Review Article

No one left behind: review of precision medicine and cystic fibrosis—how the changing approach to cystic fibrosis treatment might lead to tailored therapies for all

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Abstract: Cystic fibrosis is an autosomal recessive, multisystem disorder that has been historically associated with poor life expectancy. Due to the defective cystic fibrosis transmembrane conductance regulator protein, patients with cystic fibrosis develop viscous secretions that are difficult to clear, resulting in numerous abnormalities such as chronic airway obstruction, maldigestion and malabsorption. While our understanding of the pathophysiology and disease management have improved, pulmonary disease remains the leading cause of morbidity and mortality in patients with cystic fibrosis. However, since the introduction of precision medicine, novel therapeutic agents have been developed to target the underlying defective protein, resulting in improved disease management and life expectancy. The goal of precision medicine is to provide timely diagnosis, phenotyping, and personalized treatments, based on an individualized analysis of a patient's genome. This article reviews current and potential precision medicine treatments for patients with cystic fibrosis, including cystic fibrosis transmembrane conductance regulator modulators and other modulators designed for patients who would not benefit from currently available therapies. We will also discuss other investigational treatment modalities, such as ribosomal read-though agents and RNA therapy, which may continue the advancement of cystic fibrosis treatment. Current research into methods aimed to better predict patients' responses to personalized treatment, such as theratyping, will also be discussed. Given the benefits of applying precision medicine in cystic fibrosis, future research in this therapeutic approach will also likely benefit other life-threatening monogenetic disorders.

Keywords: Cystic fibrosis; precision medicine; cystic fibrosis transmembrane conductance regulator modulators (CFTR modulators); non-cystic fibrosis transmembrane conductance regulator modulators (non-CFTR modulators)

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Background

The rise of precision medicine has brought forth new treatment strategies that have already revolutionized the management of various diseases. In its truest form, precision medicine provides an individualized analysis of a patient's genome, which allows the clinician to understand the pathogenesis of their disease and to administer targeted treatments (1). Additionally, the goal of precision medicine is to provide timely diagnosis, phenotyping, and personalized treatments, which ideally would prevent patients from developing sequalae related to advanced disease. Extensive research in precision medicine has already resulted in therapies that improved the rate of survival for various cancer diagnoses, ranging from breast cancer to melanoma (2). Recent developments in precision medicine have also demonstrated significant benefits in patients with cystic fibrosis (CF), a rare disease that historically had been associated with devastating outcomes. Our review will demonstrate how precision medicine has changed the management of CF, providing an example to how this medical model may be potentially implemented in other genetic disorders as well.

CF

CF is a multi-system disease that is estimated to affect approximately 70,000–90,000 individuals worldwide, including 4,344 in Canada (3-5). The true number of patients with CF is unknown due to a paucity of epidemiological CF data in low- and middle-income countries, thus there may be a significant number of patients with undiagnosed CF (5). When it was first scientifically described in 1938, the predicted survival was only 6 months (6). Advances in pharmacologic and non-pharmacologic interventions have substantially improved the life expectancy of patients with CF. The median survival in 2020 for individuals living in the United States and Canada was predicted to be 50 and 54.3 years, respectively (4,7). Therefore, many newborns with CF today may live well into their fifth or sixth decade. The genetic cause of CF is the result of variants found in the CF transmembrane conductance regulator (*CFTR*) gene, located in chromosome 7. CFTR channels are responsible for the transport of chloride and bicarbonate ions across the apical membranes of most epithelial cells. These transport channels are found throughout the epithelia of the lung, pancreas, sweat glands, intestine, liver, and vas deferens (8). Insufficient chloride and bicarbonate ion transport results in thick secretions, which greatly impair the function of the affected organ. Some of the major features of CF include respiratory dysfunction, pancreatic exocrine insufficiency, and intestinal disease. Although multiple organs are in involved in CF, mortality from CF is most often caused by progressive respiratory decline. As a consequence, the severity of CF is directly proportional to the extent the lungs are affected by the disease (9).

To date, over 2,000 different *CFTR* variants worldwide have been identified (9,10). The F508del *CFTR* variant is the most common, accounting for two-thirds of all alleles identified. About 90% of CF patients carry at least one copy of the F508del variant (9). CF variants are typically classified into six classes, broadly relating to abnormal CFTR synthesis, trafficking or function (11,12). Class I variants are characterized by protein synthesis defects (such as the presence of a pre-mature stop codon), whereas class II variants (which include F508del) results in a misfolded protein, leading to protein degradation in the endoplasmic reticulum thus preventing protein expression on the cell surface. Class III variants impair channel opening (gating variants that render the channel permanently closed) and class IV variants result in reduced conduction of ions across the channels. Class V variants result in a substantial reduction in the expression of messenger ribonucleic acid (mRNA), protein, or both and class VI variants cause protein instability at the plasma membrane. In general, class I–III variants typically result in more severe multiorgan dysfunction, ranging from CF-related diabetes mellitus, pancreatic insufficiency, and impaired lung function. Conversely, class IV–VI variants are typically associated with a milder disease phenotypes (12). Although not yet commonly discussed in the literature, a seventh class has been proposed to categorize large deletion variants that may nullify the production of CFTR mRNA (13). These variants result in varying degrees of defective chloride transportation, resulting in viscous secretions that impact a variety of organs, especially those who rely on patent pathways for their proper function. Currently, the majority (80%) of patients are diagnosed within the first two years of life, mainly due to advances in neonatal screening and antenatal diagnosis (10,14). Approximately 10% of patients with CF are diagnosed in adulthood, possibly in part owing to a milder phenotype (10). *Figure 1* summarizes the class variants and their respective commercial or investigational treatment targets.

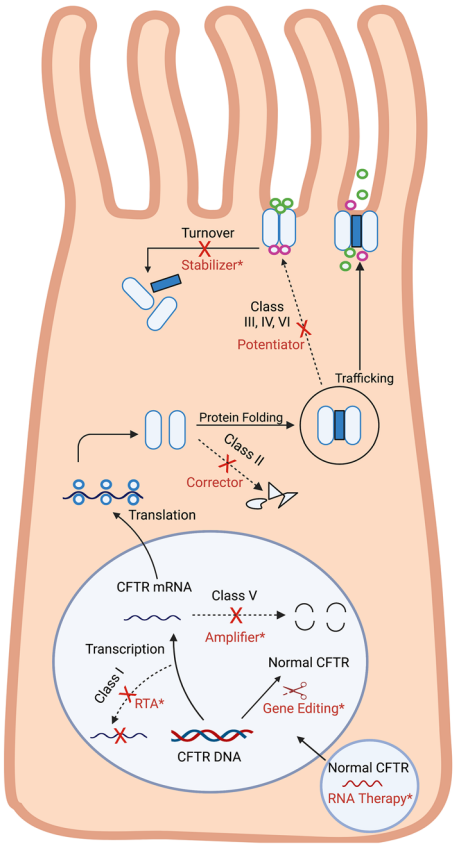

Figure 1 Class variants in cystic fibrosis and their treatment targets. *, experimental treatments. CFTR, cystic fibrosis transmembrane conductance regulator; RNA, ribonucleic acid; mRNA, messenger RNA; RTA, ribosomal read-through agents.

Objective

Traditional treatment in CF respiratory disease can be classified into three main categories: airway clearance, antimicrobials, and anti-inflammatories (15). However, these treatment modalities focus on prophylaxis or symptom control caused by the sequela of CFTR dysfunction. Since the pathology of CF begins with a defective gene, treatments targeting the *CFTR* gene and/or transport channels are the most direct ways to treat CF (15). By repairing or restoring the function of these genes or channels, patients with CF have less viscous secretions, allowing the normal function of the affected organ. Accordingly, over the last 2 decades, research into novel therapeutics that addresses the phenotypic abnormality that results from specific genotypic variants have revolutionized the field of CF. This research led to the development of CFTR modulators, a new class of medications that target the defective CFTR protein, as well as alternative non-CFTR modulators that aim to address variants in patients who are not eligible for CFTR modulators (*Table 1*). With the introduction of these modulators, the management of CF has shifted from symptom-focused treatment to precision medicine, where treatment is targeted to the patient's underlying genotype. This individualized treatment has resulted in significant improvement in health outcomes, demonstrating the importance of precision medicine in the present and future management of CF. The goal of this review is to discuss the current and the most recently developed therapeutic agents in CF, providing a concise summary for clinicians and researchers as well as emphasizing the importance of precision medicine in the treatment of rare genetic disorders.

CFTR modulators

There are numerous factors that influence CF phenotype, including genotype, modifier genes, epigenetics, and environmental factors (16). Previous heritability studies have also demonstrated that morbidity in CF is influenced by other genes that do not directly interact with *CFTR* (17-20). Due to the genetic diversity that is found within CF, high-throughput screening on chemical libraries followed by lead optimization assays were instrumental in the discovery of CFTR modulators (21,22).

CFTR variants can generally result in functional, qualitative, or quantitative defects in the chloride channel. A number of CFTR modulators have been identified since 2012, designed to target specific classes of CFTR defects on a protein level (23,24). The first modulator available for clinical use was a potentiator (ivacaftor), which improves the efficiency of CFTR functionality by reversing gating or chloride ion conduction defects and increasing intracellular levels of cAMP/cGMP (cyclic adenosine monophosphate/cyclic guanosine monophosphate), thus stimulating CFTR activity (21,25). The second class of modulators to become available for clinical care were correctors (lumacaftor, tezacaftor, elexacaftor). These compounds help to correct protein misfolding as a result of the genetic deletion seen with class II variants, allowing for increased localization of functional CFTR proteins at the apical membrane in epithelial cells.

Many variants, including F508del, result in CFTR biogenesis and channel function abnormalities, which prompted the development of potentiator and corrector

Table 1 Summary of current and potential precision medicine treatments for patients with cystic fibrosis

Precision medicine treatments	Mechanism of action	Examples
CFTR modulators	Targets defective CFTR protein through one of four mechanisms	–
Potentiator	Reversing gating defect, allowing chloride ions to flow through across the cell membrane	Ivacaftor
Corrector	Correct protein misfolding, allowing the CFTR protein to traffic to the cell membrane	Lumacaftor, tezacaftor, elexacaftor
Amplifier	Increase the number of CFTR protein	No available therapies to date
Stabilizers	Improve CFTR protein stability in the plasma membrane	Cavosonstat[†]
Ribosomal read-through agents	Suppress premature termination codons, which prevent the CFTR protein from being truncated	ELX-02[†]
RNA therapy	Deliver healthy genetic material into cells using mRNA, ACE tRNA or ASO	MRT5005[†], 4D-710[†]
Gene therapy and gene editing	Supply normal *CFTR* DNA to affected cell or use the cell's own repair mechanisms to correct the defective variants	CRISPR/Cas9 technology[†]

[†], drugs or technology that are not currently available in the market. CFTR, cystic fibrosis transmembrane conductance regulator; RNA, ribonucleic acid; mRNA, messenger RNA; ACE tRNA, anticodon-engineered suppressor transfer RNA; ASO, antisense oligonucleotides; DNA, deoxyribonucleic acid; CRISPR, clustered regularly interspaced short palindromic repeats.

combination therapy (26). Most CF patients who are eligible to receive CFTR modulator therapy require combination therapy to address protein misfolding and channel defects (26). Finally, the last class of modulators are amplifiers, which are not yet commercially available. These compounds stabilize CFTR mRNA, thus improving the rates of successful translation of the CFTR protein (27). *Table 2* summarizes the current treatment options for adults with CF, their indications as well as primary and secondary outcomes. The complete list of qualifying variants, including residual function and minimal function variants can be found in Table S1.

Potentiator

The G551D gating variant was the first to be successfully targeted using the CFTR potentiator ivacaftor, which enhances channel gating and restores CFTR activity (28,29). Patients with variants such as G551D that render the CFTR non-operational due to a persistently closed channel or other class III-VI variants, would therefore benefit from ivacaftor since this would directly target the channel defect, converting the channel from a "closed" to "open" state and improving efficiency of channel activity (30). At day 15, there were already significant improvements in sweat chloride levels (i.e., –45 mmol/L from baseline) and lung function [median absolute increase percent of predicted forced expiratory volume in 1 second (ppFEV1) of about 9%] for patients with at least one G551D *CFTR* allele (31). Ivacaftor has also been demonstrated to reduce sweat chloride level to values below the diagnostic threshold for CF (60 mmol/L), a measure of improved CFTR functionality, as well as a 55% relative reduction in the risk of pulmonary exacerbations (31). The benefits of ivacaftor have also been identified in patients with selected non-G551D gating variants, including improvements in ppFEV1 by 8.13% and sweat chloride levels by –55.82 mmol/L by 8 weeks of treatment (32). Further studies since the introduction of ivacaftor to the market demonstrate a range of possible extra-pulmonary benefits with therapy as well, ranging from improvements in chronic rhinosinusitis symptom burden to levels of fecal elastase 1, a marker of pancreatic endocrine function (33). However, most of the evidence is low quality given the limited number of patients evaluated and the lack of control groups, and thus more research is required to establish the benefits of ivacaftor on extra-pulmonary manifestations of CF (33).

Corrector

The development of correctors, including lumacaftor, tezacaftor and elexacaftor, provided an additional method

Table 2 Available modulators for adult cystic fibrosis patients, indications, primary and secondary endpoints

Modulators	Indications	Primary endpoints	Secondary endpoints
Ivacaftor	G551D, Ramsey *et al.*, 2011	↑ FEV1 10.6%	↓ 55% pulmonary exacerbations; ↑ CFQ-R 8.6 points; ↑ 2.7 kg weight; ↓ 48.1 mmol/L sweat chloride
	Non-G551D, De Boeck *et al.*, 2014	↑ FEV1 8.13%	↑ CFQ-R 12.31 points; ↑ 0.75 kg/m^2 BMI; ↓ 55.82 mmol/L sweat chloride
	R117H, Moss *et al.*, 2015	↑ FEV1 2.1%, primary outcome not met	↑ 8.4 points CFQ-R; ↑ 0.26 kg/m^2 BMI; ↓ 24.0 mmol/L sweat chloride
Lumacaftor/ivacaftor	Homozygous F508del, Wainwright *et al.*, 2015	↑ FEV1 2.6% to 4.0%	↓ 30% to 39% pulmonary exacerbations; ↑ CFQ-R 2.2 to 3.1 points; ↑ 0.24 to 0.28 kg/m^2 BMI
Tezacaftor/ivacaftor	Homozygous F508del, Taylor-Cousar *et al.*, 2017	↑ FEV1 4.0%	↓ 35% pulmonary exacerbations; ↑ CFQ-R 5.1 points; ↑ 0.06 kg/m^2 BMI; ↓ 10.1 mmol/L sweat chloride
	F508del/residual function, Rowe *et al.*, 2017	↑ FEV1 6.8%	↑ CFQ-R 11.1 points; ↓ 9.5 mmol/L sweat chloride
Elexacaftor/tezacaftor/ivacaftor	F508del/minimal function, Middleton *et al.*, 2019	↑ FEV1 13.8%	↓ 63% pulmonary exacerbations; ↑ CFQ-R 20.2 points; ↑ 1.04 kg/m^2 BMI; ↓ 41.8 mmol/L sweat chloride
	Homozyous F508del, Heijerman *et al.*, 2019	↑ FEV1 10%	↑ CFQ-R 17.4 points; ↓ 45.1 mmol/L sweat chloride

FEV1, forced expiratory volume in 1 second; CFQ-R, cystic fibrosis questionnaire-revised respiratory domain score; BMI, body mass index.

of improving the functionality of CFTR proteins by correcting protein misfolding caused by class II variants. In 2015, the combination of ivacaftor with a corrector (lumacaftor/ivacaftor) was approved by the United States Food and Drug Administration (FDA) for patients who were homozygous for F508del. In addition to improved FEV1 ranging from 2.6 to 4.0%, this combination resulted in lower rates of pulmonary exacerbations, including 61% lower rates of hospitalizations as well as a 56% drop in rates of intravenous antibiotic treatments (34). However, 10–20% patients were intolerant to the treatment due to medication side effects, including chest tightness, dyspnea and increased cough (34-37). In comparison to combination therapy, lumacaftor monotherapy was not associated with significantly improved outcomes (38). Subsequent therapies combining potentiators and correctors were developed, including a second dual combination therapy (tezacaftor/ivacaftor) in 2018 and a triple combination therapy [elexacaftor/tezacaftor/ivacaftor (ETI)] in 2019 (39,40). At week 24, the combination of tezacaftor and ivacaftor for patients homozygous for F508del was demonstrated to improve ppFEV1 by 6.8% and to reduce the rate of pulmonary exacerbations by 35% when compared to placebo (41). Tezacaftor/ivacaftor was also found to improve ppFEV1 by 6.8%, reduce sweat chloride concentrations by 9.5 mmol/L and improve quality of life, detected by an 11.1 point score increase in Cystic Fibrosis Questionnaire-Revised (CFQ-R), in patients with CF who were heterozygous for the F508del and a non-F508del, *CFTR* residual-function variant (42). ETI in particular was found to have significant benefits in patients who were heterozygous for F508del. Investigators found that when these patients were treated with the highest dose of ETI, they were found to have an increase in $ppFEV_1$ by 13.8% as early as 4 weeks post initiation of therapy (43,44). Triple combination therapy was also associated with up to 39.6 mmol/L reduction in sweat chloride concentrations alongside with improvements in quality of life, measured by 15.4 to 25.7 point increase in CFQ-R (43). For patients who are homozygous for F508del, triple therapy combination resulted in improvements in FEV1 by 11.2%, decrease in sweat chloride concentration by 46.2 mmol/L, increase in CFQ-R scores by 17.1 points and increase in BMI (body mass index) by 0.60 kg per square meter compared to tezacaftor/ivacaftor alone (39,44). Altogether, up to 90% of CF patients may benefit from these targeted therapies (45).

Within the subset of patients who are heterozygous or homozygous for F508del with very severe lung function ($ppFEV_1$ <40%), less data is available about ETI efficacy since most industry-sponsored clinical trials involving

CFTR modulators have excluded this patient population (46,47). However, since the landmark phase 3 studies, data from compassionate use of CFTR modulators in the very severe lung function population has demonstrated highly promising results where patients experience dramatic improvements in FEV1 by 15.1% and weight (range, 4.2 to 4.5 kg) such that some no longer need to remain on the lung transplant wait list (48-50). On the other hand, the efficacy of ETI in patients with very mild lung function (ppFEV1 >90%) requires further analysis, however a phase 3 open-label study of ETI in children from 6 through 11 years of age with at least one F508del variant found that ETI was both safe and efficacious in children with very mildly reduced lung function (51). These results are suggestive that ETI may be effective for all those with at least one F508del variant, regardless of the severity of their lung disease. Initial phase 3 trials did not include children younger than the age of 12, however subsequent trials found that potentiator monotherapy and combination therapies were safe and efficacious in children 6 through 11 years of age (51-54).

Recent research suggest that triple combination therapy is expected to result in significant reductions in the need for intravenous antibiotics at a population level, ranging from 16.1% to 43.6% (55). In addition, patients with F508del/unknown allele may still benefit from triple combination therapy (56). CFTR modulators may provide further benefits if they are started at a young age, although more research is required to determine their long-term effects (24). Various studies have also demonstrated ETI's benefit on non-pulmonary manifestations of CF, including improved chronic rhinosinusitis symptom burden [improvement in mean score from 34.8 to 22.4 measured by 20-item Sino-Nasal Outcome Test (SNOT-20)], possibly improved glycemic control, especially in individuals with CF-related diabetes (11.2% decrease in percent time with glucose over 200 milligrams per decilitre), increase in weight (5.6 kg), and enhanced female fertility (14 cases of conception after initiating ETI) (39,57-59).

Next generation of CFTR modulator in development

The use of CFTR modulators is a clear example of the paradigm shift as a result of precision medicine in the treatment of a genetic disorder, offering a new approach that focuses on identifying the patient's genotype and correcting the resultant phenotypic defect (60). There remains a subset of patients, however, who do not respond to currently available modulators or do not have the variants that can be targeted by these agents. Fortunately, novel CFTR modulator approaches are currently being developed that may increase the number of patients benefiting from these treatments.

Amplifier

A new class of compounds known as CFTR amplifiers are currently being developed (61). Amplifiers aim to increase the amount of CFTR mRNA, which in turn increases the amount of CFTR proteins. In patients with class V variants, the quantity of CFTR produced is reduced due to a splicing abnormality (62). While amplifiers do not improve the function of CFTR proteins, they stabilize CFTR mRNA through a co-translational mechanism that is independent of *CFTR* genotype (27). Thus, amplifiers can be used to produce more CFTR proteins for the downstream actions of other CFTR modulators. These compounds (also known as PTI-CH) were initially identified through phenotypic high-throughput screen of approximately 54,000 small molecules that exhibited functional synergy with ivacaftor and lumacaftor (63). Further research is underway to develop amplifiers that can be used clinically to complement correctors and potentiators. A phase 2 trial (NCT03591094) is currently assessing the safety and therapeutic effects of a CFTR amplifier nesolicaftor (or PTI-428) in CF patients who have two copies of the F508del variation and are being treated with tezacaftor/ivacaftor (64). One recent study found that nesolicaftor improved the response to ETI in primary human CF bronchial epithelial cells, however it is unclear whether this response will be observed in future *in vivo* models (65).

Stabilizers

The accelerated turnover of CFTR protein from the cell surface defines the underlying abnormality in patients with class VI variants. The CFTR mutant proteins are functional but have a shorter half-life in the plasma membrane (13). Several agents have been found to improve CFTR protein stability in the plasma membrane, including vasoactive intestine peptide, CFTR-associated ligand, inhibition of S-nitrosoglutathione reductase, and hepatocyte growth factor co-administered with lumacaftor (13). The first CFTR stabilizer in clinical trials cavosonstat

(N91115), an inhibitor of S-nitrosoglutathione reductase, was well tolerated by the participants, however did not demonstrate any improvement in lung function and sweat chloride concentration when combined with lumacaftor/ivacaftor or ivacaftor in phase 2 trials (NCT02589236 and NCT02724527) (13,66). Thus, further work will be needed before this agent could be considered for clinical use.

Beyond CFTR modulators—the next frontier in precision medicine

While CFTR modulators have revolutionized the treatment of CF, not all patients will benefit from therapy. Some patients are unable to tolerate the adverse side effects of their CFTR modulator, which may result in reduced adherence to their treatment (67). In addition, approximately 10% of people with CF do not have variants that would benefit from currently available CFTR modulators. In particular, patients with Class I variants, which result in aberrant transcription would therefore not be treatable using modulators. These limitations have prompted the development of specific CF therapies beyond CFTR modulation.

Ribosomal read-through agents

Currently, there are no drug therapies available for CF individuals with class I variants (68). Approximately 5–10% of all *CFTR* variants consist of premature termination or nonsense variants, resulting in the lack of CFTR protein expression (68). Researchers are currently developing read-through agents that may promote transcription as well as premature termination codon-suppressing drugs that may address the nonsense variants seen in some patients with class I variants (30). Ribosomal read-through agents (RTA) were developed as a potential treatment option for class I variants. RTAs suppress premature termination codons, which in turn prevent the protein from being truncated and allow it to be expressed in the membrane. The efficacy of RTA monotherapy is limited by the high therapeutic threshold required to correct CFTR function, which is potentially as high as 30–35% of normal CFTR function (45). Unfortunately, phase 3 trials for Ataluren, an RTA that initially had promising results, failed to demonstrate clinically significant outcomes (22). Currently, a phase 2 trial in CF patients with the G542X allele is underway for a newer RTA called ELX-02, a eukaryotic ribosomal selective glycoside, that may potentially have more successful outcomes (NCT04135495) (69).

RNA therapy

Delivering healthy genetic material into cells has been studied as a potential additional strategy to produce functional CFTR protein. Depending on the subtype, RNA (ribonucleic acid) therapy may be administered regardless of the underlying *CFTR* variant (70). There are three types of RNA that have been investigated for therapeutic use in CF: mRNA, anticodon-engineered suppressor transfer RNA (ACE tRNA) and antisense oligonucleotides (ASO).

The goal of mRNA therapy is to deliver normal *CFTR* genetic code that can be translated into healthy CFTR protein within the cytoplasm, bypassing the need for cellular transcription of mRNA from deoxyribonucleic acid (DNA). One of the critical technical challenges of delivering genetic material to targeted cells is to ensure stability of the exogenous mRNA against the host's intra- and extracellular nucleases and immune response. Different strategies have been used to increase the stability of mRNA and to reduce their immunogenicity (70). Since 1993, a variety of vector-mediated gene delivery systems have been investigated in CF, including adeno-associated virus, lentivirus, as well as non-viral agents such as exosomes and lipid nanoparticles (70,71). Clinical trials assessing gene delivery systems were able to demonstrate increased CFTR expression in nasal and bronchial epithelium, however such strategies have not demonstrated clinical benefit to date (71). Currently, there are two clinical trials investigating mRNA therapy in CF. The RESTORE-CF phase 1/2 clinical trial is examining the safety and tolerability of MRT5005, a nebulized therapy that delivers CFTR-encoded mRNA to the lungs (NCT03375047) (72,73). A second phase 1/2 clinical trial is studying the use of gene therapy 4D-710, adeno-associated virus gene therapy that carries a transgene cassette encoding human cystic fibrosis transmembrane conductance regulator gene (NCT05248230) (74).

ACE tRNAs have been designed to carry a nonsense suppressing codon. The goal of ACE tRNA is to incorporate corrected sequences in mRNA, leading to the production of normal functional CFTR proteins (75). ASO are small antisense RNA molecules that bind and correct target RNA, preventing variants such as splicing variants from disrupting mRNA production. Similar to exogenous mRNA, a major limitation to ACE tRNAs and ASOs is that they require an effective, vector-mediated gene delivery system that is able to overcome natural barriers and host

defenses (75).

Gene therapy and gene editing

Unlike CFTR modulators, which aim to restore CFTR protein function, gene therapy and gene editing have the potential to provide CF patients with wild-type CFTR protein. More specifically, gene therapy aims to supply normal *CFTR* DNA to affected cells, whereas gene editing would use the cell's own repair mechanisms to correct the defective variants. To our knowledge, CF gene therapy clinical trials have not been associated with improved outcomes, with a weak effect observed on lung function (76). Multiple gene editing tools have been developed and studied in CF, including the CRISPR (clustered regularly interspaced short palindromic repeats)/Cas9 approach to base editing and prime editing (73). While these editing tools have not yet been demonstrated to be effective in clinical settings, they nevertheless have the potential to be alternative treatment options for patients with nonsense or rare variants.

CRISPR/Cas9 technology was developed after discovering *Escherichia coli*'s defense mechanisms against exogenous DNA from bacteriophages. The goal of this strategy is to correct the DNA variants using molecular "scissors" that cut the defective DNA and replace it with the correct sequence (71). Since CRISPR/Cas9 technology is reliant on cellular DNA repair mechanisms, base editing was developed to bypass this need, thus increasing the efficiency of the system. This technique additionally allows the direct alteration of a single DNA base pair, which is particularly attractive in CF given that many *CFTR* variants could be rescued with just a single base pair change (73). Current barriers to using base editing include limits in the number of possible base-to-base conversions as well as being too large for certain gene delivery vectors (73).

Prime editing was developed to edit a specified DNA sequence using the CRISPR-Cas9 system. Variable lengths of DNA sequences can also be edited using a fusion complex composed of a catalytically impaired Cas9 protein and an engineered reverse transcriptase (73). Researchers have previously demonstrated that the F508del variant can be repaired by prime editing in patient-derived intestinal organoids (77). However, prime editing was found to have variable degrees of targeting efficiencies with resultant, undesired off-target variants (77). Further research is required before CRISPR/Cas9 technology and its associated gene-editing tools can become a viable clinical alternative to CFTR modulator therapy in CF.

Stem cell therapy

Recent advancements and discoveries in stem cell therapy has provided an additional potential avenue for treatment in individuals with CF. Researchers have examined adult and gestational stem cells for their immunomodulatory potential in context of bacterial infections as well as in the *ex vivo* production of new organs (78). Pluripotent stem cells have also been used to explore new drug development and modeling of CF pathology. While embryonic stem cells and induced-pluripotent stem cells, as well as tissue-resident adult stem cells have all been studied in CF, no stem-cell derived treatment options have yet to demonstrate clinical benefits (79). Similar to gene therapy, the delivery of stems cells to the airways remains a major obstacle that will require ongoing research.

Additional considerations: discordance between genotype and phenotype

Epigenetic modifications—DNA methylation and histone modification

While CF phenotypes can be categorized based on their class variants in order to help identify targeted treatment for *CFTR* variants, there is an emerging appreciation that most *CFTR* variants result in numerous subclasses of molecular defects, which provide an additional challenge to the development of individualized therapy in CF (80). The complexity of *CFTR* gene expression may also be influenced by epigenetic modifications, which may explain the different responses to CFTR modulators in individuals with the same *CFTR* variants.

Epigenetics are heritable changes in gene expression that do not involve modifying the DNA sequence itself (81). This can result in variable lung disease progression even amongst individuals with the same underlying *CFTR* variant. The most commonly investigated epigenetic mechanisms include DNA methylation and histone modification. The specific DNA methylations associated with lung disease severity are currently under investigation, however several studies have discovered genes that were positively or negatively associated with disease severity (81,82). One study examining histone modification on *CFTR* expression in fetal and adult tissue found that these modifications had both activating and repressing effects

that fine tunes *CFTR* expression (83). Imprinting is another epigenetic mechanism that selectively silences one copy of a gene, depending on which parent it was inherited from. One study assessing CF twins and siblings found that there may be a relationship between imprinting of chromosome 7q34 resulting in heterogeneity of disease severity despite a similar or identical genotype (84).

Additional factors influencing phenotype beyond CFTR

CFTR expression is known to be dependent on other genes that encode ion channels and transporters that regulate secretion volume and pH, as well as other epithelial fluids. Broadly termed "gene modifiers", these genes encode proteins that include amiloride-sensitive epithelial Na^+ channel (ENaC), the alternative chloride/anion channels TMEM16A and SLC26A9, and the proton pump ATP12A (30). Research on whether these targets can be used to compensate for *CFTR* variants is currently ongoing. If successful, modulating these adjunct targets could potentially be useful in treating patients with CF with a wide range of variants (28).

Future directions: further personalization of therapeutic approaches in CF beyond genetics

One challenge in the development of precision CF treatment is predicting drug response in a patient population with variant heterogeneity, despite being a monogenic disease. Previous studies have demonstrated that patients display a variety of responses to CFTR modulators, even if they have the same *CFTR* variant (34,79,85). The ability to predict which patient might most benefit from modulator use would therefore allow this intervention to be better streamlined to the right patients. Several potential strategies have been investigated to address this issue, including theratyping and 3D culture systems. Theratyping classifies *CFTR* variants according to their response to a CFTR modulator, rather than classifying *CFTR* variant based on their variant class (22,79). With this approach, theratyping would be able to further characterize complex *CFTR* variants, assess modulator responsiveness of rare *CFTR* variants that are not yet available from lung explants and compare several modulator responses of various variants (86). As a result, this approach may provide patients with rare variants a biologic rationale for treatment. One study examined the effect of gene modifier *SLC26A9*, which is thought to encode an anion channel, on the response to treatment with the CFTR modulator ivacaftor (87). After genotyping 24 patients with at least one G551D variant, those with the *SLC26A9* rs7512462 C allele were found to have a further 9.8% improvement in $ppFEV_1$ response to ivacaftor compared to individuals without this allele (87). This study highlights the potential power of theratyping to provide more granular resolution of patients based on particular SNPs (single nucleotide polymorphisms) or other rarer variants who may respond to particular treatment. However, theratyping requires further validation before it can be used widely in clinical settings (86).

Recent studies have developed 3D culture systems that allow clinicians to obtain an *in vitro* analysis of an individual's CFTR activity, allowing them to perform pre-clinical CFTR modulator screens and therefore predict drug response (6,9,22,88). Most studies assessed cultures from epithelial cells or "organoids" from bronchial and intestinal stems cells, while others have analyzed the use of nasal epithelial cells or kidney tubuloids from urine to allow the assessment of CFTR efficacy (89-91). Organoids, or mini adult organs, serve as replicate *in vivo* tissue from an individual, allowing CF disease classification and development of individualized treatments (22). As these culture systems can detect modulator responses, regardless of *CFTR* variant, this method may also allow patients with rare CF variants to have access to modulators that have not been studied based on their genetics (6).

Conclusions

Recent advancements in the treatment of CF demonstrate how precision medicine has the potential to change the treatment landscape and prognosis of severe, life-threatening diseases. With the ability to analyze patients' genomes, clinicians will be able to formulate specific treatment plans that would directly address the underlying pathogenesis of their patients' respective diseases. CF in particular has been the focus of many such studies due to the complexity behind *CFTR* variants as well as the significant clinical response that has been observed with CFTR modulators. The development of precision medicine in CF has already provided therapeutic options for CF patients with rare variants who would otherwise not benefit from current available therapy. Our review discussed the development of CFTR modulators as well as novel treatment approaches, including novel CFTR modulators and non-CFTR modulation using read-through agents, RNA, gene therapy and gene editing. Epigenetics phenomenon on *CFTR* gene

expression via DNA methylation and histone modification as well as the activity of gene modifiers, may explain in part the different responses to CFTR modulators, even amongst individuals with the same *CFTR* variants. Theratyping and 3D cultures are proposed strategies that may further characterize rare *CFTR* variants and help predict drug response on an "N-of-1" basis. While further research is required to devise viable treatment modalities for all *CFTR* variants, ongoing research of precision medicine in CF exemplifies how this approach to treatment can provide novel therapeutic options for other life-threatening monogenetic disorders as well.

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Footnote

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Supplementary

Table S1 Qualifying variants for each available modulator

Modulators	Indications	Qualifying variants
Ivacaftor	Non-G551D, De Boeck *et al.*, 2014	G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, G1349D
Tezacaftor/ivacaftor	F508del/residual function, Rowe *et al.*, 2017	2789+5G>A, 3849+10kbC>T, 3272-26A>G, 711+3A>G, E56K, P67L, E831X, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, R1070W, A455E, F1074L, D579G, D1152H, S945L, D1270N, S977F, F1052V, K1060T
Elexacaftor/tezacaftor/ivacaftor	F508del/minimal function, Middleton *et al.*, 2019	Q2X, L218X, Q525X, R792X, E1104X, S4X, Q220X, G542X, E822X, W1145X, W19X, Y275X, G550X, W882X, R1158X, G27X, C276X, Q552X, W846X, R1162X, Q39X, Q290X, R553X, Y849X, S1196X, W57X, G330X, E585X, R851X, W1204X, E60X, W401X, G673X, Q890X, L1254X, R75X, Q414X, Q685X, S912X, S1255X, L88X, S434X, R709X, Y913X, W1282X, E92X, S466X, K710X, Q1042X, Q1313X, Q98X, S489X, Q715X, W1089X, Q1330X, Y122X, Q493X, L732X, Y1092X, E1371X, E193X, W496X, R764X, W1098X, Q1382X, W216X, C524X, R785X, R1102X, Q1411X, 185+1G>T, 711+5G>A, 1717-8G>A, 2622+1G>A, 3121-1G>A, 296+1G>A, 712-1G>T, 1717-1G>A, 2790-1G>C, 3500-2A>G, 296+1G>T, 1248+1G>A, 1811+1G>C, 3040G>C (G970R), 3600+2insT, 405+1G>A, 1249-1G>A, 1811+1.6kbA>G, 3850-1G>A, 405+3A>C, 1341+1G>A, 1811+1643G>T, 3120G>A, 4005+1G>A, 406-1G>A, 1525-2A>G, 1812-1G>A, 3120+1G>A, 4374+1G>T, 621+1G>T, 1525-1G>A, 1898+1G>A, 3121-2A>G, 711+1G>T, 1898+1G>C, 182delT, 1078delT, 1677delTA, 2711delT, 3737delA, 306insA, 1119delA, 1782delA, 2732insA, 3791delC, 306delTAGA, 1138insG, 1824delA, 2869insG, 3821delT, 365-366insT, 1154insTC, 1833delT, 2896insAG, 3876delA, 394delTT, 1161delC, 2043delG, 2942insT, 3878delG, 442delA, 1213delT, 2143delT, 2957delT, 3905insT, 444delA, 1259insA, 2183AA>G, 3007delG, 4016insT, 457TAT>G, 1288insTA, 2184delA, 3028delA, 4021dupT, 541delC, 1343delG, 2184insA, 3171delC, 4022insT, 574delA, 1471delA, 2307insA, 3171insC, 4040delA, 663delT, 1497delGG, 2347delG, 3271delGG, 4279insA, 849delG, 1548delG, 2585delT, 3349insT, 4326delTC, 935delA, 1609del CA, 2594delGT, 3659delC, CFTRdele1, CFTRdele16-17b, 1461ins4, CFTRdele2, CFTRdele17a,17b, 1924del7, CFTRdele2,3, CFTRdele17a-18, 2055del9>A, CFTRdele2-4, CFTRdele19, 2105-2117del13insAGAAA, CFTRdele3-10,14b-16, CFTRdele19-21, 2372del8, CFTRdele4-7, CFTRdele21, 2721del11, CFTRdele4-11, CFTRdele22-24, 2991del32, CFTR50kbdel, CFTRdele22,23, 3121-977_3499+248del2515, CFTRdup6b-10, 124del23bp, 3667ins4, CFTRdele11, 602del14, 4010del4, CFTRdele13,14a, 852del22, 4209TGTT>AA, CFTRdele14b-17b, 991del5, A46D, V520F, Y569D, N1303K, G85E, A559T, L1065P, R347P, R560T, R1066C, L467P, R560S, L1077P, I507del, A561E, M1101K

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