

## Cystic Fibrosis

### Summary:

Cystic Fibrosis (CF) is a complex, chronic disease that primarily affects the lungs and digestive system. More than 30,000 children and adults in the United States have CF. People with CF inherit two copies of a defective gene, one copy from each parent, that produces a faulty protein, causing a buildup of thick mucus in the lungs, pancreas, and other organs. Today, because of improved medical treatments and care, more than half of people with CF are age 18 or older. Many people with CF can expect to live healthy, fulfilling lives into their 30s, 40s, and beyond.

### Objective(s):

1. Define Cystic Fibrosis
2. Understand Epidemiology, Risk Factors and Symptoms
3. Discuss pathogenesis and Diagnosis
4. Review Cystic Fibrosis Guidelines
5. Discuss Current and Future Therapies
6. What Does Cystic Fibrosis Look Like Now?

### Prepared by:

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# Cystic Fibrosis

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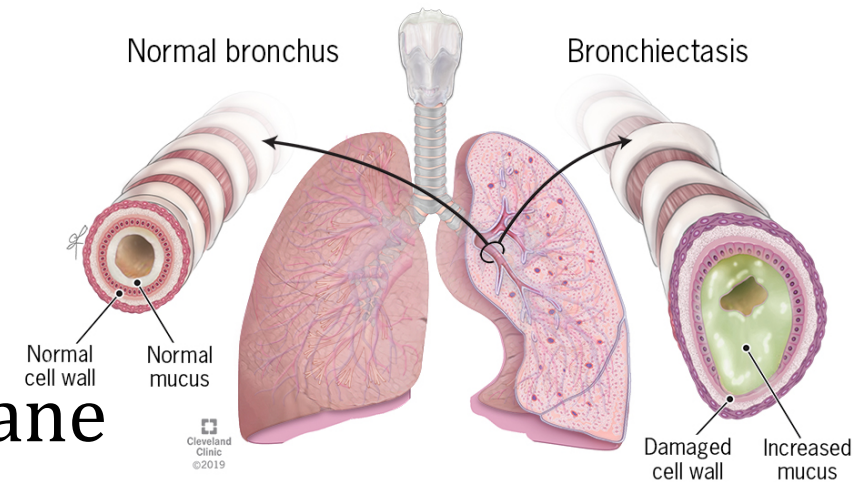
## OBJECTIVES

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# WHAT IS CYSTIC FIBROSIS?

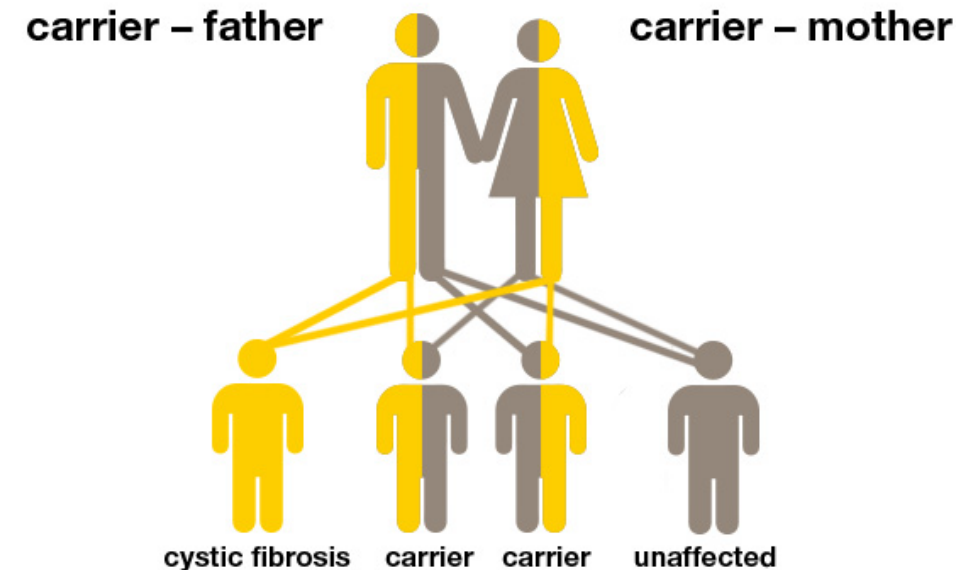
- A progressive, genetic disease
- Mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene (dysfunction in gene)
- Unable to move chloride and water to cell surface
- Results in thick and sticky mucus
- Mucus causes difficulty breathing and persistent lung infections
- Mucus causes intestinal blockages and pancreatic insufficiency



# EPIDEMIOLOGY AND RISK FACTORS

- Carrier: a person with 1 defective CF gene
- People with 2 defective genes have a 25% chance of having CF
- There are 1700 mutations that can affect the CF gene
- Common in people of north European ancestry

| Prevalence of Cystic Fibrosis |                    |
|-------------------------------|--------------------|
| United States                 | 30,000             |
| Worldwide                     | 70,000             |
| Caucasian-Americans           | 1 in 3,500 births  |
| Hispanic-Americans            | 1 in 7,000 births  |
| African-Americans             | 1 in 17,000 births |
| Asian-Americans               | 1 in 90,000 births |



# PATHOPHYSIOLOGY

- Defective CFTR protein leads to thick and sticky mucus
- Serious lung infections from bacteria being trapped in the mucus
- Lung tissue destruction from elastase release
- Mucus blocks the pancreas canaliculi and gallbladder duct leading to malabsorption
- Distal Intestinal Obstruction Syndrome (DIOS) from thickening of stool
- Imbalance of minerals in blood leading to complications: dehydration, arrhythmias, fatigue

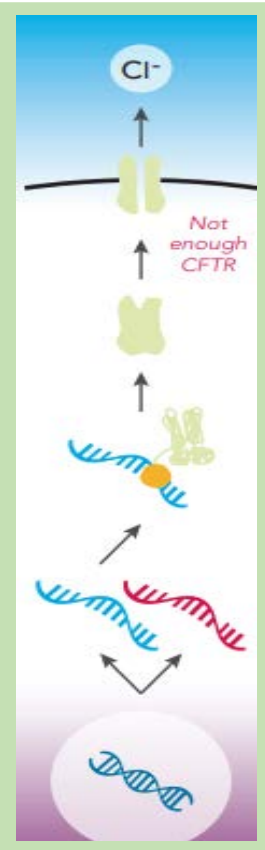
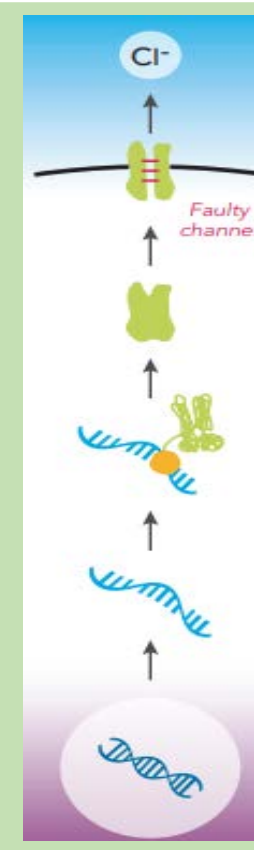
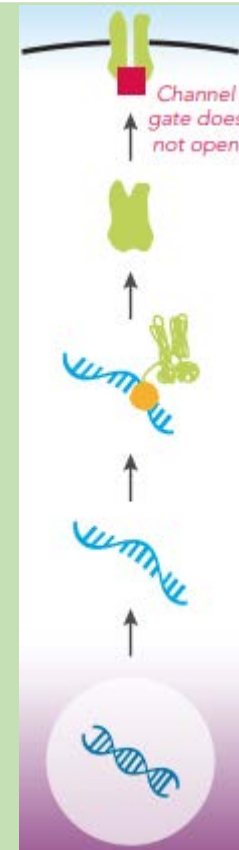
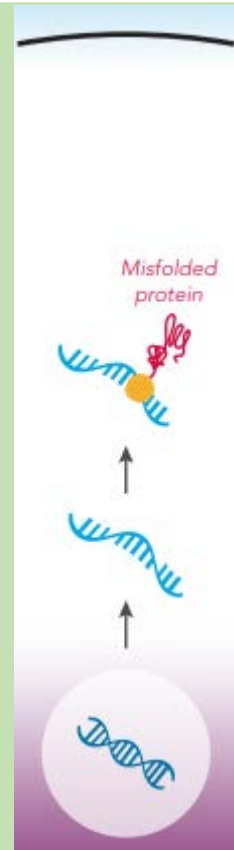
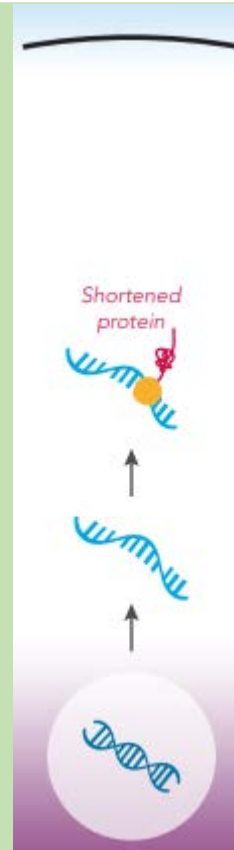


# CFTR MUTATION CLASSES



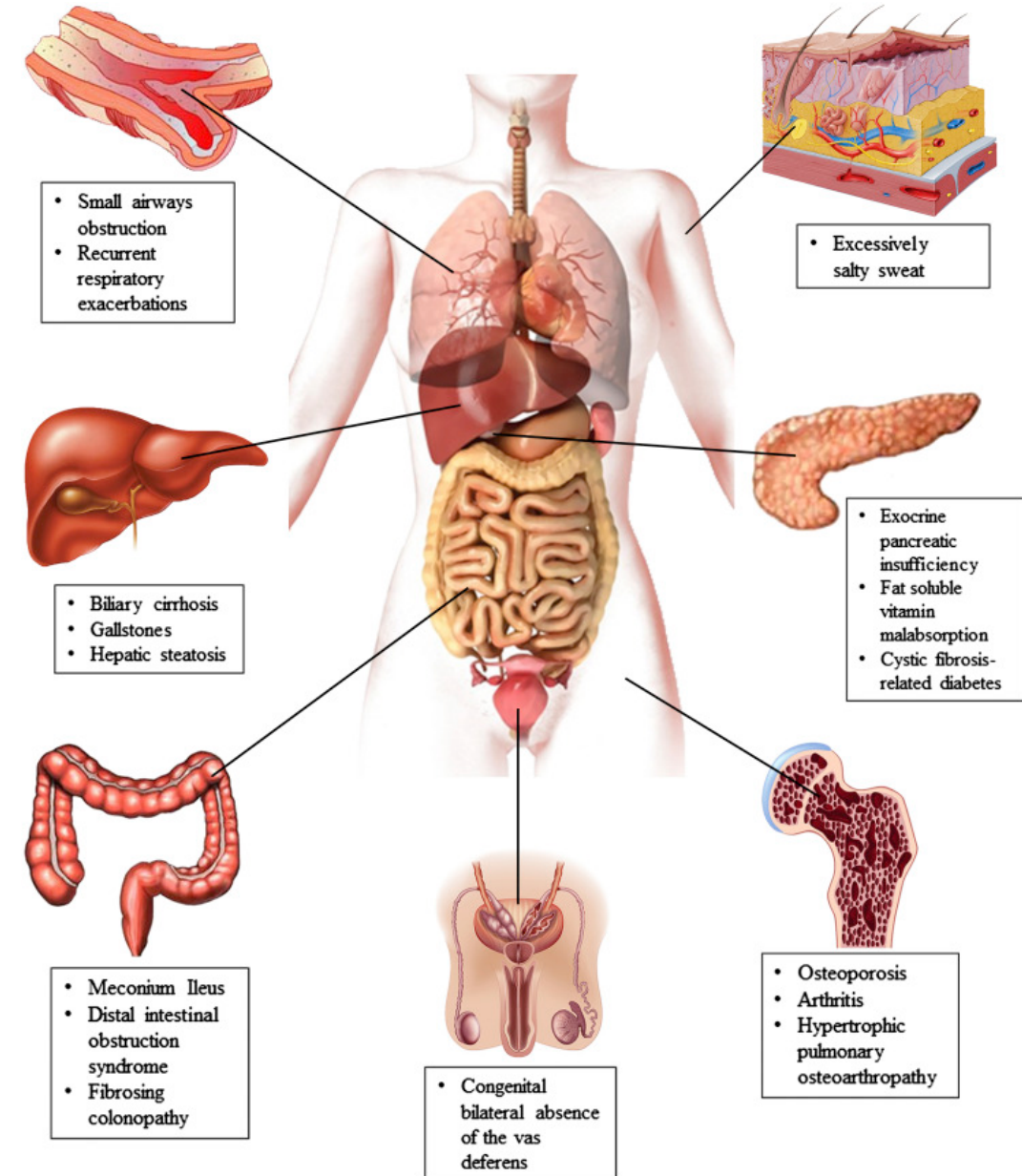
|                                                          | CLASS I                       | CLASS II                                                         | CLASS III                                                                          | CLASS IV                                                                             | CLASS V                                                                          |
|----------------------------------------------------------|-------------------------------|------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
|                                                          | No functional CFTR is created | CFTR is created but misfolds keep it from moving to cell surface | CFTR is created and moves to cell surface, but channel gate does not open properly | CFTR is created and moves to cell surface, but the function of the channel is faulty | Normal CFTR is created and moves to cell surface, but in insufficient quantities |
| % of CF patients with at least one mutation in the class | 22%                           | 88%                                                              | 6%                                                                                 | 6%                                                                                   | 5%                                                                               |

What's happening inside the cell



# SYMPTOMS

- Salty-tasting skin
- Persistent coughing, with phlegm
- Frequent lung infections
- Wheezing
- Poor growth or weight gain
- Greasy, bulky stools/difficulty with bowel movements
- Male infertility



# DIAGNOSIS

- **Newborn screening (NBS):** screens for different genetic and congenital disorders
- **Sweat chloride test:**  $\geq 60$  mmol/L, must be confirmed with genetic test
- **Genetic/carrier test:** determines if a carrier has the most common types of mutations with a blood sample or cheek swab



# COMPLICATIONS OF CYSTIC FIBROSIS

| RESPIRATORY                 | GASTROINTESTINAL                                                 | OTHER       |
|-----------------------------|------------------------------------------------------------------|-------------|
| Infection                   | Bowel problems: gallstones, intestinal blockage, rectal prolapse | Depression  |
| Chronic respiratory failure | Malnutrition                                                     | Anxiety     |
|                             | Electrolyte abnormalities                                        | Infertility |
|                             | CFRD: Cystic Fibrosis-Related Diabetes                           |             |



# Management of Respiratory Complications

1. **Bronchodilators**: helps widen airways by relaxing the muscles in the airway walls → **albuterol**
2. **Mucus thinners (mucolytics)**
  - **Hypertonic saline**: increases the amount of salt in the airways, which attract water and thins the mucus, making it easier to cough out
  - **Dornase alfa**: inhaled medication that thins the mucus. Cuts up the long DNA strands in white blood cells, which helps break up the thick, sticky mucus that leads to lung infections
3. **Airway clearance techniques**: involves coughing or huffing to help mucus out of small airways
4. **Antibiotics** (prevention and controlling lung infections)
  - Inhaled **tobramycin** and **aztreonam**: taken every other month for 28 days or alternate both every 28 days
  - Oral antibiotics (**ciprofloxacin**, **cephalexin**, **amoxicillin**, **doxycycline**): May be taken daily for acute or chronic therapy
  - IV antibiotics: for lung exacerbations
5. **Control of airway inflammation**: **NSAIDs**, inhaled and systemic **steroids** and **cromolyn**
6. **Lung transplantation**: receiving new lungs from a donor which can extend and improve the quality of life



# Management of GI Complications

## Constipation treatment (partial or full blockage/DIOS):

- Oral rehydration, osmotic laxatives, hyperosmolar contrast enemas
- A balanced electrolyte intestinal lavage solution or enema
- To prevent recurrence, regular administration of oral **polyethylene glycol 3350** may be given for 6 months– 1 year

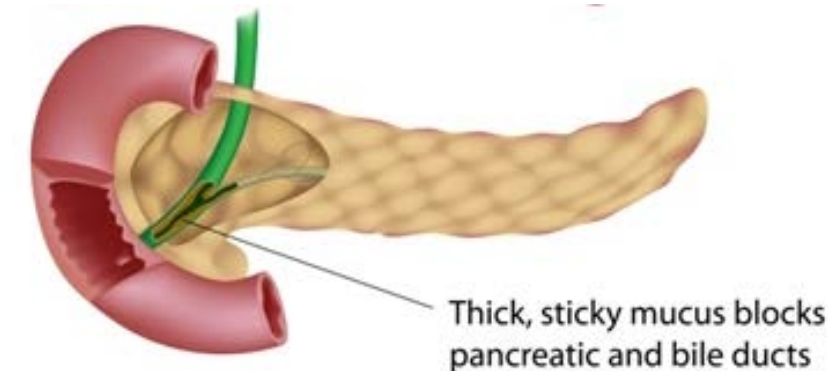
## Pancreatic insufficiency:

- Pancreatic enzyme replacement therapy (**PERT**) containing multiple combinations of proteases, lipases and amylases

## Gastroesophageal reflux disease (GERD) or acid reflux:

- Proton pump inhibitors (PPI): **omeprazole**, **lansoprazole**, etc.
- H2 blockers: **ranitidine**, **famotidine**
- Antacids: **Mylanta**®, **Maalox**®

**Cystic Fibrosis-Related Diabetes (CFRD)**: shares features with both Type 1 and 2 DM



# Management of Nutrition and Electrolytes

- The energy needs of CF patients are 1.5-2x higher than healthy patients
- The goal is to gain weight and maintain a healthy BMI
  - Adult women: BMI of 22+
  - Adult men: BMI of 23+
- Patients are encouraged to intake an additional 500 calories/day in addition to a well-balanced diet
- Supplemental vitamins ADEK and minerals including fluoride and zinc are recommended
- Sodium chloride supplementation is based on patient's age and environmental conditions



## Management of Depression/Anxiety

- CF patients and caregivers of CF patients are more likely to experience depression and anxiety
- Anxiety stems from making time for daily treatments, remembering to take medications, missing out on activities, and being hospitalized frequently



Untreated mental health problems can lead to

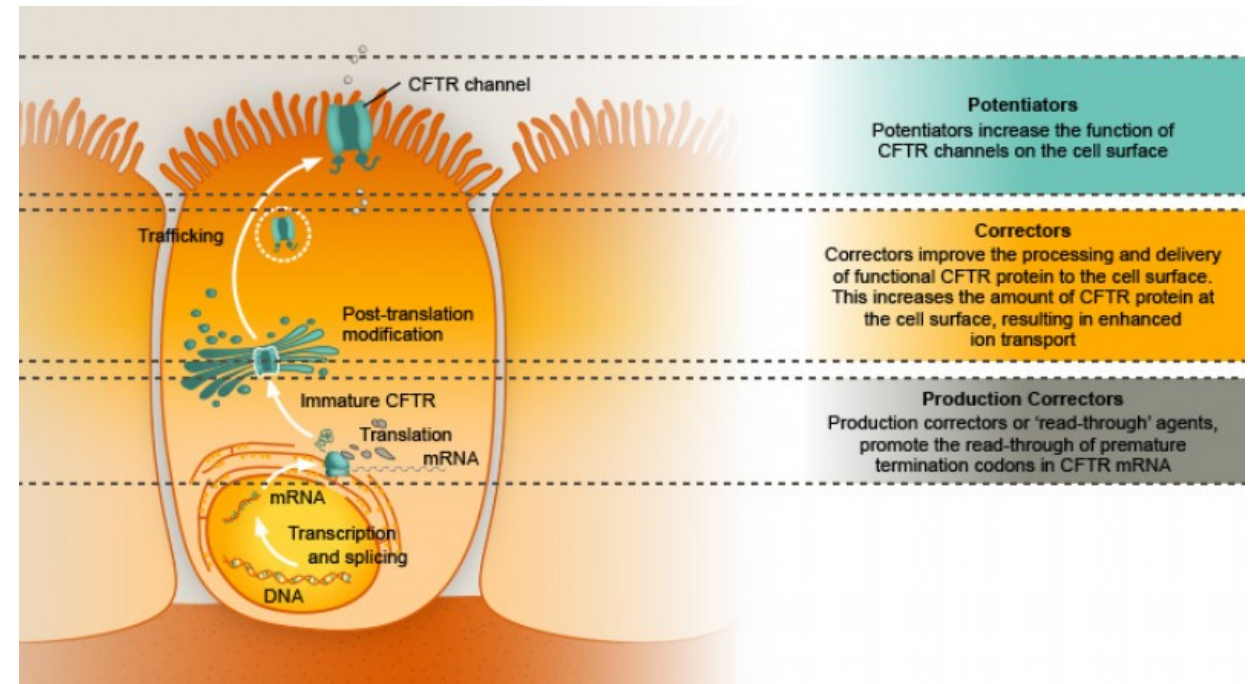
- Less adherence to treatment plans
- Worse lung function
- Lower BMI
- More hospitalizations
- Higher health care costs
- Lower quality of life

# CFTR MODULATOR THERAPY CARE GUIDELINES

## Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

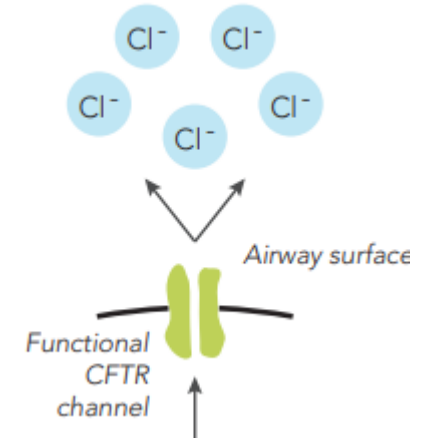
### 3 types of CFTR modulators

1. Potentiators
2. Correctors
3. Amplifiers (not available yet)



## Potentiators

Hold the CFTR protein tunnel gate open to allow chloride to flow through the cell membrane and regulate the amount of fluids at the cell surface. This helps reduce symptoms of CF by decreasing the stickiness of the mucus.



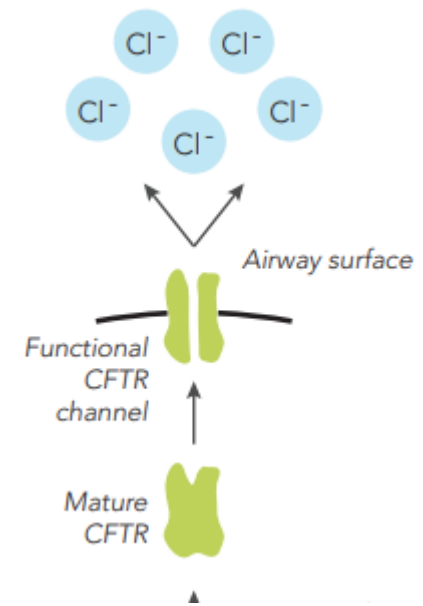
### Ivacaftor (Kalydeco®)

- Approved for ages 6 months and up
- Binds to defective protein at cell's surface
- Hold the chloride channel gate open allowing chloride to flow through
- Regulates the amount of fluids at the cell surface
- Medication shows improvement in lung function ( $\text{FEV}_1$ , FVC, BMI, and QOL (STRIVE, ENVISION trials, GOAL study))



## Correctors

Help the proteins form the correct 3D shape, move to the cell surface, and stay there longer. Correctors are used in combination with potentiators to correct the protein conformation then hold the gate open to allow chloride flow.



### Treatment Options

- Lumacaftor/Ivacaftor= Orkambi®
- Tezacaftor/Ivacaftor= Symdeko®
- Elexacaftor (corrector)/Tezacaftor (corrector)/Ivacaftor (potentiator)= Trikafta®

# ADVANCES IN CYSTIC FIBROSIS TREATMENT

## Restore CFTR Function: PHASE 2

- **ABBV-2222**: corrector (Abbvie)
  - Studied for patients who have two copies of F508del CFTR mutation
  - Studied for combination therapy with **ABBV-3067** (potentiator)
- **ABBV-3067**: potentiator (Abbvie)
  - Studied for monotherapy and in combination with **ABBV-2222** (corrector)
- **ELX-02**: restore CFTR function in patients with nonsense mutations (Eloxx Pharmaceuticals)
  - Studied for patients who have at least one copy of G542X CFTR mutation
- **PTI-428** (**amplifier**) + **PTI-801** (corrector) + **PTI-808** (potentiator) (Proteostasis Therapeutics)
  - Studied for monotherapy and in combination with each other
- **VX-121**: corrector (Vertex Pharmaceuticals)
  - Studied in combination with **tezacaftor** (corrector) and **VX-561** (potentiator)
- **VX-561**: potentiator (altered form of **Kalydeco**®) (Vertex Pharmaceuticals)
  - Studied in patients with CFTR gating mutation

| DRUG                                         | INDICATION                                                                                                                                                                                           | DOSING                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | ADR/DDI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | MONITORING                                                                                                                                                                 |
|----------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Kalydeco®<br/>(ivacaftor)</b>             | <p><b>Ages 6 months+:</b><br/>mutations in G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R.</p> <p><b>Not effective in patients with homozygous F508del mutation</b></p> | <p><b>Ages 6 months – &lt;6 years:</b></p> <ul style="list-style-type: none"> <li>• 5-7kg: 25mg granule packet q12h</li> <li>• 7-&lt;14kg: 50mg granule packet q12h</li> <li>• ≥14kg: 75mg granule packet q12h</li> </ul> <p>Mix entire packet of granules with 5ml of soft food or liquid at or below room temperature. Must be completely consumed within 1 hour.</p> <p><b>Ages 6+: 150mg q12h with fat-containing food</b></p> <p><b>Reduce dose in moderate/severe hepatic impairment and when co-administering with moderate/strong CYP3A inhibitors</b></p>                                                                                                                                           | <p><b>ADRs</b></p> <ul style="list-style-type: none"> <li>• Headache (17%)</li> <li>• URTI, nasal congestion (16%)</li> <li>• Nausea, rash (10%)</li> <li>• Rhinitis (6%)</li> <li>• Dizziness, arthralgia, bacteria in sputum (5%)</li> </ul> <p><b>DDI</b><br/>CYP3A inhibitors:</p> <ul style="list-style-type: none"> <li>• reduce Kalydeco dose to one tablet/packet twice a week with strong inhibitors</li> <li>• Reduce to one tablet/packet once daily with moderate inhibitors</li> </ul> <p>Avoid grapefruit or Seville oranges</p>                     | <ul style="list-style-type: none"> <li>• AST/ALT</li> <li>• FEV<sub>1</sub></li> <li>• Ophthalmological exams (pediatric patients)</li> </ul>                              |
| <b>Orkambi®<br/>(lumacaftor + ivacaftor)</b> | <p><b>Ages 2+ with homozygous F508del mutation in CFTR gene</b></p> <p><b>Not studied in patients with other mutations</b></p>                                                                       | <p><b>Ages ≥2-5:</b></p> <ul style="list-style-type: none"> <li>• &lt;14kg: lumacaftor 100mg/ivacaftor 125mg granule packet q12h</li> <li>• ≥14kg: lumacaftor 150mg/ivacaftor 188mg granule packet q12h</li> </ul> <p><b>Ages 6-11:</b></p> <ul style="list-style-type: none"> <li>• Two tablets (lumacaftor 100mg/ivacaftor 125mg) q12h</li> </ul> <p><b>Ages 12+:</b></p> <ul style="list-style-type: none"> <li>• Two tablets (lumacaftor 200mg/ivacaftor 125mg) q12h</li> </ul> <p><b>Reduce dose in patients with moderate/severe hepatic impairment</b></p> <p><b>When initiating Orkambi in patients taking strong CYP3A inhibitors, reduce Orkambi dose for 1<sup>st</sup> week of treatment</b></p> | <p><b>ADRs</b></p> <ul style="list-style-type: none"> <li>• Dyspnea, nasopharyngitis, nausea (13%)</li> <li>• Diarrhea (12%)</li> <li>• URTI (10%)</li> <li>• Fatigue, abnormal respiration (9%)</li> </ul> <p><b>DDI</b></p> <ul style="list-style-type: none"> <li>• CYP3A inhibitors, inducers, substrates</li> <li>• CYP2B6, CYP2C, digoxin, p-gp substrates, anti-allergies, systemic corticosteroids, antibiotics, antifungals, anti-inflammatories, antidepressants, hormonal contraceptives, oral hypoglycemic, PPIs, H2RAs, antacids, warfarin</li> </ul> | <ul style="list-style-type: none"> <li>• Blood pressure</li> <li>• Ophthalmological exams</li> <li>• AST, ALT, bilirubin</li> <li>• s/sx of respiratory effects</li> </ul> |

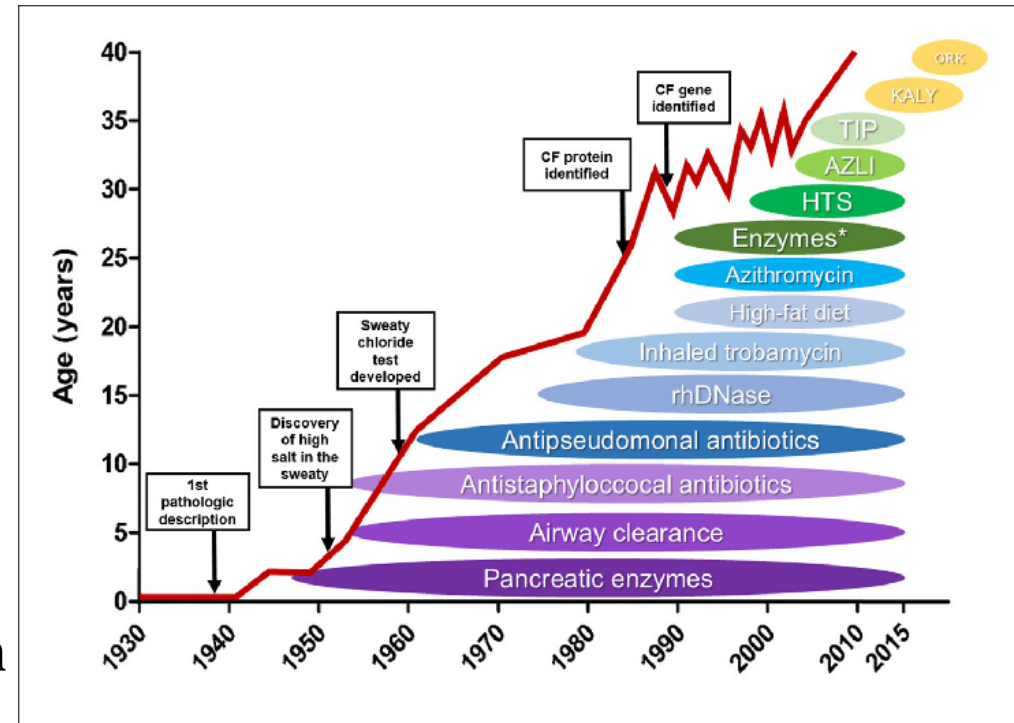
| DRUG                                                       | INDICATION                                                                                                                   | DOSING                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | ADR/DDI                                                                                                                                                                                                                                                                                                                                                                                                              | MONITORING                                                                                                     |
|------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <b>Symdeko®</b><br>(tezacaftor + ivacaftor)                | <b>Ages 6+</b> with homozygous F508del mutations or at least one mutation in CFTR gene that response to tezacaftor/ivacaftor | <p><b>Ages 6–&lt;12 years (&lt;30kg):</b></p> <ul style="list-style-type: none"> <li>Morning dose: one tablet with tezacaftor 50mg/ivacaftor 75 mg</li> <li>Evening dose: one tablet with ivacaftor 75mg</li> </ul> <p>Take ~12 hours apart</p> <p><b>Ages 6–&lt;12 (&gt;30kg) and ages 12+:</b></p> <ul style="list-style-type: none"> <li>Morning dose: one tablet with tezacaftor 100mg/ivacaftor 150mg</li> <li>Evening dose: one tablet with ivacaftor 150mg</li> </ul> <p>Take ~12 hours apart</p> <p><b>Reduce in patients with moderate/severe hepatic impairment</b></p> <p><b>Reduce when co-administered with drugs that are moderate/strong CYP3A inhibitors</b></p> | <p><b><u>ADRs</u></b></p> <ul style="list-style-type: none"> <li>Headache (15%)</li> <li>Nausea (9%)</li> <li>Sinus congestion, dizziness (4%)</li> </ul> <p><b><u>DDI</u></b></p> <ul style="list-style-type: none"> <li>CYP3A inhibitors: reduce Symdeko when co-administered with strong/moderate CYP3A inhibitors</li> <li>Avoid food containing grapefruit or Seville oranges</li> </ul>                        | <ul style="list-style-type: none"> <li>AST/ALT</li> <li>Ophthalmological exams (pediatric patients)</li> </ul> |
| <b>Trikafta®</b><br>(elexacaftor + tezacaftor + ivacaftor) | <b>Ages 12+</b> with at least one F508del mutation in the CFTR gene                                                          | <p><b>Ages 12+:</b></p> <ul style="list-style-type: none"> <li>Morning dose: two elexacaftor 100mg, tezacaftor 50mg, ivacaftor 75mg tablets</li> <li>Evening dose: one ivacaftor 150mg tablet</li> </ul> <p>Takes ~12 hours apart with fat-containing food</p> <p><b>Not recommended in patients with severe hepatic impairment</b></p> <p><b>Reduce dose in moderate hepatic impairment (risk-benefit)</b></p> <p><b>Reduce dose when co-administered with moderate/strong CYP3A inhibitors</b></p>                                                                                                                                                                             | <p><b><u>ADRs</u></b></p> <ul style="list-style-type: none"> <li>Headache (17%)</li> <li>URTI (16%)</li> <li>Abdominal pain (14%)</li> <li>Diarrhea (13%)</li> <li>Rash, increased ALT (10%)</li> </ul> <p><b><u>DDI</u></b></p> <ul style="list-style-type: none"> <li>Strong CYP3A inducers: avoid</li> <li>Strong/moderate CYP3A inhibitors: reduce Trikafta dose</li> <li>Avoid grapefruit food/drink</li> </ul> | <ul style="list-style-type: none"> <li>LFTs</li> <li>Ophthalmological exams (pediatric patients)</li> </ul>    |

# WHAT DOES CF LOOK LIKE NOW?

- **Goal of CF treatment:** minimize s/sx of condition
- Early identification and management can allow patients to live longer lives than before
- Predicted life span for a CF patient born between

2014-2018 is about **44 years** (average 16 years in 1970)

- Frequent hospitalizations and complications of disease
- Progressive respiratory insufficiency is a major cause of mortality
- Median survival post lung transplant is 8.3 years



## KEY TAKEAWAYS

- CF is a rare genetic disease that affects several body systems including lungs, pancreas, liver and skin
- Patients are tested for CF at birth
- There are many complications from CF that require management and supportive care
- CFTR modulator therapies attempt to restore CFTR function
- There have been many advances in CF treatment, leading to longer life expectancies and better QOL for patients

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THANK YOU FOR YOUR  
ATTENTION!