Narrative Review Article

Breathing Easy: Cystic Fibrosis, CFTR Modulators, and the Economic Struggle for Access

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ABSTRACT

Cystic fibrosis (CF) is a genetic disease caused by mutations to the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which causes an inability in affected cells to properly move chloride (Cl^-) and bicarbonate (HCO_3^-) across epithelial tissue, leading to symptoms such as abdominal distress and the presence of thick mucus in the lungs and airways that collect bacteria and contribute significantly to CF patient mortality. Healthcare providers have developed treatment plans designed to detect CF early and treat its symptoms. CFTR modulators such as ivacaftor, elizacaftor, and tezacaftor offer patients the ability to correct the mutations in the CFTR protein and remove symptoms entirely. However, these medications are expensive, contributing to healthcare inequality and outcomes for CF patients. To promote healthcare accessibility, Vertex Pharmaceuticals, either voluntarily or through government-mandated compulsory licensing in affected countries, could allow other companies to produce generic options at a fraction of the existing price, thereby removing economic barriers and promoting healthcare accessibility for CF patients worldwide. This review analyzes the effectiveness of CFTR modulators and how that effectiveness is counterbalanced by economic and ethical disparities, which make them inaccessible to much of the general population worldwide.

Keywords: Cystic Fibrosis, CFTR, Compulsory Licensing, Health Equity, Pharmaceuticals, Public Health, Drug Affordability

INTRODUCTION

The development of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulators has improved clinical outcomes for thousands of patients each year suffering from cystic fibrosis (CF) (1). Previous work in the field of cystic fibrosis patient care has made strides in increasing the life expectancy of patients through novel early detection techniques and patient care methodologies designed to treat the symptoms of the disease, with a particular emphasis on the mitigation of respiratory symptoms that have led to most mortality of CF patients (1). CFTR modulators were designed not to control or lessen the symptoms of disease but target the somatic mutations that cause these symptoms of disease in the first place and, in turn, provide long-term improvements to the quality of life for patients (1). However, many CF patients are unable be able to take advantage of this medical advancement due to the high prices of CFTR modulators such as ivacaftor, elexacaftor, and tezacaftor on the market (2). These CFTR

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modulators, though being straightforward to synthesize, are expensive for consumers and thus inaccessible to those from poorer households, communities, and nations (2). This economic barrier has intensified the inequality in healthcare opportunities and outlooks for those suffering from CF on an international scale (2). This narrative review explores the effectiveness of CFTR modulators in treating those suffering from CF while exploring the economic and ethical concerns that stifle their accessibility to many communities.

CYSTIC FIBROSIS

Cystic fibrosis is a type of chronic genetic disorder that primarily affects the digestive and respiratory systems. There are different forms of cystic fibrosis, with 5% of cases being intestinal, 15-20% being respiratory, and 75-80% of cases being mixed form cases (3). This autosomal recessive condition occurs when there is a genetic mutation (any one type of the over 2,000 possible mutations) in the CFTR gene, which produces membrane-bound ion channels. The two most prominent CF-causing mutations are F508del and G551D (4). A mutation to this gene results in the disruption of chloride (Cl^-) and bicarbonate (HCO_3^-) ion transportation through epithelial cells (4). With CF-causing mutations, the transportation of chloride ions is decreased, and the transportation of sodium ions is increased, leading to the typical symptoms of cystic fibrosis, including thick and dehydrated mucus alongside digestive issues. This mucus in the respiratory system does not allow for the cilia to move substances along the tract, such as bacteria, which may stick and cause infections and chronic inflammation that leads to progressive lung damage (5). Other respiratory symptoms include chronic cough, wheezing, shortness of breath, and chronic sinusitis. Digestive-related symptoms include abdominal bloating and pain, steatorrhea (oily and bulky stool), poor growth, and pancreatic insufficiency (6). Pancreatic insufficiency is a condition where the pancreas is unable to produce an adequate number of enzymes to digest food properly, leading to steatorrhea, the reduced absorption of proteins, fats, and vitamins, and ultimately malnutrition and failure to thrive (4). While individuals of any background and origin can develop cystic fibrosis, it is found to be most frequently occurring in individuals of Northern European ancestry, with the population ranging from approximately 1 in 2,500 to 1 in 6,000 (7). In America, 1 in 2,500-3,500 white newborns have cystic fibrosis (7). Cystic fibrosis screening in the United States diagnosed the following newborns with Non-European/Caucasian ethic origins: 13% of Hispanic/Latin origins, 6-7% of African Americans, and 4-5% of other races, including Asian Americans (7). The widespread nature of CF across different patient populations has necessitated the introduction of efficient, accessible diagnostic procedures that can be employed on a wide variety of patients.

DIAGNOSIS

Cystic fibrosis is diagnosed through a combination of different testing methods, involving genetic analysis, newborn screening, and sweat testing. Newborn screening (NBS) is a routine test done within 24-48 hours of the birth of a newborn to detect conditions and illnesses early on, including cystic fibrosis (8). It involves a "Heel Prick Test", where blood is taken from the infant's heel and stored on a special filter paper. The blood is then tested with Immunoreactive Trypsinogen (IRT), which tests pancreatic activity. There is also a DNA analysis that is done to check for the CFTR mutation, and a sweat test to confirm the diagnosis of cystic fibrosis (9). Sweat testing, or quantitative pilocarpine iontophoresis testing, is a more definitive method for testing cystic fibrosis; it measures the chloride concentration of the individual's sweat (10). This diagnostic method involves placing a patch of pilocarpine, a drug that activates the sweat glands, on the individual's forearm or thigh for infants. Then, the process of iontophoresis takes place, which involves an electric current of 1-4 mA being applied by a pilocarpine iontophoresis unit, driving the pilocarpine further into the skin to stimulate the muscarinic acetylcholine receptors on the sweat glands, prompting sweating (10). The sweat sample is then collected and analyzed for high chloride ion concentration as a marker for diagnosis. The test is based on the fact that CFTR gene mutations disrupt the transportation of chloride ions in epithelial cells, leading to increased chloride concentration (7).

However, socioeconomic barriers continue to exist with the diagnostic tools used to target CF. Research has shown the sweat test – which is itself the most prominent form of CF diagnosis – has limited accessibility in low-income areas due to the cost of the instruments and other necessary tools (11). Alongside this, diagnosing CF in places such as Africa is difficult because symptoms from common afflictions in the region, such as GI disorders or malnutrition, can mask the symptoms of CF, meaning many patients go undiagnosed (11). The high cost of the tools needed to diagnose CF makes many cases in low-

income areas go undiagnosed, which exacerbates the larger trend of low-income patients struggling to receive optimal care for their CF (11). Newborn screening also proves difficult because mothers in low-income areas are disincentivized from staying in the hospital following childbirth to allow their child to be tested due to the high costs of hospital stays, and many mothers (~75%) in areas such as Chad, Niger, and Ethiopia give birth in the home, with only a fraction of mothers going to a hospital for a postnatal exam (11). Genetic testing is also stifled in those regions due to the high cost of the procedure and many communities' lack of access to labs (11). This creates an issue wherein a lack of income, as well as infrastructure, impacts the ability to diagnose CF. More proficient means of diagnosis would allow more individuals suffering from CF to receive sufficient treatment.

TREATMENT

The methodology of patient care for those afflicted with CF has generally revolved around three key objectives: early detection of the disease, frequent evaluation of the patient's condition, and mitigation of symptoms following evaluation (12). To promote early detection of the disease, countries such as the United States have adopted newborn screening protocols as part of the standard of care (12). When CF is found in a newborn, they receive routine examinations to evaluate their condition and formulate care plans as the patient develops, including annual chest radiographs and imaging, cultures of the throat and lungs, and spirometry tests once age 6 (12). However, this method of treatment faces issues, as conventional imaging processes have been shown to struggle with catching abnormalities early and may only detect damage once it's severe (13). Alongside this, noninvasive oropharyngeal cultures used to detect bacterial growth in CF patient airways have been shown to lose accuracy with age and are prone to false positives (14). This shows current means of evaluation can be inaccurate, which in turn means CF patients are often unable to receive optimal care until the disease has already progressed into its later stages. Several treatments have been developed to tackle the symptoms of CF following evaluation, including anti-inflammatories, antibiotics to combat bacterial growth in the airways, mucolytic agents such as N-acetylcysteine, which can break up mucus in the airways, and osmotic agents such as inhaled mannitol as a means of airway rehydration in some countries (12). However, it must be noted that these treatments alleviate only symptoms and not the biochemical mechanisms that cause the disease itself. With CFTR modulators, however, new avenues have opened, allowing patients to target the genetic markers at the core of CF (1).

CFTR MODULATORS AND ECONOMIC BARRIERS

To change the relationship between the disease and the treatments designed to fight it, healthcare practitioners have recently adopted the use CFTR modulators in their care plans (1). CFTR modulators are drugs designed to amplify, stabilize, or otherwise correct the behavior of a defective CFTR protein in a diseased patient to help treat cystic fibrosis by tackling the biochemical root of the disease and the mutations that cause it (1). One CFTR modulator, Ivacaftor, has been approved by the FDA to treat 38 different CFTR mutations (1). Alongside that, literature has shown that CFTR modulators can work well together in groups to tackle specific mutations, as ivacaftor, alongside two other CFTR modulators, elexacaftor and tezacaftor, has been shown to have "clinically robust" results for those suffering from cystic fibrosis due to the F508del mutation (15). This is vital to the treatment of CF globally, as the F508del mutation is the most prominent mutation in the cystic fibrosis patient population, and so this treatment method, which utilizes these three CFTR modulators, could impact the greatest number of patients worldwide (16).

There have also been other advancements of note in the field of CFTR gene regulation with the same goal as CFTR modulators of targeting not symptoms, but the genetics of the patients themselves. Many of these advancements seek to use viral vectors to introduce functional copies of the CFTR gene to subjects, including helper-dependent adenoviral (HD-Ad), adeno-associated viral (AAV), lentiviral (SIV, FIV, Neuraminidase/NA, and Sendai viral) vectors. Many of these designs have proven successful in mice in a lab environment, although there are concerns regarding their behavior in human patients, low efficacy due to low viral transfer rates through the mucus of the lungs, immune response pathways, and the risk of oncogenesis (3). While some success has been found in hybridizing the vectors, with examples such as the chimeric AAV2/HBoV1 vector proving to be usable *in vivo* for ferrets before clinical trials, Abeona Therapeutics' ABO401 and Spirovant Sciences' Spiro-201 – both using modified AAV capsids as well – have proven to be most effective and

shown transfer rates 3-5x more proficient than typical AAV vectors and gone on to receive FDA approval respectively (3). These mechanisms seek to target the genetic deficiencies at the center of CF, but their viral structure has created concerns that consistent use of these medications would lead to diminished response in the patient due to immune adaptations to the vector itself, meaning these alternatives to other CFTR modulators have yet to see widespread use (3).

One issue that arises regarding the use of CFTR modulators in such a manner is their accessibility. The manufacture of elexacaftor, ivacaftor, and tezacaftor costs only between $4,628 and $6,723 per year, yet their US list prices feature over a 90% markup (2). Using these three CFTR modulators for all eligible and diagnosed CF patients across the planet would require only $489 million worth of drugs, but the US list price would cost consumers over $31 billion (2). This makes the drugs difficult to acquire for low-income patients and inaccessible to patients outside of the wealthiest nations (2). There is precedent that supports initiatives to make CFTR modulators more affordable worldwide for low-income communities and countries. The World Health Organization has previously spoken out to promote equitable accessibility of medication as a means of "attaining the highest possible standard of health" across the world (17). Vertex Pharmaceuticals, the company that has control over the production of CFTR modulators, could alleviate this inequality in accordance with the WHO's recommendations by allowing for the production of generic variants by other companies at a fraction of the price for patients (18). It can be done so through voluntary licensing agreements with other manufacturers; this allows the patent holder, in this case being Vertex Pharmaceuticals, to grant a license voluntarily to other manufacturers to produce the CFTR modulators as a generic version at a greatly reduced cost (19). Voluntary licensing may be done through organizations, such as the United Nations-backed Medicines Patent Pool, an international public health organization that aims to create greater accessibility to medicines and health technologies in middle and low-income countries. This would make the drug far more accessible to those suffering from cystic fibrosis who may not be able to pay what Vertex calls for. There is precedent for this, as the nation of Argentina – where Vertex does not have a patent for CFTR modulators – locally manufactures effective generic equivalents that retail for less than a quarter of the patented retail price, with a price of $4,000 per month as compared to $27,000 per month (18). The creation of "generics", whether by choice or at the command of governments through compulsory licensure to allow the production of generic CFTR modulators in circumvention of existing patents, could help close this gap in accessibility (Table 1).

Table 1. Analyses of CFTR Modulators in a Clinical and Economic Context

Combination	Type of Modulator	Primary Mechanism of Action	Mutations Covered	Approx. Minimum Annual Manufacturing Cost	Approx. U.S. Annual List Price	Global Accessibility Notes
Ivacaftor	Potentiator	Increases CFTR channel gating/open probability (1)	38 CFTR Gating Mutations, Including G551D (1)	~$4,000–$5,000 (2)	~$311,000 (2)	Worldwide access inhibited due to high costs and infrequent reimbursement policies (2)
Tezacaftor + Ivacaftor	Corrector + Potentiator	Tezacaftor improves effective folding; ivacaftor improves Cl- activity (1)	F508del heterozygous and selected residual-function mutations (15)	~$5,000–$6,000 (2)	~$304,000 (2)	Costly and inaccessible outside the Global North/ U.S./European Union (2)

Continued Table 1. Analyses of CFTR Modulators in a Clinical and Economic Context

Combination	Type of Modulator	Primary Mechanism of Action	Mutations Covered	Approx. Minimum Annual Manufacturing Cost	Approx. U.S. Annual List Price	Global Accessibility Notes
Elexacaftor + Tezacaftor + Ivacaftor (ETI)	Dual Corrector + Potentiator	Dual correctors correct CFTR proteins with F508del mutation; ivacaftor improves ion channel activity (15)	F508del Mutation Carriers (~90% patients w/CF) (16)	~$4,600–$6,700 (2)	~$322,000 (2)	Most effective, but patient outreach is bottlenecked by high prices (2)
Generic CFTR Modulators (Argentina)	Varies	Homologous to Vertex Products (18)	Identical targets to name-brand equivalents (18)	~$4,000–$6,000 production cost (2)	~$48,000 (18)	Significantly more affordable due to license-free manufacturing (18)

CONCLUSION

Cystic fibrosis is a complex disease. It is the product of over 2,000 possible mutations to the CFTR gene (11). These mutations can have debilitating impacts on the respiratory and digestive systems of patients at a very young age, leading to symptoms such as mucus in the respiratory tract, bloating, pancreatic insufficiency, failure to thrive, and many others (6). While healthcare providers once had to rely on treatments targeting the symptoms of cystic fibrosis, CFTR modulators such as ivacaftor, elexacaftor, and tezacaftor have provided a novel and clinically significant advancement into the future of cystic fibrosis treatment centered around the idea of targeting not symptoms, but the mutations that cause the disease itself (1). Still, these medications continue to be difficult to access for thousands of people in low-income nations and communities across the world, and so the need to remedy this inequality in healthcare accessibility and outcomes based on income is an ongoing struggle and challenge to public health (2). The World Health Organization has called for worldwide equal access to medication in its efforts to mitigate poor health outcomes exacerbated by poor economic position (17).

It is with this objective in mind that the authors conclude that these CFTR modulators must be made more affordable in accordance with the World Health Organization's objective and the larger pursuit of medical opportunity and better health outcomes worldwide. Though it is a complex issue, the creation of generic CFTR modulators could make cheaper, readily available alternatives for patients in lower-income nations and communities, as shown in Argentina, where generic equivalents are readily available (18). These generics could be produced with the permission of Vertex Pharmaceuticals or made readily available for local manufacture by governments through a compulsory license (18). Regardless, the current dynamic by which health outcomes are made worse by economic context goes against the broader mission in healthcare to bring accessibility and greater medical outcomes to patients worldwide. Closing this gap in wealth-related health outcomes could improve the quality of life of thousands of patients worldwide, regardless of economic background or location. It is through a future in cystic fibrosis treatment driven by readily available CFTR modulators that patients all over the world, regardless of wealth or status, can experience improved outcomes, cultivate a better quality of life, and breathe easy. Future research could continue to examine the greater effort of combating CF treatment inequality and the ways it continues to be exacerbated by economic policy across different communities of varying economic means. Furthermore, future work could evaluate frameworks designed to make CF diagnosis at birth easier via lower costs of diagnostic procedures and the construction of hospitals and labs in disenfranchised areas. By making diagnosis more accessible and treatment more affordable, CF treatment could approach a more holistic and

systematic methodology, improving patient outcomes worldwide.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this work.

REFERENCES

1. Lopes-Pacheco M. CFTR Modulators: the Changing Face of Cystic Fibrosis in the Era of Precision Medicine. *Frontiers in Pharmacology [Internet].* 2020 Feb 21; 10 (1662). https://doi.org/10.3389/fphar.2019.01662
2. Guo J, Wang J, Zhang J, Fortunak J, Hill A. Current prices versus minimum costs of production for CFTR modulators. *Journal of Cystic Fibrosis [Internet].* 2022 Apr 16; 21 (5). https://doi.org/10.1016/j.jcf.2022.04.007
3. Lomunova MA, Gershovich PM. Gene Therapy for Cystic Fibrosis: Recent Advances and Future Prospects. *Acta Naturae [Internet].* 2023; 15 (2): 20-31. https://doi.org/10.32607/actanaturae.11708
4. Cutting GR. Cystic fibrosis genetics: From molecular understanding to clinical application. *Nature Reviews Genetics.* 2014 Nov 18; 16 (1): 45-56. https://doi.org/10.1038/nrg3849
5. Bell SC, Mall MA, Gutierrez H, Macek M, et al. The future of cystic fibrosis care: a global perspective. *The Lancet Respiratory Medicine [Internet].* 2020 Jan; 8 (1): 65-124. https://doi.org/10.1016/S2213-2600(19)30337-6
6. Sabharwal S. Gastrointestinal Manifestations of Cystic Fibrosis. *Gastroenterology & Hepatology [Internet].* 2016; 12 (1): 43.
7. Scotet V, L'Hostis C, Férec C. The Changing Epidemiology of Cystic Fibrosis: Incidence, Survival and Impact of the CFTR Gene Discovery. *Genes [Internet].* 2020 May 26; 11 (6): 589. https://doi.org/10.3390/genes11060589
8. Dubay KS, Zach TL. Newborn Screening [Internet]. PubMed. *Treasure Island (FL): StatPearls Publishing*; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558983/ (accessed on 2025-10-02)
9. McGarry ME, Raraigh KS, Farrell P, Shropshire F, et al. Cystic Fibrosis Newborn Screening: A Systematic Review-Driven Consensus Guideline from the United States Cystic Fibrosis Foundation. *International Journal of Neonatal Screening.* 2025; 11 (2): 24. https://doi.org/10.3390/ijns11020024
10. Zubair M, Schmidt H, Sharma G. Sweat Testing [Internet]. PubMed. *Treasure Island (FL): StatPearls Publishing*; 2022. Available from: https://pubmed.ncbi.nlm.nih.gov/31613508/ (accessed on 2025-10-02)
11. Fuhrer M, Zampoli M, Abriel H. Diagnosing cystic fibrosis in low- and middle-income countries: challenges and strategies. *Orphanet Journal of Rare Diseases.* 2024 Dec 20; 19 (1). https://doi.org/10.1186/s13023-024-03506-1
12. Pittman JE, Ferkol TW. The Evolution of Cystic Fibrosis Care. *Chest [Internet].* 2015 Aug; 148 (2): 533-42. https://doi.org/10.1378/chest.14-1997
13. Borowitz D, Robinson KA, Rosenfeld M, Davis SD, et al. Cystic Fibrosis Foundation Evidence-Based Guidelines for Management of Infants with Cystic Fibrosis. *The Journal of Pediatrics [Internet].* 2009 Dec; 155 (6): S73-93. https://doi.org/10.1016/j.jpeds.2009.09.001
14. Rosenfeld M, Emerson J, Accurso F, Armstrong D, et al. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. *Pediatric Pulmonology.* 1999 Nov; 28 (5): 321-8. https://doi.org/10.1002/(SICI)1099-0496(199911)28:5<321::AID-PPUL3>3.0.CO;2-V
15. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *The Lancet [Internet].* 2019 Oct; 394 (10212). https://doi.org/10.1016/S0140-6736(19)32597-8
16. Canadian Agency for Drugs and Technologies in Health. Summary of F508del Mutation Testing [Internet]. www.ncbi.nlm.nih.gov. Canadian Agency for Drugs and Technologies in Health; 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK540352/ (accessed on 2025-10-2).
17. Chattu VK, Singh B, Pattanshetty S, Reddy KS. Access to medicines through global health diplomacy. *Health Promotion Perspectives [Internet].* 2023 Apr 30; 13 (1): 40-6. https://doi.org/10.34172/hpp.2023.05

18. Zampoli M, Verstraete J, Baird C, Calligaro G, Morrow B. Affordable Cystic Fibrosis (CF) Transmembrane Conductance Regulator Modulator Drugs for CF: All CF Lives Worldwide Matter! *American Journal of Respiratory and Critical Care Medicine*. 2023 Nov 1; 208 (9): 915-6. https://doi.org/10.1164/rccm.202307-1200VP
19. Costa E, Van Den Ham HA & Leufkens HGM. Challenges and Opportunities of adding CFTR modulators for cystic fibrosis to the WHO essential medicines list. *Journal of Cystic Fibrosis*. 2025; 24 (5): 920-922. https://doi.org/10.1016/j.jcf.2025.06.006