



HAL
open science

Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis

Kevin Southern, Carlo Castellani, Elise Lammertyn, Alan Smyth, Donald Vandevanter, Silke van Koningsbruggen-Rietschel, Jürg Barben, Amanda Bevan, Edwin Brokaar, Sarah Collins, et al.

► To cite this version:

Kevin Southern, Carlo Castellani, Elise Lammertyn, Alan Smyth, Donald Vandevanter, et al.. Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. *Journal of Cystic Fibrosis*, 2023, 22 (1), pp.17-30. 10.1016/j.jcf.2022.10.002 . hal-04029667

HAL Id: hal-04029667

<https://hal.science/hal-04029667>

Submitted on 14 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Standards of care for *CFTR* variant-specific therapy (including modulators) for people with cystic fibrosis



Kevin W. Southern a *, Carlo Castellani b , Elise Lammertyn c , Alan Smyth d , Donald VanDevanter e , Silke van Koningsbruggen-Rietschel g , Jürg Barben h , Amanda Bevani , Edwin Brokaar j , Sarah Collins k , Gary J. Connett l , Thomas W.V. Daniels m , Jane Davies n , Dimitri Declercq o , Silvia Gartnerp , Andrea Gramegnaq , Naomi Hamiltonr , Jenny Hauser s , Nataliya Kashirskaya t , Laurence Kessler u , Jacqueline Lowdon v , Halyna Makukh w , Clémence Martin x , Lisa Morrison y , Dilip Nazareth z , Jacqueliën Noordhoek aa , Ciaran O’Neill bb , Elizabeth Owen cc , Helen Oxley dd , Karen S. Raraigh ee , Caroline Raynal ff , Karen Robinson gg , Jobst Roehmel hh , Carsten Schwarz ii , Isabelle Sermet jj , Michal Shteinberg kk , Ian Sinha ll , Constance Takawira z , Peter van Mourik mm , Marieke Verkleij nn , Michael D. Waller oo , Alistair Duff v

a *Women and Children’s Health, University of Liverpool, Liverpool, United Kingdom*

b *Cystic Fibrosis Center, IRCCS Istituto Giannina Gaslini, Genoa, Italy*

c *Cystic Fibrosis Europe & the Belgian Cystic Fibrosis Association, Brussels, Belgium*

d *Lifespan & Population Health, School of Medicine, University of Nottingham and the NIHR Nottingham Biomedical Research Unit, Nottingham, United Kingdom*

e *Case Western Reserve University School of Medicine, Cleveland, United States*

g *CF Centre Cologne, Children’s Hospital, Faculty of Medicine and University of Cologne, Kerpener Str. 62, Cologne 50937, Germany*

h *Division of Paediatric Pulmonology & CF Centre, Children’s Hospital of Eastern Switzerland, Claudiusstr. 6, St. Gallen 9006, Switzerland*

i *University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom*

j *Haga Teaching Hospital, The Hague, The Netherlands*

k *Royal Brompton & Harefield Hospitals, London, United Kingdom*

l *National Institute for Health Research, Southampton Biomedical Research Centre, Southampton Children’s Hospital, Southampton, United Kingdom*

m *University Hospital Southampton, Tremona Road, Southampton, Hampshire, United Kingdom*

n *National Heart & Lung Institute, Imperial College London and Royal Brompton Hospital, Guy’s & St Thomas’ NHS Trust, London, United Kingdom*

o *Cystic Fibrosis Reference Centre, Ghent University Hospital, Ghent, Belgium and Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium*

p *Hospital Universitari Vall d’Hebron, Barcelona, Spain*

q *Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Respiratory Unit and Adult Cystic Fibrosis Center, Fondazione IRCCS CàGranda Ospedale Maggiore Policlinico, Milano, Italy*

r *Inverness, Scotland, United Kingdom*

s *Tasmanian Adult Cystic Fibrosis Unit, Royal Hobart Hospital, Hobart, Tasmania, Australia*

t *Research Centre for Medical Genetics, Moscow Regional Research and Clinical Institute, Moscow, Russia*

u *Department of Endocrinology, diabetes and nutrition, Alsace Adult CF centre, University Hospital Strasbourg, France*

v *Leeds Children's Hospital, Leeds, United Kingdom*

w *SI "Institute of Hereditary Pathology of Ukrainian NAMS", Lviv, Ukraine*

x *Respiratory Medicine and Cystic Fibrosis National Reference Center Cochin Hospital AP-HP, Université Paris Cité Institut Cochin Inserm U1016, Paris France*

y *West of Scotland Adult CF Unit, Queen Elizabeth University Hospital, Glasgow, Scotland, United Kingdom*

z *Liverpool Adult CF Unit, Liverpool Heart and Chest Hospital, United Kingdom*

aa *CF Europe, Brussels, Belgium*

bb *Centre for Public Health, Queens University Belfast, Belfast, United Kingdom*

cc *Dietetics, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, United Kingdom*

dd *Manchester Adult CF Centre, Manchester University NHS Foundation Trust, United Kingdom*

ee *McKusick-Nathans Department of Genetic Medicine, Johns Hopkins University, Baltimore, United States*

ff *Laboratory of molecular genetics, University Hospital of Montpellier and INSERM U1046 PHYMEDEXP, Montpellier, France*

gg *Johns Hopkins University, Baltimore, United States Abbreviations: CFTR, Cystic fibrosis transmembrane conductance regulator; VST, Variant-specific therapy.*

hh *Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité-Universitätsmedizin Berlin, Germany*

ii *Division of Cystic Fibrosis, CF Centre Westbrandenburg, Campus Potsdam, Potsdam, Germany*

jj *1 INSERM U1151, Institut Necker Enfants Malades, Paris, France, and Centre de Références Maladies Rares, Mucoviscidose et Maladies apparentées, Hôpital Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris (AP-HP)-Centre, Paris, France, and AP-HP, Hôpital Universitaire Necker-Enfants Malades, Service de Pneumologie Pédiatrique, Centre de Référence pour les Maladies Respiratoires Rares de l'Enfant, France and European Respiratory Network for Lung Disease, Paris, France*

kk *Pulmonology Institute and CF Center, Carmel Medical Center and the Technion- Israel Institute of Technology Faculty of Medicine, Haifa, Israel*

ll *Respiratory Department, Alder Hey Children's NHS Foundation Trust, Liverpool, UK and Women and Children's Health, University of Liverpool, Liverpool, United Kingdom*

mm *Department of Pulmonology, University Medical Center Utrecht, Utrecht, The Netherlands*

nn *Department of Pediatric Psychology, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands*

oo *King's College Hospital NHS Foundation Trust, London, UK and King's College London, London, United Kingdom*

☆ **Abbreviations not commonly used in the field of cystic fibrosis:**

CFRD = CF-related diabetes, CFSPID = CF Screening Positive, Inconclusive Diagnosis, CFTR-RD = CFTR related disorder, VST = variant-specific therapy, VUS = variant of uncertain significance

***Corresponding author.**

E-mail address:

kwsouth@liv.ac.uk (K.W. Southern) .

Keywords:

Cystic fibrosis CFTR Variant-specific therapy CFTR modulators Guidelines

a b s t r a c t

Cystic fibrosis (CF) has entered the era of variant-specific therapy, tailored to the genetic variants in the *Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)* gene. CFTR modulators, the first variant-specific therapy available, have transformed the management of CF.

The latest standards of care from the European CF Society (2018) did not include guidance on variant-specific therapy, as CFTR modulators were becoming established as a novel therapy. We have produced interim standards to guide healthcare professionals in the provision of variant-specific therapy for people with CF.

Here we provide evidence-based guidance covering the spectrum of care, established using evidence from systematic reviews and expert opinion. Statements were reviewed by key stakeholders using Delphi methodology, with agreement ($\geq 80\%$) achieved for all statements after one round of consultation. Issues around accessibility are discussed and there is clear consensus that all eligible people with CF should have access to variant-specific therapy.

1. Introduction

1.1. Background

The European Cystic Fibrosis Society (ECFS) defines standards of care for cystic fibrosis (CF). The last update [1], whilst comprehensive, did not include standards for the provision of variant-specific therapy (VST) that has emerged over the past decade and represents a significant treatment for many people with CF (pwCF). CF is a result of disease-causing variants affecting the *CF Trans-membrane Conductance Regulator (CFTR)* gene. VST for CF is a new class of drug, of which CFTR modulators are the first agents licensed to treat the basic defect. A VST is a systemic agent, generally taken orally, that corrects the molecular defect arising from the pathogenic *CFTR* gene variant. These agents are distinct from genetic therapies (DNA, RNA) or therapies that treat the clinical sequelae of CFTR disease (e.g., antibiotics, dornase alfa). VST results in greater CFTR quantity and/or function. Several different terms are used to describe VST, to some degree reflecting the mechanism of action (Table 1). In this paper we provide evidence-based guidance for pwCF and their healthcare workers regarding variant-specific therapy. We consider the different challenges of these therapies and provide statements to guide pwCF, CF teams and policymakers (Table 2).

1.2. Methods

This guidance was completed without support or funding from the pharmaceutical industry. Conflicts of interest of contributors are described completely and the process was undertaken with transparency (Supplementary Table 1).

A core author group (KS, CC, EL, AS, DV, SvK) was selected by the ECFS Standards of Care Committee, who defined the outline of the paper. Three to four contributing authors were selected by the ECFS Standards of Care Committee and invited to write each section. Their contributions were reviewed internally by the core author group and the ECFS Board. The process was undertaken in partnership with the CF Cochrane Review Group and systematic reviews were prioritized when available to inform the guidance (see www.cochrane.org/ for detailed methodology). Sections were reviewed internally by the core group and changes incorporated. The section authors also generated statements (Table 2) which were reviewed by a wider group of stakeholders using a modified Delphi methodology [2]. Contributors from a range of backgrounds were asked to review statements and state if they agreed or disagreed (yes/no/cannot answer). If they disagreed, they were asked to explain why and provide an alternative version. Consensus was achieved when 80% of contributors agreed with a statement (respondents who ticked “cannot answer” were not included in the calculation, as stakeholders commented a “cannot answer” response was not the same as a “disagree”). This threshold of 80% agreement has been used in previous Delphi exercises in CF [2]. All comments on statements were reviewed by the core panel, even if agreement was achieved.

In total, 32 statements were generated by the contributing author group and were reviewed by the Delphi consultation between January and February 2022 (65 respondents from 24 countries, see list in Supplementary Table 2). Respondents were physicians (46.2%), other healthcare professionals (26.2%), scientists (12.3%), pwCF and their families (10.8%) and patient organization representatives (4.6%). An acceptable (> 80%) agreement was achieved for all statements in the first round of consultation. Two statements were removed, despite achieving agreement. One statement (on the theme of adherence) was removed because it was repetitive, and one (on the theme of exercise) was removed due to comments and a lack of supporting evidence. After round 1 of the Delphi consultation, several statements were edited for clarity without changing the meaning (Supplementary Table 3).

Table 1

Common nomenclature for CFTR gene variant specific therapy. Several terms have been used to describe emerging therapies for pwCF. In this quickly evolving area, some terms and their application can be unclear and inconsistent.

Name	Abbreviation (if applicable)	Definition/Comments
Variant-specific therapy	VST	A systemic therapy, generally administered orally, that corrects the molecular defect associated with a disease-causing <i>CFTR</i> gene variant ¹ .
Premature termination codon therapy	PTC	A therapy (for example, ataluren) for a variant that results in little or no CFTR protein product, known as a class 1 variant ² (most commonly nonsense or stop codon variants).
Corrector		An agent (or combination of agents) that improves the processing of mutant CFTR to increase the quantity of CFTR protein at the cell membrane. This is generally associated with class 2 <i>CFTR</i> variants (most commonly F508del). Lumacaftor and tezacaftor are examples of correctors.
Potentiator		An agent (for example, ivacaftor) that improves CFTR protein function by addressing gating defects, often associated with class 3 and 4 <i>CFTR</i> variants (most commonly G551D).
CFTR modulator		An agent that increases the quantity and improves the function of CFTR protein. These agents include both correctors and potentiators, and combinations thereof. Sometimes referred to as "small molecule CFTR modulators".
Highly Effective Modulator Therapy	HEMT	A term to describe certain CFTR modulator therapies based on efficacy.
Triple therapy		A therapy that includes three separate agents (for example a combination of correctors and potentiator, as in elexacaftor-tezacaftor-ivacaftor) for pwCF. ³

¹ The term "variant" to describe a DNA change is now preferred, rather than the term 'mutation,' to avoid any negative connotation.

² Classification and characterization of *CFTR* gene variants is described in more detail in Section 2.

³ As new therapies emerge, larger combinations may become available with four or even five agents.

Table 2

Consensus statements.

1	For individuals with clinical features consistent with CF, disease-causing variants of the <i>CFTR</i> gene are those characterized as "CF-causing" or "varying clinical consequences" by an established and validated program (for example, CFTR2 or CFTR-France).
2	Individuals under consideration for CFTR modulator use should have molecular diagnostic testing of the <i>CFTR</i> gene that includes, at minimum, the most frequent variants known to be CF-causing in their population of origin. Further analysis may include exonic regions, intron-exon junctions, and presence of copy number variants, in the case of incomplete genotype after initial molecular testing.
3	<i>CFTR</i> gene variants should be considered of uncertain clinical significance in the absence of epidemiological or laboratory evidence. These variants should undergo further evaluation to determine their pathogenic or benign status and potential responsiveness to VST.
4	PwCF aged six years and older, with one or two F508del variants, should have daily treatment with triple modulator therapy (elexacaftor-tezacaftor-ivacaftor).
5	PwCF and at least one responsive non-F508del variant should be considered for mono (ivacaftor), dual (tezacaftor-ivacaftor) or triple CFTR modulator therapy (elexacaftor-tezacaftor-ivacaftor).
6	Children with CF with eligible <i>CFTR</i> gene variants should be offered treatment with ivacaftor from 4 months of age.
7	Children with CF who are homozygous for the F508del variant, aged 2–5 years, should be offered treatment with dual modulator therapy (Lumacaftor-ivacaftor).
8	Parent/careers of pre-school children with CF should be aware of the efficacy data and safety profile of VST before treatment start.
9	Before initiating treatment, pwCF and their families should have a detailed discussion with the CF team, outlining the impact of taking CFTR modulator therapy, backed up with written information.
10	Before starting CFTR modulator therapy, a detailed drug history should be obtained and cross checked with prescribing information about potential drug interactions.
11	Patients should be followed up at least every 3 months after initiating CFTR modulator therapy to monitor progress and screen for side effects.
12	CF teams should monitor adherence to CFTR modulator therapy, for example, by using pharmacy dispensing data.
13	Before commencing and once established on a VST, pwCF, in partnership with the physiotherapy team, may need to adapt and optimise their airway clearance technique and sinus treatments.
14	For pwCF starting a VST, the management of CFRD should be reviewed and adapted on an individual basis, considering clinical and nutritional status.
15	PwCF on VST should continue to receive regular monitoring of nutritional status and dietary intake, according to changing energy requirements.
16	Frequency of support of nutritional assessment should be individualized, depending on age, clinical status and CFTR modulator therapy.
17	CF teams should be familiar with the wide-ranging psychological impact of VST and prepare, advise and support pwCF and their caregivers as required, involving the CF psychologist when indicated.
18	Symptoms of depression and anxiety should be assessed pre-VST and no later than 3 months after starting.
19	Prior to initiating VST in women with CF, contraception and fertility should be reassessed, and appropriate counselling provided.
20	The decision to use VST during pregnancy should weigh the risk to maternal health in the event of withholding therapy and the lack of data regarding safety to the foetus.
21	Women treated with VST planning to breastfeed should be informed regarding lack of data on safety during breastfeeding.
22	PwCF and <i>CFTR</i> gene variant(s) with unclear response to modulator therapy should be offered referral to a centre with capacity for <i>ex vivo</i> testing of <i>CFTR</i> response, to potentially establish an individualized treatment plan, including with modulator therapies.
23	All pwCF with non-responsive <i>CFTR</i> gene variants should continue to receive high-quality CF-specialist multi-disciplinary care at a specialist or accredited CF centre.
24	It is important that pwCF and non-responsive <i>CFTR</i> gene variants are informed of clinical trials and supported to participate in trials.
25	For pwCF after solid organ transplant, VST should be considered for eligible patients after discussion of the potential risks and benefits between the patient, the CF team, and the transplant team.
26	For patients with a diagnosis of CFTR-related disorder, there is no evidence to support the use of VST outside of clinical trials.
27	For infants with an unclear diagnosis following newborn screening for CF (CRMS/CFSPID), the use of VST is not indicated.
28	For new high-cost CF therapies, a robust health technology assessment should evaluate the impact on pwCF and society.
29	Evidence used to inform reimbursement decisions using public money should be transparent and available to the public.
30	The CF community should advocate globally for equitable access to new therapies with proven efficacy for all pwCF.

2. Disease causing variants of the *CFTR* gene and standards for *CFTR* gene testing

Karen Raraigh, Nataliya Kashirskaya, Caroline Raynal, Halyna Makukh

2.1. Definitions and nomenclature

It is important that the names given to gene abnormalities are precise and accurate. The Human Genome Variation Society (HGVS) sets standards to describe genetic changes in all genes [3]. The term “mutation” is no longer recommended, as it assumes a disease state and has a somewhat negative connotation. Instead, the term “variant” is preferred. Variants are classified as disease-causing (pathogenic), non-disease-causing (benign), or of uncertain significance [3, 4]. Variants should be described at the DNA level using HGVS nomenclature (e.g., c.1652G > A); although protein (e.g., p.Gly551Asp) and legacy (e.g., G551D) names are also widely recognized. In this paper, we describe variants by their HGVS name initially, then use the legacy name.

CFTR disease-causing variants that lead to a CF phenotype [1] impair quantity and/or function of *CFTR*, when found in *trans* with a known CF-causing variant, according to a validated *CFTR* gene database (such as CFTR2 [5] and CFTR-France [6]) (Statements 1 and 2, Table 2). Depending on the related phenotype observed [7], these variants are classified as CF-causing variants that consistently cause CF [6, 8], or variants of varying clinical consequences (VVCC) that result in either 1) no disease, 2) CF in some individuals, or 3) a *CFTR*-related disorder (*CFTR*-RD) [6, 8, 9].

Variants with a lack of consistent data to determine if they are pathogenic or benign are classified as variants of uncertain significance (VUS) (Statement 3, Table 2).

2.2. Standards for *CFTR* gene testing

A DNA panel of common CF-causing variants are typically assessed for first level testing. Ideally, the variants included should reflect the person’s ancestry [10]. More extensive second level testing includes analysis of *CFTR* coding sequences, intronic flanking regions, and deep-intronic regions where disease-causing variants have been described [11–15].

The diagnosis of CF is confirmed by a positive newborn screening result (i.e., elevated immunoreactive trypsinogen [IRT]) or when a person has clinical features of CF plus sweat chloride > 59 mmol/L and/or two disease-causing variants identified in *trans* (i.e., on opposite alleles) [1]. However, in the context of CF symptoms, laboratory features, or abnormal *CFTR* bioassays, the absence of two disease-causing variants does not rule out CF. Further sequencing of the entire *CFTR* gene [16, 17] or transcript analysis on nasal epithelial cells [18] should be performed to search for additional disease-causing variants. It is also recommended to search for complex alleles (i.e., two or more *CFTR* variants associated in *cis* on the same allele) in those whose genotype does not correlate with expected phenotype and in people bearing variants known to be involved in complex alleles that may impact on the effectiveness of VST [17, 19, 20].

2.3. Molecular consequences and functional classes of variants

Variants have different molecular consequences, depending on type and location in the *CFTR* gene [21], and have traditionally been classified by functional impact from Class I to VI [22, 23]. Though generally useful, this system does not capture nuances that may impact response to VST. Recent proposals for more accurate classification group variants by the effect on *CFTR* quantity or function (Fig. 1) [24], or divide Class I variants into those amenable to read-through therapies (i.e., nonsense) and those unlikely to be corrected by small molecules (no mRNA production; i.e., frameshifts, large deletions/duplications) [25].

Pathogenicity of rare variants and VUS may be investigated by groups with well-established protocols by evaluating *in vivo* CFTR function using intestinal current measurement [26] or nasal potential difference [27], *ex vivo* organoid forskolin-induced swelling (FIS) [28], or variant testing in a heterologous cell system *in vitro* [8]. Notably, the potential impact of any variant on *CFTR* splicing—which may compromise CFTR modulator efficacy—must be considered prior to functional evaluation to avoid misinterpretation of results [29, 30]. It is possible that developments in the field may identify agents that address splicing defects.

A list of *CFTR* variants and eligibility for VST is included in the appendix (Supplementary Table 4). It should be acknowledged that some of the licensed variants included in this list are characterized as non-CF causing (i.e., causing a CFTR-RD or non-disease causing) [5, 6] and others are known or suspected to affect splicing or have characteristics that may decrease the expected clinical benefit of VST [29, 30]. A clear diagnosis of CF is a pre-requisite to prescription of these agents. This issue is further discussed in Section 12.

3. Who is eligible for variant-specific therapy?

3.1. Kevin W Southern, Karen Robinson, Alan Smyth and Ian Sinha

Emerging CFTR modulator therapies for pwCF have been licensed for specific variants of the *CFTR* gene, based on data from clinical trials and *in vitro* testing. This variant-focused approach to licensing may oversimplify a complex situation since many CF-causing variants are not easily characterized and their response to VST may be unpredictable. This has led to the concept of “theratyping” to chart individual clinical response to VST, regardless of *CFTR* variant. This approach offers therapeutic options to pwCF with rare variants [31] (see Section 11). The evidence for VST in pre-school children is reviewed in Section 4.

The first VST licensed was the “potentiator” ivacaftor in 2012, initially for pwCF with at least one c.1652G > A variant (legacy name: G551D). The evidence base for the use of this therapy in pwCF older than 6 years of age is strong, with a good safety profile [32]. Ivacaftor is now licensed for infants with CF aged 4 months and older (see detail in Section 4). G551D is a class III or “gating” variant, with CFTR protein correctly located in the cell membrane but non-functioning. Ivacaftor addresses the gating defect, enabling some salt transport. Ivacaftor has subsequently been approved for other less-common variants with a similar molecular pathobiological characterization based on *in vitro* laboratory evidence or *in vivo* clinical trial data (Supplementary Table 4).

The most common CF-causing variant is c.1521_1523delCTT (legacy name: F508del) [33]. The first VST to be licensed for this variant was a combination of lumacaftor (initially termed a corrector) and ivacaftor. There is good evidence that lumacaftor-ivacaftor treatment results in improved respiratory function in pwCF with two F508del variants, albeit with a lower magnitude of improvement than was observed with ivacaftor treatment amongst pwCF and the G551D variant [33]. Lumacaftor-ivacaftor has a reasonable safety profile but is associated with transient respiratory symptoms and a small but clinically significant rise in blood pressure in adults. Another dual therapy, tezacaftor-ivacaftor, has similar efficacy but a better safety profile [33]. Both dual therapies were licensed for pwCF with two F508del variants. Tezacaftor-ivacaftor has since been approved for certain combinations of F508del and another variant (Supplementary Table 4).

The addition of elexacaftor to tezacaftor-ivacaftor resulted in further improvement in clinical outcomes for pwCF with two F508del variants already established on dual therapy, as well

as pwCF with one F508del variant who were modulator naïve [34–36]. The impact on modulator-naïve pwCF was particularly notable, with rapid improvements in all outcomes measured, including a disease-specific quality of life measure. Elexacaftor-tezacaftor-ivacaftor, often called triple therapy, is associated with a reasonable safety profile, and no rise in blood pressure was reported in the initial trial [33]. Subsequent studies of elexacaftor-tezacaftor-ivacaftor in 6–11-year-olds confirmed the safety profile reported in adults and provided evidence of efficacy, leading to an extension of the licence to this age group [37].

A frequently asked question is whether it is appropriate to transfer patients established on effective monotherapy or dual therapy onto triple therapy? A study of adult pwCF with F508del and another variant responsive to either ivacaftor alone or tezacaftor-ivacaftor demonstrated significant further improvement in outcomes when they commenced triple therapy [36, 38]. This supports the rationale that all pwCF, aged 6 years and older, who have one or two F508del variants should have access to daily elexacaftor-tezacaftor-ivacaftor therapy (Statement 4, Table 2).

PwCF carrying non-F508del *CFTR* gene variants should be considered for modulator therapy if *in vitro* or clinical trial data support potential responsiveness to any of the therapeutic options: mono (ivacaftor), dual (tezacaftor-ivacaftor or lumacaftor-ivacaftor) or triple modulator therapy (elexacaftor-tezacaftor-ivacaftor) (Statement 5, Table 2) (Supplementary Table 4). Several *CFTR* gene variants are non-responsive to current modulator therapy (see Section 11) and there is no currently approved effective VST for pwCF have premature truncation codon variants (e.g. non-sense) or other large deletions or duplications [39].

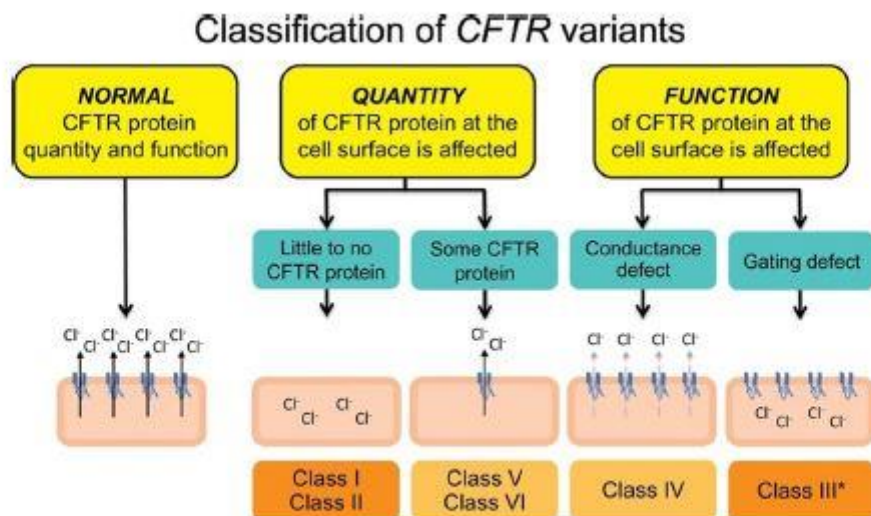


Fig. 1. A functional classification of *CFTR* gene variants (Adapted from Foil et al. [24]).

4. Modulator therapy for pre-school children with CF

4.1. Isabelle Sermet, Jane C Davies and Silvia Gartner

CFTR modulator therapies, in particular ivacaftor and elexacaftor-tezacaftor-ivacaftor, have significantly impacted the course of CF in older children and will likely improve their survival. Most infants and young children with CF still await trials to confirm eligibility for these treatments. In Europe, ivacaftor is licensed for children with CF aged 4 months and older, with at least one of 10 *CFTR* variants (Statement 6, Table 2) (Supplementary Table 4). Lumacaftor-ivacaftor is licensed for 2–5-year-olds who are homozygous for F508del (Supplementary Table 4).

Ivacaftor led to significant improvements in sweat chloride, growth and in some cases pancreatic function biomarkers (increased faecal elastase-1, decreased serum trypsinogen) in clinical trials in pre-school children [40–42]. These improvements appeared within weeks and were maintained during the open-label extension

for > 2 years [43]. Measurement of respiratory function based on multiple breath washout also demonstrated significant improvement in lung clearance index (LCI) [44]. This is encouraging because elevated LCI, which measures the inhomogeneity of lung ventilation, is an indicator of progression of CF airway disease later in life [45, 46]. An ongoing open-label trial is currently assessing the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in infants with CF aged < 4 months (clinicaltrials.gov NCT02725567).

Lumacaftor-ivacaftor also led to better growth and reduced sweat chloride in children aged 2–5 years (Statement 7, Table 2). Treatment effects were smaller than those seen with ivacaftor but were maintained long term [47, 48]. There were no significant improvements in LCI [47].

Both therapies are formulated as granules for younger children, are well tolerated and have pharmacokinetic profiles similar to those in older children. Moderate alanine transaminase elevations were reported in some infants, which did not increase with longer treatment duration [40-43, 47-49]. This supports more frequent tests of liver function early in treatment. Preclinical studies showed cataracts in juvenile rats, and cases of non-congenital lens opacities have been reported in paediatric patients on ivacaftor. Although other risk factors were sometimes present, possible causation cannot be excluded. Therefore, baseline and follow-up ophthalmological examinations are recommended in children with CF treated with therapies containing ivacaftor (Statement 8, Table 2).

Elexacaftor-tezacaftor-ivacaftor is in phase 3 trials for children with CF aged 2–5 years, with results expected at the end of 2022 (clinicaltrials.gov NCT04537793). In summary, data from younger children have largely mirrored those from older populations, although the more limited baseline disease means that measuring efficacy is more challenging. CF organ disease progression in infants is largely irreversible which highlights the need to begin VST as early as possible. It is unknown whether treatment of infants could prevent various aspects of CF, such as structural lung disease, chronic infection, hepatobiliary disease, pancreatic/intestinal dysfunction and glucose intolerance [50]. This has only been shown in the animal model to date [51]. The goal should be to determine the safety and effectiveness of early life initiation in order to provide VST following neonatal screening, to potentially slow down disease evolution considerably.

5. Monitoring the introduction and maintenance of variant-specific therapy (CFTR modulators)

5.1. Gary J Connett, Amanda Bevan, Edwin Brokaar

Before starting CFTR modulator therapy, families and individuals with CF should discuss with the CF team the reasons for which treatment is being considered. There should also be discussion, backed up with written information, about when and how to take the medication (Statement 9, Table 2). There should be opportunities to address any emerging concerns or uncertainties about medication use as part of routine and annual assessments. A drug history, cross-checked with prescribing information about potential drug interactions, must be obtained before starting treatment (Statement 10, Table 2) and should also enquire about the use of complementary and alternative medicines. St. John's wort (*Hypericum perforatum*) for example, is an herbal remedy used for anxiety and depression and a strong CYP3A inducer that might decrease modulator efficacy. Drugs that inhibit CYP3A-mediated drug catabolism, including some used regularly in CF care such as anti-fungal azoles and the macrolide antibiotics erythromycin and clarithromycin, can result in significant increases in modulator exposure and modulator dose should be adjusted accordingly. Dose adjustments should also be considered for patients with severe liver disease according to the Child-Pugh Score for assessing the correct dose reduction.

Blood pressure measurements and liver function tests, in addition to standard care, should be obtained at baseline, then every 3 months for the first year of treatment and at least annually thereafter (Statement 11, Table 2). More frequent liver function monitoring should be considered in those with significant underlying liver disease.

Transaminitis (raised liver enzymes) is reported in up to 25% of patients established on CFTR modulator therapy. Elevations are usually transient and mild, but in 2% to 5% of cases are above 3 times the upper limit of normal (ULN) [52]. Current prescribing guidance suggests that with bilirubin levels $> 2 \times$ ULN with transaminases $> 3 \times$ ULN, or if transaminase levels $> 5 \times$ ULN, dosing should be interrupted until levels return to normal. The risks of restarting treatment on long-term liver function should be assessed on a case-by-case basis and the decision to restart taken working in partnership with the patient and their family, taking into account objective measures of effectiveness. Acute cholecystitis is a rare possible side effect of treatment [53], probably because of the effects of increased bile flow on stones and biliary sludge.

Respiratory side effects such as chest tightness and dyspnoea have been reported, especially after introduction of Lumacaftor- ivacaftor treatment and in adults with more severe lung disease [54]. These adverse effects are less problematic with other modulator combinations, but it is advisable to initiate treatment after optimising other aspects of care including routine respiratory treatments.

Increased sputum production can occur shortly after initiating treatment and patients should be warned about this phenomenon. This transient phenomenon is sometimes referred to as ‘the purge’ and is discussed in the airway clearance section (Section 6).

Other side effects include gastrointestinal symptoms, headache, and rash, which are often transient or resolve after dose reduction or interruption. Rash might occur more commonly in those taking hormonal contraceptives. Muscle pain (myositis) can also occur and be associated with raised creatinine kinase (CK) levels. Monitoring should be considered if the patient is taking other medicines, such as statins, which can also increase CK levels [55].

Rarer side effects reported include menstrual irregularities, testicular pain, and sinus pain. Such events are usually transient, but unsettling for pwCF.

Whilst quality of life measures suggest significant improvements in wellbeing for most patients receiving modulator therapy, there have also been reports of mental health, neurocognitive and neuropsychiatric events. Careful consideration is required to assess whether these events are pharmacologically derived, or due to changes in life circumstances as a result of modulator use (described in Section 9).

Monitoring response to VST by standard clinical measures can inform dosing regimens. Measuring LCI might be informative in pwCF with normal spirometry (i.e., a forced expiratory volume in one second [FEV₁] above 90% of predicted) [56]. Repeat sweat testing provides evidence of a treatment effect on CFTR activity but does not predict clinical response [57].

The continued effectiveness of modulators depends on maintaining high levels of adherence to these therapies. CF services should routinely access pharmacy dispensing data as part of adherence monitoring (Statement 12, Table 2). The benefit of withdrawing concomitant treatments, such as mucoactive agents is being evaluated in a number of trials including CF STORM (EudraCT- 2020-005864-77) and CF SIMPLIFY (Clinicaltrials.gov identifier NCT04378153). Monitoring and supporting adherence to such treatments, when clinically indicated, remains important.

As with all new therapies, the safe use of modulator treatment and recognition of rare side effects depends upon responsible clinicians providing regular follow-up and reporting all potentially related adverse reactions to their relevant medicine regulatory authorities.

6. Managing airway clearance during introduction of variant-specific therapy

6.1. Lisa Morrison, Jenny Hauser, Naomi Hamilton

VST has been shown to increase airway surface liquid, ciliary beat frequency, mucociliary transport, and reduce mucus viscosity [58]. It is important that the healthcare team reflects carefully on airway clearance techniques to determine their role, effectiveness, and optimal prescription for pwCF established on VST (Statement 13, Table 2).

Some individuals experience a period of “sputum purging” following VST commencement [59]. We recommend a review of optimal airway clearance techniques, prior to commencing VST. Outpatient review or an inpatient stay may be considered by the healthcare team and the pwCF, before and during this purge phase, with appropriate symptom treatment. Transient adverse effects have been reported on commencement of VST in some pwCF, including chest tightness, inability to tolerate increase in airway secretions, an initial decline in FEV₁, haemoptysis or decreased oxygen levels [54]. This may reflect significant disease, and increased physiotherapy support will be required for these individuals.

Comments posted by pwCF on social media suggest that a purge can be immediate and profound, although on occasion less apparent (Fig. 2). PwCF established on dual CFTR modulator therapy who then switch to triple therapy may also experience a purge and should have adequate physiotherapy support as needed.

There is no evidence to support discontinuation of physiotherapy management for pwCF on established VST. However, pwCF regularly experience reduced airway secretions and improved respiratory symptoms. An individualized approach to rationalizing therapies could therefore ease the relative burden of care whilst upholding optimal health outcomes. This should be done in partnership with the pwCF, their physiotherapist and health-care team. Maintaining routine airway clearance techniques will ensure that pwCF continue to achieve optimal benefit from VST. It is important that pwCF are proactive in their airway clearance management and remain receptive to their individual symptoms. In some cases, it may be appropriate to consider alternative approaches to maintaining respiratory health, including exercise as an adjunct to airway clearance particularly in those individuals with stable respiratory health. Whilst exercise is important for all pwCF, there is no evidence to support it replacing formal airway clearance techniques. Clinical trials are needed to answer this frequently asked question and modulator therapy has thrown this into sharper perspective.

In addition to the impact on the lungs, pwCF on VST have reported improvements in chronic rhinosinusitis symptoms. These include improvements in CT scan appearances (relating to sinus architecture) and patient-reported outcomes, specifically rhinorrhoea, postnasal drip, thick nasal discharge, and fatigue [60 , 61].

7. Managing glucose intolerance following the introduction of variant-specific therapy

7.1. Sarah Collins, Dilip Nazareth, Laurence Kessler

7.1.1. Effect of CFTR modulators on CFRD

Cystic fibrosis-related diabetes (CFRD) is a common complication, present in over 50% of adult pwCF [62]. CFRD is associated with poorer clinical outcomes, including accelerated pulmonary function decline and excess morbidity [63]. The aetiology is likely multi-factorial secondary to pancreatic damage, resulting in alpha and beta cell loss and dysfunction, manifested as a decreased first- phase insulin secretion.

CFTR modulator therapy has been shown to impact glucose handling. Ivacaftor has a significant beneficial effect on glycaemia [64–67] and the combinations of ivacaftor and Lumacaftor or tezacaftor have also shown a small benefit in glucose handling [68–71]. Elexacaftor-tezacaftor-ivacaftor has been shown to improve continuous glucose monitoring (CGM) markers of glycaemia in pwCF with and without known CFRD [72]. Hence, it is important to monitor glucose handling in pwCF established on VST.

7.1.2. Screening for CFRD

The significance of early glucose abnormalities in pwCF remains controversial [73], however, weight and lung function decline have been shown to precede a diagnosis of CFRD [74]. A prospective 4-year study reported the degree of glucose intolerance to be a strong determinant of future lung function decline in pwCF [75], justifying early screening.

Guidelines propose definitions of glucose tolerance abnormalities in pwCF based on 2-hour blood glucose levels following oral glucose tolerance testing (OGTT). This should be performed annually in adults. From the age of 10 years onwards, children with CF should be screened annually for glucose tolerance abnormalities [76]. Several studies report the usefulness of determining 1-hour (T 1) blood glucose levels following OGTT, enabling earlier hyper- glycaemia to be detected [77]. T 1 hyperglycaemia is correlated with hyperglycaemia detected by continuous glucose monitoring (CGM) [78].

There is increasing evidence of the use of CGM in CF and several studies report links between CGM abnormalities and clinical deterioration [79, 80].

In the era of modulator therapy, it remains to be determined whether an OGTT is the most appropriate test. Attention should be paid to tests assessing dynamic glucose handling over time.

7.1.3. Management of CFRD

While changes in glucose handling have been observed with CFTR modulator therapy, the impact upon CFRD management is not fully established. Glucose levels should be closely monitored, and treatment modified, as required. Similarly, nutritional status should be closely monitored [81], with appropriate dietary modifications recommended where applicable (Statement 14, Table 2). Improvements in survival will result in people living with CFRD for longer. Therefore, close ongoing monitoring of diabetes- related complications is important, especially for microvascular disease.

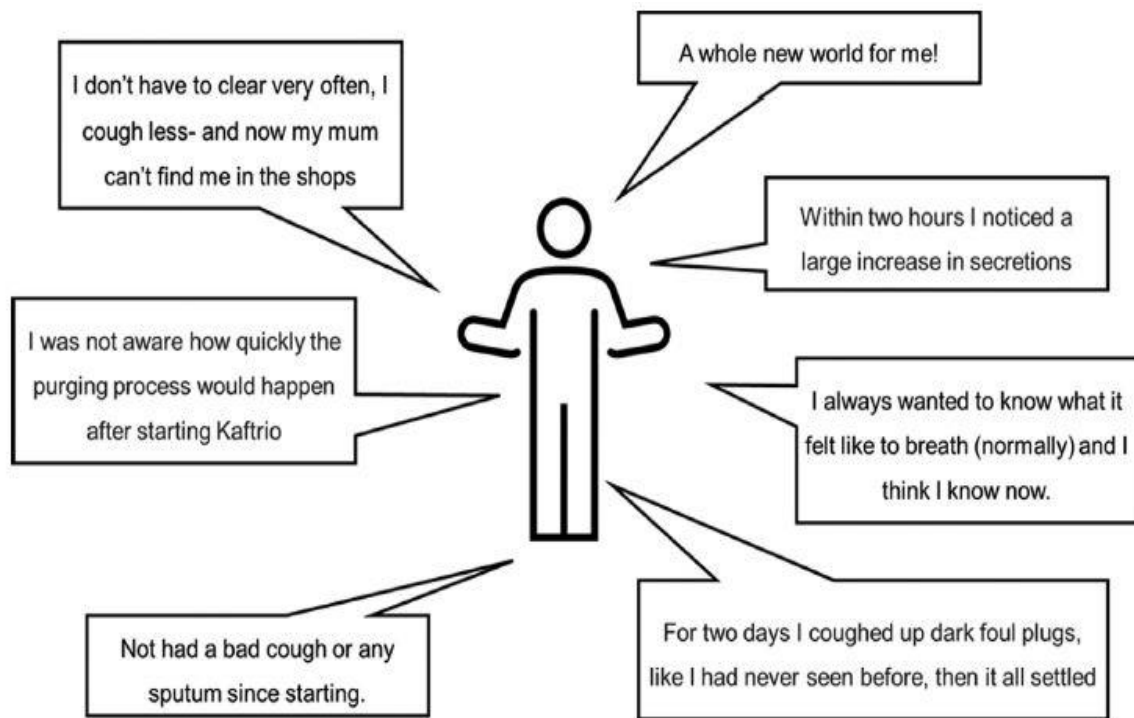


Fig. 2. Comments from pwCF upon starting VST.

8. Monitoring and supporting nutritional issues during variant-specific therapy

8.1. Jacqueline Lowdon, Elizabeth Owen, Dimitri DeClerq

8.1.1. Nutritional status and monitoring

In addition to improving respiratory outcomes, clinical trials have demonstrated significant nutritional impact, although precise mechanisms remain unclear. More significant effects on anthropometric parameters have been seen for pwCF on ivacaftor or elexacaftor-tezacaftor-ivacaftor than for those on dual CFTR modulator therapy [82]. Improvements in weight, height and BMI were reported as secondary or exploratory outcomes in the randomized controlled trials (RCTs) underpinning approval of CFTR modulators. PwCF with one or two G551D variants in phase 3 trials of ivacaftor had sustained increases in weight and BMI [32]. PwCF with one or two F508del variants aged ≥ 12 years on elexacaftor-tezacaftor-ivacaftor had significant increases in weight and BMI [82]. Real-world studies of pwCF treated with ivacaftor also found consistent increases in weight and BMI [83]. Data on linear growth and body composition is limited for elexacaftor-tezacaftor-ivacaftor. Longitudinal data is needed to establish whether the effects of elexacaftor-tezacaftor-ivacaftor on anthropometric status are sustained beyond 48 weeks, and to assess the effects on body composition.

8.1.2. Dietary and nutritional issues

Changes reported in nutritional status may be multifactorial. In pwCF with G551D taking ivacaftor, there have been reports of decreased energy expenditure, increased small intestine pH and decreased gut inflammation [40, 84, 85]. Data from clinical trials and real-world studies of pwCF are needed to determine the long-term effects and the physiological mechanisms with different modulators. As evidence is lacking regarding macronutrient requirements, it is recommended that current practice continues to assess energy requirements individually, depending on age and clinical status (Statements 15–16, Table 2) [82, 86]. If there are concerning trends in weight/BMI/body composition, the focus should shift from a diet of quantity to a diet of quality.

Working closely with their dietitian and CF team supports pwCF to maintain a healthy weight/BMI/body composition and a high quality, balanced diet. Emerging data suggest vitamin levels can be affected by CFTR modulator therapy and longer-term data are required to quantify the impact on need for vitamin supplementation [86, 87]. Similarly the need for salt supplementation on VST should be monitored closely, as per the usual practice of the CF service.

Early initiation of ivacaftor may mitigate existing pancreatic damage and prevent or delay further damage in young children with CF [40, 41, 43]. Further research characterizing the impact of VST on children is paramount, especially the role of faecal elastase measurement for monitoring pancreatic function. At present, there is no evidence to warrant reducing or stopping pancreatic enzyme replacement therapy (PERT) upon commencement of VST although this is an important question for pwCF.

9. Identifying and managing psychological issues during the introduction of variant-specific therapy

9.1. Helen Oxley, Alistair Duff, Marieke Verkleij

VST can have positive psychological benefits as well as physical ones [88]. However, there can also be adverse indirect psychological impact for pwCF and caregivers, who report adjustment issues. Feeding and eating are known issues for pwCF and managing changes in weight and eating behaviors associated with VST will remain challenging. The wider CF team needs to be aware of, and sympathetic to, patients having complex feelings about the future and the past that can be difficult to verbalise (Statement 17, Table 2) [89]. CF psychologists should guide the team on the amount of support required and be involved in delivering highly specialized help for adjustment problems, behavior change and psychological well-being. All team members must be patient and give patients every opportunity to air their feelings, without judgement. These reactions have mostly been reported in adults, however children and young people with CF are now transitioning onto VST and need further careful psychological consideration as do all those who are as yet ineligible for, or unable to start VST.

Worsening of depression and anxiety symptoms including suicidal ideation and suicide attempts requiring hospitalization have been reported by some pwCF who have commenced VST [90–92]. Signals for mental health and neurocognitive adverse events have been reported with the four currently available CFTR modulator therapies [54], as well as reports of “mental foginess” [93]. PwCF are known to have 2–3 times the risk of developing elevated symptoms of depression and anxiety than the general population [94]. Depression and anxiety are in turn associated with negative health outcomes, worse treatment adherence and greater healthcare utilization [94–100]. Therefore, pwCF and parent-caregivers should be screened in accordance with established CF mental health guide- lines and treatment recommendations [98], prior to, and during, VST but no later than 3 months after commencement (Statement 18, Table 2).

Early studies reported sub-optimal adherence to VST, but more recent data shows 89% and 83% adherence at 6 and 12 months respectively [101]. This is thought to result from high costs, good communication, knowledge and monitoring, and optimistic perspectives from the media and patient associations. When first prescribed VST, patients may consider that they will adhere to such effective therapy, but good intentions do not always lead to lasting behavior change. Evidence-based strategies for improving and maintaining optimal adherence remain relevant. Understanding barriers to, and facilitators of, adherence remains important as the landscape shifts. The CF team can improve their ability to support pwCF through this journey by practising patient-centred communication skills such as active listening, expressing empathy, and recognising unique challenges. For pwCF who have not yet commenced VST, it remains essential to focus on optimal adherence to traditional therapies to remain as well as possible. Often obscured are feelings of pressure and responsibility and some patients fear judgement over their struggles to adhere whilst others find it difficult to acknowledge the consequences of their sub-optimal adherence as they pursue a “normal” daily life.

10. Fertility and breast feeding

10.1. *Andrea Gramegna, Connie Takawira, Michal Shteinberg*

Women with CF have increased rates of subfertility due to multifactorial causes, including endocrine as well as barrier abnormalities [102, 103].

A rise in pregnancy rates has been reported following ivacaftor therapy [104]. More recently, unintentional pregnancies have been recorded within weeks of commencing elexacaftor-tezacaftor-ivacaftor [104–107]. Women with CF report under-utilizing contraception, and unintentional pregnancies are a recognized issue [108, 109].

Prior to commencing VST, women should be counselled about the risk of unintentional pregnancy (Statement 19, Table 2). Contraceptive use should be reviewed and, if necessary, modified to address potential drug interactions.

In men with CF, complete bilateral absence of vas deferens (CBAVD) causes infertility [110]. Animal model work suggests that exposure to VST *in utero* may correct this abnormality. This possibility should be considered in male CF infants, born to CF mothers on VST, as transplacental drug transfer is possible [51].

10.2. *The use of VST during pregnancy*

Data regarding safety of VST during pregnancy is limited. Withholding VST during or before pregnancy is an option but has been associated with clinical deterioration in pregnant and non-pregnant women [111–113]. Available animal and human data have not identified teratogenicity, but the components of VST have all been demonstrated to cross the placenta in animals [114]. This transplacental transfer had minor effects on pregnancy outcomes at normal human doses and has not been associated with toxicity to foetal chromosomes or organogenesis [112]. Two case series report data on pregnancy and VST. Nash et al. describe 64 pregnancies exposed to ivacaftor, Lumacaftor-ivacaftor or tezacaftor-ivacaftor and Taylor-Cousar et al. describe 45 pregnancies exposed to elexacaftor-tezacaftor-ivacaftor [112, 113]. Data from these case series suggest miscarriage rates similar to those of the general population and no related complications in infants following *in utero* exposure [112, 113]. The decision to continue or withhold VST during pregnancy should be made between the CF team and the woman with CF, considering the risks for the mother and the baby (Statement 20, Table 2). Babies with CF exposed to modulator therapy *in utero* may have a reduced serum IRT and this may lead to a false negative newborn screening result.

10.3. *Breast feeding*

Data on the safety of VST in breastfeeding remain lacking. The product characteristics of elexacaftor-tezacaftor-ivacaftor report all three components to be present in breastmilk in animal studies with no adverse effects reported at equivalent human doses. One case report detected measurable levels of Lumacaftor and ivacaftor in the breastmilk of a breastfeeding mother with CF on this dual therapy [115]. Transient elevations in liver enzymes and bilirubin in the non-CF infant were reported [115]. In a further survey, no adverse effects were reported in 26 infants exposed to elexacaftor-tezacaftor-ivacaftor during breastfeeding, although eye examination was only undertaken in two of these infants [113].

The decision as to whether to breastfeed while on VST should be taken after discussion between the CF team and the mother, with review of all available information (Statement 21, Table 2). For breastfeeding mothers on VST, monitoring of the infant (eye examination and liver function) should be considered.

11. Standards for patients with non-responsive *CFTR* gene variants

11.1. Peter van Mourik, Michael D. Waller, Jobst Roehmel

Approximately 10–20% of pwCF worldwide carry CF genotypes that render them ineligible for CFTR modulator therapies, including those with nonsense (premature stop) variants where clinical benefit from novel read-through agents has not been demonstrated [116, 117]. Ancestral and geographical variations in the prevalence of non-responsive *CFTR* variants lead to varying proportions of pwCF with genotypes eligible for modulator therapies. This can lead to inequitable treatment opportunities [118, 119]. Marketing authorization often restricts the use of currently licensed modulators for unapproved *CFTR* variants, with clinical trial and efficacy data lacking for other, mostly rare, *CFTR* variants. *Ex vivo* CFTR function measurements can potentially determine the function of rare *CFTR* variants and assess possible responsiveness to approved modulator therapies [120]. However, this approach is not routinely available in clinical practice.

Recent studies report that improvements in *ex vivo* biomarkers of CFTR function such as intestinal organoids and nasal epithelial cells correlate with improvements in outcomes such as increased FEV₁ and decreased sweat chloride concentration [120–126]. When *ex vivo* studies suggest that a *CFTR* variant may have some response to a specific therapy, then a clinical n-of-1 trial of that therapy is warranted [127] with clear endpoints of improvement in respiratory function and quality of life measures (Statement 22, Table 2).

In the absence of available VST, it is essential that pwCF continue to receive high quality care delivered by a specialist CF multi-disciplinary team at a specialist or accredited CF centre (Statement 23, Table 2) [128]. Maintaining high quality care is imperative for all pwCF in the era of VST.

Experimental therapeutics in development and in clinical trials offer new possibilities to correct the underlying CF defect or disease sequelae. This may improve treatment options for all pwCF, especially those who have had limited benefit from commercially available CFTR modulators. Healthcare providers should remain up to date regarding current and future clinical studies. PwCF should be informed about eligible research studies and be actively encouraged to participate (<https://apps.cff.org/trials/pipeline>) (Statement 24, Table 2).

12. The use of variant-specific therapies outside licence indications (for example, post-transplant or for patients with a CFTR-RD, CFSPID designation etc.)

12.1. Thomas Daniels, Carsten Schwarz, Carlo Castellani

12.1.1. PwCF and solid organ transplantation

VST has been shown to significantly improve several aspects of CF, however clinical trials of VST did not include pwCF who had been recipients of solid organ transplants (SOT). In Europe for example, elexacaftor-tezacaftor-ivacaftor is not recommended for use in transplanted pwCF, whereas the FDA label does not advise against use in the transplanted population.

In liver-transplanted pwCF, healthcare teams must consider the risk for liver toxicity and significant interactions with medications commonly used after liver transplant. VST side effects (such as raised transaminases) and interactions should be monitored. Decisions about starting VST should be made on a case-by-case basis and after careful consideration by the CF team and the transplant team, in partnership with the patient (Statement 25, Table 2). In most cases, the significant benefits in terms of pulmonary function and exacerbation rate will be considered to outweigh the risk of possible side effects. A recent report from the US

patient registry reported indications and outcomes for 94 pwCF who had started elexacaftor-tezacaftor-ivacaftor after lung transplantation (median duration, 4.6 years) [129]. A significant number (42%) stopped elexacaftor-tezacaftor-ivacaftor due to side effects (median, 56 days after starting).

In lung-transplanted pwCF, it may be considered that the transplanted lung has no CFTR dysfunction (although a donor may be a CF carrier), therefore any abnormality of the transplanted lung should not ordinarily be considered an indication for VST. It could be considered for use in exceptional circumstances when there is evidence of significant extrapulmonary CF disease despite maximal medical therapy. One such extrapulmonary manifestation is chronic rhinosinusitis (CRS) which causes very unpleasant symptoms and reduces quality of life. Elexacaftor-tezacaftor-ivacaftor has been shown to improve CRS symptoms (as measured using the Sino-Nasal Outcome Tool and the Respiratory Domain of the CFQ-R) [60]. CRS has been associated with increased risk for Chronic Lung Allograft Dysfunction (CLAD). It remains controversial whether aggressive treatment of CRS after lung transplant reduces the risk of developing CLAD [130, 131]. However, in selected post-lung transplant patients where CRS persists despite maximal medical therapy, a trial of VST should be considered and monitored accordingly. Another extrapulmonary manifestation of CF which may warrant consideration of VST is malnutrition. In lung-transplanted pwCF, BMI < 20 kg/m² and > 28 kg/m² has been associated with worse survival in a registry study, with the greatest effects seen at the extremes of BMI [132]. VST has a positive effect on nutritional status for pwCF without SOT [34]. Consideration of the use of VST to improve nutrition in malnourished lung transplant recipients when other standard methods of nutritional support have failed is recommended, with the associated caveats and monitoring listed above.

VST is associated with improvements in glycaemic control [72] and better glycaemic control is generally associated with better health outcomes [133]. Preliminary data from a US registry study suggests elexacaftor-tezacaftor-ivacaftor in post-lung transplant recipients also improves glycaemic control in this group [129].

Intestinal manifestations for extrapulmonary CF are often under-appreciated but have a major impact on quality of life [134]. These problems frequently persist after lung transplantation [135]. The effects of VST on gastrointestinal manifestations of CF in pre-transplant recipients is less well established, with effects failing to reach statistical significance in clinical trials [136]. However, given the marked effect on QoL of gastrointestinal symptoms and their persistence after lung transplantation, it would be reasonable to consider a trial of VST in those for whom all other treatment options have failed.

If a trial of elexacaftor-tezacaftor-ivacaftor is considered, it is worth noting the potential interaction between E-T-I and calcineurin inhibitors (especially tacrolimus) reported by Ramos and colleagues [129]. In a subset of 55 subjects not takingazole antifungal medication, 30 required a dose change of tacrolimus (7% required an increased dose, 47% a decreased dose, and 38% required no dose change). This experience reinforces the importance of careful monitoring of tacrolimus levels.

12.1.2. CFTR related disorders (CFTR-RD) and CF screen positive, inconclusive diagnosis (CFSPID)

CFTR-RD are clinical conditions associated with CFTR dysfunction that do not fulfil the diagnostic criteria for CF [9]. Their phenotype is usually mono-organ, and their genotype includes at least one variant with a level of residual CFTR function greater than typical CF {Sermet, unpublished #1465}. Hypothetically, CFTR modulators might be beneficial, depending on the CFTR gene variants associated with CFTR-RD. However, no recommendation can be made until 1) clear indications on CFTR-RD standards of diagnosis and care are made available to the medical community, 2) *in vivo* and *ex vivo* evidence of CFTR rescue in CFTR-RD variants are documented, and 3) VST clinical trials are undertaken in these populations and improved outcomes demonstrated (Statement 26, Table 2).

Infants with an unclear diagnosis following a positive CF newborn screening result are given the designation “CF Screening Positive, Inconclusive Diagnosis”(CFSPID) [137]. These infants are healthy and most remain healthy with no sequelae of the neonatal testing. Some children may receive a diagnosis of CF as they grow or

develop clinical manifestations consistent with CFTR-RD. Children with a CFSPID designation who convert to a CF diagnosis should be considered for VST, if they have an eligible genotype (Statement 27, Table 2).

13. Assessment of cost-effectiveness and the ethics of access

13.1. Ciaran O'Neill, Jürg Barben, Clemence Martin

Various governments use cost-effectiveness analyses to assess the relative value for money of novel therapies compared to other uses of healthcare resources. Industry undertakes such analyses –often alongside clinical trials–which they present as part of a business case to evaluation boards (such as NICE in the UK), who advise government. This often forms part of the negotiation around the price at which a drug may be adopted for reimbursement in a publicly funded system (Statement 28, Table 2).

Cost-effectiveness analysis is intended to provide a rigorous and transparent process by which evidence can be generated and informed decisions made. However, increasingly, where the cost-effectiveness ratio breaches accepted thresholds for approval, decisions around the price at which drugs are approved for reimbursement are made behind closed doors. This enables access at a price below that listed without compromising the manufacturer's ability to negotiate with other potential purchasers. From the perspective of an individual country this model may allow them to access novel therapies at below list price. From the perspective of industry, it may allow them to act more effectively as a discriminating monopoly to maximize their profits and invest in further research and development. From the perspective of the user of these therapies it may afford access to life changing therapies that would not otherwise be available.

There are, however, risks and ethical considerations associated with this approach. Within one country, reimbursing therapy that breaches accepted norms for cost-effectiveness effectively gives preferential access to healthcare resources to one patient group over others in society. This may be facilitated by advocacy groups who can readily present patients who would benefit from the new therapy, while policy makers struggle to present to the public those patients who lose because their care can no longer be purchased. A further issue is that not all profits are reinvested in R&D and that the exercise of monopoly power and secrecy around pricing may serve to deter competition in this market.

Pricing of new medicines usually begins in the US as this is the largest market. After FDA approval in terms of safety and efficacy, the company sets a price they consider appropriate. Competition is then limited by patent law which can be extended in the case of rare and orphan diseases. The US price sets a benchmark that may influence price negotiations in other jurisdictions. Patents are neither bad nor good. They can benefit or harm a society and its economy. But they only make sense if the overall benefit for the general public outweighs the harm. This is the only way to politically justify states granting a monopoly to individuals or companies, who can turn it into a business free of competition (Statement 29, Table 2).

The considerable benefits of VST have been somewhat diminished by global inequities in access. Cost is undoubtedly a factor, and the field should reflect on how future developments can benefit all eligible pwCF, regardless of their circumstance or location (Statement 30, Table 2) [138 , 139].

14. Conclusion

VST represents a paradigm shift for the management of pwCF with eligible *CFTR* gene variants. *CFTR* modulators are the first agents to clearly show that correcting the underlying molecular defect is possible, and that this results in profound and significant improvement in clinical outcomes. As with most novel therapies, introduction of these agents has been complex, and this remains an emerging area. This paper provides clear evidence-based and pragmatic guidance for pwCF and their CF teams.

Author credit

The core committee (KWS, CC, AD, AS, SvKR, DvD, EL) established the framework for the exercise and identified experts to produce each section (highlighted in the paper). All members of the faculty contributed to the delphi process and had oversight of the final paper. Fiona Dunlevy provided overall administrative support and medical writing skills to produce a consistent document. Conflict of interest statements are fully recorded in supplemental materials.

Acknowledgments

The authors thank Fiona Dunlevy, who provided editorial support and coordinated the Delphi consultation. We also thank the ECFS board who supported the project. We thank the team at the CF Cochrane Review Group for support throughout this project. We also thank the ECFS board and CF Europe for their contribution.

References

- [1] Castellani C, Duff AJA, Bell SC, Heijerman HGM, Munck A, Ratjen F, et al. ECFS best practice guidelines: the 2018 revision. *J Cyst Fibros* 2018;17:153– 78. doi: [10.1016/j.jcf.2018.02.006](https://doi.org/10.1016/j.jcf.2018.02.006) .
- [2] Munck A, Mayell SJ, Winters V, Shawcross A, Derichs N, Parad R, et al. Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID): a new designation and management recommendations for infants with an inconclusive diagnosis following newborn screening. *J Cyst Fibros* 2015;14:706–13. doi: [10.1016/j.jcf.2015.01.001](https://doi.org/10.1016/j.jcf.2015.01.001) .
- [3] den Dunnen JT, Dalgleish R, Maglott DR, Hart RK, Greenblatt MS, McGowan-Jordan J, et al. HGVS recommendations for the description of sequence variants: 2016 update. *Hum Mutat* 2016;37:564–9. doi: [10.1002/humu.22981](https://doi.org/10.1002/humu.22981) .
- [4] Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405– 24. doi: [10.1038/gim.2015.30](https://doi.org/10.1038/gim.2015.30) .
- [5] US CF Foundation J.H.U., The Hospital for Sick Children,. The Clinical and Functional TRanslation of CFTR (CFTR2). 2011. <https://cftr2.org/Date> accessed: 19/8/2022
- [6] Claustres M, Theze C, des Georges M, Baux D, Girodon E, Bienvenu T, et al. CFTR-France, a national relational patient database for sharing genetic and phenotypic data associated with rare CFTR variants. *Hum Mutat* 2017;38:1297–315. doi: [10.1002/humu.23276](https://doi.org/10.1002/humu.23276) .
- [7] Castellani C, Cuppens H, Macek M Jr, Cassiman JJ, Kerem E, Durie P, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. *J Cyst Fibros* 2008;7:179–96. doi: [10.1016/j.jcf.2008.03.009](https://doi.org/10.1016/j.jcf.2008.03.009) .

- [8] Sosnay PR, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. *Nat Genet* 2013;45:1160–7. doi: [10.1038/ng.2745](https://doi.org/10.1038/ng.2745) .
- [9] Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, et al. Recommendations for the classification of diseases as CFTR-related disorders. *J Cyst Fibros* 2011;10(Suppl 2):S86–102. doi: [10.1016/S1569-1993\(11\)60014-3](https://doi.org/10.1016/S1569-1993(11)60014-3) .
- [10] Dequeker E, Stuhmann M, Morris MA, Casals T, Castellani C, Claustres M, et al. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders—updated European recommendations. *Eur J Hum Genet* 2009;17:51–65. doi: [10.1038/ejhg.2008.136](https://doi.org/10.1038/ejhg.2008.136) .
- [11] Highsmith WE, Burch LH, Zhou Z, Olsen JC, Boat TE, Spock A, et al. A novel mutation in the cystic fibrosis gene in patients with pulmonary disease but normal sweat chloride concentrations. *N Engl J Med* 1994;331:974–80. doi: [10.1056/NEJM199410133311503](https://doi.org/10.1056/NEJM199410133311503) .
- [12] Chillon M, Dork T, Casals T, Gimenez J, Fonknechten N, Will K, et al. A novel donor splice site in intron 11 of the CFTR gene, created by mutation 1811 + 1.6kbA→G, produces a new exon: high frequency in Spanish cystic fibrosis chromosomes and association with severe phenotype. *Am J Hum Genet* 1995;56:623–9 .
- [13] Faa V, Incani F, Meloni A, Corda D, Masala M, Baffico AM, et al. Characterization of a disease-associated mutation affecting a putative splicing regulatory element in intron 6b of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. *J Biol Chem* 2009;284:30024–31. doi: [10.1074/jbc.M109.032623](https://doi.org/10.1074/jbc.M109.032623) .
- [14] Costantino L, Claut L, Paracchini V, Coviello DA, Colombo C, Porcaro L, et al. A novel donor splice site characterized by CFTR mRNA analysis induces a new pseudo-exon in CF patients. *J Cyst Fibros* 2010;9:411–18. doi: [10.1016/j.jcf.2010.08.009](https://doi.org/10.1016/j.jcf.2010.08.009) .
- [15] Bergougnoux A, Deletang K, Pommier A, Varilh J, Houriez F, Altieri JP, et al. Functional characterization and phenotypic spectrum of three recurrent disease-causing deep intronic variants of the CFTR gene. *J Cyst Fibros* 2019;18:468–75. doi: [10.1016/j.jcf.2018.10.012](https://doi.org/10.1016/j.jcf.2018.10.012) .
- [16] Bonini J, Varilh J, Raynal C, Theze C, Beyne E, Audrezet MP, et al. Small-scale high-throughput sequencing-based identification of new therapeutic tools in cystic fibrosis. *Genet Med* 2015;17:796–806. doi: [10.1038/gim.2014.194](https://doi.org/10.1038/gim.2014.194) .
- [17] Raraigh KS, Aksit MA, Hetrick K, Pace RG, Ling H, O’Neal W, et al. Complete CFTR gene sequencing in 5,058 individuals with cystic fibrosis informs variant-specific treatment. *J Cyst Fibros* 2021;21:463–70. doi: [10.1016/j.jcf.2021.10.011](https://doi.org/10.1016/j.jcf.2021.10.011) .
- [18] Costa C, Pruliere-Escabasse V, de Becdelievre A, Gameiro C, Golmard L, Guittard C, et al. A recurrent deep-intronic splicing CF mutation emphasizes the importance of mRNA studies in clinical practice. *J Cyst Fibros* 2011;10:479–82. doi: [10.1016/j.jcf.2011.06.011](https://doi.org/10.1016/j.jcf.2011.06.011) .

- [19] Baatallah N, Bitam S, Martin N, Serval N, Costes B, Mekki C, et al. Cis variants identified in F508del complex alleles modulate CFTR channel rescue by small molecules. *Hum Mutat* 2018;39:506–14. doi: [10.1002/humu.23389](https://doi.org/10.1002/humu.23389) .
- [20] Sondo E, Cresta F, Pastorino C, Tomati V, Capurro V, Pesce E, et al. The L467FF508del complex allele hampers pharmacological rescue of mutant CFTR by elxacaftor/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. doi: [10.3390/ijms23063175](https://doi.org/10.3390/ijms23063175) .
- [21] Bareil C, Bergougnoux A. CFTR gene variants, epidemiology and molecular pathology. *Arch Pediatr* 2020;27(Suppl 1):eS8–eS12. doi: [10.1016/S0929-693X\(20\)30044-0](https://doi.org/10.1016/S0929-693X(20)30044-0) .
- [22] Veit G, Avramescu RG, Chiang AN, Houck SA, Cai Z, Peters KW, et al. From CFTR biology toward combinatorial pharmacotherapy: expanded classification of cystic fibrosis mutations. *Mol Biol Cell* 2016;27:424–33. doi: [10.1091/mbc.E14-04-0935](https://doi.org/10.1091/mbc.E14-04-0935) .
- [23] Welsh MJ, Smith AE. Molecular mechanisms of CFTR chloride channel dysfunction in cystic fibrosis. *Cell* 1993;73:1251–4. doi: [10.1016/0092-8674\(93\)90353-r](https://doi.org/10.1016/0092-8674(93)90353-r) .
- [24] Foil KE, Powers A, Raraigh KS, Wallis K, Southern KW, Salinas D. The increasing challenge of genetic counseling for cystic fibrosis. *J Cyst Fibros* 2019;18:167–74. doi: [10.1016/j.jcf.2018.11.014](https://doi.org/10.1016/j.jcf.2018.11.014) .
- [25] De Boeck K., Amaral M.D. Progress in therapies for cystic fibrosis. *The Lancet Respiratory medicine*. 2016;4:662–74. DOI:10.1016/S2213-2600(16)00023-0
- [26] Derichs N, Sanz J, Von Kanel T, Stolpe C, Zapf A, Tummler B, et al. Intestinal current measurement for diagnostic classification of patients with questionable cystic fibrosis: validation and reference data. *Thorax* 2010;65:594–9. doi: [10.1136/thx.2009.125088](https://doi.org/10.1136/thx.2009.125088) .
- [27] Rowe SM, Clancy JP, Wilschanski M. Nasal potential difference measurements to assess CFTR ion channel activity. *Methods Mol Biol* 2011;741:69–86. doi: [10.1007/978-1-61779-117-8_6](https://doi.org/10.1007/978-1-61779-117-8_6) .
- [28] Boj SF, Vonk AM, Statia M, Su J, Vries RR, Beekman JM, et al. Forskolin-induced swelling in intestinal organoids: an in vitro assay for assessing drug response in cystic fibrosis patients. *J Vis Exp* 2017;120:55159. doi: [10.3791/55159](https://doi.org/10.3791/55159) .
- [29] Joynt AT, Evans TA, Pellicore MJ, Davis-Marcisak EF, Aksit MA, Eastman AC, et al. Evaluation of both exonic and intronic variants for effects on RNA splicing allows for accurate assessment of the effectiveness of precision therapies. *PLoS Genet* 2020;16:e1009100. doi: [10.1371/journal.pgen.1009100](https://doi.org/10.1371/journal.pgen.1009100) .
- [30] Raraigh KS, Lewis MH, Collaco JM, Corey M, Penland CM, Stephenson AL, et al. Caution advised in the use of CFTR modulator treatment for individuals harboring specific CFTR variants. *J Cyst Fibros* 2022;21:856–60. doi: [10.1016/j.jcf.2022.04.019](https://doi.org/10.1016/j.jcf.2022.04.019) .

- [31] Crawford KJ, Downey DG. Theratyping in cystic fibrosis. *Curr Opin Pulm Med* 2018;24:612–17. doi: [10.1097/MCP.0000000000000521](https://doi.org/10.1097/MCP.0000000000000521) .
- [32] Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev* 2019;1:CD009841. doi: [10.1002/14651858.CD009841.pub3](https://doi.org/10.1002/14651858.CD009841.pub3) .
- [33] Southern KW, Murphy J, Sinha IP, Nevitt SJ. Corrector therapies (with or without potentiators) for people with cystic fibrosis with class II CFTR gene variants (most commonly F508del). *Cochrane Database Syst Rev* 2020;12:CD010966. doi: [10.1002/14651858.CD010966.pub3](https://doi.org/10.1002/14651858.CD010966.pub3) .
- [34] Middleton PG, Mall MA, Drevinek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del Allele. *N Engl J Med* 2019;381:1809–19. doi: [10.1056/NEJMoa1908639](https://doi.org/10.1056/NEJMoa1908639) .
- [35] Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, 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, randomized, phase 3 trial. *Lancet* 2019;394:1940–8. doi: [10.1016/S0140-6736\(19\)32597-8](https://doi.org/10.1016/S0140-6736(19)32597-8) .
- [36] Nichols DP, Paynter AC, Heltshe SL, Donaldson SH, Frederick CA, Freedman SD, et al. Clinical effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: a clinical trial. *Am J Respir Crit Care Med* 2022;205:529–39. doi: [10.1164/rccm.202108-1986OC](https://doi.org/10.1164/rccm.202108-1986OC) .
- [37] Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, et al. A phase 3 open-label study of elexacaftor/tezacaftor/ivacaftor in children 6 through 11 years of age with cystic fibrosis and at least one F508del Allele. *Am J Respir Crit Care Med* 2021;203:1522–32. doi: [10.1164/rccm.202102-0509OC](https://doi.org/10.1164/rccm.202102-0509OC) .
- [38] Barry PJ, Mall MA, Alvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple therapy for cystic fibrosis phe508del-gating and -residual function genotypes. *N Engl J Med* 2021;385:815–25. doi: [10.1056/NEJMoa2100665](https://doi.org/10.1056/NEJMoa2100665) .
- [39] Aslam A, Jahnke N, Remington T, Southern KW. Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis. *Paediatr Respir Rev* 2017;24:32–4. doi: [10.1016/j.prrv.2017.04.001](https://doi.org/10.1016/j.prrv.2017.04.001) .
- [40] Davies JC, Cunningham S, Harris WT, Lapey A, Regelman WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2–5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med* 2016;4:107–15. doi: [10.1016/s2213-2600\(15\)00545-7](https://doi.org/10.1016/s2213-2600(15)00545-7) .
- [41] Rosenfeld M, Wainwright CE, Higgins M, Wang LT, McKee C, Campbell D, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to < 24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med* 2018;6:545–53. doi: [10.1016/S2213-2600\(18\)30202-9](https://doi.org/10.1016/S2213-2600(18)30202-9) .

- [42] Davies JC, Wainwright CE, Sawicki GS, Higgins MN, Campbell D, Harris C, 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;203:585–93. doi: [10.1164/rccm.202008-3177OC](https://doi.org/10.1164/rccm.202008-3177OC) .
- [43] Rosenfeld M, Cunningham S, Harris WT, Lapey A, Regelman WE, Sawicki GS, et al. An open-label extension study of ivacaftor in children with CF and a CFTR gating mutation initiating treatment at age 2-5years (KLIMB). *J Cyst Fibros* 2019;18:838–43. doi: [10.1016/j.jcf.2019.03.009](https://doi.org/10.1016/j.jcf.2019.03.009) .
- [44] Ratjen F, Klingel M, Black P, Powers MR, Grasemann H, Solomon M, et al. Changes in lung clearance index in preschool-aged patients with cystic fibrosis treated with ivacaftor (goal): a clinical trial. *Am J Respir Crit Care Med* 2018;198:526–8. doi: [10.1164/rccm.201802-0243LE](https://doi.org/10.1164/rccm.201802-0243LE) .
- [45] Davies G, Stanojevic S, Raywood E, Duncan JA, Stocks J, Lum S, et al. An observational study of the lung clearance index throughout childhood in cystic fibrosis: early years matter. *Eur Respir J* 2020;56:20 0 0 0 06. doi: [10.1183/13993003.00006-2020](https://doi.org/10.1183/13993003.00006-2020) .
- [46] Hardaker KM, Panda H, Hulme K, Wong A, Coward E, Cooper P, et al. Abnormal preschool Lung Clearance Index (LCI) reflects clinical status and predicts lower spirometry later in childhood in cystic fibrosis. *J Cyst Fibros* 2019;18:721–7. doi: [10.1016/j.jcf.2019.02.007](https://doi.org/10.1016/j.jcf.2019.02.007) .
- [47] McNamara JJ, McColley SA, Marigowda G, Liu F, Tian S, Owen CA, et al. Safety, pharmacokinetics, and pharmacodynamics of Lumacaftor and ivacaftor combination therapy in children aged 2–5 years with cystic fibrosis homozygous for F508del-CFTR: an open-label phase 3 study. *Lancet Respir Med* 2019;7:325–35. doi: [10.1016/s2213-2600\(18\)30460-0](https://doi.org/10.1016/s2213-2600(18)30460-0) .
- [48] Hoppe J.E., Chilvers M., Ratjen F., McNamara J.J., Owen C.A., Tian S., et al. Long-term safety of Lumacaftor-ivacaftor in children aged 2-5 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a multicentre, phase 3, open-label, extension study. *Lancet Respir Med*. 2021;9:977–88. DOI:[10.1016/S2213-2600\(21\)00069-2](https://doi.org/10.1016/S2213-2600(21)00069-2)
- [49] European Medicines Agency. Orkambi Summary of Product Characteristics. 2015. https://www.ema.europa.eu/en/documents/product-information/orkambi-epar-product-information_en.pdf Date accessed: 29/3/22
- [50] Ferkol TW. Prevention of cystic fibrosis: the beginning of the end? *Sci Transl Med* 2019;11:2361. doi: [10.1126/scitranslmed.aax2361](https://doi.org/10.1126/scitranslmed.aax2361) .
- [51] Sun X, Yi Y, Yan Z, Rosen BH, Liang B, Winter MC, et al. In utero and postnatal VX-770 administration rescues multiorgan disease in a ferret model of cystic fibrosis. *Sci Transl Med* 2019;11:eaau7531. doi: [10.1126/scitranslmed.aau7531](https://doi.org/10.1126/scitranslmed.aau7531) .
- [52] NIH Cystic fibrosis agents. Livertox: clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012 .

- [53] Safirstein J, Grant JJ, Clausen E, Savant D, Dezube R, Hong G. Biliary disease and cholecystectomy after initiation of elexacaftor/ivacaftor/tezacaftor in adults with cystic fibrosis. *J Cyst Fibros* 2021;20:506–10. doi: [10.1016/j.jcf.2020.07.014](https://doi.org/10.1016/j.jcf.2020.07.014) .
- [54] Dagenais RVE, Su VCH, Quon BS. Real-world safety of CFTR modulators in the treatment of cystic fibrosis: a systematic review. *J Clin Med* 2020;10:23. doi: [10.3390/jcm10010023](https://doi.org/10.3390/jcm10010023) .
- [55] Valiyil R, Christopher-Stine L. Drug-related myopathies of which the clinician should be aware. *Curr Rheumatol Rep* 2010;12:213–20. doi: [10.1007/s11926-010-0104-3](https://doi.org/10.1007/s11926-010-0104-3) .
- [56] Davies JC, Sermet-Gaudelus I, Naehrlich L, Harris RS, Campbell D, Ahluwalia N, et al. A phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor in combination with ivacaftor in participants 6 through 11 years of age with cystic fibrosis homozygous for F508del or heterozygous for the F508del-CFTR mutation and a residual function mutation. *J Cyst Fibros* 2021;20:68–77. doi: [10.1016/j.jcf.2020.07.023](https://doi.org/10.1016/j.jcf.2020.07.023) .
- [57] Sermet-Gaudelus I, Nguyen-Khoa T, Hatton A, Hayes K, Pranke I. Sweat chloride testing and Nasal Potential Difference (NPD) are primary outcome parameters in treatment with Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators. *J Pers Med* 2021;11:729. doi: [10.3390/jpm11080729](https://doi.org/10.3390/jpm11080729) .
- [58] Birket SE, Chu KK, Houser GH, Liu L, Fernandez CM, Solomon GM, et al. Combination therapy with cystic fibrosis transmembrane conductance regulator modulators augment the airway functional microanatomy. *Am J Physiol Lung Cell Mol Physiol* 2016;310:L928–39. doi: [10.1152/ajplung.00395.2015](https://doi.org/10.1152/ajplung.00395.2015) .
- [59] Papworth Hospital NHS Foundation Trust. Kaftrio: turning around the lives of patients with cystic fibrosis. 2020. <https://royalpapworth.nhs.uk/our-hospital/latest-news/kaftrio-patients-cystic-fibrosis-Alex-StobbsRoyal> Date accessed: 29/3/22
- [60] DiMango E, Overdevest J, Keating C, Francis SF, Dansky D, Gudis D. Effect of highly effective modulator treatment on sinonasal symptoms in cystic fibrosis. *J Cyst Fibros* 2021;20:460–3. doi: [10.1016/j.jcf.2020.07.002](https://doi.org/10.1016/j.jcf.2020.07.002) .
- [61] Sergeev V, Chou FY, Lam GY, Hamilton CM, Wilcox PG, Quon BS. The extrapulmonary effects of cystic fibrosis transmembrane conductance regulator modulators in cystic fibrosis. *Ann Am Thorac Soc* 2020;17:147–54. doi: [10.1513/AnnalsATS.201909-671CME](https://doi.org/10.1513/AnnalsATS.201909-671CME) .
- [62] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009;32:1626–31. doi: [10.2337/dc09-0586](https://doi.org/10.2337/dc09-0586) .
- [63] Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective. *Lancet Respir Med* 2020;8:65–124. doi: [10.1016/S2213-2600\(19\)30337-6](https://doi.org/10.1016/S2213-2600(19)30337-6) .

- [64] Christian F, Thierman A, Shirley E, Allen K, Cross C, Jones K. Sustained glycemic control with ivacaftor in cystic fibrosis-related diabetes. *J Investig Med High Impact Case Rep* 2019;7:2324709619842898. doi: [10.1177/2324709619842898](https://doi.org/10.1177/2324709619842898) .
- [65] Tsabari R, Elyashar HI, Cymberknowh MC, Breuer O, Armoni S, Livnat G, et al. CFTR potentiator therapy ameliorates impaired insulin secretion in CF patients with a gating mutation. *J Cyst Fibros* 2016;15:e25–7. doi: [10.1016/j.jcf.2015.10.012](https://doi.org/10.1016/j.jcf.2015.10.012) .
- [66] Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, et al. Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. *J Cyst Fibros* 2020;19:68–79. doi: [10.1016/j.jcf.2019.05.015](https://doi.org/10.1016/j.jcf.2019.05.015) .
- [67] Hayes D Jr, McCoy KS, Sheikh SI. Resolution of cystic fibrosis-related diabetes with ivacaftor therapy. *Am J Respir Crit Care Med* 2014;190:590–1. doi: [10.1164/rccm.201405-0882LE](https://doi.org/10.1164/rccm.201405-0882LE) .
- [68] Thomassen JC, Mueller MI, Alejandre Alcazar MA, Rietschel E, van Koningsbruggen-Rietschel S. Effect of Lumacaftor/ivacaftor on glucose metabolism and insulin secretion in Phe508del homozygous cystic fibrosis patients. *J Cyst Fibros* 2018;17:271–5. doi: [10.1016/j.jcf.2017.11.016](https://doi.org/10.1016/j.jcf.2017.11.016) .
- [69] Flume PA, Liou TG, Borowitz DS, Li H, Yen K, Ordonez CL, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. *Chest* 2012;142:718–24. doi: [10.1378/chest.11-2672](https://doi.org/10.1378/chest.11-2672) .
- [70] Wainwright CE, Elborn JS, Ramsey BW. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015;373:1783–4. doi: [10.1056/NEJMc1510466](https://doi.org/10.1056/NEJMc1510466) .
- [71] Li A, Vigers T, Pyle L, Zemanick E, Nadeau K, Sagel SD, et al. Continuous glucose monitoring in youth with cystic fibrosis treated with Lumacaftorivacaftor. *J Cyst Fibros* 2019;18:144–9. doi: [10.1016/j.jcf.2018.07.010](https://doi.org/10.1016/j.jcf.2018.07.010) .
- [72] Scully KJ, Marchetti P, Sawicki GS, Uluer A, Cernadas M, Cagnina RE, et al. The effect of elexacaftor/tezacaftor/ivacaftor (ETI) on glycemia in adults with cystic fibrosis. *J Cyst Fibros* 2022;21:258–63. doi: [10.1016/j.jcf.2021.09.001](https://doi.org/10.1016/j.jcf.2021.09.001) .
- [73] Chan CL. Continuous glucose monitoring in cystic fibrosis-Benefits, limitations, and opportunities. *J Cyst Fibros* 2021;20:725–6. doi: [10.1016/j.jcf.2021.07.016](https://doi.org/10.1016/j.jcf.2021.07.016) .
- [74] Lanng S, Thorsteinsson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Pediatr* 1992;151:684–7. doi: [10.1007/BF01957574](https://doi.org/10.1007/BF01957574) .
- [75] Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. *Am J Respir Crit Care Med* 2000;162:891–5. doi: [10.1164/ajrccm.162.3.9904075](https://doi.org/10.1164/ajrccm.162.3.9904075) .

- [76] Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes* 2018;19(Suppl 27):64–74. doi: [10.1111/pedi.12732](https://doi.org/10.1111/pedi.12732) .
- [77] Brodsky J, Dougherty S, Makani R, Rubenstein RC, Kelly A. Elevation of 1-hour plasma glucose during oral glucose tolerance testing is associated with worse pulmonary function in cystic fibrosis. *Diabetes Care* 2011;34:292–5. doi: [10.2337/dc10-1604](https://doi.org/10.2337/dc10-1604) .
- [78] Elidottir H, Diemer S, Eklund E, Hansen CR. Abnormal glucose tolerance and lung function in children with cystic fibrosis. Comparing oral glucose tolerance test and continuous glucose monitoring. *J Cyst Fibros* 2021;20:779–84. doi: [10.1016/j.jcf.2021.01.002](https://doi.org/10.1016/j.jcf.2021.01.002) .
- [79] Chan CL, Ode KL, Granados A, Moheet A, Moran A, Hameed S. Continuous glucose monitoring in cystic fibrosis—a practical guide. *J Cyst Fibros* 2019;18(Suppl 2):S25–31. doi: [10.1016/j.jcf.2019.08.025](https://doi.org/10.1016/j.jcf.2019.08.025) .
- [80] Chan CL, Vigers T, Pyle L, Zeitler PS, Sagel SD, Nadeau KJ. Continuous glucose monitoring abnormalities in cystic fibrosis youth correlate with pulmonary function decline. *J Cyst Fibros* 2018;17:783–90. doi: [10.1016/j.jcf.2018.03.008](https://doi.org/10.1016/j.jcf.2018.03.008) .
- [81] Petersen MC, Begnel L, Wallendorf M, Litvin M. Effect of elxacaftortezacaftor-ivacaftor on body weight and metabolic parameters in adults with cystic fibrosis. *J Cyst Fibros* 2022;21:265–71. doi: [10.1016/j.jcf.2021.11.012](https://doi.org/10.1016/j.jcf.2021.11.012) .
- [82] Bailey J, Rozga M, McDonald CM, Bowser EK, Farnham K, Mangus M, et al. Effect of CFTR modulators on anthropometric parameters in individuals with cystic fibrosis: an evidence analysis center systematic review. *J Acad Nutr Diet* 2021;121:1364–78 e2. doi: [10.1016/j.jand.2020.03.014](https://doi.org/10.1016/j.jand.2020.03.014) .
- [83] Duckers J, Leshner B, Thorat T, Lucas E, McGarry LJ, Chandarana K, et al. Realworld outcomes of ivacaftor treatment in people with cystic fibrosis: a systematic review. *J Clin Med* 2021;10. doi: [10.3390/jcm10071527](https://doi.org/10.3390/jcm10071527) .
- [84] Stallings VA, Sainath N, Oberle M, Bertolaso C, Schall JJ. Energy balance and mechanisms of weight gain with ivacaftor treatment of cystic fibrosis gating mutations. *J Pediatr* 2018;201:229–37 e4. doi: [10.1016/j.jpeds.2018.05.018](https://doi.org/10.1016/j.jpeds.2018.05.018) .
- [85] Gelfond D, Heltshe S, Ma C, Rowe SM, Frederick C, Uluer A, et al. Impact of CFTR modulation on intestinal pH, motility, and clinical outcomes in patients with cystic fibrosis and the G551D mutation. *Clin Transl Gastroenterol* 2017;8:e81. doi: [10.1038/ctg.2017.10](https://doi.org/10.1038/ctg.2017.10) .
- [86] Burgel PR, Munck A, Durieu I, Chiron R, Mely L, Prevotat A, et al. Real-life safety and effectiveness of Lumacaftor-ivacaftor in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2020;201:188–97. doi: [10.1164/rccm.201906-1227OC](https://doi.org/10.1164/rccm.201906-1227OC) .
- [87] Sommerburg O, Hammerling S, Schneider SP, Okun J, Langhans CD, Leutz-Schmidt P, et al. CFTR modulator therapy with Lumacaftor/ivacaftor alters plasma concentrations of lipid-soluble vitamins A and E in patients with cystic fibrosis. *Antioxidants (Basel, Switzerland)* 2021;10. doi: [10.3390/antiox10030483](https://doi.org/10.3390/antiox10030483) .

- [88] Martin C, Burnet E, Ronayette-Preira A, de Carli P, Martin J, Delmas L, et al. Patient perspectives following initiation of elexacaftor-tezacaftor-ivacaftor in people with cystic fibrosis and advanced lung disease. *Respir Med Res* 2021;80:100829. doi: [10.1016/j.resmer.2021.100829](https://doi.org/10.1016/j.resmer.2021.100829) .
- [89] Cystic Fibrosis Trust. Emotional and social impact of Kaftrio. 2020. <https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/Emotional%20and%20social%20impact%20of%20Kaftrio%20Nov%202020.pdf> Date accessed: 28 February 2022
- [90] Talwalkar JS, Koff JL, Lee HB, Britto CJ, Mulenos AM, Georgiopoulos AM. Cystic fibrosis transmembrane regulator modulators: implications for the management of depression and anxiety in cystic fibrosis. *Psychosomatics* 2017;58:343–54. doi: [10.1016/j.psymb.2017.04.001](https://doi.org/10.1016/j.psymb.2017.04.001) .
- [91] Tindell W, Su A, Oros SM, Rayapati AO, Rakesh G. Trikafta and psychopathology in cystic fibrosis: a case report. *Psychosomatics* 2020;61:735–8. doi: [10.1016/j.psymb.2020.06.021](https://doi.org/10.1016/j.psymb.2020.06.021) .
- [92] McKinzie CJ, Goralski JL, Noah TL, Retsch-Bogart GZ, Prieur MB. Worsening anxiety and depression after initiation of Lumacaftor/ivacaftor combination therapy in adolescent females with cystic fibrosis. *J Cyst Fibros* 2017;16:525–7. doi: [10.1016/j.jcf.2017.05.008](https://doi.org/10.1016/j.jcf.2017.05.008) .
- [93] Heo S, Young DC, Safirstein J, Bourque B, Antell MH, Diloreto S, et al. Mental status changes during elexacaftor/tezacaftor /ivacaftor therapy. *J Cyst Fibros* 2022;21:339–43. doi: [10.1016/j.jcf.2021.10.002](https://doi.org/10.1016/j.jcf.2021.10.002) .
- [94] Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Sole A, et al. Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries. *Thorax* 2014;69:1090–7. doi: [10.1136/thoraxjnl-2014-205983](https://doi.org/10.1136/thoraxjnl-2014-205983) .
- [95] Ploessl C, Pettit RS, Donaldson J. Prevalence of depression and antidepressant therapy use in a pediatric cystic fibrosis population. *Ann Pharmacother* 2014;48:488–93. doi: [10.1177/1060028013514846](https://doi.org/10.1177/1060028013514846) .
- [96] Smith BA, Modi AC, Quittner AL, Wood BL. Depressive symptoms in children with cystic fibrosis and parents and its effects on adherence to airway clearance. *Pediatr Pulmonol* 2010;45:756–63. doi: [10.1002/ppul.21238](https://doi.org/10.1002/ppul.21238) .
- [97] Verkleij M, de Winter D, Hurley MA, Abbott J. Implementing the International Committee on Mental Health in Cystic Fibrosis (ICMH) guidelines: screening accuracy and referral-treatment pathways. *J Cyst Fibros* 2018;17:821–7. doi: [10.1016/j.jcf.2018.02.005](https://doi.org/10.1016/j.jcf.2018.02.005) .
- [98] Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE, et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. *Thorax* 2016;71:26–34. doi: [10.1136/thoraxjnl-2015-207488](https://doi.org/10.1136/thoraxjnl-2015-207488) .

- [99] Snell C, Fernandes S, Bujoreanu IS, Garcia G. Depression, illness severity, and healthcare utilization in cystic fibrosis. *Pediatr Pulmonol* 2014;49:1177–81. doi: [10.1002/ppul.22990](https://doi.org/10.1002/ppul.22990) .
- [100] Schechter MS, Ostrenga JS, Fink AK, Barker DH, Sawicki GS, Quittner AL. Decreased survival in cystic fibrosis patients with a positive screen for depression. *J Cyst Fibros* 2021;20:120–6. doi: [10.1016/j.jcf.2020.07.020](https://doi.org/10.1016/j.jcf.2020.07.020) .
- [101] Olivereau L, Nave V, Garcia S, Perceval M, Rabilloud M, Durieu I, et al. Adherence to Lumacaftor-ivacaftor therapy in patients with cystic fibrosis in France. *J Cyst Fibros* 2020;19:402–6. doi: [10.1016/j.jcf.2019.09.018](https://doi.org/10.1016/j.jcf.2019.09.018) .
- [102] Shteinberg M, Lulu AB, Downey DG, Blumenfeld Z, Rousset-Jablonski C, Perceval M, et al. Failure to conceive in women with CF is associated with pancreatic insufficiency and advancing age. *J Cyst Fibros* 2019;18:525–9. doi: [10.1016/j.jcf.2018.10.009](https://doi.org/10.1016/j.jcf.2018.10.009) .
- [103] Shteinberg M, Taylor-Cousar JL, Durieu I, Cohen-Cymbereknoh M. fertility and pregnancy in cystic fibrosis. *Chest* 2021;160:2051–60. doi: [10.1016/j.chest.2021.07.024](https://doi.org/10.1016/j.chest.2021.07.024) .
- [104] Esan OB, Schluter DK, Phillips R, Cosgriff R, Paranjothy S, Williams D, et al. Pregnancy rates and outcomes in women with cystic fibrosis in the UK: comparisons with the general population before and after the introduction of disease-modifying treatment, 2003-17. *BJOG* 2022;129:743–51. doi: [10.1111/1471-0528.16957](https://doi.org/10.1111/1471-0528.16957) .
- [105] O'Connor KE, Goodwin DL, NeSmith A, Garcia B, Mingora C, Ladores SL, et al. Elexacaftor/tezacaftor/ivacaftor resolves subfertility in females with CF: a two center case series. *J Cyst Fibros* 2021;20:399–401. doi: [10.1016/j.jcf.2020.12.011](https://doi.org/10.1016/j.jcf.2020.12.011) .
- [106] Kendle AM, Roekner JT, Santillana EC, Kis LE, Cain MA. Cystic fibrosis transmembrane conductance regulator modulators during pregnancy: a case series. *Cureus* 2021;13:e17427. doi: [10.7759/cureus.17427](https://doi.org/10.7759/cureus.17427) .
- [107] Cystic Fibrosis Foundation. Clinical Considerations: fertility and CFTR Modulators. 2022. <https://www.ecfs.eu/sites/default/files/Clinical%20Considerations%20Fertility%20and%20Modulators.04122022.pdf> Date accessed: 9 May 2022
- [108] Kazmerski TM, Sawicki GS, Miller E, Jones KA, Abebe KZ, Tuchman LK, et al. Sexual and reproductive health behaviors and experiences reported by young women with cystic fibrosis. *J Cyst Fibros* 2018;17:57–63. doi: [10.1016/j.jcf.2017.07.017](https://doi.org/10.1016/j.jcf.2017.07.017) .
- [109] Godfrey EM, Mody S, Schwartz MR, Heltshe SL, Taylor-Cousar JL, Jain R, et al. Contraceptive use among women with cystic fibrosis: a pilot study linking reproductive health questions to the Cystic Fibrosis Foundation National Patient Registry. *Contraception* 2020;101:420–6. doi: [10.1016/j.contraception.2020.02.006](https://doi.org/10.1016/j.contraception.2020.02.006) .
- [110] Gaillard DA, Carre-Pigeon F, Lallemand A. Normal vas deferens in fetuses with cystic fibrosis. *J Urol* 1997;158:1549–52 .

- [111] Trimble AT, Donaldson SH. Ivacaftor withdrawal syndrome in cystic fibrosis patients with the G551D mutation. *J Cyst Fibros* 2018;17:e13–ee6. doi: [10.1016/j.jcf.2017.09.006](https://doi.org/10.1016/j.jcf.2017.09.006) .
- [112] Nash EF, Middleton PG, Taylor-Cousar JL. Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators—an international survey. *J Cyst Fibros* 2020;19:521–6. doi: [10.1016/j.jcf.2020.02.018](https://doi.org/10.1016/j.jcf.2020.02.018) .
- [113] Taylor-Cousar JL, Jain R. Maternal and fetal outcomes following elexacaftortezacaftor-ivacaftor use during pregnancy and lactation. *J Cyst Fibros* 2021;20:402–6. doi: [10.1016/j.jcf.2021.03.006](https://doi.org/10.1016/j.jcf.2021.03.006) .
- [114] European Medicines Agency. Kaftrio Summary of Product Characteristics. 2020. <https://www.ema.europa.eu/en/medicines/human/EPAR/kaftrio> Date accessed: 1 July 2021
- [115] Trimble A, McKinzie C, Terrell M, Stringer E, Esther CR Jr. Measured fetal and neonatal exposure to Lumacaftor and ivacaftor during pregnancy and while breastfeeding. *J Cyst Fibros* 2018;17:779–82. doi: [10.1016/j.jcf.2018.05.009](https://doi.org/10.1016/j.jcf.2018.05.009) .
- [116] Kerem E, Konstan MW, De Boeck K, Accurso FJ, Sermet-Gaudelus I, Wilschanski M, et al. Ataluren for the treatment of nonsense-mutation cystic fibrosis: a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet Respir Med* 2014;2:539–47. doi: [10.1016/S2213-2600\(14\)70100-6](https://doi.org/10.1016/S2213-2600(14)70100-6) .
- [117] Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. *J Cyst Fibros* 2022;21:456–62. doi: [10.1016/j.jcf.2022.01.009](https://doi.org/10.1016/j.jcf.2022.01.009) .
- [118] McGarry ME, McColley SA. Cystic fibrosis patients of minority race and ethnicity less likely eligible for CFTR modulators based on CFTR genotype. *Pediatr Pulmonol* 2021;56:1496–503. doi: [10.1002/ppul.25285](https://doi.org/10.1002/ppul.25285) .
- [119] De Boeck K, Zolin A, Cuppens H, Olesen HV, Viviani L. The relative frequency of CFTR mutation classes in European patients with cystic fibrosis. *J Cyst Fibros* 2014;13:403–9. doi: [10.1016/j.jcf.2013.12.003](https://doi.org/10.1016/j.jcf.2013.12.003) .
- [120] Silva IAL, Railean V, Duarte A, Amaral MD. Personalized medicine based on nasal epithelial cells: comparative studies with rectal biopsies and intestinal organoids. *J Pers Med* 2021;11:421. doi: [10.3390/jpm11050421](https://doi.org/10.3390/jpm11050421) .
- [121] Berkers G, van Mourik P, Vonk AM, Kruisselbrink E, Dekkers JF, de Winterde Groot KM, et al. Rectal organoids enable personalized treatment of cystic fibrosis. *Cell Rep* 2019;26:1701–8 1701-8 e3. doi: [10.1016/j.celrep.2019.01.068](https://doi.org/10.1016/j.celrep.2019.01.068) .
- [122] Ramalho AS, Furstova E, Vonk AM, Ferrante M, Verfaillie C, Dupont L, et al. Correction of CFTR function in intestinal organoids to guide treatment of cystic fibrosis. *Eur Respir J* 2021;57:1902426. doi: [10.1183/13993003.02426-2019](https://doi.org/10.1183/13993003.02426-2019) .
- [123] Dekkers JF, Berkers G, Kruisselbrink E, Vonk A, de Jonge HR, Janssens HM, et al. Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis. *Sci Transl Med* 2016;8:344ra84. doi: [10.1126/scitranslmed.aad8278](https://doi.org/10.1126/scitranslmed.aad8278) .

- [124] Muilwijk D, Bierlaagh M, van Mourik P, Kraaijkamp J, van der Meer R, van den Bor R, et al. Prediction of real-world long-term outcomes of people with CF homozygous for the F508del mutation treated with CFTR modulators. *J Pers Med* 2021;11:1376. doi: [10.3390/jpm11121376](https://doi.org/10.3390/jpm11121376) .
- [125] Anderson JD, Liu Z, Odom LV, Kersh L, Guimbellot JS. CFTR function and clinical response to modulators parallel nasal epithelial organoid swelling. *Am J Physiol Lung Cell Mol Physiol* 2021;321:L119–LL29. doi: [10.1152/ajplung.00639.2020](https://doi.org/10.1152/ajplung.00639.2020) .
- [126] Sette G, Lo Cicero S, Blacona G, Pierandrei S, Bruno SM, Salvati V, et al. Theratyping cystic fibrosis in vitro in ALI culture and organoid models generated from patient-derived nasal epithelial conditionally reprogrammed stem cells. *Eur Respir J* 2021;58:2100908. doi: [10.1183/13993003.00908-2021](https://doi.org/10.1183/13993003.00908-2021) .
- [127] Magaret AS, Mayer-Hamblett N, VanDevanter D. Expanding access to CFTR modulators for rare mutations: the utility of n-of-1 trials. *J Cyst Fibros* 2020;19:1–2. doi: [10.1016/j.jcf.2019.11.011](https://doi.org/10.1016/j.jcf.2019.11.011) .
- [128] Mahadeva R, Webb K, Westerbeek RC, Carroll NR, Dodd ME, Bilton D, et al. Clinical outcome in relation to care in centers specializing in cystic fibrosis: cross sectional study. *BMJ* 1998;316:1771–5. doi: [10.1136/bmj.316.7147.1771](https://doi.org/10.1136/bmj.316.7147.1771) .
- [129] Ramos KJ, Guimbellot JS, Valapour M, Bartlett LE, Wai TH, Goss CH, et al. Use of elexacaftor/tezacaftor/ivacaftor among cystic fibrosis lung transplant recipients. *J Cyst Fibros* 2022;21:745–52. doi: [10.1016/j.jcf.2022.04.009](https://doi.org/10.1016/j.jcf.2022.04.009) .
- [130] Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment—a consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019;38:493–503. doi: [10.1016/j.healun.2019.03.009](https://doi.org/10.1016/j.healun.2019.03.009) .
- [131] Vital D, Hofer M, Benden C, Holzmann D, Boehler A. Impact of sinus surgery on pseudomonas airway colonization, bronchiolitis obliterans syndrome and survival in cystic fibrosis lung transplant recipients. *Respiration* 2013;86:25–31. doi: [10.1159/000339627](https://doi.org/10.1159/000339627) .
- [132] Fernandez R, Safaeinili N, Kurihara C, Odell DD, Jain M, DeCamp MM, et al. Association of body mass index with lung transplantation survival in the United States following implementation of the lung allocation score. *J Thorac Cardiovasc Surg* 2018;155:1871–9. doi: [10.1016/j.jtcvs.2017.11.031](https://doi.org/10.1016/j.jtcvs.2017.11.031) .
- [133] Benhalima K, Standl E, Mathieu C. The importance of glycemic control: how low should we go with HbA1c? Start early, go safe, go low. *J Diabetes Complicat* 2011;25:202–7. doi: [10.1016/j.jdiacomp.2010.03.002](https://doi.org/10.1016/j.jdiacomp.2010.03.002) .
- [134] Rowbotham NJ, Smith S, Leighton PA, Rayner OC, Gathercole K, Elliott ZC, et al. The top 10 research priorities in cystic fibrosis developed by a partnership between people with CF and healthcare providers. *Thorax* 2018;73:388–90. doi: [10.1136/thoraxjnl-2017-210473](https://doi.org/10.1136/thoraxjnl-2017-210473) .

[135] Gilljam M, Chaparro C, Tullis E, Chan C, Keshavjee S, Hutcheon M. GI complications after lung transplantation in patients with cystic fibrosis. *Chest* 2003;123:37–41. doi: [10.1378/chest.123.1.37](https://doi.org/10.1378/chest.123.1.37) .

[136] Fajac I, Daines C, Durieu I, Goralski JL, Heijerman H, Knoop C, et al. Nonrespiratory health-related quality of life in people with cystic fibrosis receiving elexacaftor/tezacaftor/ivacaftor. *J Cyst Fibros* 2022;13:S1568–993. doi: [10.1016/j.jcf.2022.08.018](https://doi.org/10.1016/j.jcf.2022.08.018) .

[137] Barben J, Castellani C, Munck A, Davies JC, de Winter-de Groot KM, Gartner S, et al. Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). *J Cyst Fibros* 2021;20:810–19. doi: [10.1016/j.jcf.2020.11.006](https://doi.org/10.1016/j.jcf.2020.11.006) .

[138] Guo J, Wang J, Zhang J, Fortunak J, Hill A. Current prices versus minimum costs of production for CFTR modulators. *J Cyst Fibros* 2022;21:866–72. doi: [10.1016/j.jcf.2022.04.007](https://doi.org/10.1016/j.jcf.2022.04.007) .

[139] Zampoli M, Kashirskaya N, Karadag B, Filho L, Paul GR, Noke C. Global access to affordable CFTR modulator drugs: time for action!. *J Cyst Fibros* 2022;21:e215–16. doi: [10.1016/j.jcf.2022.03.006](https://doi.org/10.1016/j.jcf.2022.03.006) .

