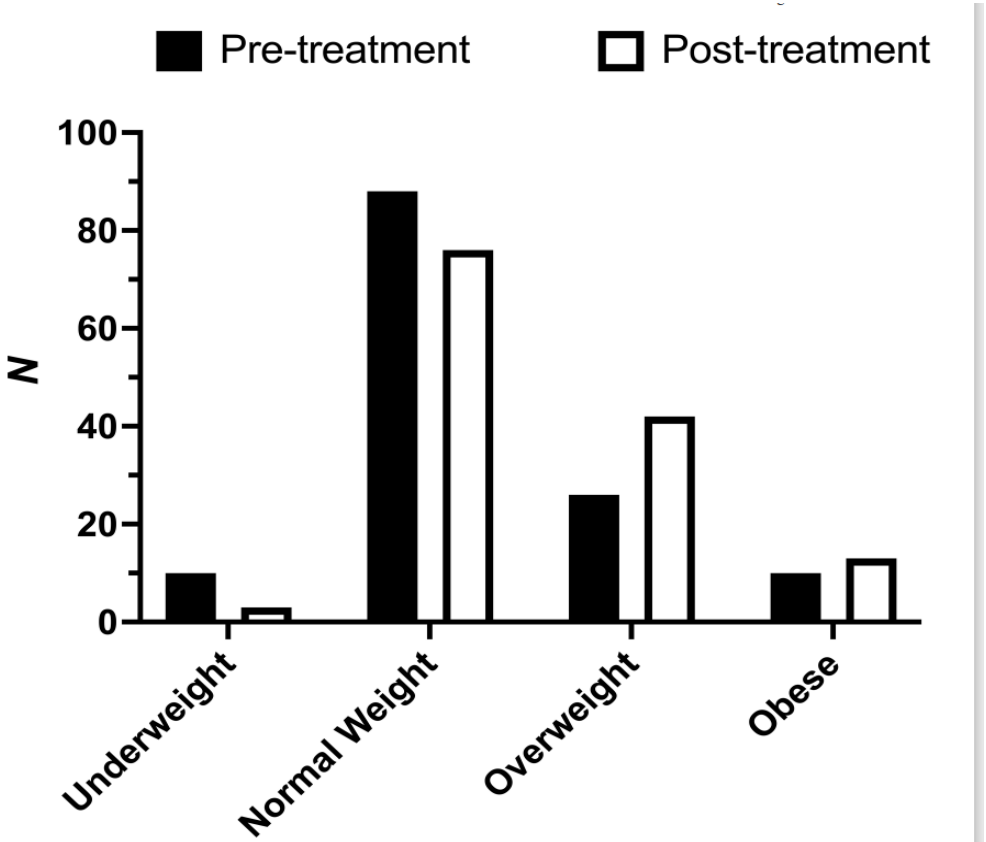


Figure 1.
Effect of elexacaftor-tezacaftor-ivacaftor on rates of underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25–29.9), and obesity (BMI ≥ 30). *N* = 134. *P* < 0.001 for difference in weight category distribution.

Cure efficaci non ancora per tutti: ma la ricerca non si ferma

Nuovi modulatori o nuove indicazioni
- **VX121-TEZ-IVA**
- **VX 561 (D-IVA)**

Terapie genetiche
- **mRNA, gene transfer, gene editing**
- **ELX-02 (glicoside non atb)**

Advances in the Cystic Fibrosis Drug Development Pipeline

CFTR Modulators	mRNA-Based Therapies	Gene-Based Therapies
Ivacaftor [1]	Aminoglycoside read-through nonsense mutation (ELX-02) [2]	CFTR Gene Transfer Vectors: • Recombinant adeno-associated viral vectors (rAAV) (4D-710) [2] • Liposomal vector (pGM169/GL67A) [2] • Lentiviral vector [3]
Lumacaftor/Ivacaftor [1]	Depletion of termination factor, eRF1 (SRI-37240) [3]	
Tezacaftor/Ivacaftor [1]	Inhaled CFTR mRNA (MRT5005 [2] VX-522 [2] ARCT-032 [2] ReCode [3])	
Elexacaftor/Tezacaftor/Ivacaftor [1]	Short-interfering RNAs (siRNAs) [3]	Zinc-finger nucleases (ZFN) [3]
Deuticaftor (VX561) [2]		Transcription activator-like effector nucleases (TALENS) [3]
Varzacaftor (VX-121)/tezacaftor/ Deuticaftor [2]		Clustered Regularly Interspersed Palindromic Repeats (CRISPR)/CRISPR-associated nuclease 9 (CAS9) [3]
Navocaftor (ABBV-3067), galicaftor (ABBV-2222) and ABBV-576 [2] *		

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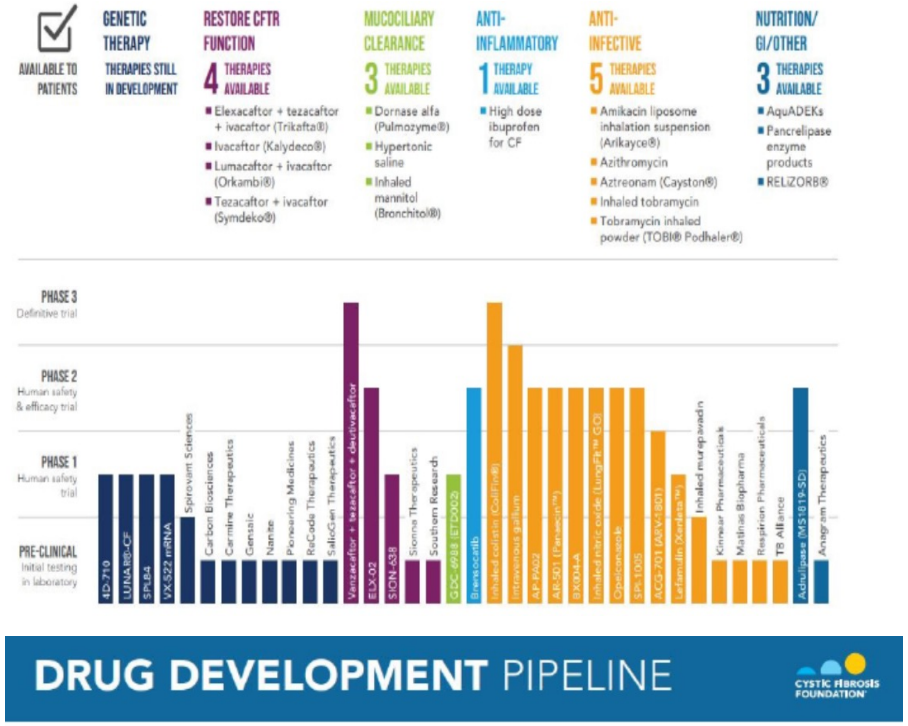

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Sviluppo di terapie target su pz non eleggibili per i modulatori disponibili: Priorità

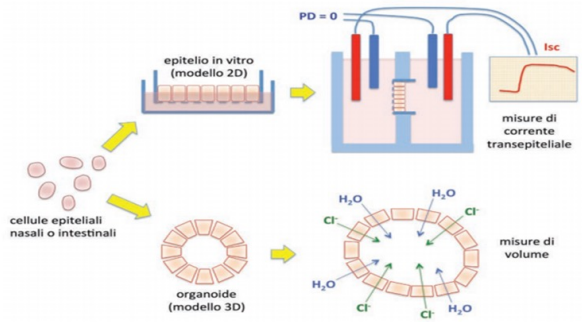
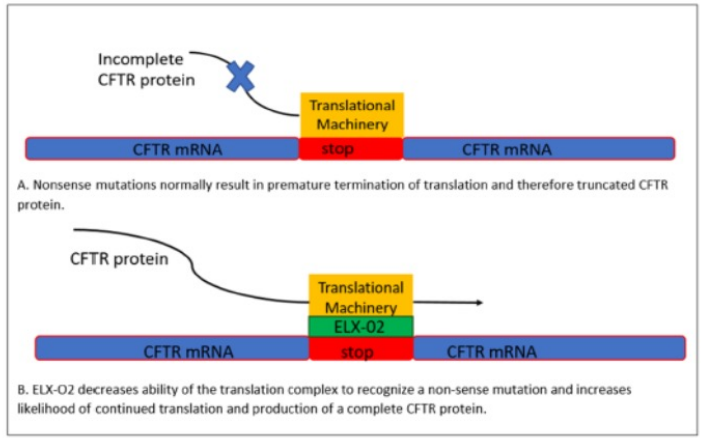


Figura 3. Modelli cellulari per la medicina personalizzata.
In molti casi, soprattutto per pazienti con mutazioni rare con sensibilità farmacologica sconosciuta, è importante prelevare le cellule del paziente stesso per effettuare valutazioni in vitro. Le cellule nasali, prelevate mediante "brushing", o intestinali, prelevate mediante biopsia rettale, possono essere coltivate su membrana porosa oppure seminate all'interno di una matrice gelatinosa. Nella prima condizione si formano degli strati cellulari che riproducono la struttura dell'epitelio in vivo. Su questi modelli bidimensionali (2D) è possibile valutare la funzione di CFTR e la risposta a farmaci misurando la corrente ionica transepiteliale. Nella seconda condizione si formano gli organoidi, strutture cave (sferiche) ripiene di un liquido conseguente alla secrezione operata da CFTR. Il rigonfiamento dell'organoide permette di valutare l'effetto di modulatori farmacologici di CFTR.

Terapie personalizzate

Nel 2019 CFF: Path to a cure



Riparare la proteina

The era of CFTR modulators: improvements made and remaining challenges

The collaborative working model adopted by the CF community to date, which has underpinned substantial progress, needs to further continue to address health inequities and to ensure that the pipeline of new treatments remains active and successful. The NIHR Respiratory Translational Research Collaboration established the CF National Research Strategy Group specifically to identify areas of unmet need and provide potential solutions to challenges. The group of people with genetic variants unsuitable for CFTR modulator drugs remains a high priority and trials of genetic therapies will be a major focus of the next few years. The recent JLA Priority setting partnership (PSP) illustrated this, identifying treatment for this subgroup as the top priority research area. Knowledge arising from the PSP will be used to support the design and funding of both national and international research efforts to ensure that the progress made to date is further built upon, until (to quote the CF Trust) the hope for 'a life unlimited' by CF becomes a reality.

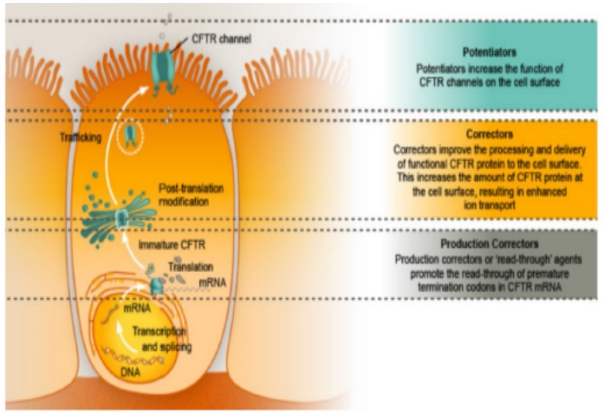


FIGURE 3 Site and mechanism of action of different CFTR modulator drugs

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Nuovi studi sono necessari per identificare terapie efficaci per tutte le persone con FC senza accesso a HEMT (15% ca)
-Mutazioni di stop
-Delezioni

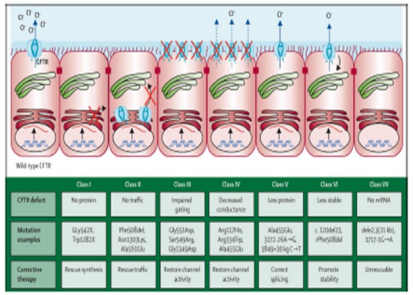

FIGURE 2 Classes of CFTR mutations and their respective therapeutic strategies. CFTR mutations are grouped into seven functional classes, with the expectation that the same type of modulator will be applicable to all the defects in one class. Class VII mutations are not expected to be rescuable by a modulator. A therapeutic strategy for Class VII mutations could be stimulation of alternative chloride channels, gene therapy, gene editing or the addition of messenger ribonucleic acid. rPhe508del = rescued Phe508del

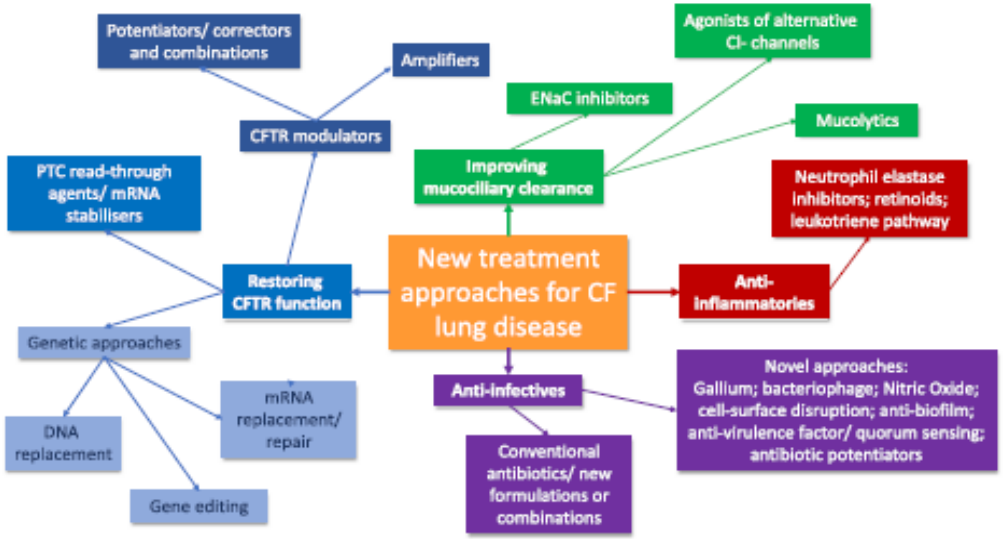

Fig. 2 | A large number of new approaches to CF therapy are progressing through from preclinical to clinical trial stages. Further detail can be found in the following review articles: CFTR modulator therapies[128], genetic therapies[129], mRNA-directed approaches and read-through agents[130], mucoactive and airway hydrating drugs[110,112], anti-infectives[110] and anti-inflammatories[114].

Future studies should identify effective therapies for all people with cystic fibrosis, regardless of the genetic variant. For example, therapies are needed for people with genetic variants that are not modulator responsive such as premature termination codons, large deletions or frameshifts that produce little or no stable protein.[113] Although multiple gene replacement programs, both virally and non-virally based, have been attempted,[154] none have demonstrated efficacy. The availability of gene editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) CRISPR-associated protein 9 may lead to functional *CFTR* repair in intestinal or pulmonary epithelia.[155] All genetic based therapies face the challenge of developing efficient vectors that can deliver stable product to the target stem cells in the airway or intestinal tract.[113]

Future therapies for cystic fibrosis

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