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Cystic Fibrosis

An APCCMPD Ambulatory Care Curriculum Teaching Script

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Review Literature review current through June 2026
Update Last updated June 2026

Citation Dorgan D. Cystic Fibrosis [teaching script]. Jagpal S, Kim B, Jagana R, Miles M, Izquierdo M, Steinbach T, assoc eds. Mathai SK, ed. Association of Pulmonary and Critical Care Medical Program Directors; Published 2026.
https://apccmpd.memberclicks.net/assets/AmbulatoryCareWorkgroup/Year_2_Scripts/02%20Cystic%20Fibrosis_2026_Final.pdf

Cystic Fibrosis

Scenario 1

Mr. D is a 32-year-old man who presents to your clinic with a new diagnosis of possible cystic fibrosis (CF). He first developed respiratory symptoms at age 12, with frequent cough (small amount of sputum production), intermittent dyspnea, wheezing, and nasal congestion with frequent sinus pressure, which was labeled asthma and allergic rhinitis for years. He also has acute respiratory infections 1-3 times per year and was often given oral antibiotics for "bronchitis." He has never had steatorrhea or difficulty maintaining weight, although he did have pancreatitis in college once, which was attributed to alcohol. However, he says he has never been a heavy alcohol user. He and his wife have been unsuccessfully trying to have children.

Question 1: What testing would you recommend to determine whether Mr. D has CF?

Question 2: Our patient is confirmed to have CF based on a positive sweat chloride test and by genetic testing. What further testing would be appropriate?

Question 3: Mr. D's testing returned with no significant abnormalities except for a sputum culture that grew mucoid *Pseudomonas aeruginosa*. What baseline pulmonary therapies should be initiated? What therapies specific to *Pseudomonas* should be initiated?

Question 4: Mr. D asks whether he should call his primary care physician or the pulmonary clinic when he has a respiratory infection. What would you advise that he do?

Question 5: How can we help decide whether he also has asthma or whether his history of unexplained dyspnea and wheezing were all due to undiagnosed CF?

Scenario 2

Mr. W is a 19-year-old man with CF (F508del homozygous) diagnosed in infancy. He has been treated at a CF center throughout his life. He has been active throughout his childhood and felt healthy from a respiratory standpoint most of the time, but he does have exacerbations requiring IV antibiotics 1-2 times per year. He has pancreatic insufficiency and takes pancreatic enzymes. Thus, he is generally able to maintain his weight apart from transient drops associated with exacerbations. He had an adenovirus infection just before turning 18, and his health has been worse since. He doesn't feel quite as sick as when he has an acute exacerbation. His sputum is not as thick, dark, and copious as when he has a "typical exacerbation," but he does have more sputum production than his prior baseline. His weight is also below his baseline, but not dropping as much as usual for an exacerbation. His baseline FEV1 used to be 75-80% predicted, but lately it

has been 55-60%. He has received two courses of IV antibiotics with a slight improvement in symptoms and FEV1 increase to the low 60s but has not returned to his prior state of health at any point.

Question 6: Assuming he is on all of the usual CF maintenance medications, is this his new baseline health status or can we do anything else for him? What other testing should we consider?

Scenario 3

Ms. H is a 36-year-old woman with CF who presents to clinic with complaints of decreased stool output and cramping abdominal pain (diffuse, but worse on the right side of her abdomen) along with an occasional sense of bloating in her abdomen. She has a decreased appetite and mild nausea without vomiting. No fevers, chills, or night sweats, but she has lost about 5 pounds, which she attributes to decreased appetite. No respiratory symptoms beyond her baseline cough and sputum production.

Question 7: What is the most likely cause of Ms. H's symptoms? Would you recommend any other diagnostic testing?

Question 8: What treatment approach is most likely to help her?

Question 9: This patient has sufficient bowel movements after a "clean out" as described above. Her abdominal imaging no longer shows significant stool burden. However, she is continuing to lose weight. How should we expand our differential?

Scenario 4

Mr. S is a 48-year-old man with CF (F508del homozygous). He has been surprisingly healthy for someone with his genotype. He has never been consistent about using respiratory therapies and rarely has acute pulmonary exacerbations; he can't remember the last time he needed antibiotics. His lung function has gradually declined over the years, with FEV1 currently 55% predicted, but he isn't bothered much by respiratory symptoms, so he hasn't been willing to use nebulizers frequently or do much for airway clearance. He has pancreatic insufficiency and takes pancreatic lipase. He now returns to clinic for the first time in several years, and early in the conversation says he saw on Instagram that there might be some new treatment for CF; he wants to hear more about it.

Question 10: What "new" treatments are available for CF? How do they work? What are the potential side effects and complications? Is it appropriate for him to start one of the new treatments?

Scenario 5

A 26-year-old woman with CF and worsening respiratory disease (frequent exacerbations, FEV1 30% predicted) presents to clinic with right-sided chest pain that started yesterday. She had been feeling worse in the preceding few days, with some increased cough and sputum production, but had not felt as bad as she usually does with a CF exacerbation.

Question 11: What are the potential causes of her chest pain? What should we do next?

Cystic Fibrosis

Educational Objectives:

1. Review the initial presentation and workup for cystic fibrosis (CF).
2. Review potential complications and management of CF.
3. Discuss mechanisms and indications for cystic fibrosis transmembrane regulator (CFTR) modulators.

Scenario 1:

Mr. D is a 32-year-old man who presents to your clinic with a new diagnosis of possible cystic fibrosis (CF). He first developed respiratory symptoms at age 12, with frequent cough (small amount of sputum production), intermittent dyspnea, wheezing, and nasal congestion with frequent sinus pressure, which was labeled asthma and allergic rhinitis for years. He also has acute respiratory infections 1-3 times per year and was often given oral antibiotics for "bronchitis." He has never had steatorrhea or difficulty maintaining weight, although he did have pancreatitis in college once, which was attributed to alcohol. However, he says he has never been a heavy alcohol user. He and his wife have been unsuccessfully trying to have children.

Question 1: What testing would you recommend to determine whether Mr. D has CF?

Guidelines (<https://www.sciencedirect.com/science/article/pii/S0022347616310484>) for CF diagnosis recommend starting with sweat chloride testing, followed by CFTR genetic testing if sweat chloride is in the indeterminate range (30-59). As seen on the flow chart in the following Figure 1, there are further steps in the diagnostic algorithm.

An appropriate clinical picture combined with a sweat chloride ≥ 60 mmol/L and/or two CF-causing mutations is considered diagnostic of CF. An appropriate clinical picture includes disease affecting 1 or more organ systems:

Pulmonary: bronchiectasis and/or chronic sinusitis

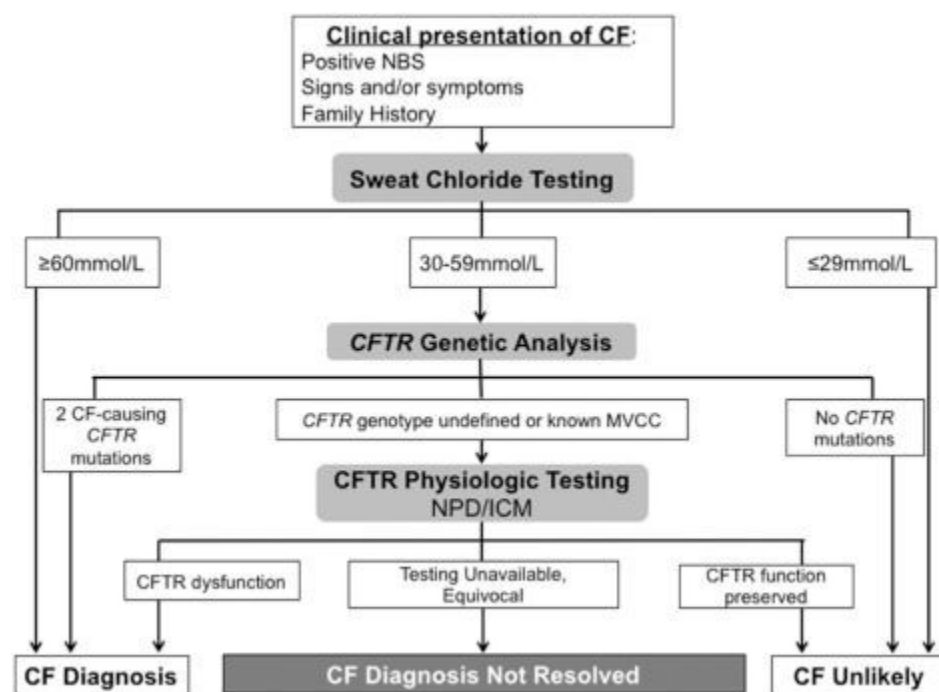
GI: pancreatitis and/or pancreatic insufficiency

GU: Congenital bilateral absence of vas deferens (CBAVD)

If sweat chloride testing is positive (≥ 60 mmol/L), it is still recommended that full CFTR genetic testing be done, since new therapies for CF are mutation-specific. Knowing the exact CFTR mutations can impact treatment decisions. Also, there are some mutations (e.g., a splicing mutation called 3849+10kbC->T) that are known to lead to false-negative sweat chloride (≤ 30 mmol/L). These mutations tend to lead to a milder clinical phenotype that is less likely to be diagnosed in childhood. Therefore, in cases where clinical suspicion for CF is high despite a negative or indeterminate sweat chloride test, genetic testing should be performed in consultation with a dedicated CF center.

When ordering CFTR genetic testing, the ideal scenario is to have full CFTR gene sequencing plus deletion/duplication analysis and intron polyT analysis. Commercial labs and several private genetic testing companies (ex: Ambry and Invitae) perform this more detailed testing. Many companies also allow simultaneous genetic testing for primary ciliary dyskinesia if that is also on your differential diagnosis. Complete genetic testing is indicated because the common CF mutations identified with initial screening tests are associated with more severe disease. If someone with adequate access to healthcare has made it to adulthood without CF being diagnosed, then they are unlikely to have solely the common mutations. At that point, complete genetic testing is needed.

Figure 1. Diagnostic Workup for CF



Diagnostic algorithm for CF testing.

Adapted from Farrell P, White T. Introduction to Cystic Fibrosis Foundation Consensus Guidelines for Diagnosis of Cystic Fibrosis. J Pediatr. 2017 <https://doi.org/10.1016/j.jpeds.2016.09.064>.¹

To look up a CFTR mutation to know if it is potentially disease-causing, you can start your search at websites such as <https://cftr2.org/>.

Question 2: Our patient is confirmed to have CF based on a positive sweat chloride test and by genetic testing. What further testing would be appropriate?

Guidelines recommend obtaining sputum cultures in all CF patients. Both bacterial culture and AFB cultures are indicated to identify potential pathogens of concern. Assessment of respiratory symptoms, physical examination, sputum cultures and spirometry are done on quarterly clinic visits at accredited cystic fibrosis centers. Other tests that are recommended as part of annual labs in CF that the cystic fibrosis center is likely to obtain are listed in Table 1.

Table 1. Screening for multi-organ manifestations of CF

CF	Guideline-based screening
Liver disease	LFTs annually
Pancreatic insufficiency/malabsorption	Vitamins A, D, and E annually, fecal elastase when clinically appropriate
Diabetes	Oral glucose tolerance test annually and can obtain HgbA1c
Cystic fibrosis exacerbations and pulmonary colonization	Sputum culture and AFB. CXR every 2-4 years
Osteopenia/Osteoporosis	DEXA scan every 5 years or less based on bone health
Colorectal Cancer	Colonoscopy every 5 years, starting at age 40
Mental Health	Depression and Anxiety Screening

Adapted from the Clinical Care Checklist for Adult Care in Cystic Fibrosis <https://www.cff.org/medical-professionals/adult-care-clinical-care-guidelines>

Question 3: Mr. D's testing returned with no significant abnormalities except for a sputum culture that grew mucoid *Pseudomonas aeruginosa*. What baseline pulmonary therapies should be initiated? What therapies specific to *Pseudomonas* should be initiated?

Chronic medications for maintenance of lung health in CF patients are as follows²:

1. Inhaled bronchodilators (SABA or LAMA)
2. Mucous modification as part of airway clearance regimen
 - a. Inhaled mannitol/Bronchitol- A DPI formulation of mannitol that was approved by FDA in 2020 for hydration and mobilization of respiratory secretions
 - b. Nebulized hypertonic saline - Hydrates respiratory secretions to help mobilize mucus more effectively; improves lung function and decreases exacerbations
 - c. Nebulized DNase/dornase/Pulmozyme - Breaks down DNA in sputum, which decreases sputum viscosity (since DNA is highly viscous) to help mobilize sputum; improves lung function and decreases exacerbations
 - d. Acetylcysteine and cromolyn – acetylcysteine has mucolytic, anti-inflammatory and antioxidant properties and can be combined with cromolyn to modify mucous

Airway clearance therapies (There have been no head-to-head trials comparing these various modalities)

- a. Percussion and postural drainage
- b. Positive expiratory pressure devices (PEP)
- c. Active cycle of breathing technique
- d. Autogenic drainage (AD)
- e. Oscillatory PEP devices (OPEP)
- f. High-frequency chest compression (HFCC) devices
- g. Exercise
3. Inhaled corticosteroids (ICS) or inhaled corticosteroid long-acting beta agonist (ICS/LABA) combination if the patient has asthma or asthma overlap syndrome.
4. Azithromycin: Recommended for patients with chronic *Pseudomonas aeruginosa* infection for the initial 18 months. Patients need to be screened for nontuberculous mycobacteria before initiation and at 12-month intervals.
5. Inhaled **cyclic** antipseudomonal antibiotics for chronic colonization:

- a. Nebulized and powdered inhaler tobramycin - Approved for CF patients with *Pseudomonas aeruginosa* in their sputum; improves lung function and decreases exacerbations
 - b. Nebulized aztreonam lysine (Cayston) - Approved for CF patients with *Pseudomonas aeruginosa* in their sputum; improves lung function and decreases exacerbations
 - c. Inhaled Colistin - Not FDA approved but used for CF patients with *Pseudomonas aeruginosa* in their sputum; improves lung function and decreases exacerbations
6. **CFTR Modulators:** A mutation-specific gene modulator is recommended for all eligible patients. CFTR modulators have been proven to improve lung function and decrease exacerbations. Recently, generic versions of these medications have become available globally.

Assuming this is his first infection with *Pseudomonas*, attempts at eradication should be made which would include inhaled tobramycin for 28 days. Oral antibiotics have not been shown to increase the rate of eradication if not having a true exacerbation but are commonly prescribed in conjunction with nebulized tobramycin for eradication attempts. If eradication fails and the patient is considered to have chronic pseudomonas colonization repeat cultures positive despite attempts at eradication and a mucoid phenotype, the team would initiate cyclic inhaled antipseudomonal antibiotics every other month and initiate chronic azithromycin for at least the first year (if the patient has concomitant bronchiectasis.)³ Every other month administration of inhaled tobramycin has been shown to decrease rates of resistance when compared to continuous administration. In Europe, inhaled colistin has been employed continuously without observed increases in antimicrobial resistance. During the month off tobramycin, some providers employ additional inhaled therapies, but no significant benefits have been proven with this strategy.

Question 4: Mr. D asks whether he should call his primary care physician or the pulmonary clinic when he has a respiratory infection. What would you advise that he do?

Whereas the general population tends to do well with watchful waiting in the context of respiratory infections (since most are self-limited viral infections), more aggressive use of antibiotics is warranted in CF. This is because patients are colonized with bacterial pathogens and viral infections can more easily lead to secondary bacterial infection in CF patients. While antibiotics are not automatically prescribed for every infection, it is preferred to have patients contact their CF program rather than primary care as long-term outcomes are better with a more aggressive approach to antibiotic use.

Question 5: How can we help decide whether he also has asthma or whether his history of unexplained dyspnea and wheezing were all due to undiagnosed CF?

CFTR mutation carriers are at increased risk of asthma compared to non-carriers. CF patients have an increased risk of asthma. It can be difficult to differentiate the patients with asthma from those without since asthma symptoms can also manifest in CF patients without asthma. If clear allergic triggers for respiratory symptoms are present, this suggests an asthmatic component to the respiratory disease in some CF patients. Pre- and post-bronchodilator testing can be helpful as well. In some patients the diagnostics are ambiguous, but they may be labeled as having asthma based on clinical response to asthma

medications. Many CF clinicians are also routinely monitoring for eosinophilia and considering biologic therapy for asthma for patients on a personalized basis.

Scenario 2:

Mr. W is a 19-year-old man with CF (F508del homozygous) diagnosed in infancy. He has been treated at a CF center throughout his life. He has been active throughout his childhood and felt healthy from a respiratory standpoint most of the time, but he does have exacerbations requiring IV antibiotics 1-2 times per year. He has pancreatic insufficiency and takes pancreatic enzymes. Thus, he is generally able to maintain his weight apart from transient drops associated with exacerbations. He had an adenovirus infection just before turning 18, and his health has been worse since. He doesn't feel quite as sick as when he has an acute exacerbation. His sputum isn't as thick, dark, and copious as when he has a "typical exacerbation," but he does have more sputum production than his prior baseline. His weight is also below his baseline, but not dropping as much as usual for an exacerbation. His baseline FEV1 used to be 75-80% predicted, but lately it has been 55-60%. He has received two courses of IV antibiotics with a slight improvement in symptoms and FEV1 increase to the low 60s but has not returned to his prior state of health at any point.

Question 6: Assuming he is on all the usual CF maintenance medications, is this his new baseline health status or can we do anything else for him? What other testing should we consider?

This may be his new baseline, but a decline in lung function not responding to IV antibiotics warrants further assessment to determine if there are any modifiable causes. This can include re-checking sputum bacterial cultures to determine if there is a new pathogen or increased resistance of previously identified pathogens, checking sputum AFB cultures, checking sputum fungal cultures, and checking IgE as an initial assessment for ABPA. Readdressing adverse effects of smoking, vaping, use of nicotine products and assessment of work-related exposures are important every visit. Gradual loss of lung function by 2 to 3 % forced expiratory volume in 1 second (FEV1) annually is noted in cystic fibrosis patients. This has been changing in the era of gene-modulating drugs. Adherence to airway clearance therapies and gene-modulating medications is of vital importance. Nationally, there has been a decline in adherence to airway clearance therapies as people with CF have been prescribed highly effective CFTR modulators, but it is worth noting that CF progresses even while patients are on CFTR modulators. Guidelines recommend continued airway clearance therapies.

Scenario 3:

Ms. H is a 36-year-old woman with CF who presents to clinic with complaints of decreased stool output and cramping abdominal pain (diffuse, but worse on the right side of her abdomen) along with an occasional sense of bloating in her abdomen. She has a decreased appetite and mild nausea without vomiting. No fevers, chills, or night sweats, but she has lost about 5 pounds, which she attributes to decreased appetite. No respiratory symptoms beyond her baseline cough and sputum production.

Question 7: What is the most likely cause of Ms. H's symptoms? Would you recommend any other diagnostic testing?

Her symptoms are most likely due to distal intestinal obstruction syndrome (DIOS), which used to be called meconium ileus equivalent. DIOS is more common in patients with pancreatic insufficiency and is caused by inspissated intestinal contents that completely or partially block the small intestinal lumen, most commonly at the ileocecal junction. Patients typically present with abdominal pain and a palpable "mass" of intestinal contents in the right lower quadrant. An abdominal x-ray and/or CT scan of the abdomen may show impacted stool in the distal small intestine and ascending colon, as well as possible small bowel dilation and/or air-fluid levels. In addition to abdominal imaging studies, it may be helpful to get a CBC, BMP, LFTs, amylase, lipase, and urine studies to assess for other causes of abdominal pain.

Question 8: What treatment approach is most likely to help her?

Patients with DIOS usually respond well to rehydration and treatment with osmotic laxatives and/or enemas. Surgery is a last resort for management of DIOS and is reserved for patients with peritoneal signs on exam or evidence of intestinal ischemia. If surgery is necessary, the goal is to remove as little bowel as possible; in some cases, the stool can be manually mobilized through the intestine during a laparotomy to avoid resecting bowel. It is extremely important to work with surgery teams closely and offer CF specific literature as needed.

Question 9: This patient has sufficient bowel movements after a "clean out" as described above. Her abdominal imaging no longer shows significant stool burden. However, she is continuing to lose weight. How should we expand our differential?

The differential diagnosis for abdominal pain in CF can include any of the things that can cause abdominal pain in patients without CF. However, here are some things for which CF patients are at increased risk:

- Acute pancreatitis
- Gallstones (cholelithiasis) and inflammation of gallbladder (cholecystitis)
- Complications of frequent use of antibiotics, including *C. difficile* colitis or small intestinal bacterial overgrowth
- Adhesions (if they required prior surgery for meconium ileus or other abdominal pathology)
- GI malignancies, even at a relatively young age. Colon cancer screening is recommended starting at age 40 in people with CF.
- Intussusception is possible in adults with CF, typically with inspissated intestinal contents acting as the lead point.
- Fibrosing colonopathy is characterized by severe fibrosis of the intestine and has historically been associated with high doses of pancreatic enzymes. It is much less common since the 1990s, although it is unclear how much of this is due to changes in the dosing of pancreatic enzymes or due to changes in how enzymes are manufactured. It is now considered an extremely rare condition.

CT of the abdomen and pelvis with lab work would help evaluate the above possibilities.

Scenario 4:

Mr. S is a 48-year-old man with cystic fibrosis (F508del homozygous). He has been surprisingly healthy for someone with his genotype. He has never been consistent about using respiratory therapies and rarely has acute pulmonary exacerbations; he can't remember the last time he needed antibiotics. His lung function has gradually declined over the years, with FEV1 currently 55% predicted, but he isn't bothered much by respiratory symptoms, so he hasn't been willing to use nebulizers frequently or do much for airway clearance. He has pancreatic insufficiency and takes pancreatic lipase. He now returns to clinic for the first time in several years, and early in the conversation says he saw on Instagram that there might be some new treatment for CF; he wants to hear more about it.

Question 10: What "new" treatments are available for CF? How do they work? What are the potential side effects and complications? Is it appropriate for him to start one of the new treatments?

There are new medications approved in recent years targeting the genetic mutations that cause CF, and it is likely that Mr. S has been seeing the news about Trikafta and Alyftrek.

1. Kalydeco (ivacaftor) - FDA approved in 2012
2. Orkambi (lumacaftor/ivacaftor) - FDA approved in 2015
3. Symdeko (tezacaftor/ivacaftor) - FDA approved in 2018
4. Trikafta (elexacaftor/tezacaftor/ivacaftor) - FDA approved in 2019
5. Alyftrek (vancacaftor/tezacaftor/deutivacaftor) - FDA approved in 2025

To understand the mechanism for these drugs, it helps to outline how CFTR mutations lead to absent or decreased CFTR function.

CFTR is a chloride-ion transport protein in the epithelial lining of cells. Specific CFTR mutations lead to dysfunction at different points in CFTR transcription, translation, cellular processing, and actual function as an ion channel. Figure 2 shows different classes into which CFTR mutations are grouped.

Figure 2. CFTR Mutation Classes

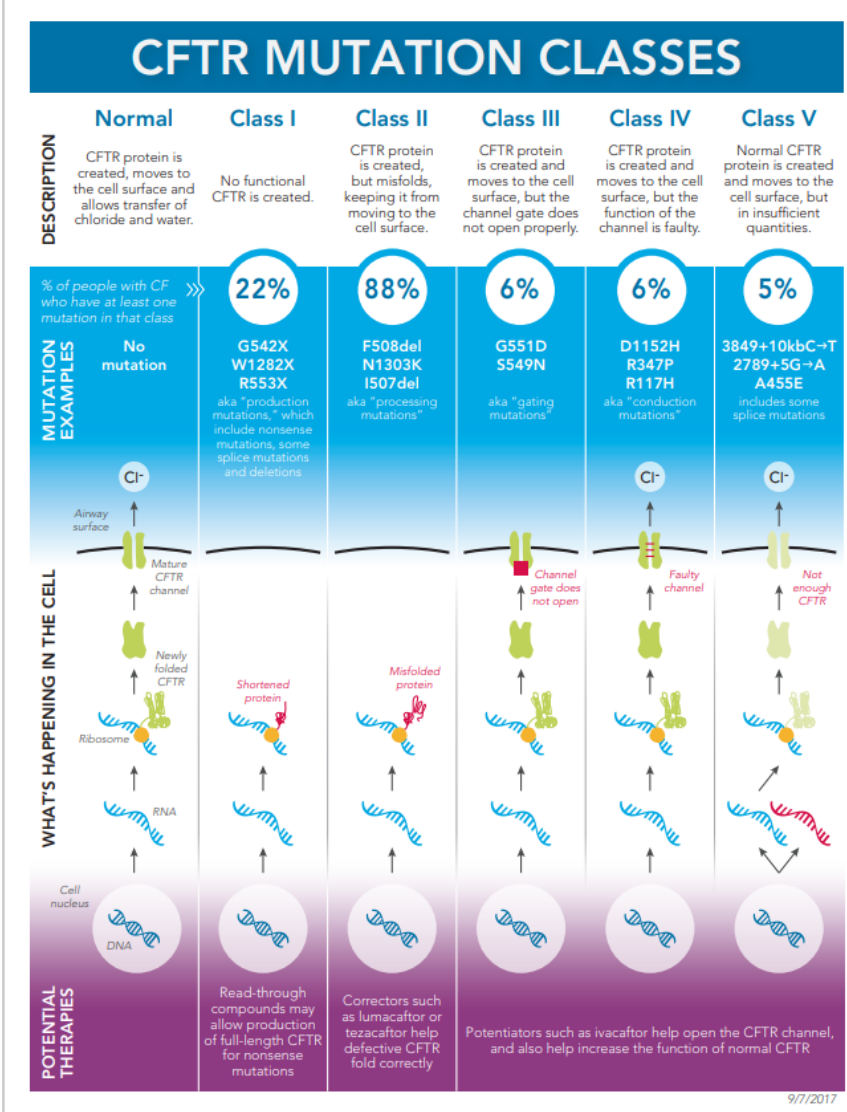


Figure 2 is from the CFF website. <https://www.cff.org/sites/default/files/2021-12/Know-Your-CFTR-Mutations-Infographic.pdf>

Table 2 takes information from 2022 - Patient Registry Annual Data Report 6 (published by the CF foundation) and lists currently available modulators, genotypes for which they are approved and major side effects.

Table 2. CFTR Modulators and Further Data

Drug	FDA approval	Mutation classes approved in	Major side effects
ivacaftor	Age 1 month or older if contains 1 of 97 mutations	3,4,5	Cataracts and LFT elevation
lumacaftor/ivacaftor	Homozygous for F508del Ages 1+	2	Cataracts, LFT elevation, respiratory symptoms
tezacaftor/ivacaftor	Homozygous for F508 or one of 153 approved mutations for ages 6 +	2,3,5	Cataracts and LFT elevation
elexacaftor/tezacaftor/ivacaftor	Homozygous or heterozygous for F508del Approved for ages 2+.	2	Cataracts and LFT elevation

Table information adapted from Vertex Healthcare provider website. <https://www.vertextreatmentshcp.com/>

Ivacaftor (Kalydeco) is called a CFTR potentiator, producing increased chloride-channel activity when CFTR protein is at the cell surface. By itself, it does not help class I or II mutations, but can improve CFTR function in Class III, IV, and V.

Lumacaftor, elexacaftor, and tezacaftor are called **CFTR correctors**. They help stabilize CFTR with F508del mutations to interfere with lysosomal degradation so it can reach the cell surface, where Ivacaftor can potentiate its function. Lumacaftor/ivacaftor (Orkambi) was approved first but was difficult for patients to tolerate; many patients had chest tightness, wheezing, and dyspnea on Orkambi. Tezacaftor/ivacaftor (Symdeko) has been noted to have no increase in respiratory events which includes chest discomfort, wheezing, and dyspnea. In fact, in a pooled analysis of the existing trials noted respiratory events were 11.3% in patients treated with tezacaftor/ivacaftor vs 14.7% in placebo.⁴

Elexacaftor/tezacaftor/ivacaftor (Trikafta) was approved by the FDA in October 2019 as the first **triple combination** therapy. It was approved for individuals with cystic fibrosis that are 2 years old or older who have at least one allele with the F508del mutation. The most notable side effect that requires monitoring and medication adjustment is elevation in LFTs and hepatic impairment. This is the first in the class of highly effective modulator therapy (HEMT).

Elexacaftor/tezacaftor/ivacaftor has received approval in all patients with at least one copy of F508del, although it received approval based on improvement of FEV1 by 13.3% in patient with F508del and minimal function mutation. This is not a mutation in which ivacaftor or tezacaftor/ivacaftor have been proven helpful. Elexacaftor/tezacaftor/ivacaftor has been shown to increase the FEV1 of homozygous F508del patients by 11% as compared to those already receiving tezacaftor/ivacaftor. The predicted life survival for CF patients

has increased from 43 years to 65 years since the approval of the first CFTR modulator. The addition of elexacaftor/tezacaftor/ivacaftor and the expansion of the gene modulator drugs to younger age groups has expanded the eligibility of patients with CF for modulator therapy to approximately 93.9% of CF patients in the 2022 CF registry.^{6,7} Of the 93.9%, 11.09% are eligible but have not received a prescription for the drugs. The non-responders are in classes 1 and 6. Thus, non-responder patients (which is estimated to be 6% of the population) are unlikely to receive approval for modulators and will require genetic-based therapies (which are on the horizon with technologies such as inhaled lipid mRNA-based therapies).

Another advantage of modulators is that they can be taken orally, which is far more convenient for CF patients whose other treatments (nebulizers, airway clearance modalities, etc.) are time intensive.

The main disadvantages to CFTR modulators are cost (all cost approximately \$300,000 per year). However, they are currently covered by insurance with a qualifying mutation, and generic/biosimilar medications are now being introduced. The need to monitor LFTs for potential hepatotoxicity, and less common adverse events, particularly weight gain.

Scenario 5:

A 26-year-old woman with CF and worsening respiratory disease (frequent exacerbations, FEV1 30% predicted) presents to clinic with right-sided chest pain that started yesterday. She had been feeling worse in the preceding few days, with some increased cough and sputum production, but had not felt as bad as she usually does with a CF exacerbation.

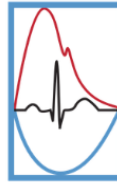
Question 11: What are the potential causes of her chest pain? What should we do next?

Spontaneous pneumothorax can develop in cystic fibrosis. Although most respiratory infections associated with CF are airway infections associated with bronchiectasis, pneumonia is also a possibility and can often cause chest pain in CF patients. Starting with a chest x-ray is a reasonable approach in this clinical setting.

Of course, if there are pulmonary embolism risk factors, a CT angiogram of the chest may also be appropriate.

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[Cystic Fibrosis Foundation. Patient Registry. Cystic Fibrosis Foundation website. Accessed March 11, 2026. https://www.cff.org/medical-professionals/patient-registry](https://www.cff.org/medical-professionals/patient-registry)



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