# CFTR-RD
# Acute Recurrent or Chronic Pancreatitis

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# Disclosures



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# CFTR gene

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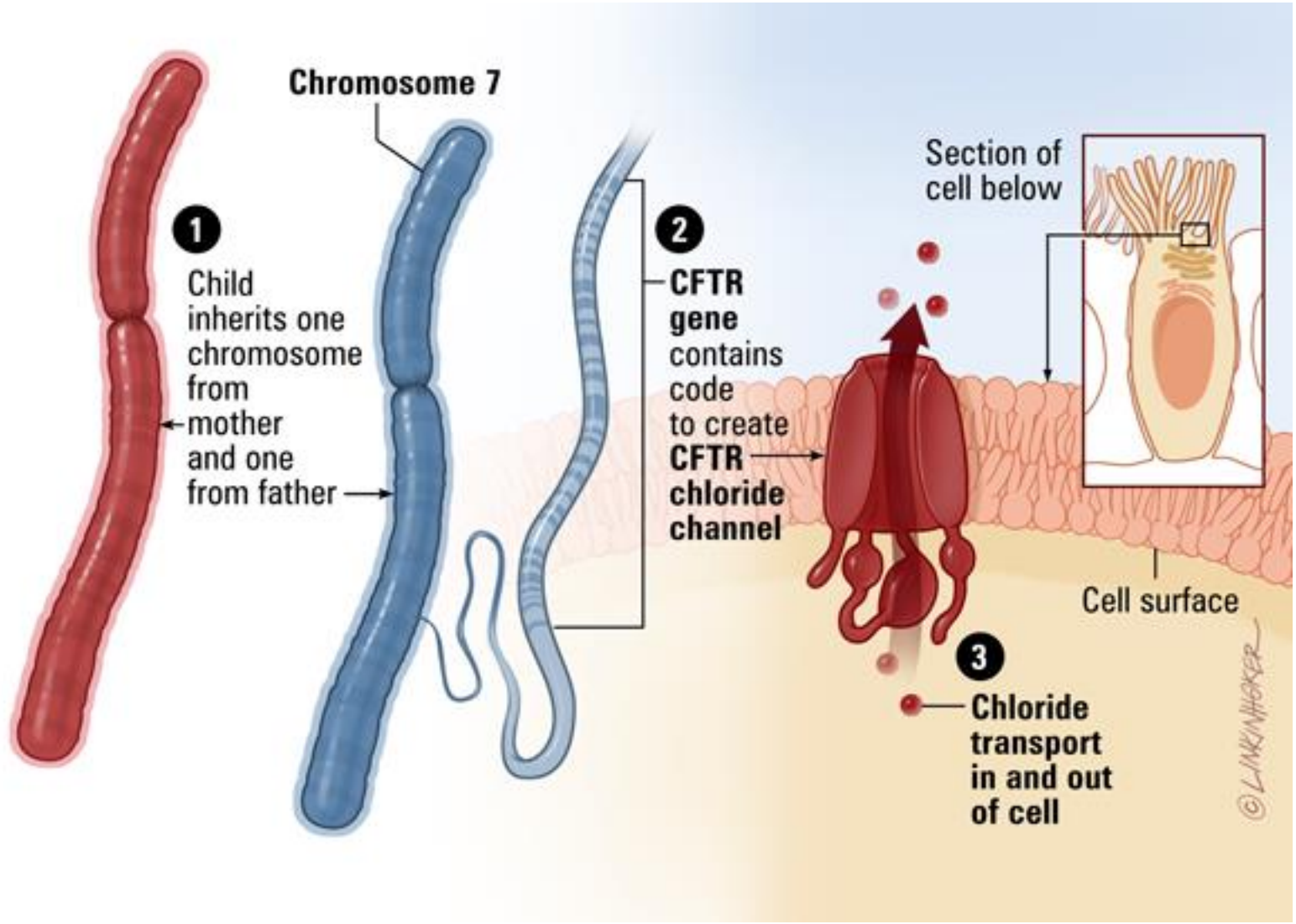


https://hopkinscf.org/

# Mendelian Inheritance

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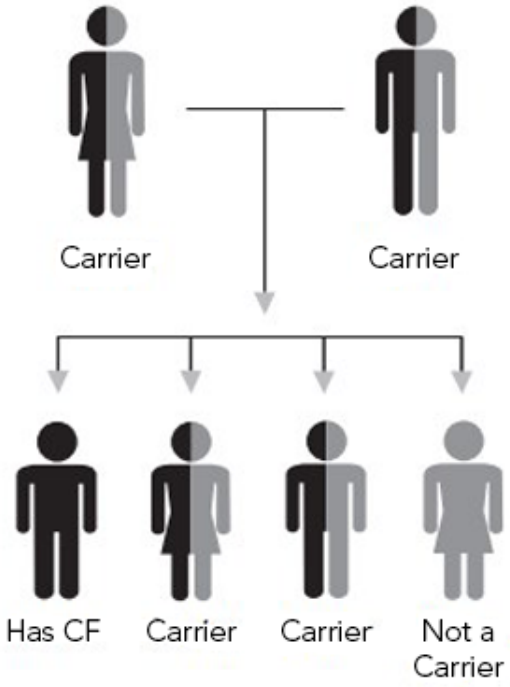
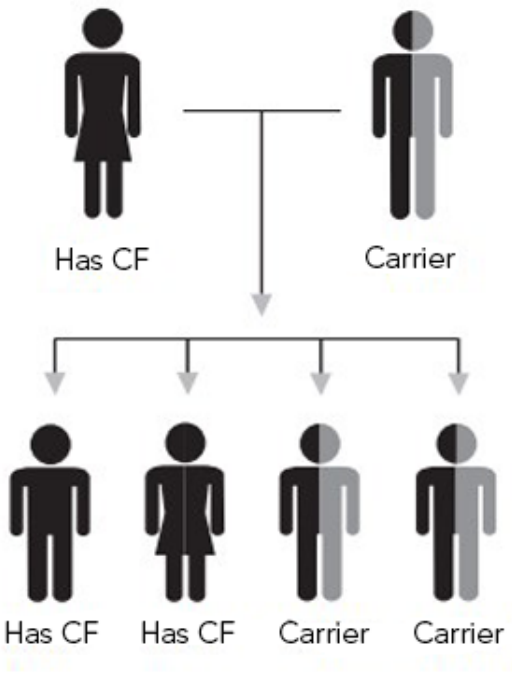
## How a Person Gets CF

To have CF, you must inherit two copies of the CFTR gene that contain mutations – one copy from each parent. That means that each parent must either have CF or be a carrier of a CFTR gene mutation.

When two people who are carriers have a child, there is a 25 percent chance of having a child with CF.




When one parent has CF and one parent is a carrier, there is a 50 percent chance of having a child with CF.

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# CF is Caused by Defects in CFTR Gene

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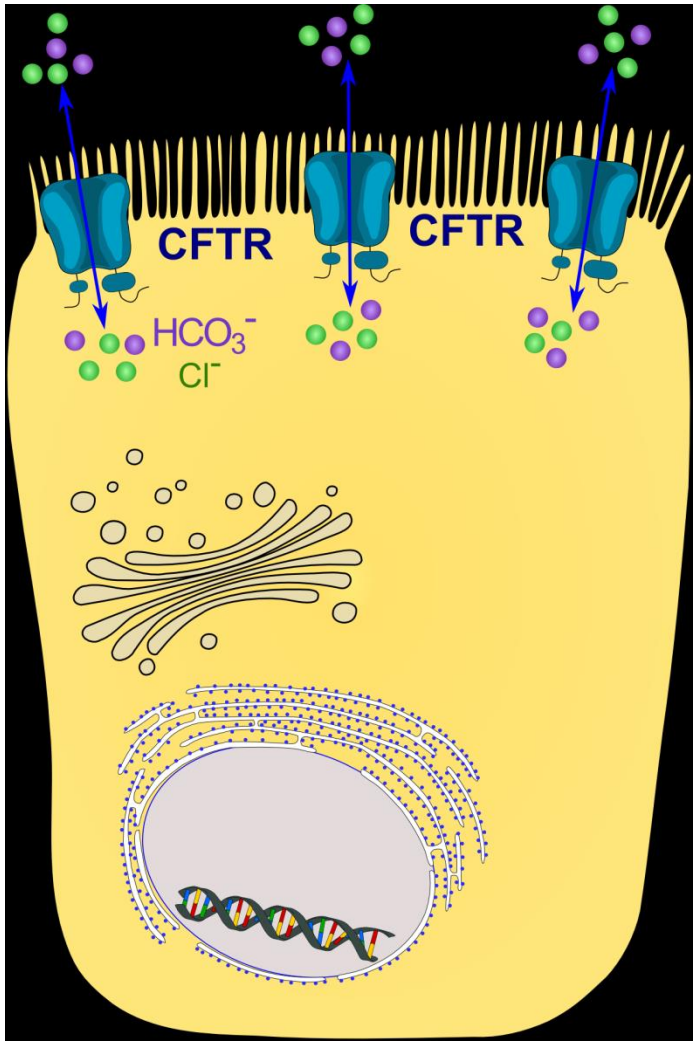
- CFTR = Cystic Fibrosis Transmembrane conductance Regulator
- CFTR transports anions (Cl, HCO3)
- Active in epithelium of trachea/lungs, pancreas, intestine, sweat glands, bile ducts, vas deferens, etc
- Helps maintain proper fluidity and electrolyte composition of secretions



# CFTR Channel-Functional

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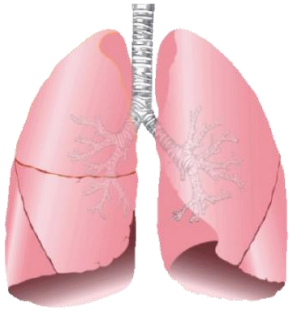

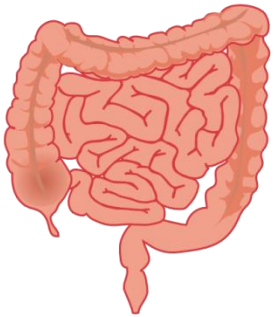

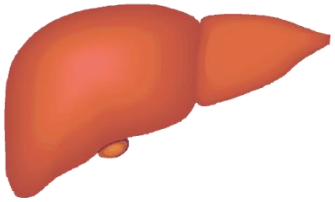

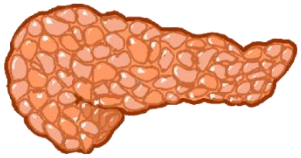

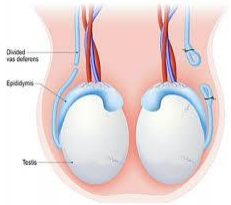

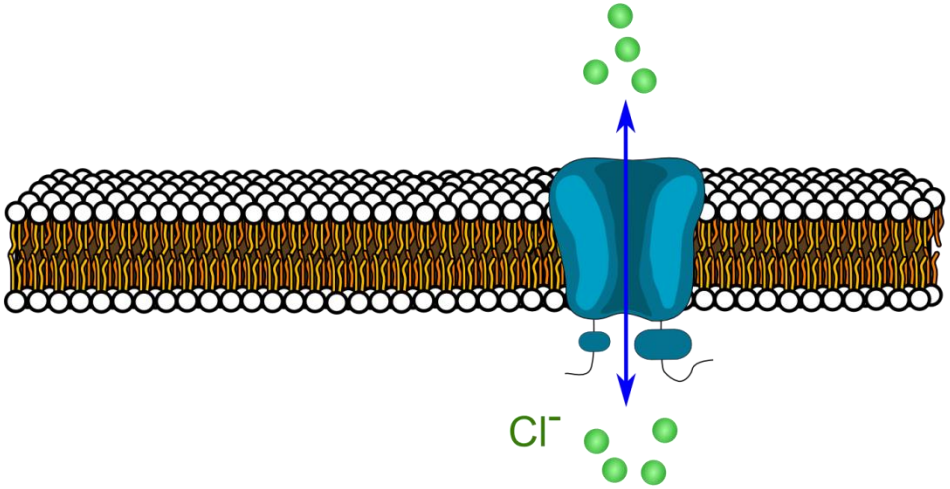


CFTR

# CFTR Channel-Defective

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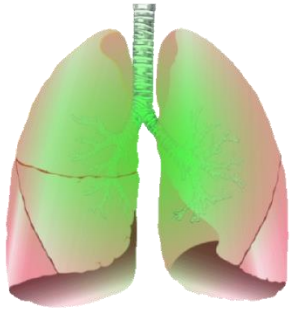
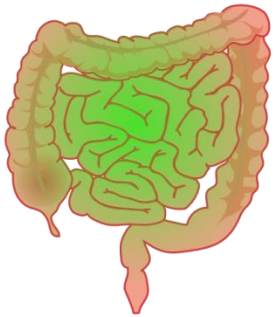
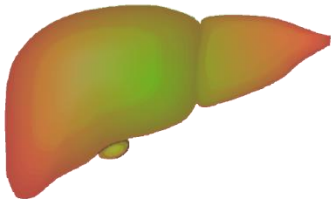
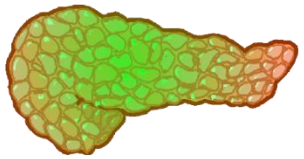
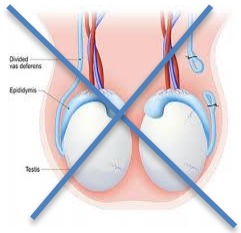


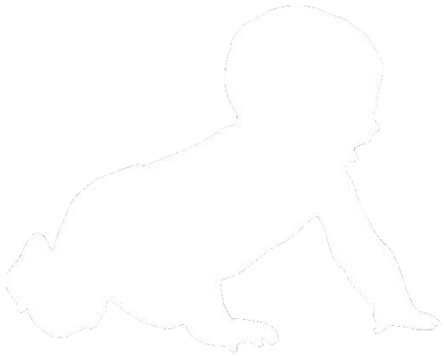


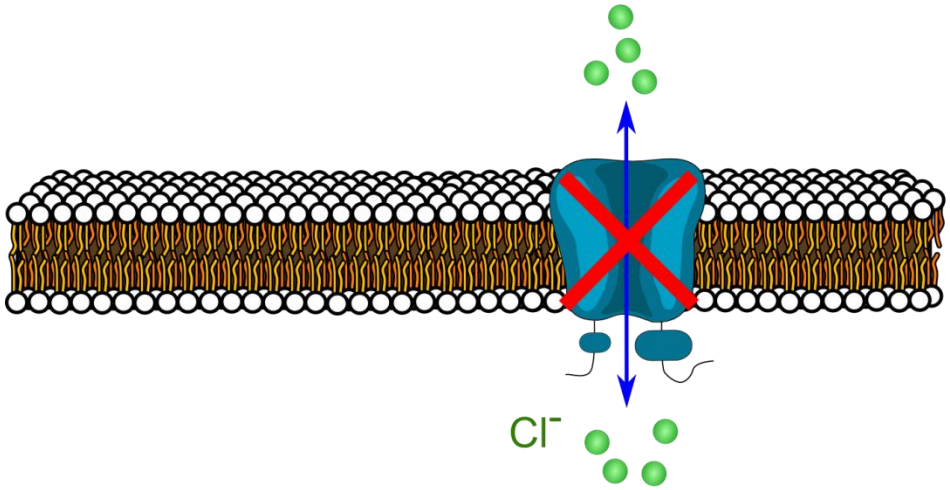






cystic fibrosis






CFTR

# Cystic Fibrosis

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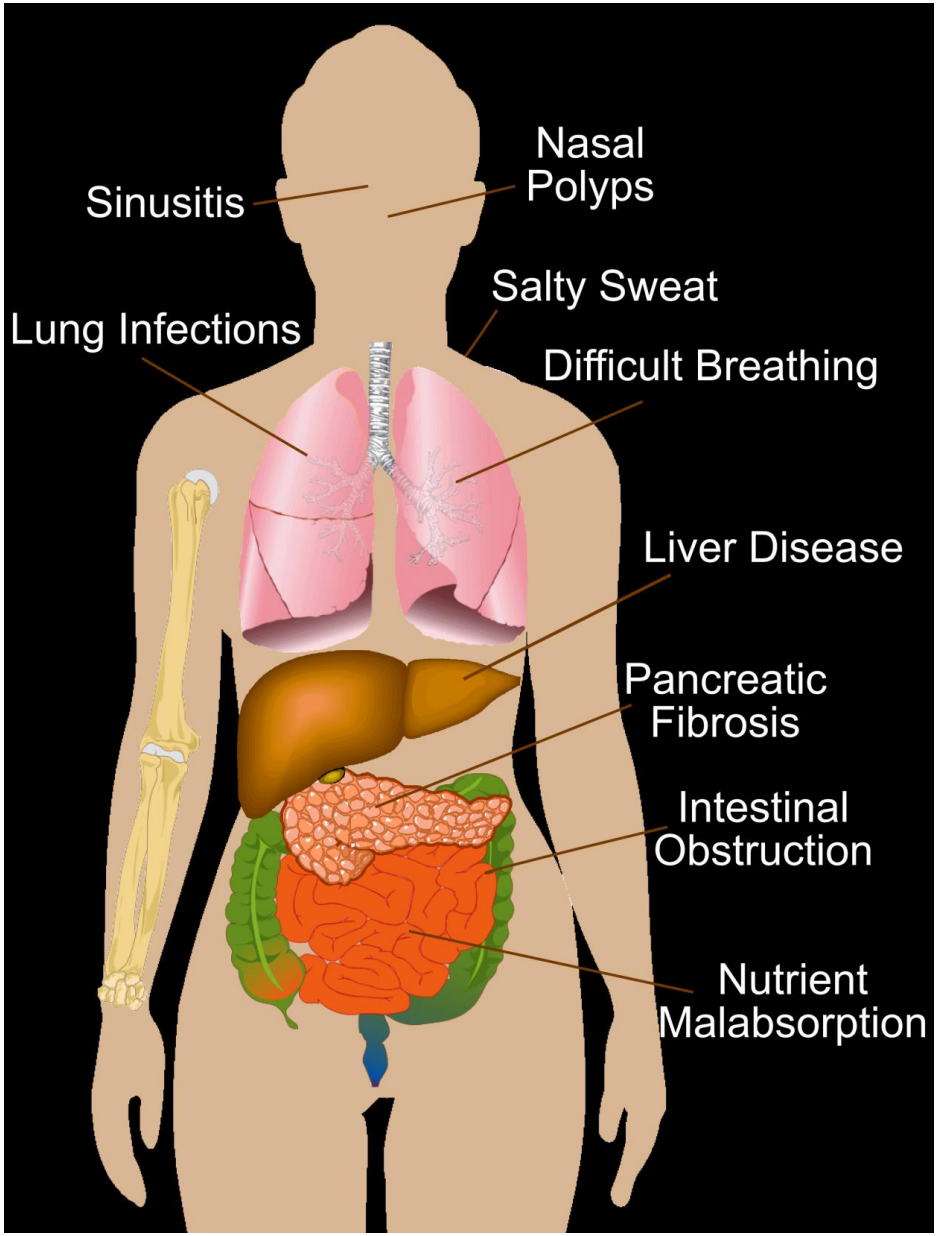

# Pancreas and Lungs in CF

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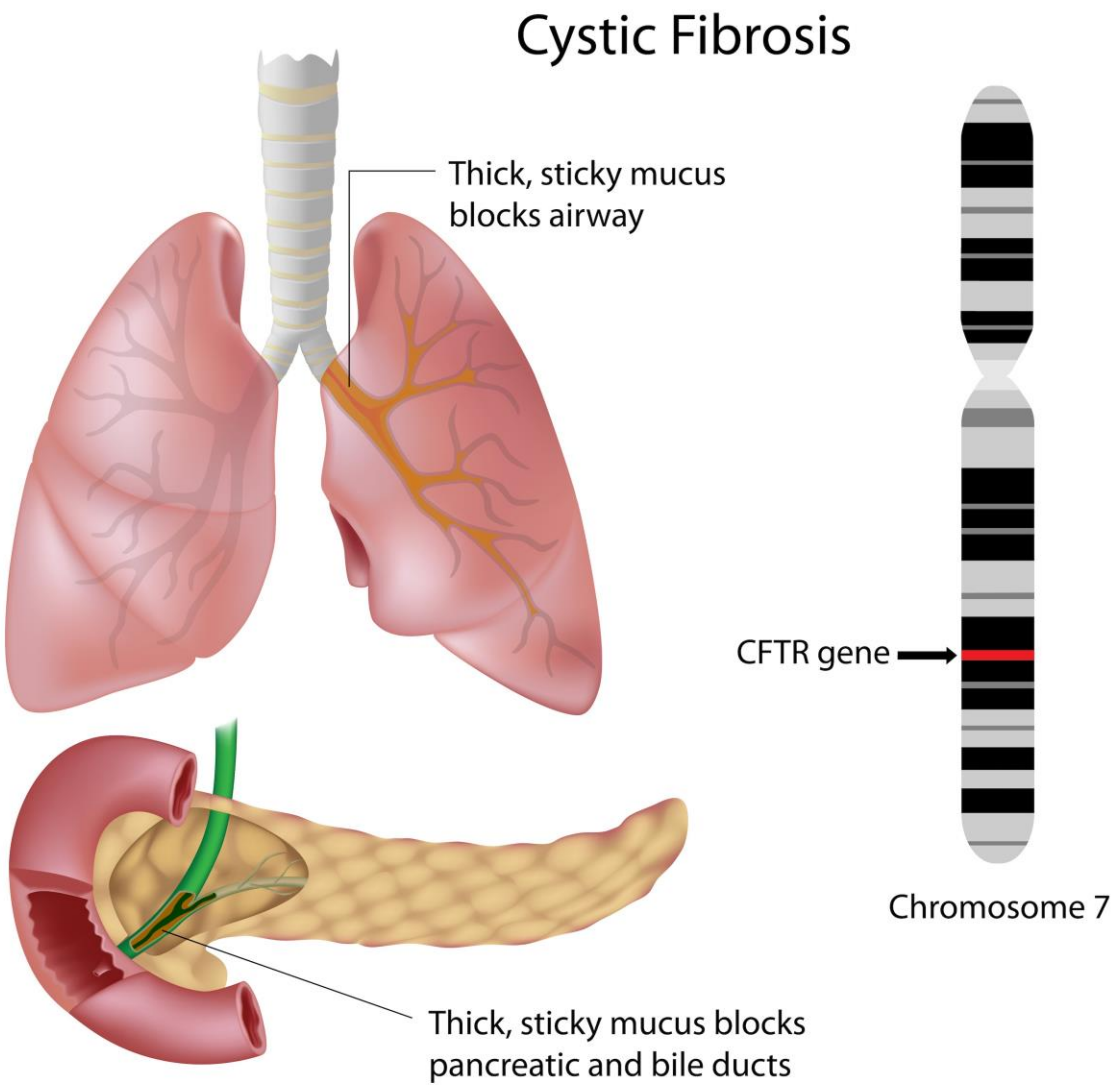


- Early exocrine pancreatic insufficiency in majority; increased risk for ARP in pancreatic sufficient CF
- CF-related diabetes increases as patients age; adds to morbidity and mortality

# CF-Causing Mutations

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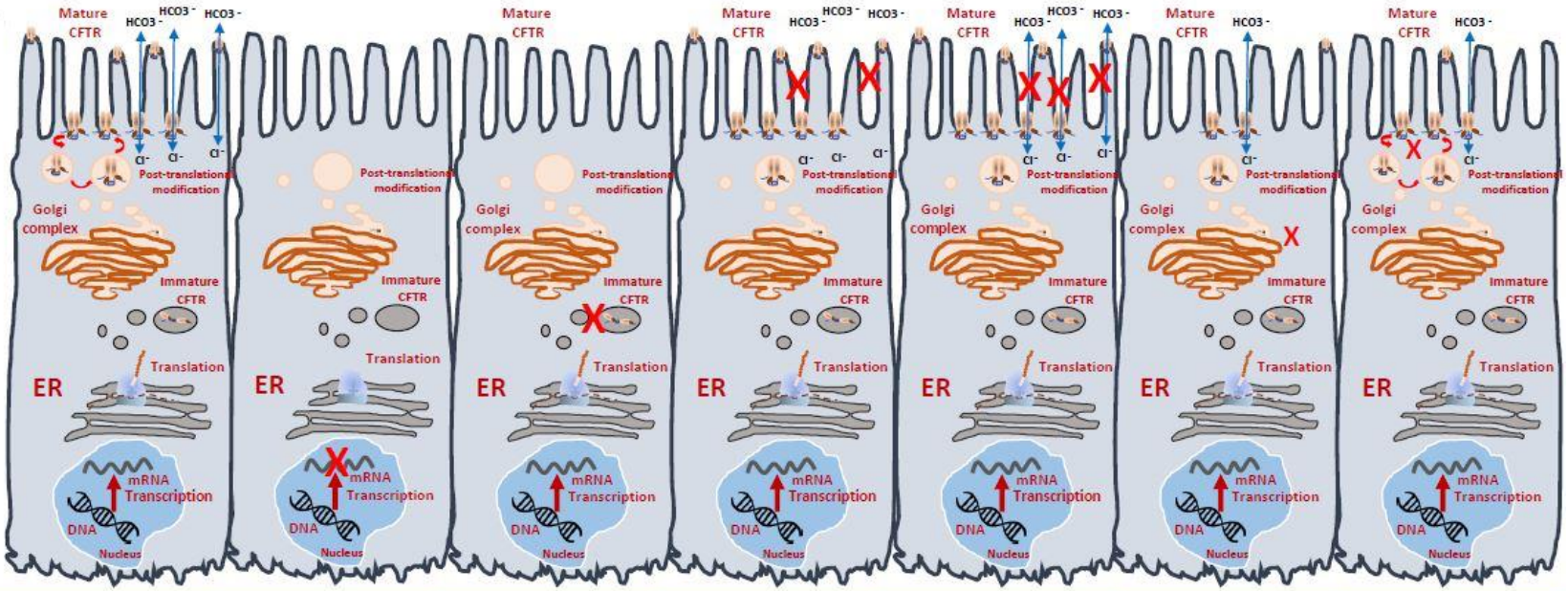
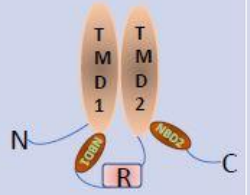
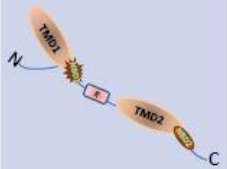
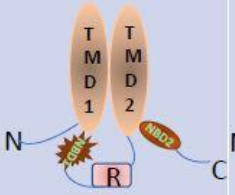
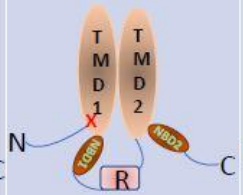
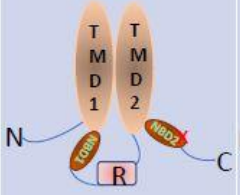
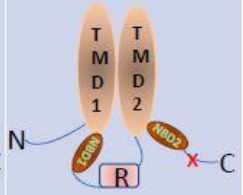



| WT | I | II | III | IV | V | VI |
|---|---|---|---|---|---|---|
|  | No CFTR biosynthesis |  |  |  |  |  |
| **Mutations** | G542X | ΔF508 | G551D | R117H | 3849+10kbC-T<br>A455E | Q1412X |
| **Pancreas** | PI | PI | PI | PS/PI | PS | PI |
| **Phenotype** | No synthesis | Trafficking/ Processing | Defective activation/ Reduced gating | Decreased conductance | Reduced protein synthesis | Rapid turnover of the CFTR channel |

# Testing for CF

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- Newborn screening
- Sweat test-**Gold standard
  - <29 mmol/L—Normal
  - 30-59 mmol/L—Borderline or Intermediate
  - > 60 mmol/L—Abnormal
- NPD
- Beta-adrenergic sweat test

# Diagnosis of CF

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| DIAGNOSTIC DEFINITIONS | |
|---|---|
| **Cystic Fibrosis** | CF is diagnosed when an individual has both a clinical presentation of the disease and evidence of CFTR dysfunction. |
| **Cystic Fibrosis Related Metabolic Syndrome (CRMS)/ Cystic Fibrosis Screen Positive, Inconclusive Diagnosis (CFSPID)** | Definitions for CRMS and CFSPID have been combined. CRMS/CFSPID applies to **infants** who have a **positive NBS** test for CF<br>AND either:<br>• A sweat chloride value <30 mmol/L and 2 CFTR mutations, at least 1 of which has unclear phenotypic consequences<br>OR<br>• An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations |
| **CFTR - Related Disorder** | A monosymptomatic clinical entity associated with CFTR dysfunction that does not fulfill the diagnostic criteria for CF |

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# Diagnosis of CF

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| SWEAT CHLORIDE RANGES | | |
|---|---|---|
| **Diagnosis** | **≥ 60mmol/L** | A positive newborn screen, clinical features consistent with CF, or a positive family history |
| **Intermediate Range** | **30-59mmol/L** | A positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range on two separate occasions may have CF. They should be considered for extended CFTR gene analysis and/or CFTR functional analysis. |
| **Unlikely** | **≤ 29mmol/L** | A positive newborn screen, and a sweat chloride of less than 30mmol/L indicates that CF is unlikely.<br><br>Clinical features that may be consistent with CF, a sweat chloride less than 30mmol/L, indicates that CF is less likely. It may however be considered if evolving clinical criteria and/or CFTR genotyping support CF and not an alternative diagnosis. |

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# CFTR-RD



- Do not fit diagnostic criteria for CF (only monosymptomatic presentation such as ARP)
- Sweat Cl results are intermediate
- Genetic testing determines unknown *CFTR* mutations or *CFTR* genotype that is undefined (CFTR2 database)

# Take home points

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- Patients with CF may present with recurrent pancreatitis
- Include Sweat Cl in work-up
- Look for other symptoms of CFTR dysfunction
- If diagnosed with CF, patients need to be followed by CF center

# Remaining Questions

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- Are CFTR Mutations (non-CF causing) contributing to disease?
  - Impact on disease onset and progression
  - Interplay with other gene mutations and environmental factors to influence disease phenotype
- Would patients with CFTR-RD be candidates for CFTR modulator therapies?