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Cystic fibrosis: therapeutic developments and market trends within the broader landscape of lung disease

Abstract

The paper examines the CF therapeutic market, recent trends, and CF research pipelines, focusing on this rare genetic disorder primarily affecting the lungs. The first part sharpens the definition of CF as a chronic pulmonary disease, explores the physical changes involved, looks at its distributional pattern, and discusses the effects of CF on people's survival. The market analysis includes the market size, differences among countries or regions, and what future trends are likely to happen. Treatments, including CFTR modulators and add-on therapies, are paid for, plus new advances like gene editing and those using mRNA, ENaC inhibitors, and microbiome targeting. There is a special emphasis on both mutation-specific and mutation-agnostic approaches during the development of clinical and preclinical products. Regulations and policies for gaining drug approval and for patients to access these drugs are addressed, along with incentives for orphan drugs and difficulties with reimbursement. The essay also looks at the current barriers to equal access, lower costs, and global fairness in healthcare. It ends by highlighting the impact of involving technology and individual medicine, which can transform treatment for all CF patients worldwide.

Keywords: cystic fibrosis (CF), CFTR modulators, gene therapy, orphan drug policy, global healthcare access, personalized medicine

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Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; COPD, chronic obstructive pulmonary disease; FDA, food and drug administration; EMA, European Medicines Agency; HTA, health technology assessment; HTA, compound annual growth rate; LNP, lipid nanoparticle; mRNA, messenger ribonucleic acid; ENaC, epithelial sodium channel; IND, investigational new drug; VOC, volatile organic compound; PERT, pancreatic enzyme replacement therapy; FEV, forced expiratory volume in one second; CFF, Cystic Fibrosis Foundation; ECFS, European Cystic Fibrosis Society; HTAI, Health Technology Assessment International; ISPOR, International society for pharmacoeconomics and outcomes research; QALY, quality-adjusted life year; AI, artificial intelligence; ML, machine learning; NDA, new drug application; NOC/c, notice of compliance with conditions; LMICs, low- and middle-income countries; iPSC, induced pluripotent stem cells; COVID-1, coronavirus disease 2019; US, United States; UK, United Kingdom; EU, European Union; CAD, Canadian Dollar; USD, United States Dollar; EUR, Euro

Introduction

Diseases of the lungs are among the most significant sources of morbidity and mortality globally, with millions of deaths each year and a high financial burden on the healthcare system worldwide. These diseases fall into a large group of progressive and long-term cumulative disorders such as cystic fibrosis (CF), chronically obstructive pulmonary disease (COPD), and asthma. CF is one such rare life-shortening genetic lung-dominant disease with the hallmark of the mucus trap leading to recurrent infections and progressive pulmonary deterioration. Even though it is an orphan disease with low prevalence owing to its rarity of occurrence, its clinical and financial importance has multiplied in the last few decades. This is mainly due to increased patient numbers due to its occurrence and increased life expectancy because of innovations in its treatment and more demand for highly specific therapeutics from the growing market. In this review article, we will evaluate the positioning of CF among the vast group of lung diseases, find out the market value and product trends, the current and emerging treatments, and the current issues and prospects of the drug market in CF.

Disease: cystic fibrosis within lung diseases

Cystic fibrosis (CF) is a genetic disease mainly involving the lungs but has systemic consequences affecting the gastrointestinal tract and other organ.[1] It is a progressive lung disease because of its long-term sequelae for respiratory status.[1,2] CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that maps on chromosome.[2,3] CFTR is a protein that acts as a chloride channel that ensures the proper balance of salt and water on the surface of epithelia, such as the lung airways. In normal individuals, CFTR enables the efflux of chloride ions from epithelial structures into the airways that hydrate mucus. In normal lung tissue, the airway epithelium is composed of ciliated cells and goblet cells in cooperation with one another to trap material and sweep the material away from the lungs, with the assistance of well-hydrated mucus to facilitate effective mucociliary clearance.[3] In CF patients, CFTR gene mutations result in the expression of an abnormal protein that does not perform its job of chloride transport or is not expressed at all, with the consequence of drying out mucus secretions.[3–7]

Consequently, CF patients develop the secretion of thick, sticky mucus throughout the airways.[1] This mucus blocks the bronchioles, compromises mucociliary clearance, and promotes an environment favorable for recurrent bacterial infections, as shown in Figure 1.[8] This progresses with chronic inflammation, airway remodeling, bronchiectasis, and progressive deterioration of lung function over time.[8] Pseudomonas aeruginosa and Staphylococcus aureus are common respiratory pathogens that cause recurrent pulmonary exacerbations. The progressive lung destruction is the central cause of morbidity and mortality among CF patients.

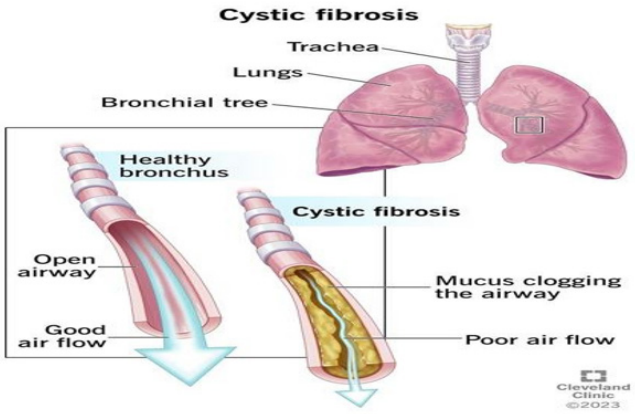

Figure 1 Image of thick, viscous mucus in the airways.[8]

This figure visually represents the abnormal accumulation of thick and sticky mucus in the airways of a cystic fibrosis (CF) patient. It illustrates how impaired mucociliary clearance promotes infections and lung damage.

Cystic fibrosis is among the best-studied monogenic lung diseases.[3] It is a member of the class of chronic pulmonary disorders and shares several features with the other disorders in this class, including inflammation, obstructive lung function, and long-term therapy needs. CF is distinct from other disorders because of its monogenic cause, its onset early in life (in infancy or childhood), and the systemic nature of its expression. While the respiratory system is the primary system involved in the disease process, the pancreas, intestines, liver, and reproductive tract become involved because of the pan-epithelial expression of CFTR.[7] In the healthy state, pancreatic ducts secrete enzymes, intestines absorb nutrients from the moist lining, liver bile ducts drain normally, and male reproductive ducts remain intact to facilitate the transport of sperm. This can be seen in Figure 2 below.

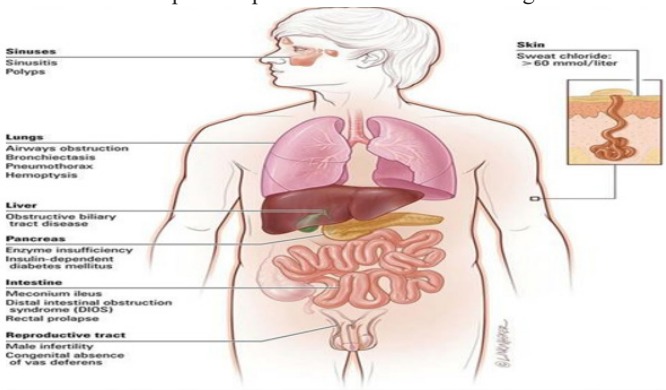

Figure 2 Common clinical manifestations of cystic fibrosis.[7]

A diagram summarizing systemic manifestations of CF, including effects on the lungs, pancreas, liver, intestines, and reproductive system due to CFTR dysfunction.

The incidence and prevalence of CF differ significantly by ethnicity and geographic region.[4] In the United States alone, it is estimated that 30,000 people have CF, with 1,000 new diagnoses each year, as reported by the Cystic Fibrosis Foundation. The estimated incidence is 1 per 3,500 live births. The same is observed in the European Union and the United Kingdom combined, with more than 48,000 people affected.[4–6] In Australia, the number is reported as 1 in 2,500 births, one of the highest per capita occurrences in the world. In the Asian and African communities, CF is less prevalent, with lower incidence and carrier frequencies. Figure 3 is a geographic representation of CF occurrence worldwide, focusing on the high number of cases found in North America, the European continent, and the region of Oceania.

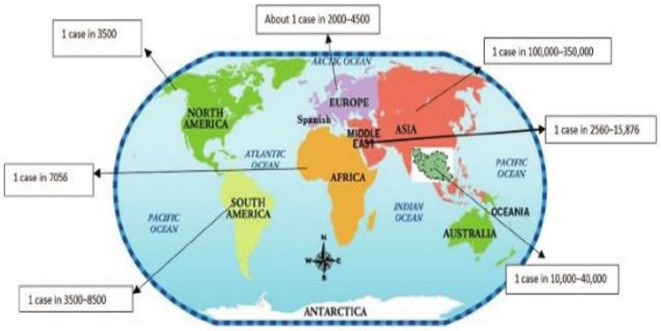

Figure 3 Global distribution of CF outbreaks.[4]

This figure shows a world map highlighting regional prevalence rates of cystic fibrosis, with the highest concentrations in Europe, North America, and Oceania, and the lowest in East Asia and Africa.

CF patients' survival rate has increased considerably over the last four decades due to growth in screening, the use of antibiotics, airway clearance methods, and, more recently, CFTR modulator therapies. During the 1960s, the mean life expectancy of people with CF was below 10 years. The median predicted survival in high-income nations is more than 47 years, with the possibility of patients surviving up into the 60s and beyond. The improvement has changed the nature of CF from childhood to adulthood in most parts of the world. It hence presents new issues regarding long-term disease care, comorbidities, and access to specialized treatment for older CF patients.[4,5]

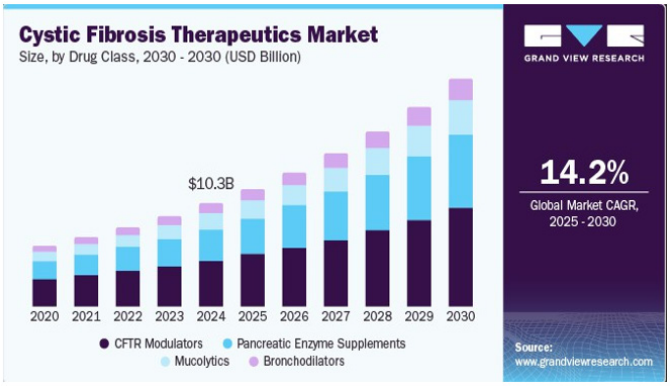

Figure 4 CF Therapeutics Markets.[5]

A bar or pie chart representing the estimated market value of cystic fibrosis therapeutics, showing past and projected growth, key segments, or revenue breakdowns by therapy types or drug classes.

Despite the improvement, inequalities in outcomes persist.[7] In the United States, for instance, socioeconomic status, race, and type of insurance continue to influence access to state- of-the-art therapy.[7] Hispanic and Black patients with CF have been found to have worse clinical outcomes and more delayed diagnoses than White patients.[6,7] In the developing world, access to CF diagnostic and treatment services is restricted and leads to underreporting and profoundly lower survival rates. International efforts such as the CFTR2 Project and country CF registries seek to gather comprehensive epidemiological information to inform treatment policies and address inequalities in care.[9]

Market size

The worldwide cystic fibrosis (CF) therapeutics market had an estimated value of around USD 10.3 billion in 2024 and is expected

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to grow to USD 22.7 billion by the year 2030 with a 14.2% compound annual growth rate (CAGR) in the forecast period.[5] The growth is mainly due to the growing uptake of CFTR modulators, the growth in the number of adult CF patients, and increased newborn screening programs that facilitate early diagnosis and treatment.[6]

The North American region is the biggest CF therapeutics market, capturing nearly 65% of the world's revenue.[4,5] The United States is the market leader, with an estimated valuation of USD 5.8 billion in 2023,[10–14] backed by the early FDA approval of drugs, extensive insurance coverage, and infrastructural provision for CF care (Figure 5).[15] CFTR modulators capture the most significant prescription in the US due mainly to the comprehensive adoption of Trikafta and prior-generation medications like Orkambi and Kalydeco.[7] Reimbursement schemes and orphan drug benefits have brought speedier market entry into nearly all eligible patients.[15]

The CF market in Europe is around USD 2.7 billion in 2023.[5–15] The United Kingdom, Germany, and France contribute most significantly. While the European Medicines Agency (EMA) has approved all the significant CFTR modulators, access remains inconsistent owing to the variability of the national reimbursement mechanisms. France and the Netherlands adopted early access, but some countries like Poland and Hungary experienced more than 12 months' delay after EMA approval.[15] The increase in the number of national CF registries and pan-European collaborative structures is likely to facilitate regional growth.[5]

The Asia-Pacific region is presently below the level of market representation but is expected to grow with a 15.2% CAGR, the highest in the world (Figure 5).[15] The market will be USD 550 million in 2023 and will be dominated by Australia, Japan, and South Korea regarding accessibility of treatment and diagnosis.[5,15] CF is underdiagnosed in China and India because of a lack of awareness and infrastructure.[6] But increased genetic testing capacity and collaborations with international partners are expected to spur market growth in the next decade.[6] Figure 6 delineates regional market size and growth rates expected in the US, Europe, Asia-Pacific, and the world as a whole[4]. North America remains the leader in absolute value and product variety compared to other regions.[4,5] Nevertheless, the growth rate of the Asia- Pacific market indicates a trend toward more extensive global market participation, particularly with the assistance of nonprofit foundations and research consortia.[4]

Figure 5 CF Market Share.[4]

A regional comparison of CF therapeutic market share, illustrating the dominance of North America, with details on Europe and Asia-Pacific's emerging roles.

The primary drivers of CF market growth are the broadening of drug eligibility criteria, clinical outcomes improvement, and improving patient survival.[8] CFTR modulator drugs that began as a treatment for a limited population of patients with the G551D mutation now aim for more than 90% of genetically identified people.[9] With the increases in treatment success, patients' lifespans have increased, with the median predicted age of patients in high-income nations surpassing 47 years.[8,9] With more people surviving into adulthood, there is a need for long-term therapeutics that drives a stable base of the market.[9] Newborn screening programs have also influenced the timing of treatment and diagnosis.[9,10] Earlier treatment has been associated with improved pulmonary status, less rate of exacerbations, and a decrease in intubations and hospitalizations that ultimately translates into payer acceptance of high-priced therapies. Nations with universal newborn screening, like the US, Australia, and regions of Western Europe, have reported an increased prevalence of CF due to improved detection (Figure 6).[10]

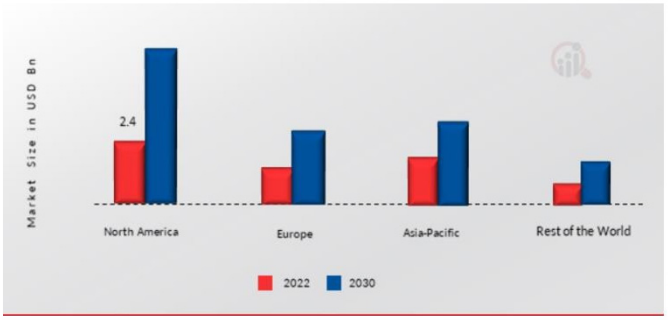

Figure 6 CF Market Share by Region.[4]

This figure shows growth rates and market sizes by global regions. It emphasizes the stronghold of North America in absolute value and the high CAGR in the Asia-Pacific region.

Another key driver is the deep pipeline of clinical innovation.[9] Biopharmaceutical firms have invested heavily in next-generation medicines such as gene editing, mRNA platforms, ENaC inhibitors, and anti-inflammatory drugs. Under US and EU regulations, Orphan drug benefits guarantee market protection and financial assistance for developing drugs for rare diseases that support a competitive and profitable innovation cycle.[8–10] In spite of encouraging trends, there continue to be substantial market barriers.[9] Therapies for CF are among the most expensive in the rare disease market.[9,10] Trikafta's annual list price is over USD 311,000 per patient in the United States, and in Europe, the list price of EUR 200,000–250,000 varies across countries and negotiated discounting.[4,8] Pricing is restricted in most low- and middle-income nations and has raised ethical concerns regarding equity and affordability.[4,8,9,10]

Moreover, geographic inequalities in care infrastructure and diagnosis constrain growth in markets like Southeast Asia, Latin America, and sub-Saharan Africa.[4,5] Most of these regions have no national newborn screening programs, clinical specialists, or diagnostic facilities with the capacity for CFTR mutation identification.[4,7] The result is extensive underdiagnosis and untreated disease.[7] Public-private alliances and non-governmental organizations have set in to reverse the deficits, but the problems remain rooted in structure (Figure 7).[4,5,8]

Reimbursement heterogeneity is a second restraint.[7] In the European region, various health technology assessment (HTA) organizations evaluate CF medications variably, resulting in variable coverage among member countries.[7] This fragmentation hinders market uptake and slows early access among more conservative cost-benefit threshold countries.[7]

Clinical-own product: approved treatments

Cystic fibrosis (CF) treatment is based on a multi-class drug therapy involving the underlying genetic defect as well as secondary infection

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and symptom relief of mucus blockage and pancreatic insufficiency.[11] The treatment paradigm currently comprises CFTR modulators, inhaled antibiotics, mucolytics, and pancreatic enzyme substitution.[11] The most significant change in the care of CF has been the development of CFTR modulators from Vertex Pharmaceuticals, which has created a leading presence within the treatment marketplace.[12]

Aerosolized antibiotics for the treatment of *P. aeruginosa* infection in CF patients.

Antibiotics	Type of Antibiotic	Mechanism of Action	Formulations	Trade Name	Nebulization Time	Dosage	Frequency
Tobramycin	Aminoglycosides	Inhibition of protein synthesis	Solution for nebulization	Tobramycin	15 min	300 mg/5 mL	Twice daily
				Tobi	15 min	300 mg/5 mL	Twice daily
				Bramitob	15 min	300 mg/4 mL	Twice daily
				Vantobra	4 min	170 mg/1.7 mL	Twice daily
Aztreonam lysine	Monobactams	Inhibition of bacterial cell wall synthesis	Solution for nebulization	Cayston	2-3 min	75 mg/1 mL	Three times daily
Levofloxacin	Fluoroquinolones	DNA gyrase and topoisomerase IV	Solution for nebulization	Quinsair	5 min	240 mg/3 mL	Twice daily
Colistimethate sodium *	Polymyxins	Disruption of bacterial cell membrane	Solution for nebulization	Promixin	3 min	80 mg/3 mL	Twice/Three times daily
				Colfinair	3-4 min	80 mg/3 mL	Twice/Three times daily

Figure 7 Inhaled antibiotics for chronic lung infections in CF.

A comparative visual showing various inhaled antibiotics used in CF treatment, such as TOBI, Colistin, and Cayston, including delivery methods and target pathogens like *P. aeruginosa*.

CFTR modulators

CFTR modulators are small-molecule treatments that target the action of the defective CFTR protein.[12] They fall into potentiators, correctors, and amplifiers based on their actions. Trikafta (elexacaftor/tezacaftor/ivacaftor) is the most commonly prescribed triple-combination CFTR modulator.[13] Formed by Vertex Pharmaceuticals, Trikafta received FDA approval in October 2019 for patients aged six and older with one F508del mutation, representing about 90% of the CF population.[3] The FDA approval was increased in 2021 for patients aged six and older.[3] Trikafta combines the action of two correctors (lumacaftor and ivacaftor) that augment CFTR protein processing and trafficking with a potentiator (ivacaftor) that increases the chloride channel opening at the cell's surface.[12] The yearly list price is about USD 311,000 per patient in the US. Global net product sales in 2023 exceeded USD 8.7 billion and is the highest-selling CF treatment on record.[3] Symdeko (tezacaftor/ivacaftor and ivacaftor) was approved in 2018 for treating patients six and older with two copies of the F508del mutation or one mutation responsive to ivacaftor.[12] Symdeko is a dual combination therapy generally used if Trikafta is unavailable or in mutation-specific situations. The yearly cost is approximately USD 292,000, with sales of USD 576 million in 2023.[3,13]

The first dual-combination drug that received the FDA approval in 2015 is Orkambi (lumacaftor/ivacaftor).[3] It is used for patients aged 2 and above with the F508del homozygous mutation.[3,12,13] Although it is less tolerable with chest discomfort and hepatotoxicity, it was used extensively before Trikafta's approval.[12] It is priced similarly at an annual list price of USD 272,000 and has continuously decreased sales with a figure of USD 453 million in 2023.[3]

The first CFTR potentiator approved in 2012 was Kalydeco (ivacaftor), which had an original indication for patients with the G551D mutation.[9,10] The label has been extended to treat more than 97 mutations, both gating and residual function variants.[3] It is used in patients who are 1 month and older.[3] Kalydeco's action increases CFTR channel opening and enhances chloride transport in responsive mutations in the cells. It costs around USD 311,000 annually and saw sales of USD 552 million in 2023.[3] These modulators have been presented in the Table 1.[14–24]

Table 1 Therapeutic cystic fibrosis transmembrane conductance regulator modulators

	Market name USA/EU	Year Approved USA (FDA)/ EU (EMA)	Indication (age)	CF mutations	CF population %	Lung $ppFEV_1$	Lung exacerbation reduction %	Estimated annual cost USD/EUR
Ivacaftor	Kalydeko	2012/2014	>6 months	Class III, gating mutation, residual function and conduction mutations (class IV)	3–5	10.6–12.5 (week 24)	55	311000/260000
Lumacaftor/ ivacaftor	Orkambi	2015/2018	>12 years >6 years	Class II, F508del homozygous	45–50	2.6–4.0	30–39	272000/226000
Tezacaftor/ ivacaftor with ivacaftor	Symdeko/ Symkevi	2018/2018	>6 years	Class II, F508del homozygous, heterozygous, other mutations	45–50	4.0–6.8	35	292000/242000
Elexacaftor/ tezacaftor/ ivacaftor with ivacaftor	Trikafta/ Kaftrio	2019/2020	>6 years	Class II, at least one copy of F508del mutation and one copy with residual function mutation	85–90	10.4–13.8	63	311000/260000

EU, European Union; FDA, Food and Drug Administration, EMA, European medicines Agency; CF, cystic fibrosis; $ppFEV_1$, percentage predicted forced expiratory volume in 1 s.

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Antibiotics

Inhaled antibiotics play a vital role in controlling Pseudomonas aeruginosa and Staphylococcus aureus colonization in patients with CF, decreasing bacterial load, slowing the rate of deterioration of lung function, and lessening the frequency of exacerbations. TOBI is an aminoglycoside antibiotic in inhalation solution and powder forms. Novartis produced it for the first time when it was approved in 1997; TOBI Podhaler was added in 2013.[25,26] Tobramycin acts against P. aeruginosa and is used in patients 6 years and older. It is given in 28-day on/off treatment cycles.[24] Prices range by formulation but average USD 10,000–15,000 per year. It is still widely used, particularly in treating early or long-term colonization.[25–34]

Colistin (colistimethate sodium) is an off-label and compounded agent used as an inhaled drug. Colobreathe (dry powder of colistimethate) from Forest Laboratories is approved in Europe (2012).[35] It is typically reserved for patients becoming resistant or intolerant of the tobramycin.[36] Colistin is priced between USD 5,000–12,000 per year per formulation and delivery route.[25] Aztreonam lysine for inhalation (Cayston) is manufactured by Gilead Sciences and approved by the FDA in 2010.[36] It is explicitly used in P. aeruginosa infections in seven and older patients. It is delivered using the Altera nebulizer system thrice for 28 days.[35,36] Aztreonam is directed against beta-lactam-resistant strains and is typically used in rotation with tobramycin.[35] The cost is around USD 17,000–20,000 annually, and it is commonly used in the adult population with confirmed colonization.[25]

Mucolytics and enzyme replacements

The mucolytics decrease mucus viscosity for improved airway clearance.[17] Replacements of enzymes play a critical role in the treatment of pancreatic insufficiency, which is a common CF complication.[16] Pulmozyme (dornase alfa) is a Genentech-produced recombinant human DNase I that received FDA approval in 1993.[18] It degrades extracellular DNA in sputum and thins mucus.[18] It is given once daily by nebulization and is approved for patients 5 years of age and older.[18] Annual cost ranges from USD 25,000–30,000. It is still a standard adjunct therapy for airway clearance and is employed in children and adults.[17,29]

Creon (pancrelipase) is a pancreatic enzyme replacement therapy (PERT) used to treat exocrine pancreatic insufficiency. It is produced by AbbVie and approved by the FDA in 2009 under enzyme regulation modernization.[19,20] Creon is composed of lipase, protease, and amylase of porcine origin and is orally administered with meals.[18–20] It is prescribed in nearly 90% of CF patients and is vital for maintaining nutritional status.[29] Average yearly costs range from USD 8,000 to 15,000 based on dosage frequency and patient weight.[29]

In real-life outcomes of these therapies, significant increases in lung function, nutritional status, and quality of life have been observed. CFTR modulators, most notably Trikafta, have produced 10–14% increases in FEV1, significant decreases in pulmonary exacerbations, and increased body mass index (BMI) within the initial 6–12 months of treatment.[18,20,29] CFF Patient Registry observational studies corroborate long-term benefits across age groups and genotypes.[20]

Side effects differ by class of therapy. CFTR modifiers potentially cause increased liver enzymes, rash, and mood changes, but antibiotics potentially result in ototoxicity, bronchospasm, or bacterial resistance.[21,22,29] Adherence is a ubiquitous problem, particularly among adolescents and young adults, with daily regimen burdens frequently exceeding 2 hours.[29] Oral CFTR modifiers have enhanced adherence compared with inhaled treatments.[29]

Innovation and products in development

The therapeutics pipeline for cystic fibrosis (CF) has grown far beyond CFTR modulators and now includes next-generation gene-editing technologies, mRNA treatments, ENaC inhibitors, and treatments targeting the microbiome.[35] Clinical trials of various phases represent continued efforts toward the remaining 10% of patients not responsive to current CFTR modulator therapy and alternative or complementary therapies for all patients with CF.[27]

Gene editing: Vertex pharmaceuticals and CRISPR therapeutics

Vertex Pharmaceuticals is collaborating with CRISPR Therapeutics on gene-editing programs to correct CFTR mutations at the genomic level.[26,27] Their most advanced candidate is the inhaled mRNA-based gene-edited therapy drug VX-522, delivered through lipid nanoparticles (LNPs) (Figure 8).[33] It is for patients not suitable for current modulator therapy, such as patients with nonsense of minimal function mutations. The treatment employs the delivery of messenger RNA encoding a functional CFTR gene into the lungs using LNPs.[27,33] Up to 2024, VX-522 is undergoing clinical trials in Phase I. The trial assesses the safety, tolerability, and CFTR protein expression evidence in patients older than 18.[29,33] Vertex and CRISPR have laid long-term goals for in vivo gene editing methods to repair the CFTR DNA with the CRISPR-Cas9 directly.[33] Successful insertion of the CFTR gene into epithelial cells has already been shown in preclinical trials but is not yet up for human trials.[1] The development is underway with the FDA's orphan drug and fast-track status.[1] The process of editing the gene is revealed in Figure 8 below.

Figure 8 Conceptual representation of gene editing.[11]

Illustrates a schematic of gene editing using mRNA-based delivery (VX-522), showing how functional CFTR genes are introduced to correct CFTR dysfunction.

mRNA therapy: Translate bio and sanofi

Translate Bio, which Sanofi bought in 2021, is developing MRT5005, an inhaled mRNA treatment intended to substitute for defective CFTR protein by delivering functional CFTR mRNA into airway epithelial cells.[21] In contrast with CFTR modulators that act on the residual function of CFTR, MRT5005 presents novel mRNA transcripts irrespective of mutation class.[21,29] The first Phase I/II trial (NCT03375047) included CF patients with a range of CFTR mutations, even patients without CFTR production.[29] While the initial dosing provided incremental improvement in FEV1, the treatment was generally well tolerated with no dose- limiting toxicities.[30] Sanofi laid out plans for optimizing formulation and delivery systems for subsequent trials, focusing on the durability of response and delivery efficiency (Figure 9). The development of CF mRNA therapies follows platforms used with mRNA-based COVID-19 vaccines,

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providing an investment area of interest with built-in manufacturing infrastructure and familiarity with regulatords.[30,31] MRT5005 is in clinical development with updated protocols pending review by the regulators (Figure 10).[21]

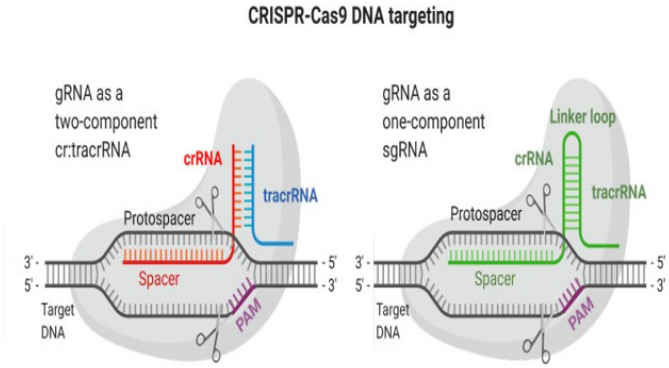

Figure 9 CRISPR Therapeutics gene targeting.[1]

A schematic representation of CRISPR-Cas9 technology for editing the CFTR gene, aiming at correcting mutations at the DNA level in CF patients.

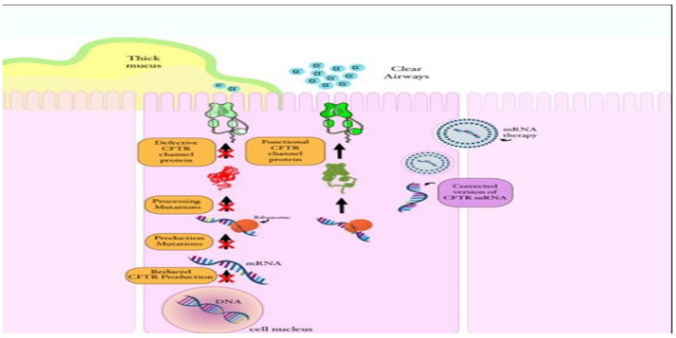

Figure 10 CFTR mutations and mRNA therapy.[21]

A diagram displaying how mRNA-based therapies like MRT5005 can replace defective CFTR protein regardless of mutation type, expanding therapeutic reach.

ENaC inhibitors

The epithelial sodium channel (ENaC) is integral to the hydration of the airway surface.[32] Hyperabsorption of sodium in CF dehydrates the airway surface and enhances the consequences of defective chloride transport.[31] ENaC inhibitors seek to rehydrate the airways regardless of CFTR functional status and thus are appropriate for all CF genotypes.[34] Ensifentrine is a dual PDE3/4 and ENaC inhibitor developed by Verona Pharma and is in Phase II trials.[37] Ensifentrine is an inhaled drug showing bronchodilation, inflammation reduction, and enhanced mucociliary clearance (Figure 11).[37] Although primarily focused on COPD development, Verona is investigating its potential in the CF space with orphan drug designation in the US and EU. Spirovant Sciences is developing SP-101, a new inhaled ENaC antisense oligonucleotide that blocks ENaC mRNA translation. SP-101 is in preclinical development, with the expected submission of an IND in late 2024.[37] Preclinical models have already demonstrated a reduction of ENaC expression and enhanced mucociliary transport.[38]

Anti-inflammatory therapies

Chronic neutrophilic inflammation of the CF lung is responsible for progressive damage to the tissue irrespective of infection status. Anti-inflammatory treatment seeks to decrease inflammation in the airways with minimal immunosuppression. Lenabasum, a medication developed by Corbus Pharmaceuticals, is an oral CB2 cannabinoid receptor agonist that works to decrease inflammatory cytokine secretion. It achieved a decrease in pulmonary exacerbations and inflammatory biomarkers in a Phase II (NCT03451045) clinical trial in patients with CF.[38–40] Still, it failed the primary endpoint of the Phase III clinical trial. This caused Corbus in 2021 to cease CF development.[41] The information remains of value as a potential guide for pursuing inflammatory pathway targets in the future.[41] LAU-7b from Laurent Pharmaceuticals is an oral derivative of fenretinide that modulates lipid metabolism and reduces inflammation (Figure 12). It entered a Phase II clinical trial (NCT02141958), demonstrating promise in the slowing of lung function worsening.[40] A Phase III trial is set to follow with support from Canadian and European health agencies.[39]

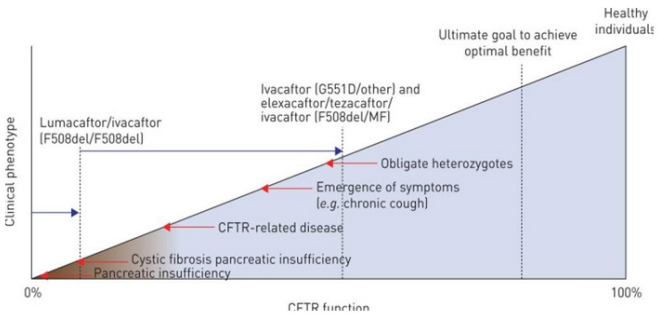

Figure 11 The relationship between ENaC inhibitors and CFTR in CF.[37]

Shows how ENaC inhibitors modulate airway hydration and reduce sodium absorption, improving mucus clearance independently of CFTR functionality.

Compounds being tried to treat inflammation in CF.

Compound Name	Mechanism of Action
LAU-7b (retinoid)	Reduces inflammation [48]
Bresoxatib	Neutrophil enzyme inhibitors [48]
Lonodelestat	
Anakinra	IL-1 receptor blockade, biologic agents [6]
Rilonacept	
Canakinumab	

Figure 12 Anti-inflammatory Therapies.[40]

Illustrates therapeutic approaches to modulate chronic inflammation in CF lungs, including cannabinoid receptor agonists and lipid modulators.

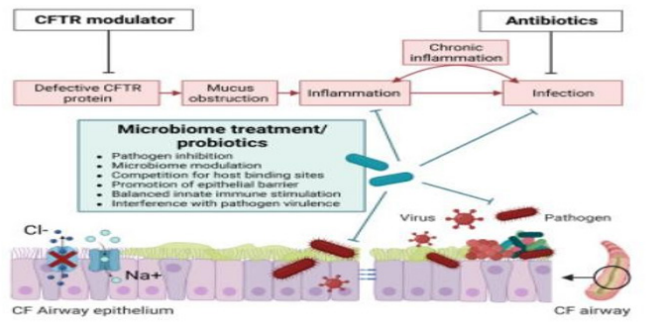

Figure 13 Microbiome-Targeted Therapies.[43]

This figure displays approaches targeting the CF lung microbiome, such as phage therapy, mRNA-antibiotic co-delivery, and breath biomarker-guided interventions.

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Microbiome-targeted therapies

The lung microbiome of CF contributes significantly to its disease pathogenesis.[43] Pseudomonas, Staphylococcus, and Burkholderia species cause long-term infections that result in biofilm production, antibiotic resistance, and inflammation.[42,43] Therapeutics that target the microbiome seek to modulate the microbial population toward better clinical outcomes.[43,44]

ReCode Therapeutics is creating RCTX-001, its lipid nanoparticle-based treatment co-delivering CFTR mRNA with antibiotics with the potential to remake the local microbiome as it restores ion transport.[41] Improved bacterial clearance and mucus hydration have already been observed using preclinical models.[41] Spirosure explores the utilization of volatile organic compound (VOC) breath biomarkers to inform treatment decisions and modulate the microbiome. Although not a treatment product, it is in phase I validation trials and can inform directed microbiome interventions in subsequent trials. Anagenex is cultivating synthetic phage- based antimicrobials for P. aeruginosa in preclinical trials. The therapies specifically kill pathogens with minimal damage to commensal flora, decreasing the risk of resistance.[43]

Mutation spectrum and therapeutic diversity

New treatments are expanding the treatment model through targeting different CFTR mutations and other non-CFTR pathways.[45] While currently approved modulators target only predominantly the F508del mutation and certain gating mutations,[46] treatments are under development for those with nonsense, splicing, and minimum function mutations who previously received little or none of the proper treatment.[47] These developments aim to close the clinical care gap by bringing treatment to patients who have been excluded from therapy.[48,49]

A number of drugs currently being investigated at various stages of clinical development work through different biological mechanisms, involving gene correction, sodium transport, inflammation, and microbiome.[47] A few are mutation-agnostic, and treatment may be based on a patient's phenotype, not his or her genes, and therefore expand the population being reached by best available treatments to a larger, more heterogeneous population.[46,47] Geographic trial coverage is irregular and mainly takes place within the United States, Western Europe, Canada, and Australia.[16] Limited coverage exists for trials within Asia, Africa, and much of Latin America, an indicator of present imbalances between global research capacity and availability for experimental treatments.[16] Enhanced international coverage for clinical development will be required to provide new treatments to patients in the world at large Table 2.

Table 2 Mucolytic and Antibiotic therapy for chronic CF management

Medication	Dosage and Administration	Potential Side Effects	Monitoring Parameters	Comments
Dornase alpha	All age groups: 2.5 mg daily via selected nebulizer Dosage of 2.5 mg 2x daily may be used in selected patients	Cough, rhinitis, dyspnea, rash, chest pain, voice disorder, fever, dyspepsia	FEV_1 Side effects	Review manufacturer instructions for nebulizer selection and medication administration
Hypertonic saline	Adults and pediatric patients: Administer 4 mL of 7% solution 2x daily via nebulizer May consider 3% or 3.5% concentrations if 7% solution not tolerated	Bronchospasm	FEV_1, electrolytes	
Mannitol (inhaled)	For adults aged ≥18 y: Administer 400 mg 2x daily via DPI, with later dose administered 2-3 h prior to bedtime	Bronchospasm Risk of hemoptysis in ~10% of adults Cough, oropharyngeal pain, vomiting, bacteria in sputum, fever, arthralgia	FEV_1, SpO_2, hemoptysis	Must pass BTT prior to treatment start Must administer 10 capsules (1 capsule = 40 mg) via provided inhaler device Pretreat with SABA 5-15 min prior to each dose Contraindicated if hypersensitivity to gelatin or mannitol
Tobramycin (inhaled)	For ages ≥6 y: Administer in cycles of 28 days on and 28 days off Nebulizer: 300 mg 2x daily Podhaler: 112 mg 2x daily	Bronchospasm, cough, shortness of breath, sore throat, fever, dysphonia, headache, hemoptysis, nasal congestion May cause nephrotoxicity, ototoxicity (hearing loss, tinnitus), and muscle weakness	Renal function, auditory function and audiogram, serum concentrations of tobramycin	Cautious use if known or suspected auditory, vestibular, renal, or neuromuscular dysfunction present
Aztreonam (inhaled)	Inhale 75 mg 3x daily via nebulizer in cycles of 28 days on and 28 days off (pediatric dosing same as adult)	Bronchospasm, pharyngolaryngeal pain, cough, nasal congestion, wheeze, fever, skin rash, abdominal pain, vomiting		Use only with Altera nebulizer system Space doses at least 4 hours apart Recommend pretreating with bronchodilator
Azithromycin	Infants aged ≥6 mo to <18 y: Administer 3x weekly 10-mg/kg/dose (maximum 500-mg/dose) or fixed dosing 3x weekly 18 to <36 kg: 250 mg ≥36 kg: 500 mg Adults: Administer 3x weekly <40 kg: give 250 mg; ≥40 kg: give 500 mg	Diarrhea, nausea, abdominal pain, vaginitis May cause QTc prolongation, ventricular tachycardia, Clostridium difficile, drug-induced liver injury, ototoxicity (hearing loss, tinnitus), or delayed hypersensitivity reactions	Hepatic function, signs/symptoms of hepatitis, audiogram with prolonged use, ECG for QTc prolongation	Considered off-label use for CF Must screen for non-TB mycobacterial infection prior to use Potential for DDIs-may require dose adjustment Cautious use in myasthenia gravis; exacerbations and new onset of symptoms have occurred

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Regulatory, policy, and access considerations

A set of accelerated review pathways and policy incentives throughout the United States, Canada, and the European Union has enhanced cystic fibrosis (CF) treatments.[49] These policies facilitate the development and timely availability of medicines for orphan diseases, particularly diseases with few or no available treatment alternatives. Accelerated review mechanisms like the fast-tracking designation, breakthrough therapy designation, and orphan drug designation have helped CF products, specifically CFTR modulators, receive speedy development timelines and prolonged market protection.[49]

The Food and Drug Administration (FDA) has a number of designations within the United States that have facilitated CF drug approval.[48] The 1983 Orphan Drug Act's incentives include seven years' protection of the market, clinical trial tax credits, fee waiver for users, and grant support for clinical trials.[48] All the four CFTR modulators developed by Vertex-- Kalydeco, Orkambi, Symdeko, and Trikafta--were given orphan drug designation.[48,49]

Breakthrough Therapy Designation was also received by Trikafta, which accelerated its development and review status based on its significant improvement over the then-available treatments.[48] FDA's accelerated approval pathway facilitated review of Vertex's submission materials on a rolling schedule, and Trikafta was approved within less than six months after it filed for its NDA.[48]

In Canada, Health Canada makes orphan drug incentives available through its route of Notice of Compliance with Conditions (NOC/c).[16] Although the Canadian orphan drug system is less advanced than the FDA's and the EMA's, Trikafta obtained approval under NOC/c in June 2021, around a year and a half after US approval.[16] Trikafta's approval by Health Canada hinged on internal evaluations of clinical benefit, cost-effectiveness, and public-payer negotiations. Cystic Fibrosis Canada played a fundamental advocacy role in driving earlier access, with its efforts leading to a commitment to list Trikafta on the drug plans of the provinces by 2022.[3]

The European Medicines Agency (EMA) has aided CF drug development with its Regulation on Orphan Medicinal Products that began in 2000.[26] The regulation offers 10 years of market protection, fee waivers, and access to centralized review.[26,37] Kalydeco gained EMA approval in 2012, Orkambi in 2015, Symkevi (Symdeko) in 2018, and Kaftrio (Trikafta) in 2020. Centralized approval does not ensure access across European nations because of the involvement of national health technology assessment (HTA) bodies that individually assess cost-effectiveness and price negotiation.[26] This has delayed market access in Poland, Hungary, and Slovakia, as Trikafta was approved but not reimbursed until 2022 or beyond.[37]

Pricing policies and insurance arrangements play a significant role as determinants of access.[16] Table 3 illustrates that the list price of Trikafta in the United States is more than USD 311,000 per year per patient, with negotiated prices across Europe between EUR 200,000– 250,000 based on country-level negotiations.[16] The price per individual in Canada is calculated as CAD 300,000 per year, with cost-sharing arrangements that vary for public and private payers.[26] Such differences account for unequal access between regions and income quintiles.

Table 3 Preclinical CF Therapeutic Candidates

Drug/Candidate Name	Developer	Mechanism of action	Target Mutation/Class	Status	Delivery method
SP-101	Spirovant Sciences	ENaC antisense oligonucleoti de inhibits sodium absorption	Mutation-agnostic	Preclinic al	Inhalation
VX-522 (Gene Edited)	Vertex & CRISPR Therapeutics	LNP-based mRNA therapy encoding functional CFTR protein	Minimal function and nonsense mutations	IND-enabling	Inhalation via LNP
RCTX-001	ReCode Therapeutics	Co-delivery of CFTR mRNA + antibiotics targeting microbiome	Mutation-agnostic	Preclinic al	Lipid nanopartic le (LNP)
Synthetic Phage Therapy	Anagenex	Targeted phage antimicrobial s reduce biofilm and resistance	Chronic P. aeruginosa colonization	Preclinic al	Inhalation
VOC Biomarker Platform	Spirosure	Breath-based volatile compound detection to guide microbiome therapy	Diagnostic platform	Phase I Validatio n	Non- invasive (breath sensor)
Gene- correcting CRISPR Therapy	Vertex/CRISP R	CRISPR-Cas9 for in vivo gene editing of CFTR gene	Frameshift/nonsen se mutations	Preclinic al	Inhaled or vector-mediated

Source: Author.

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In the United States, patients typically rely on public programs like Medicaid or private insurance.[16] Most insurance plans include Trikafta but with high co-pays, step therapy requirements, and prior authorization that may limit or postpone access.[7] Nonprofit foundations like the HealthWell Foundation and CF Patient Assistance Foundation for eligible patients provide financial assistance. Meanwhile, most European nations have a nationwide health system that wholly or partly reimburses CF drugs following HTA approval, but the negotiation process causes a time gap in patients' access.[37]

Disparities in insurance appear in all regions. Uninsured and underinsured patients struggle greatly within the US, especially in non-Medicaid-expansion states.[7] The status is even worse in developing nations: low diagnostic capacity, the absence of local CF expertise, and the lack of approved therapies translate into unavailable advanced care.[4,5] Numerous CFTR modulators are unavailable in such regions as sub-Saharan Africa, Southeast Asia, and South America due to a lack of infrastructure and purchasing power.[10] Advocacy groups have played a vital role in enhancing access to CF treatment and informing health policy.[8] The US Cystic Fibrosis Foundation (CFF) has spent more than USD 500 million on drug development for CF under its Venture Philanthropy Model, funding specific research projects at companies such as Vertex and directly funding research within these companies.[7] The foundation runs the CFF Patient Registry, an essential tool for post-marketing surveillance and clinical outcomes analysis.[9]

CFF's policy team advocates on the federal and state levels on Medicaid expansion, insurance reforms, and medication pricing policy.[7] Its Compass initiative offers one-on-one insurance and financial counseling to thousands of CF families each year.[7,8] EURORDIS (Rare Diseases Europe) advocates for fair access to orphan drugs within the European Union and has advocated harmonizing the EU member states' reimbursement policies.[26] Clinical research, guideline development, and data collection are supported by the European Cystic Fibrosis Society (ECFS) and are enabled by the ECFS Patient Registry, which makes pan-European drug access and outcomes surveillance possible.[5]

International advocacy groups cooperate as well. The Global Registry Harmonization Group standardizes data definitions and outcomes across CF registries in Australasia, Europe, and North America to provide improved evidence for access determinations and international health equity.[6] In the face of supportive regulation, orphan drug prices have prompted concerns among policymakers.[19] The prices of CFTR modulators aren't always indicative of development costs when public financing and philanthropy were heavily involved in the early stages of this work.[25] In the United States, pending federal policies like the Inflation Reduction Act and value-based pricing talks potentially influence CF drug prices and public payers' negotiation leverage in the future.[26]

The HTAi organization and the ISPOR organization have set up working groups to create international best practices for evaluating the value of treatments for rare diseases.[29] These conversations encompass how quality-adjusted life years (QALYs), disease severity, and societal value should all be integrated into cost-effectiveness analyses.[39] As evident in Figure 9, the history of FDA approval of significant CF therapies demonstrates the speed provided by incentives.[1] The bundling of approvals following 2012 coincides with the general adoption of accelerated track and breakthrough designations as a period of paradigm-shifting in the care of CF.[1] Although there has been universal improvement in the facilitation of regulation and drug development globally, inequities in access persist. Policy responses need to reconcile incentives for innovation with business models that accommodate sustainable and equitable access to life-prolonging treatments.[1–3]

Future outlook and market opportunities

The CF treatment landscape is set for further change but still has substantive gaps regarding treatment availability, universal access, and affordability.[42] Whilst CFTR modulator therapies have transformed the lives of many, there are still around 10% of CF patients in the world who cannot access them because of their mutation profiles. These individuals have nonsense, splicing, or minimal function mutations that the current small-molecule therapies cannot treat.[45] These individuals form a high-priority area for innovation and unmet clinical needs.[45]

Geographic differences continue to limit access to specialized CF treatment.[41] Even without CFTR modulators in low- and middle-income countries (LMICs), access to basic CF treatment is restricted.[41,47] Structural barriers like newborn screening programs, lack of trained CF specialists, and poor reimbursement policies widen health inequalities.[38,41] There is little or no access to approved CF medications in most sub-Saharan Africa, Southeast Asia, and South America.[37] These marketplace opportunities offer humanitarian issues and long- term business opportunities for organizations that produce lower-cost formulations, extended access programs, or price-tiered programs.

Affordability is an inherent challenge even among high-income countries.[46] The current pricing of CFTR modulators—more than USD 300,000 per year per patient in specific markets—is not sustainable for most public and private payers.[49] With more patients surviving and needing lifelong treatment, pressures against budgets within world health systems will grow.[44] This has drawn greater interest in value-based pricing, outcome-based reimbursement programs, and cost-containment policies.[35]

One of the most encouraging developments is the transition towards personalized therapy in treating CF.[50] Genomic diagnostics, mutation-associated screening, and biomarker-based stratification have enabled more individualized treatment regimens.[43] Ultra-orphan CFTR mutations are being addressed with therapy by companies using customized methods that use patient-derived organoids, induced pluripotent stem cells (iPSCs), and genotype-to-phenotype modeling.[18,43,45] These methods enhance clinical targeting and decrease the risk of nonresponse and side effects of the therapy.[45]

The coupling of machine learning (ML) and artificial intelligence (AI) drives accelerated drug development in CF.[9] Large datasets of CF patient registries, clinical trials, and real-world evidence are used to train AI models that predict mutation responses, improve drug candidates, and elucidate synergistic combinations.[2] Atomwise, Exscientia and Insitro already have CF- associated discovery programs underway using AI that decrease the time and cost of early-stage development.[49]

Firms are also investigating platform therapeutics with the potential for modular adaptation in various genetic targets.[7] Scalability is being engineered into mRNA delivery systems, lipid nanoparticles, and gene editing vectors with the potential for immediate applicability to new subsets of patients.[32] This flexibility is increasingly necessary as CF therapy shifts toward treating previously untreated mutations.[10,11]

As evident from Figure 10, the number of patients who become candidates for next- generation therapies is predicted to grow in the next 10 years.[37] Enhanced mutation screening, earlier diagnoses, and life expectancy worldwide fuel it.[37] Growth in the eligible population

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will propel sustained demand for advanced therapeutics worldwide, mainly in markets with increased health investment and improved regulation.

Industry forecasts predict sustained growth in the market up to 2035 based on a synergy of therapeutical innovation, geographic market growth, and patient retention for chronic patients.[42] Strategic investments in clinical infrastructure capacities, scale of production, and inter-industry collaborations will play a vital role in maintaining this trend and addressing the changing needs of a diversified CF population of patients.[38,47]

Conclusion

Cystic fibrosis is a model for the ways in which genetic understanding has enabled therapy innovation in the realm of chronic lung disease. The shift towards mutation-based therapy from a disease-centred treatment approach has transformed clinical outcomes and transformed the CF drug landscape. CFTR modulators —notably Trikafta and its forerunners— are setting the gold standard for personalized therapy with supportive complementary antibiotics, mucolytics, and enzyme replacers remaining vital components of disease treatment. The pipeline is hurtling forward with pace, with gene editing, mRNA therapy, and ENaC inhibitors offering new hope for the 10% of patients not addressed by current approved treatments. Accelerated approval has been made possible due to regimes of regulatory policies and orphan drug legislation but unequal access remains both between and within countries due to costs and infrastructure issues. Reducing such inequalities will require sustained advocacy, international health collaborations, and price reforms. Additional investment in precision therapy and platform technologies will be required to enable all individuals with CF—not just by mutation but by geography—to gain access to the next generation of life-extending therapies.

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Conflicts of interest

There are no conflicts of interest.

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