JAMA | Review

Cystic Fibrosis
A Review

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IMPORTANCE Cystic fibrosis, a genetic disorder defined by variants in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene, affects more than 30 000 individuals in the US and approximately 89 000 worldwide. Absent or decreased function of the CFTR protein is associated with multiorgan dysfunction and shortened life expectancy.

OBSERVATIONS CFTR is an anion channel in the apical membrane of epithelial cells. Loss of function leads to obstructed exocrine glands. Of people with cystic fibrosis in the US, approximately 85.5% have the gene variant F508del. Manifestations of cystic fibrosis in patients with the F508del gene variant begin in infancy with steatorrhea, poor weight gain, and respiratory symptoms (coughing, wheezing). As people with cystic fibrosis age, chronic respiratory bacterial infections cause loss of lung function and bronchiectasis. With the availability of universal newborn screening in multiple countries including the US, many people with cystic fibrosis are asymptomatic at diagnosis. With multidisciplinary care teams that included dietitians, respiratory therapists, and social workers, treatment of cystic fibrosis can slow disease progression. Median survival has improved from 36.3 years (95% CI, 35.1-37.9) in 2006 to 53.1 years (95% CI, 51.6-54.7) in 2021. Pulmonary therapies for patients with cystic fibrosis consist of mucolytics (eg, dornase alfa), anti-inflammatories (eg, azithromycin), and antibiotics (such as tobramycin delivered by a nebulizer). Four small molecular therapies, termed *CFTR modulators*, that facilitate CFTR production and/or function have received regulatory approval. Examples are ivacaftor and elexacaftor-tezacaftor-ivacaftor. For example, in patients with 1 F508del variant, the combination of ivacaftor, tezacaftor, and elexacaftor improved lung function from −0.2% in the placebo group to 13.6% (difference, 13.8%; 95% CI, 12.1%-15.4%) and decreased the annualized estimated rate of pulmonary exacerbations from 0.98 to 0.37 (rate ratio, 0.37; 95% CI, 0.25-0.55). Improved respiratory function and symptoms have lasted up to 144 weeks in postapproval observational studies. An additional 177 variants are eligible for treatment with the elexacaftor-tezacaftor-ivacaftor combination.

CONCLUSION Cystic fibrosis affects approximately 89 000 people worldwide and is associated with a spectrum of disease related to exocrine dysfunction, including chronic respiratory bacterial infections and reduced life expectancy. First-line pulmonary therapies consist of mucolytics, anti-inflammatories, and antibiotics, and approximately 90% of people with cystic fibrosis who are 2 years or older may benefit from a combination of ivacaftor, tezacaftor, and elexacaftor.

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Cystic fibrosis is an autosomal recessive, genetic disease characterized by reduced or absent function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein that affects more than 30 000 individuals in the US and approximately 89 000 in registries worldwide.[1,2] More than 2000 sequence variants of the *CFTR* gene (OMIM 602421) have been identified. Of these, approximately 700 have been shown to cause disease.[3]

The clinical features of cystic fibrosis result from reduced or absent function of the CFTR protein, a regulated anion channel located in the apical membrane of epithelia in multiple organs, including the lungs, liver, gastrointestinal tract, and pancreas.[4,5] The clinical manifestations of CFTR dysfunction and resultant organ damage include pancreatic insufficiency with malnutrition, biliary cirrhosis, absence of the vas deferens resulting in azoospermia, chronic sinusitis, and chronic endobronchial bacterial infections associated with obstructive airway disease.[6] Identifying the structure and function of CFTR has facilitated development of small molecule CFTR modulator drugs that improve the health of more than 90% of people with cystic fibrosis.[7] This review summarizes

Box. Commonly Asked Questions on the Management of Cystic Fibrosis

How have the new medicines, termed *CFTR modulators*, affected the lives of people with cystic fibrosis?

Modulator combination therapies such as elexacaftor-tezacaftor-ivacaftor, which received initial regulatory approval in 2019, have been highly effective leading to a marked improvement in lung function as measured by forced expiratory volume in the first second, reductions in respiratory symptoms such as cough and sputum production, and hospitalizations. People with cystic fibrosis also experience weight gain and improvements in several measures of quality of life including reduction in school or work absenteeism.

Do all people with cystic fibrosis have access to highly effective modulators?

People with cystic fibrosis must carry at least 1 copy of a cystic fibrosis gene variant responsive to a modulator therapy such as elexacaftor-tezacaftor-ivacaftor to be eligible to receive the therapy. Approximately 90% of people with cystic fibrosis have the gene variant F508del, which is responsive to the elexacaftor-tezacaftor-ivacaftor combination, but there remain many people with cystic fibrosis who do not yet have access to elexacaftor-tezacaftor-ivacaftor, including children younger than 2 years, people with rare gene variants unresponsive to therapy, and people living in geographic regions without access to the approved drugs.

Are there research efforts to find therapies for all people with cystic fibrosis?

There are multiple research programs across the world trying to develop gene-agnostic therapies for which all people with cystic fibrosis will be eligible including gene therapy, gene editing, messenger RNA therapy, and alternative ion channels to bypass the CFTR protein. Most of these approaches are in preclinical stages.

current evidence regarding clinical manifestations and pulmonary treatments of cystic fibrosis (**Box**).

Methods

We searched PubMed for English-language studies of practical guidelines, meta-analyses, or clinical or randomized clinical trials of cystic fibrosis published from January 1, 2012, to December 31, 2022, and updated the search through March 31, 2023.

A total of 1002 articles were retrieved. A second literature search from January 1, 2002, to December 31, 2022, focused on CFTR modulators and resulted in 26 additional articles. Current practice guidelines were reviewed. We manually inspected reference lists of selected articles for other relevant sources. Articles of highest priority for inclusion were meta-analyses, randomized clinical trials, longitudinal studies with longer follow-up, and studies relevant to general medical practice. The 115 articles included 24 were randomized clinical trials; 6 were pediatric single-arm intervention trials; 7 were meta-analyses; 24 were reviews; 14 were longitudinal observational studies; 9 were cross-sectional studies;15 were guidelines or consensus documents; 6 were basic science studies; 3 were registry studies; and 7 were other (1 autopsy case series, 1 economic analysis, 1 protocol, and 4 prescribing information).

Discussion and Observations

Epidemiology

Worldwide, approximately 89 000 individuals are living with cystic fibrosis, including approximately 31 450 people in the US.[1,2] The prevalence of cystic fibrosis is similar between the US (7.97 per 100 000) and European Union (7.37 per 100 000).[8] Among people with cystic fibrosis in the US, approximately 3.5% identified as Black or African American, 91.4% as White, and 5.1% as other, which included people who identified as American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, some other race, or 2 or more races. Among people with cystic fibrosis in the US, approximately 9.8% identified as Hispanic ethnicity and approximately 91.2% as non-Hispanic ethnicity.[1]

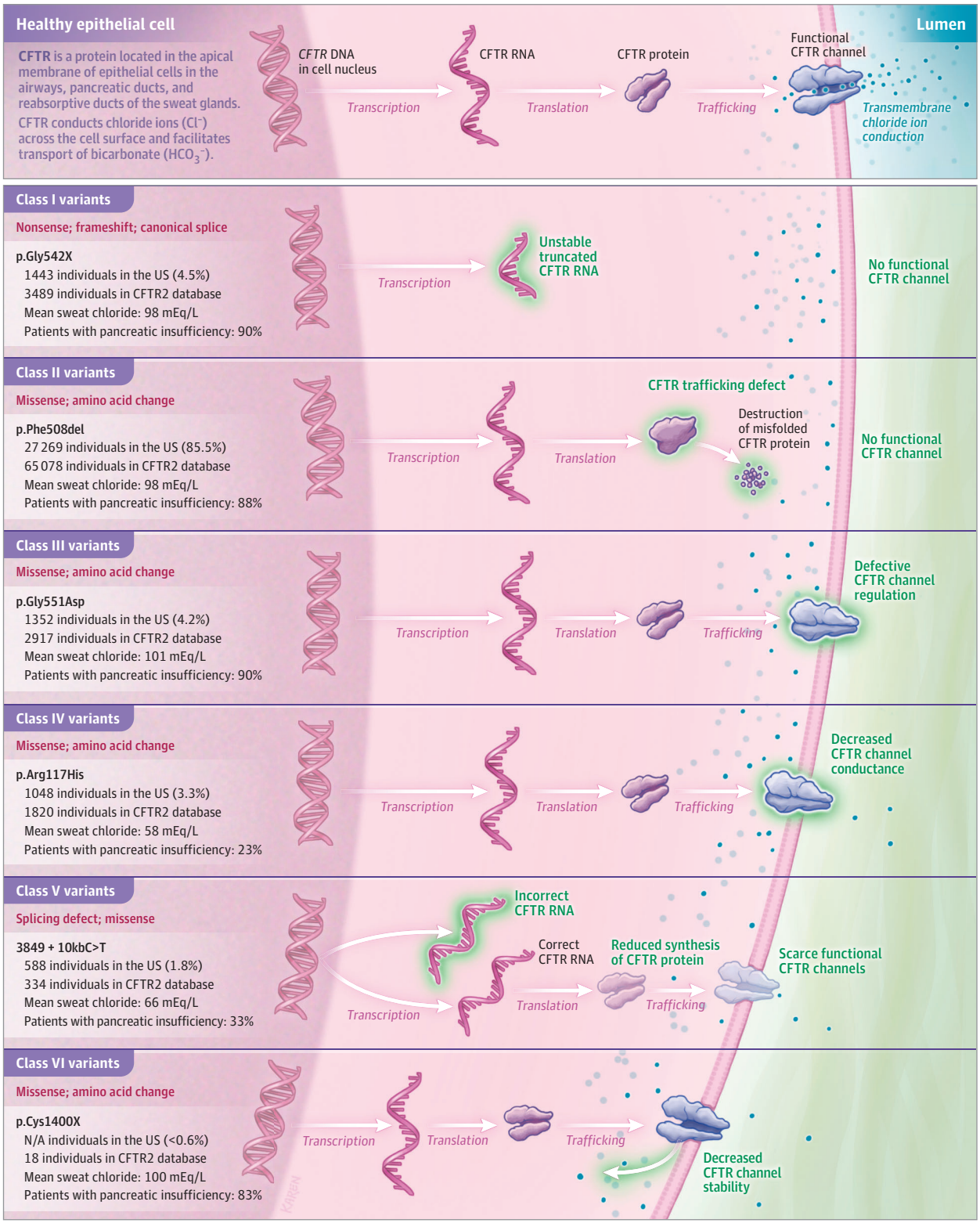
Approximately 85.5% of people in the US have the phenylalanine deleted at position 508 (p.Phe508del) gene variant, also known as F508del.[1] A meta-analysis described 24 to 54 *CFTR* gene variants in regions from South Asia, the Middle East, and East Asia, but populations of non-European ancestry are likely underestimated due to ascertainment bias.[2,9] In populations from 10 countries in Latin America, F508del was the most frequent *CFTR* variant, ranging from 23% to 59%.[10] Rare variants (<1% of individuals) in Latin American populations reflect diverse Native, African, and European heritages.[10]

Pathophysiology

Pathophysiological changes in cystic fibrosis are primarily due to loss of CFTR protein function and its essential role as an anion channel in apical epithelia. Loss of function of the CFTR protein alters hydration and pH concentration in exocrine ducts, leading to obstructed and dilated exocrine glands in multiple organs.[11] Reduced CFTR function in the sweat gland leads to increased salt losses and higher chloride concentrations in sweat.[12] The mucinous obstruction of pancreatic acini and ducts biliary ducts and glandular obstruction of the vas deferens and submucosal glands in the airways leads to organ destruction and fibrosis.[13-15] The endobronchial space of airways in people with cystic fibrosis typically becomes infected initially with bacterial pathogens such as *Staphylococcus aureus* and *Haemophilus influenzae* and later with *Pseudomonas aeruginosa*.[16] These infections are associated with a neutrophilic inflammatory response and persistent mucopurulent plugging that leads to bronchiectasis.[17] With the availability of CFTR modulator therapies, the pathogenesis of clinical disease is changing, and early intervention may partially prevent development of multiorgan pathology. In utero administration of the CFTR modulator ivacaftor to ferret fetuses with the glycine at residue 551 replaced by the aspartic acid (p.Gly551Asp; legacy G551D) variant reduced meconium ileus and improved pancreatic exocrine function, growth, and survival.[18]

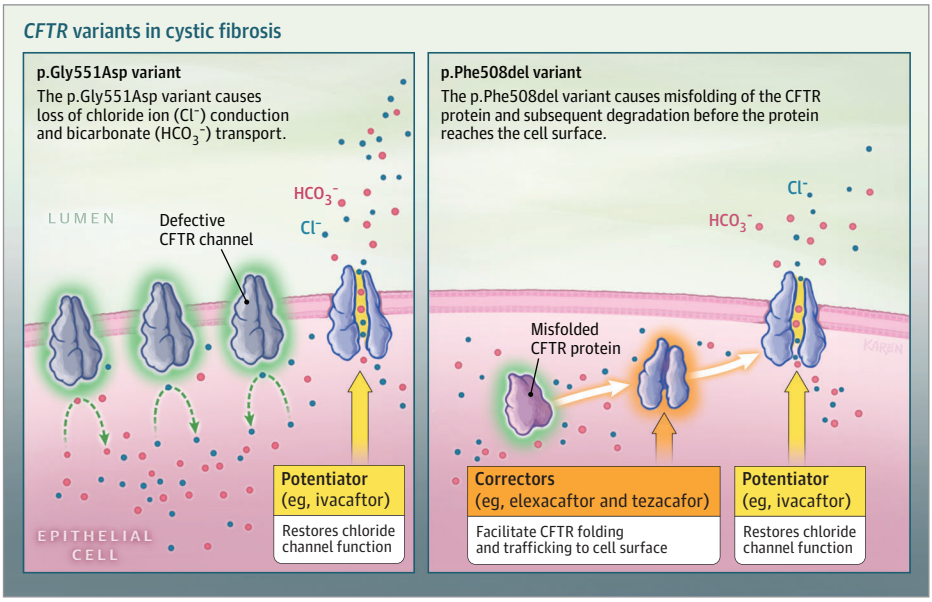
More than 700 disease-causing gene variants of *CFTR* have been identified.[3,6] The most common are grouped into 6 classes by the processes through which they can cause CFTR dysfunction (**Figure 1**).[19,20] Three classes (I, II, III) typically result in minimal or no CFTR and are often associated with the highest sweat-chloride values, severe lung disease, and pancreatic insufficiency whereas classes IV, V, and VI are associated with some residual protein function, may have lower sweat chloride, and milder disease. Although there are examples in which single variants affect multiple mechanisms, matching of cystic fibrosis variants with biological pathways

Figure 1. Cystic Fibrosis Transmembrane Conductance Regulator Variant Classes[1,5,6,19]



Cystic fibrosis transmembrane conductance regulator (*CFTR*) variants can be generally classified in 6 mechanistic classes based on how they alter CFTR RNA transcription, protein trafficking, channel function, and stability.[5,19] Reported prevalence, and clinical features (sweat chloride, pancreatic insufficiency) are summarized for exemplar variants per class.[1,6] The CFTR2 database provides information on all the *CFTR* variants and updates it as information becomes available.[6] The figure is adapted from Boyle and De Boeck.[5] N/A indicates number not available.

Figure 2. Cystic Fibrosis Transmembrane Conductance Regulator Modulator Therapy Functions[21-24]



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

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

have aided in the development of CFTR modulator therapies.[21] Modulator therapies that increase the quantity of CFTR protein at the cell surface are termed *correctors*, and those that augment channel function are termed *potentiators* (**Figure 2**).

Clinical Presentation

Because disease-causing variants of the *CFTR* gene result in a range of protein dysfunction, the clinical presentation and rate of disease progression are variable (Figure 1).[5,21] More than 80% of people with cystic fibrosis and 2 severe gene variants have consequences of exocrine pancreatic insufficiency including protein and fat maldigestion, steatorrhea, and poor growth.[25] Both upper and lower airway disease begin in infancy with cough, increased respiratory rate, or wheezing or crackles on chest auscultation.[26] As patients become infected with pathogens such as *S aureus* and subsequently *P aeruginosa,* they frequently experience acute pulmonary exacerbations, characterized by cough, sputum production, and dyspnea, which require more frequent airway clearance treatments (**Table 1**) and often hospitalization.[44] Chronic endobronchial infections and inflammation lead to a decline in lung function, characterized by a decrease in the forced expiratory volume in the first second (FEV_1) of expiration and forced vital capacity (FVC) on spirometry. Most patients with cystic fibrosis develop an obstructive pattern on spirometry. Recurrent pulmonary infections cause bronchiectasis, a major cause of morbidity and mortality.[7] In addition, patients with advanced cystic fibrosis may develop pulmonary hypertension, which is associated with decreased survival.[49] Adults in the US have been reported to have increased risk of comorbidities[1] including cystic fibrosis–related diabetes (29.2%),[50] liver disease with cirrhosis (4.1%),[51] and osteoporosis (7.5%).[52] People with cystic fibrosis who have at least 1 copy of a *CFTR* variant with residual function often have later onset of lung disease yet have comparable disease progression with those with minimally functional variants.[53]

Of 563 infants diagnosed by newborn screening in the US in 2021, 88.3% were asymptomatic at the time of diagnosis.[1] Among the 216 individuals diagnosed at ages older than 6 months, the most common presenting symptoms were acute or persistent respiratory abnormalities (50.2%) such as cough or wheeze, nasal polyps or sinus disease (15.5%), congenital bilateral absence of the vas deferens or infertility (9%), steatorrhea or abnormal stools (7.7%), failure to thrive (6.9%), and digital clubbing (2.6%).[1]

Assessment and Diagnosis

Diagnostic criteria for cystic fibrosis consist of 1 or more organ-specific manifestations and elevated sweat chloride levels or genetic confirmation of 2 disease-causing variants in the *CFTR* gene. Most newborn screening methods include measurement of immunoreactive trypsinogen (IRT) from a bloodspot, followed by DNA testing for *CFTR* variants, but the thresholds that define IRT elevation and selection of *CFTR* variants can vary across the US, affecting the prevalence of positive screening results.[54,55]

Sweat chloride testing is the main diagnostic test for cystic fibrosis with high sensitivity (99%) and specificity (93%) and has established guidelines for technical quality and accuracy at specialized cystic fibrosis centers.[12,56] Elevated chloride concentration of collected sweat (≥60 mEq/L) is consistent with the diagnosis. Intermediate sweat chloride levels (30-59 mEq/L) require further biochemical, genetic testing, or nasal potential difference measurement and long-term follow-up at specialized centers because some patients may later be diagnosed with definite cystic fibrosis, ranging from 6% to 48% based on prospective and retrospective case series and registry studies.[12,57-59]

Treatment

Long-term Therapies

For patients with cystic fibrosis, at least quarterly visits with a specialized, multidisciplinary team, including physicians, nurses, social workers, and dietitians, are recommended to monitor for disease progression and treat multiorgan manifestations.[29,30,49,60,61] Annual screening for psychosocial health concerns is recommended in

Table 1. Long-term Pulmonary Therapies for Cystic Fibrosis

Therapy	Mechanism of action	Indication	Mode of administration and frequency	Evidence summary
Mucociliary clearance				
Airway clearance techniques such as chest physiotherapy and oscillating devices	Augmented mucociliary clearance of the lung and facilitate cough to remove mucus obstruction from airways; mechanical loosening of airway secretions	Mechanical exercise and devices to relieve retained airway secretions in conjunction with standard maintenance nebulized therapies	Maintenance typically 2/d and increases with pulmonary exacerbations[27]	In a meta-analysis of 38 studies (n =1114) of multiple oscillating devices for airway clearance techniques, there was no clear evidence of one mode superior to another[28]
Dornase alfa	Reduced viscosity of airway secretions through cleaving of extracellular DNA in sputum	Recombinant DNase enzyme used in conjunction with maintenance airway clearance techniques	Recommended as part of maintenance therapy: 2.5-mg nebulized 1/d[29,30]	In a meta-analysis of 15 studies (n = 2447), dornase alfa improved lung function and reduced pulmonary exacerbations vs placebo[31]
Inhaled hypertonic saline	Not established. Proposed mechanisms include airway surface hydration through improved sputum rheological properties and antimicrobial properties	Concentrated saline solution inhaled used in conjunction with standard maintenance airway clearance therapies	Recommended as part of maintenance therapy[29] 7%: 4 mL-nebulized 2/d; Bronchodilator pretreatment recommended to reduce symptoms of cough and wheeze associated with administration	Meta-analysis of 17 randomized controlled trials (n = 966) found evidence of reduced frequency of pulmonary exacerbations, but low evidence for improvement in FEV_1[32] In recent trials among young children, 7% hypertonic saline use improved lung clearance index, a measure of lung function[33,34]
Mannitol	Not directly established; proposed mechanisms are to act as a hyperosmolar agent to rehydrate the airway surface and improve sputum viscosity	Nebulized sugar alcohol as add-on maintenance therapy to manage patients who have passed a tolerance test Mannitol was approved in 2019 for age ≥18 y in the US	400-mg inhaled 2/d	A meta-analysis of 6 studies (n = 784) reported that mannitol improved measures of lung function with moderate quality evidence[35] Inhaled mannitol was associated with mean absolute improvement of lung function relative to placebo in adults ($ppFEV_1$ difference, 1.21%; 95% CI, 0.07%-2.36%; P = .04)[36]
Anti-inflammatory				
Azithromycin	Proposed anti-inflammatory mechanisms include reducing IL-4 and IL-8, suppressing neutrophil activity, and decreasing production of tumor necrosis factor[37]	Macrolide antibiotic as add-on maintenance therapy for patients who are chronically infected with *Pseudomonas aeruginosa* and consideration of use for those without *P aeruginosa*[29,30]	Limited data, but largest trials have used <40 kg: 250 mg 3/wk and ≥40 kg: 500 g 3/wk[38]	A 2012 Cochrane review of 10 studies (n = 959) found azithromycin improved mean FEV_1 by approximately 4% vs placebo for patients infected with *P aeruginosa* and reduced exacerbations[38] Hospital days for exacerbations were reduced with azithromycin vs placebo among infants, 3-6 mo (mean difference, 6.3; 95% CI; −10.5 to −2.1)[39]
High-dose ibuprofen	Not directly established; proposed mechanisms include reduced airway inflammation as an inhibitor of cyclooxygenase-1 and cyclooxygenase-2; blocks release of leukotriene B_4, a proinflammatory molecule that promotes neutrophil activity; inhibition of neutrophil chemotaxis and NF-κB–mediated inflammation[29]	Patients aged 6-18 y to reduce annual decline in lung function; US national guidelines recommend use in children with attention to concentration levels, but insufficient evidence for use in adults[29]	Dose adjusted for peak plasma concentrations of 50 to 100 µg/mL; approximately 20 to 30 mg/kg 2/d Maximum dose: 1600 mg 2/d Requirement for annual ibuprofen levels has reduced acceptance of therapy by patients and caregivers	A 2019 Cochrane review of 4 trials (n = 287) found ibuprofen treatment vs placebo reduced annual rates of lung function decline, particularly in children[40]
Inhaled antibiotics for chronic *P aeruginosa*				
Inhaled tobramycin	Active against most gram-negative bacilli through binding of bacterial ribosome and inhibiting protein synthesis[41]	Guideline-recommended inhaled maintenance therapy for patients with chronic *Pseudomonas aeruginosa* infection[29]	300-mg nebulized or 112-mg dry powder inhaler 2/d for 28 d alternating with 28 d off	A 2022 meta-analysis of inhaled antibiotics to treat *P aeruginosa* in included 18 trials (n = 3024); among the 12 included, tobramycin had the best available evidence of the antipseudomonal antibiotics reviewed and tobramycin use was associated with improved lung function and reduced exacerbations [42]

(continued)

Table 1. Long-term Pulmonary Therapies for Cystic Fibrosis (continued)

Therapy	Mechanism of action	Indication	Mode of administration and frequency	Evidence summary
Inhaled aztreonam lysine	Inhibits synthesis of bacterial cell walls; active against gram-negative bacteria and stable against β-lactamases[43]	Inhaled maintenance therapy for patients with chronic *P aeruginosa* infection[29]	75-mg nebulized 3/d for 28 d alternating with 28 d off	A 2022 meta-analysis of inhaled antibiotics to treat *P aeruginosa* included 18 trials (n = 3024); Of 18 trials, 1 trial found moderate-quality evidence for aztreonam use for improved lung function (mean difference, FEV_1, −3.4%; 95% CI, −6.63% to −0.17%) with fewer hospitalizations vs inhaled tobramycin[42]
Pulmonary exacerbations				
Management of pulmonary exacerbations, clinically presenting as recurrent episodes of clinical symptoms including increased cough, sputum production, dyspnea, decreased energy level and appetite, weight loss, and/or decreases in measures of spirometry[44,45]	Antibiotic therapy for 10- to 14-d courses associated with decreased bacterial density in sputum and improved lung function[46]	Guideline-recommended increased frequency for airway clearance therapy sessions and antibiotic courses[44]	Antibiotics based on respiratory microbiological cultures; increased frequency of airway clearance; hospitalization may be needed	A 2021 trial of adults (n = 982) treated for pulmonary exacerbation found lung function change from treatment initiation was noninferior at 10 d vs 14 d of therapy among early responders within 7 to 10 d of therapy (mean $ppFEV_1$ change, 12.8% vs 13.4%; difference, −0.65%; 95% CI, −3.3% to 2.0%) and noninferior at 14 vs 21 d of therapy for later responders (difference, −0.10%; 95% CI, −1.3% to 1.1%)[47] Lung function improvement was higher for those treated in the hospital vs at home (mean $ppFEV_1$ change, 8.0%; 95% CI, 6.7% to 9.4% vs 5.0%; 95% CI, 3.5% to 6.5%)[48]

Abbreviations: NF-κB, nuclear factor kappa-B; $ppFEV_1$, predicted percent of forced expiratory volume in the first second of expiration.

children aged 12 years or older.[62] Monitoring for comorbidities includes annual oral glucose tolerance testing (≥10 years) for cystic fibrosis–related diabetes,[50] dual-energy x-ray absorptiometry scanning every 2 to 5 years (>8 years) for bone density, and colonoscopy every 5 years (≥40 years) for colorectal cancer.[63]

Disease progression is measured by monitoring for trends in nutritional status (height, weight, body mass index [BMI], calculated as weight in kilograms divided by height in meters squared), lung health (spirometry, respiratory microbiology, chest imaging), and assessments for pulmonary exacerbations. Exacerbations manifest as an acute worsening of respiratory symptoms and lung function (percent predicted FEV_1 [$ppFEV_1$]) and usually require oral or intravenous antibiotic treatments specific for respiratory microbiology, increased airway clearance therapies (eg, high-frequency oscillatory percussive devices), and high-calorie, high-protein diets to limit permanent loss of lung function.[44,47] In a randomized clinical trial of 982 participants with cystic fibrosis and pulmonary exacerbation defined by providers as necessitating intravenous antibiotic treatment, antibiotic therapy duration of 10 days was noninferior to 14 days, based on the outcome of lung function (change in $ppFEV_1$) among those who had improved lung function and symptoms within 7 to 10 days of treatment (mean $ppFEV_1$ change, 12.8% vs 13.4%; difference, −0.65%; 95% CI, −3.3% to 2.0%). In addition, those without improved lung function or symptoms within days 7 to 10 days, 21 days of intravenous antibiotics was not superior to 14 days[47] (mean $ppFEV_1$ change, 3.3% vs 3.4%; difference, −0.10%; 95% CI, −1.3% to 1.1%).[47] In subsequent analysis, lung function improvement was higher for those treated in the hospital (mean $ppFEV_1$ change, 8.0%; 95% CI, 6.7% to 9.4%) vs at home (mean $ppFEV_1$ change, 5.0%; 95% CI, 3.5% to 6.5%).[48]

Long-term pharmacological pulmonary therapies such as mucolytics to thin secretions to facilitate clearance from the upper and lower airways (such as dornase alfa), airway surface liquid hydration (inhaled hypertonic saline, mannitol), and anti-inflammatory drugs (azithromycin, ibuprofen) have been based on phase 3 randomized, placebo-controlled clinical trials (Table 1). In a clinical trial of 968 patients with cystic fibrosis, dornase alfa compared with placebo increased the mean percent change in FEV_1 by 5.8% (SE, 0.7%) vs 0% (SE, 0.6%) and reduced the proportion of patients with 1 or more pulmonary exacerbations from 89 (27%) to 61 (19%).[64] In a clinical trial of 164 participants, 7% hypertonic saline compared with 0.9% saline reduced pulmonary exacerbations (mean exacerbations per participant, 0.39 [7% saline] vs 0.89 [0.9% saline]); difference, 0.5; 95% CI, 0.14-0.86; $P = .02$).[65] In a randomized clinical trial of 185 patients chronically infected with *P aeruginosa*, azithromycin, compared with placebo, significantly improved lung function from baseline ($ppFEV_1$, 4.4% vs −1.8%; mean difference, 6.2%; 95% CI, 2.6%-9.8%) at end of 168 days of treatment.[66]

CFTR Modulator Therapies

CFTR modulator therapies act by 2 mechanisms to enhance CFTR function. Potentiators, like ivacaftor, increase the probability that the protein channel is open, so chloride or bicarbonate can flow more easily through the cell membrane (Figure 2). Correctors, like lumacaftor, tezacaftor, and elexacaftor, improve channel quantity at the cell surface by helping the protein fold properly, enabling

transport to the cell surface (Figure 2). Severe variants such as F508del need both potentiators and correctors to improve channel quantity and function (Figure 2). Four modulators are currently approved by US and European drug regulatory agencies, and eligibility for each treatment depends on the specific *CFTR* genetic variants present (**Table 2**). Ivacaftor is available as a monotherapy, and lumacaftor-ivacaftor, tezacaftor-ivacaftor, and elexacaftor-tezacaftor-ivacaftor are available as combination therapies (Table 2).

Ivacaftor (formerly VX-770) was the first CFTR modulator tested in randomized clinical trials of patients with cystic fibrosis in 2006. Ivacaftor was tested first for patients with cystic fibrosis who have a *G551D-CFTR* variant where the CFTR protein is transported to the cell membrane, but the CFTR channel does not open properly. In a randomized clinical trial of 161 patients with at least 1 copy of G551D, compared with placebo, patients at 24 weeks' follow-up had improved $ppFEV_1$ (10.1% vs −0.4%; mean difference, 10.5%; 95% CI, 8.5%-12.5%), a 55% reduction in pulmonary exacerbations (28 vs 44; rate ratio, 0.43; 95% CI, 0.27-0.68), and increased weight (3.1 kg vs 0.4 kg; mean difference, 2.7 kg; 95% CI, 1.3-4.1 kg).[68] Respiratory symptoms were scored on a 100-point scale on the respiratory domain of the Cystic Fibrosis Questionnaire revised (CFQ-R), for which higher numbers indicate a lower effect of these symptoms on quality of life (minimal clinically important difference, 4 points).[81] Ivacaftor improved respiratory symptom scores by 8.6 points relative to placebo (5.9 vs −2.7; mean difference, 8.6; $P < .001$). Ivacaftor is approved for patients 4 months or older.

For people with 2 copies of the F508del variant, ivacaftor alone did not improve CFTR activity or demonstrate clinical efficacy.[82] These patients required the combination of corrector and potentiator medications. Randomized, placebo-controlled clinical trials of first-generation correctors, lumacaftor or tezacaftor, in combination with ivacaftor demonstrated modest improvements in $ppFEV_1$ and reduction in pulmonary exacerbations in patients homozygous for the F508del variant.[73,74,77,83,84] For example, in a clinical trial of 509 patients homozygous for the F508del variant, the tezacaftor-ivacaftor combination drug compared with placebo improved $ppFEV_1$ (3.4% vs −0.6%; mean difference, 4%; 95% CI, 3.1% to 4.8%) and reduced the pulmonary exacerbations annualized rate (0.64 vs 0.99 events per year; rate ratio, 0.65; 95% CI, 0.48 to 0.88) at 24 weeks' follow-up.[70] The tezacaftor-ivacaftor combination reduced sweat chloride (−9.9 vs 0.2 mEq/L; mean difference, −10.1 mEq/L; 95% CI, −11.4 to −8.8 mEq/L) for patients homozygous for the *F508del* variant, but had no effect in patients with 1 copy.[53,77,85,86]

The combination of a second-generation corrector, elexacaftor (formerly VX-445) with the first-generation corrector tezacaftor (formerly VX-661) had an additive effect in stabilizing the nascent CFTR protein and facilitated increased expression of the mature CFTR protein channel at the cell surface.[87,88] When the 2 correctors were combined with the potentiator, ivacaftor, in phase 3 randomized trials, this triple combination was effective and had similar clinical responses for people with cystic fibrosis who were either homozygous for the F508del variant or who had 1 copy of the F508del variant and 1 copy of a minimal function variant on the second allele (Table 2).[22,23] In a randomized clinical trial of 107 patients who were homozygous for the F508del variant, the elexacaftor-tezacaftor-ivacaftor combination compared with tezacaftor-ivacaftor alone increased $ppFEV_1$ (10.4% vs 0.4%; difference, 10.0%; 95% CI, 7.4% to 12.6%), decreased sweat chloride concentration (−43.4 vs 1.7 mEq/L; difference, −45.1; 95% CI, −50.1 to −40.1 mEq/L), and improved respiratory symptom scores above the 4-point minimally important clinical difference for CFQ-R (16 vs −1.4; difference, 17.4; 95% CI, 11.8 to 23) at 4 weeks' follow-up.[22]

In a randomized clinical trial[23] of 403 patients heterozygous for the F508del variant and a minimal function variant, elexacaftor-tezacaftor-ivacaftor compared with placebo improved $ppFEV_1$ (13.6% vs −0.2%; mean difference, 13.8%; 95% CI, 12.1% to 15.4%) at 4 weeks and through 24 weeks (13.9% vs −0.4%; mean difference, 14.3%; 95% CI, 12.7% to 15.8%).[23] The elexacaftor-tezacaftor-ivacaftor combination decreased the pulmonary exacerbations annualized rate (0.37 vs 0.98; rate ratio, 0.37; 95% CI, 0.25 to 0.55), increased absolute change in body mass index from baseline (1.13 vs 0.09; difference, 1.04; 95% CI, 0.85 to 1.23), improved respiratory symptom scores by CFQ-R (17.5 vs −2.7; difference, 20.2 points; 95% CI, 17.5 to 23.0) and decreased sweat chloride concentration (−42.2 vs −0.4 mEq/L; difference, −41.8 mEq/L; 95% CI, −44.4 to −39.3 mEq/L) at 24 weeks' follow-up.[22,23] Preliminary open-label observational studies involving people taking elexacaftor-tezacaftor-ivacaftor therapy have reported similar results at up to 144 weeks of follow-up.[89]

Elexacaftor-tezacaftor-ivacaftor is approved for patients aged 2 years or older; approximately 90% of people with cystic fibrosis, including for those with variants that have demonstrated in vitro culture response to treatment.[80,90-92] This technique known as *theratyping* has increased access to therapy with modulator drugs among people with rare (<1%) *CFTR* variants.[92]

Ivacaftor and its combination CFTR modulator were generally well tolerated and had similar safety profiles in phase 3 studies involving younger age groups (Table 2).[69-71,74,75,80,90,91,93,94] Compared with placebo, elexacaftor-tezacaftor-ivacaftor had a similar incidence of adverse events (93.1% vs 96.1%) including headache (17%), upper respiratory tract infection (16%), abdominal pain (14%), diarrhea (13%), exanthem (10%), increased alanine transaminase (10%), or aspartate transaminase (9%).[23] Serious adverse events were less common in the treatment group (13.9% vs 20.9%).[23] For all CFTR modulator therapies, liver function monitoring is recommended quarterly for the first year of treatment and then annually.[67,72,76,78] Ophthalmologic examinations for children are recommended annually based on toxicology studies of ivacaftor that identified cataracts in juvenile rats, although this adverse effect was not observed in human trials.[67] Drug interactions are important considerations because ivacaftor and combination therapies are both substrates and inducers in the cytochrome P450 (*CYP3A*) pathway (Table 2).[67,72,76,78]

Prognosis

In 2021, the median age of survival in the US was approximately 53.1 years (95% CI, 51.6-54.7 years) for people born from 2017 through 2021. In comparison, for people with cystic fibrosis born from 2001 through 2006, life expectancy was approximately 36.3 years (95% CI, 35.1-37.9 years). The US annual mortality rate was 1.5 deaths per 100 in 2006 and 0.7 deaths per 100 in 2021.[1] Registry data across multiple other countries such as the UK, Germany, and Canada have reported similar improvements in life expectancy. Current life expectancy in the UK, Germany, and Canada is approximately 47 to 53 years.[95]

Newborn screening for early diagnosis of cystic fibrosis has been associated with improved health.[12] A prospective, observational

Table 2. *CFTR* Modulator Therapies for Cystic Fibrosis

Modulator name	Common eligible genotypes (prevalence in US)[1]	Ages approved and adult dosing	Efficacy	Adverse effects	Monitoring and drug interactions
Ivacaftor	Approved use for use with ≥1 copy of G551D (4.2%) R117H (3.3%) 3849 + 10kbC→T (1.8%)[a] 2789 + 5G→A (1.5%)[a] D1152H (1.1%) 3272-26A→G (0.8%)[a] L206W (0.7%) A455E (0.6%) For all eligible 97 variants, refer to prescribing information[67]	Approved for ages ≥1 mo; Dose for ages ≥6 y: one 150-mg tablet every 12 h; for ages 4 mo to 6 y, see prescribing information67	For patients with a *G551D-CFTR* variant, ivacaftor vs placebo increased mean absolute change from baseline lung function ($ppFEV_1$) through wk 24 (10.4% vs −0.2%; 95% CI, 8.6% to 12.6%; $P < .001$) and wk 48 (10.1% vs −0.4%; 95% CI, 8.5% to 12.5%; $P < .001$); reduced pulmonary exacerbations at wk 28 (rate ratio, 0.38; 95% CI, 0.22 to 0.64; $P < .001$); and improved weight gain from baseline to wk 28 (difference, 2.8 kg; 95% CI, 1.8 to 3.7; $P < .001$); reduced sweat chloride concentration (−48.7 vs −0.06 mEq/L; mean difference, −48 mEq/L; $P < .001$)[68] In an open-label, single-arm study of children (aged 2-5 y) who received ivacaftor and had 1 gating gene variant, mean-weight-for-age *z* score increased 0.2 from baseline at wk 24 ($P < .001$)[69] In single-arm study of infants (12-24 mo) receiving ivacaftor, mean weight-for-age z score was maintained 0.15 (95% CI, −0.05 to 0.36) from baseline[70] Ivacaftor for 4 mo-<12 mo, mean weight-for-age *z* score increased 0.52 (95% CI, 0.23 to 0.82) from baseline[71]	AEs were similar for ivacaftor vs placebo to 48 wk (82 vs 78 participants), but lower incidence of cough (33% vs 42%), pulmonary exacerbation (13% vs 33%) in the treated group; AEs more commonly reported for ivacaftor vs placebo: headache (22.9%), respiratory tract infection (22.9%), nasal congestion (17%), rash (14.5%), dizziness (12%), increased hepatic enzyme levels led to study drug discontinuation for 1 in the ivacaftor group vs 4 in the placebo group[68]	Elevated transaminases: ALT or AST assessed prior to initiation and every 3 mo for first y of treatment, then annually; increase monitoring frequency for history of elevations; interrupt dose if ALT or AST >5 × ULN Cataracts: reported in pediatric patients; baseline and follow-up eye examinations recommended for patients ≤18 y Drug interactions: reduce ivacaftor dose or avoid CYP3A inhibitors (eg, ketoconazole, voriconazole, clarithromycin, erythromycin, food containing grapefruit); avoid coadministration with strong CYP3A inducers (eg, rifampin, phenobarbital, St John's wort) that decrease ivacaftor exposure; caution and monitoring for medications categorized as CYP2C9 substrates (eg, warfarin, glipizide) and CYP3A and/or P-gp substrates (eg, digoxin, cyclosporine, tacrolimus) Ivacaftor may increase exposure of such medications
Lumacaftor-ivacaftor	*F508del* homozygous (44.1%)	Approved for ages ≥1 y Dose for ages ≥12 y: 2 tablets combined of 200-mg lumacaftor and 125-mg ivacaftor every 12 h Doses for ages 1 y to 11 y, refer to prescribing information[72]	In pooled analysis of 2 studies, lumacaftor-ivacaftor vs placebo improved: mean absolute difference of $ppFEV_1$ (range, 2.8 to 3.3, $P < .001$); reduced pulmonary exacerbations rate (range, 0.61 to 0.70; $P = .001$); increased absolute change in BMI (range, 0.24 to 0.28; $P < .001$).[73,74]	Incidence of AEs were similar in lumacaftor-ivacaftor-treated and placebo groups up to 24 wk, but higher proportion of patients who discontinued study drug because of an AE in lumacaftor-ivacaftor group (4.2% vs 1.6%)[73] Common AEs: dyspnea (13%), nasopharyngitis (13%), nausea (13%), rash (7%), and elevated blood creatine phosphokinase (7%); elevation of liver transaminases, rash; and drug interactions have also been reported[74,75]	Patients: caution use and consider reduced dose in patients with advanced liver disease; increased monitoring for respiratory symptoms at initiation in patients with $ppFEV_1$ < 40% Elevated transaminases (ALT, AST, bilirubin): same monitoring as per ivacaftor and interrupt dose if ALT or AST >3 × ULN with bilirubin >2 × ULN Blood pressure: periodically measure blood pressure in all patients for elevations Drug interactions: same as ivacaftor above; and interacts with CYP3A substrates or CYP3A substrates with narrow therapeutic index, including reducing effects of hormonal contraceptives Cataracts: same monitoring as ivacaftor
	F508del homozygous (44.1%); or 1 copy of all variants for ivacaftor; or 1 copy of additional 57 variants; for all eligible variants, refer to prescribing information[76]	Approved for ages ≥6 y Dose for ages ≥12 y: 1 tablet tezacaftor 100 mg/ivacaftor 150 mg in AM; 1 tablet ivacaftor 150 mg in PM Doses for ages 6 y to 11 y, refer to prescribing information[76]	Tezacaftor-ivacaftor vs placebo improved mean absolute difference of $ppFEV_1$ (3.4% vs −0.6%, $P < .001$) through wk 24; reduced pulmonary exacerbation rate (0.65; 95% CI, 0.48, 0.88; $P = .005$)[77] Tezacaftor-ivacaftor improved $ppFEV_1$ (6.8%, $P < .001$) vs placebo[53]	Most AEs deemed unrelated to study drug; common adverse drug reactions (occurring in ≥3% of patients) were headache, nausea, sinus congestion, and dizziness; study drug interruption most commonly from elevated liver transaminases[53]	Elevated transaminases (ALT, AST, bilirubin): same monitoring as per lumacaftor-ivacaftor Cataracts: same monitoring as ivacaftor Drug Interactions: same as ivacaftor; reduce dose with strong or moderate CYP3A inhibitors; avoid coadministration with strong CYP3A inducers and food containing grapefruit

(continued)

Table 2. *CFTR* Modulator Therapies for Cystic Fibrosis (continued)

Modulator name	Common eligible genotypes (prevalence in US)[1]	Ages approved and adult dosing	Efficacy	Adverse effects	Monitoring and drug interactions
Elexacaftor-tezacaftor-ivacaftor	≥1 copy of F508del (85.5%); G85E (0.7%) or all variants for tezacaftor-ivacaftor (except as indicated)[a] or of additional 30 CFTR variants; all eligible variants, refer to prescribing information[78]	Approved for ages ≥2 y Dose for ages ≥12 y: 2 tablets, each containing 100-mg elexacaftor, 50-mg tezacaftor, and 75-mg ivacaftor in AM; 1 tablet of 150-mg ivacaftor in PM Doses for ages 2 y to 11 y, refer to prescribing information[78]	In patients who were *F508del* homozygous, elexacaftor-tezacaftor-ivacaftor vs placebo increased: absolute change in lung function ($ppFEV_1$) from baseline at 29 d (13.8 vs 0.4; difference, 11.0; 95% CI, 7.9 to 14.0; P < .001)[22] In patients with *F508del*-minimal function genotypes, elexacaftor-tezacaftor-ivacaftor vs placebo increased absolute change in lung function ($ppFEV_1$) from baseline at wk 4 (13.6% vs −0.2%; mean difference, 13.8%; 95% CI, 12.1% to 15.4%; *P* < .001) and through wk 24 (13.9% vs −0.4%; mean difference, 14.3%; 95% CI, 12.7% to 15.8%; P < .001)[23] In participants with *F508del*-gating or *F508del*-residual function variants, elexacaftor-tezacaftor-ivacaftor vs active control increased lung function ($ppFEV_1$) from active control by 3.5 percentage points (95% CI, 2.2 to 4.7)[79] In children aged 6-11 y, elexacaftor-tezacaftor-ivacaftor improved the lung clearance index (−2.29 vs −0.02 units; *P* < .001)[80]	Similar incidence of AEs seen in elexacaftor-tezacaftor-ivacaftor vs placebo; common AEs (≥5% of patients and higher than placebo by ≥1%): headache (17%), upper respiratory tract infection (16%), abdominal pain (14%), diarrhea (13%), rash (10%), increased ALT levels (10%), increased nasal congestion, blood creatine phosphokinase levels (9%), and AST increased (9%); rash led to 1% study drug discontinuation vs <1% placebo[23]	Elevated transaminases (ALT, AST, bilirubin): same monitoring as per lumacaftor-ivacaftor and tezacaftor-ivacaftor; more frequent monitoring for people with advanced liver disease or history of elevations Cataracts: same monitoring as ivacaftor Drug Interactions: same as tezacaftor-ivacaftor; reduce dose with strong or moderate CYP3A inhibitors; avoid coadministration with strong CYP3A inducers and food containing grapefruit

Abbreviations: AE, adverse effect; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; *CFRT*, cystic fibrosis transmembrane conductance regulator; $ppFEV_1$, predicted percent of forced expiratory volume in the first second of expiration; ULN, upper limit of normal.

[a] Variants eligible for ivacaftor and tezacaftor-ivacaftor only and not eligible for elexacaftor-tezacaftor-ivacaftor therapy.

study of 231 infants with cystic fibrosis diagnosed by universal newborn screening in the US demonstrated that infants diagnosed during newborn screening had minimal respiratory symptoms and were able to achieve normal weight for age by 1 year, although their mean lengths were lower than the World Health Organization standard growth curves for healthy infants.[96] A retrospective cohort study comparing the longitudinal outcomes of 9571 infants in the same birth cohort before and after implementation of the cystic fibrosis newborn screening program by state found that a newborn screening program was associated with higher median weight (6.0, 95% CI, 3.1-8.4) and median height (6.6; 95% CI, 3.8-9.3) percentiles in the first year of life and was associated with older age at onset of chronic *P aeruginosa* infection (hazard ratio [HR], 0.69; 95% CI, 0.54-0.89), but no association with lung function ($ppFEV_1$) at age 6 years.[97]

Observational data showed that modulator therapy was associated with improved health.[98,99] Among 2509 patients with cystic fibrosis from the US and UK who were followed up from 2011 (pretreatment baseline) to 2016, the 635 patients treated with ivacaftor maintained higher lung function and higher BMI compared with the 1874 patients not treated with ivacaftor.[98] Patients who received ivacaftor had an FEV_1 decline of −0.7% at the 5-year follow-up compared with 8.3% in the group that did not receive ivacaftor. In the PROMISE[99] observational study of 487 people with cystic fibrosis who were treated with elexacaftor-tezacaftor-ivacaftor, sustained improvement in lung function, measured by $ppFEV_1$, was observed at the 6-month follow-up compared with pretreatment baseline (90.9% vs 80.5%; difference, 9.8%; 95% CI, 8.8% to 10.8%). In this cohort, elexacaftor-tezacaftor-ivacaftor use was associated with improved CFTR function as measured by sweat chloride concentration (after treatment, 45.7 mEq/L vs baseline, 88.0 mEq/L; difference, −41.7 mEq/L; 95% CI, −43.8 to −39.6 mEq/L).[99] In a prospective observational study of people with cystic fibrosis with advanced lung disease (defined as $ppFEV_1$ < 40%), elexacaftor-tezacaftor-ivacaftor use was associated with an absolute change from baseline $ppFEV_1$ of 15.1%.[100] The proportion of people with cystic fibrosis who required supplemental oxygen declined from 43.4% at initiation to 23.4% after 3 months of elexacaftor-tezacaftor-ivacaftor treatment and requirements for noninvasive ventilation were reduced from 28.1% to 19.8%.[100] The 2021 Cystic Fibrosis Foundation Patient Registry[1] reported a decline in number of lung transplants from 197 in 2006 to 54 in 2021.

Improvements in longevity observed in cystic fibrosis are not equal by race or ethnicity in the US. Hispanic patients compared with non-Hispanic patients had significantly higher mortality after adjustment for clinical and socioeconomic factors (9.1% vs 3.3%; HR, 2.8; 95% CI, 1.7 to 4.6).[101] These differences in outcomes may be due in part to delayed diagnosis and care initiation. Among 6354 infants born between 2010 through 2018, initiating cystic fibrosis care occurred later among infants described as American Indian and Native Alaskan, Asian, Black or African American, and/or other race, and/or Hispanic ethnicity (group 1), compared with infants described as White and not Hispanic (group 2). The median age at the first clinical evaluation for cystic fibrosis among infants in group 1 was 31 days (IQR, 19-49 days) vs 22 days (IQR, 14-36) for those in group 2. Delayed cystic fibrosis care was associated with worse nutrition. Measured by weight-for-age *z* scores at 1 year of age, the median *z* score for group 1 was −0.11 (IQR, −0.75 to 0.59) vs 0.062 (IQR, −0.57 to 0.65) for group 2.[102] *CFTR* genetic panels and selection of variants tested differ by state and often represent the most common variants. In a cross-sectional study of 7 *CFTR* genetic panels used in newborn screening, detection of at least 1 *CFTR* variant was lowest in infants identified as Black, Asian, and Hispanic compared with infants categorized as non-Hispanic White

for all panels (41.9%-93.1% vs 87.5%-97.0%).[103] Panel choice by state may contribute to inequities in delays in diagnosis of cystic fibrosis. The *CFTR* genetic variants present in Black patients (69.7%) and Hispanic patients (75.6%) have fewer matching *CFTR* modulators available for treatment compared with the variants present in White patients (92.4%).[104]

Practical Considerations and Application of Evidence

As health improves, particularly after initiation of elexacaftor-tezacaftor-ivacaftor, people with cystic fibrosis have expressed interest in reducing the number of treatments.[105] Randomized clinical trials and observational studies are underway to identify therapies that can be reduced or eliminated in patients receiving CFTR modulator therapies. The SIMPLIFY study[105] included 2 independently conducted randomized, clinical trials assessing the noninferiority of discontinuing vs continuing 6 weeks of either hypertonic saline (184 discontinued vs 186 continued) or dornase alfa (240 discontinued vs 234 continued). In the hypertonic saline trial, discontinuing hypertonic saline was non-inferior to continuing with respect to the 6-week change in $ppFEV_1$ (−0.19% vs 0.14%; difference, −0.32%; 95% CI, −1.25 to 0.60). In the dornase alfa trial, discontinuing dornase alfa was noninferior to continuing with respect to the 6-week change in $ppFEV_1$ (0.18% vs 0.16%; difference, 0.35%: 95% CI, −0.45% to 1.14%).[105] The SIMPLIFY study is the first step toward understanding the need for standard therapies for people receiving modulators.

Wholesale acquisition costs of CFTR modulators can range from $272 623 to $311 741 per year and raise concerns about affordability and access.[106] However, the final reimbursement cost is based on agreements with health authorities or private payers and is variable. In the US, CFTR modulator therapies were prescribed to 91% (range, 75.9%-100%) of people with eligible *CFTR* variants in 2021, funded by both private and public payers.[1] More than 40 countries, including Australia, Europe, Israel, New Zealand, and North America have regulatory and reimbursement approvals permitting access to elexacaftor-tezacaftor-ivacaftor combination therapy. However, other global areas such as India, and in regions of Central and South America, the Middle East, and Southern Africa are awaiting approval for elexacaftor-tezacaftor-ivacaftor, which could widen disparities in cystic fibrosis outcomes between high-income and low- and middle-income countries.[107]

Several knowledge gaps about modulator therapies must be addressed. Long-term pharmacovigilance is needed to understand the safety of these drugs including drug-drug interactions and effects such as weight gain, elevated blood pressure, mental health effects, and liver function abnormalities.[94] The long-term safety and effectiveness of CFTR modulators prenatally and in infants younger than 4 months is unknown.[108]

Adults comprise 58.3% of the total US cystic fibrosis population. As this population ages, expanded services will be needed across multiple subspecialities to manage comorbidities and age-related complications including gastrointestinal cancers, diabetes, obesity, and hypertension.[1,50,63,94,109] Rates of pregnancy in women with cystic fibrosis have increased from 210 in 2011 to 675 in 2021, underscoring the importance of attending to reproductive health.[1,110] The association of cystic fibrosis with mental health has been characterized in observational studies, but interventional studies are needed.[62,111,112] In an observational study of 1005 patients with cystic fibrosis, patients who tested positive (mean hazard rate, 29.4 deaths per 1000 patients per year) for any depression screening tool had a higher 5-year mortality rate than those who tested negative for depression (mean hazard rate, 15.7 deaths per 1000 patients per year; unadjusted HR, 2.0; 95% CI, 1.3-3.0), but the association was attenuated and no longer statistically significant after adjustment for potential confounders (adjusted HR, 1.4; 95% CI, 0.9-2.2).[111]

Future studies should identify effective therapies for all people with cystic fibrosis, regardless of the genetic variant. For example, therapies are needed for people with genetic variants that are not modulator responsive such as premature termination codons, large deletions or frameshifts that produce little or no stable protein.[113] Although multiple gene replacement programs, both virally and non-virally based, have been attempted,[114] none have demonstrated efficacy. The availability of gene editing technologies such as clustered regularly interspaced short palindromic repeats (CRISPR) CRISPR–associated protein 9 may lead to functional *CFTR* repair in intestinal or pulmonary epithelia.[115] All genetic based therapies face the challenge of developing efficient vectors that can deliver stable product to the target stem cells in the airway or intestinal tract.[113]

Limitations

This review has several limitations. First, some relevant publications may have been missed. Second, this was not a systematic review. Third, the review focused on CFTR modulators for which long-term safety and efficacy data are not available. Fourth, topics such as lung transplant, the effect of COVID-19, digital health, or management of cystic fibrosis–related comorbidities such as diabetes or liver disease were not covered.

Conclusions

Cystic fibrosis affects approximately 89 000 identified people worldwide and is associated with a spectrum of disease related to exocrine dysfunction, including chronic respiratory bacterial infections and reduced life expectancy. First-line pulmonary therapies consist of mucolytics, anti-inflammatories, and antibiotics, and approximately 90% of people with cystic fibrosis 2 years and older benefit from a combination of ivacaftor, tezacaftor, and elexacaftor.

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