Cystic Fibrosis Insights

Objectives

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

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1. To recognize that defective CFTR is the underlying cause of CF
2. To relate the CFTR defect to the systemic, multi-organ clinical manifestations in CF
3. To review clinical outcomes related to morbidity and mortality in CF

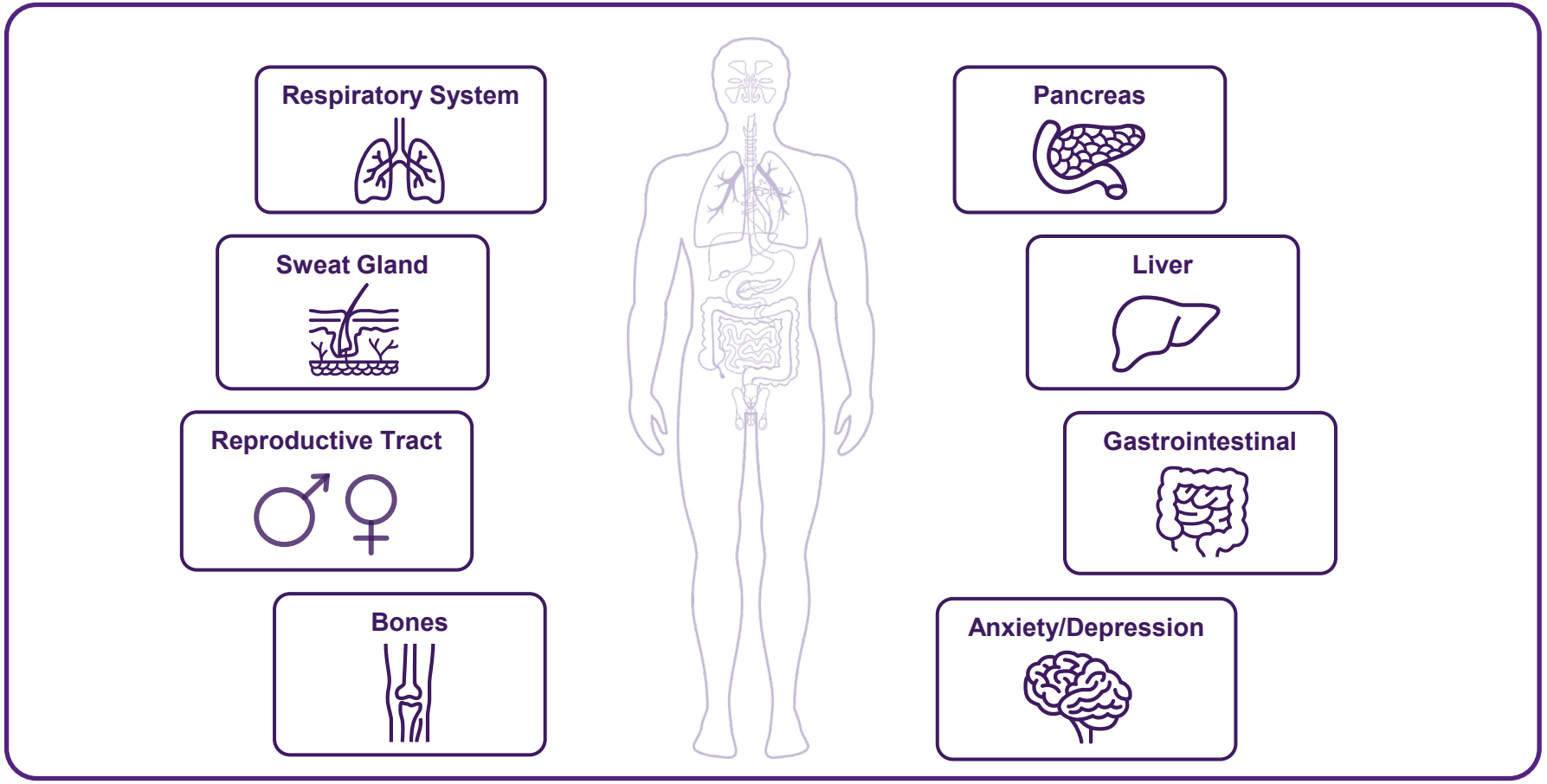
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

CF Overview and Epidemiology

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

CF Is a Life-Shortening Disease With Clinical Manifestations Throughout the Body[1–3]

- Median predicted survival age for people with CF in Canada born between 2017 and 2021 was 57.3 years[1]
- Median age at death for those who died in 2021 was 38.7 years[1]

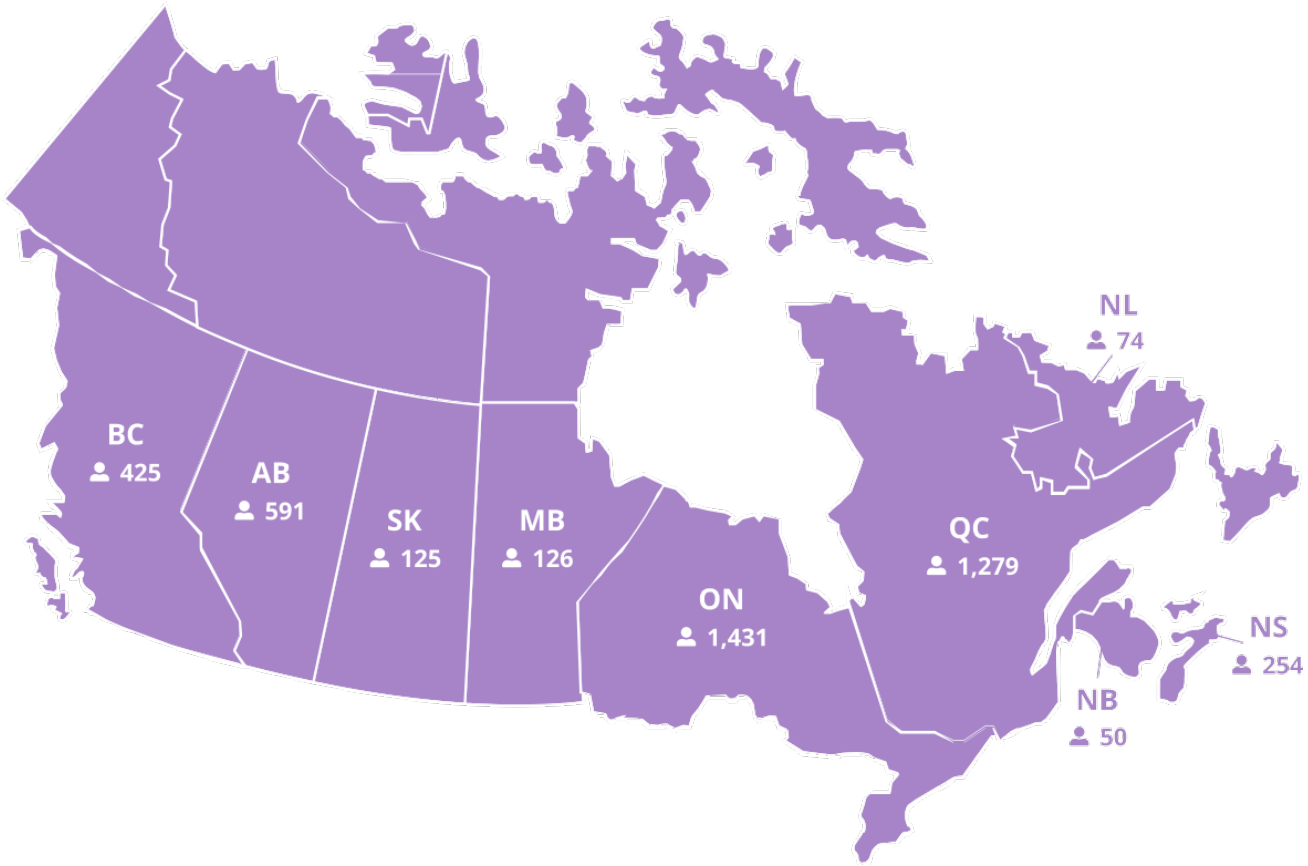


CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023
2. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. 3. Shteinberg M, et al. *Lancet*. 2021;397:2195-2211.

Number of People With CF by Canadian Provinces

4,338 people with CF are included in the 2021 Canadian CF Patient Registry



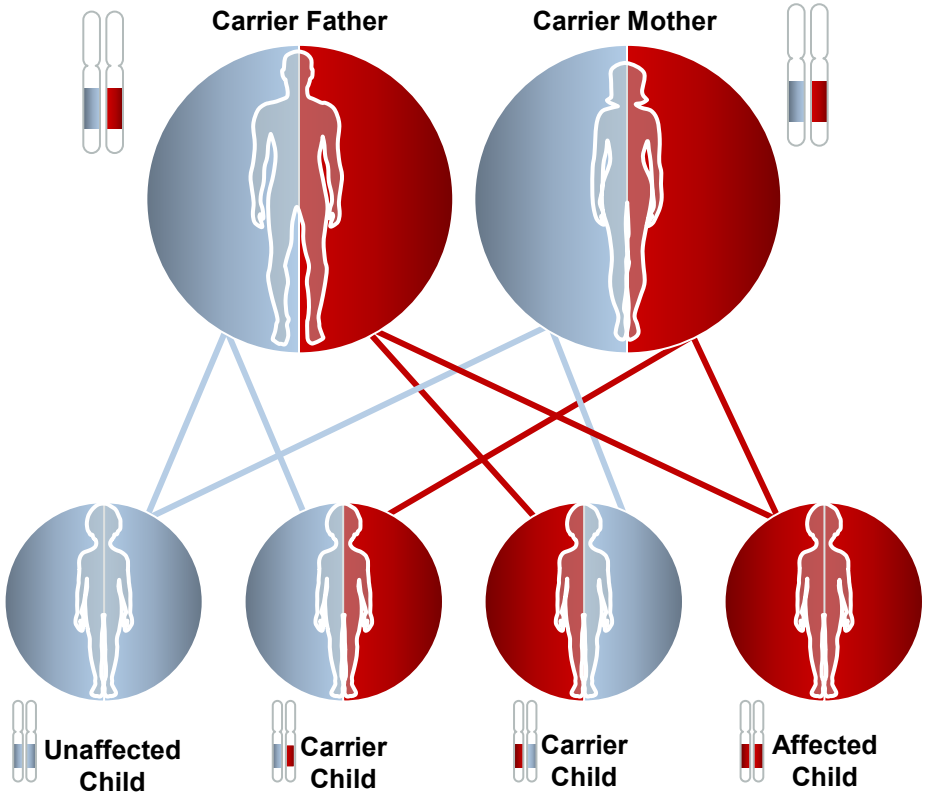
CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator

Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Genetics and Role of Defective CFTR in CF

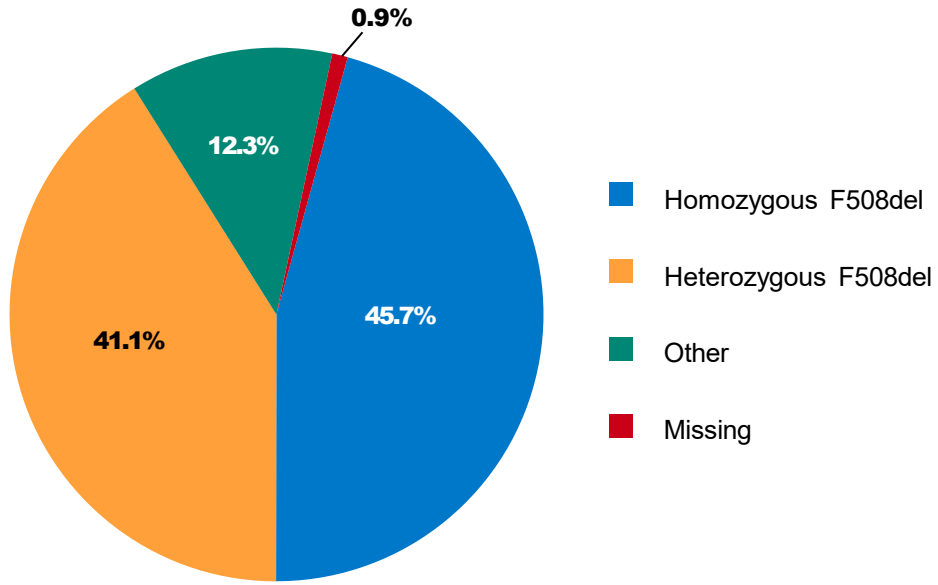
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

CF Has an Autosomal Recessive Inheritance Pattern



Both copies of the *CFTR* gene must carry a disease-causing mutation for CF to be the outcome

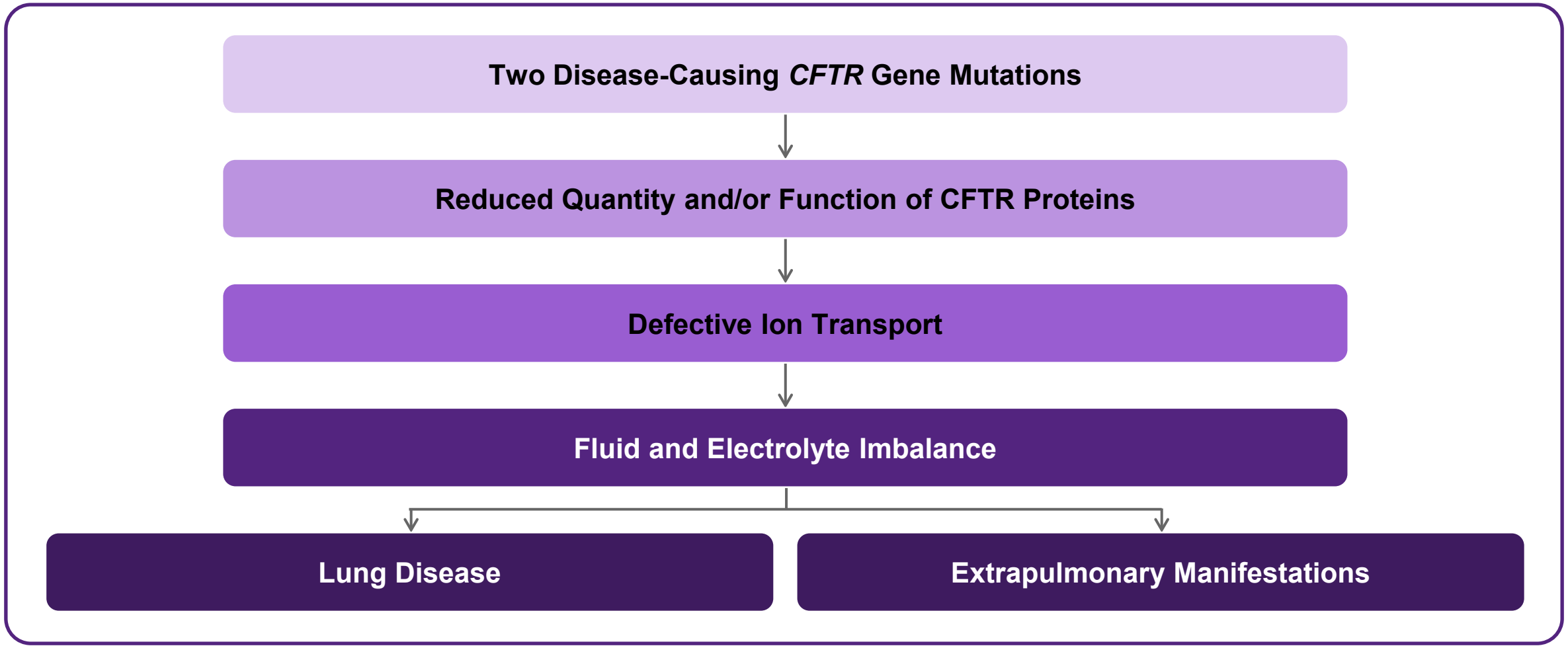
Distribution of Genotypes in Canada, 2021. [N = 4,338][2]



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. National Institutes of Health. Cystic Fibrosis. https://medlineplus.gov/genetics/condition/cystic-fibrosis/#inheritance. Accessed March 2023. 2. Image adapted from Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Pathophysiological Cascade of CF[1,2]



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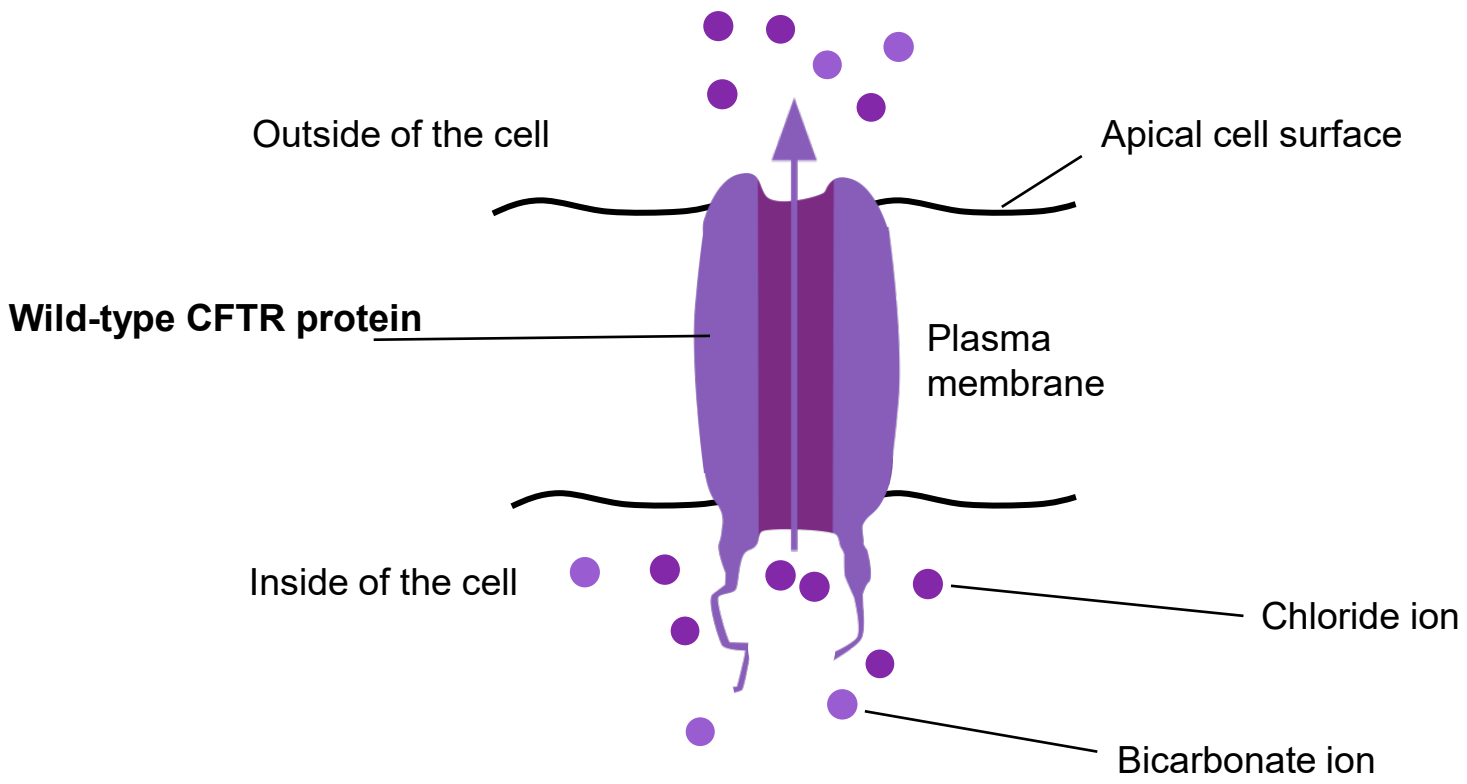
1. Ratjen FA. *Respir Care*. 2009;54(5):595-605. 2. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904.

CFTR Protein Functions at the Epithelial Cell Surface as an Ion Channel

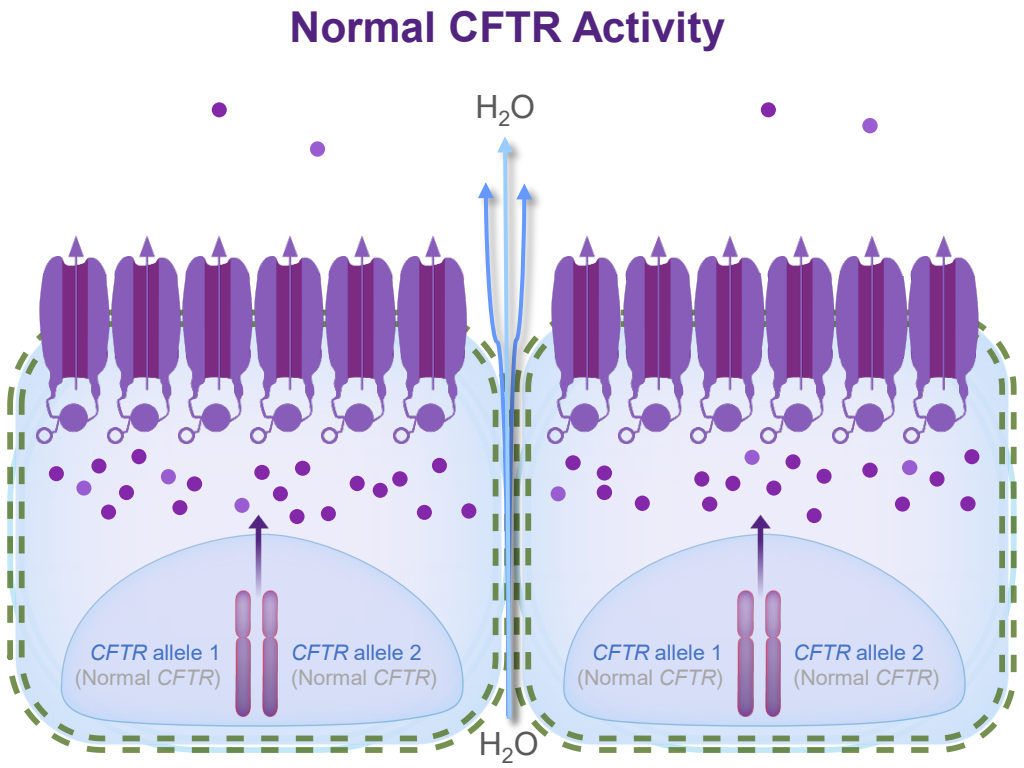


The CFTR protein functions at the apical surface of epithelial cells as a channel primarily mediating the appropriate movement of chloride and bicarbonate ions into and out of the cell

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Derichs N. *Eur Respir Rev*. 2013;22(127):58-65.

Total CFTR Activity Is Determined by Quantity and Function of CFTR at the Cell Surface



- CFTR-mediated ion transport helps maintain appropriate water and salt balance[1]
- Maintaining water and salt balance requires both adequate **quantity** and **function** of CFTR proteins at the cell surface[1,2]

CFTR Quantity X **CFTR Function** = **Total CFTR Activity**[3]

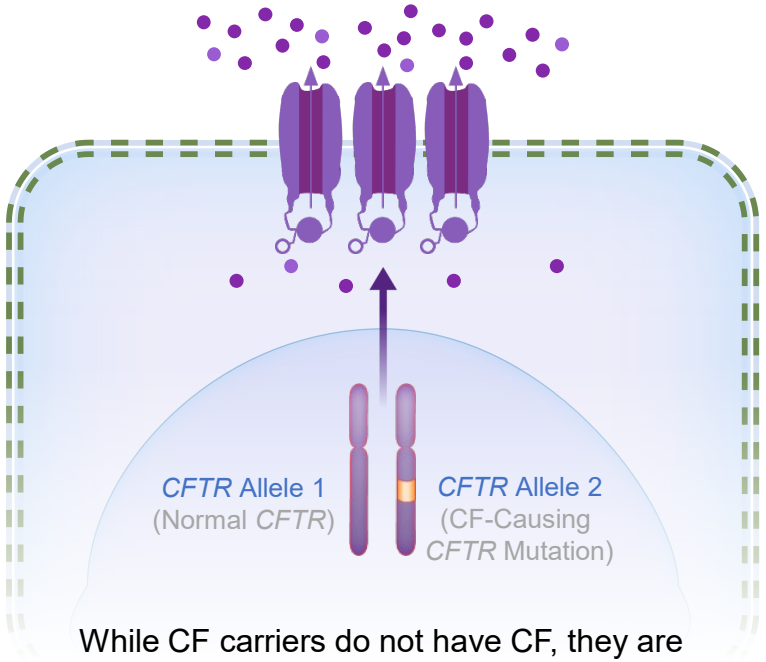
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. MacDonald KD, et al. *Paediatr Drugs*. 2007;9(1):1-10. 2. Derichs N. *Eur Respir Rev*. 2013;22(127):58-65. 3. Clancy JP. *Pediatr Pulmonol*. 2018;53(S3):S4-S11.

CF Results From Insufficient CFTR Protein Activity

CF Carrier
Normal *CFTR* Allele + *CFTR* Allele Mutation

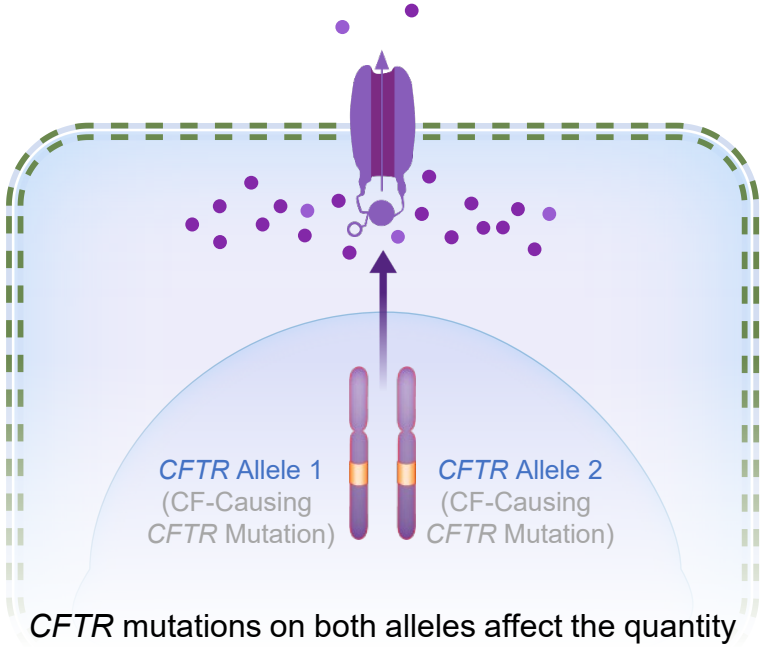
Sufficient CFTR Activity[1]



While CF carriers do not have CF, they are at increased risk for developing CF-related conditions in multiple organ systems[1–3]

CF Disease
CFTR Allele Mutation + *CFTR* Allele Mutation

Insufficient CFTR Activity[4]

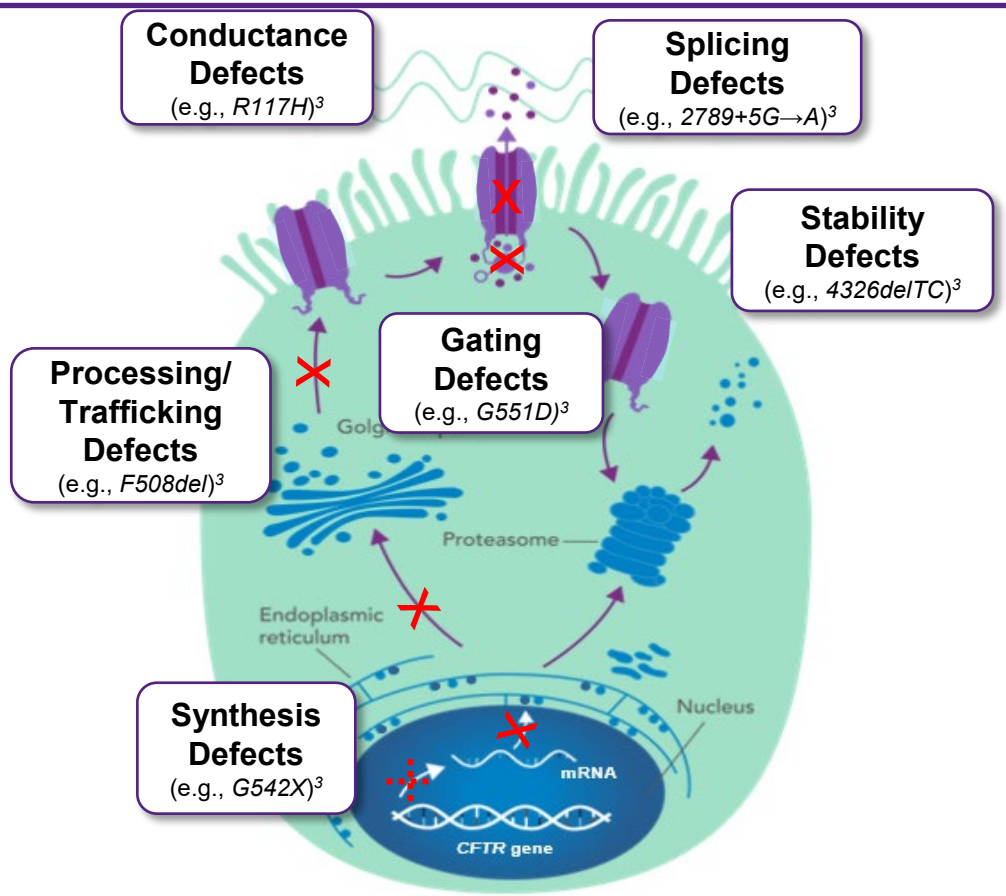


CFTR mutations on both alleles affect the quantity and/or function of the CFTR protein resulting in insufficient total CFTR activity[4–6]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Claustres M. *Reprod Biomed Online*. 2005;10(1):14-41. 2. Miller AC, et al. *Proc Natl Acad Sci USA*. 2020;117(3):1621-1627. 3. Çolak Y, et al. *Eur Respir J*. 2020;56(3):2000558.
4. Boyle MP, Boeck KD. *Lancet Respir Med*. 2013;1(2):158-163. 5. Rogan MP, et al. *Chest*. 2011;139(6):1480-1490. 6. Derichs N. *Eur Respir Rev*. 2013;22(127):58-65.

CFTR Protein Defects Can Reduce Total CFTR Activity Resulting in CF Disease[1–3]



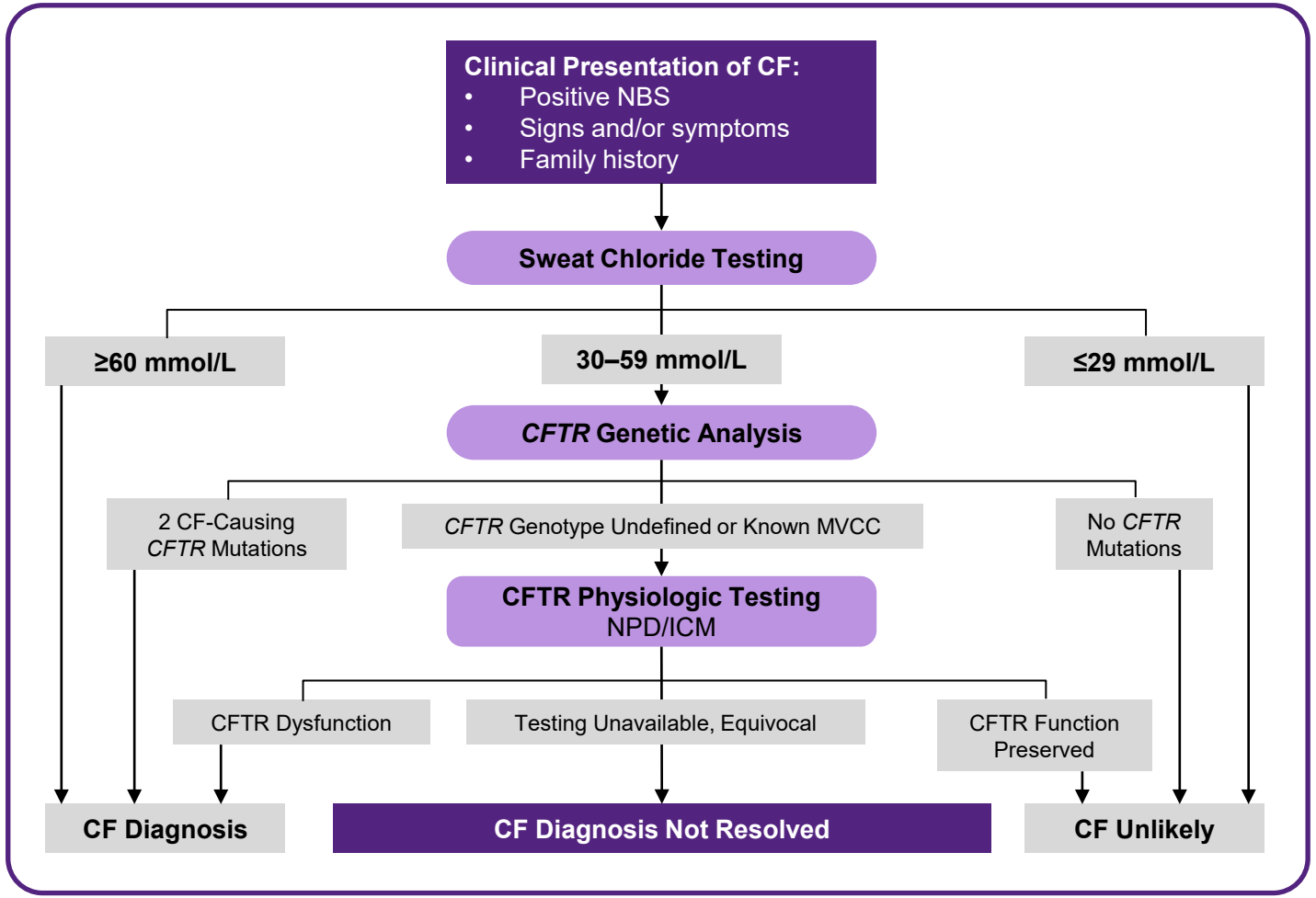
- Some CFTR protein defects result in little to no total CFTR activity[1]
- Other CFTR protein defects result in some CFTR activity[1]
- A single *CFTR* mutation can result in multiple defects in the CFTR protein[2]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Derichs N. *Eur Respir Rev*. 2013;22(127):58-65. 2. Ratjen F, et al. *Nat Rev Dis Primers*. 2015;1:15010. 3. Boyle MP, Boeck KD. *Lancet Respir Med*. 2013;1(2):158-163.

Diagnosis of CF

- Early diagnosis through newborn screening (NBS) enables early access to care and facilitates better outcomes[1]
- In 2021, NBS detected:
  - **68.4%** of all new diagnoses[1]
  - **60.5%** were diagnosed before the age of one[1]
- Upon a positive NBS result, the diagnosis of CF is primarily based on demonstration of abnormal CFTR function by measurement of sweat chloride concentration[2]



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ICM, intestinal current measurement; MVCC, mutations of varying clinical consequence; NPD, nasal potential difference.

1. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023.. 2. Farrell PM, et al. *J Pediatr*. 2017;181S:S4-S15.e1.

Clinical Phenotype Is Influenced by Multiple Factors

CFTR Genotype and the Resulting Amount of Total CFTR Activity[1,2]

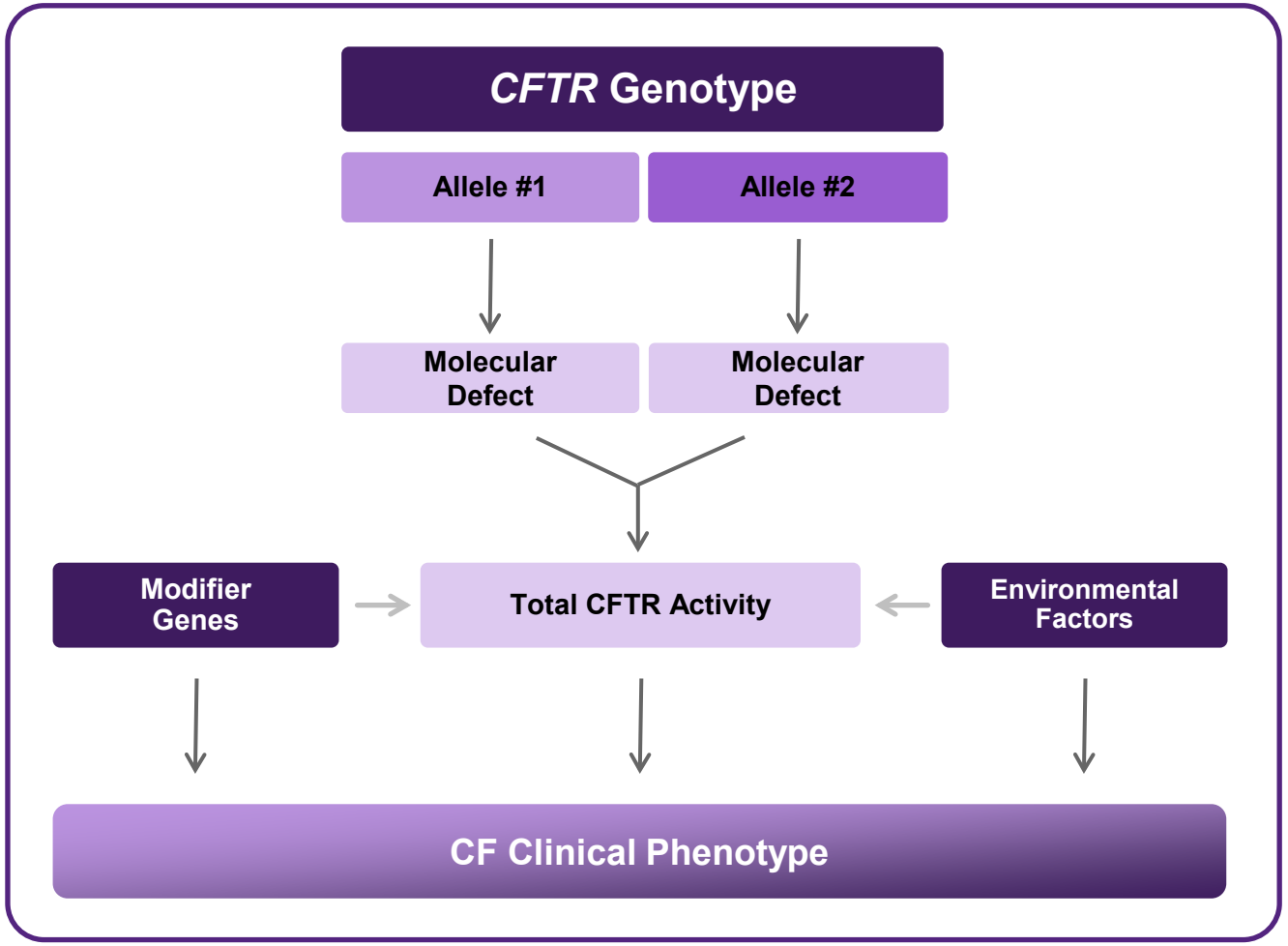
- The amount of CFTR activity resulting from mutations on both alleles will impact the overall CF clinical phenotype
- The presence of a complex allele (more than 1 *CFTR* mutation in a single allele) may also contribute to reduction in CFTR activity

Modifier Genes[2,3]

- Many modifier genes have been identified that affect the function of various organs and have an impact on CF disease manifestations

Environmental Factors[4]

- Exposure to cigarette smoke and other toxins, pulmonary bacterial colonization, and infection may affect phenotype and other outcomes



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1. Rogan MP et al. *Chest*. 2011;139(6):1480-1490. 2. Castellani C, et al. *J Cyst Fibros*. 2008;7(3):179-196. 3. Cutting GR, et al. *Nat Rev Genet*. 2015;16(1):45-56. 4. Cutting GR. *Annu Rev Genomics Hum Genet*. 2005;6:237-260.

Symptoms of CF Can Begin at an Early Age and Lead to Increasingly Complicated Disease*

Infancy

- Meconium Ileus (up to 20%)[1]
- Pancreatic Insufficiency (85%)[1]
- Lung Infection[2]
- Lung Structural Changes (e.g., bronchiectasis)[3]

Childhood/ Adolescence

- Chronic Lung Infection[2]
- Lung Structural Changes (increasing prevalence with age)[3]
- Sinus Disease (~19%)[2]
- CF-Related Diabetes (~5%)[2]
- CF-Related Liver Disease[2,4]
- Gastroesophageal Reflux Disease (~30%)[2]
- Anxiety Disorder (~13%)/Depression (~10%)[2]

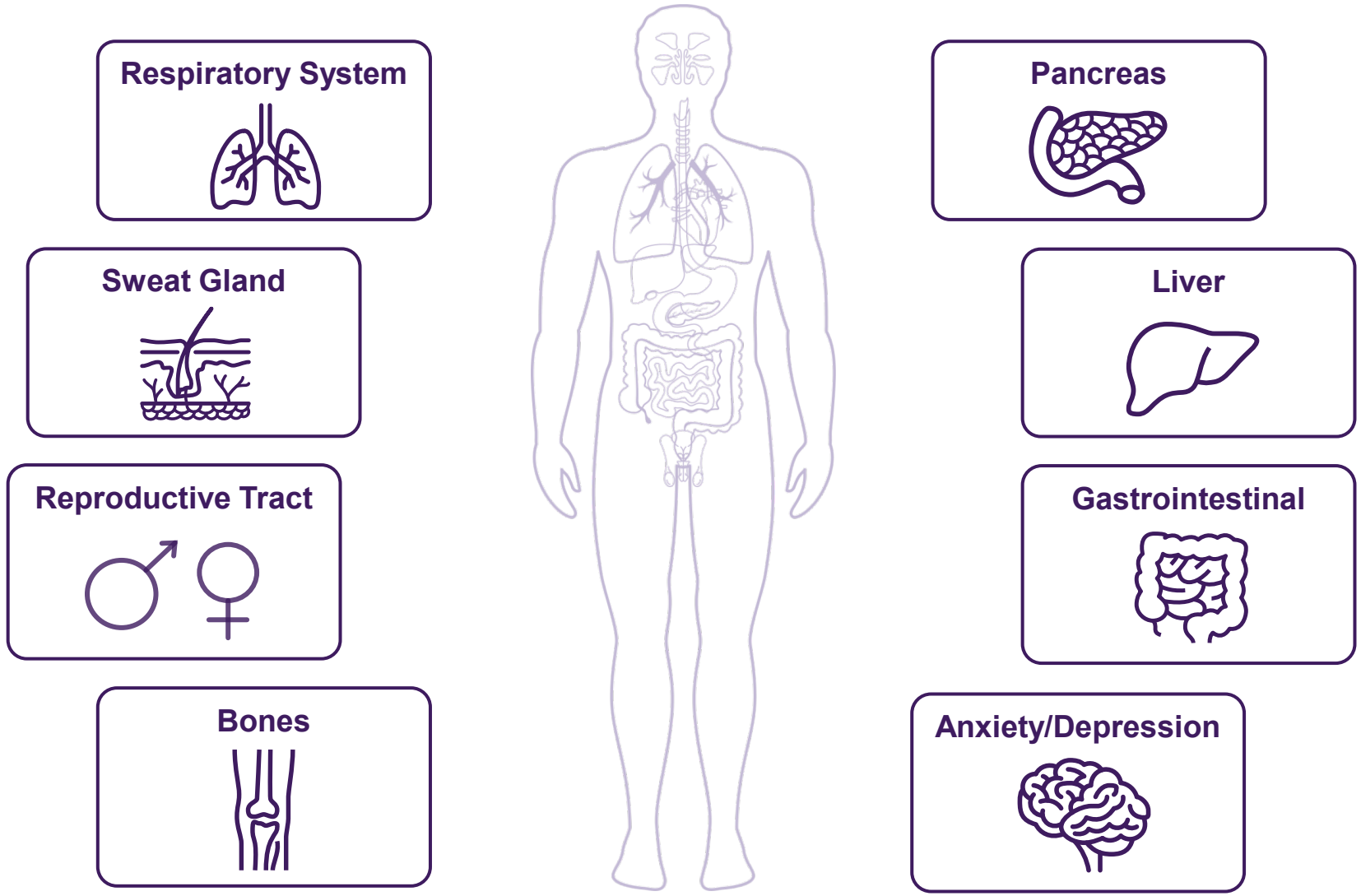
Adulthood

- Chronic Lung Infection[2]
- Lung Structural Changes[5]
- Sinus Disease (~52%)[2]
- CF-Related Diabetes (~29%)[2]
- CF-Related Liver Disease[1]
- Gastroesophageal Reflux Disease (~42%)[2]
- Distal Intestinal Obstructive Syndrome (~2%)[2]
- Osteopenia (18%)[2]
- Anxiety Disorder (~28%)/Depression (~30%)[2]
- Infertility[6]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.
*Information from US sources referenced below

1. Slae M, Wilschanski M. *Frontline Gastroenterol*. 2021;21(7):622-628. 2. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023. 3. Stick SM, et al. *J Pediatr*. 2009;155(5):623-628. 4. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29(12):1954-1962. 5. de Jong PA, et al. *Thorax*. 2006;61(1):80-85. 6. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904.

Clinical Manifestations of CF



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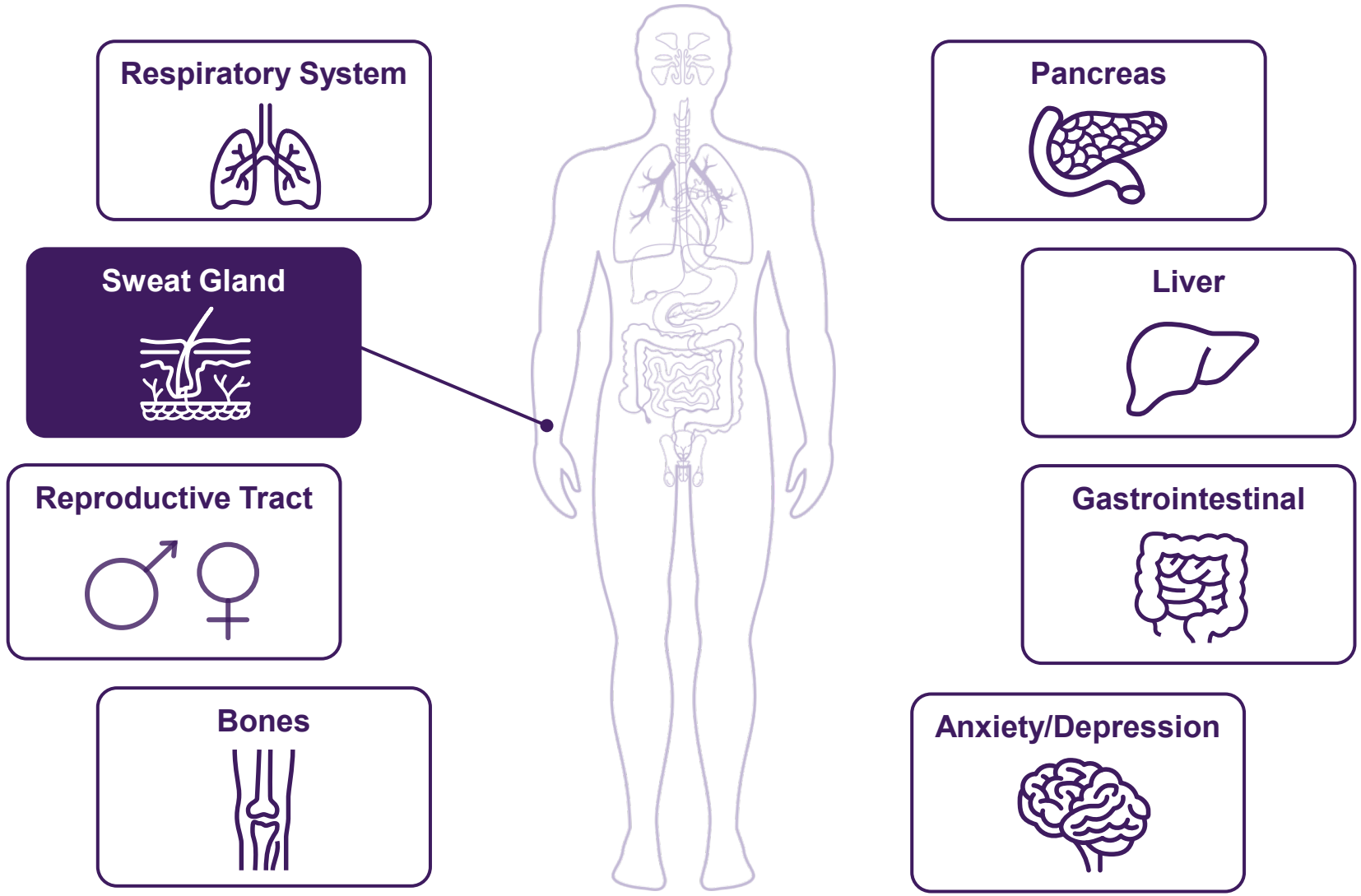
Clinical Manifestations of CF



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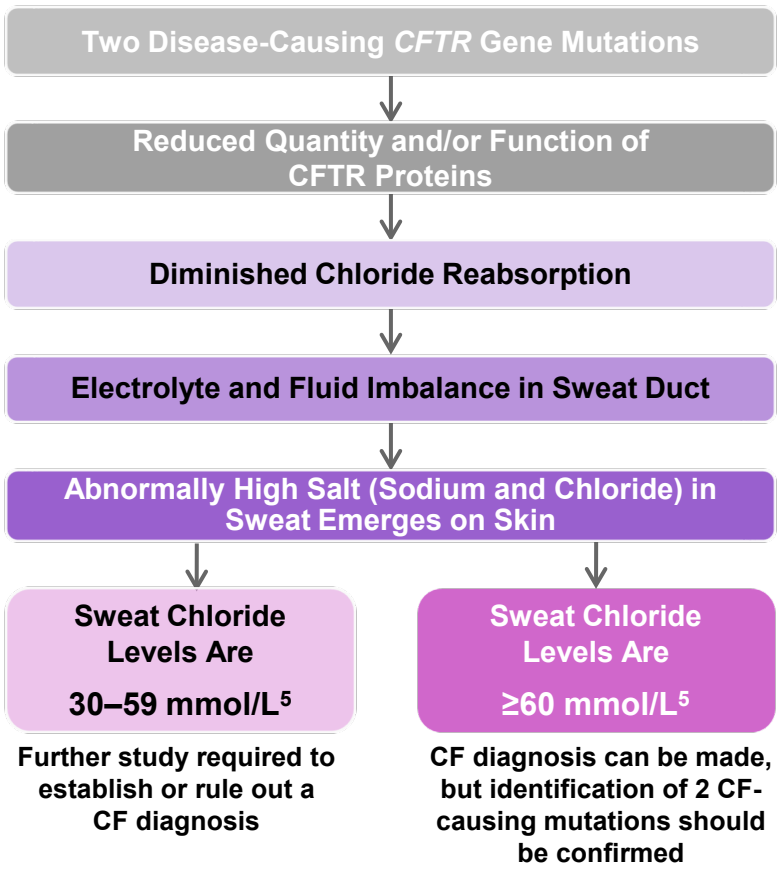
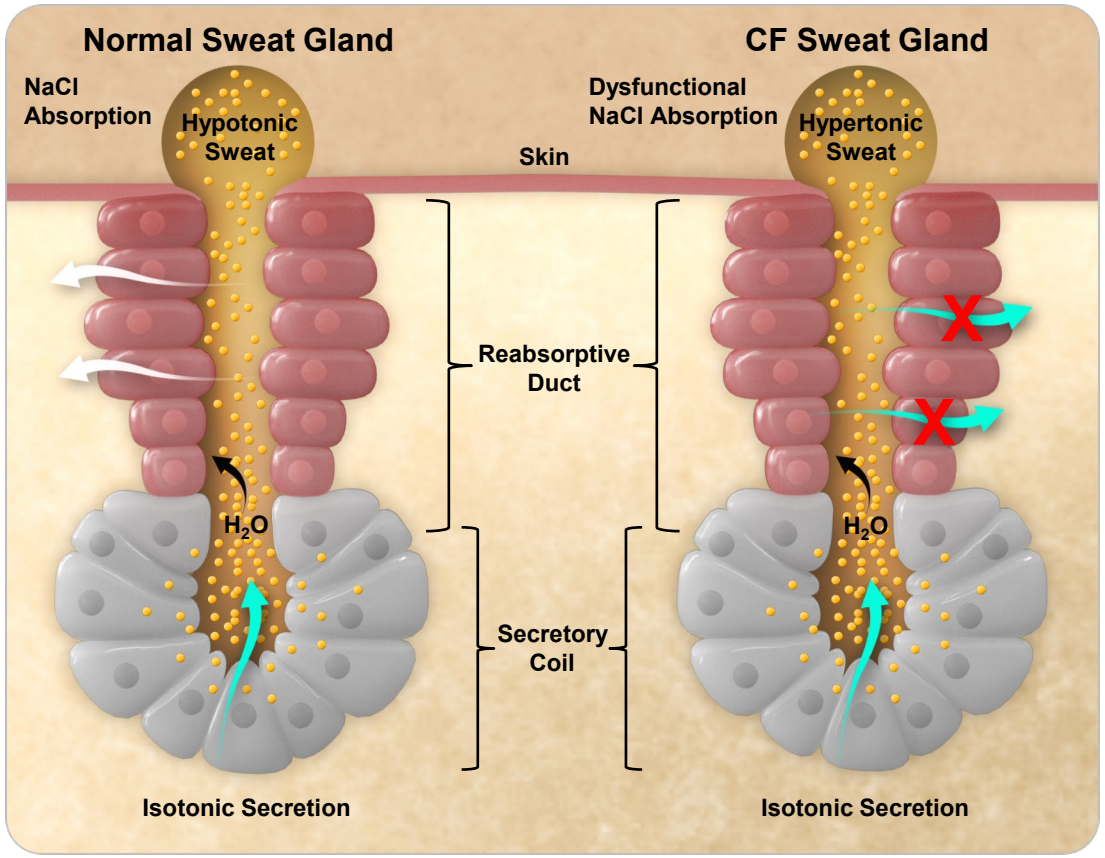
Elevated Sweat Chloride Levels Are a Hallmark of CF Disease and Diagnosis[1–4]

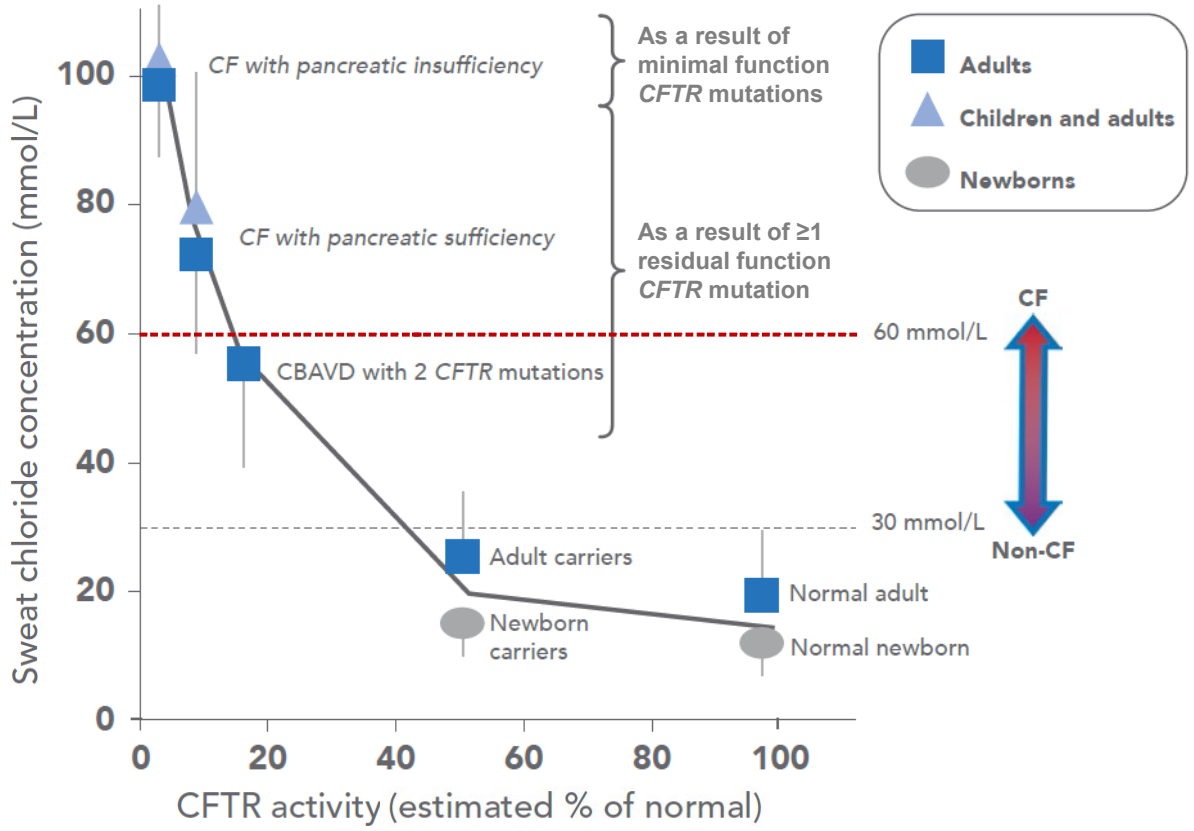




CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

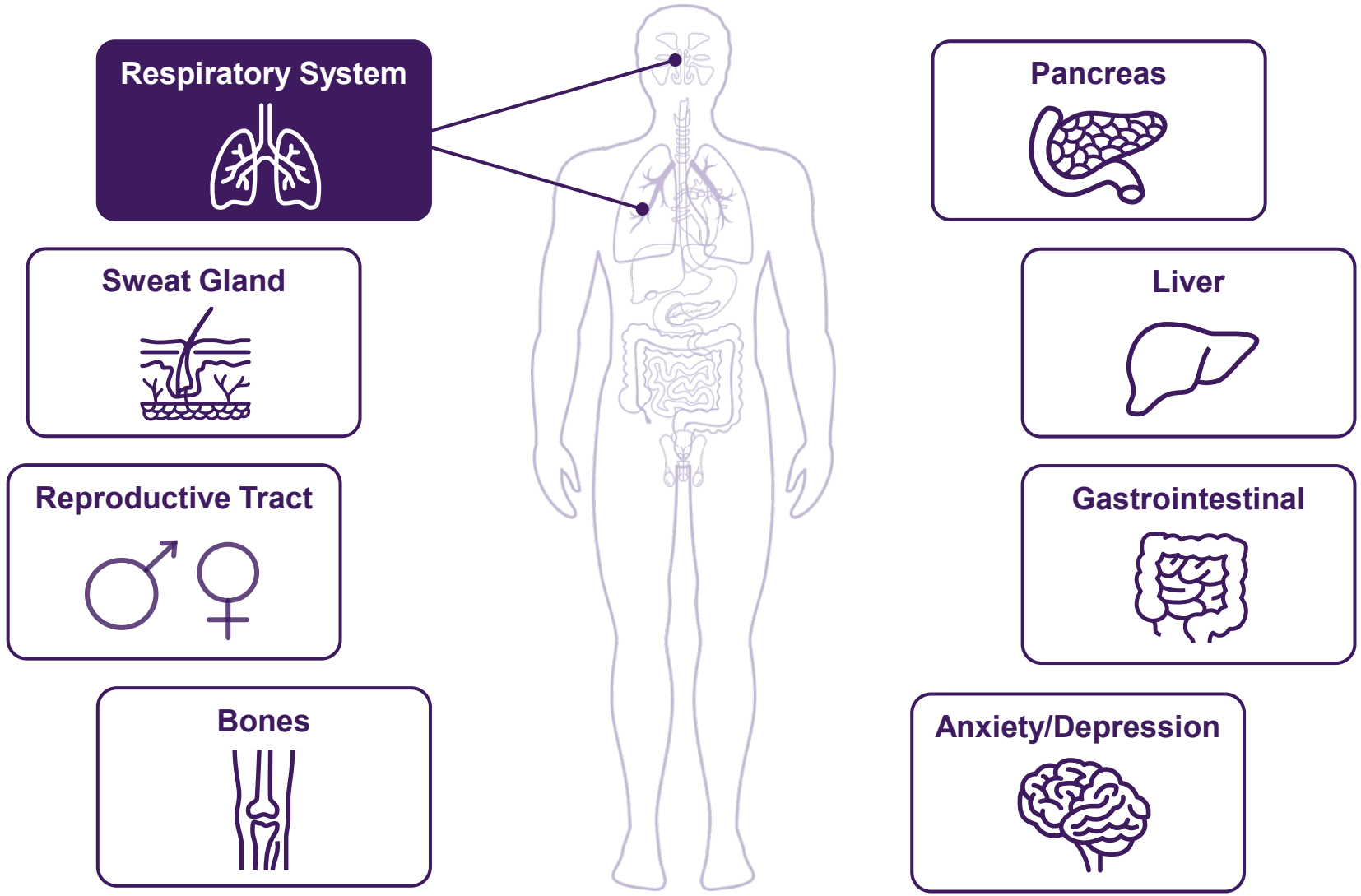
1. Quinton PM. *Acta Physiologica Sinica*. 2007;59:397-415. 2. Rowe SM, et al. *Proc Am Thorac Soc*. 2007;4(4):387-398. 3. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. 4. Derichs N. *Eur Respir Rev*. 2013;22(127):58-65. 5. Farrell PM, et al. *J Pediatr*. 2017;181S:S4-S15.

Sweat Chloride Concentration Is Associated With Clinical Phenotype at the Population Level[1,2]



CBAVD, congenital bilateral absence of the vas deferens; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.
Assumptions: (A) sweat chloride levels are vs. predicted CFTR activity; (B) normal individuals are assumed to have 100% CFTR activity; (C) carriers are assumed to have 50% CFTR activity.
1. Rowe SM, et al. *Proc Am Thorac Soc*. 2007;4(4):387-398. 2. Farrell PM, et al. *J Pediatr*. 2017;181S:S4-S15.

Clinical Manifestations of CF



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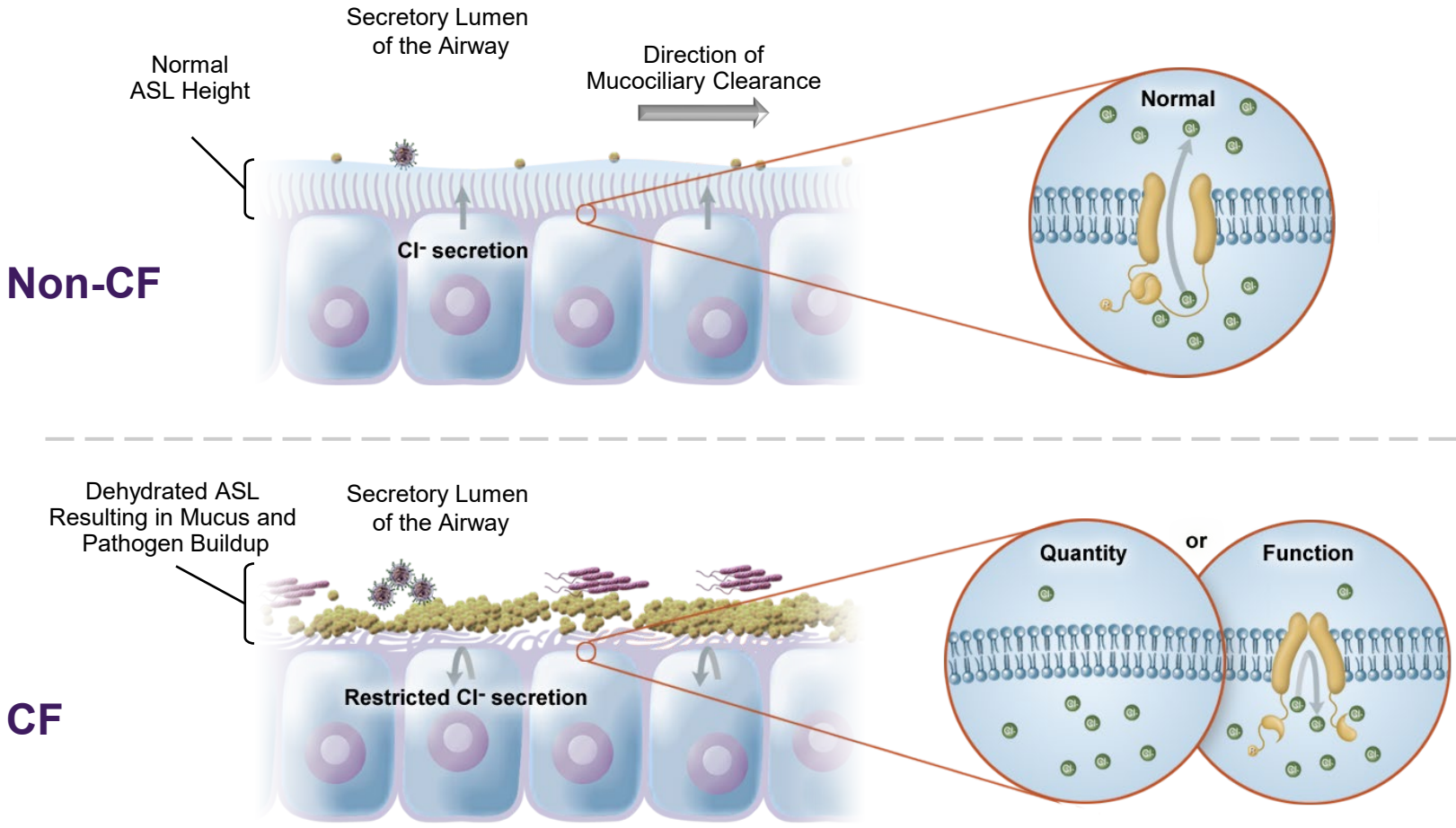
Effect of Decreased Total CFTR Activity on the Airway



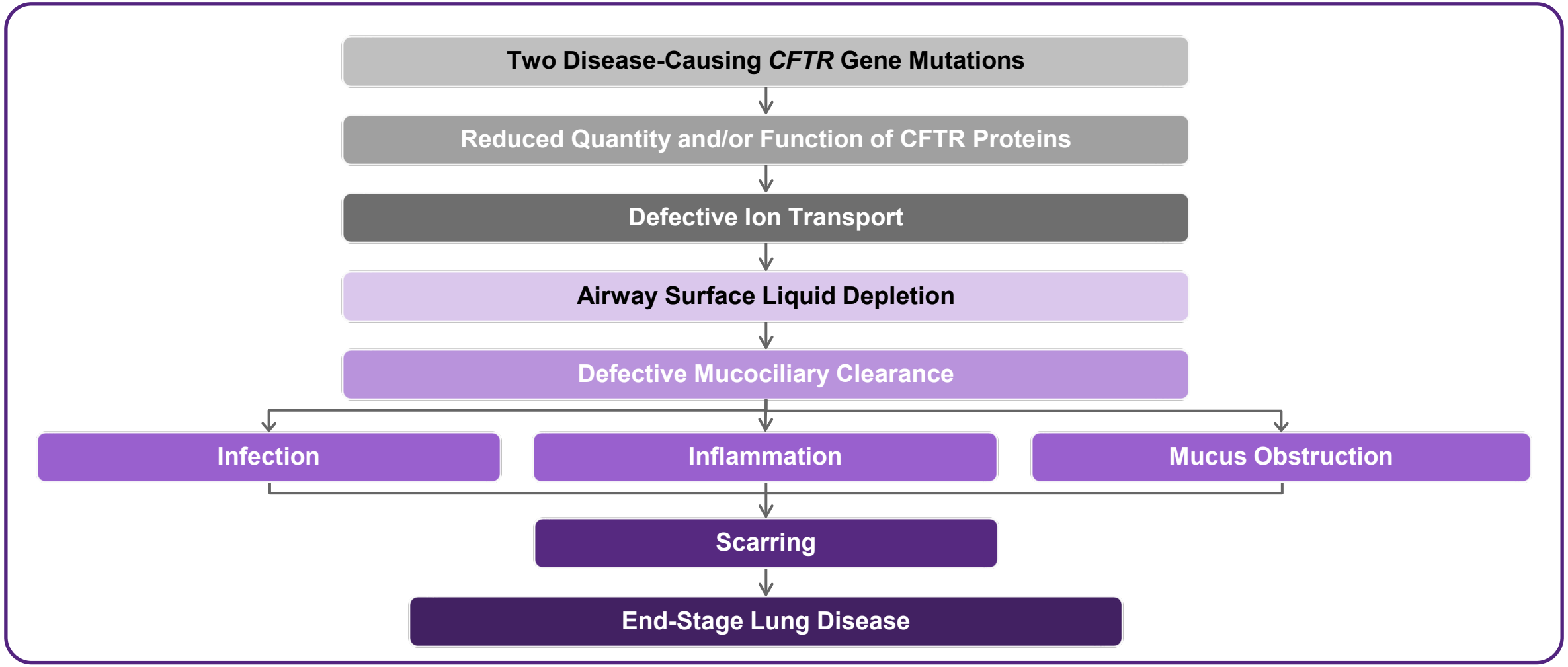
Normal activity of CFTR proteins allows chloride ions to be secreted into the lumen of the airway[1,2]

A much-reduced number of chloride ions are secreted into the lumen of the airway due to defects in the quantity and/or function of CFTR proteins[1,2]

ASL, airway surface liquid; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; Cl^-, chloride.

1. Rowe SM, et al. *N Engl J Med*. 2005;352(19):1992-2001. 2. Proesmans M, et al. *Eur J Pediatr*. 2008;167(8):839-849.

CF Lung Disease Pathophysiological Cascade[1,2]



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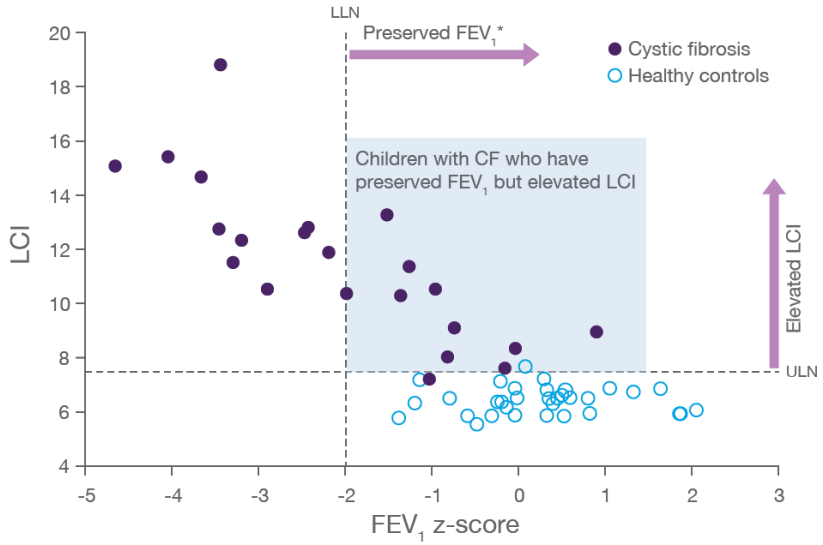
1. Ratjen FA. *Respir Care*. 2009;54(5):595-605. 2. Derichs N. *Eur Respir Rev*. 2013;22(127):58-65.

Early Progressive Lung Disease Can Be Evident Despite Normal FEV_1

- FEV_1 effectively measures disease progression in later-stage lung disease but is relatively insensitive to early localized or small airway obstructions[1–3]
- Evidence of often irreversible structural lung abnormalities can be observed in people with CF prior to decline or changes in FEV_1[3–7]

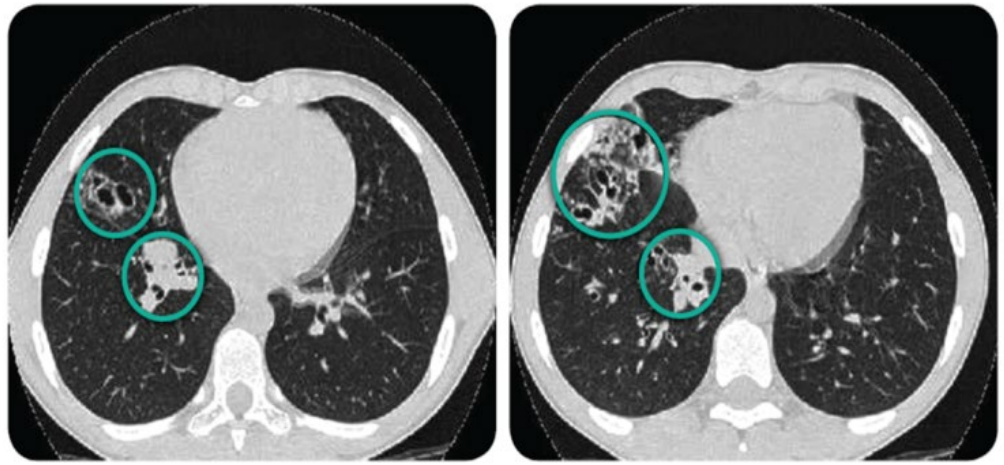
Lung Clearance Index (LCI)



95% (21/22) of children with CF (aged 6–16 years) had an abnormal LCI, while 50% (11/22) had preserved FEV_1[6]

Figure adapted with permission from Aurora P, et al. 2004[6]

Computed Tomography (CT)



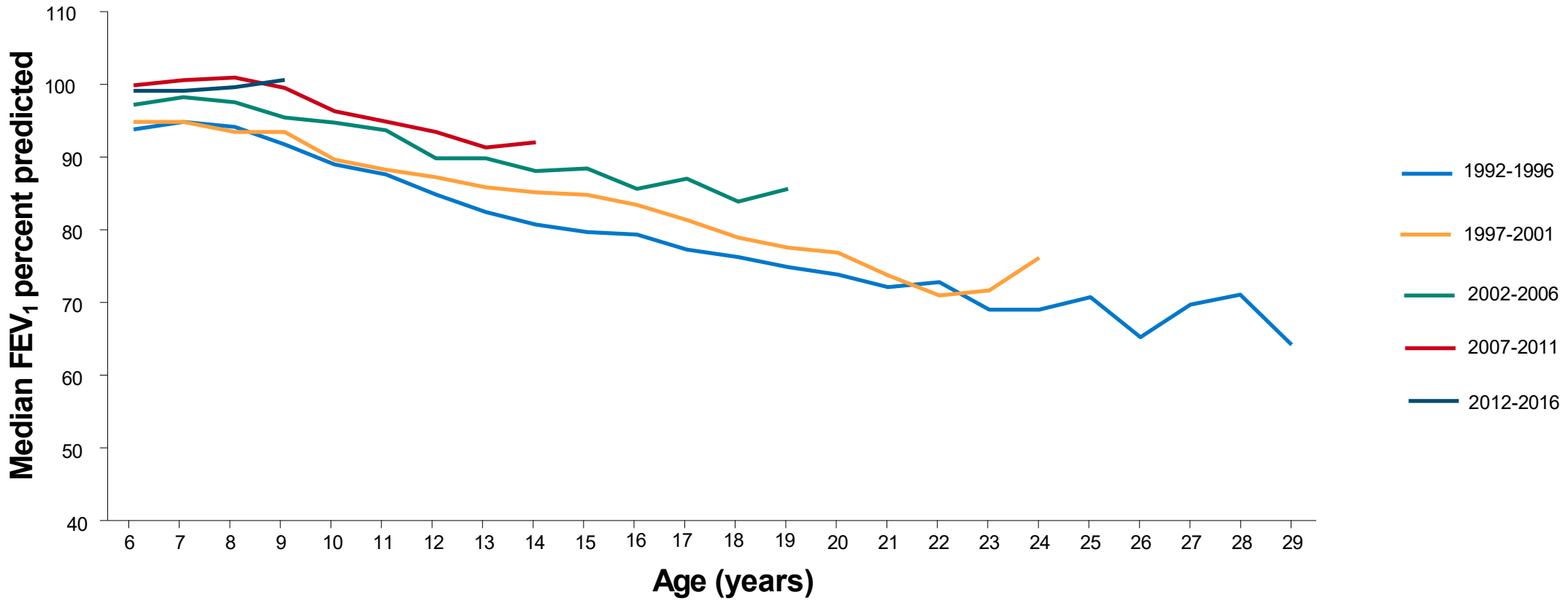
CT of peripheral and focal end-stage lesions in right middle and lower lobes in a 13-year-old person with CF with FEV_1 96% predicted[7]

Images reproduced with permission from de Jong PA, et al. 2004[7]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 second; LLN, lower limit of normal; ULN, upper limit of normal.

1. Tiddens HA. *Pediatr Pulmonol*. 2002;34(3):228-231. 2. Horsley A. *Respir Med*. 2009;103(6):793-799. 3. Gustafsson PM, et al. *Thorax*. 2008;63(2):129-134. 4. Owens CM, et al. *Thorax*. 2011;66(6):481-488.
5. Ellemunter H, et al. *Respir Med*. 2010;104(12):1834-1842. 6. Aurora P, et al. *Thorax*. 2004;59(12):1068-1073. 7. de Jong PA, et al. *Eur Respir J*. 2004;23(1):93-97.

Median ppFEV$_1$ by Age and Birth Cohort[1]



FEV$_1$ level is an independent predictor of the risk for mortality[2]

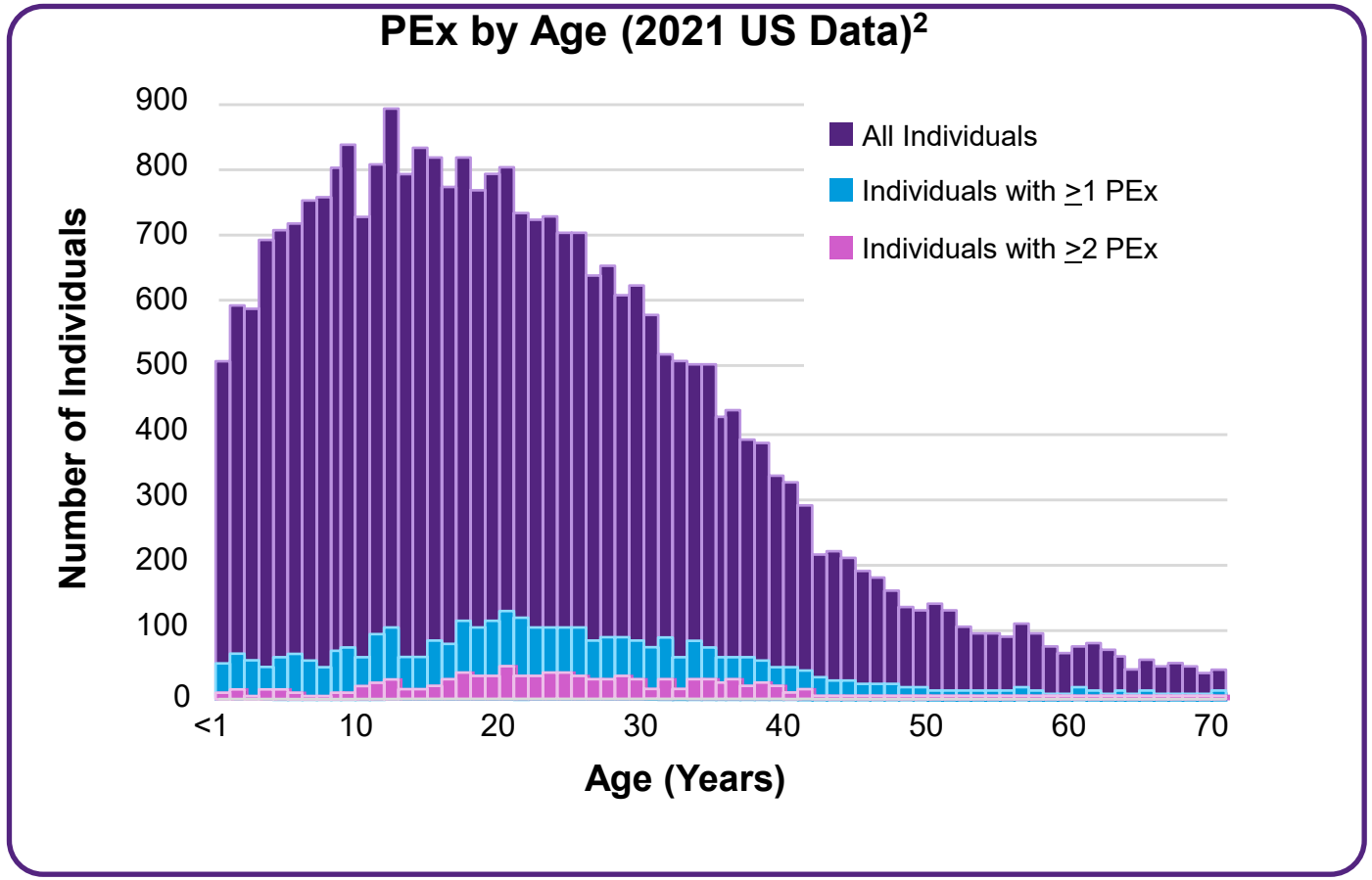
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FEV$_1$, forced expiratory volume in 1 second; ppFEV$_1$, percent predicted forced expiratory volume in 1 second.

1. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023
2. Kerem E, et al. *N Engl J Med*. 1992;326(18):1187-1191.

Pulmonary Exacerbations (PEx) Affect Lung Function and Quality of Life

- PEx are characterized by acute worsening of respiratory symptoms (e.g., cough, sputum production, shortness of breath)[1]
- Major clinical consequences:
  - Often result in hospitalization (median of 8.0 days/year in adults)[2]
  - Irreversible and progressive loss of lung function[3–6]
  - Increased risk for future PEx[7]
  - Reduced health-related quality of life[8]
  - Increased risk of death[9–12]

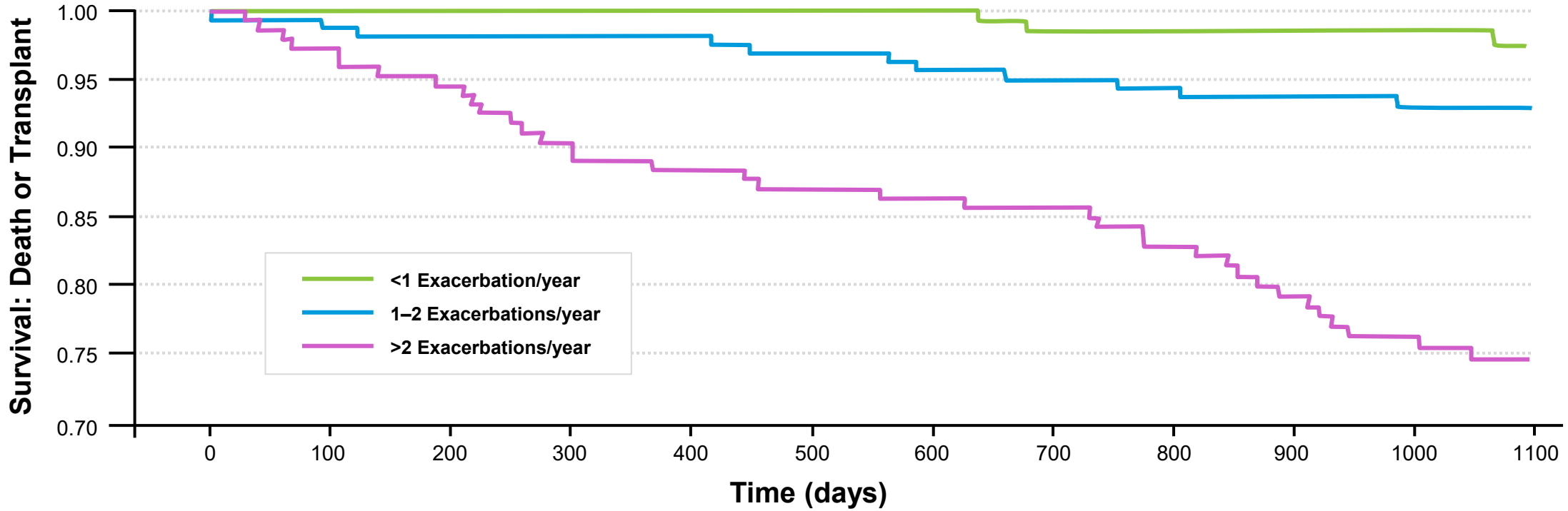
Canada observed a 41.6% decrease in hospitalizations for pulmonary exacerbation between 2017 and 2021[13]



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Goss CH, Burns JL. *Thorax*. 2007;62(4):360-367. 2. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.. 3. Sanders DB, et al. *Am J Resp Crit Care Med*. 2010;182(5):627-632. 4. Collaco JM, et al. *Am J Respir Crit Care Med*. 2010;182(9):1137-1143. 5. Sanders DB, et al. *Pediatr Pulmonol*. 2011;46(4):393-400. 6. Waters V, et al. *Eur Respir J*. 2012;40(1):61-66. 7. VanDevanter DR, et al. *J Cyst Fibros*. 2015;14:763-769. 8. Britto MT, et al. *Chest*. 2002;121(1):64-72. 9. Liou TG, et al. *Am J Epidemiol*. 2001;153(4):345-352. 10. de Boer K, et al. *Thorax*. 2011;66(8):680-685. 11. Buzzetti R. *J Cyst Fibros*. 2012;11(1):24-29. 12. Stephenson AL, et al. *Eur Respir J*. 2015;45(3):670-679. 13. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

People With CF With >2 PEx per Year Have Increased Risk of Lung Transplant and/or Mortality



Kaplan-Meier plot comparing time to death or lung transplant over 3 years per exacerbation group.
Analyses were adjusted for age, sex, BMI, infection with *Burkholderia cepacia*, transmissible *P. aeruginosa*, baseline FEV_1, CF comorbidities, and maintenance therapies.

Image adapted with permission from de Boer K, et al. 2011[1]

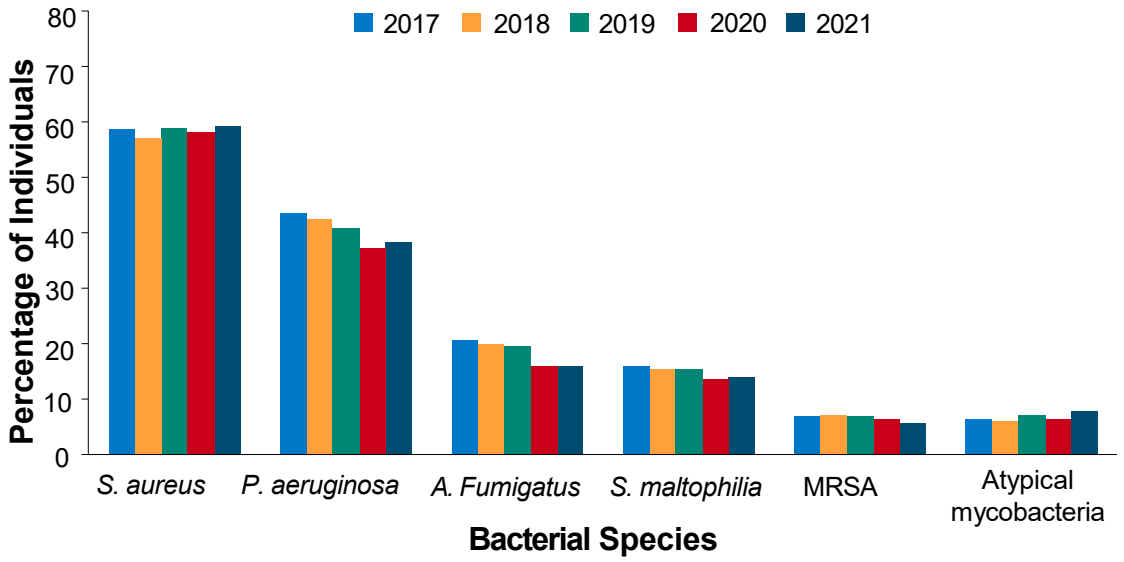
BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 second; PEx, pulmonary exacerbations; US, United States.

de Boer K, et al. *Thorax*. 2011;66(8):680-685.

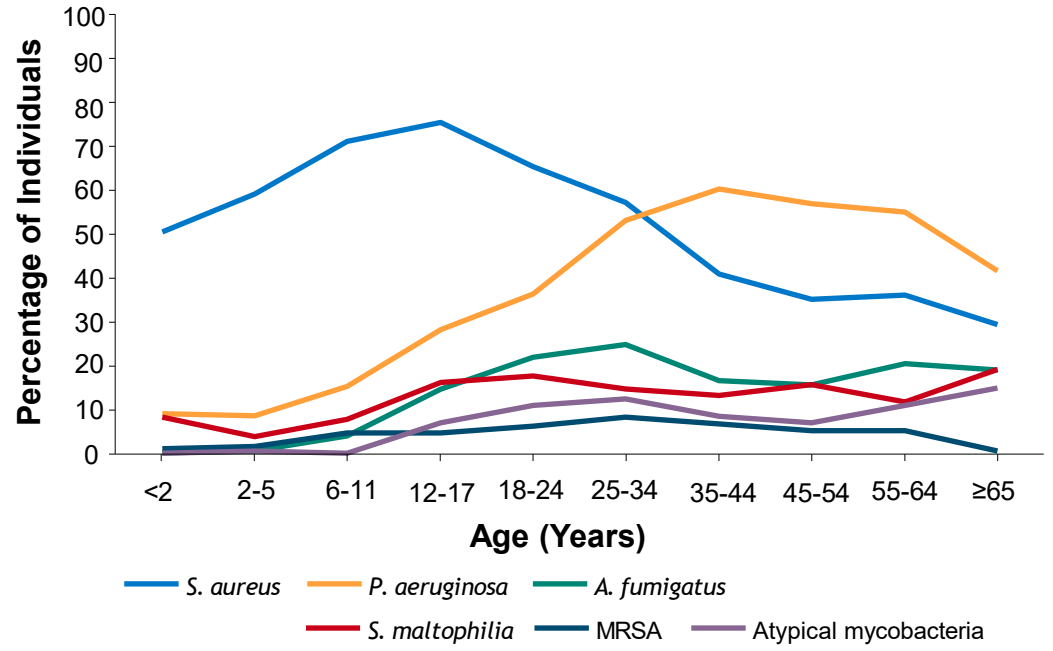
Chronic Infections in the Respiratory Tract Drive Lung Damage in People With CF

Bacteria establishes a chronic presence in the airways and is associated with chronic inflammation, leading to respiratory tissue injury and subsequent loss of lung function[1]

Prevalence of Respiratory Microorganisms, 2017–2021[2]



Prevalence of Respiratory Microorganisms by Age Cohort, 2021[2]



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; MRSA, methicillin-resistant *S. aureus*..

1. Doring G, et al. *J Cyst Fibros*. 2012;11(6):461-479. 2. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

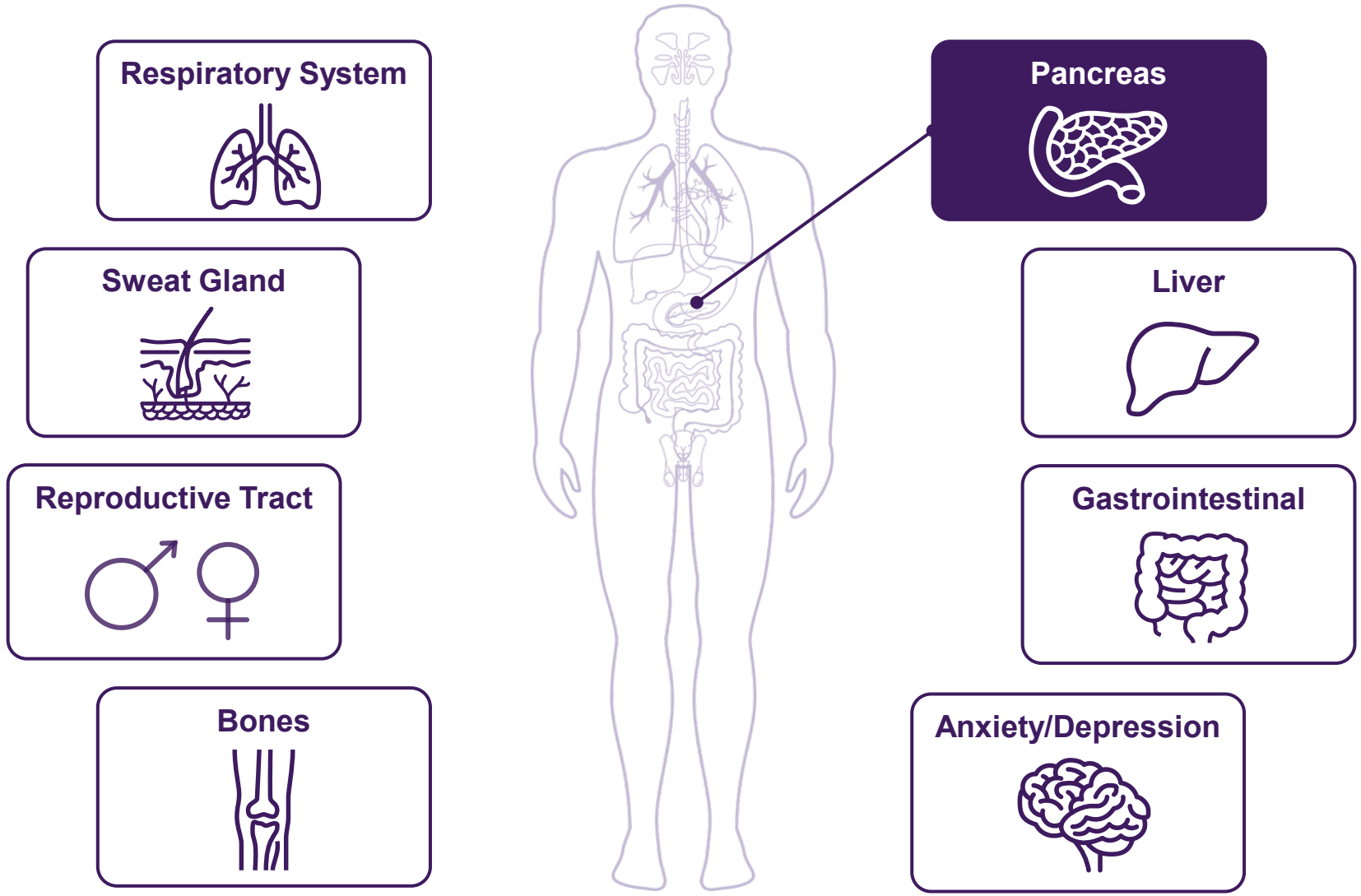
Sinonasal Manifestations

- Common symptoms of sinus disease include[1]:
  - Nasal congestion and discharge
  - Headache
  - Mouth breathing
  - Anosmia
  - Hyposmia
- Nasal polyps are also frequently identified[1]
- The unified airway model suggests that disease processes in the upper airway can influence those of the lower airway and vice versa[2,3]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

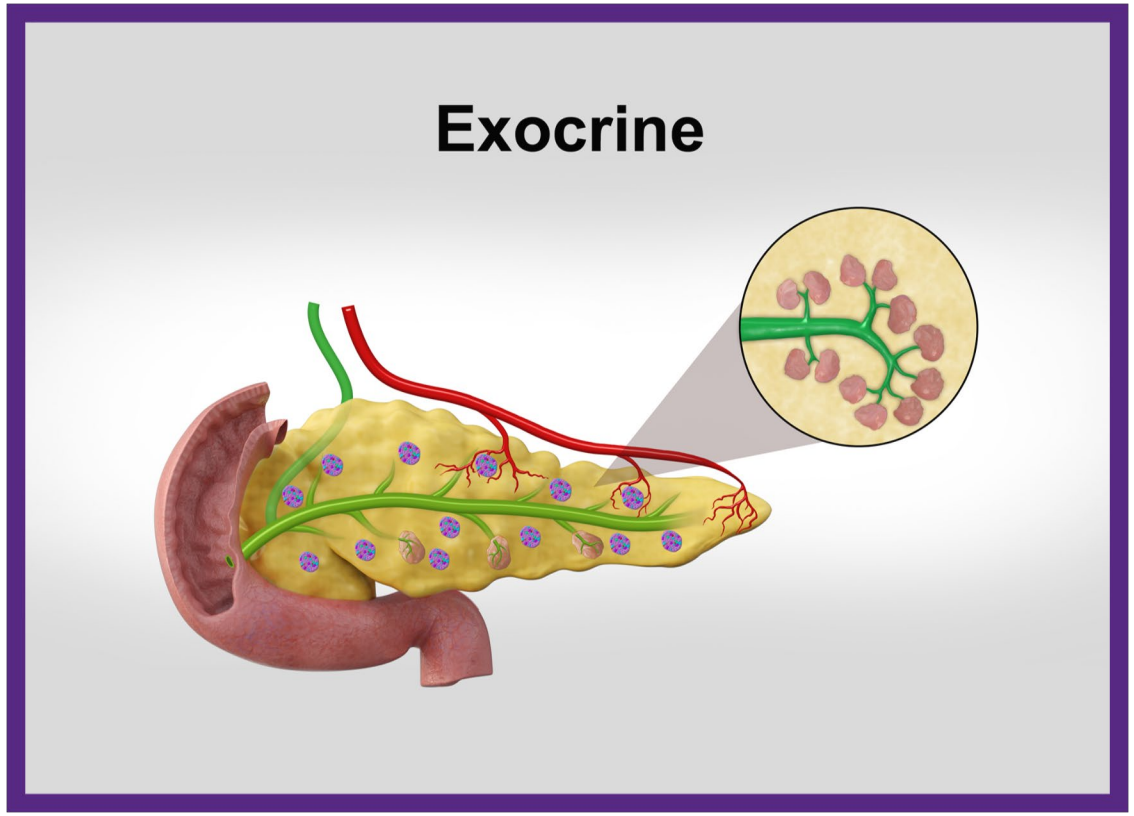
1. Oomen KP, et al. *Int J Otolaryngol*. 2012;2012:789572. 2. Chang EH. *Int Forum Allergy Rhinol*. 2014;4(2):132-137. 3. Okafor S, et al. *Immunol Allergy Clin North Am*. 2020;40(2):371-383.

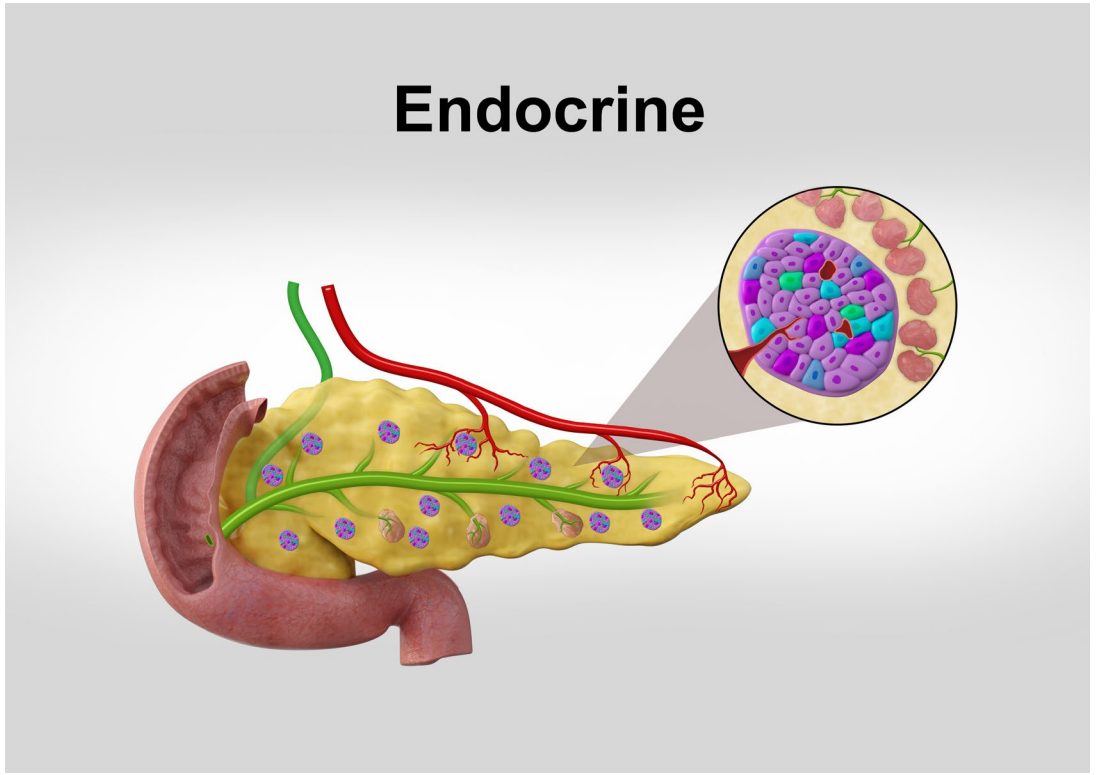
Clinical Manifestations of CF



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Pancreatic Disease in CF

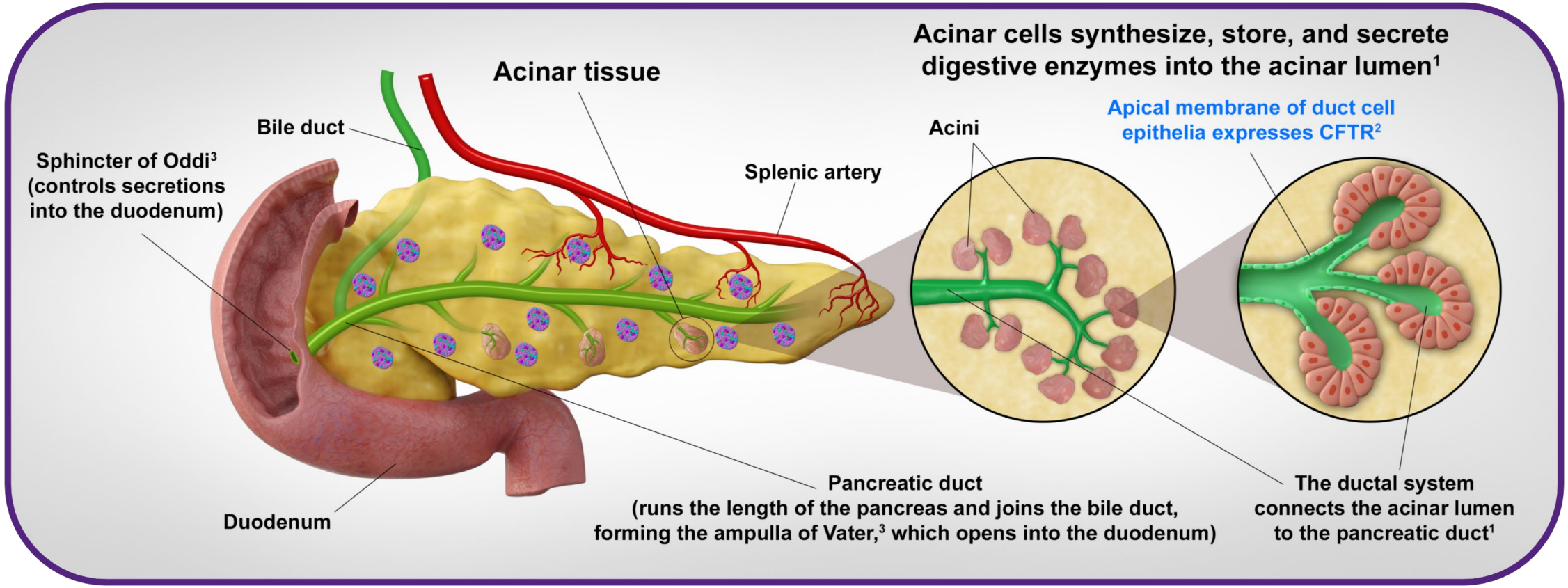




CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Exocrine Pancreas: Structure and Function

- The exocrine function of the pancreas is to produce and secrete digestive enzymes, water, and bicarbonate into the duodenum[1]
- Around 85% of pancreatic mass is exocrine[1]

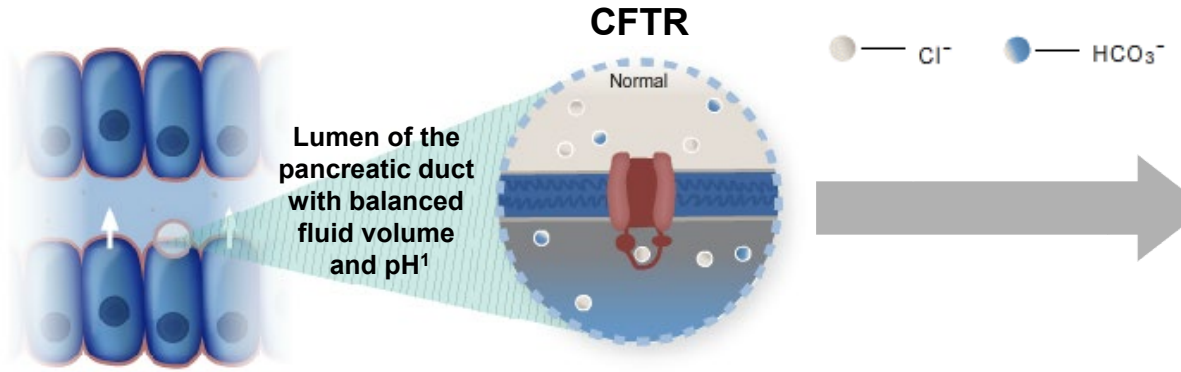


CFTR, cystic fibrosis transmembrane conductance regulator.

1. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. 2. Ishiguro H, et al. *J Gen Physiol*. 2009;133(3):315-326. 3. Avisse C, et al. *Surg Clin North Am*. 2000;80(1):201-212.

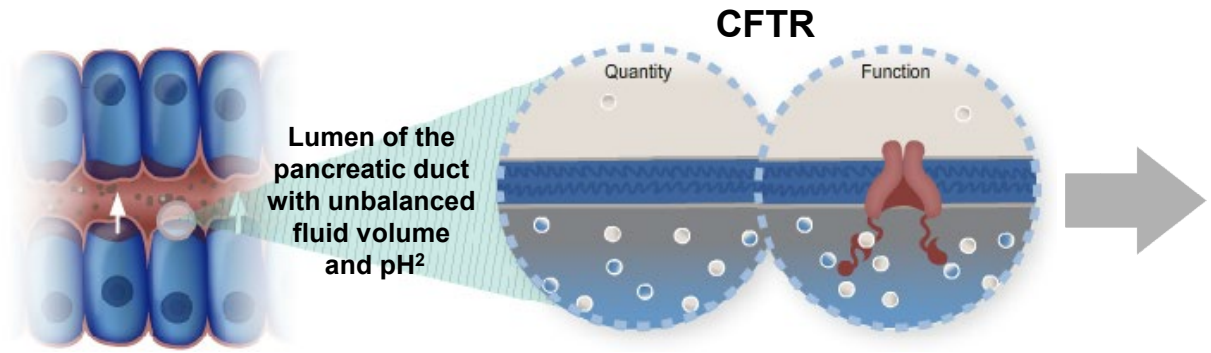
Exocrine Pancreas: Pathophysiology

Normal (Non-CF)



- HCO_3^- and Cl^- secreted into the lumen of pancreatic ducts[1,2]
- Normal food digestion and nutrient absorption[1]

CF



- Loss of CFTR function in the pancreatic duct[2]
- Restricted HCO_3^- and Cl^- secretion alter fluid and pH balance[2]
- Inflammation[2]
- Impaired ability to dissolve protein-rich acinar secretion[2]
- Protein precipitation[2]
- Plugging of small ducts[2]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; Cl^-, chloride; HCO_3^-, bicarbonate.

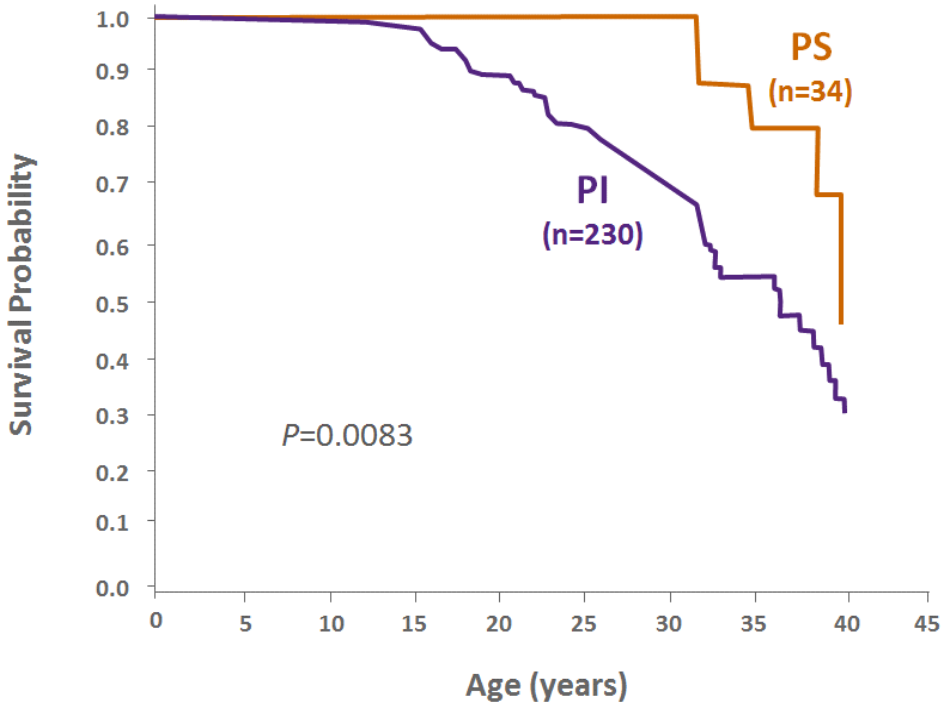
1. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. 2. Wilschanski M, et al. *Gut*. 2007;56:1153-1163.

Exocrine Pancreatic Insufficiency Manifestations in CF

- Pancreatic damage develops early in life, with damage found in neonates and fetuses at 17 weeks gestation[1]
- Approximately 85–90% of infants with CF are pancreatic insufficient (PI) within the first year of life[2]
- Some people with pancreatic sufficiency may become PI later in life[3]
- Loss of exocrine pancreatic function is a major cause of malnutrition due to malabsorption[4]
- Steatorrhea, an indicator of PI, occurs when lipase secretion from the exocrine pancreas is <4% of the lowest levels seen in people with normal pancreatic function[5]

Poor nutritional status in CF is highly correlated with lung function deterioration and is a strong predictor of mortality[4]

Kaplan-Meier Survival Curves for People With Pancreatic Sufficiency vs Insufficiency[6,*]

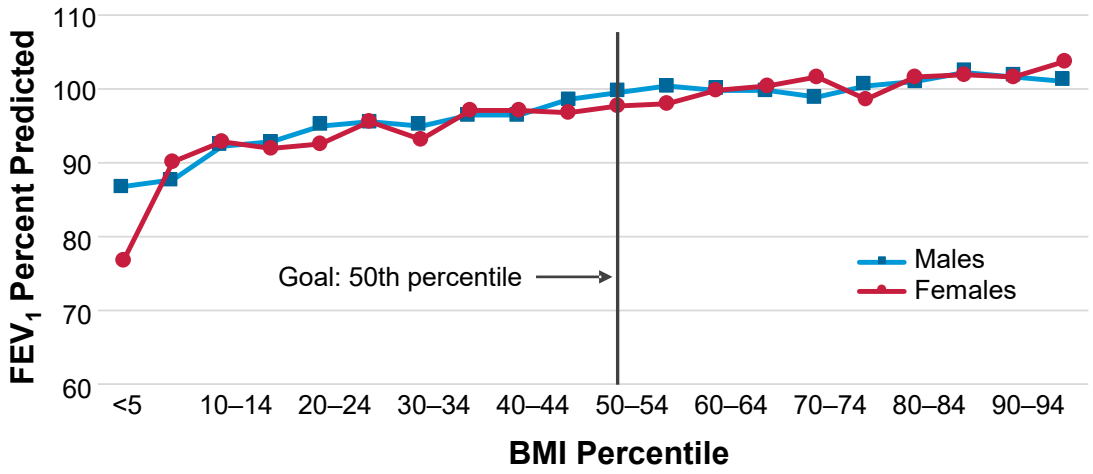


*Pancreatic status was based on genotype: *F508del* homozygous = PI; mutations associated with "mild" status = PS.
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; PI, pancreatic insufficient; PS, pancreatic sufficient.

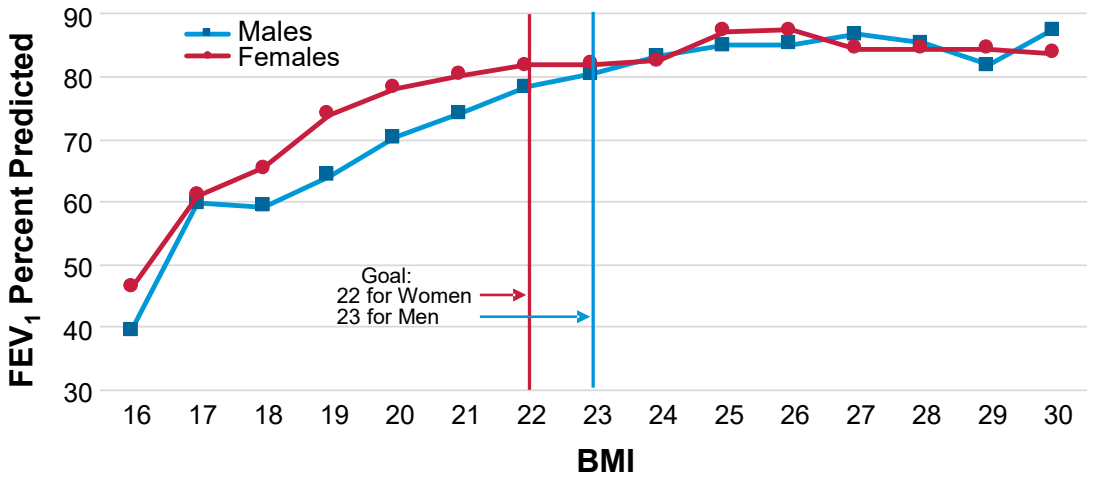
1. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29(12):1954-1962. 2. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. 3. Durno C, et al. *Gastroenterology*. 2002;123(6):1857-1864.
4. De Lisle RC, Borowitz D. *Cold Spring Harb Perspect Med*. 2013;3(9):a009753. 5. Gaskin KJ, et al. *Gastroenterology*. 1984;86(1):1-7. 6. Davis PB, et al. *Pediatr Pulmonol*. 2004;38:204-209.

Growth and Nutritional Status Are Associated With Pulmonary Function in People With CF

ppFEV$_1$ vs BMI Percentile for Children Aged 6–19 Years (US 2021 Data)



ppFEV$_1$ vs BMI Value for Adults Aged 20–40 Years (US 2021 Data)

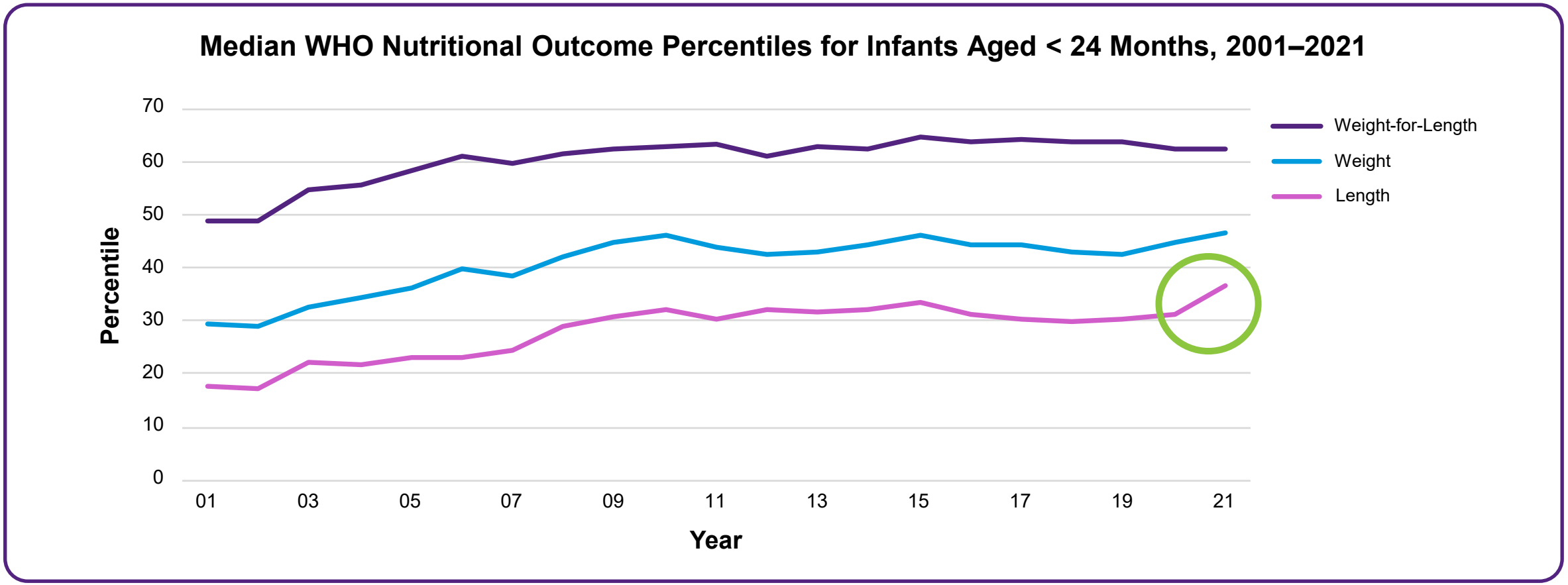


BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ppFEV$_1$, percent predicted forced expiratory volume in one second; vs, versus.

Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.

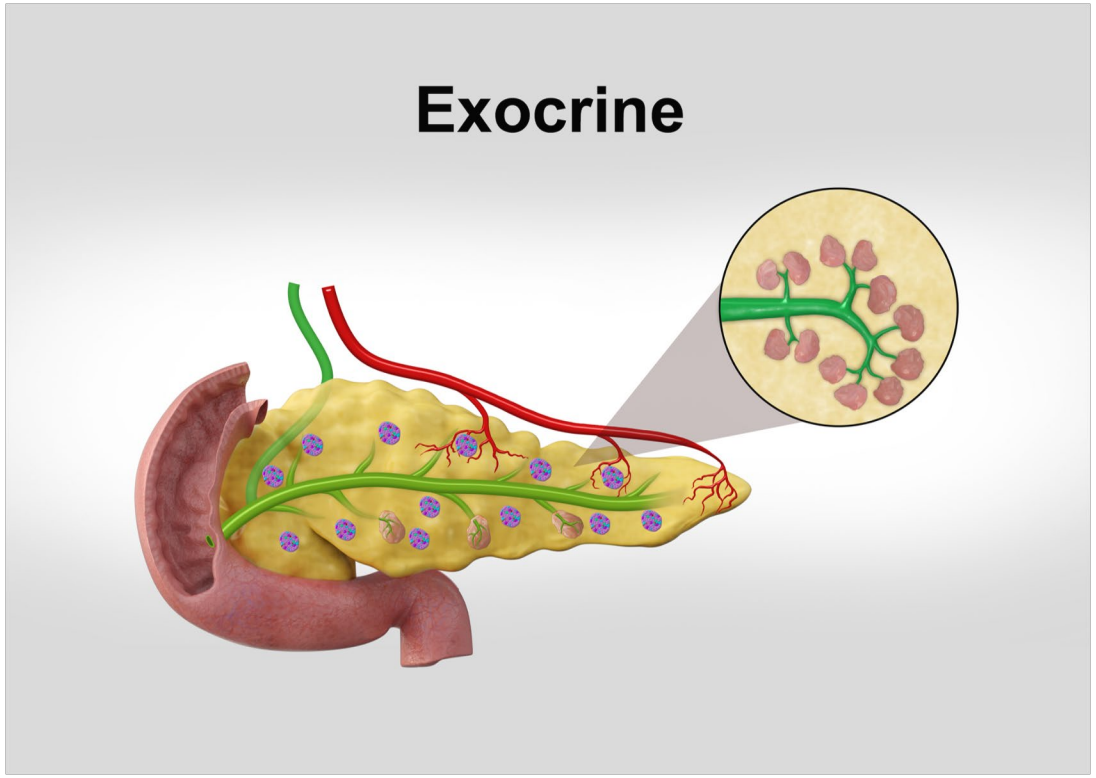
Length Percentiles for Infants With CF in the US

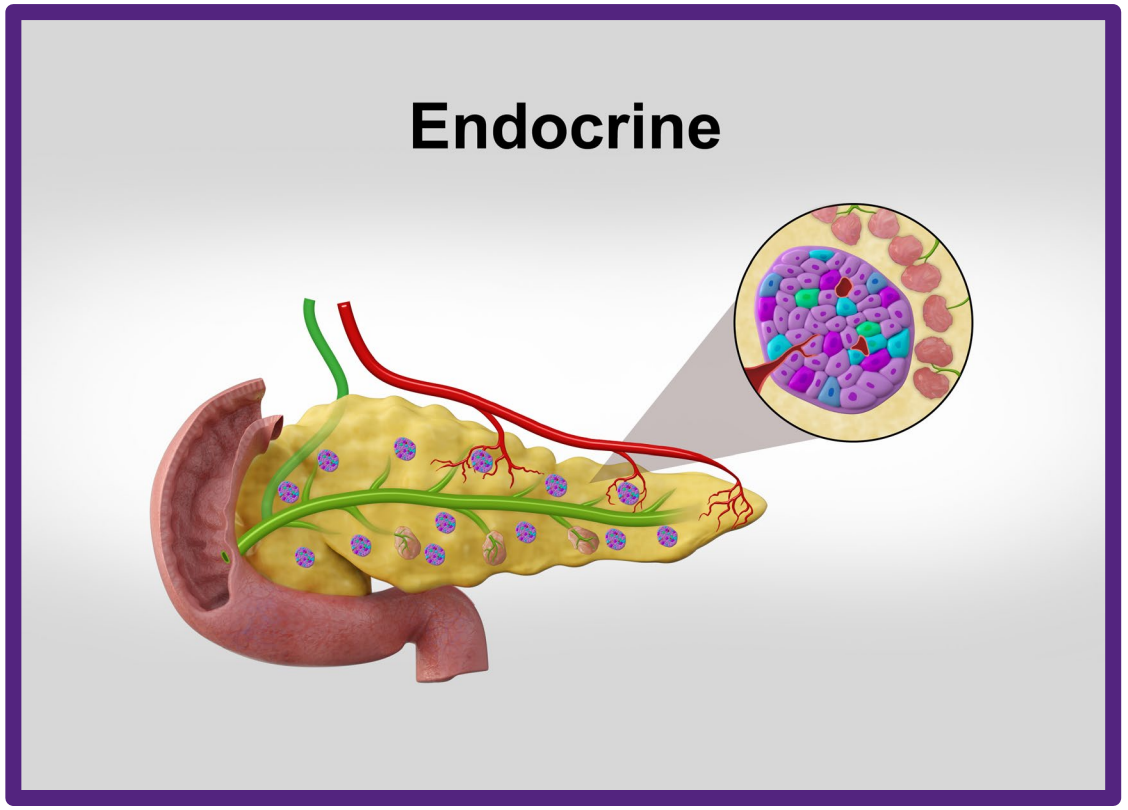
Length percentiles for infants with CF has increased for the first time since 2010 but remains below what is expected for the US population



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; US, United States; WHO, World Health Organization.
Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.

Pancreatic Disease in CF

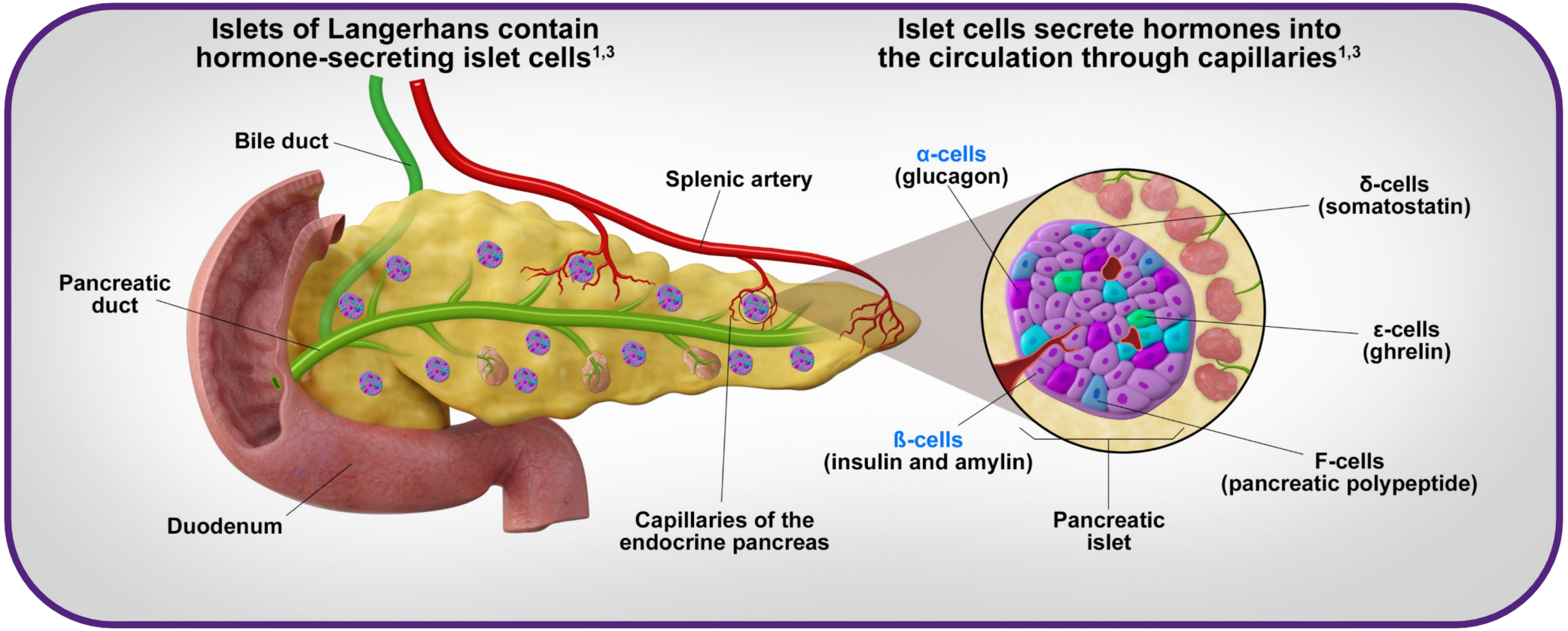




CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Endocrine Pancreas: Structure and Function

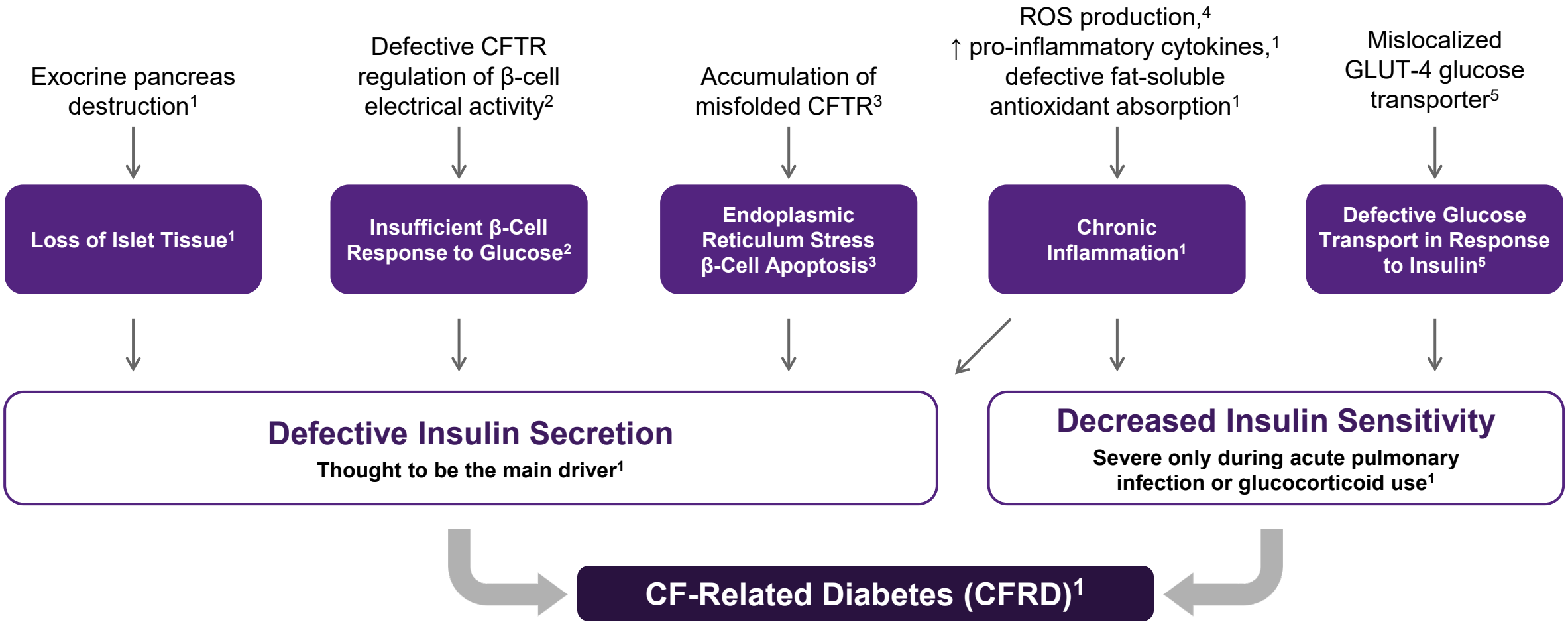
- The endocrine function of the pancreas is to produce and secrete hormones (e.g., insulin, glucagon) into the bloodstream[1,2]
- Endocrine islet cells comprise 1% to 2% of pancreatic mass[1]



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Begg DP, et al. *Adv Physiol Educ*. 2013;37(1):53-60. 2. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. 3. Nussey S, et al. The Endocrine Pancreas. In: *Endocrinology: An Integrated Approach*. Oxford: BIOS Scientific Publishers; 2001.

Potential Mechanisms of Endocrine Pancreas Pathophysiology in CF



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GLUT-4, glucose transporter-4; ROS, reactive oxygen species.

1. Barrio R. *Eur J Endocrinol*. 2015;172(4):R131-R141. 2. Guo JH, et al. *Nat Commun*. 2014;5:4420. 3. Ali BR. *Med Hypotheses*. 2009;72(1):55-57. 4. Galli F, et al. *Biochim Biophys Acta*. 2012;1822(5):690-713.
5. Hardin DS, et al. *Am J Physiol Endocrinol Metab*. 2001;281(5):E1022-E1028.

Comparison of CFRD With Type 1 and Type 2 Diabetes

Despite some shared features with type 1 and type 2 diabetes mellitus, CFRD is a distinct clinical entity

Parameter	CFRD	Type 1 Diabetes	Type 2 Diabetes
Prevalence	35% (of CF population)*	0.2%	11%
Peak Age of Onset	18–24 Years	Childhood, Youth	Adults
Usual Body Weight	Normal to Underweight	Normal	Obese
Insulin Deficiency	Severe, Not Complete	Nearly Complete	Partial, Variable
Insulin Sensitivity	Somewhat Decreased	Somewhat Decreased	Severely Decreased
Autoimmune Etiology	No	Yes	No
Microvascular Complications	Yes	Yes	Yes
Macrovascular Complications	No	Yes	Yes
Metabolic Syndrome	No	No	Yes
Major Cause of Death	Pulmonary	Cardiovascular	Cardiovascular

*In the 2021 Canadian CF Patient Registry, CFRD is reported in 2.8% of children and in 32.6% adults[1]
CF, cystic fibrosis; CFF, Cystic Fibrosis Foundation; CFRD, cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator;
Table adapted with permission from Moran A, et al. *Pediatr Diabetes*. 2018;19(Suppl 27):64-74.
1. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Clinical Sequelae of CF Pancreatic Disease

Exocrine
Pancreatic Insufficiency

- Steatorrhea[1]
- Fat-soluble Vitamin Deficiency[1]
- Malabsorption → Malnutrition[1]
- Weight Loss/Failure to Thrive[2]
- Lung Function Decline[3]
- Increased Mortality[4]

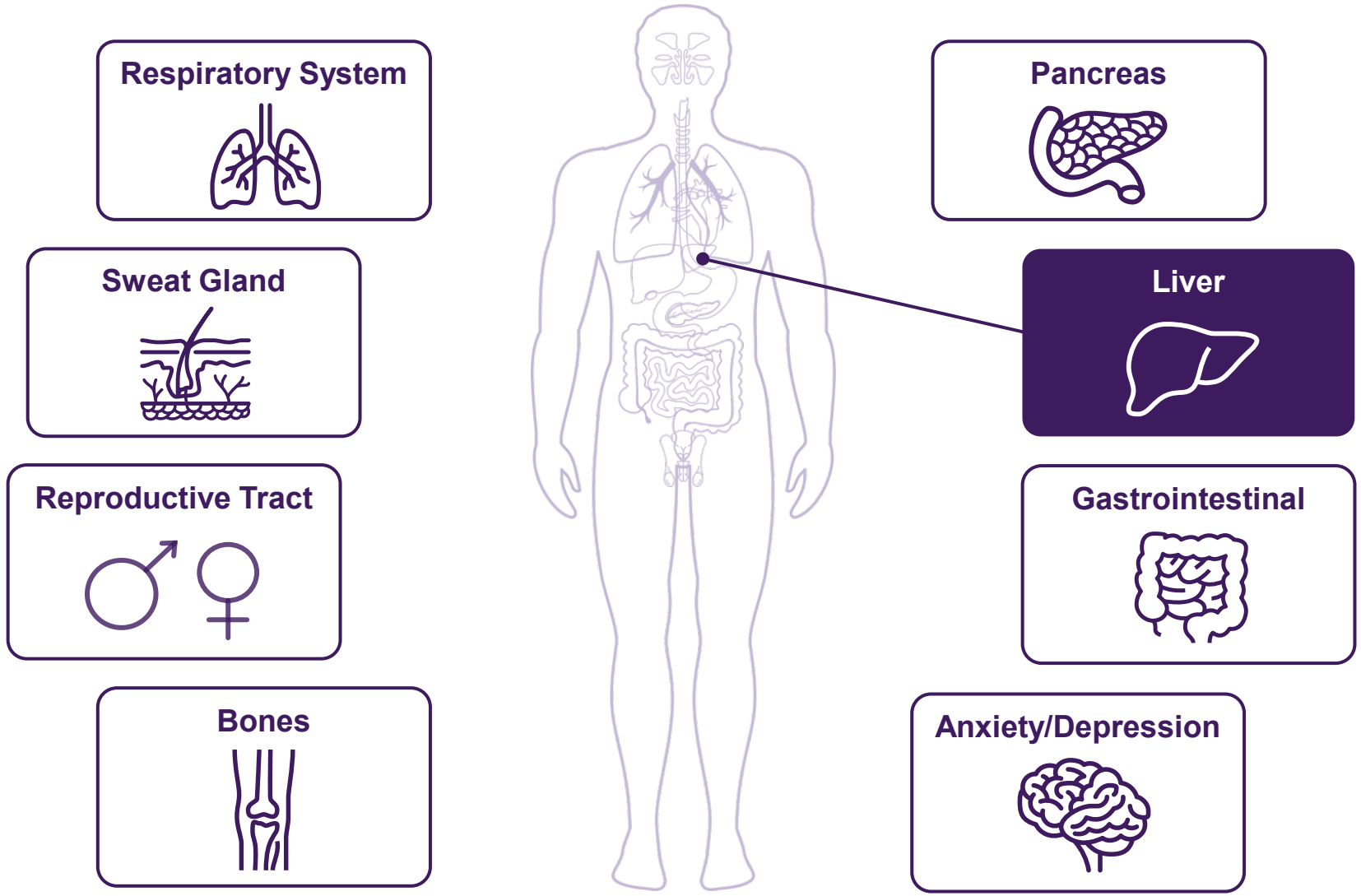
Endocrine
Pancreatic Insufficiency

- CFRD[1,5]
- Protein Catabolism[5]
- Weight Loss/Failure to Thrive[5]
- Lung Function Decline[5]
- Increased Mortality[5]

CF, cystic fibrosis; CFRD, cystic fibrosis–related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator.

1. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. 2. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023. 3. Schaedel C, et al. *Pediatr Pulmonol*. 2002;33(6):483-491. 4. Davis PB, et al. *Pediatr Pulmonol*. 2004;38:204-209. 5. Moran A, et al. *Diabetes Care*. 2010;33(12):2697-2708.

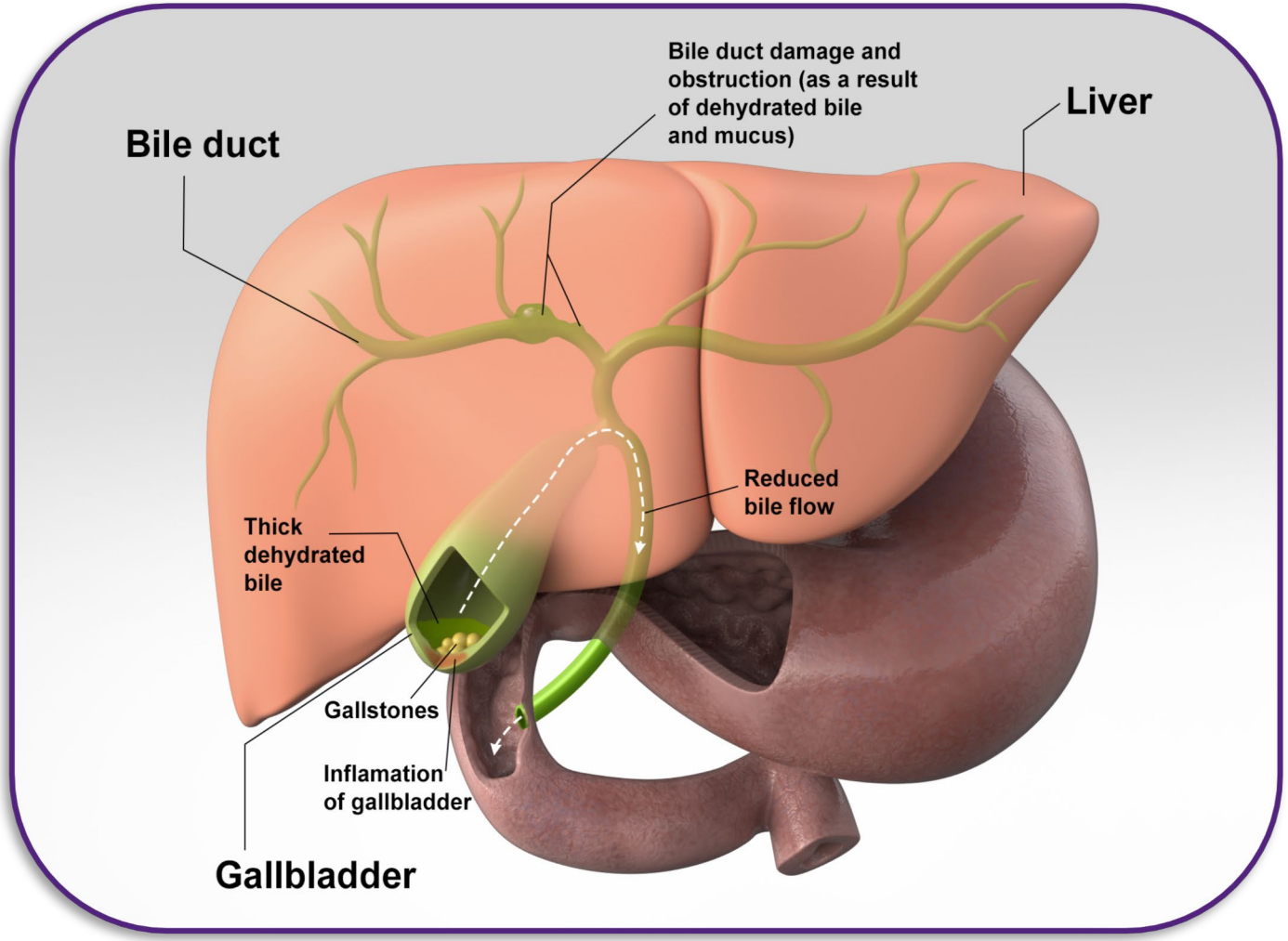
Clinical Manifestations of CF



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

CF-Related Liver Disease (CFLD) or Hepatobiliary Disease

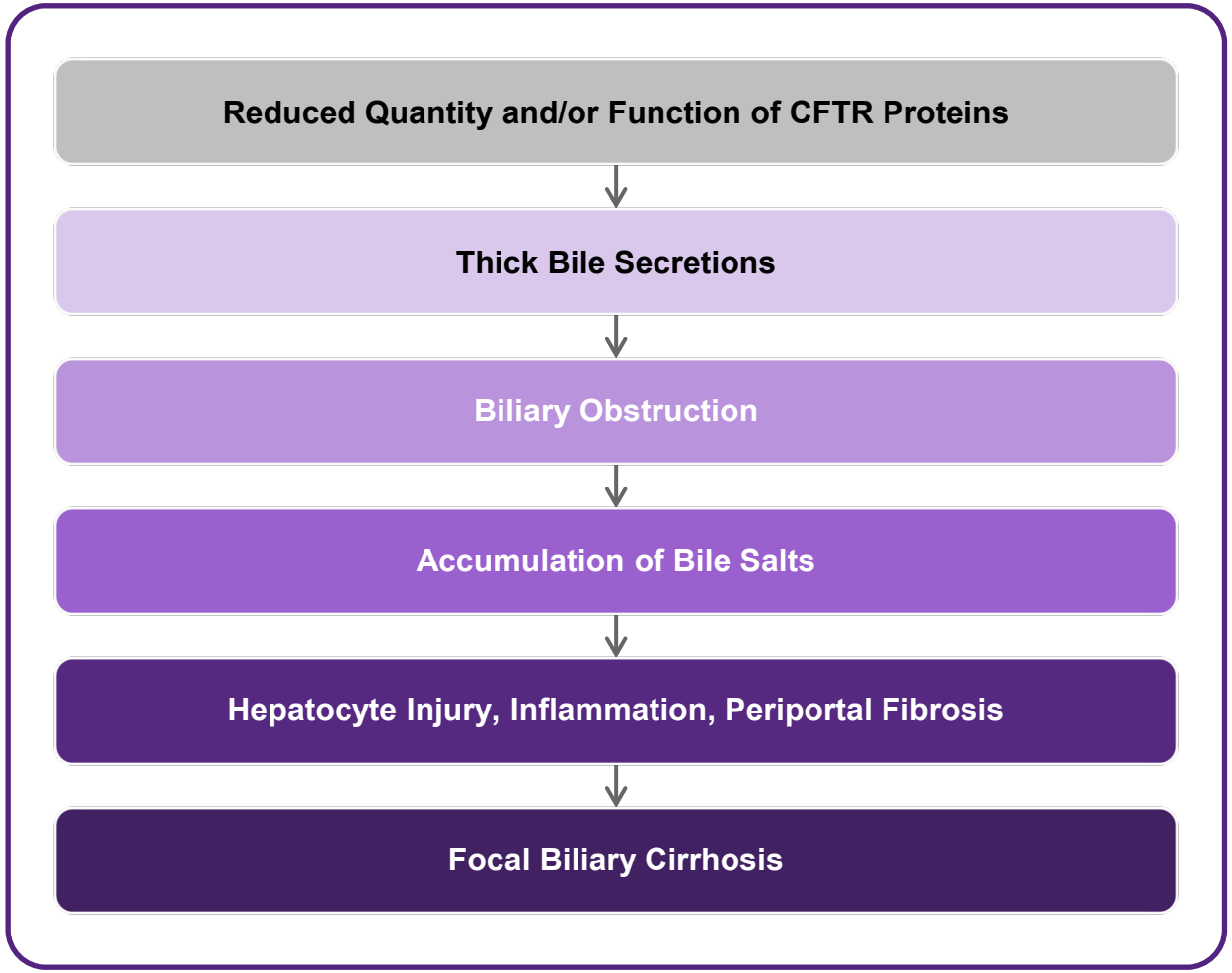
- CFTR is expressed on the apical surface of cholangiocytes and gallbladder epithelial cells but not hepatocytes[1]
- Highest incidence is in the first 10 years of life with clinically significant hepatobiliary manifestations reported in 15–30% of children[2,3]
- Steatosis, the most common identified histological abnormality, is found in up to 70% of liver biopsies from children with suspected CFLD[3]
- In 2021, liver disease/liver failure accounted for 2.6% of overall mortality in the US[4]



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; US, United States.

1. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913. 2. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 3. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29(12):1954-1962. 4. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.

Pathophysiology of CFLD

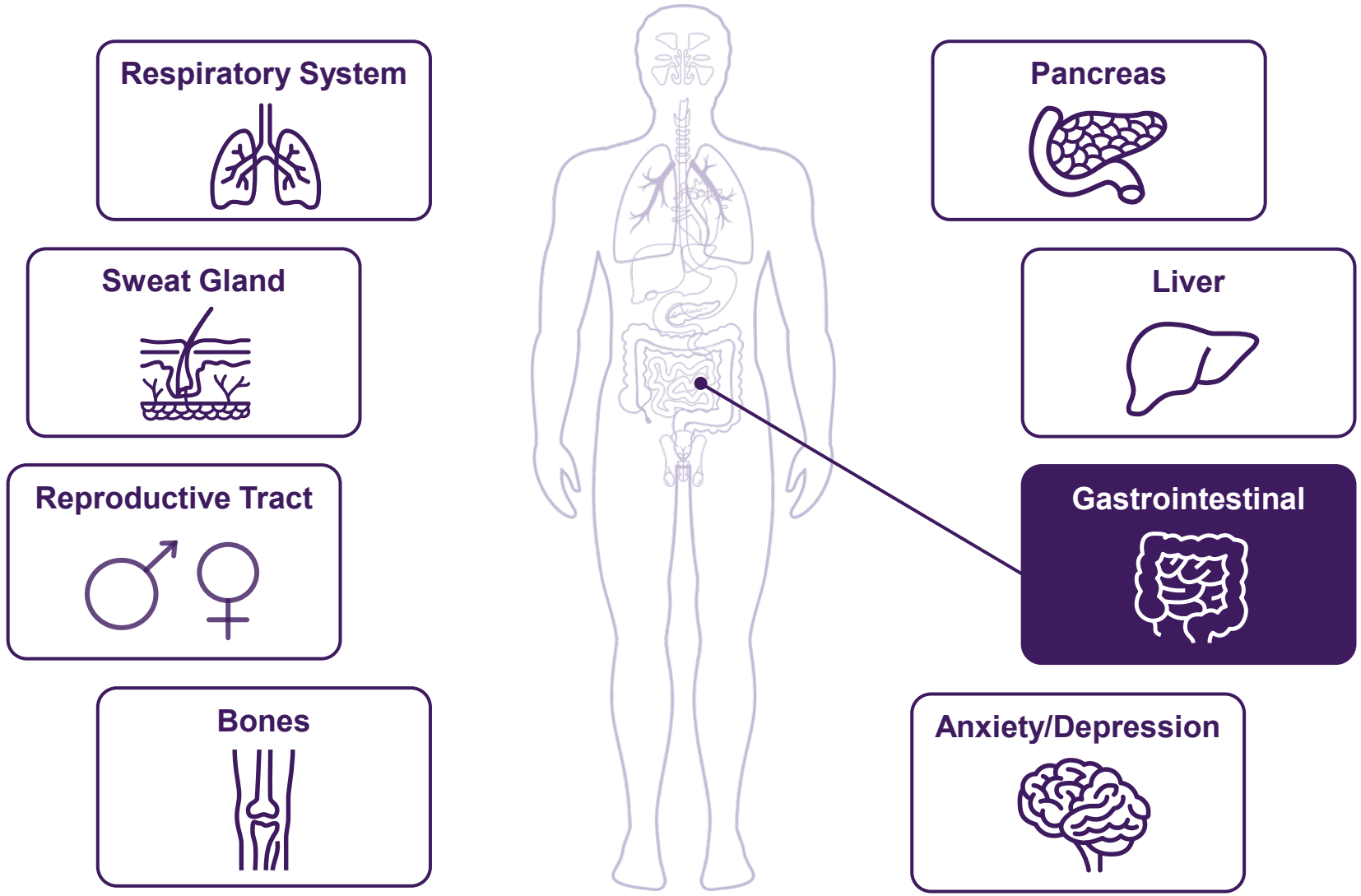


- Impaired CFTR function leads to bile salt accumulations due to thickened, inspissated bile secretions and biliary obstructions from plugging[1]
- Biliary dysfunction likely contributes to hepatocyte injury and inflammation resulting in hepatic fibrosis[2–4]
- A small subset of people progress from focal biliary cirrhosis to multilobular cirrhosis, leading to development of portal hypertension, splenomegaly, hypersplenism, and associated complications of gastric or esophageal variceal bleeding[5,6]
- Biliary cirrhosis and portal hypertension can be coexisting risk factors for early mortality[1,7]

CF, cystic fibrosis; CFLD, cystic fibrosis–related liver disease; CFTR, cystic fibrosis transmembrane conductance regulator.

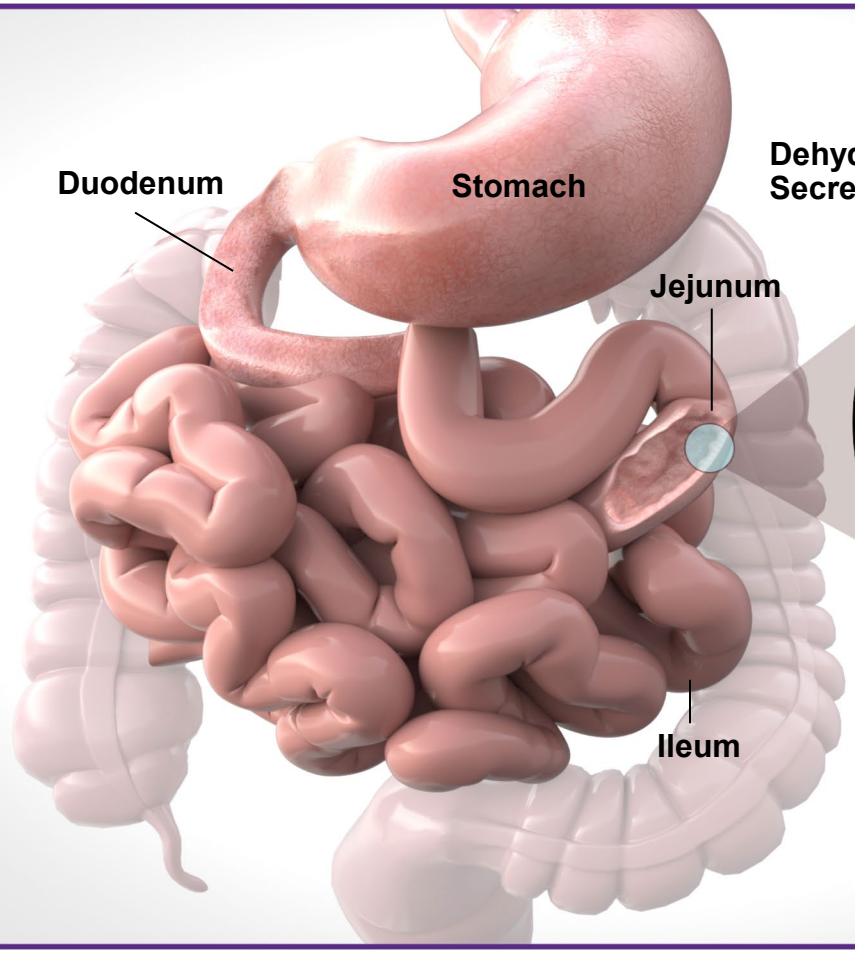
1. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29(12):1954-1962. 2. Flass T, Narkewicz MR. *J Cyst Fibros*. 2013;12(2):116-124. 3. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913. 4. Sokol RJ, et al. *J Pediatr Gastroenterol Nutr*. 1999;28:S1-S13. 5. Ooi CY, Durie PR. *Nat Rev Gastroenterol Hepatol*. 2016;13(3):175-185. 6. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 7. Kamal N, et al. *Curr Opin Gastroenterol*. 2018;34(3):146-151.

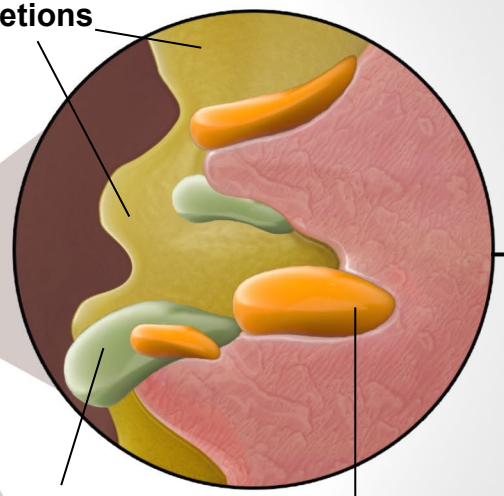
Clinical Manifestations of CF



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Intestinal Dysregulation in CF Results From CFTR Protein Dysfunction in Intestinal Epithelia As Well As Other Organs[1,2]





CFTR mutations in intestinal epithelia, as well as the pancreas and hepatobiliary system, all contribute to the electrolyte and fluid imbalance leading to dehydrated secretions in the GI tract

Dysfunction of the pancreas and hepatobiliary system due to CFTR protein defects have downstream consequences in the intestinal lumen

Altered bicarbonate secretion by the pancreas results in more highly acidic intestinal contents

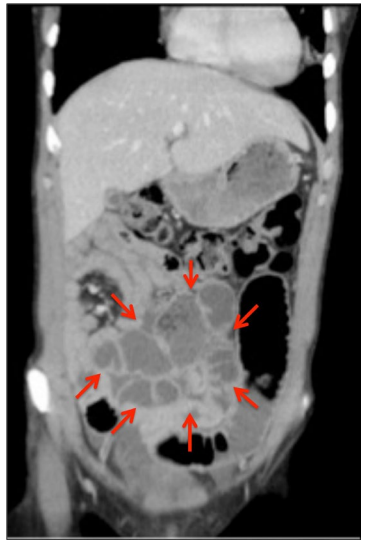
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GI, gastrointestinal.

1. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 2. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913.

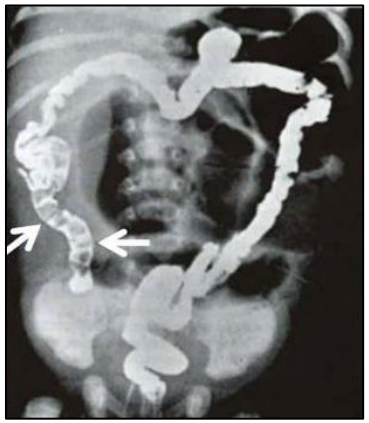
Gastrointestinal Complications of CF[1–3]

- Meconium ileus (MI)
  - Intestinal obstruction of abnormal meconium, typically at the terminal ileum[2,3]
- Distal intestinal obstruction syndrome (DIOS)
  - Complete or incomplete fecal obstruction of the ileocecum[1]
- Gastroesophageal reflux disease (GERD)
- Constipation
- Rectal prolapse
- Intussusception
- Small intestine bacterial overgrowth
- GI cancers

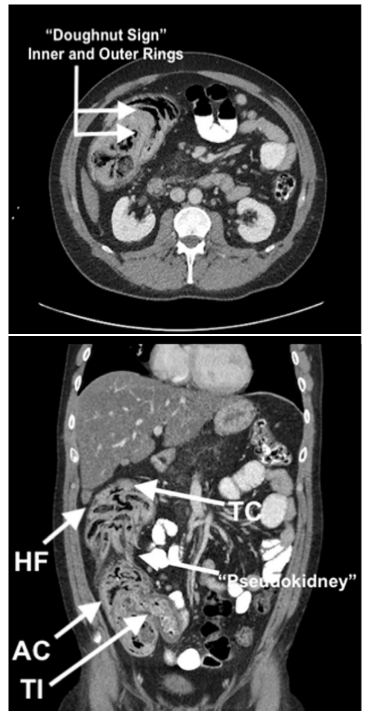
Distal Intestinal Obstruction Syndrome[4]



Meconium Ileus[5]



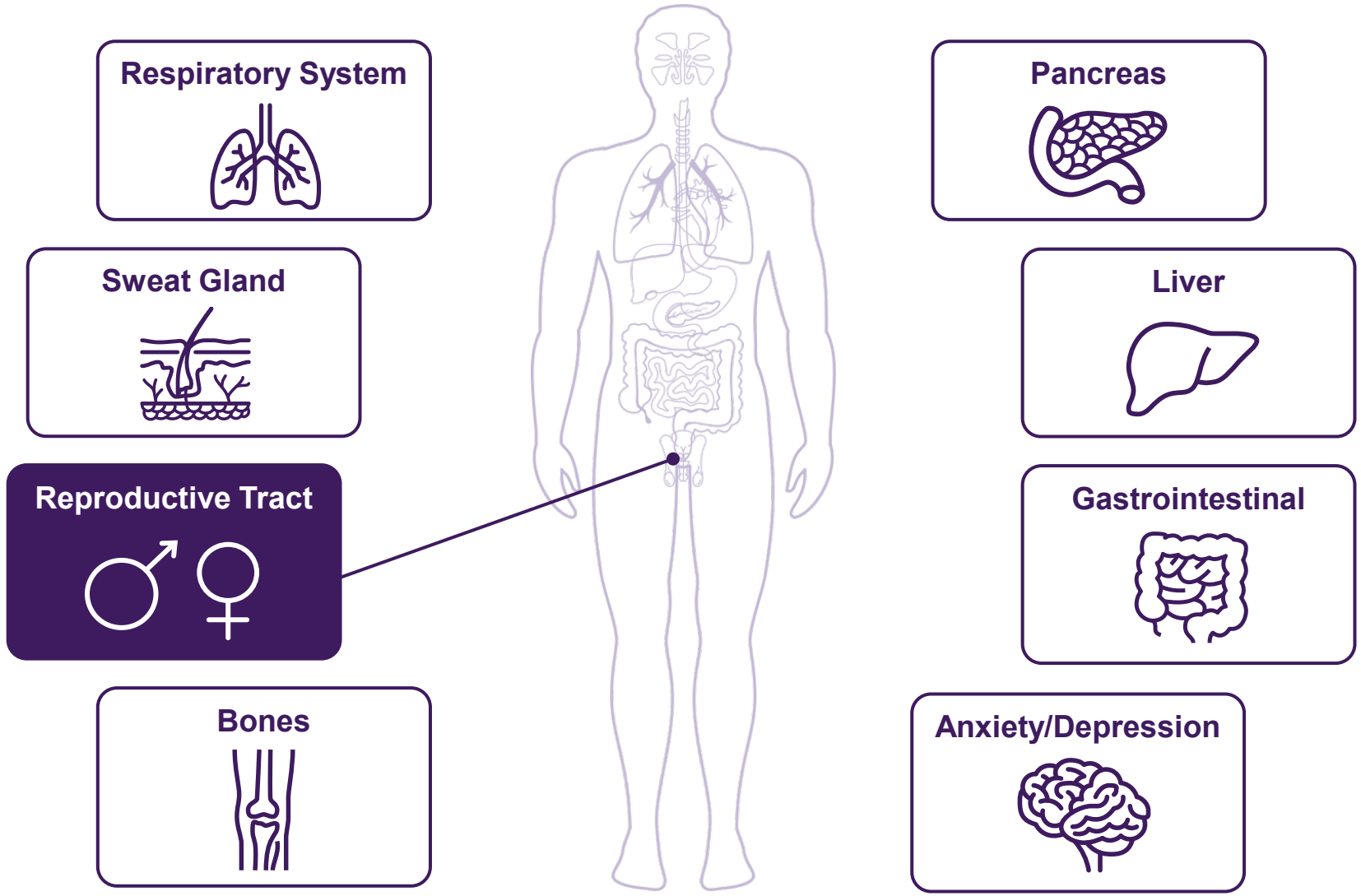
Intussusception[6]



AC, ascending colon; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; GI, gastrointestinal; HF hepatic flexure; TC, transverse colon; TI, terminal ileum.

1. Gelfond D, Borowitz D. *Clin Gastroenterol Hepatol*. 2013;11(4):333-342. 2. Kelly T, Buxbaum J. *Dig Dis Sci*. 2015;60(7):1903-1913. 3. Haller W, et al. *J Gastroenterol Hepatol*. 2014;29:1344-1355.
4. Mavilia M. *Clin J Gastroenterol*. 2019;12:571-573. 5. Feldman M, et al. eds. Sleisenger & Fordtran's *Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management*. 9th ed. Philadelphia, PA: Saunders; 2010:931-953.
6. Adewale AT, et al. *J Cyst Fibros*. 2019;18(2):e11-e13.

Clinical Manifestations of CF



CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Fertility in CF

Male

- Over 98% of men with CF are infertile[1]
  - Predominantly due to obstructive azoospermia caused by congenital bilateral absence of vas deferens (CBAVD)[1,2]
  - Some infertility seen regardless of obstruction[1]
- Role for CFTR in transporting bicarbonate associated with sperm motility[1]
- *CFTR* mutations may also influence spermatogenesis due to fluid and electrolyte modifications in the epididymis[1]

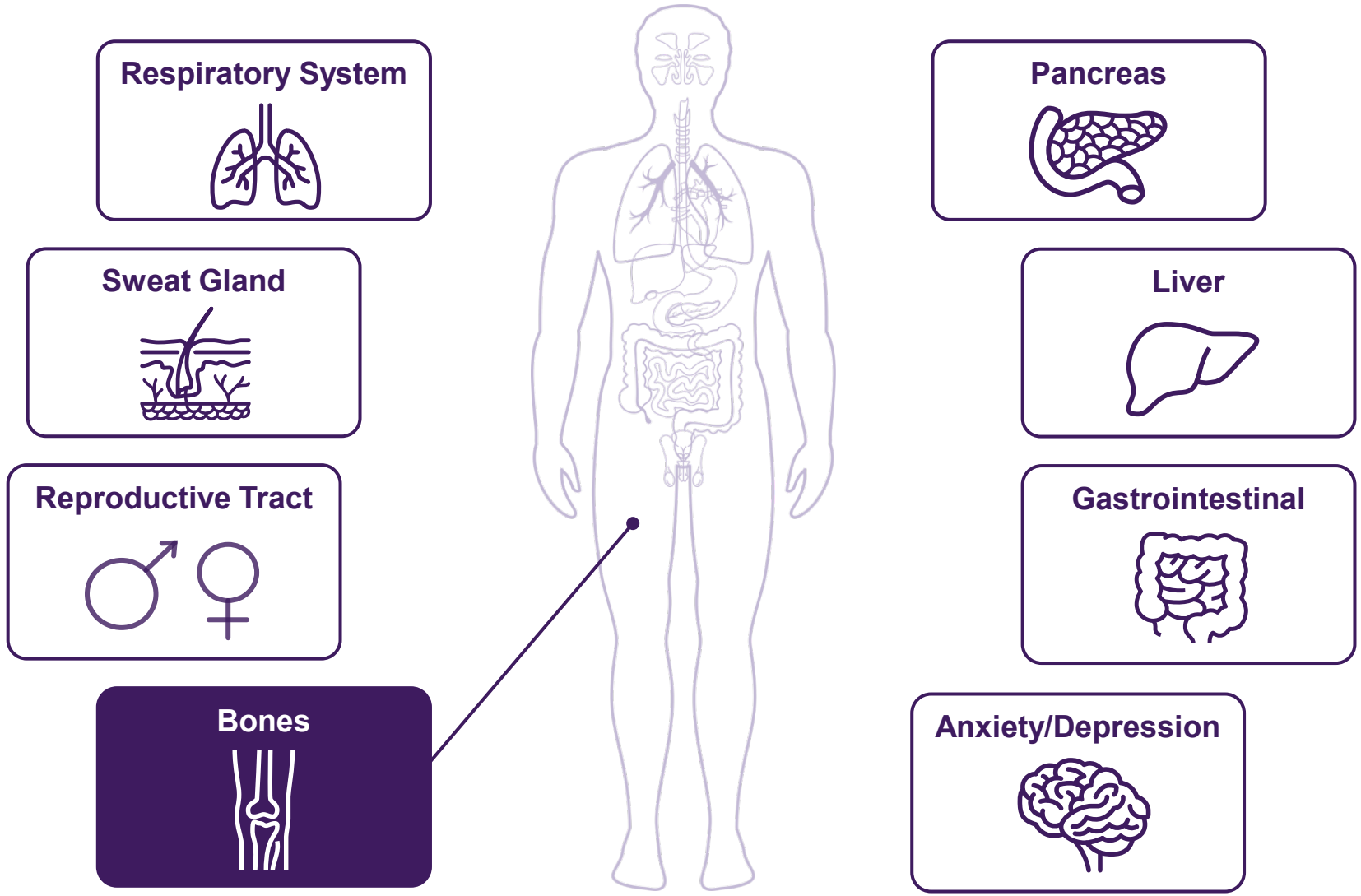
Female

- Infertility in women with CF is not as common as the rates seen in men[1]
- Typically normal anatomy[1]
- Ovulation disturbances and delayed menarche[1]
- Large amounts of CFTR in the cervix[1]
  - Most common abnormality is thick, dehydrated cervical mucus that impairs cervical penetration by sperm
- Alterations of uterine HCO_3^- concentrations can result in failure of sperm capacitation and fertilization[1]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; HCO_3^-, bicarbonate.

1. Ahmad A, et al. *Curr Opin Obstet Gynecol*. 2013;25(3):167-172. 2. Rutherford AJ. *J R Soc Med*. 2007;100 (Suppl 47):29-34.

Clinical Manifestations of CF

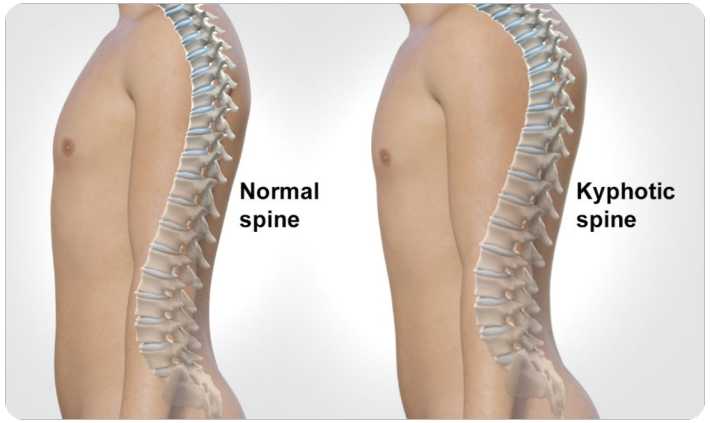


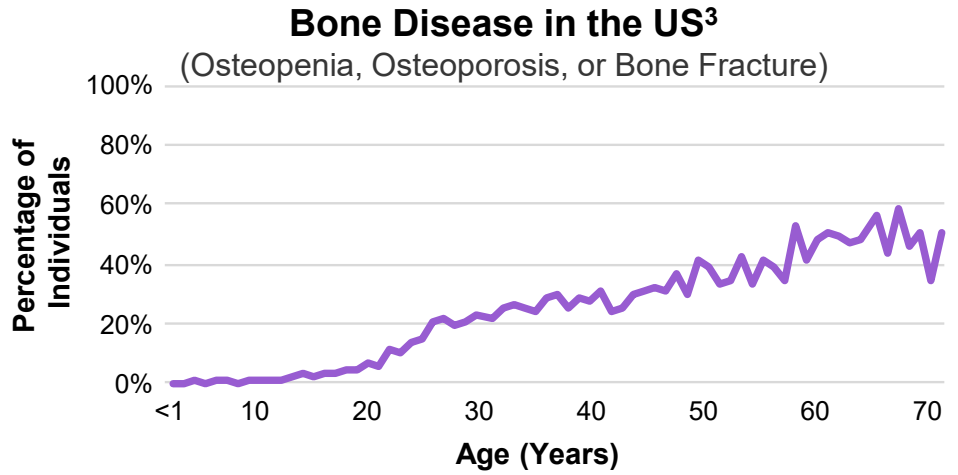
CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

CF-Related Bone Disease (CFBD)

- Characterized by decreased bone mineral density (BMD), increased fracture rates and kyphosis[1]
  - Most common fractures are vertebral and rib
  - Can lead to kyphosis and accelerated decline in lung function

- **Possible Causes of CFBD[1]**
  - CFTR dysfunction
  - Pancreatic insufficiency
  - Malnutrition and poor growth
  - Vitamin D, vitamin K, and calcium insufficiency
  - CF-related diabetes
  - Sex steroid deficiency and delayed puberty
  - Chronic inflammation
  - Moderate to severe lung disease
  - Lack of exercise, especially weight-bearing
  - Tobacco, alcohol, and caffeine
  - Organ transplant and immunosuppressive therapy
  - Glucocorticoids and other medications

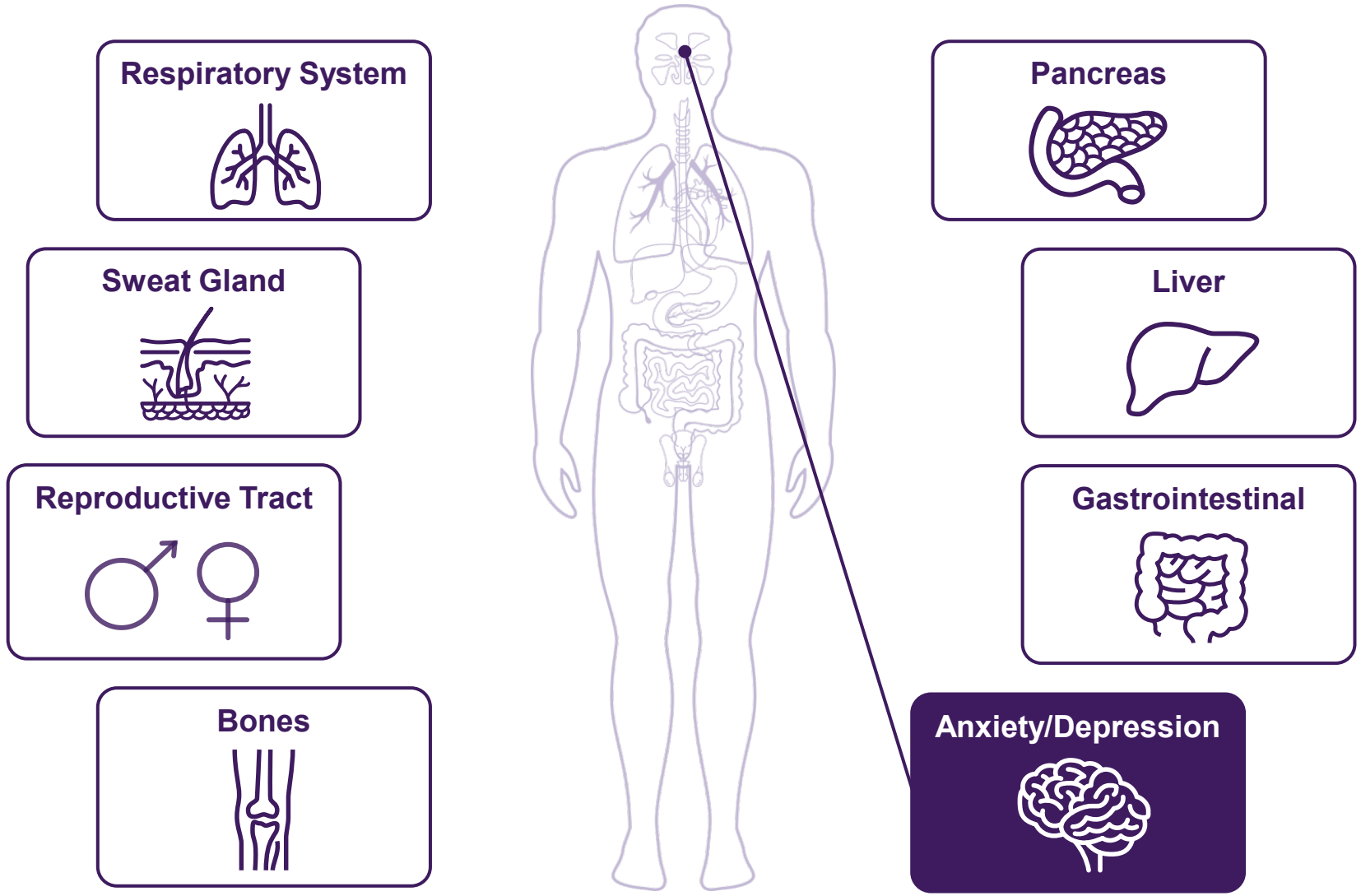




CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Gore AP, et al. *J Osteoporos*. 2010;2011:926045. 2. National Institutes of Health. Kyphosis. https://medlineplus.gov/ency/article/001240.htm. Accessed March 2023.. 3. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023.

Clinical Manifestations of CF

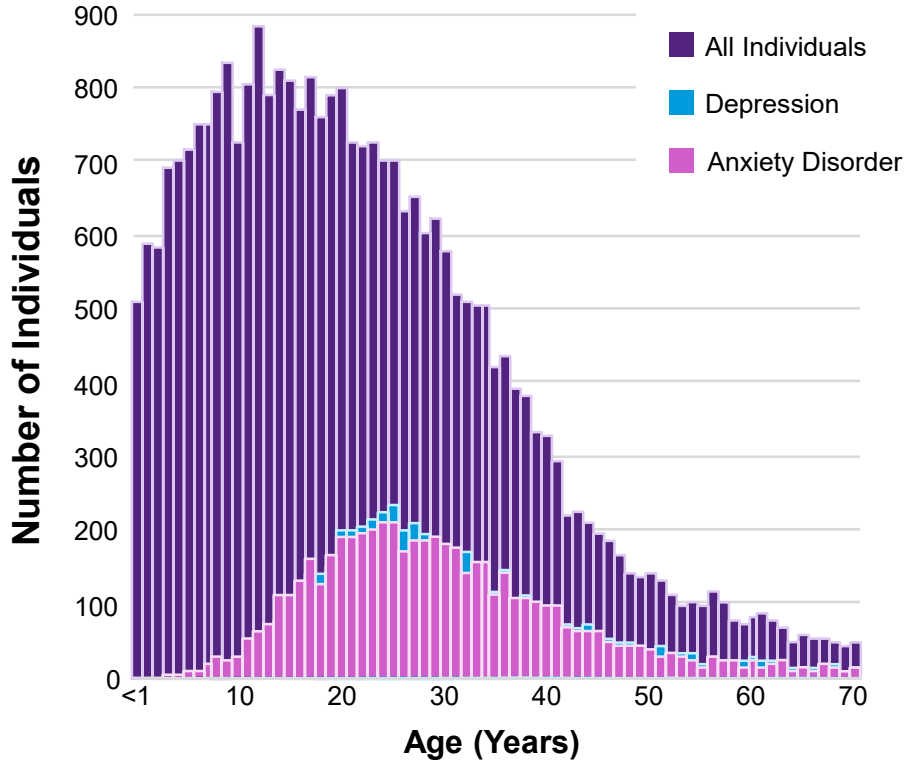


CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

Anxiety and Depression in CF

Prevalence of anxiety and depression peaks in early adulthood, when lung disease often worsens[1]

Anxiety and Depression in People With CF in the US[1]



- Symptoms of depression and anxiety in adolescents, adults, and caregivers with CF are 2–3 times greater than in community samples[2]
- Psychological distress in people with CF has been associated with worse adherence, poorer pulmonary function, increased hospitalizations, and decreased health-related quality of life[2]

In 2021 in Canada, there were 654 (15.1%) individuals with cystic fibrosis with a recorded complication depression or anxiety in the CF Registry. 75 of these diagnoses were children and 579 were adults, representing 4.9% of all children and 20.5% of all adults living with cystic fibrosis[3]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. Cystic Fibrosis Foundation. 2021 Patient Registry Annual Data Report, 2022. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf. Accessed March 2023. 2. Quittner AL, et al. *Thorax*. 2016;71:26-34.
3. Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report. https://www.cysticfibrosis.ca/registry/2021AnnualDataReport.pdf. Accessed March 2023

Summary

1. CF is a systemic, multi-organ genetic disease caused by mutations in the *CFTR* gene that affect the quantity and/or function of CFTR protein[1,2]
2. CFTR protein channels transport ions, such as chloride and bicarbonate, to regulate fluid and electrolyte balance in epithelial tissues throughout the body, such as the lungs, sinuses, pancreas, intestine, biliary ducts, reproductive system, and sweat glands[3]
3. Symptoms of CF manifest throughout life with great variability among individuals, although lung disease is the primary cause of morbidity and mortality[1]

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

1. O'Sullivan BP, Freedman SD. *Lancet*. 2009;373(9678):1891-1904. 2. Derichs N. *Eur Respir Rev*. 2013;22(127):58-65. 3. MacDonald KD, et al. *Pediatr Drugs*. 2007;9(1):1-10.