

REVIEW ARTICLE

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Cystic Fibrosis

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CARE FOR PATIENTS WITH CYSTIC FIBROSIS HAS UNDERGONE TRANSFORMATIVE changes over the past decade and serves as an example of how an understanding of the functional consequences of a genetic disease can lead to improved outcomes in affected persons. Substantial progress had been made through the implementation of therapies addressing key downstream manifestations of the disease such as mucus accumulation in the airways and persistent airway infections. In addition, the introduction of small-molecule drugs that address the underlying molecular defects — cystic fibrosis transmembrane conductance regulator (CFTR) modulators — has resulted in unprecedented improvements in the health of many persons with cystic fibrosis. Here, we summarize recent advancements, highlight how they may affect clinical care in the future, and describe unmet needs in the care of persons with cystic fibrosis.

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GENETICS

Cystic fibrosis is an autosomal recessive disease caused by variants in the *CFTR* gene. *CFTR* encodes for an ion channel, CFTR, that is involved in regulation of the water–electrolyte balance on the surface of many organ systems, including the upper and lower airways, intestine, pancreas, biliary tree, cervix, vas deferens, and sweat glands.^{1,2} The incidence of cystic fibrosis is approximately 1 in 3500 to 1 in 5000 live births in Northern Europe, Australia, and North America, with substantial regional variation. Approximately 35,000 persons in the United States have cystic fibrosis.³

The number of *CFTR* variants that have been described as of this writing has increased to more than 2000; an ongoing effort supported by the Cystic Fibrosis Foundation has led to the annotation of more than 700 disease-causing variants.⁴ Understanding the functional consequences of gene variants at the protein level is crucial not only to clarify a potential association with disease manifestations, but also to define whether a given variant could respond to disease-modifying therapies. Deletion of three base pairs in *CFTR* leading to the loss of the amino acid phenylalanine at position 508 (F508del) of the protein is the most common cystic fibrosis–causing variant. Approximately 85% of all cystic fibrosis–related alleles in the United States are F508del.⁵ Frequencies of less common cystic fibrosis–related variants can vary in geographic regions depending on the race and ethnic mix of the population. Non-White persons are overrepresented in the population of persons with rare *CFTR* variants. The higher frequency of rare variants affects diagnosis and the availability of current treatment options with disease-modifying drugs for non-White persons, even though F508del is also the most common identified variant in Black and Hispanic patients with cystic fibrosis in the United States.⁶

CFTR PROTEIN

Cystic fibrosis–causing variants have different implications with respect to CFTR production, processing, expression, and function. They can result in premature termination codons with reduced or absent CFTR formation (class I variant); premature degradation due to protein misfolding (class II); abnormalities of channel gating (class III), conductance (class IV), or both; reduced transcript, promoter, or splicing abnormalities (class V); or accelerated turnover from the cell surface (class VI). Although this classification has been helpful, a given variant can cause more than one molecular defect. For instance, although F508del primarily results in defective protein folding (class II), it also has reduced channel conductance (class IV) and increased cell-surface turnover (class VI); all these features can be potential drug targets. Current CFTR modulator therapy is mainly, but not exclusively, effective in class III (the potentiator ivacaftor) and in the class II variant F508del (a combination of correctors with ivacaftor, such as elexacaftor–tezacaftor–ivacaftor)^{7,8} (Fig. 1).

PATHOPHYSIOLOGY AND ORGAN MANIFESTATIONS OF CYSTIC FIBROSIS

CFTR is involved in the regulation of transepithelial ion transport and water–electrolyte homeostasis in many organ systems. In the sweat glands, normal CFTR activity results in chloride ion absorption from primarily isotonic perspiration; CFTR dysfunction in persons with cystic fibrosis causes impaired chloride absorption in the sweat-gland ducts and consequently elevated sweat chloride concentrations.^{1,2} The absence or dysfunction of CFTR in airway epithelium leads to decreased chloride and bicarbonate secretion at the apical membrane, the inability of alternative chloride channels such as TMEM16A (also called anoctamin 1 and ANO1) to compensate, and persistent sodium absorption through loss of CFTR-mediated inhibition of the epithelial sodium channel, which causes absorption of airway-surface fluid.⁹ The consequences of this fluid imbalance in the lungs are thickened secretions and reduced mucociliary transport, resulting in mucus retention and plugging of airways. Mucus plugging alone can cause an inflamma-

Figure 1 (facing page). Classes of CFTR Variants.

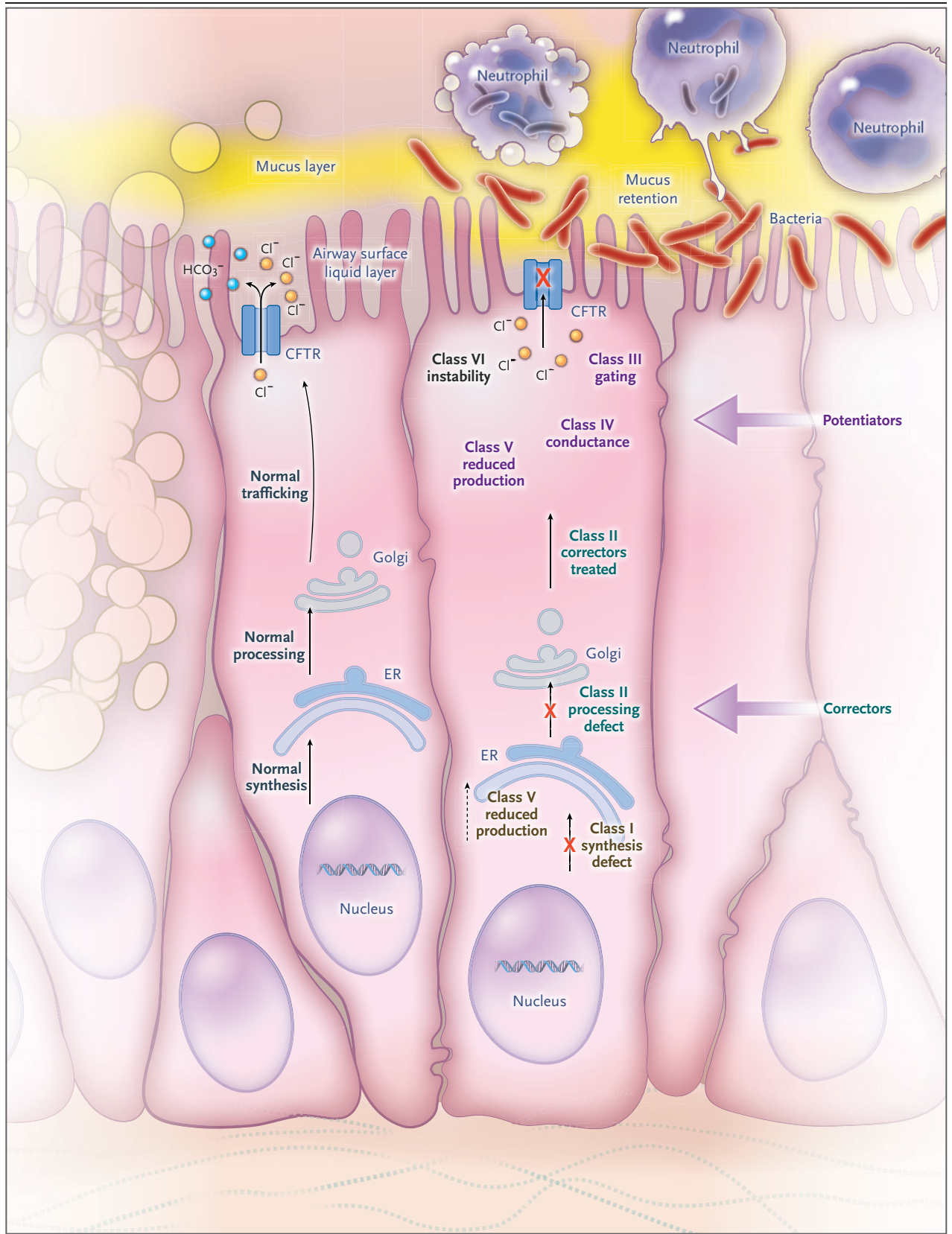
Shown are the classes of CFTR variants causing cystic fibrosis and targets for current CFTR modulators. CFTR deficiency in airway epithelium causes a reduction in the layer of airway surface liquid, mucus accumulation, influx of neutrophils, and bacterial infection. Correctors improve trafficking and processing of CFTR protein to the apical membrane of the cell. Potentiators improve function of CFTR expressed at the cell membrane. ER denotes endoplasmic reticulum; Cl⁻ chloride, and HCO₃⁻ bicarbonate.

tory response in the airways even in the absence of pathogens.^{10,11} Mucus retention also favors recurrent and persistent bacterial infections with consecutively increased mucus production and inflammation, a cycle leading to the development of structural lung damage (bronchiectasis).^{1,2}

Studies involving pigs with cystic fibrosis have shown the importance of bicarbonate secretion for the release and unfolding of mucins from submucosal glands, with the absence of CFTR resulting in mucus bands stuck to the glandular lumen.^{12,13} Bicarbonate deficiency also affects bacterial killing, and together with impaired mucociliary clearance it promotes bacterial infection of the lower airways. Chronic lung disease with progressive decline in lung function and ultimately respiratory failure continues to be the major cause of death, but cystic fibrosis is a multiorgan disease (Fig. 2).

In classic cystic fibrosis, thickened secretions cause pancreatic autodigestion and fatty replacement of the organ. Pancreatic insufficiency affects approximately 80% of persons with cystic fibrosis; can cause abdominal gas and bloating, steatorrhea, and weight loss; and is usually defined by reduced fecal elastase-1 content in stool. In some persons with cystic fibrosis — usually those carrying so-called milder variants (class IV through VI) — pancreatic insufficiency may develop later in life or never. Pancreatic function may not be normal in these persons, and pancreatic-sufficient persons with cystic fibrosis have a higher risk of acute pancreatitis than pancreatic-insufficient persons with cystic fibrosis.²³

Cystic fibrosis–related diabetes increases in prevalence with age and affects approximately a quarter of persons with cystic fibrosis who are older than 30 years of age. Current guidelines recommend annual screening for cystic fibrosis–



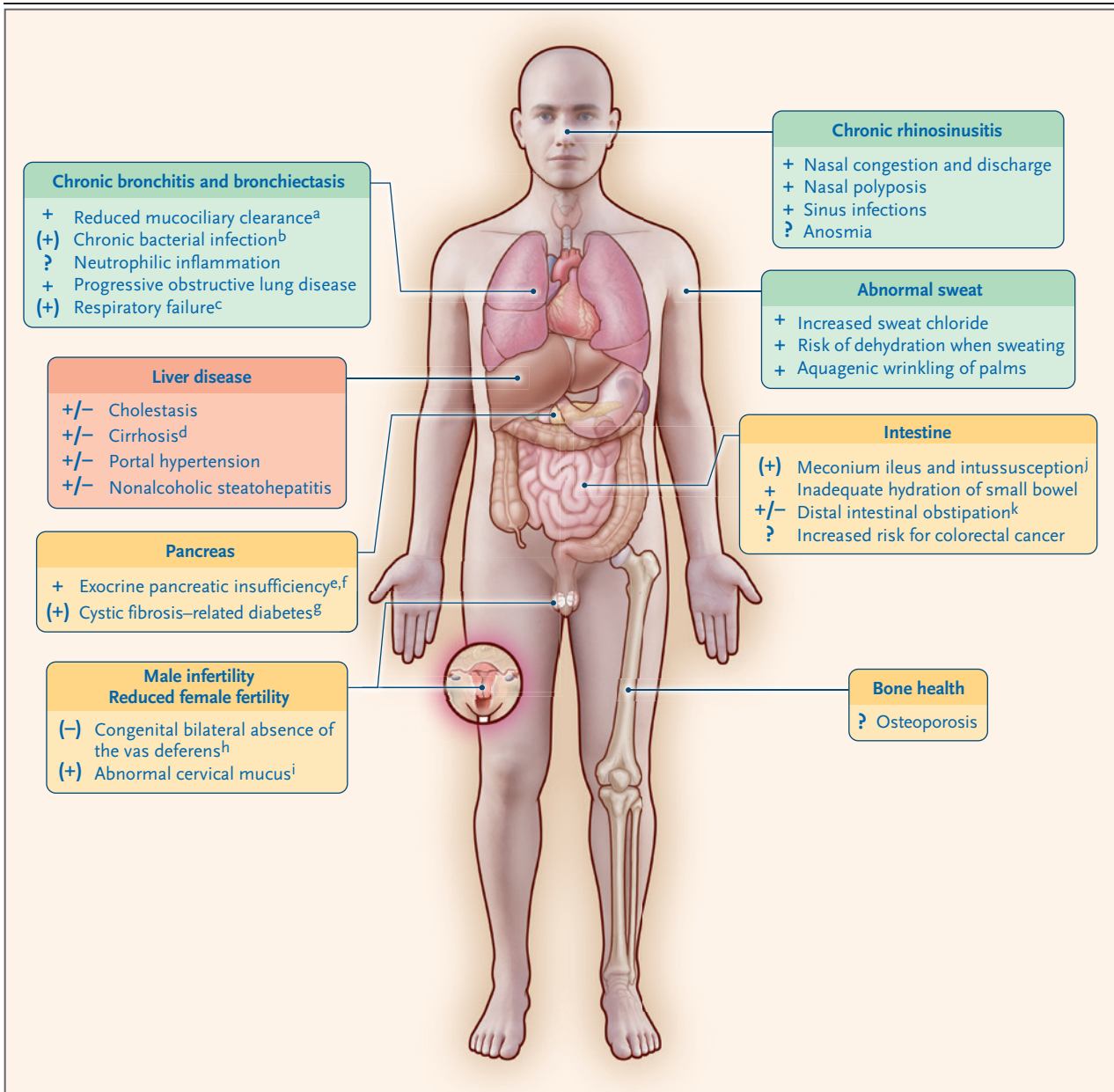


Figure 2. Effects of CFTR Modulators on Manifestations of Cystic Fibrosis in Main Organs and on Symptoms.

Shown are the effects of highly effective CFTR modulators on specific organ-related manifestations and symptoms. The + sign indicates beneficial effects, (+) potentially beneficial effects, – deleterious effects, (–) potentially deleterious effects, and ? unclear effects. With regard to the particular effect of CFTR modulators, the superscript “a” denotes an improvement in central and peripheral lung mucociliary clearance¹⁴; “b” a reduction (by 2 to 3 log units) in the count of pathogens associated with chronic cystic fibrosis but rarely clearance¹⁵; “c” a reduction in premature mortality, a reduction in the need for lung transplantation, and likely delayed onset of severe end-stage lung disease with respiratory failure⁵; “d” an increased risk of liver-related toxic effects (although the risk of development of cirrhosis may be lower among patients treated with CFTR modulators than among those not treated with CFTR modulators)¹⁶; “e” an improvement in the nutritional status in patients with cystic fibrosis with pancreatic insufficiency^{17,18}; “f” preservation of pancreas function if started in early life¹⁹; “g” an improvement in glucose tolerance but not insulin secretion²⁰; “h” possible prevention of congenital bilateral absence of the vas deferens if initiated prenatally²¹; “i” an increased potential for pregnancy among women with cystic fibrosis²²; “j” possible reduction in the echogenicity of the echogenic bowel if started antenatally¹⁹; and “k” a transient increase in the risk of distal intestinal obstruction. The green shading indicates overall predominantly beneficial effects of CFTR modulators; the red shading, overall potentially deleterious effects; and the yellow shading, not yet known whether beneficial for organ-related manifestations.

related diabetes with oral glucose-tolerance testing.²⁴

Cystic fibrosis–related liver disease ranges from steatosis associated with increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels to focal biliary fibrosis or to severe cholestasis and advanced liver cirrhosis with portal hypertension warranting liver transplantation. Cystic fibrosis–related liver disease tends to be focal in nature, and currently there is no well-established biomarker to predict the development of severe liver involvement. In addition, no preventive treatment strategies have been shown to be efficacious. Noncirrhotic portal hypertension without synthetic liver dysfunction, which is common in persons with cystic fibrosis, may not warrant liver transplantation.²⁵

DIAGNOSIS

NEWBORN SCREENING

The diagnosis of cystic fibrosis is based on one or more organ manifestations that are consistent with the disease and either objective evidence of CFTR dysfunction (such as a positive sweat chloride test) or two disease-causing *CFTR* variants. Although the classic presentation associated with failure to thrive in infancy leads to early clinical suspicion, the diagnosis can be delayed in pancreatic-sufficient patients and those who present with monosymptomatic disease. Early diagnosis can ensure timely initiation of treatment. This has been the main rationale for newborn screening programs that have now been implemented in many countries, including all states in the United States. Most screening programs use blood trypsinogen levels, which are elevated in infants with cystic fibrosis, as the initial test followed by genetic testing for common *CFTR* variants on the same blood spot for screen-positive cases.²⁶ Some programs such as those in California now include extended gene sequencing in patients in whom only one *CFTR* variant is detected on initial testing. This approach increases the likelihood of detecting pathogenic variants in non-White populations and reduces the number of patients for whom confirmatory sweat testing is warranted.²⁷ However, newborn screening does not always result in a clear diagnosis. Current guidelines suggest conducting clinical follow-up for infants who

had a positive screening test for cystic fibrosis but received an inconclusive diagnosis because approximately 20% of these infants will subsequently meet diagnostic criteria for cystic fibrosis.²⁸

SWEAT TEST

Sweat chloride testing is recommended to confirm the diagnosis both in newborn-screening positive infants and in persons with symptoms suggestive of cystic fibrosis.²⁹ Increased chloride ion concentrations in sweat (≥ 60 mmol per liter) are characteristic of cystic fibrosis, but *CFTR* expression and function can vary among organs, especially in variants with residual *CFTR* functions including noncanonical splicing variants. Therefore, a sweat chloride level below the diagnostic threshold does not necessarily rule out cystic fibrosis. *CFTR* dysfunction is a spectrum, with some persons having only limited organ involvement (e.g., men with congenital bilateral absence of the vas deferens).³⁰ In cases of diagnostic uncertainty, *in vivo* tests of *CFTR* function such as the nasal potential difference and intestinal current measurement can aid in the diagnosis,³¹ but these tests are rarely warranted and are not widely available, even in specialized centers.

EPIDEMIOLOGY

Improved outcomes over the past decades have changed the prevalence of cystic fibrosis, and there is now a growing population of adults with the disease. Cystic fibrosis, which was previously considered to be a disease affecting White persons, has been diagnosed in persons of many ethnic backgrounds on all continents.³² Reliable estimates of prevalence are not available for major parts of Asia and Africa and most low- and middle-income countries because many cases go unrecognized.

TREATMENT

CFTR MODULATORS

The potentiator ivacaftor is effective in persons with cystic fibrosis carrying variants with residual *CFTR* expression in which channel conductance is reduced, such as the G551D variant. Although the exact mechanisms of action are unknown for the *CFTR* modulators, ivacaftor binds to *CFTR* and is thought to thereby in-

crease the probability of opening the channel. Ivacaftor has led to unprecedented improvements in respiratory outcomes, including lung function, the risk of pulmonary exacerbation, and respiratory symptoms as well as nutritional status and other manifestations of cystic fibrosis.^{17,33-35} However, only approximately 5% of persons with cystic fibrosis carry disease-causing variants that respond to ivacaftor monotherapy.

In patients with F508del, the most common variant, combination therapy with corrector drugs that ameliorate the protein-folding defect and allow for transport of the channel to the cell surface and ivacaftor to improve channel gating are warranted to achieve clinical benefit. The first-generation corrector drugs lumacaftor and tezacaftor had modest benefits when combined with ivacaftor, and these benefits were observed only in persons with cystic fibrosis homozygous for F508del.³⁶⁻³⁹ In contrast, the triple-combination therapy elxacaftor–tezacaftor–ivacaftor benefits persons with cystic fibrosis who have either one or two F508del alleles and results in improvements in lung function exceeding those previously observed with ivacaftor in gating variants.^{18,40-42}

Given the impressive responses observed with ivacaftor and elxacaftor–tezacaftor–ivacaftor, these are now commonly referred to as highly effective modulator therapy, but CFTR chloride conduction, while improving, does not always normalize with these drugs and even more effective therapies could potentially become available in the future. Additional CFTR variants have subsequently been found to be responsive to elxacaftor–tezacaftor–ivacaftor in vitro testing with the use of a cultured cell–based assay. These findings have led to expansion of the label in the United States,⁴³ although there are concerns about clinical efficacy for some of these variants.⁴⁴ Individual testing to assess the response to CFTR modulator therapies can also be performed with patient-derived tissues, and both nasal epithelial cells obtained through brushing and intestinal organoids generated from rectal-biopsy specimens have been used for this purpose in persons with rare variants. The individual response to highly effective modulator therapy varies, and in vitro testing with the use of patient-derived tissues or genetic tools could be used to predict clinical benefit to current and future CFTR modulators. Given the high treat-

ment costs with current modulators, this personalized medicine strategy will probably be cost-effective.⁴⁵

The use of highly effective modulator therapy to treating cystic fibrosis as early as possible is attractive.⁴⁶ Elxacaftor–tezacaftor–ivacaftor is now available for children 2 years of age and older,⁴⁷ and studies involving children 12 months to less than 24 months of age (ClinicalTrials.gov number, NCT05882357) are currently under way. Maintained pancreatic function has been reported in infants with cystic fibrosis who were exposed to intrauterine elxacaftor–tezacaftor–ivacaftor.¹⁹ These findings are supported by data from a study involving ferrets with cystic fibrosis that showed that certain organ manifestations can be prevented or rescued with antenatal initiation of highly effective modulator therapy.²¹

THE THERAPY FOR SYMPTOMS

Major advances in the care of patients with cystic fibrosis have been associated with treatment of symptoms, even before the introduction of CFTR modulators. Besides nutritional management with a high-calorie, high-fat diet and pancreatic enzyme replacement in patients with pancreatic insufficiency, many of the previously recommended therapies focused on management and prevention of respiratory manifestations. Cystic fibrosis–related lung disease manifests as chronic mucus retention, airway infection, inflammation, and acute respiratory events. The intermittent worsening of symptoms such as productive cough is defined as pulmonary exacerbation. Pulmonary exacerbations are associated with loss of lung function and are an independent predictor of death. Preventing and treating these events is therefore one of the main therapeutic goals.⁴⁸ Mucus plugging of the small airways is the earliest manifestation of CFTR dysfunction in the lungs in both animal models of cystic fibrosis and in affected infants.⁴⁶ Therefore, therapies to improve mucus clearance are important components of maintenance therapy in patients with cystic fibrosis.

MUCOACTIVE THERAPIES

Either active or passive airway-clearance techniques are considered part of standard of care even though the evidence of their efficacy is not strong.⁴⁹ Inhalation of the mucolytic drug dornase alfa (recombinant human DNase) has been

shown to improve lung function and to reduce the frequency of pulmonary exacerbations.⁵⁰ Dornase alfa lowers the viscosity of airway secretions by breaking down free DNA strands that are mainly derived from neutrophils entering the airways as part of the inflammatory response. Nebulized inhaled hypertonic saline, which ameliorates dehydration of airway secretions and mucociliary clearance, improves lung function and reduces exacerbations among children and adults. Nebulized hypertonic saline is also beneficial for infants and young children in whom data on other therapies for treating symptoms are currently lacking⁵¹⁻⁵³ (Table 1).

LUNG INFECTION

Acute and chronic infections of the airway in persons with cystic fibrosis are caused by a large variety of pathogens, among which *Staphylococcus aureus* (both methicillin-susceptible and methicillin-resistant *S. aureus*) and *Pseudomonas aeruginosa* are the most common. Other gram-negative bacteria include *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and achromobacter species, which have all been linked to worse outcomes in persons who have chronic infection with these organisms.⁵⁸ In cystic fibrosis, as in other chronic airway diseases, atypical mycobacteria can cause clinically significant lung damage and are challenging to treat.⁵⁹ Regular microbiologic testing of airway secretions is performed to detect new infections and to guide treatment decisions. Early infections with pathogens including *P. aeruginosa*, whether symptomatic or not, are targeted with the aim of eradication of these pathogens from the airways.⁶⁰ Maintenance therapy with inhaled antibiotics has been shown to be beneficial in chronic *P. aeruginosa* infection and is considered to be the standard of care⁶¹ (Table 1).

ACUTE PULMONARY EXACERBATIONS

Pulmonary exacerbations are treated with oral or intravenous antibiotic therapies and intensified airway clearance.⁴⁸ Fungi such as *Aspergillus fumigatus* are commonly found in airway secretions in persons with cystic fibrosis. Chronic infection with *A. fumigatus* is associated with an increased frequency of cystic fibrosis–related pulmonary exacerbations, but treatment with antifungal agents remains controversial.⁶² *A. fumigatus* can also cause allergic bronchopulmonary

aspergillosis, which manifests as therapy-resistant airway obstruction and is treated with systemic glucocorticoids alone or in combination with antifungal agents.⁶³ Biologic agents including the anti-IgE monoclonal antibody omalizumab have been used in patients with cystic fibrosis–related allergic bronchopulmonary aspergillosis, but robust data from clinical trials are lacking.⁶⁴

LUNG TRANSPLANTATION

Bilateral lung transplantation is a surgical option for persons who have cystic fibrosis and severe advanced lung disease.⁶⁵ Although lung transplantation may not always result in a survival benefit, it may be performed to improve quality of life. Even though persons with cystic fibrosis and severe pulmonary disease (forced expiratory volume in 1 second [FEV₁] <40% of the predicted value) were excluded from most clinical trials of CFTR modulators, most patients with cystic fibrosis who were on the waiting list for a lung transplant were removed from the list when treatment was initiated clinically.⁶⁶

In the United States, the number of lung transplantations in persons with cystic fibrosis in 2021 had decreased to approximately 20% of those performed in 2019.⁵ Although some of this decline may also have been related to reduced transplantation activities during the coronavirus disease 2019 (Covid-19) pandemic, the expected effects of highly effective modulator therapy on progression of chronic disease and on survival would result in an increased average patient age at transplantation. Continuation of CFTR modulators may be indicated for nonrespiratory indications in some transplant recipients, although one study showed that one third of persons with cystic fibrosis stopped treatment after lung transplantation owing to side effects or lack of perceived benefits.⁶⁷ Noneligibility for CFTR modulators may contribute to the existing ethical and racial disparity in outcomes among patients; this disparity is also reflected in underuse of lung transplantation in vulnerable populations.⁶⁸

CYSTIC FIBROSIS CARE IN THE ERA OF CFTR MODULATOR THERAPY

MODELS OF CARE

Multidisciplinary care at specialized cystic fibrosis centers and standardized treatment guidelines based on evidence from clinical trials

Table 1. Commonly Used Maintenance Therapies for Cystic Fibrosis.

Therapy and Patient's Age and Weight	Dose	Comments
CFTR modulators		
Monotherapy (CFTR gating or splice variants): ivacaftor (Kalydeco)		
Adults	150 mg every 12 hr	Dose adjustment for moderate or severe hepatic impairment or if coadministered with strong CYP3A inhibitors. ⁵⁴ With all modulators, monitor for liver-related toxic effects, elevated creatine kinase level, hypertension, and cataracts.
Children		
1 to <2 mo, ≥3 kg (≥7 lb)	5.8 mg every 12 hr	
2 to <4 mo, ≥3 kg (≥7 lb)	13.4 mg every 12 hr	
4 to <6 mo, ≥5 kg (≥11 lb)	25 mg every 12 hr	
6 mo to <6 yr		
5 kg to <7 kg (11 to <15 lb)	25 mg every 12 hr	
7 kg to <14 kg (15 to <31 lb)	50 mg every 12 hr	
≥14 kg (≥31 lb)	75 mg every 12 hr	
≥6 yr	150 mg every 12 hr	
Double combination (for F508del–F508del): lumacaftor–ivacaftor (Orkambi)		
Risk of transient dyspnea with lumacaftor–ivacaftor. Dose adjustment also for moderate or severe hepatic impairment or if coadministered with strong CYP3A inhibitors. ⁵⁵		
Adults	400 mg daily + 250 mg twice daily	
Children		
1–2 yr		
7 to <9 kg (15 to <20 lb)	75 mg + 94 mg every 12 hr	
9 to <14 kg (20 to <31 lb)	100 mg + 125 mg every 12 hr	
≥14 kg (≥31 lb)	150 mg + 188 mg every 12 hr	
2–5 yr		
<14 kg (<31 lb)	100 mg + 125 mg every 12 hr	
≥14 kg (≥31 lb)	150 mg + 188 mg every 12 hr	
6–11 yr		
≥12 yr	200 mg + 250 mg every 12 hr	
400 mg + 250 mg every 12 hr		
Double combination (for F508del–F508del or F508del–residual function variant): tezacaftor–ivacaftor (Symdeko, or Symkevi in some countries)		
Dose adjustment for moderate or severe hepatic impairment or if coadministered with moderate or strong CYP3A inhibitors. Concomitant use with strong CYP3A inducers not recommended. ⁵⁶		
Adults	100 mg daily + 150 mg twice daily	
Children		
6–11 yr		
<30 kg (<66 lb)	50 mg daily + 75 mg twice daily	
≥30 kg (≥66 lb)	100 mg daily + 150 mg twice daily	
≥12 yr	100 mg daily + 150 mg twice daily	

Triple combination (one or two F508del alleles): elxacaftor-tezacaftor-ivacaftor (Trikafta, or Kaftrio in some countries)		Dose adjustment for moderate hepatic impairment and not recommended for severe hepatic impairment. Dose adjustment if coadministered with moderate or strong CYP3A inhibitors. Concomitant use with strong CYP3A inducers not recommended. ⁵⁷
Adults	200 mg daily + 100 mg daily + 150 mg twice daily	
Children		
2 to <6 yr		
<14 kg (<31 lb)	80 mg daily + 40 mg daily + 60 mg (morning) and 59.5 mg (evening)	
≥14 kg (≥31 lb)	100 mg daily + 50 mg daily + 75 mg twice daily	
6 to <12 yr		
<30 kg (<66 lb)	100 mg daily + 50 mg daily + 75 mg twice daily	
≥30 kg (≥66 lb)	200 mg daily + 100 mg daily + 150 mg twice daily	
Mucoactive agents		
Human recombinant DNase	2.5 mg once daily by inhalation	Approved for patients ≥6 yr. Has also been studied in younger children.
Hypertonic saline solution (7%)	4 ml daily by inhalation	Approved for patients ≥6 yr. Has also been studied in younger children.
Mannitol dry powder	400 mg twice daily by inhalation	Approved for adults only.
Antipseudomonas antibiotics		
Tobramycin solution or powder	300 mg twice daily by inhalation, or 112 mg twice daily, for 28 days on-off cycles	Also used to attempt eradication of early infection.
Inhaled aztreonam	75 mg inhaled every 8 hr, for 28 days	
Antiinflammatory therapy		
Azithromycin	250–500 mg, three times weekly by mouth	Long-term treatment may induce macrolide resistance.
Children		
<25 kg (55 lb)	10 mg/kg/dose, three times weekly by mouth	
25 kg (55 lb) to <40 kg (88 lb)	250 mg, three times weekly by mouth	
≥40 kg (88 lb)	500 mg, three times weekly by mouth	
Treatment for pancreatic insufficiency		
Pancreatic enzyme–replacement therapy	Lipase units should not exceed 10,000 per kg of body weight per day for patients >12 mo	Should be taken with all meals and snacks, and adjusted according to the fat content of food consumed.
Fat-soluble vitamins (vitamins D, A, K, and E)	Should be supplemented as needed	
Treatment for constipation or distal intestinal obstruction syndrome		
Osmotic stool softeners	Polyethylene glycol 3350 at 0.5 to 1.0 g/kg/day to a maximum of 40 g/day	To prevent episodes of distal intestinal obstruction syndrome, improve adherence to pancreatic enzyme–replacement therapy and adequately adjust the dose and timing of intake.

improved outcomes for persons with cystic fibrosis in the past, but none of the recommended therapies for treating symptoms have been studied in the context of CFTR modulators. Therefore, important questions to address in the era of highly effective modulator therapy include what disease manifestations are potentially reversible and what the need for additional therapies for treating symptoms will be. Reducing treatment burden has been identified as a key priority by persons with cystic fibrosis.⁶⁹ One recent trial involving adults with cystic fibrosis in clinically stable condition who had received CFTR modulators and who had an FEV₁ that was of 60% of the predicted value or greater and children 12 to 17 years of age with an FEV₁ that was at least 70% of the predicted value showed that discontinuing either dornase alfa or hypertonic saline did not have detrimental effects on lung function in the short term.⁷⁰ However, the long-term effects of discontinued or reduced therapies for treating symptoms are currently unclear. Therapies for treating symptoms, including mechanical airway-clearance techniques, for persons with cystic fibrosis treated with highly effective modulator therapy may become more important for those with advanced lung disease, acute exacerbations, or both. Similarly, it is unclear how aggressively clinicians need to promote achievement of previously defined nutritional goals in patients who are already receiving or awaiting highly effective modulator therapy.

CARE OF ADULTS WITH CYSTIC FIBROSIS

Only half a century ago, most persons with a diagnosis of cystic fibrosis did not reach adulthood, but the median age of survival now is above 50 years in Canada, Australia, New Zealand, European countries, and the United States, and may further increase with the broad use of CFTR modulators.^{71,72} CFTR modulator therapy will not only result in delayed disease manifestations and healthier children with cystic fibrosis but will also have a considerable effect on the care of adults with cystic fibrosis. We anticipate an increasing number of adults with mild-to-moderate disease and an aging cystic fibrosis population at risk for age-related complications and coexisting conditions.⁷³

Clinics for adults with cystic fibrosis are faced with growing numbers of patients with

complications that were previously not encountered in cystic fibrosis care, such as microvascular and macrovascular complications of diabetes, obesity, and hypertension.⁷⁴ The higher level of clinical stability may also challenge the concept of frequent follow-up visits. Different care models, including strategies for home monitoring, are therefore currently being explored to meet patients' needs while ensuring that events known to trigger disease progression are adequately captured and addressed.

HIGHLY EFFECTIVE MODULATOR THERAPY

EFFECTS ON THE LUNGS

Although highly effective modulator therapy reduces the risk of acute pulmonary exacerbation, its role in addressing established, chronic airway infection with opportunistic pathogens is yet to be defined.⁷⁵ An observational trial of ivacaftor suggested initial improvement but a rebound phenomenon involving infection and inflammation after 1 year of therapy.⁷⁶ One complicating factor is that highly effective modulator therapy often results in the patient's inability to provide an expectorated sputum sample, which affects the clinician's ability to perform routine microbiologic surveillance. A recent study involving persons with cystic fibrosis who had received elxacaftor–tezacaftor–ivacaftor showed a considerable reduction in densities of typical cystic fibrosis pathogens in sputum after 1 month of therapy, but most patients remained infected with the pathogens that were present before the initiation of elxacaftor–tezacaftor–ivacaftor.¹⁵ It can therefore be assumed that there will be an ongoing need for effective antimicrobial agents targeting multiresistant pathogens, at least for most patients with established structural cystic fibrosis–related lung disease, and potentially also a need for antiinflammatory therapy.

Cystic fibrosis–related lung disease is routinely monitored by means of pulmonary-function testing, but spirometry is insensitive for detecting early or mild disease. Other tools that have been developed include the multiple-breath washout–derived lung-clearance index, a measure of ventilation inhomogeneity. The lung-clearance index is increased in persons with cystic fibrosis, even in the context of a normal

FEV₁, and has been shown to decrease with therapies such as highly effective modulator therapy, probably because of resolution of peripheral mucus plugging in airways, as supported by imaging techniques.⁷⁷⁻⁸⁰ Currently, computed tomography (CT) of the chest is the most sensitive type of imaging to capture structural lung disease, but radiation-free methods would be more suitable for frequent follow-up. New magnetic resonance imaging (MRI) techniques, including ultrashort echo-time MRI and functional MRI, have been shown to be sensitive in detecting changes in the lungs and other organs in persons with cystic fibrosis. These techniques are currently being evaluated in the context of highly effective modulator therapy.^{81,82}

EFFECTS ON THE PANCREAS

When initiated early, CFTR modulator therapy has the potential to prevent or delay the onset of pancreatic insufficiency. Although functional recovery of the pancreas is unlikely to occur in adults, exocrine function in infants and preschool children treated with ivacaftor can improve so that continuation of pancreatic enzyme-replacement therapy, which is generally initiated as early as a diagnosis is established, may not be warranted.⁸³ Registry data from the United States and United Kingdom show that the incidence of cystic fibrosis-related diabetes decreased in the 4 to 5 years after the introduction of ivacaftor to the market.⁸⁴ Highly effective modulator therapy, including elexacaftor-tezacaftor-ivacaftor, may result in improved glycemic control, but a recent observational study showed no associated change in insulin secretion 12 to 18 months after the initiation of elexacaftor-tezacaftor-ivacaftor.²⁰

EFFECTS ON NUTRITION

Nutritional guidelines for patients with pancreatic insufficiency have focused on achieving weight and body-mass index (BMI) goals, because a positive relationship between BMI and survival is well documented.⁸⁵ Recommended diets are high in fat and calories as well as salt to compensate for losses in sweat. However, BMI is not a measure of body composition, and current recommendations may lead to a disproportional increase in body-fat percentage despite normal weight or BMI. This so-called normal-

weight obesity has been shown to have inverse correlations with lung function in persons with cystic fibrosis.^{86,87} CFTR modulator therapy is associated with weight gain and may result in obesity and related long-term metabolic complications.⁸⁸ Monitoring of triglyceride and cholesterol levels in an aging population is warranted and may help guide nutritional recommendations.

EFFECTS ON THE LIVER

Although it is unclear whether CFTR modulator therapy can have beneficial effects on the course of cystic fibrosis-related liver disease, it can cause isolated, often transient elevation of ALT, AST, and bilirubin levels and may potentially cause severe liver injury in patients with preexisting cystic fibrosis-related liver disease.¹⁶ Monitoring of liver involvement in persons with cystic fibrosis has been challenging in the past, and better monitoring tools are needed to understand the risk-benefit ratio of CFTR modulator therapy in patients with established, severe, cystic fibrosis-related liver disease.

EFFECTS ON FERTILITY

Since the introduction of CFTR modulators, an increased incidence of pregnancy has been reported among women with cystic fibrosis, probably because of drug-related changes in the thickened secretions in the cervix and fallopian tubes.²² Male infertility is unlikely to be affected by these drugs owing to absence of the vas deferens.

EFFECTS ON OTHER ORGAN SYSTEMS

Whether CFTR modulators will reduce other manifestations of cystic fibrosis, including bone disease⁸⁹ and renal complications owing to frequent and prolonged courses of antibiotic therapy, is unclear. The use of high-dose nephrotoxic and ototoxic aminoglycoside antibiotics can also lead to hearing loss.

EFFECTS ON MENTAL HEALTH

Mental health has been a focus in the care of patients with cystic fibrosis because anxiety and depression are common in persons with this disease.^{90,91} Regular screening for anxiety and depression, close monitoring, preventive or supportive interventions, and antidepressant phar-

Table 2. Data from Clinical Trials on the Frequency of Adverse Events Associated with CFTR Modulators.*

Adverse Event	Ivacaftor	Lumacaftor–Ivacaftor	Tezacaftor–Ivacaftor	Elexacaftor–Tezacaftor–Ivacaftor
Elevated ALT and AST levels	Common	Common	Uncommon	Uncommon
Elevated creatine kinase level	Uncommon	Uncommon	Uncommon	Common
Rash	Common	Common	Uncommon	Common
Cataracts	Uncommon	Uncommon	Uncommon	Uncommon
Neurologic symptoms, depression, or anxiety	Uncommon	Uncommon	Uncommon	Uncommon
Nausea and vomiting	Uncommon	Common	Uncommon	Uncommon
Abdominal pain	Common	Common		Common
Distal intestinal obstruction syndrome	Uncommon	Uncommon		Uncommon
Increase in cough or chest tightness	Uncommon	Common	Common	Uncommon
Decrease in FEV ₁	Uncommon	Common		Uncommon

* Data are modified from the Canadian clinical consensus guideline for initiation, monitoring and discontinuation of CFTR modulator therapies for patients with cystic fibrosis.⁹⁵ Common events occur in more than 10% of patients. For all reported side effects of each CFTR modulator, refer to the specific product monographs. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and FEV₁ forced expiratory volume in 1 second.

macotherapy are recommended.⁹² Although concern has been raised regarding the potential effects of elexacaftor–tezacaftor–ivacaftor on mental health, results of recent studies did not suggest worsening of depression and anxiety after initiation of elexacaftor–tezacaftor–ivacaftor.^{93,94}

SAFETY CONCERNS AND SIDE EFFECTS

CFTR modulators have an overall favorable safety profile. The frequency of adverse events reported in clinical trials is shown in Table 2.⁹⁵ Respiratory-related adverse events appear to occur more frequent with lumacaftor–ivacaftor than with other CFTR modulators. The CFTR modulators are substrates and inducers of the cytochrome P450 enzyme and interact with other drugs that are metabolized in this pathway. Dose adjustment, discontinuation of the CFTR modulator, or adjustment to the full dose from a lower starting dose according to published protocols is advisable in patients with clinically significant side effects and drug–drug interactions.⁹⁶

FUTURE DIRECTIONS

Small molecule–based CFTR pharmacotherapy has been a huge success story, but there is an unmet need to also develop therapies for persons with cystic fibrosis who are not eligible to

receive these medications, who do not have a response to them, or who cannot receive them without adverse effects. For example, there is currently no CFTR-targeting therapy for cystic fibrosis caused by stop codon variants (class I), but read-through drugs could overcome the consequences of premature termination codons. Splice modulation for CFTR variants that affect messenger RNA (mRNA) splicing can be targeted directly or with antisense oligonucleotides. The noncanonical splicing variant 3849+10 kb C→T results in insertion of an intronic sequence that includes a premature stop codon; an antisense oligonucleotide that can increase non-aberrant splicing is currently in clinical development.⁹⁷ Major efforts are also under way to develop therapies such as nucleic acid–based therapies and alternative ion channel modulators that could potentially benefit all persons with cystic fibrosis, regardless of CFTR defect. Gene editing and replacement therapies can target CFTR deficiency by delivery to the lung through the tracheobronchial tree. Preliminary evidence from studies of an adeno-associated viral vector suggest greater lower-airway CFTR expression with this approach than with previous approaches in an early-phase study.^{98,99} Much has been learned about mRNA delivery to target cells during the Covid-19 pandemic, and clinical studies have been initiated with in-

haled CFTR mRNA.¹⁰⁰ Although these novel therapies could potentially ensure that all persons with cystic fibrosis can be treated effectively, access to highly effective modulator therapy and other expensive medications in development varies widely, and strategies need

to be developed to ensure that the current gap in patient outcomes between affluent geographic regions and low- and middle-income countries is closed.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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