

Cystic fibrosis: new challenges and perspectives beyond elexacaftor/tezacaftor/ivacaftor

Vito Terlizzi^{ID} and Miquéias Lopes-Pacheco

Ther Adv Respir Dis

2025, Vol. 19: 1–20

DOI: 10.1177/
17534666251323194

© The Author(s), 2025.

Article reuse guidelines:
sagepub.com/journals-
permissions

Abstract: Over the past decade, major clinical advances have been made in the healthcare and therapeutic development for cystic fibrosis (CF), a lethal genetic disease caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR modulators represent innovative treatments that directly target the primary defects in the mutated CFTR protein and have demonstrated significant clinical benefits for many people with CF (pwCF) who are eligible for these treatments. In particular, the triple combination therapy composed of elexacaftor, tezacaftor, and ivacaftor (ETI) has changed the CF therapeutic landscape by significantly improving lung function, quality of life, and predicted survival rates. Here, we provided a comprehensive summary of the impact of ETI on clinical outcomes and the need for further research on long-term efficacy, side effects, pregnancy, possible drug–drug interactions, and extra-pulmonary manifestations. Moreover, a significant number of pwCF are unresponsive to these drugs or cannot afford their high costs. We, therefore, discussed health inequity issues and alternative therapeutic strategies under development aiming to obtain effective therapies for all pwCF.

Keywords: CFTR modulator, efficacy, health inequity, outcomes, safety, therapy development

Received: 12 September 2024; revised manuscript accepted: 7 February 2025.

Cystic fibrosis: Clinical features, diagnosis, and treatment

Cystic fibrosis (CF) is a multisystem disease caused by mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) protein.^{1,2} It affects more than 100,000 individuals worldwide, with substantial regional variability. It is also considered a lethal genetic disease with high prevalence in people of European descent, although CF also occurs in other populations.^{3–5} CFTR variants that cause deficient or dysfunctional CFTR protein disrupt chloride/bicarbonate secretion, sodium reabsorption, and water transport, leading to epithelial surface lining dehydration and mucus hyperconcentration. Typically, CF is characterized by elevated sweat chloride concentration (SCC), obstructive lung disease, chronic bacterial infections of lower airways and sinuses, bronchiectasis,

and male infertility due to obstructive azoospermia.^{1,2}

More than 2100 CFTR variants have been recorded (<http://www.genet.sickkids.on.ca/app>, accessed on January 2, 2025), although to date 1167 are annotated on the CFTR2 website (<https://cftr2.org/>, accessed on January 2, 2025) and differentiated in CF causing (n. 1085), variants of varying clinical consequence (VVCC) (n. 55), and non-CF-causing (n. 27).

Furthermore, according to their impact on the production, trafficking, functioning, or stability of the CFTR mRNA and/or protein, they are typically categorized into six classes: variants of classes I–III usually result in little to no CFTR activity, leading to potentially severe clinical outcomes and more often pancreatic insufficiency,

Correspondence to:

Vito Terlizzi
Department of Pediatric
Medicine, Cystic Fibrosis
Regional Reference
Center, Meyer Children's
Hospital IRCCS, Viale
Gaetano Pieraccini 24,
Florence, Italy
vito.terlizzi@meyer.it

Miquéias Lopes-Pacheco
Department of Pediatrics,
Cystic Fibrosis and Airway
Disease Research Center,
Emory University School of
Medicine, Atlanta, GA, USA

while variants from classes IV–VI allow significant residual CFTR function leading to milder phenotypes and more often pancreatic sufficiency.^{6,7} However, a mixture of deficiencies in different *CFTR* alleles has been reported reflecting the composite defects in mutant CFTR biology.^{7–11}

The diagnosis of CF is based on positive newborn screening (NBS), clinical features consistent with CF, or a positive family history, in the presence of a high SCC and/or two *CFTR*-causing variants in trans (i.e., on two different alleles).¹² The age at diagnosis is strongly influenced by the presence or absence of a national or regional CF NBS program. However, over the last decade, the proportion of children diagnosed with CF through NBS has increased to almost 90% throughout Europe,³ while in the U.S., the median age at first CF clinic visit has decreased to 21 days in 2023.¹³ This is a real success given that identifying CF earlier is crucial to prevent the evolution of disease and potential complications. However, a late diagnosis of CF is possible in the presence of recurrent respiratory tract infections and diffuse bronchiectasis, infertility in males, severe sinusitis, or recurrent pancreatitis. These people with CF (pwCF) are more likely to harbor residual function variants or VVCC, in trans with a CF-causing variant, associated with a milder phenotype.¹⁴ Furthermore, a delayed diagnosis with worse clinical outcomes is reported in people of color or living in underprivileged regions. They are more likely to carry (ultra)rare *CFTR* variants, omitted from CF NBS panels, leading to disparities in care.¹⁵ Until one decade ago, CF management primarily centered on symptom relief and slowing disease progression. The major efforts were on preventing malnutrition and bacterial infections in infants, emphasizing the importance of initiating care as soon as the diagnosis was made.¹⁶ Several chest physiotherapy techniques are known to promote the expectoration of mucus, such as autogenic drainage or using devices that create positive pressure (positive expiratory pressure therapy (PEEP) or high-pressure PEEP therapy) or a vibration (oscillating devices). They are recommended in all pwCF from the first months of life, with positive short-term effects, increasing lung function and sputum expectoration.¹⁶

To date, while the survival and quality of life of pwCF have significantly improved, lung disease remains the most common cause of morbidity

and death, especially in pwCF ineligible for CFTR modulators—a novel class of drugs targeting the fundamental defect(s) caused by *CFTR* pathogenic variants.^{1,5} Nevertheless, mucoactive drugs remain crucial for reducing secretion build-up, preventing infections, and slowing lung damage.¹⁷ Inhaled antibiotic therapy is still the key for eradicating pathogen bacteria, such as *Pseudomonas aeruginosa* (*Pa*), or maintaining long-term control in case of chronic infections.¹⁸

In this paper, a narrative review of the literature was performed, using the MEDLINE/PubMed database, including English-language studies, published from 2019 (i.e., when the first paper on elxacaftor/tezacaftor/ivacaftor (ETI) efficacy was published) to 2024. We aimed to explore the changes in CF with the advent of ETI, the new challenges for clinicians, and future perspectives.

CFTR modulators: Potentiators and correctors approved for clinical use

The introduction of CFTR modulator therapies has revolutionized the course and treatment of CF, impacting the health and quality of life of pwCF.¹⁹ These drugs target defects in the structure and function of the CFTR protein.⁵ However, CFTR modulators are only effective for specific variants since they cause different defects in the CFTR protein. On this basis, they have been classified into five main groups: potentiators, correctors, amplifiers, stabilizers, and read-through agents.⁵

Until late 2024, there were three correctors and one potentiator available in the market. The potentiator Ivacaftor (IVA; Kalydeco®; VX-770) is effective on variants causing defective gating/conductance by facilitating the opening of the CFTR channel and increasing CFTR-mediated chloride and bicarbonate secretion.²⁰ In 2022, 1146 (2.1%) out of 54,546 Europeans with CF were eligible for IVA.³ In the first study on the efficacy of IVA in pwCF carrying at least one G551D variant, it was associated with impressive improvements by 2 weeks and maintained through week 48, with a reduction of SCC of 48.1 mmol/L and positive effects on percent predicted forced expiratory volume (ppFEV1), respiratory exacerbations, weight, and respiratory symptoms. All enrolled adults with CF had an SCC lower than the cutoff point for the diagnosis of CF, which is 60 mmol/L.²¹ These results were later confirmed

in increasingly younger individuals with other gating variants²² or with variants with residual function,^{23,24} so that the indication is currently expanded to include pwCF who are as young as 1 month old and have at least one *CFTR* variant responsive to IVA based on clinical data, in vitro assay data or both.^{25,26} Furthermore, in infants aged 4 to <12 months with CF and pancreatic insufficiency, a partial recovery of pancreatic function has been reported.²⁷

IVA is on the market also in combination with *CFTR* correctors. These molecules enhance the folding of mutant *CFTR* protein, rescuing its trafficking to the cell surface.^{5,28} Lumacaftor (LUM), Tezacaftor (TEZ), and Elexacaftor (ELX) are currently approved in different combinations. The combination LUM-IVA (Orkambi[®]) has proven moderately effective in F508del-homozygotes individual with an improvement in ppFEV1 ranging from 2.6 to 4.0 percentage points more in the treated group, although some adverse effects have been reported.²⁹ Furthermore, it led to a weight gain and a significant reduction in the frequency of pulmonary exacerbations (PEx), CF-related hospitalizations, and extra-pulmonary complications such as CF-related diabetes, CF bone disease, and *CFTR* function, measured as a decline in SCC of 17.8–21.4 mmol/L in real-world settings.^{30,31} Although these improvements are less relevant than the benefits of IVA in pwCF with gating variants, LUM-IVA was the first hope for F508del-homozygous individuals, who represented 44% of Americans with CF in 2022.³

Co-treatment TEZ-IVA (Symdeko[®] or Symkevi[®]) is effective both in F508del-homozygous individuals and in residual-function heterozygous compounds, thus expanding the possibility of access to *CFTR* modulators.^{32,33} Furthermore, TEZ has better pharmacokinetic properties and fewer adverse effects than LUM.^{32,33} However, it was quickly replaced by the latest and most effective *CFTR* modulator, that is the triple combination ELX-TEZ-IVA (ETI; Kaftrio[®] or Trikafta[®]). In 2019, two randomized, double-blind, placebo-controlled trials reported the impact of ETI on pwCF with at least one F508del, resulting in an improvement of ppFEV1 of 14.3 and 10.0 points after 24 weeks of treatment and a decline of SCC of 41.8 mmol/L and 45.1 mmol/L in F508del/*CFTR* minimal function and F508del-homozygous

individuals, respectively.^{34,35} Benefits of ETI are also on chest computer tomography (CT) scores, CF-related diseases, inflammatory markers, and circulating levels of fat-soluble vitamins,^{36–38} thus significantly transforming the lives of eligible pwCF.^{39,40}

How have *CFTR* modulators changed the face of CF?

The CF Foundation Patient Registry currently provides updated preliminary data to 2023 on 33,288 pwCF.¹³ First of all, the enormous impact of ETI is clear from the increase in the predicted survival⁴¹ and the dramatic decline in the number of pwCF undergoing lung transplants. While the median survival is lower for ineligible pwCF and an individual variability is known, among those born in 2019–2023 it is 61 years, which is almost doubled compared to the years 1999–2003.¹³ Furthermore, a recent study by Lopez et al showed a median projected survival for pwCF initiating ETI between the ages of 12 and 17 years to 82.5 years—an increase of 45.4 years compared with best supportive care alone.⁴¹

This is one of the main factors why the number of adults with CF has steadily increased over the past 10 years, representing 60.4% of Americans with CF in 2023.¹³ It is, therefore, expected that they will experience increasingly common non-pulmonary complications, which are more prevalent in adults, such as CF liver involvement, CF-related diabetes, osteoporosis, depression, anxiety, cardiovascular diseases, and cancer, among others.⁴² Collaboration with specialists from a wide range of disciplines will be necessary, as will greater involvement in primary care.^{16,43,44}

Indeed, before the advent of ETI, CF was one of the major indications for lung transplantation worldwide. Over the last years, most pwCF on ETI with advanced lung disease and listed for lung transplantation were removed from the waiting list. Furthermore, those who were under active evaluation for transplantation listing showed such an improvement that they were no longer considered for it.^{45,46} Data from the French registry showed that lung transplantation for CF was reduced by 55% in 2020 as compared with 2018–2019.⁴⁶ Likewise, in 2023 only 61 lung transplants were reported in the Cystic Fibrosis Foundation (CFF) registry.¹³

CFTR modulator therapies may enhance female fertility by improving physical and psychological status as well as by normalizing the cervical micro-environment.⁴⁷ For these reasons, the number of pregnancies with CF is continuously increasing. Between 2003 and 2023, pregnancies in women with CF in the U.S. moved from 162 to 675.¹³ This highlights the importance of counseling on contraceptive use and family planning before initiation and at routine intervals in ETI therapy.

Registry data also highlight how the prevalence of *Pa* infections has markedly decreased, from 44% in 2018 to 25% in 2023.¹³ Similar data were also for other bacteria typical in pwCF, such as *Stenotrophomonas maltophilia* (from 12% to 5%), *Methicilin-resistant Staphylococcus aureus* (from 25% to 14%), *Achromobacter xylosoxidans* (from 6% to 2%), *Burkholderia cepacia complex* (from 3% to 1%), and *Nontuberculosis mycobacteria* (from 14% to 10%).^{13,48} This trend and the ever-increasing attention to infection prevention and control have also helped reduce the number of PEx in pwCF.¹³

The advent of CFTR modulators and, in particular, of ETI has also disrupted some milestones in the clinical course of the disease. Early use of IVA, LUM-IVA, and even more ETI may allow restoration of pancreatic function in pwCF with pancreatic insufficiency,⁴⁹ an entity historically considered irreversible. Likewise, pwCF with pancreatic insufficiency on ETI can now develop more often acute pancreatitis due to an increased acinar reserve.⁵⁰ Finally, ETI appears to have the potential of reducing the risk of pancreatitis in pwCF with *CFTR* variants with a residual function by increasing CFTR-mediated chloride secretion.⁵¹

ETI treatment can improve bronchial wall thickening and mucous plugging in studies using magnetic resonance imaging (MRI)⁵² and CT,³⁷ up to complete or partial resolution of cystic bronchiectasis,^{53,54} always described as permanent dilatation of the airways on high-resolution CT scan.

ETI can also have a beneficial impact on glucose metabolism in individuals with CF-related diabetes, leading to a possible need for reduction or cessation of insulin therapy.⁵⁵ These data highlight the need for close surveillance, as well as for the possibility of underestimating the risk of some complications. While CF is commonly associated

with malnutrition,¹⁶ in the era of CFTR modulators, overweight and obesity are progressively becoming a significant critical issue, especially in adults with CF.⁵⁶ They seem associated with male sex, older age at diagnosis, and pancreatic sufficiency, being also risk factors for cardiovascular and metabolic diseases.⁵⁶

Differences in the intestinal microbiome of pwCF compared to healthy controls are known, influencing growth and disease progression in children. Recent reports show that ETI consistently improves microbiome diversity in children, showing taxonomic and functional changes, and reducing measures of intestinal inflammation and antibiotic resistance genes.^{57,58} Long-term and large case series studies are needed. Multiomic approaches (genomics, metabolomics, microbiomics, and proteomics) have been extensively used to unravel CF pathological mechanisms; however, only a few studies have explored these technologies to identify novel biomarkers associated with CFTR modulator responses (Table 1). Integrative multiomics could add a valuable perspective on how to individualize CF care.

What are the new challenges for the clinicians beyond elexacaftor/tezacaftor/ivacaftor?

New technologies in healthcare always come with new challenges. CF care has significantly changed, and clinicians must face new dilemmas and question marks (Table 2). Data on the efficacy and safety of ETI, particularly in the pediatric population, remain scarce, highlighting the need for registry or real-world studies reflecting the experiences of pwCF. Clinical trials exclude groups of pwCF with milder or advanced lung disease and include a small number of young children and babies so that regulatory approval for pediatric age is extrapolated on efficacy data obtained in adults with CF.⁶⁶ Recent real-world studies show that changes in outcomes can be different from those reported in clinical trials.^{67–69} Furthermore, among the pediatric clinical trials for ETI, the one by Mall et al.⁷⁰ is placebo-controlled and includes the lung clearance index (LCI) as the primary outcome, a much more sensitive tool than ppFEV1 to detect improvements with interventions or significant structural or functional abnormalities.⁷¹ While LCI is a very promising tool for tracking lung function in children or adults with CF with milder disease or

Table 1. Omics studies assessing the effects of CFTR modulators on samples of people with CF.

Modulator	Approach	Samples	Main finding(s)	Ref
IVA	Transcriptomics	Peripheral blood mononuclear cells of pwCF carrying at least one G551D allele	Identification of 239 genes that were differentially expressed after IVA treatment. These genes were associated with differentiation, microbial infection, inflammation, toll-like receptor signaling, and metabolism.	59
	Proteomics	Peripheral blood mononuclear cells of pwCF carrying at least one G551D allele	A total of 21 differentially expressed proteins associated with plasma membrane. IVA treatment increased levels of ENO1 and PFN1 (related to monocyte migration across epithelia and endothelia) and ICAM3 and CORO1A (related to leukocyte migration).	60
		Leukocytes of pwCF carrying residual function variants	IVA treatment led to downregulation of proteins associated with leukocyte transendothelial migration and regulation of actin cytoskeleton pathways.	61
		Plasma of pwCF carrying at least one G551D allele	IVA treatment changed expression of proteins involved in lipid digestion and transport and extracellular matrix organization. Lung function improvement was correlated with decreased levels of calprotectin and G-CSF and increased levels of calreticulin, and RGMA. Increased weight was correlated with increased levels of IGF-1, leptin and afamin and decreased levels of PSP.	62
LUM-IVA	Transcriptomics	Whole blood samples of F508del-homozygous pwCF	A total of 36 genes were differentially expressed before and after LUM-IVA treatment. Treatment reduced expression of cell-death genes and normalized protein synthesis expression. MMP-9 and SOCS3 were the top two genes more affected, demonstrating decreased expression after LUM-IVA.	63
ETI	Transcriptomics	Nasal epithelia of pwCF carrying at least one F508del allele	Identification of 136 differentially expressed genes and 27 enriched pathways related to the top 20 differentially expressed genes.	64
	Proteomics	Sputum of pwCF carrying at least one F508del allele	A total of 110 proteins were differentially expressed before and after ETI treatment (80 increased and 30 reduced). Reduction in abundance of many proteins involved in pro-inflammatory neutrophilia.	65
ETI, elexacaftor-tezacaftor-ivacaftor; IVA, ivacaftor; LUM-IVA, lumacaftor-ivacaftor.				

normal ppFEV1, it might underestimate lung disease severity in pwCF with established obstructive lung disease.

A high level of heterogeneity in treatment response to ETI is described.⁷² The associated factors are still poorly understood. CFTR modulators

require at least 10 g of fat to be taken in order to ensure it is properly absorbed, which is a task not easily achievable in children. Moreover, these molecules are metabolized by cytochrome P450 subtypes CYP3A4 and CYP3A5, which are inhibited by several drugs commonly co-administered in pwCF.⁷³ New insights also emerge about

Table 2. Priorities and challenges in the era of CFTR modulators.

- Start modulator therapy as soon as possible according to legislative guidelines
- Consider MRI as a radiation-free option for monitoring disease progression in pwCF on CFTR modulators expected to live longer
- Preserving and monitoring lung function and disease progression before starting CFTR modulators with more sensitive and noninvasive approaches such as LCI or lung MRI
- Early lung disease monitoring with LCI in children and adults with milder lung disease or normal spirometry
- Need for registry or real-world efficacy data in pediatric age
- Monitoring long-term patient outcomes and safety
- Understanding biological mechanisms underlying CFTR modulators correlated adverse events
- Early identify factors associated with variable clinical response to CFTR modulators
- Optimizing the therapeutic effect and ETI exposure
- Maintain high adherence to treatments especially for pwCF with advanced lung disease before starting
- ETI and chronic *Pseudomonas aeruginosa* infection
- Reducing the therapeutic burden in pwCF with mild-moderate lung disease after starting ETI
- Monitor the emergence and evolution of more frequent or new CF-associated conditions, such as CF liver involvement, depression, cardiovascular diseases, cancer, and obesity
- Caution in the interpretation of IRT values and sweat tests in infants exposed to ETI during pregnancy
- Expand and standardize the prescribing of ETI for pwCF with drug-responsive CFTR variants
- Intensify the research for effective CFTR modulators for pwCF currently not eligible for ETI

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane regulator; ETI, ellexacaftor/tezacaftor/ivacaftor; IRT, immunoreactive trypsinogen; LCI, lung clearance index; MRI, magnetic resonance imaging.

the influence of variants in *cis* with F508del in pwCF and their responses to CFTR modulators.^{74–76} For instance, the L467F in complex allele with F508del showed no rescue by the LUM-IVA modulator combination⁷⁴ and was also unresponsive to ETI therapy^{74,75} in primary nasal epithelial cells.⁷⁶ Clinicians should investigate the presence of *cis* variants in pwCF with reduced or absent response to modulators, as well as ensure correct absorption of the drug or incompletely understood drug–drug interactions that may interfere with outcomes. It would be even more desirable to predict the CFTR modulator's efficacy in patient-derived tissues, such as primary bronchial cells, primary nasal cells, or rectal biopsy-derived organoids. First data on the use of plasma quantitation of ETI have been reported,⁷⁷ aiming to optimize the therapeutic effect and the drug exposure, minimizing adverse events.

The majority of pwCF in clinical trials experienced adverse events.^{34,35} Most of them were mild or moderate in severity, consistent with CF manifestations or common childhood infections. However, close monitoring is necessary especially for liver tests, given that an increase in transaminases is observed in approximately 10%–26% of children^{69,70} and 5% of adults⁷⁸ on ETI therapy, causing a suspension of the drug very rarely.⁶⁹ In pwCF with liver involvement, ETI is associated with

improvement in liver stiffness and fibrosis indices, probably reducing the development of advanced CF liver disease.⁷⁹ Longer observations with larger cohorts are needed to confirm this data.

Furthermore, ETI may significantly increase serum cholesterol by enhancing its absorption, as evidenced by a correlation between serum cholesterol and phytosterol levels.^{80,81} These metabolic changes and the increased prevalence of overweight and obesity among pwCF (from 10% to 21% among children with CF and from 18% to 42% among adults)¹³ may lead to a higher risk of co-morbidities, such as metabolic disorders and cardiovascular disease, especially with chronic administration in the pediatric population.

Worrying albeit rare adverse events have also been reported, such as raised intracranial pressure,^{69,82} neuropsychiatric effects on mental health,^{83,84} drug reaction with eosinophilia and systemic symptoms like syndrome, musculoskeletal injuries, or severe decrease in platelet count.⁸⁵ Research is also continuing in pwCF eligible for ETI, as demonstrated by recent data on vanzacaftor–tezacaftor–deutivacaftor (VTD), a once-daily dosing combination with fewer drug interactions than ETI.⁸⁶ While recent data from phase III trials ensured the approval of VTD as a novel therapy for pwCF harboring at least one F508del allele or another

responsive *CFTR* variants,^{87,88} the long-term effects remain to be investigated.

Even with the recently published evidence-based standards of care for *CFTR* variant-specific therapies,⁸⁹ understanding biological mechanisms underlying adverse events, optimizing the drug exposure or early identification of pwCF at greatest risk of adverse events will be among the major challenges of coming years.

Little data are yet available on long-term efficacy. Daines et al. demonstrated in children aged >12 years and adults with CF in ETI at week 144, durable clinical benefits, with a good safety profile.⁹⁰ Nevertheless, in a 5-year single-center retrospective study, pwCF who received IVA showed an acute improvement in lung function, with a subsequent decline and the need to optimize care again.⁹¹ Clinicians must closely monitor the lung function, SCC, and nutritional status of pwCF in ETI, especially for those with advanced lung disease (ppFEV1 ≤ 40% or waiting for a lung transplant) before starting the drug, and efforts must be directed to maintain high adherence with treatments. In fact, concerning overall improvement after *CFTR* modulators, the risk of reduced treatment adherence is a critical factor.^{92,93} Reducing the therapeutic burden is a priority for pwCF, especially for those with mild-moderate lung disease.³⁹

The SIMPLIFY study demonstrated that in pwCF undergoing ETI and having a relatively well-preserved pulmonary function, discontinuing daily hypertonic saline or dornase alfa for 6 weeks did not lead to clinically significant differences in pulmonary function compared to continuing treatment.^{94,95} However, the follow-up period was very short and included pwCF had very mild lung disease, with a ppFEV1 of 96.9%. Other ongoing projects, such as CF STORM (52-week trial) and NEEMO (prospective observational study with 12-month assessments up to 5 years) will address the safety of stopping additional treatments in pwCF on ETI.

Nevertheless, while IVA treatment resulted in a decrease in sputum *Pa* density and total bacteria burden, the infection rebounded after 1 year of the drug and with the same strain of bacterium.⁹⁶ Likewise in pwCF in ETI, *Pa* remains detectable by amplicon sequencing throughout the respiratory tract.^{97,98} For this reason, a recent paper by experts on this focus concluded that pwCF on

CFTR modulators may still need inhaled antibiotics to maintain long-term control of *Pa* infections.¹⁹ Furthermore, another challenge in the era of *CFTR* modulators, especially with ETI, is the definition of *Pa* chronic infection. Many pwCF on ETI fail to produce sputum, being needed to monitor airway infections. Such investigations include the use of induced sputum, for pwCF colonized by *Pa* before starting the drug and with multiple negative cultures indicating a possible clearance. A clear guideline is desirable on this topic.^{19,99}

Caution and careful monitoring are necessary in case of infants exposed to ETI in utero and while breastfeeding.⁴⁷ More cases are reported on the safety of ETI in pregnancy⁴⁷; for instance, congenital bilateral cataracts in newborns exposed to the drug have been reported, highlighting the need for cataract screen at birth.¹⁰⁰ Furthermore, decreased blood immunoreactive trypsinogen (IRT) levels in newborn carriers exposed to ETI have been shown,¹⁰¹ as a case of false negative CF NBS in a CF child born from a mother taking *CFTR* modulator therapy during pregnancy.¹⁰² Passing ETI through the placenta and into breast milk can have beneficial effects by preventing pancreatic insufficiency and even resolving meconium ileus in fetuses with CF.¹⁰³ This implies caution in the interpretation of IRT values and SCC in infants exposed to the drug.

Finally, the increased projected survival for pwCF starting ETI at a young age has brought attention to the risk of colorectal cancer.¹⁰⁴ Lack of *CFTR* expression promotes carcinogenic processes such as intestinal inflammation and deleterious gut microbiome changes. For this reason, the CFF Foundation recently recommended treating this population as a high-risk group, using a colonoscopy-only screening strategy starting at age 40 in pwCF without transplant and at age 30 after transplant. Screening should be considered every 5 years if negative and every 3 years or sooner for individuals with adenomatous polyps.¹⁰⁴

Health inequities to access to *CFTR* modulators

While ETI has become a standard of care for children aged 2 or 6 years and older in most high-income countries,⁸⁶ significant global disparities persist in access to these life-saving drugs, especially due to the high cost of the drug.^{105–108} It is clear that the age of starting ETI impacts clinical

Table 3. CFTR modulators in people with CF (updated to March 2025).

CFTR modulator	Commercial name	Current FDA approval	Current EMA approval
IVA	Kalydeco®	Age ≥ 1 month; weight ≥ 5 kg; 77 responsive variants	Age ≥ 4 months; weight ≥ 5 kg; 10 responsive variants
LUM-IVA	Orkambi®	Age ≥ 1 year; F508del/F508del	Age ≥ 1 year; F508del/F508del
TEZ-IVA	Symdeko® (USA) Symkevi® (Europe)	Age ≥ 6 years; F508del/F508del and 26 other responsive variants	Age ≥ 6 years; F508del/F508del and 14 other responsive variants
ETI	Trikafta® (USA) Kaftrio® + Kalydeco® (Europe)	Age ≥ 2 years; F508del/Any and 271 other responsive variants	Age ≥ 2 years; at least one non-class I variant
VTD	Alyftrek®	Age ≥ 6 years; F508del/Any and 31 other responsive variants	Not approved

CFTR, cystic fibrosis transmembrane regulator; EMA: European Medicines Agency; FDA, food and drug administration.

outcomes and survival.^{41,66} A study in Canada showed the projected benefits of ETI on the number of deaths would be halved if the access were delayed to 2025, compared to 2021.¹⁰⁹

The different access possibilities for pwCF and the reimbursement of these drugs are regulated by national regulatory agencies, such as the European medicines agency (EMA) in Europe and by the FDA in the U.S., based on results from phase III double-blind Randomized controlled trials (RCTs). However, there are differences in the extension indications (Table 3). For instance, the FDA has accepted pre-clinical evidence, considering a recovery of the CFTR function ≥10% based on chloride transport; on the contrary, EMA does not deem preclinical data sufficient to expand the label of CFTR modulators without confirmatory clinical data.^{107,110} So initial approvals and regulatory review process are expected to be faster in the U.S., where CFTR modulators are approved 267 days earlier than in the European Union.¹¹¹ So in most European countries, ETI is prescribed only in pwCF aged ≥2 or 6 years, with at least one F508del, while in the U.S., pwCF with 271 other responsive CFTR variants are eligible. However, in March 2025 an extension was approved, making ETI prescribable in Europe in all pwCF aged 2 years and over, with at least one non-class I mutation (Table 3). Cromwell et al have recently reported meaningful improvements in lung function in Americans with CF on ETI, carrying 92 out of these 177 CFTR variants, corresponding to 5.2% of U.S. Registry participants.¹¹² Similarly, the French compassionate

program showed that ETI is effective in a large number of pwCF with rare CFTR variants, including variants that were not previously approved by the FDA.^{113,114}

Even more worrying, although the situation moves rapidly, ETI is not yet licensed and reimbursed in several low-middle income European countries or Central and South America, India, the Middle East, and Southern Africa, while in other countries pwCF have access via a mechanism called “a named patient supply program” (Table 4). In other countries, “legal wars” are necessary to obtain the drug, with delays in starting therapy, also due to the difficulty of carrying out the CFTR genetic test. This may force families to migrate to countries where legislative guidelines allow economic coverage of the drug. Race, ethnic diversity, or the knowledge of regional epidemiology and information on CFTR eligible variants are crucial factors influencing eligibility for CFTR modulators, penalizing low- and middle-income countries or favoring populations where F508del is common, such as the U.S. and Northern European populations.¹⁰⁵ In 2023, only 8% of the American population was ineligible for a modulator based on their genotype.¹³ However, in 2022, Guo et al estimated that only 12% of the world’s total CF population is receiving these drugs.⁴ In countries with mixed ethnicity or with a low prevalence of F508del, such as Brazil¹¹⁵ and Italy,¹⁶ where over 50% and 30% of pwCF, respectively, have a CFTR variant other than F508del, a larger number of pwCF may not be eligible for CFTR modulators. They have

Table 4. Countries where elexacaftor/tezacaftor/ivacaftor (ETI) was licensed and reimbursed as of the 13th December 2024 and age for ETI access (<https://www.vrtx.com/medicines/cystic-fibrosis-facts-and-figures/>).

Country	Age for ETI access	Subregion
Andorra	6+	Western Europe
Australia	2+	Oceania
Albania	no access	Southern Europe
Austria	2+	Western Europe
Belarus	no access	Eastern Europe
Belgium	6+	Western Europe
Bosnia and Herzegovina	2+	Southern Europe
Brazil	6+	South America
Bulgaria	6+	Eastern Europe
Canada	2+	North America
Chile	No data ^a	South America
Colombia	No data ^a	South America
Croatia	6+	Southern Europe
Cyprus	6+	Southern Europe
Czech Republic	2+	Eastern Europe
Denmark	2+	Northern Europe
Egypt	No data ^b	Africa
El Salvador	No data ^b	Central America
England and British overseas territories	2+	Northern Europe
Estonia	2+	Northern Europe
Faroe Islands	2+	Northern Europe
Finland	2+	Northern Europe
France and French overseas territories	2+	Western Europe
Germany	2+	Western Europe
Greece	2+	Southern Europe
Greenland	2+	Northern Europe
Honduras	No data ^b	Central America

(Continued)

Table 4. (Continued)

Country	Age for ETI access	Subregion
Hungary	2+	Eastern Europe
Iceland	6+	Northern Europe
Ireland	2+	Northern Europe
Italy	6+	Southern Europe
Ivory Coast	No data ^b	Africa
Kenya	No data ^b	Africa
Kuwait	no data	Middle East
Latvia	2+	Northern Europe
Lebanon	No data ^b	Middle East
Liechtenstein	6+	Western Europe
Lithuania	2+	Northern Europe
Luxembourg	2+	Western Europe
Malta	6+	Southern Europe
Mexico	No access	Central America
Moldova	No access	Eastern Europe
Monaco	No data	Western Europe
Montenegro	2+	Southern Europe
Nepal	No data ^b	Asia
Netherlands	6+	Western Europe
New Zealand	6+	Oceania
North Macedonia	No data ^a	Southern Europe
Northern Ireland	2+	Northern Europe
Norway	2+	Northern Europe
Oman	No data	Middle East
Poland	12+	Eastern Europe
Portugal	6+	Southern Europe
Qatar	No data	Middle East
Romania	2+	Eastern Europe
Russia	6+	Eastern Europe
Saudi Arabia	No data	Southern Europe
San Marino	No data	Southern Europe

(Continued)

Table 4. (Continued)

Country	Age for ETI access	Subregion
Scotland	2+	Northern Europe
Serbia	No data ^a	Southern Europe
Slovakia	12+	Eastern Europe
Slovenia	6+	Southern Europe
South Africa	6+	Africa
Spain	2+	Southern Europe
Sri Lanka	No data ^b	Asia
Sweden	2+	Northern Europe
Switzerland	6+	Western Europe
Tanzania	No data ^b	Africa
Tunisia	No data ^b	Africa
Turkey	No data ^a	Southern Europe
Uganda	No data ^b	Africa
Ukraine	No access ^b	Eastern Europe
United Arab Emirates	No data	Middle East
United Kingdom	2+	Northern Europe
United States	2+	North America
Uruguay	6+	South America
Vatican City	No data	Southern Europe
Wales	2+	Northern Europe
^a Named patient supply available.		
^b Donation program.		

significant physical, mental, and social impacts from their disease and, as recently reported, the current therapeutic options have left them feeling scared, forgotten, and neglected.¹¹⁶ Clinicians must consider these aspects, and increasingly greater psychological support will be desirable, especially in adolescence. These inequities are added to the already known worldwide differences about the prescription ETI post liver transplantation¹¹⁷ or to the absence or limited neonatal screening programs in some areas¹¹⁸ or to the different access to liver and lung transplants.⁴³ For these reasons, in 2024, differences in patient clinical status and survival could be attributable not

only to intrinsic disease severity but also to these disparities. The delay and unlikely universal availability of CFTR modulators in the next years will lead to further widening of global disparities in CF outcomes.¹⁰³

Accordingly, there is an urgent need to reduce the cost of CFTR modulators to negotiate agreements also in low- and middle-income countries. As reported by Guo et al., the annual estimated minimum production cost of ETI is 5676 \$–90% lower than the current market price (>300,000\$ in the U.S.).¹¹⁹

What are the future perspectives beyond ellexacaftor/tezacaftor/ivacaftor?

Despite the therapeutic success of currently approved CFTR modulators, particularly IVA and ETI, the complete restoration of the function in the lungs and other affected organs is not achieved by these drugs. Indeed, experimental evidence revealed that these drugs are unable to fully recover CFTR protein stability and traffic defects as well as channel gating activity for several variants, including F508del and G551D.^{20,120–123} In intestinal organoids and primary nasal epithelial cells, improvement of CFTR function attains only ~50% with ETI treatment, indicating that there is still scope for further improvement.¹²⁴ Accordingly, pwCF still face a progressive deterioration of their lung function and complications, albeit at a slower pace.¹²⁵ Moreover, several CFTR variants are only moderately rescued (below clinically relevant levels) or unresponsive at all for the currently available modulator therapies. Individuals carrying these CF genotypes will be “bad” or only “mild” responders in whom disease progress will remain at an accelerated pace.¹²⁶

While the identification of specific therapies for (ultra)rare CFTR variants poses substantial challenges due to the high variability of CFTR variants and the small number of individuals carrying these genotypes, the implementation of “theratyping” (i.e., matching single variants with effective modulators) has significantly facilitated the characterization of CFTR variants in which the molecular defect(s) was(were) understudied as well as the assessment of available CFTR modulator efficacy to expand their benefit for pwCF carrying (ultra)rare genotypes.^{127,128} Translational models using patient’s own cells have been developed and these consist of useful tools to

understand and predict clinical responsiveness at an individual level. Among those, the most suitable models are represented by the 2D and 3D cultures of nasal epithelial cells and rectal biopsies-derived intestinal organoids.¹²⁹ In addition to recapitulating several features of the parental organ, these models were demonstrated to be practical, reliable, and easy to obtain and handle.¹²⁹ Indeed, various studies have reported good correlations of the data on patient-derived cell models with clinical features of pwCF (before and after starting ETI therapy).^{130–138}

In parallel, the CF drug discovery pipeline continues to expand with various small molecules under investigation in early-stage clinical studies. For instance, Sionna Therapeutics is initiating two phase I trials of two CFTR correctors (SION-719 and SION-451), which are described as highly potent NBD1 stabilizers. The company has also signed an agreement with AbbVie to expand and accelerate the development of the corrector ABBV-2222 and the potentiator ABBV-3067 that present complementary mechanisms to Sionna's compounds. Fair Therapeutics will assess the safety and efficacy of the triple combination composed by the amplifier PTI-428, the corrector PTI-801, and the potentiator PTI-808 in pwCF carrying rare genotypes. The amplifier PTI-428 was found to selectively enhance CFTR translation by stabilizing CFTR mRNA,¹³⁹ while the corrector PTI-801 was demonstrated to share a common mechanism to ELX to rescue F508del-CFTR.¹²³ The individuals enrolled in this clinical study were selected based on their intestinal organoid responses to these CFTR modulators. Novartis has developed the CFTR potentiator icenticaftor, which demonstrated clinical benefit for patients with chronic obstructive pulmonary disease in a phase II study.¹⁴⁰

Several other CFTR correctors and potentiators are in pre-clinical studies with promising results. The corrector ARN23765 demonstrated picomolar potency and lengthened CFTR rescue in vitro at concentrations 5000 lower than LUM.¹⁴¹ Rescue of F508del-CFTR processing and function was enhanced by the combination of TEZ with the corrector MCG1516A.¹⁴² The compound 4172 and its analogs, in combination with LUM and the corrector 3151, increased the processing and function of several CFTR variants.¹⁴³ IDOR-4 is a macrocyclic CFTR corrector that demonstrated a complementary mechanism of action to clinically

approved CFTR modulators.¹⁴⁴ Apigenin, Asp-11, CP-628006, and LSO-24 are CFTR potentiators from different chemotypes that were proposed to potentiate CFTR gating activity by a different mechanism than that of IVA.^{143–148}

Another class of small molecules under development for CF are the read-through agents. These compounds enable the translation machinery to “over-read” a premature termination codon (PTC), thus allowing the insertion of an amino acid to continue the translation to the normal end of the transcript.²⁰ ELX-02 demonstrated promising read-through activity in vitro,^{149,150} but clinical data of pwCF carrying G542X taking this compound exhibited only modest improvement in lung function. TLN468 is another agent that allowed the expression of several nonsense CFTR variants in which processing and function were enhanced by the combination with CFTR modulators.¹⁵¹ SRI-41315 is suggested to induce read-through activity by pausing protein translation at PTCs due to eRF1 suppression.¹⁵² Another alternative for these variants consists in the design of synthetic tRNAs able to decode PTCs, thus introducing an amino acid into the nascent polypeptide chain that enables the translation of the full-length protein. This approach can rescue both mRNA and full-length protein expression.^{153–155} Finally, antisense oligonucleotides (ASOs) represent an additional option under development not only for nonsense variants but also for those with splicing defects.¹⁵⁶ These chemically modified synthetic RNA-like molecules act by complementary base pairing to the target sequence and demonstrated promising results for CFTR variants, including W1282X and 3849 + 10 kb C>T.^{156–159} As ASOs are very small and considerably stable, it is expected that they could be delivered without the need for a vehicle.

A growing number of studies have demonstrated the feasibility of gene therapy using CFTR cDNA or mRNA to enable patient cells to produce a functional copy of CFTR.^{160–165} The major advantage of these approaches is the possibility of using them in a variant-agnostic manner (i.e., anyone with CF could receive this treatment regardless of the underlying CFTR variants). Some promising gene therapeutic products include the 4D-710 (from 4D Molecular Therapeutics), SP-101 (Spirovant Sciences), ARCT-032 (from Arcturus Therapeutics), RCT2100 (from ReCode Therapeutics) and

VX-522 (from Vertex Pharmaceuticals). The 4D-710 and SP-101 are adeno-associated viral vectors containing WT-CFTRΔR cDNA. The SP-101 demonstrated to restore CFTR-mediated chloride transport in primary human airway epithelial from pwCF,¹⁶⁶ while the 4D-710 is being assessed in adults with CF ineligible or unable to tolerate adverse events of currently available modulator therapies. On the other hand, ARCT-032, RCT2100, and VX-522 are lipid nanoparticles containing the CFTR mRNA that can be delivered to the airway by aerosolization.

Other strategies to directly edit and repair the mutated DNA include homology-directed repair^{165,167–169} and base or prime editing using clustered regularly interspaced short palindromic repeated and associated proteins (CRISPR/Cas).^{170–174} The ultimate goal of these approaches is to correct cells in which CFTR is expressed and has a fundamental role in the epithelial surface lining homeostasis or to reprogram stem cells that could be administered *in vivo* to differentiate and repopulate the epithelium.²⁰ While gene editing holds substantial promise with several publications demonstrating its feasibility, there are still various obstacles to translating this approach into the clinical scenario for CF.

Finally, modulation of alternative (non-CFTR) channels/transporters has been investigated as a potential approach to circumvent the absence of CFTR-mediated chloride and bicarbonate secretion. Some of the main targets include ENaC, TMEM16A, SLC26A4, SLC26A9, and ATP12A.^{20,175} By inhibiting or enhancing the functional expression of these channels/transporters, it is expected that the epithelial surface liquid homeostasis could be restored. This approach can also serve as CFTR variant-agnostic therapeutics.

Conclusion

It is undeniable that “highly effective” modulator therapies have revolutionized the lives of many pwCF by transforming what was described as an early-age lethal disease into a more manageable chronic condition. However, these therapeutic regimens have brought new dilemmas and questions since these individuals are presenting a healthier profile, and more accurate and sensitive biomarkers will be needed to stratify subtle lung disease alterations and monitor disease progression. Several approaches are under investigation with LCI, CT,

and MRI of the lungs already demonstrating to be sensitive measurements for young children and adults with mild disease. Moreover, as pwCF are also living longer, there is an increasingly appreciated need for further studies of the appearance of extra-pulmonary manifestations (CF-related diabetes, osteoporosis, intestinal cancer, and others) and the impact of CFTR modulators on these.

Therotyping efforts remain vital to expand the access of currently available modulator therapies to a greater CF population since a significant number of pwCF carry (ultra)rare *CFTR* variants and these are usually excluded from traditional clinical trial designs. However, there are also pwCF-carrying *CFTR* variants that are refractory for these therapies. These include not only canonical splice, PTC, frameshift, and large deletion/insertion variants, but also missense variants with folding and/or gating defects that are unresponsive to currently available modulators. Therefore, alternative therapeutic strategies are required to overcome such defects. While there are several obstacles to overcome in these alternative strategies, significant progress has also been made to translate them into clinical practice. The joint effort of the entire CF scientific community is the most complete way to have effective therapies for all pwCF.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Vito Terlizzi: Conceptualization; Investigation; Methodology; Project administration; Writing – original draft.

Miquéias Lopes-Pacheco: Conceptualization; Investigation; Methodology; Project administration; Writing – original draft.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Available by contacting the corresponding author.

ORCID iD

Vito Terlizzi  <https://orcid.org/0000-0003-1106-4424>

References

- Grasemann H and Ratjen F. Cystic fibrosis. *N Engl J Med* 2023; 389: 1693–1707.
- Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989; 245: 1066–1073.
- ECFS 2022 Annual Data Report
- Guo J, Garratt A and Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. *J Cyst Fibros* 2022; 21: 456–462.
- Lopes-Pacheco M. CFTR modulators: the changing face of cystic fibrosis in the era of precision medicine. *Front Pharmacol* 2020; 10: 1662.
- Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet* 2015; 16: 45–56.
- Veit G, Avramescu RG, Chiang AN, et al. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Mol Biol Cell* 2016; 27: 424–433.
- Cheng SH, Gregory RJ, Marshall J, et al. Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. *Cell* 1990; 63: 827–834.
- Dalemans W, Barbry P, Champigny G, et al. Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. *Nature* 1991; 354: 526–528.
- Lukacs GL, Chang XB, Bear C, et al. The delta F508 mutation decreases the stability of cystic fibrosis transmembrane conductance regulator in the plasma membrane. Determination of functional half-lives on transfected cells. *J Biol Chem* 1993; 268: 21592–21598.
- Jensen TJ, Loo MA, Pind S, et al. Multiple proteolytic systems, including the proteasome, contribute to CFTR processing. *Cell* 1995; 83: 129–135.
- Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr* 2017; 181S: S4–S15.e1.
- Cystic Fibrosis Foundation Patient Registry Highlights 2023.
- Barry PJ and Simmonds NJ. Diagnosing cystic fibrosis in adults. *Semin Respir Crit Care Med* 2023; 44: 242–251.
- Wu M, Davis JD, Zhao C, et al. Racial inequities and rare CFTR variants: Impact on cystic fibrosis diagnosis and treatment. *J Clin Transl Endocrinol* 2024; 36: 100344.
- Terlizzi V and Farrell PM. Update on advances in cystic fibrosis toward a cure and implications for primary care clinicians. *Curr Probl Pediatr Adolesc Health Care* 2024: 101637.
- Terlizzi V, Castellani C, Taccetti G, et al. Dornase alfa in cystic fibrosis: indications, comparative studies and effects on lung clearance index. *Ital J Pediatr*. 2022; 48: 141.
- Burgel PR, Ballmann M, Drevinek P, et al. Considerations for the use of inhaled antibiotics for *Pseudomonas aeruginosa* in people with cystic fibrosis receiving CFTR modulator therapy. *BMJ Open Respir Res* 2024; 11: e002049.
- Oliver KE, Carlon MS, Pedemonte N, et al. The revolution of personalized pharmacotherapies for cystic fibrosis: what does the future hold? *Expert Opin Pharmacother* 2023; 24: 1545–1565.
- Van Goor F, Hadida S, Grootenhuys PD, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci USA*. 2009; 106: 18825–18830.
- Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011; 365: 1663–1672.
- De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. *J Cyst Fibros*. 2014; 13: 674–680.
- McGarry ME, Illek B, Ly NP, et al. In vivo and in vitro ivacaftor response in cystic fibrosis patients with residual CFTR function: N-of-1 studies. *Pediatr Pulmonol* 2017; 52: 472–479.
- Guimbellot J, Solomon GM, Baines A, et al. Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *J Cyst Fibros* 2019; 18: 102–109.

25. Kalydeco (Ivacaftor) prescribing information. Boston, MA: Vertex Pharmaceuticals Incorporated, 2020.
26. Durmowicz AG, Lim R, Rogers H, et al. The U.S. Food and Drug Administration's experience with ivacaftor in cystic fibrosis. Establishing efficacy using in vitro data in lieu of a clinical trial. *Ann Am Thorac Soc* 2018; 15: 1–2.
27. Davies JC, Wainwright CE, Sawicki GS, et al. Ivacaftor in infants aged 4 to <12 months with cystic fibrosis and a gating mutation. Results of a two-part phase 3 clinical trial. *Am J Respir Crit Care Med* 2021; 203: 585–593.
28. Heneghan M, Southern KW, Murphy J, et al. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). *Cochrane Database Syst Rev* 2023; 11(11): CD010966.
29. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med*. 2015; 373:220–231.
30. Graeber SY, Dopfer C, Naehrlich L, et al. Effects of lumacaftor-ivacaftor therapy on cystic fibrosis transmembrane conductance regulator function in Phe508del homozygous patients with cystic fibrosis. *Am J Respir Crit Care Med* 2018; 197: 1433–1442.
31. Yaacoby-Bianu K, Schnapp Z, Koren I, et al. Real life evaluation of the multi-organ effects of Lumacaftor/Ivacaftor on F508del homozygous cystic fibrosis patients. *BMC Pharmacol Toxicol* 2022; 23: 80.
32. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med* 2017; 377: 2013–2023.
33. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual function heterozygotes with cystic fibrosis. *N Engl J Med* 2017; 377: 2024–2035.
34. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019; 394: 1940–1948.
35. Middleton PG, Mall MA, Drevinek P, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single F508del allele. *N Engl J Med* 2019; 381: 1809–1819.
36. McNally P, Lester K, Stone G, et al. Improvement in lung clearance index and chest computed tomography scores with elexacaftor/tezacaftor/ivacaftor treatment in people with cystic fibrosis aged 12 years and older – the RECOVER trial. *Am J Respir Crit Care Med* 2023; 208: 917–929.
37. Mainz JG, Lester K, Elnazir B, et al. Reduction in abdominal symptoms (CFAbd-Score), faecal M2-pyruvate-kinase and Calprotectin over one year of treatment with Elexacaftor-Tezacaftor-Ivacaftor in people with CF aged ≥12 years – The RECOVER study. *J Cyst Fibros* 2024; 23: 474–480.
38. Francalanci M, Terlizzi V, Fevola C, et al. Nutritional status and circulating levels of fat-soluble vitamins in cystic fibrosis patients: a cohort study and evaluation of the effect of CFTR modulators. *Children (Basel)*. 2023; 10:252.
39. Hisert KB, Birket SE, Clancy JP, et al. Understanding and addressing the needs of people with cystic fibrosis in the era of CFTR modulator therapy. *Lancet Respir Med* 2023; 11: 916–931.
40. Bacalhau M, Camargo M, Magalhães-Ghiotto GAV, et al. Elexacaftor-tezacaftor-ivacaftor: a life-changing triple combination of CFTR modulator drugs for cystic fibrosis. *Pharmaceuticals (Basel)* 2023; 16: 410.
41. Lopez A, Daly C, Vega-Hernandez G, et al. Elexacaftor/tezacaftor/ivacaftor projected survival and long-term health outcomes in people with cystic fibrosis homozygous for F508del. *J Cyst Fibros* 2023; 22: 607–614.
42. Burgel PR, Paillasseur JL, Durieu I, et al. Multisystemic effects of elexacaftor-tezacaftor-ivacaftor in adults with cystic fibrosis and advanced lung disease. *Ann Am Thorac Soc* 2024; 21: 1053–1064.
43. Burgel PR, Burnet E, Regard L, et al. The changing epidemiology of cystic fibrosis: the implications for adult care. *Chest* 2023; 163: 89–99.
44. Auth R, Catanese S and Banerjee D. Integrating Primary Care into the Management of Cystic Fibrosis. *J Prim Care Community Health* 2023; 14: 21501319231173811.
45. Carnovale V, Iacotucci P, Terlizzi V, et al. Effectiveness and safety of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease with the Phe508del/minimal function genotype. *Respir Med* 2021; 189: 106646.
46. Burgel PR, Durieu I, Chiron R, et al.; French Cystic Fibrosis Reference Network Study Group.

- Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *Am J Respir Crit Care Med* 2021; 204: 64–73.
47. Taylor-Cousar JL. CFTR modulators: impact on fertility, pregnancy, and lactation in women with cystic fibrosis. *J Clin Med* 2020; 9: 2706.
 48. Terlizzi V, Tomaselli M, Giacomini G, et al. *Stenotrophomonas maltophilia* in people with Cystic Fibrosis: a systematic review of prevalence, risk factors and management. *Eur J Clin Microbiol Infect Dis* 2023; 42: 1285–1296.
 49. McKay IR and Ooi CY. The exocrine pancreas in cystic fibrosis in the era of CFTR modulation: a mini review. *Front Pediatr* 2022; 10: 914790.
 50. Gould MJ, Smith H, Rayment JH, et al. CFTR modulators increase risk of acute pancreatitis in pancreatic insufficient patients with cystic fibrosis. *J Cyst Fibros* 2022; 21: 600–602.
 51. Ramsey ML, Gokun Y, Sobotka LA, et al. Cystic fibrosis transmembrane conductance regulator modulator use is associated with reduced pancreatitis hospitalizations in patients with cystic fibrosis. *Am J Gastroenterol* 2021; 116: 2446–2454.
 52. Wucherpfennig L, Triphan SMF, Wege S, et al. Magnetic resonance imaging detects improvements of pulmonary and paranasal sinus abnormalities in response to elexacaftor/tezacaftor/ivacaftor therapy in adults with cystic fibrosis. *J Cyst Fibros* 2022; 21: 1053–1060.
 53. Middleton PG and Simmonds NJ. Cystic fibrosis modulator therapy can reverse cystic bronchiectasis. *Respirol Case Rep* 2023; 11: e01172.
 54. Cazier P, Chassagnon G, Dhote T, et al. Reversal of cylindrical bronchial dilatations in a subset of adults with cystic fibrosis treated with elexacaftor-tezacaftor-ivacaftor. *Eur Respir J* 2024; 63: 2301794.
 55. Taelman V, Declercq D, Van Biervliet S, et al. Effect of 18 months elexacaftor-tezacaftor-ivacaftor on body mass index and glycemic control in adults with cystic fibrosis. *Clin Nutr ESPEN* 2023; 58: 73–78.
 56. Gramegna A, Aliberti S, Contarini M, et al. Overweight and obesity in adults with cystic fibrosis: an Italian multicenter cohort study. *J Cyst Fibros* 2022; 21: 111–114.
 57. Reasoner SA, Bernard R, Waalkes A, et al. Longitudinal profiling of the intestinal microbiome in children with cystic fibrosis treated with elexacaftor-tezacaftor-ivacaftor. *mBio* 2024; 15: e0193523.
 58. Marsh R, Santos CD, Yule A, et al. Impact of extended elexacaftor/Tezacaftor/Ivacaftor therapy on the gut microbiome in cystic fibrosis. *J Cyst Fibros*. 2024; 23: 967–976.
 59. Sun T, Sun Z, Jiang Y, et al. Transcriptomic responses to ivacaftor and prediction of ivacaftor clinical responsiveness. *Am J Respir Cell Mol Biol* 2019; 61: 643–652.
 60. Hisert KB, Schoenfelt KQ, Cooke G, et al. Ivacaftor-induced proteomic changes suggest monocyte defects may contribute to the pathogenesis of cystic fibrosis. *Am J Respir Cell Mol Biol* 2016; 54: 594–597.
 61. Pedrazzi M, Vercellone S, Barberis E, et al. Identification of potential leukocyte biomarkers related to drug recovery of CFTR: clinical applications in cystic fibrosis. *Int J Mol Sci* 2021; 22(8): 3928.
 62. Hoppe JE, Wagner BD, Kirk Harris J, et al. Effects of ivacaftor on systemic inflammation and the plasma proteome in people with CF and G551D. *J Cyst Fibros* 2022; 21: 950–958.
 63. Kopp BT, Fitch J, Jaramillo L, et al. Whole-blood transcriptomic responses to lumacaftor/ivacaftor therapy in cystic fibrosis. *J Cyst Fibros* 2020; 19: 245–254.
 64. Yue M, Weiner DJ, Gaietto KM, et al. Nasal epithelium transcriptomics predict clinical response to elexacaftor/tezacaftor/ivacaftor. *Am J Respir Cell Mol Biol* 2024; 71: 730–739.
 65. Maher RE, Barry PJ, Emmott E, et al. Influence of highly effective modulator therapy on the sputum proteome in cystic fibrosis. *J Cyst Fibros* 2024; 23: 269–277.
 66. Gifford AH, Taylor-Cousar JL, Davies JC, et al. Update on clinical outcomes of highly effective modulator therapy. *Clin Chest Med* 2022; 43: 677–695.
 67. Daccò V, Rosazza C, Mariani A, et al. Effectiveness and safety of elexacaftor/tezacaftor/ivacaftor treatment in children aged 6–11 years with cystic fibrosis in a real-world setting. *Pediatr Pulmonol* 2024; 59(11): 2792–2799.
 68. Urquhart DS, Dowle H, Moffat K, et al. Lung clearance index (LCI2.5) changes after initiation of Elexacaftor/Tezacaftor/Ivacaftor in children with cystic fibrosis aged between 6 and 11 years: The “real-world” differs from trial data. *Pediatr Pulmonol* 2024; 59: 1449–1453.

69. Terlizzi V, Fevola C, Presti S, et al. Reported adverse events in a multicenter cohort of patients ages 6–18 years with cystic fibrosis and at least one F508del allele receiving elexacaftor/tezacaftor/ivacaftor. *J Pediatr* 2024; 274: 114176.
70. Mall MA, Brugha R, Gartner S, et al. Efficacy and safety of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis heterozygous for F508del and a minimal function mutation: a phase 3b, randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2022; 206: 1361–1369.
71. Bayfield KJ, Douglas TA, Rosenow T, et al. Time to get serious about the detection and monitoring of early lung disease in cystic fibrosis. *Thorax* 2021; 76: 1255–1265.
72. Alicandro G, Gramegna A, Bellino F, et al. Heterogeneity in response to Elexacaftor/Tezacaftor/Ivacaftor in people with cystic fibrosis. *J Cyst Fibros* 2024; S1569–1993(24)00057-2.
73. Kaftrio European Medicines Agency, <https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio>
74. Baatallah N, Bitam S, Martin N, et al. Cis variants identified in F508del complex alleles modulate CFTR channel rescue by small molecules. *Hum Mutat* 2018; 39: 506–514.
75. Terlizzi V, Centrone C, Ferrari B, et al. Modulator therapy in cystic fibrosis patients with cis variants in F508del complex allele: a short-term observational case series. *J Pers Med* 2022; 12: 1421.
76. Sondo E, Cresta F, Pastorino C, et al. The L467F-F508del complex allele hampers pharmacological rescue of mutant CFTR by Elexacaftor/Tezacaftor/Ivacaftor in cystic fibrosis patients: the value of the ex vivo nasal epithelial model to address non-responders to CFTR-modulating drugs. *Int J Mol Sci* 2022; 23: 3175.
77. Pigliasco F, Cafaro A, Stella M, et al. Simultaneous quantification of ivacaftor, tezacaftor, and elexacaftor in cystic fibrosis patients' plasma by a novel LC-MS/MS method. *Biomedicines* 2023; 11: 628.
78. Tewkesbury DH, Athwal V, Bright-Thomas RJ, et al. Longitudinal effects of elexacaftor/tezacaftor/ivacaftor on liver tests at a large single adult cystic fibrosis centre. *J Cyst Fibros* 2023; 22: 256–262.
79. Terlizzi V, Fevola C, Cecchetti M, et al. Effect of elexacaftor-tezacaftor-ivacaftor on liver transient elastography, fibrosis indices and blood tests in children with cystic fibrosis. *J Cyst Fibros* 2025; S1569–1993(24)01861-7.
80. Castaldo A, Iacotucci P, Bagnasco S, et al. Liver biochemical indexes and cholesterol metabolism in cystic fibrosis patients with F508del/CFTR variant genotype after elexacaftor/tezacaftor/ivacaftor treatment. *Sci Rep* 2024; 14: 17422.
81. Castaldo A, Gelzo M, Iacotucci P, et al. One year of treatment with elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis homozygous for the F508del mutation causes a significant increase in liver biochemical indexes. *Front Mol Biosci* 2024; 10: 1327958.
82. Southern KW, Barben J, Goldring S, et al. Raised intracranial pressure in three children with cystic fibrosis receiving elexacaftor-tezacaftor-ivacaftor modulator therapy. *Am J Respir Crit Care Med* 2023; 208: 103–105.
83. VanElzakker MB, Tillman EM, Yonker LM, et al. Neuropsychiatric adverse effects from CFTR modulators deserve a serious research effort. *Curr Opin Pulm Med* 2023; 29: 603–609.
84. Sermet-Gaudelus I, Benaboud S, Bui S, et al. Behavioural and sleep issues after initiation of elexacaftor-tezacaftor-ivacaftor in preschool-age children with cystic fibrosis. *Lancet* 2024; 404(10448): 117–120.
85. Manciuilli T, Bresci S, Mencarini J, et al. Prevalence of adverse events in cystic fibrosis patients treated with elexacaftor/tezacaftor/ivacaftor: Experience of the regional referral center in Tuscany, Italy. *Pediatr Pulmonol* 2023; 58: 3626–3629.
86. Uluer AZ, MacGregor G, Azevedo P, et al. Safety and efficacy of vanzacaftor-tezacaftor-deutivacaftor in adults with cystic fibrosis: randomised, double-blind, controlled, phase 2 trials. *Lancet Respir Med* 2023; 11: 550–562.
87. Keating C, Yonker LM, Vermeulen F, et al. Vanzacaftor-tezacaftor-deutivacaftor versus elexacaftor-tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103): results from two randomised, active-controlled, phase 3 trials. *Lancet Respir Med* 2024; S2213–2600(24)00411-9.
88. Hoppe JE, Kasi AS, Pittman JE, et al. Vanzacaftor-tezacaftor-deutivacaftor for children aged 6–11 years with cystic fibrosis (RIDGELINE Trial VX21-121-105): an analysis from a single-arm, phase 3 trial. *Lancet Respir Med* 2024; S2213–2600(24)00407-7.

89. Southern KW, Castellani C, Lammertyn E, et al. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *J Cyst Fibros* 2023; 22: 17–30.
90. Daines CL, Tullis E, Costa S, et al. Long-term safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis and at least one F508del allele: 144-week interim results from a 192-week open-label extension study. *Eur Respir J* 2023; 62: 2202029.
91. Mitchell RM, Jones AM, Stocking K, et al. Longitudinal effects of ivacaftor and medicine possession ratio in people with the Gly551Asp mutation: a 5-year study. *Thorax* 2021; 76: 874–879.
92. Davis CS and Cogen JD. Can clinical benefits of modulators effectively “modulate” adherence in people with CF? *Thorax* 2021; 76: 854–855.
93. Gold LS, Hansen RN, Mayer-Hamblett N, et al. The cost of simplifying treatments for cystic fibrosis: Implications of the SIMPLIFY trial. *J Manag Care Spec Pharm* 2024; 30: 26–33.
94. Mayer-Hamblett N, Ratjen F, Russell R, et al. 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. *Lancet Respir Med* 2023; 11: 329–340.
95. Donaldson SH, Corcoran TE, Pilewski JM, et al. The effect of discontinuing hypertonic saline or dornase alfa on mucociliary clearance in elexacaftor/tezacaftor/ivacaftor treated people with cystic fibrosis: The SIMPLIFY-MCC Study. *J Cyst Fibros* 2024; 23: 457–460.
96. Hisert KB, Heltshe SL, Pope C, et al. Restoring cystic fibrosis transmembrane conductance regulator function reduces airway bacteria and inflammation in people with cystic fibrosis and chronic lung infections. *Am J Respir Crit Care Med* 2017; 195: 1617–1628.
97. Armbruster CR, Hilliam YK, Zemke AC, et al. Persistence and evolution of *Pseudomonas aeruginosa* following initiation of highly effective modulator therapy in cystic fibrosis. *mBio*. 2024; 15: e0051924.
98. Nichols DP, Morgan SJ, Skalland M, et al. Pharmacologic improvement of CFTR function rapidly decreases sputum pathogen density, but lung infections generally persist. *J Clin Invest* 2023; 133: e167957.
99. Elborn JS, Blasi F, Burgel P-R, et al. Role of inhaled antibiotics in the era of highly effective CFTR Modulators. *Eur Respir Rev* 2023; 32: 220154.
100. Jain R, Wolf A, Molad M, et al. Congenital bilateral cataracts in newborns exposed to elexacaftor-tezacaftor-ivacaftor in utero and while breast feeding. *J Cyst Fibros* 2022; 21: 1074–1076.
101. Patel P, Yeley J, Brown C, et al. Immunoreactive trypsinogen in infants born to women with cystic fibrosis taking elexacaftor-Tezacaftor-Ivacaftor. *Int J Neonatal Screen* 2023; 9: 10.
102. Fortner CN, Seguin JM and Kay DM. Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking CFTR modulator therapy during pregnancy. *J Cyst Fibros* 2021; 20: 835–836.
103. Szentpetery S, Foil K, Hendrix S, et al. A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus. *J Cyst Fibros* 2022; 21: 721–724.
104. Raza Z, Islam BN, Hachem CY, et al. Evolving data on risk and current screening recommendations for colorectal cancer in cystic fibrosis: pre- and posttransplant. *Pediatr Pulmonol* 2024; 59(Suppl. 1): S91–S97.
105. Zampoli M, Morrow BM and Paul G. Real-world disparities and ethical considerations with access to CFTR modulator drugs: mind the gap! *Front Pharmacol* 2023; 14: 1163391.
106. Zampoli M, Sykes J, Verstraete J, et al. Global disparities in cystic fibrosis outcomes prior to CFTR modulators: a CF registries cohort study in South Africa and Canada. *J Cyst Fibros* 2024; 23: 334–340.
107. Mall MA, Burgel PR, Castellani C, et al. Cystic fibrosis. *Nat Rev Dis Primers* 2024; 10: 53.
108. Guo J, King I and Hill A. International disparities in diagnosis and treatment access for cystic fibrosis. *Pediatr Pulmonol* 2024; 59: 1622–1630.
109. Stanojevic S, Vukovojac K, Sykes J, et al. Projecting the impact of delayed access to elexacaftor/tezacaftor/ivacaftor for people with Cystic Fibrosis. *J Cyst Fibros* 2021; 20: 243–249.
110. Costa E, Girotti S, Pauro F, et al. The impact of FDA and EMA regulatory decision-making process on the access to CFTR modulators for

- the treatment of cystic fibrosis. *Orphanet J Rare Dis* 2022; 17(1): 188.
111. Costa E, Girotti S, Mathieu C, et al. Differential times of submission and approval of CFTR modulators for the treatment of Cystic Fibrosis in the United States and the European Union. *J Cyst Fibros* 2024; 24: 125–132.
112. Cromwell EA, Ostrenga JS, Sanders DB, et al. Impact of the expanded label for elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with no F508del variant in the United States. *Eur Respir J* 2024; 64(5): 2401146.
113. Burgel PR, Sermet-Gaudelus I, Girodon E, et al. The expanded French compassionate programme for elexacaftor-tezacaftor-ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. *Lancet Respir Med* 2024; 12: 888–900.
114. Burgel PR, Sermet-Gaudelus I, Durieu I, et al. The French Compassionate Program of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis with advanced lung disease and no F508del CFTR variant. *Eur Respir J* 2023; 61(5): 2202437.
115. Registro Brasileiro De Fibrose Cística – REBRAFC http://portalgbefc.org.br/ckfinder/userfiles/files/Rebrafc_2021_REV_fev24.pdf
116. Kramer-Golinkoff E, Camacho A, Kramer L, et al. A survey: understanding the health and perspectives of people with CF not benefiting from CFTR modulators. *Pediatr Pulmonol* 2022; 57: 1253–1261.
117. Testa I, Indolfi G, Brugha R, et al. Safety and efficacy of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis following liver transplantation: a systematic review. *J Cyst Fibros* 2024; 23: 554–560.
118. Munck A, Berger DO and Southern KW. European survey of newborn bloodspot screening for CF: opportunity to address challenges and improve performance. *J Cyst Fibros* 2023; 22: 484–495.
119. Guo J, Wang J, Zhang J, et al. Current prices versus minimum costs of production for CFTR modulators. *J Cyst Fibros* 2022; 21: 866–872.
120. Jih KY and Hwang TC. Vx-770 potentiates CFTR function by promoting decoupling between the gating cycle and ATP hydrolysis cycle. *Proc Natl Acad Sci USA* 2013; 110(11): 4404–4409.
121. Veit G, Roldan A, Hancock MA, et al. Allosteric folding correction of F508del and rare CFTR mutants by elexacaftor-tezacaftor-ivacaftor (Trikafta) combination. *JCI Insight* 2020; 5(18): e139983.
122. Capurro V, Tomati V, Sondo E, et al. Partial rescue of F508del-CFTR stability and trafficking defects by double corrector treatment. *Int J Mol Sci.* 2021; 22: 5262.
123. Ferreira FC, Amaral MD, Bacalhau M, et al. PTI-801 (posenacaftor) shares a common mechanism with VX-445 (elexacaftor) to rescue p.Phe508del-CFTR. *Eur J Pharmacol.* 2024; 967: 176390.
124. Mall MA, Mayer-Hamblett N and Rowe SM. Cystic fibrosis: emergence of highly effective targeted therapeutics and potential clinical implications. *Am J Respir Crit Care Med* 2020; 201: 1193–1208.
125. Flume PA, Wainwright CE, Elizabeth Tullis D, et al. Recovery of lung function following a pulmonary exacerbation in patients with cystic fibrosis and the G551D-CFTR mutation treated with ivacaftor. *J Cyst Fibros* 2018; 17: 83–88.
126. Sawicki GS, McKone EF, Pasta DJ, et al. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med* 2015; 192: 836–842.
127. Clancy JP, Cotton CU, Donaldson SH, et al. CFTR modulator theratyping: current status, gaps and future directions. *J Cyst Fibros* 2019; 18: 22–34.
128. Silva IAL, Laselva O and Lopes-Pacheco M. Advances in preclinical in vitro models for the translation of precision medicine for cystic fibrosis. *J Pers Med* 2022; 12: 1321.
129. Bacalhau M, Camargo M and Lopes-Pacheco M. Laboratory tools to predict CFTR modulator therapy effectiveness and to monitor disease severity in cystic fibrosis. *J Pers Med* 2024; 14: 93.
130. Graeber SY, van Mourik P, Vonk AM, et al. Comparison of organoid swelling and in vivo biomarkers of cftr function to determine effects of lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for the F508del mutation. *Am J Respir Crit Care Med* 2020; 202: 1589–1592.
131. Park JK, Shrivastava A, Zhang C, et al. Functional profiling of CFTR-directed therapeutics using pediatric patient-derived nasal epithelial cell models. *Front Pediatr* 2020; 8: 536.
132. Mitropoulou G, Brandenberg N, Hoehnel S, et al. Rectal organoid-guided CFTR modulator therapy restores lung function in a cystic fibrosis

- patient with the rare 1677delTA/R334W genotype. *Eur Respir J* 2022; 60(6): 2201341.
133. Terlizzi V, Pesce E, Capurro V, et al. Clinical consequences and functional impact of the rare S737F CFTR variant and its responsiveness to CFTR modulators. *Int J Mol Sci* 2023; 24: 6576.
 134. Dreano E, Burgel PR, Hatton A, et al. Theratyping cystic fibrosis patients to guide elxacaftor/tezacaftor/ivacaftor out-of-label prescription. *Eur Respir J*. 2023; 62: 2300110.
 135. Kondratyeva E, Melyanovskaya Y, Efremova A, et al. Clinical and genetic characteristics of a patient with cystic fibrosis with a complex allele [E217G;G509D] and functional evaluation of the CFTR channel. *Genes (Basel)* 2023; 14: 1705.
 136. Lefferts JW, Bierlaagh MC, Kroes S, et al. CFTR function restoration upon elxacaftor/tezacaftor/ivacaftor treatment in patient-derived intestinal organoids with rare CFTR genotypes. *Int J Mol Sci* 2023; 24: 14539.
 137. Terlizzi V, Colangelo C, Marsicovetere G, et al. Effectiveness of elxacaftor/tezacaftor/ivacaftor therapy in three subjects with the cystic fibrosis genotype Phe508del/unknown and advanced lung disease. *Genes (Basel)* 2021; 12: 1178.
 138. Comegna M, Terlizzi V, Salvatore D, et al. Elxacaftor-tezacaftor-ivacaftor therapy for cystic fibrosis patients with the F508del/unknown genotype. *Antibiotics (Basel)* 2021; 10: 828.
 139. Dukovski D, Villella A, Bastos C, et al. Amplifiers co-translationally enhance CFTR biosynthesis via PCBP1-mediated regulation of CFTR mRNA. *J Cyst Fibros* 2020; 19: 733–741.
 140. Martinez FJ, Criner GJ, Gessner C, et al. Icenticaftor, a CFTR potentiator, in COPD: a multicenter, parallel-group, double-blind clinical trial. *Am J Respir Crit Care Med* 2023; 208: 417–427.
 141. Pedemonte N, Bertozzi F, Caci E, et al. Discovery of a picomolar potency pharmacological corrector of the mutant CFTR chloride channel. *Sci Adv* 2020; 6: eaay9669.
 142. Lopes-Pacheco M, Bacalhau M, Ramalho SS, et al. Rescue of mutant CFTR trafficking defect by the investigational compound MCG1516A. *Cells* 2022; 11: 136.
 143. Vaccarin C, Veit G, Hegedus T, et al. Synthesis and biological evaluation of pyrazole-pyrimidones as a new class of correctors of the cystic fibrosis transmembrane conductance regulator (CFTR). *J Med Chem* 2024; 67(16): 13891–13908.
 144. Marchesin V, Monnier L, Blattmann P, et al. A uniquely efficacious type of CFTR corrector with complementary mode of action. *Sci Adv* 2024; 10: eadk1814.
 145. Moran O, Galletta LJ and Zegarra-Moran O. Binding site of activators of the cystic fibrosis transmembrane conductance regulator in the nucleotide binding domains. *Cell Mol Life Sci* 2005; 62: 446–460.
 146. Phuan PW, Son JH, Tan JA, et al. Combination potentiator ('co-potentiator') therapy for CF caused by CFTR mutants, including N1303K, that are poorly responsive to single potentiators. *J Cyst Fibros* 2018; 17: 595–606.
 147. Liu J, Berg AP, Wang Y, et al. A small molecule CFTR potentiator restores ATP-dependent channel gating to the cystic fibrosis mutant G551D-CFTR. *Br J Pharmacol* 2022; 179: 1319–1337.
 148. Bacalhau M, Ferreira FC, Silva IAL, et al. Additive Potentiation of R334W-CFTR function by novel small molecules. *J Pers Med* 2023; 13: 102.
 149. Crawford DK, Mullenders J, Pott J, et al. Targeting G542X CFTR nonsense alleles with ELX-02 restores CFTR function in human-derived intestinal organoids. *J Cyst Fibros* 2021; 20: 436–442.
 150. Chen J, Thrasher K, Fu L, et al. The synthetic aminoglycoside ELX-02 induces readthrough of G550X-CFTR producing superfunctional protein that can be further enhanced by CFTR modulators. *Am J Physiol Lung Cell Mol Physiol* 2023; 324: L756–L770.
 151. Karri S, Cornu D, Serot C, et al. TLN468 changes the pattern of tRNA used to read through premature termination codons in CFTR. *J Cyst Fibros* 2024; 23(6): 1185–1194.
 152. Sharma J, Du M, Wong E, et al. A small molecule that induces translational readthrough of CFTR nonsense mutations by eRF1 depletion. *Nat Commun* 2021; 12: 4358.
 153. Lueck JD, Yoon JS, Perales-Puchalt A, et al. Engineered transfer RNAs for suppression of premature termination codons. *Nat Commun* 2019; 10: 822.
 154. Ko W, Porter JJ, Sipple MT, et al. Efficient suppression of endogenous CFTR nonsense mutations using anticodon-engineered transfer RNAs. *Mol Ther Nucleic Acids* 2022; 28: 685–701.

155. Albers S, Allen EC, Bharti N, et al. Engineered tRNAs suppress nonsense mutations in cells and in vivo. *Nature* 2023; 618(7966): 842–848.
156. Levin AA. Treating disease at the RNA level with oligonucleotides. *N Engl J Med* 2019; 380: 57–70.
157. Michaels WE, Bridges RJ and Hastings ML. Antisense oligonucleotide-mediated correction of CFTR splicing improves chloride secretion in cystic fibrosis patient-derived bronchial epithelial cells. *Nucleic Acids Res* 2020; 48: 7454–7467.
158. Oren YS, Irony-Tur Sinai M, Golec A, et al. Antisense oligonucleotide-based drug development for Cystic Fibrosis patients carrying the 3849+10 kb C-to-T splicing mutation. *J Cyst Fibros* 2021; 20: 865–875.
159. Kim YJ, Sivetz N, Layne J, et al. Exon-skipping antisense oligonucleotides for cystic fibrosis therapy. *Proc Natl Acad Sci USA* 2022; 119: e2114858118.
160. Vidović D, Carlon MS, da Cunha MF, et al. RAAV-CFTRΔR rescues the cystic fibrosis phenotype in human intestinal organoids and cystic fibrosis mice. *Am J Respir Crit Care Med* 2016; 193: 288–298.
161. Alton EW, Beekman JM, Boyd AC, et al. Preparation for a first-in-man lentivirus trial in patients with cystic fibrosis. *Thorax* 2017; 72: 137–147.
162. Guan S, Munder A, Hedtfeld S, et al. Self-assembled peptide-poloxamine nanoparticles enable in vitro and in vivo genome restoration for cystic fibrosis. *Nat Nanotechnol* 2019; 14: 287–297.
163. Rowe SM, Zuckerman JB, Dorgan D, et al. Inhaled mRNA therapy for treatment of cystic fibrosis: Interim results of a randomized, double-blind, placebo-controlled phase 1/2 clinical study. *J Cyst Fibros* 2023; 22: 656–664.
164. Marquez Loza LI, Cooney AL, Dong Q, et al. Increased CFTR expression and function from an optimized lentiviral vector for cystic fibrosis gene therapy. *Mol Ther Methods Clin Dev* 2021; 21: 94–106.
165. Vaidyanathan S, Baik R, Chen L, et al. Targeted replacement of full-length CFTR in human airway stem cells by CRISPR-Cas9 for pan-mutation correction in the endogenous locus. *Mol Ther* 2022; 30: 223–237.
166. Excoffon KJ, Lin S, Narayan PKL, et al. SP-101, A novel adeno-associated virus gene therapy for the treatment of cystic fibrosis, mediates functional correction of primary human airway epithelia from donors with cystic fibrosis. *Hum Gene Ther* 2024; 35(17–18): 695–709.
167. Vaidyanathan S, Salahudeen AA, Sellers ZM, et al. High-efficiency, selection-free gene repair in airway stem cells from cystic fibrosis patients rescues CFTR function in differentiated epithelia. *Cell Stem Cell* 2020; 26: 161–171.e4.
168. Suzuki S, Crane AM, Anirudhan V, et al. Highly Efficient gene editing of cystic fibrosis patient-derived airway basal cells results in functional CFTR correction. *Mol Ther* 2020; 28: 1684–1695.
169. Santos L, Mention K, Cavusoglu-Doran K, et al. Comparison of Cas9 and Cas12a CRISPR editing methods to correct the W1282X-CFTR mutation. *J Cyst Fibros* 2022; 21: 181–187.
170. Geurts MH, de Poel E, Amatngalim GD, et al. CRISPR-based adenine editors correct nonsense mutations in a cystic fibrosis organoid biobank. *Cell Stem Cell* 2020; 26: 503–510.e7.
171. Anzalone AV, Koblan LW and Liu DR. Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors. *Nat Biotechnol* 2020; 38: 824–844.
172. Krishnamurthy S, Traore S, Cooney AL, et al. Functional correction of CFTR mutations in human airway epithelial cells using adenine base editors. *Nucleic Acids Res* 2021; 49: 10558–10572.
173. Schene IF, Joore IP, Baijens JHL, et al. Mutation-specific reporter for optimization and enrichment of prime editing. *Nat Commun* 2022; 13: 1028.
174. Doman JL, Sousa AA, Randolph PB, et al. Designing and executing prime editing experiments in mammalian cells. *Nat Protoc* 2022; 17: 2431–2468.
175. Pinto MC, Silva IAL, Figueira MF, et al. Pharmacological modulation of ion channels for the treatment of cystic fibrosis. *J Exp Pharmacol* 2021; 13: 693–723.