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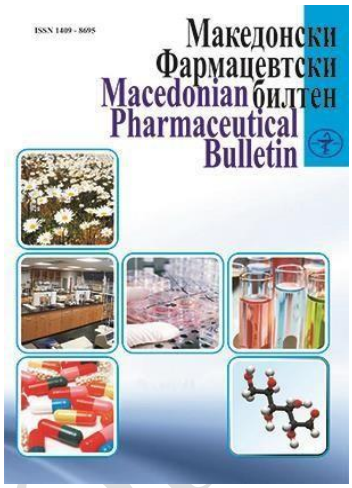

Title: CFTR modulators and the changing natural history of cystic fibrosis

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CFTR modulators and the changing natural history of cystic fibrosis

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Abstract

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by CFTR mutations, where defective chloride transport leads to viscous secretions and progressive multisystem dysfunction. Persistent infection and inflammation compromise lung function, making respiratory involvement the primary driver of morbidity and mortality in people with CF (pwCF). Advances in CFTR modulator therapy, potentiators and correctors, have transformed disease management and its clinical course. Ivacaftor, the first approved potentiator, showed significant benefits in patients with gating mutations, while lumacaftor–ivacaftor and tezacaftor–ivacaftor improved outcomes in F508del homozygotes. More recently, the triple therapy elexacaftor–tezacaftor–ivacaftor (ETI) and the newer vanzacaftor–tezacaftor–deutivacaftor (VTD) have further improved respiratory outcomes, nutritional parameters, and patient quality of life, with VTD offering once daily dosing. Modulator therapy reduces pulmonary exacerbations, improves radiological findings, and benefits sinonasal health. Effects on extrapulmonary manifestations are variable: liver disease outcomes remain uncertain, pancreatic function may partially recover with early treatment, and glucose metabolism shows improvement, though risks of obesity are emerging. The extension of life expectancy brings forward new concerns, notably cardiovascular conditions, mental health issues and malignancies. CFTR modulators have revolutionized CF care in pwCF, extending survival and improving overall quality of life. They represent a

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paradigm shift, underscoring the importance of early intervention, individualized nutritional support, and updated surveillance strategies for long term health. Challenges remain for the patients with rare or nonsense mutations not responsive to current modulators, highlighting the need for novel therapeutic approaches.

Keywords: Cystic fibrosis, CFTR modulators, ivacaftor, elexacaftor–tezacaftor–ivacaftor (ETI), people with cystic fibrosis (pwCF), vanzacaftor–tezacaftor–deutivacaftor (VTD)

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Introduction

Cystic fibrosis (CF) is a life-threatening autosomal recessive genetic disease affecting approximately 56,000 individuals in Europe and more than 160,000 worldwide (Guo et al., 2022; Lopes-Pacheco et al., 2020). It is caused by mutations in the CFTR gene, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel expressed in epithelial cells across multiple organs (Lopes-Pacheco et al., 2016; Riordan et al., 1989; Rommens et al., 1989). Dysfunction of this channel results in impaired ion transport and the production of thick, viscous secretions in exocrine glands (Saint-Criq and Gray, 2017). Mutations in the CFTR gene lead to absent or deficient CFTR protein function at the cell surface. As an epithelial chloride channel, CFTR plays a critical role in regulating salt and water absorption and secretion. Failure to maintain chloride transport in affected organs underlies the multisystem pathology characteristic of CF. Clinical manifestations may begin as early as the intrauterine period and progress throughout life.

The aim of this review is to critically examine how CFTR modulators have transformed the natural history of cystic fibrosis. It seeks to synthesize current evidence on their impact across respiratory, nutritional, reproductive, and psychosocial domains, while also addressing emerging challenges such as cardiovascular comorbidities and malignancy risk. Furthermore, the paper aims to identify persisting unmet needs among patients with rare mutations, the burden of supportive therapies, and inequities in global access, thereby outlining future directions for gene-based strategies and rational simplification of care.

This paper was conducted as a narrative literature review. Relevant publications were identified through searches of PubMed, Scopus, Web of Science, and Google Scholar. The search strategy included terms such as cystic fibrosis, CFTR modulators, natural history, respiratory manifestations, nutrition, fertility, and malignancies.

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Inclusion criteria comprised peer-reviewed articles, clinical trials, systematic reviews, and consensus guidelines published between 1995 and 2026**,** focusing on CFTR modulators and their clinical impact. Exclusion criteria were case reports without broader relevance, non-peer reviewed sources, and studies not addressing CFTR modulators. Extracted data were synthesized thematically to illustrate the paradigm shift in CF care, from a uniformly fatal childhood disease to a chronic condition with prospects for curative therapies.

Multisystem clinical manifestations of cystic fibrosis

Respiratory manifestations in cystic fibrosis

Respiratory disease represents the most prominent and clinically significant component of CF, determining long-term morbidity and mortality. CFTR dysfunction leads to secretion of thick, viscous mucus that disrupts mucociliary clearance and forms endobronchial plaques, which obstruct airflow (Stoltz et al., 2015; Turcios, 2020). This dense mucus favors microbial colonization, with pathogens such as *Haemophilus influenzae, Staphylococcus aureus, Pseudomonas aeruginosa, Burkholderia cepacia, Klebsiella* species, and fungi including *Candida* and *Aspergillus.* Persistent infection drives neutrophil-dominated inflammation, releasing proteases and reactive oxygen species, resulting in progressive airway damage and ultimately bronchiectasis (Mall et al., 2024).

Bronchiectasis develops early, affecting nearly one in three children by age three. Even before symptoms emerge, inflammation and infection are present, with CT abnormalities detectable in infants as early as three months (Khan et al., 1995; Schultz & Stick, 2015). Pulmonary function tests typically show obstructive ventilatory failure with declining FEV_1, hyperinflation, and air trapping, though restrictive changes may appear in advanced disease (Walicka-Serzysko et al., 2023). Additional modalities such as lung clearance index, chest CT, and MRI detect early abnormalities before spirometry changes.

Clinically, pwCF experience alternating phases of exacerbation and remission. Exacerbations manifest as cough, sputum, dyspnea, chest pain, anorexia, weight loss, hemoptysis, and measurable declines in lung function. These episodes profoundly affect quality of life, contribute to psychological distress, and drive healthcare utilization and costs (Smirnova et al., 2024; Stanford et al., 2021).

Early recognition, aggressive infection management, optimization of airway clearance, and the advent of highly effective CFTR modulators have significantly altered the natural history of CF respiratory disease. Nevertheless, vigilant monitoring remains essential, as respiratory dysfunction continues to be the leading cause of morbidity and mortality,

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alongside multisystem involvement of the pancreas, liver, intestines, reproductive tract, and sweat glands.

Gastrointestinal manifestations in cystic fibrosis

Gastrointestinal manifestations affect about 85% of patients with CF, reflecting systemic CFTR dysfunction. Impaired ion transport leads to dehydrated secretions, reduced bicarbonate output, and abnormal motility, resulting in complications ranging from neonatal meconium ileus to chronic malabsorption and dysbiosis (Gabel et al., 2019). Acidic intestinal fluid damages the mucosa, inactivates pancreatic enzymes, and disrupts nutrient absorption (Henena et al., 2021; Ng et al., 2021). Thick mucus predisposes to obstruction, with distal intestinal obstructive syndrome and chronic constipation reported in up to half of patients. Dysbiosis and small intestinal bacterial overgrowth are common, exacerbated by frequent antibiotic use (Dorsey and Gonska, 2017).

Pancreatic involvement begins in utero, with ductal obstruction and progressive tissue damage leading to exocrine pancreatic insufficiency (EPI) in ~85% of patients, often present at birth (Ramsey et al., 2024; Sankararaman et Schindler, 2023). Loss of endocrine function contributes to CF-related diabetes mellitus (CFDM).

CF-related liver disease (CFLD) is the third leading cause of CF mortality, accounting for ~3% of deaths. It is associated with male sex, meconium ileus, severe CFTR mutations, and pancreatic insufficiency (Boëlle et al., 2019; Stonebraker et al., 2016). Pathophysiology involves dehydrated bile, ductal obstruction, inflammation, and progressive fibrosis, which may advance to biliary cirrhosis, portal hypertension, and complications such as variceal bleeding (Kobelska-Dubiel et al., 2014).

Reproductive system involvement in cystic fibrosis

CFTR dysfunction disrupts the normal development and function of reproductive ducts, leading to structural abnormalities and impaired gamete transport. More than 95% of men with CF are infertile due to CBAVD, although spermatogenesis is typically preserved (McGlynn et al., 2023). This results in obstructive azoospermia, with semen analysis showing low volume, acidic pH, and absent spermatozoa. Assisted reproductive technologies, such as surgical sperm retrieval and *in vitro* fertilization, enable many men with CF to achieve biological parenthood (Jarzabek et al., 2004).

In women, fertility is generally preserved, but thick cervical mucus, inadequate hydration of secretions, altered microbiota, malnutrition, and delayed puberty can impair conception. Despite these challenges, many women with CF can conceive naturally,

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particularly with improved nutritional status and the advent of highly effective CFTR modulators (Jain et al., 2021).

Sweat gland involvement in cystic fibrosis

CFTR plays a critical role in chloride reabsorption within sweat ducts. In CF, defective CFTR prevents chloride and sodium reabsorption, resulting in sweat with markedly elevated salt concentrations. This produces the characteristic salty taste of the skin and forms the basis of the sweat chloride test, a cornerstone diagnostic tool. Elevated sweat chloride is still considered a reliable measure of CFTR malfunction, widely applied in clinical trials and serving as a parameter in monitoring treatment efficacy with CFTR modulators (Saint-Criq & Gray, 2017).

CFTR mutations and modulator therapies

Since the discovery of the CFTR gene in 1989, more than 2,000 variants have been identified (Cystic Fibrosis Mutation Database, 2025). To facilitate clinical and therapeutic interpretation, these mutations are commonly classified into six functional categories, reflecting their impact on protein synthesis, folding, trafficking, gating, conductance, or stability (Veit et al., 2016). Importantly, many mutations display pleiotropic effects and may therefore be assigned to more than one class.

In North Macedonia, the distribution of CFTR mutations is dominated by F508del, accounting for approximately 72.3% of cases, followed by several other variants with lower prevalence, including G542X, N1303K, G1349D, G126D, V456F, and 621+1G>T (Fustik et al., 2020). Table 1 summarizes the major classes of CFTR genetic mutations, their underlying molecular defects, representative examples, and currently approved modulator therapies.

Table 1.

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CFTR modulators

CFTR modulators are developed to correct the malfunctioning of the CFTR protein.

In CF, the CFTR protein may be synthesized in reduced amounts, fail to traffic correctly to the cell surface, or undergo accelerated degradation. Importantly, however, synthesis does occur, providing a therapeutic target for intervention. By correcting folding and trafficking defects or by potentiating channel activity at the cell membrane, modulators restore chloride and water transport across epithelial surfaces (Lopes Pacheco et al., 2020).

In the treatment of pwCF, these drugs are classified according to their mechanism of action into potentiators and correctors. Potentiators increase the probability of CFTR channel opening, thereby enhancing chloride and water transport. Correctors facilitate proper three-dimensional folding and trafficking of the CFTR protein to the membrane, ensuring its functional expression. (Lopes Pacheco et al., 2021; Okiyoneda et al., 2013; Van Goor et al., 2009).

This classification highlights the complementary mechanisms by which modulators restore CFTR function, forming the foundation for combination therapies that have transformed outcomes in CF care.

As the first mutation-specific CFTR modulator, ivacaftor represented a major therapeutic milestone, approved in 2012 by both the FDA and EMA (Ramsey et al., 2011).

The initial indication targeted individuals aged ≥12 years carrying the G551D mutation, a gating defect that prevents proper channel opening. Although this subgroup represented fewer than 10% of pwCF, the robust improvements in CFTR-mediated ion transport led to rapid extension of its use to additional gating variants (G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R) and the Class IV mutation R117H (Yu et al., 2012).

In addition to its effects on gating mutations, ivacaftor has demonstrated efficacy in residual function and splice mutations, where some CFTR protein reaches the cell surface but either in insufficient quantities or with inadequate chloride conductance (Kerem et al., 2021; Rowe et al., 2017).

Today, ivacaftor is licensed for pwCF from one month of age with responsive mutations, either as monotherapy or in combination with other modulators, with age-specific indications defined by genotype (Guimbellot et al., 2021; McNally et al., 2024).

Clinical trials and long-term follow-up demonstrate significant benefits of ivacaftor therapy. Treatment improves respiratory function, including FEV1, and is associated with fewer exacerbations and reduced microbial colonization with highly resistant pathogens,

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notably *Pseudomonas aeruginosa* (McKone et al., 2014; Heltshe et al., 2015). Patients also show improved nutritional status, reflected in higher BMI and better appetite, as well as enhanced physical endurance and overall well-being (Edgeworth et al., 2017), which contribute to improved health-related quality of life (Sawicki et al., 2016; Quittner et al., 2015).

Additionally, studies indicate restoration of pancreatic activity, reductions in systemic inflammatory markers, and favorable structural changes in lung tissue observed on imaging (Adam et al., 2016; Ronan et al., 2018). According to Bessonova et al. (2018), sustained use of ivacaftor has been linked to lower transplantation rates and improved longevity in individuals with CF.

Beyond its CFTR-modulating role, Rubin et al. (2026) reported that ivacaftor exerts CFTR-independent antioxidant effects. Specifically, it mitigates oxidative stress by scavenging lipid radicals, thereby interrupting lipid peroxidation and preventing ferroptosis, a lipid-driven cell death pathway. This additional property may contribute to protection against progressive tissue injury in the CF lung.

Lumacaftor, categorized among CFTR correctors, acts by stabilizing the misfolded CFTR protein and promoting its delivery to the cell membrane. In primary bronchial epithelial cell models (Van Goor et al., 2011), it prevents degradation of the CFTR protein by cellular quality control mechanisms. However, lumacaftor alone did not produce significant improvements in lung function among patients homozygous for the F508del mutation (Clancy et al., 2012). Clinically meaningful outcomes were observed only when lumacaftor was combined with ivacaftor, a CFTR potentiator that augments channel activity (Boyle et al., 2014).

In 2015, the lumacaftor–ivacaftor (LUM/IVA) combination was first approved by the FDA for pwCF homozygous for the F508del mutation aged ≥12 years (Wainwright et al., 2015). In parallel, the EMA granted approval in 2015 for the same indication, with subsequent extensions to younger age groups following similar timelines (McNamara et al., 2019; Milla et al., 2017; Rayment et al., 2022).

Tezacaftor, developed as a second-generation CFTR corrector from lumacaftor, offers improved pharmacokinetics and a more favorable safety profile. It acts as a stabilizer of the CFTR protein, correcting its misfolded conformation and ensuring proper three-dimensional structure. Because its effect is limited to protein folding, tezacaftor is not used alone. ivacaftor maintains the channel in an open state, thereby enabling chloride and water

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transport across epithelial cells and promoting the thinning of the dense secretions in the airways (Rowe et al., 2017).

Tezacaftor–ivacaftor (TEZ/IVA) is indicated for pwCF who are homozygous for the F508del mutation or carry one of the residual function variants responsive to therapy in combination with F508del. Since the F508del mutation also impairs channel gating through alterations in the CFTR regulatory domain, effective treatment requires a corrector–potentiator combination. Although clinical trials in patients homozygous for F508del demonstrated comparable outcomes with both TEZ/IVA and LUM/IVA (Taylor-Cousar et al., 2020; Donaldson et al., 2018), TEZ/IVA showed advantages over LUM/IVA. The TEZ/IVA regimen is associated with fewer drug–drug interactions and a more favorable safety profile. Both regimens were approved for pwCF homozygous for F508del from ≥1 year of age (McElvaney et al., 2023).

Since LUM/IVA and TEZ/IVA provided only moderate benefits in F508del homozygotes, new correctors with complementary mechanisms were developed to increase efficacy through triple combinations. The addition of elexacaftor to TEZ/IVA created the triple therapy elexacaftor–tezacaftor–ivacaftor (ETI), which marked the greatest advance in CFTR modulation.

In 2019, the FDA approved ETI for pwCF aged 12 years and older carrying at least one F508del allele (Hoy, 2019). Clinical data from that year confirmed notable improvements in lung function together with sweat chloride reductions below diagnostic thresholds (Middleton et al., 2019). Follow-up studies consistently demonstrated gains in nutritional status, and patient-reported quality of life, while registry analyses documented fewer exacerbations and hospitalizations. In 2019, regulatory submissions were also initiated in Europe, paving the way for EMA approval in 2020 for pwCF with at least one F508del mutation (European Medicines Agency, 2020). Indications were subsequently broadened to include individuals with one or two F508del alleles, thereby extending therapy to approximately 80% of the CF population (Cystic Fibrosis Foundation, 2025). Regulatory milestones further lowered the age limit to 6–11 years in January 2022 and to 2–5 years in November 2023 (Zemanick et al., 2021; Goralski et al., 2023). These expansions established ETI as the most transformative advance in CF care, ensuring access from early childhood and delivering sustained clinical benefits across the majority of patients.

Over time, randomized controlled trials gradually included pwCF without F508del mutations, thereby broadening ETI indications. A pivotal French observational study (Burgel et al., 2023) demonstrated clinical benefits in pwCF with extensive pulmonary damage and

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non-F508del variants, suggesting ETI may be effective in ~50% of patients lacking F508del. Splice mutations and the N1303K variant have shown clear responsiveness to CFTR modulators, lending support to the FDA's practice of relying on in vitro findings when broadening access for rare genotypes (Gentzsch et al., 2024; Graeber et al., 2023). Extending this evidence-based approach to other regulatory authorities would promote wider availability, with variant lists updated regularly as new data continue to emerge.

By 2025, EMA approved combined ETI–ivacaftor regimen for pwCF aged ≥2 years who do not carry two Class I CFTR variants (Drai et al., 2026). For patients with genotypes unresponsive to ETI, including those with two nonsense variants, alternative modulators or novel therapeutic strategies remain necessary.

Vanzacaftor–tezacaftor–deutivacaftor

Vanzacaftor–tezacaftor–deutivacaftor (VTD) represents a next-generation CFTR modulator therapy. Deutivacaftor is a new potentiator with a longer half-life than ivacaftor, while vanzacaftor is a novel corrector identified through pharmacological screening. VTD is administered once daily and has demonstrated enhanced restoration of CFTR-mediated chloride transport *in vitro* (Uluer et al., 2023).

VTD has been tested in pwCF with at least one F508del variant and was recently approved in the US and Europe for patients aged ≥6 years (Hoppe et al., 2025). Clinical results showed non-inferiority to ETI in ppFEV1, with favorable safety and tolerability. Although sweat chloride improvements were modest, their clinical relevance remains uncertain. Once-daily dosing may reduce treatment burden and improve adherence. Importantly, thirty-one CFTR variants that did not respond to ETI showed measurable responsiveness to VTD, based on data obtained from cell-based assays using Fischer Rat Thyroid (FRT) cells — a model derived from rat thyroid tissue that naturally lacks CFTR gene expression. These findings highlight the potential of VTD to address genotypes unresponsive to current modulators and reinforce the value of *in vitro* systems in guiding therapeutic expansion (Gentzsch et al., 2024; Graeber et al., 2023; Keating et al., 2025). Current clinical trials are assessing whether the age threshold can be lowered to extend eligibility to children aged two years and older, potentially broadening therapeutic access during early childhood.

Furthermore, in pwCF carrying the complex allele L467F;F508del, VTD showed superior efficacy compared to ETI (Kondratyeva et al., 2025). This highlights VTD as a promising alternative for patients with complex genotypes or limited response to ETI.

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Overall, VTD is positioned as a next-generation CFTR modulator therapy, offering broader applicability, simplified dosing, and potential benefits for patients with variants unresponsive to ETI, thereby extending therapeutic options in CF care.

CFTR Modulators: benefits and clinical outcomes

Cystic fibrosis was historically a condition that almost invariably resulted in fatal outcomes during early childhood. Advances in diagnostics, multidisciplinary care, and especially the emergence of novel therapies have progressively improved survival prospects for pwCF. Adults now represent 56% of patients with CF, exceeding the proportion of pediatric patients (European CF Patient Registry, 2026). The introduction of CFTR modulators has further expanded the ability to reshape disease progression in eligible individuals. Data from the European CF Patient Registry demonstrate a pronounced and exponential improvement in median predicted survival, with estimates indicating that half of those born with CF in 2022 may achieve a life expectancy of 68.2 years (Zolin, 2023).

Highly effective modulator therapies have delivered significant improvements across multiple aspects of pulmonary disease and represent a milestone in reducing disease-related morbidity and mortality, as confirmed in real-world clinical studies.Reduced production of thick secretions and enhanced mucociliary clearance achieved with CFTR modulators lead to fewer exacerbations, fewer hospitalizations, and reduced need for antibiotics. Clinical evidence confirms improvements in ppFEV1 as a measure of lung function. (Gushue et al., 2023).

A decline in bronchial colonization with highly resistant pathogens such as *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) has been observed, linked to reduced airway inflammation and decreased mucus viscosity. However, chronic P. aeruginosa infection tends to persist in patients treated with modulators, highlighting the need for larger, long-term studies to assess the impact on antibiotic burden (Burgel et al., 2024).

Radiological improvements have also been demonstrated. CT imaging has shown reductions in bronchial wall thickening, mucus plugging, and hyperinflation. Similarly, MRI has revealed improved ventilation and perfusion, along with reductions in mucus plugging and bronchiectasis (Klimeš et al., 2024). These findings confirm that CFTR modulators not only improve symptoms and function but also produce objective structural changes visible on imaging.

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Studies of sinus and nasal involvement show significant improvements in pwCF receiving modulator therapy, including relief of chronic rhinosinusitis symptoms and improvements in radiological and endoscopic findings (Stone et al., 2024). This underscores the positive impact of modulators on the upper airways, which is crucial for overall respiratory health and quality of life.

The influence of CFTR modulators on hepatobiliary disease in CF remains complex and not fully established. Modulators improve bile flow by correcting the underlying protein defect in cholangiocytes. Evidence suggests associations with improved liver stiffness (measured by ultrasound and transient elastography) and reduced incidence of cirrhosis compared with other treatments, indicating a positive long-term impact on liver health (Eldredge et al., 2024; Manioudaki et al., 2025).

Nevertheless, elevations in transaminases and bilirubin are recognized adverse effects that may necessitate temporary or permanent discontinuation of therapy. Interestingly, clinical trials of newer triple regimens with VTD did not report transaminase elevations among the most frequent adverse events.

In summary, CFTR modulators represent a transformative advance in CF care, delivering improvements in survival, lung function, infection control, radiological outcomes, upper airway health, and hepatobiliary involvement, while continuing to require careful monitoring for potential adverse effects.

CFTR modulators have the potential not only to improve pulmonary function but also to deliver meaningful benefits for hepatobiliary health in pwCF.

The degree of pancreatic involvement in CF depends on the type of CFTR mutation and the level of CFTR function. Milder variants are associated with recurrent pancreatitis, whereas severe variants typically lead to exocrine pancreatic insufficiency (EPI) and cystic fibrosis–related diabetes (CFRD) (O'Donnell et al., 2024). The mechanisms by which CFTR modulators improve exocrine pancreatic function are not fully understood. It is hypothesized that the observed reduction in pancreatitis episodes reflects restoration of acinar function, thereby improving EPI. Evidence supports a decrease in RP frequency among patients with pancreatic insufficiency treated with CFTR modulators (Ramsey et al., 2024).

Initiating therapy at a younger age is associated with the greatest improvements, suggesting the potential to alter long-term pancreatic damage previously considered irreversible. Conversely, cases have been reported in which patients with established EPI developed pancreatitis after starting modulator therapy. For this reason, pancreatitis should be

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considered in the differential diagnosis of abdominal pain following treatment initiation, even in patients with EPI (O'Donnell et al., 2024).

Studies also suggest partial recovery of pancreatic function markers. Pivotal Ivacaftor trials demonstrated increases in fecal elastase levels in children under six years of age, indicating partial restoration of pancreatic function (Davies et al., 2016). However, recovery potential appears limited beyond approximately 12 years of age, both for ivacaftor and ETI.

Historically, malnutrition has been a major determinant of CF severity. With the advent of CFTR modulators, the nutritional and functional profile of patients has changed significantly. ETI therapy is associated with increases in BMI in certain age groups. While this reduces the risk of undernutrition, it simultaneously raises the risk of overweight and obesity (Bailey et al., 2021). In adults, fat mass gain appears to exceed lean mass gain, whereas in children weight gain is more evenly distributed, resulting in greater interindividual variability (Steinack et al., 2023). Pediatric studies also demonstrate beneficial effects on nutritional status, although outcomes vary. Gaschignard et al. (2023) reported that lumacaftor–ivacaftor improved nutritional status without necessarily being linked to increased dietary intake.

Nutritional support should therefore be individualized, with greater emphasis on healthy diet from early childhood. The traditional recommendation for a high-calorie diet is now considered outdated in the context of highly effective modulator therapy. These findings highlight that new therapies not only alter disease trajectory but also necessitate revision of nutritional strategies to ensure optimal health and long-term stability in pwCF.

As life expectancy continues to rise, pwCF are expected to face new medical challenges for which evidence remains limited, including cardiovascular disease, malignancies, and mental health disorders.

Cardiovascular risk factors such as hypertension, dyslipidemia, and insulin resistance (Ratti et al., 2025) have become a reality for pwCF in the era of highly effective CFTR modulators. Improved nutritional status and prolonged survival have shifted the metabolic profile, with overweight and obesity increasingly observed in this population. While higher BMI has historically been associated with better pulmonary outcomes, excess adiposity introduces new long-term vascular complications.

This evolving metabolic profile highlights the need for systematic cardiovascular surveillance in CF care. Multidisciplinary teams should incorporate cardiology expertise, and metabolic screening to mitigate long-term complications. Preventive strategies focusing on

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balanced nutrition, physical activity, and early detection of metabolic abnormalities will be essential to ensure that gains in survival are matched by sustained quality of life.

CFTR modulators have significantly improved clinical outcomes and overall quality of life for pwCF. However, their widespread and prolonged use has revealed potential adverse effects on mental health, including depression, anxiety, sleep disturbances, and behavioral changes (VanElzakker et al., 2023). Evidence in pediatric populations remains limited, but careful monitoring is warranted given the ongoing developmental stages. In some countries, national protocols already incorporate standardized questionnaires to assess neuropsychiatric impact, even in children.

A broadened approach to mental health in CF care should therefore be prioritized. International guidelines from the European Cystic Fibrosis Society and the Cystic Fibrosis Foundation recommend annual screening for depression and anxiety in all individuals with CF aged ≥12 years, as well as in at least one primary caregiver of children with CF (Quittner et al., 2015). Validated tools such as the PHQ-9 and GAD-7 are brief, reliable, and widely available, enabling systematic surveillance across diverse healthcare settings.

Beyond screening, a multidisciplinary model is essential, integrating pulmonologists, psychologists, psychiatrists, social workers, and nutritionists to ensure early detection and intervention. A stepped care framework, ranging from supportive interventions for mild cases to cognitive behavioral therapy, interpersonal therapy, and pharmacological treatment for moderate to severe cases, has been proposed and validated in CF populations **(**Quittner et al., 2016**;** Ramsey et al., 2024).

Future priorities include longitudinal studies to clarify the incidence and mechanisms of neuropsychiatric effects in both pediatric and adult cohorts, as well as policy development to ensure equitable access to mental health services. Patient and family education should also be emphasized, empowering caregivers to recognize early warning signs and seek timely support.

Surveillance protocols must be updated, families and patients provided with timely information, and health-promoting measures emphasized from early childhood (Ticona et al., 2023).

The growing adult CF population has brought fertility and pregnancy into the center of clinical attention. Historically, infertility was common, particularly in men due to congenital bilateral absence of the vas deferens (CBAVD), and in women as a result of malnutrition, chronic pulmonary disease, and altered cervical mucus (Jarząbek et al., 2004). With improved survival, nutritional status, and the introduction of highly effective CFTR modulators, fertility

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rates among pwCF are increasing, and pregnancy is becoming a realistic option for many women.

Recent evidence suggests that CFTR modulators may improve menstrual regularity and fertility potential in women with CF (Taylor-Cousar et al., 2020). Pregnancy outcomes have also improved, with better maternal lung function, nutritional status, and neonatal survival compared to earlier decades (Montemayor et al., 2022). Nevertheless, uncertainties remain regarding the safety of CFTR modulators during pregnancy and lactation. Registry data and case reports indicate potential benefits, but systematic studies are needed to balance maternal health gains with possible fetal risks.

In males with CF, preliminary reports suggest potential improvements in spermatogenesis and semen parameters in some individuals, although CBAVD remains a structural barrier to fertility (Clarke et al., 2022). Importantly, modulators may enhance overall health, nutritional status, and sexual function, indirectly supporting reproductive potential.

Future priorities in reproductive health for pwCF include the establishment of international pregnancy registries, the development of evidence-based guidelines for reproductive counseling, and the integration of fertility and pregnancy management into multidisciplinary CF care models. These measures are essential to address the evolving needs of women with CF, who increasingly consider pregnancy a realistic option in the era of highly effective modulator therapy.

Equally, male fertility requires focused attention. Although CBAVD remains a structural barrier to natural conception, preliminary reports suggest potential improvements in spermatogenesis and semen parameters in some individuals treated with CFTR modulators. Moreover, modulators may indirectly support reproductive potential by enhancing overall health, nutritional status, and sexual function. Expanding access to assisted reproductive technologies and establishing registries to capture fertility outcomes in men are critical steps to ensure that reproductive health strategies in CF care are comprehensive and equitable.

Malignancies have become a significant concern in CF care, also. The most common cancers are gastrointestinal, particularly colorectal cancer, which occurs 5–10 times more frequently than in the general population, often with onset in the third decade of life. This earlier age of presentation has led to consensus recommendations for proactive colorectal cancer screening in pwCF (Hadjiliadis et al., 2018).

Other reported malignancies include pancreatic and hepatobiliary cancers**,** gynecological cancers (such as cervical neoplasia), and hematological malignancies. Case

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series have documented that cancer is now among the leading causes of mortality in adults with CF, with median age at diagnosis around 25 years (Appelt et al., 2022). Epidemiological data further confirm increased cancer incidence both in transplanted and non-transplanted CF populations, underscoring the need for systematic surveillance (Rousset-Jablonski et al., 2022).

Importantly, while CFTR modulators have not been shown to directly increase cancer risk, their impact on survival means that more patients live into age ranges where malignancies naturally emerge. This demographic shift highlights the need for integrated cancer surveillance protocols within CF care models.

As the last step in addressing new challenges, future healthcare models are emerging as a necessary priority in the era of highly effective CFTR modulators (Haesebaert et al., 20205). Initiatives such as the HORIZON Project in France aim to reassess standard care and develop integrated approaches that address not only physical parameters but also psychosocial realities of patients and families. This reflects the broader transformation in CF care, where improved survival, shifting nutritional profiles, evolving reproductive health, and emerging comorbidities demand multidisciplinary strategies and updated guidelines.

CFTR modulators are no longer simply disease-modifying therapies; they are reshaping the demographic, nutritional, reproductive, and long-term health profile of pwCF.

Conclusion

Cystic fibrosis has undergone a profound transformation, evolving from a fatal hereditary disease most often manifesting in early childhood into a chronic condition with steadily improving quality of life and significantly extended survival. The introduction of CFTR modulators represents not only a therapeutic breakthrough but also a paradigm shift, redefining expectations for lung function, nutrition, reproductive health, and overall well-being in the majority of patients.

Survival has markedly improved, with adults now comprising the majority of the CF population. This demographic transition introduces new challenges, including fertility and pregnancy considerations, a nutritional shift from historical malnutrition toward risks of overweight and obesity, the emergence of cardiovascular comorbidities and malignancies. Mental health has likewise become a central dimension of long-term care, reflecting the psychosocial burden of chronic disease management.

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Nevertheless, the greatest challenge remains for patients with rare and nonsense mutations who do not respond to existing modulators, the ongoing reliance on burdensome supportive therapies, and inequities in global access to modulator treatment. The next era of CF care must therefore be defined by innovation in gene-based strategies, rational simplification of therapeutic regimens, and a commitment to equitable distribution of life-changing therapies.

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Резиме

CFTR модулатори и промена на природниот тек на цистична фиброза

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Клучни зборови: цистична фиброза, CFTR модулатори, ivacaftor, elexacaftor/tezacaftor/ivacaftor (ETI), пациенти со ЦФ pw(CF), vanzacaftor/tezacaftor/deutivacaftor (VTD)

Цистичната фиброза (ЦФ) е автозомно рецесивно генетско заболување предизвикано од мутации во цистична фибриза трансмембранскиот регулаторен (CFTR) ген, при што нарушениот транспорт на хлорни јони доведува до создавање на густи и вискозни секрети и прогресивно мултисистемско оштетување. Перзистентната инфекција и хроничната воспалителна реакција постепено ја нарушуваат белодробната функција, и води до респираторни компликации, кои претставуваат главна причина за морбидитет и морталитет кај лицата со ЦФ (pwCF). Значаен напредок во лекувањето на pwCF е постигнат со воведувањето на CFTR модулаторите, кои ја менуваат природната еволуција на болеста. Зависно од нивниот механизам на дејство овие лекови се поделени на потенцијатори и коректори. Ивакафтор, првиот одобрен потенцијатор, покажа значително подобрување кај пациентите со „gating“ мутации. Подоцна, комбинациите лумакафтор–ивакафтор и тезакафтор–ивакафтор доведоа до подобри клинички исходи кај пациенти хомозиготи за мутацијата F508del. Најновите високоефикасни модулатори, тројната комбинација елексакафтор/тезакафтор/

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ивакафтор (ETI) и поновата комбинација ванзакафтор/тезакафтор/деутивакафтор (VTD), дополнително ги подобруваат белодробната функција, нутритивниот статус и квалитетот на животот, при што VTD овозможува еднократно дневно дозирање. Терапијата со CFTR модулатори значително го намалува бројот на белодробни егзацербации, ги подобрува радиолошките наоди и позитивно влијае врз хроничниот синузитис. Ефектите врз екстрапулмоналните манифестации се варијабилни. Досегашните податоци не даваат јасен доказ за значително подобрување на заболувањето на црниот дроб, додека раното започнување на терапијата може да овозможи делумно обновување на панкреасната функција. Дополнително, забележано е подобрување на метаболизмот на глукозата, иако истовремено се појавуваат нови предизвици, како што е зголемената зачестеност на прекумерната телесна тежина и дебелината. Со продолжувањето на животниот век на пациентите со ЦФ, сè поголемо значење добиваат и долгорочните компликации, вклучувајќи кардиоваскуларни заболувања, нарушувања на менталното здравје и малигни заболувања. CFTR модулаторите претставуваат револуционерен напредок во третманот на ЦФ, овозможувајќи значително продолжување на преживувањето и подобрување на квалитетот на животот. Тие претставуваат промена на терапевтската парадигма, нагласувајќи ја важноста на раната интервенција, индивидуализираниот нутритивен пристап и современите стратегии за долгорочно следење на пациентите. Сепак, лекувањето на пациентите со ретки или „nonsense“ мутации кои не реагираат на достапните модулатори, останува предизвик, што ја нагласува потребата од развој на нови терапевтски пристапи.

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Table 1. Classes of CFTR mutations and available modulator therapies

Mutation Class	Molecular Defect	Example Mutations	Modulator Type	Representative Drugs
Class I (defective protein synthesis)	No CFTR protein production	G542X, W1282X	*No approved modulators* (read-through agents under investigation)	—
Class II (defective processing/trafficking)	Misfolded protein fails to reach cell membrane	F508del	Correctors + Potentiators	LUM/IVA; TEZ/IVA; ETI; VTD
Class III (defective channel gating)	Protein present but channel does not open	G551D, S549N	Potentiators	Ivacaftor
Class IV (reduced conductance)	Channel opens but ion transport is impaired	R117H	Potentiators	Ivacaftor
Class V (reduced protein expression)	Decreased quantity of CFTR protein	A455E	Potentiators ± Correctors	Ivacaftor; ETI (selected cases)
Class VI (reduced stability)	Protein reaches membrane but is rapidly degraded	4326delTC	Correctors + Potentiators	ETI; VTD

* Lumacaftor/ivacaftor (LUM/IVA); tezacaftor/ivacaftor (TEZ/IVA); elexacaftor/tezacaftor/ivacaftor (ETI); vanzacaftor/tezacaftor/deutivacaftor (VTD)

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