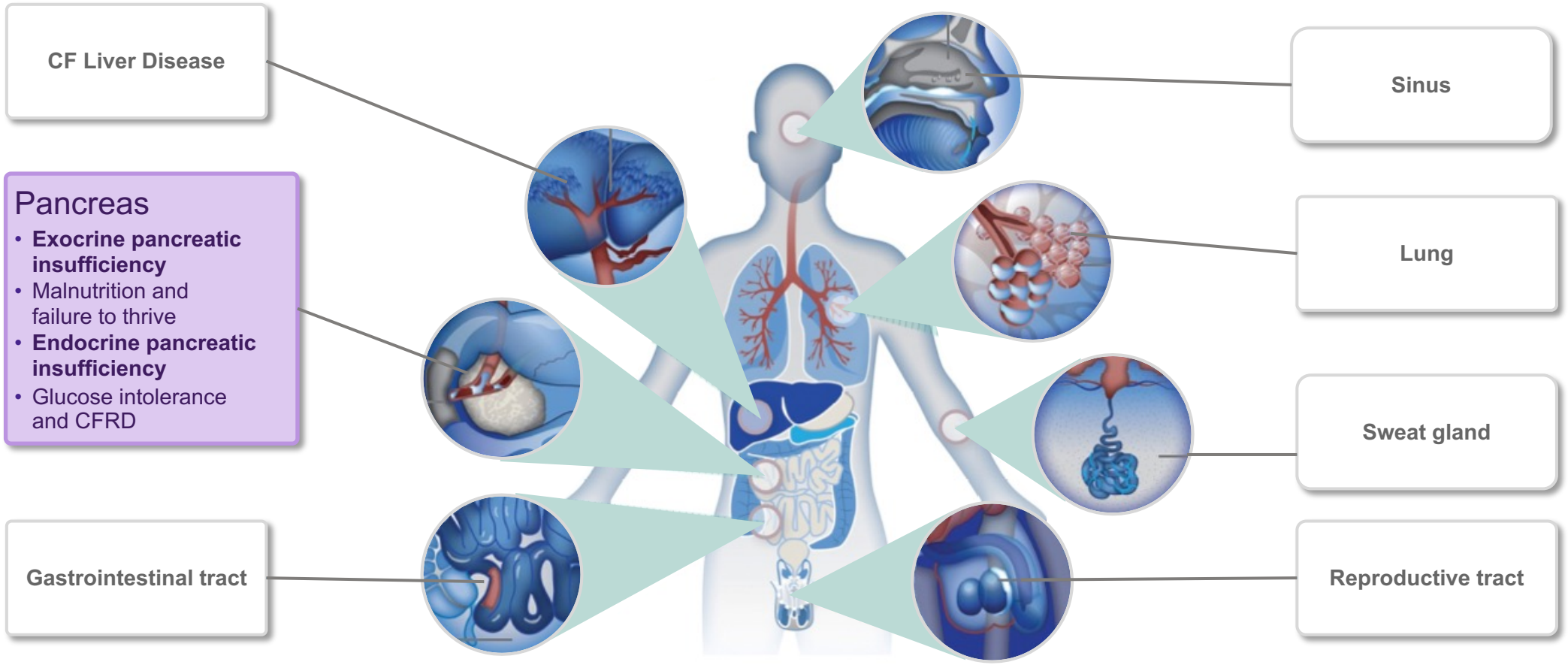
Pancreatic Disease in Cystic Fibrosis

CF is a Genetic Disease that Manifests Clinically Throughout the Body[1–6]



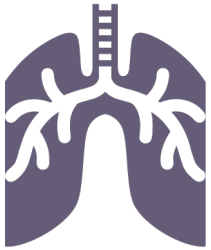
1. Wilschanski M. *Curr Gastroenterol Rep*. 2008;10:316-323. 2. O'Sullivan BP, et al. *Lancet*. 2009;373:1891-1904. 3. Wilschanski M, et al. *Cold Spring Harb Perspect Med*. 2013;3:a009746.
4. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962. 5. Haller W, et al. *J Gastroenterol Hepatol*. 2014;29:1344-1355. 6. Cutting GR. *Nat Rev Genet*. 2015;16:45-56.

Pancreatic Manifestations of CF

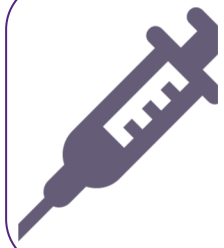
Pancreatic damage develops early in life, with damage found in neonates and fetuses at 17 weeks gestation[1]

Approximately 85–90% of infants with CF are pancreatic insufficient (PI) within the first year of life[2]

In most cases of CF, loss of exocrine pancreatic function early in life is a major cause of malnutrition[3]



In infants with CF, early malnutrition affects subsequent growth patterns and negatively impacts pulmonary outcomes[4]



CF-related diabetes is the most common co-morbidity associated with CF in adolescents and adults[5]

CFTR, cystic fibrosis transmembrane conductance regulator.

1. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962. 2. O'Sullivan BP, et al. *Lancet*. 2009;373:1891-1904. 3. De Lisle RC, et al. *Cold Spring Harb Perspect Med*. 2013;3:a009753. 4. Sanders DB, et al. *J Cyst Fibros*. 2018;17:528-535. 5. Moran A, et al. *Pediatr Diabetes*. 2018;19(Suppl 27):64-74.

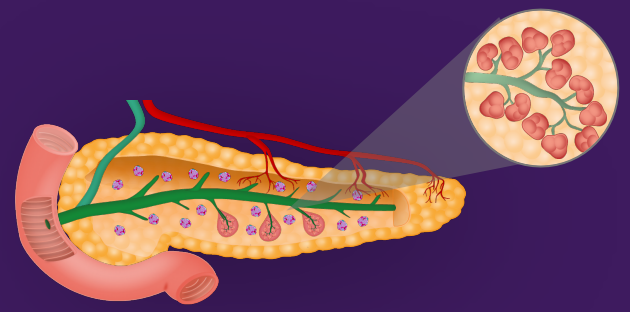
Pancreatic Phenotype is Strongly Correlated with *CFTR* Genotype

- Patients carrying two *CFTR* mutations that result in a CFTR protein with little-to-no CFTR activity have exocrine pancreatic insufficiency early in life[1,2]
- Patients carrying at least one *CFTR* mutation that confers some residual CFTR activity may have pancreatic sufficiency[1]
- Some patients with pancreatic sufficiency may become pancreatic insufficient later in life[3]
- Pancreatic function in CF may also be influenced by CFTR modifier genes (e.g. *SLC26A9*)[4]

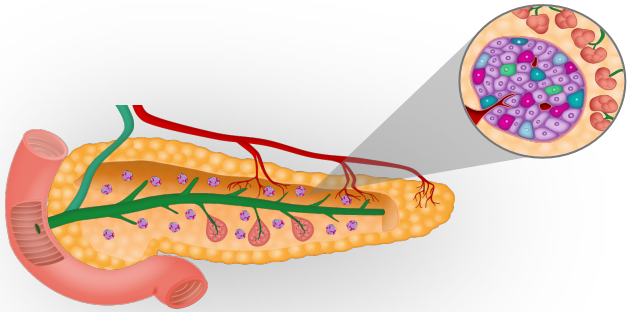
1. Ahmed N, et al. *Gut*. 2003;52:1159-1164. 2. Wilschanski M. *Curr Gastroenterol Rep.* 2008;10:316-323. 3. Cutting GR. *Annu Rev Genomics Hum Genet*. 2005;6:237-260. 4. Miller MR, et al. *J Pediatr*. 2015;166:1152-1157.

Pancreatic Disease in CF

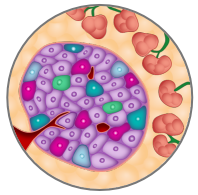
Exocrine



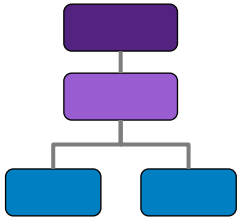
Endocrine



Exocrine Pancreatic Disease in CF



Structure and Function



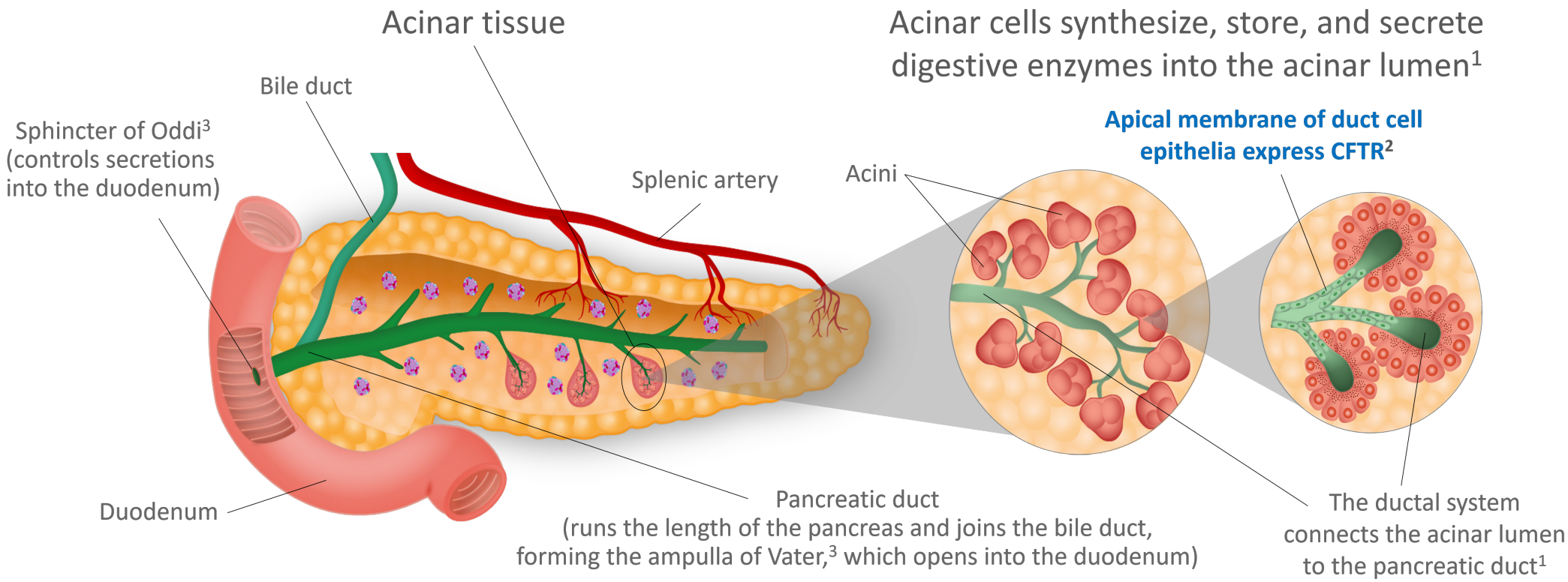
Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

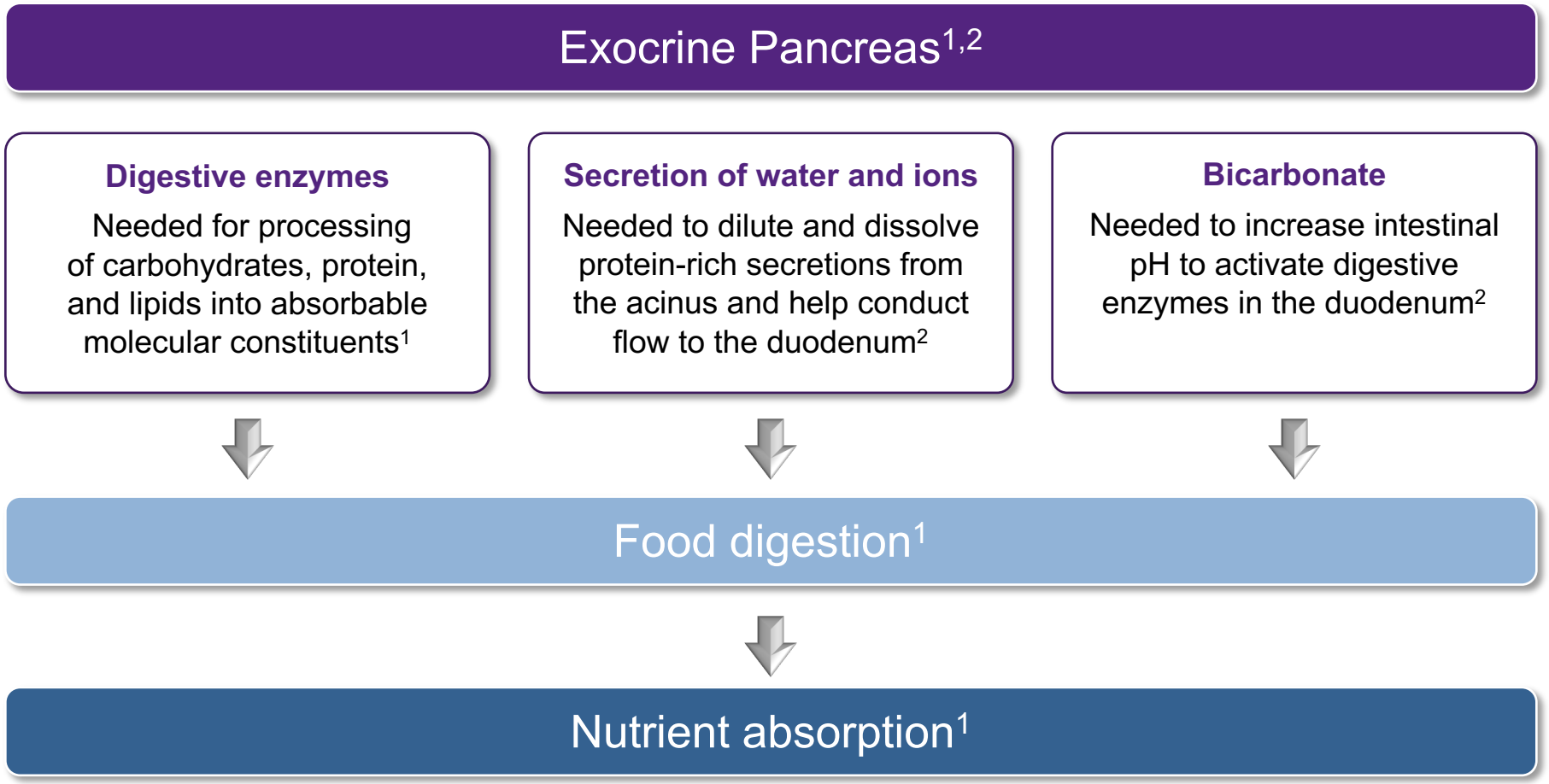
Exocrine Pancreas: Structure and Function

- 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]



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

Exocrine Pancreas Secretions are Essential for Food Digestion and Subsequent Nutrient Absorption



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

Key Pancreatic Enzymes

Amylase
(carbohydrate digestion)[1]

- Secreted by both salivary gland and pancreas[2,3]
- Carbohydrate digestion not impacted by absence of pancreatic amylase due to salivary amylase and brush border enzymes[1,4]
- High serum levels may be associated with pancreatic inflammation or pancreatic insult[5]

Lipase
(fat digestion)[1]

- High serum levels associated with pancreatic inflammation or insult; consistent low levels reflect a nonfunctioning pancreas[5,6]
- Decreased lipase activity causes steatorrhea and fat malabsorption[7]
- Overt steatorrhea does not occur until approximately 90% of glandular function is lost[4]

Trypsinogen
(breaks down protein)[3]

- An inactive pancreatic protease activated to trypsin in the intestinal lumen[8]
- Consistently high serum levels reflect inflammation in a functional pancreas; consistently low levels reflect a non-functional pancreas[6]

Elastase
(breaks down protein)[3]

- A protease secreted by the pancreatic acinar cells that is not broken down during intestinal transit[4,9]
- Fecal elastase values can fluctuate over time[9]

1. Ledder O, et al. *J Gastroenterol Hepatol*. 2014;29:1954-1962. 2. Gillard BK, et al. *Clin Chemistry*. 1983;29:1119-1123. 3. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.
4. Normatov I, et al. *Pediatr Ann*. 2019;48:e441-e447. 5. Banks PA, et al. *Am J Gastroenterol*. 2006;101:2379-2400. 6. Augarten A, et al. *Eur J Gastroenterol Hepatol*. 2008;20:164-168. 7. Wilschanski M, et al. *Gut*. 2007;56:1153-1163.
8. Berg JM, et al. (eds). Chapter 10.5. In: *Biochemistry*. 5th Edition. New York, NY: W H Freeman; 2002. 9. Meyts I, et al. *J Cyst Fibrosis*. 2002;1:265-268.

Serum Amylase Isoenzymes by Age

- Total serum amylase is low at birth and reaches adult values by 3-4 years of age
- Salivary-like amylase isoenzyme is 1/3 of adult values at birth, increases at 3 months; reaches adult values by 3 years of age
- **Pancreatic amylase isoenzyme is minimal at birth, increases by 7–9 months and reaches adult values by 5–9 years of age**

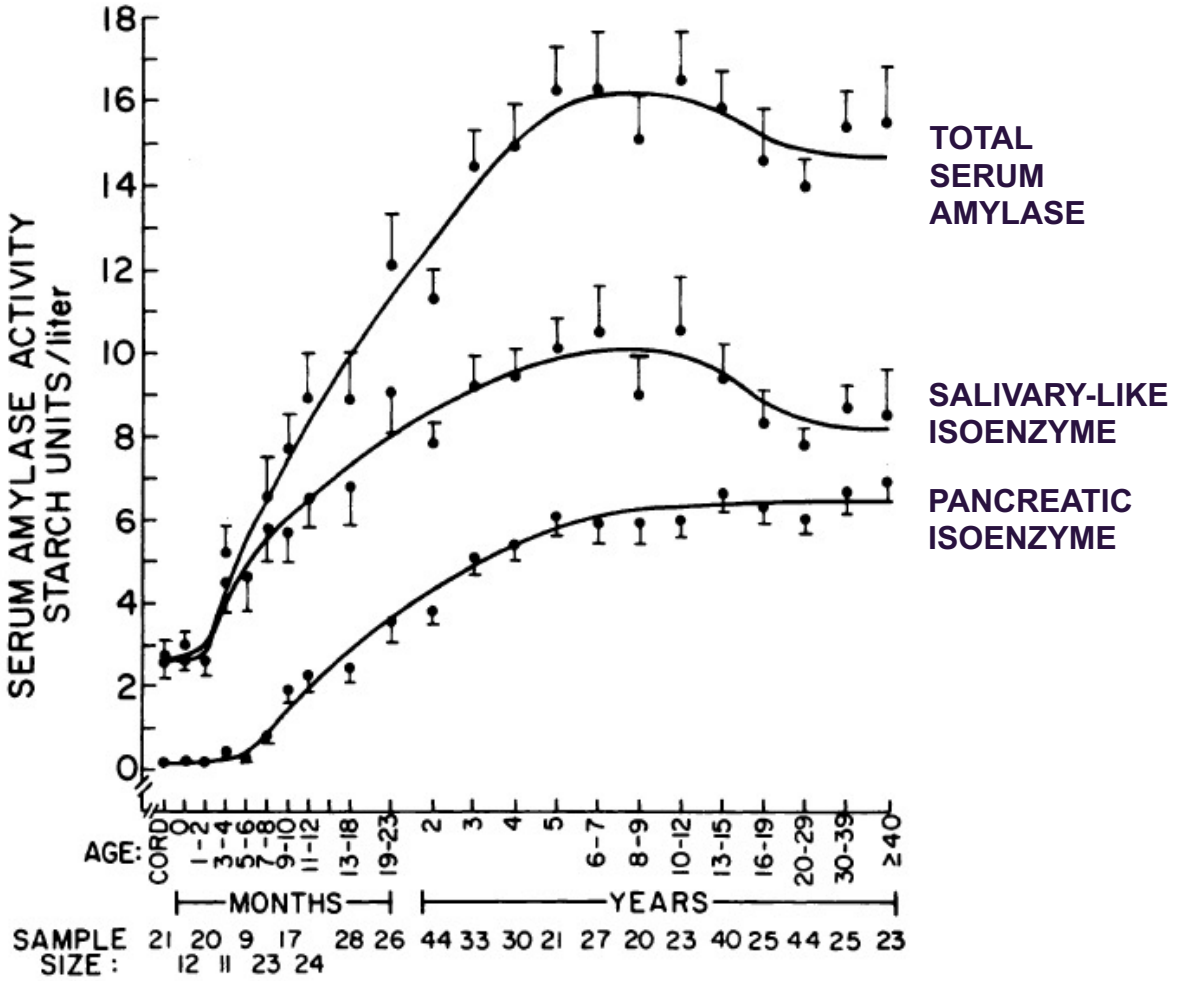
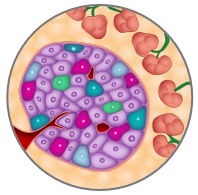
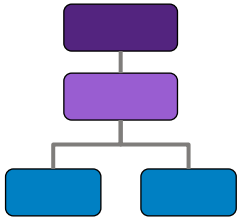


Figure reproduced with permission from Gillard BK, et al. 1983.
Gillard BK, et al. *Clin Chem.* 1983;29:1119-1123.

Exocrine Pancreatic Disease in CF



Structure and Function

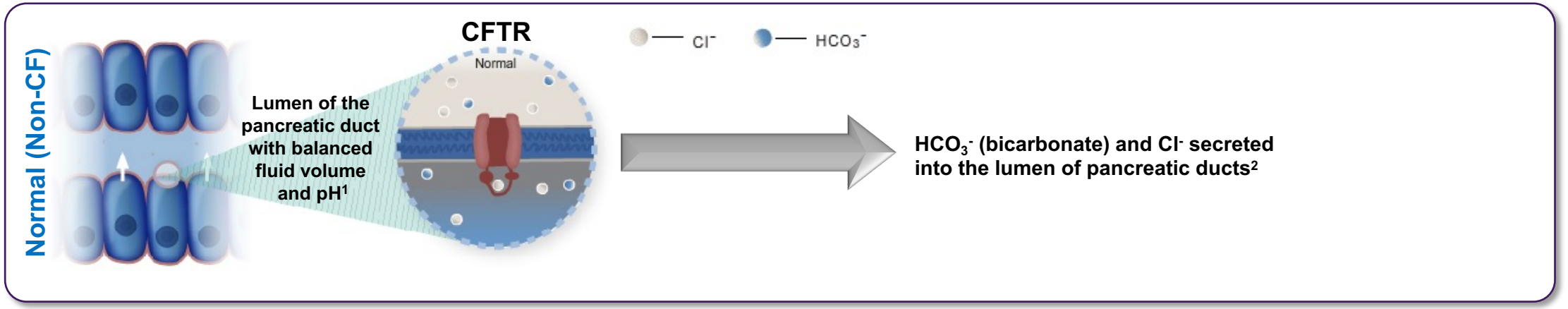


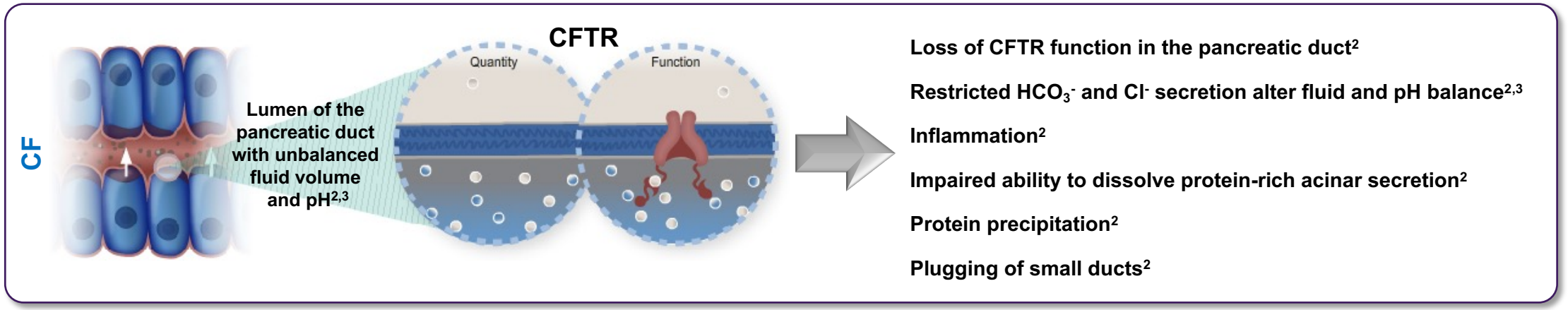
Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

Exocrine Pancreas: Pathophysiology





CFTR, cystic fibrosis transmembrane conductance regulator.

1. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010. 2. Wilschanski M, et al. *Gut*. 2007;56:1153-1163. 3. Derichs N. *Eur Respir Rev*. 2013;22:58-65.

Exocrine Pancreas: Pathophysiology

Reduced quantity and/or function of CFTR protein[1,2]

↓

Decreased chloride and bicarbonate secretion[1,2]

↓

Reduced volume and more acidic fluid[1,2]

↓

Precipitation of secreted proteins[1,2]

↓

Obstruction of pancreatic ducts[1,2]

↓

Progressive pancreatic damage, destruction of acinar tissue and atrophy[1,2]

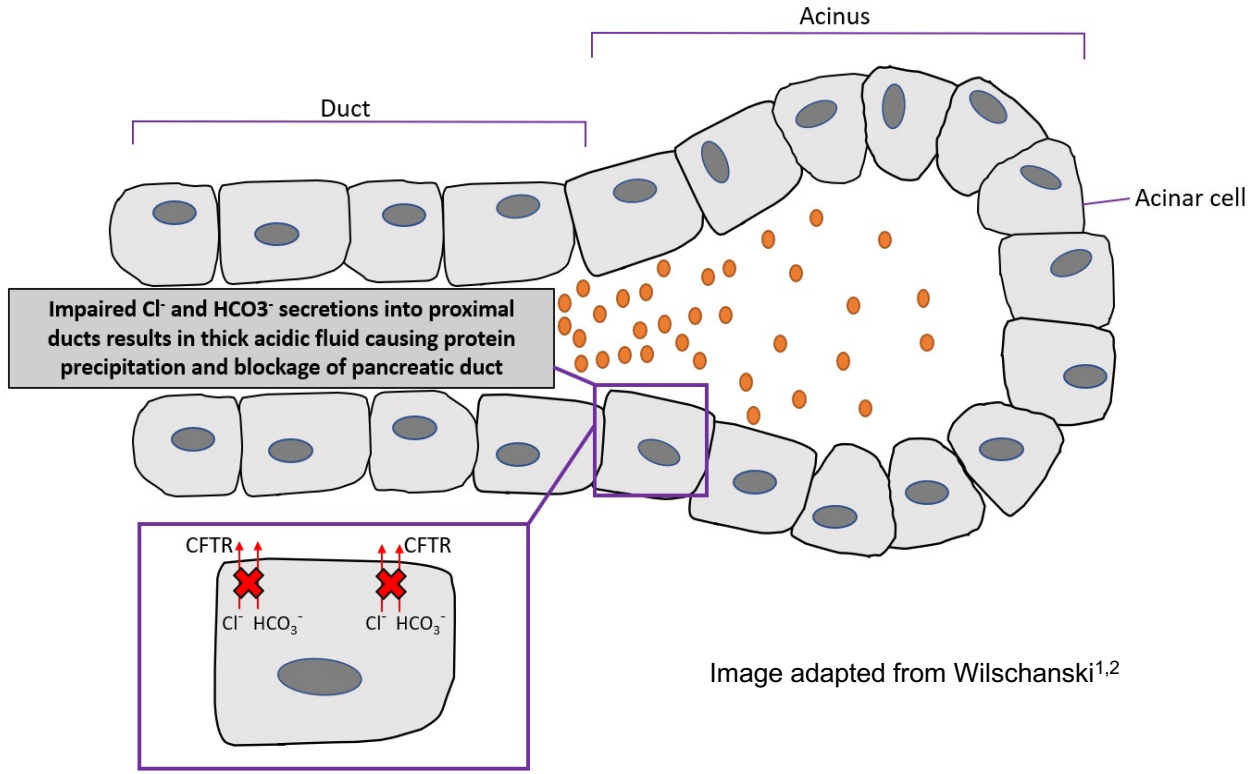
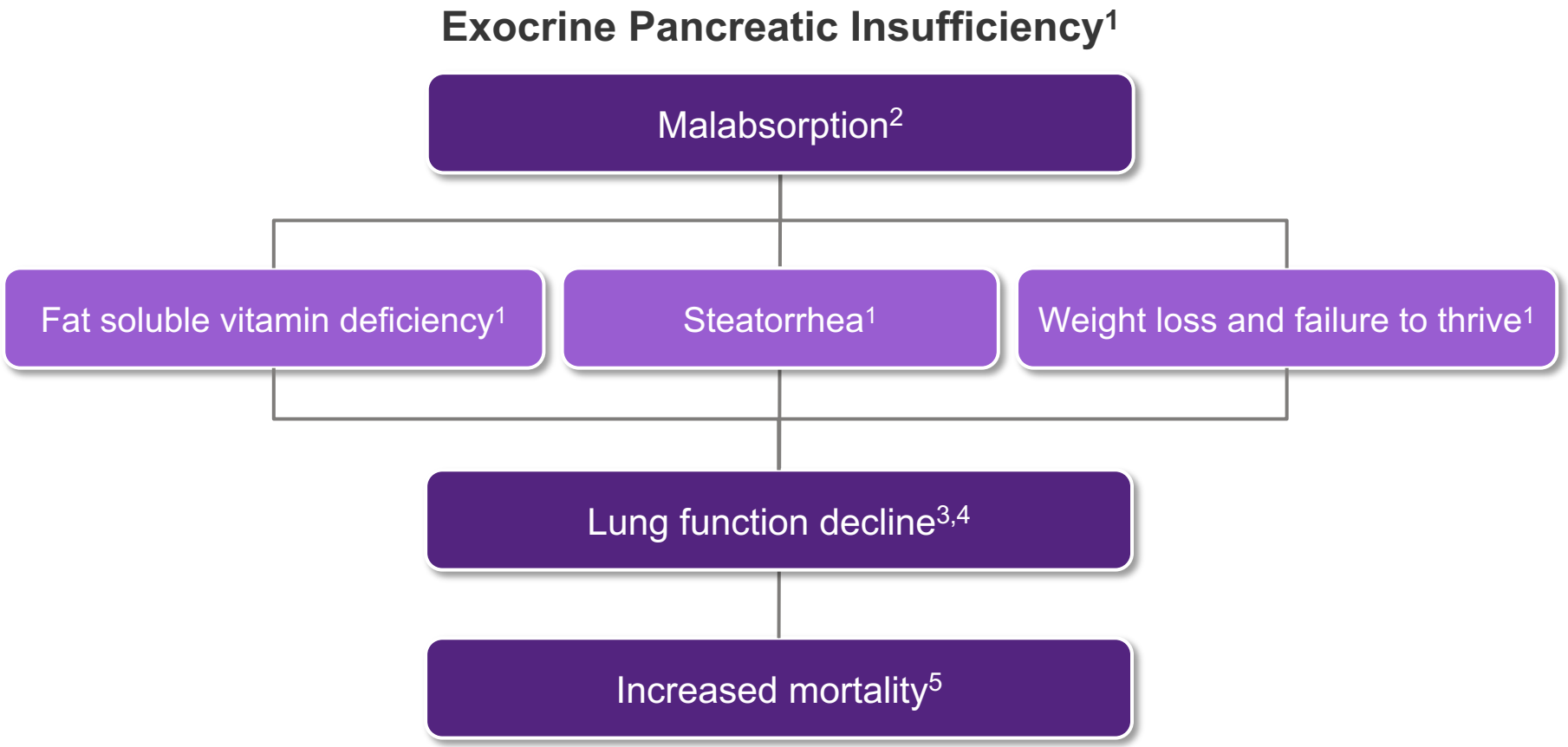


Image adapted from Wilschanski[1,2]

CFTR, cystic fibrosis transmembrane conductance regulator.

1. Wilschanski M, et al. *Gut*. 2007;56:1153-1163. 2. Wilschanski M, et al. *Cold Spring Harb Perspect Med*. 2013;3:a009746.

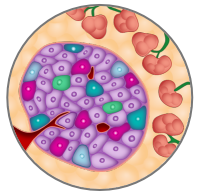
Manifestations of CF Exocrine Pancreatic Insufficiency



Not all manifestations in the pancreas fall along a continuum
Clinical manifestations may vary in individual patients

1. O'Sullivan BP, et al. *Lancet*. 2009;373:1891-1904. 2. Gelfond D, et al. *Clin Gastroenterol Hepatol*. 2013;11:333-342. 3. Konstan MW, et al. *J Pediatr*. 2003;142:624-630. 4. Peterson ML, et al. *Pediatrics*. 2003;112:588-592. 5. Davis PB, et al. *Pediatr Pulmonol*. 2004;38:204-209.

Exocrine Pancreatic Disease in CF



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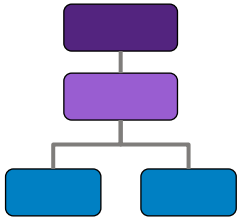


Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

Exocrine Pancreatic Function Tests

- Direct test of pancreatic function with duodenal aspiration is done infrequently
  - An invasive and complicated procedure[1]
- Indirect exocrine pancreatic function tests undertaken in patients with CF include:
  - Immunoreactive trypsinogen (IRT)[2]
  - Human pancreatic fecal elastase-1 (FE-1)[1]
  - Pancreatitis-associated protein (PAP)[3]
  - Intestinal pH[4]
  - 72-hour quantitative fecal fat (coefficient of fat absorption)[5]

1. Daftary A, et al. *J Cyst Fibros*. 2006;5:71-76. 2. Durie PR, et al. *Pediatr Res*.1986;20:209-213. 3. Sarles J, et al. *J Pediatr*. 2005;147:302-305.
4. Bodewes FA, et al. *J Cystic Fibros*. 2015;14:169-177. 5. Borowitz D, et al. *J Pediatr Gastroenterol Nutr*. 2007;44:219-223.

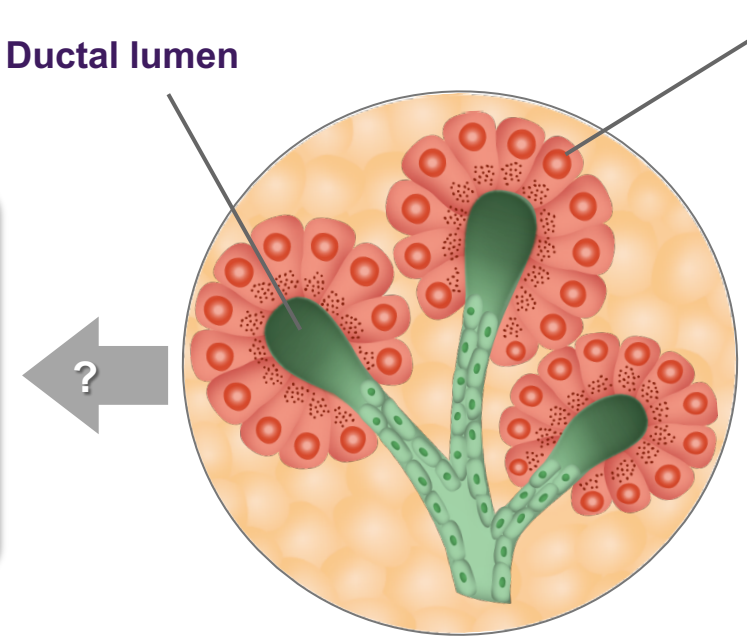
Immunoreactive Trypsinogen (IRT) Test

- Elevated levels of serum IRT are seen in neonates and infants with CF[1,2] [non-CF range (16.6–46.2 µg/liter)][1]
  - Associated with pancreatic inflammation, ductal obstruction and/or acinar cell damage and pancreatitis[1–3]
- Serum IRT can be measured by radioimmunoassay[1] or ELISA[4]
- Newborn screening for CF normally involves IRT measurement followed by DNA analysis or a second IRT measurement for confirmation; measurement of sweat chloride at 2 to 4 weeks confirms diagnosis[5]
- Consistently low trypsinogen levels (below normal) after 7 years of age can reflect a non-functional pancreas and can distinguish pancreatic insufficiency from pancreatic sufficiency[1]

ELISA, enzyme-linked immunosorbent assay; PI, pancreatic insufficiency; PS, pancreatic sufficient.

1. Durie PR, et al. *Pediatr Res*. 1986;20:209-213. 2. Wilschanski M, et al. *Gut*. 2007;56:1153-1163. 3. Augarten A, et al. *Eur J Gastroenterol Hepatol*. 2008;20:164-168. 4. MP Biomedicals. Human Immunoreactive Trypsinogen (IRT) Elisa kit. https://www.amsbio.com/human-immunoreactive-trypsinogen-amse01i0460 (last accessed November 2020). 5. Farrell PM, et al. *J Pediatr*. 2008;153:S4-S14.

Proposed Mechanism of Elevated Serum Trypsinogen Levels in CF



Increased ductal concentrations of pancreatic trypsinogen, with back diffusion into the systemic circulation?

?

?

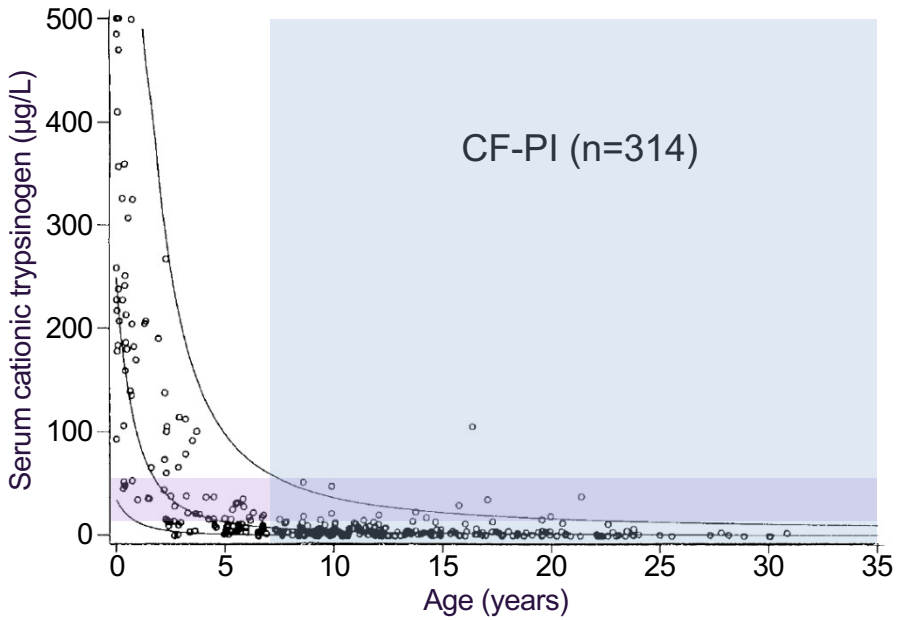
Regurgitant release of trypsinogen into the circulation from obstructed acinar-ductal units?

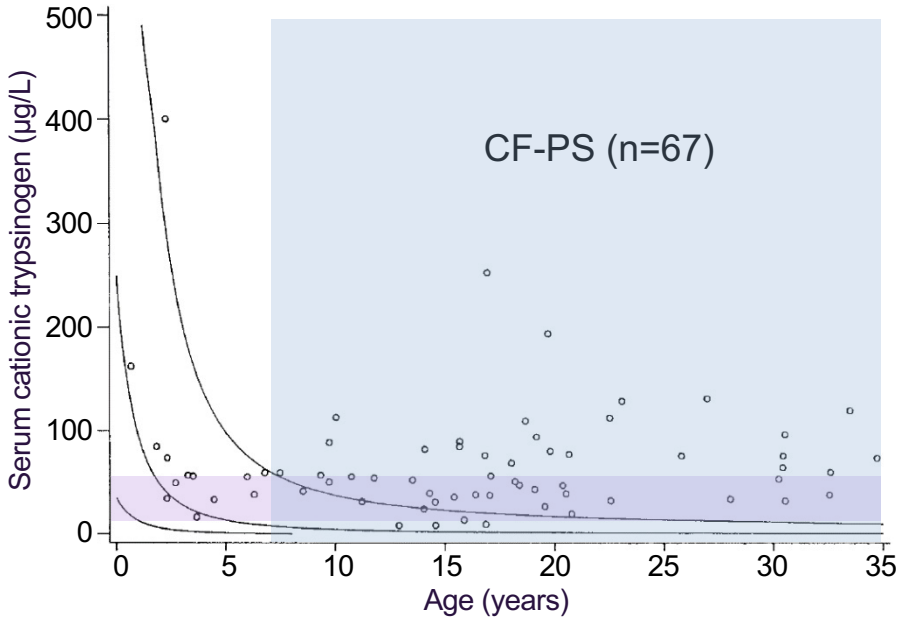
Trypsinogen enters systemic circulation

1. Couper RTL, et al. *J Pediatr*. 1995;127:408-413.

Serum Trypsinogen Levels by Age and Pancreatic Status

Observational Cross-Sectional Study*





- Rapid age-related decline in levels of serum trypsinogen in CF-PI patients
- In patients under 7 years of age, serum trypsinogen failed to distinguish CF-PS vs CF-PI patients
- After 7 years of age, serum trypsinogen was significantly higher in PS patients compared with the group with PI (P<0.001) and can reliably distinguish between these groups

CF-PI, CF with pancreatic insufficiency; CF-PS, CF with pancreatic sufficiency. *Individual serum trypsinogen values (µg/L), plotted against age, for CF-PI patients (left graph) and CF-PS patients, superimposed on the mathematically derived equation for the CF-PI group (right graph). The least squares mean and 95% confidence limits of the derived equation are shown.

Figures reprinted with permission from Durie PR, et al. 1986. Durie PR, et al. *Pediatr Res*. 1986;20:209-213.

Fecal Elastase-1 (FE-1) Test

FE-1 test is the most commonly used test to screen for pancreatic exocrine insufficiency in CF[1]

Levels of FE-1 can be measured using a monoclonal ELISA[2,3]

- FE-1 is species-specific; therefore, human FE-1 can be differentiated from the porcine elastase present in PERT

In CF, FE-1 <200 µg/g is indicative of PI[4]

- An FE-1 cut-off of 200 µg/g has a sensitivity of 99% in diagnosing PI in a pediatric population with CF[5]
- FE-1 has higher sensitivity for detecting moderate to severe PI, but lower in the cases of mild PI[6]

ELISA, enzyme-linked immunosorbent assay; PERT, pancreatic enzyme replacement therapy; PI, pancreatic insufficiency.

1. Singh VK, et al. *J Cyst Fibros*. 2017;16(Suppl 2):S70-S78. 2. Meyts I, et al. *J Cyst Fibros*. 2002;1:265-268. 3. Borowitz D, et al. *J Pediatr Gastroenterol Nutr*. 2007;44:219-223. 4. Borowitz D, et al. *J Pediatr*. 2004;145:322-326. 5. Cade A, et al. *Pediatr Pulmonol*. 2000;29:172-176. 6. Daftary A, et al. *J Cyst Fibros*. 2006;5:71-76.

Fecal Elastase-1 (FE-1) Test (Continued)

Advantages

- The test is highly sensitive (near 100%) and specific for PI, but less sensitive in PS patients
- Patients do not have to stop PERT to assess for endogenous FE-1
- Easy to perform and non-invasive
- Results can be available within 3 hours

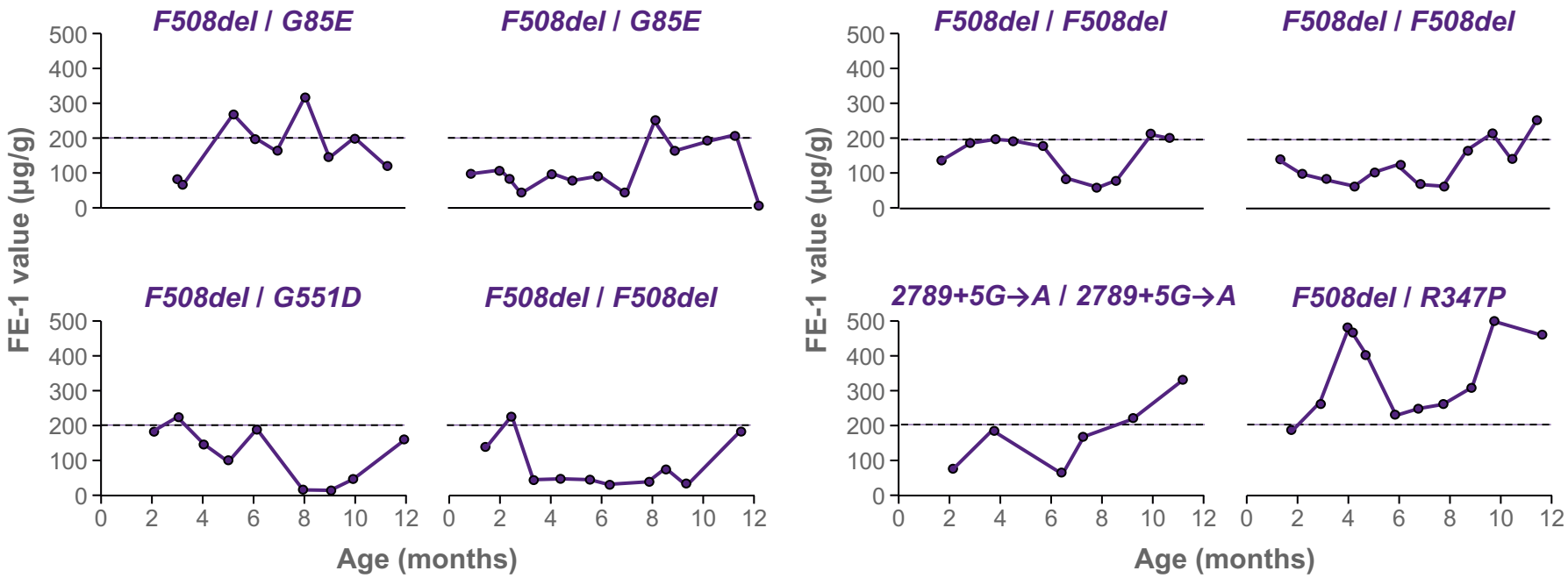
Limitations

- Diarrheal stools, intestinal inflammation, or enteropathy may confound result interpretation
- Unable to distinguish primary exocrine PI from exocrine PI secondary to intestinal villous damage
- Lack of consensus regarding an appropriate threshold level to indicate PI

FE-1, fecal elastase-1; PERT, pancreatic enzyme replacement therapy; PI, pancreatic insufficient; PS, pancreatic sufficiency.

Daftary A, et al. *J Cyst Fibros*. 2006;5:71-76.

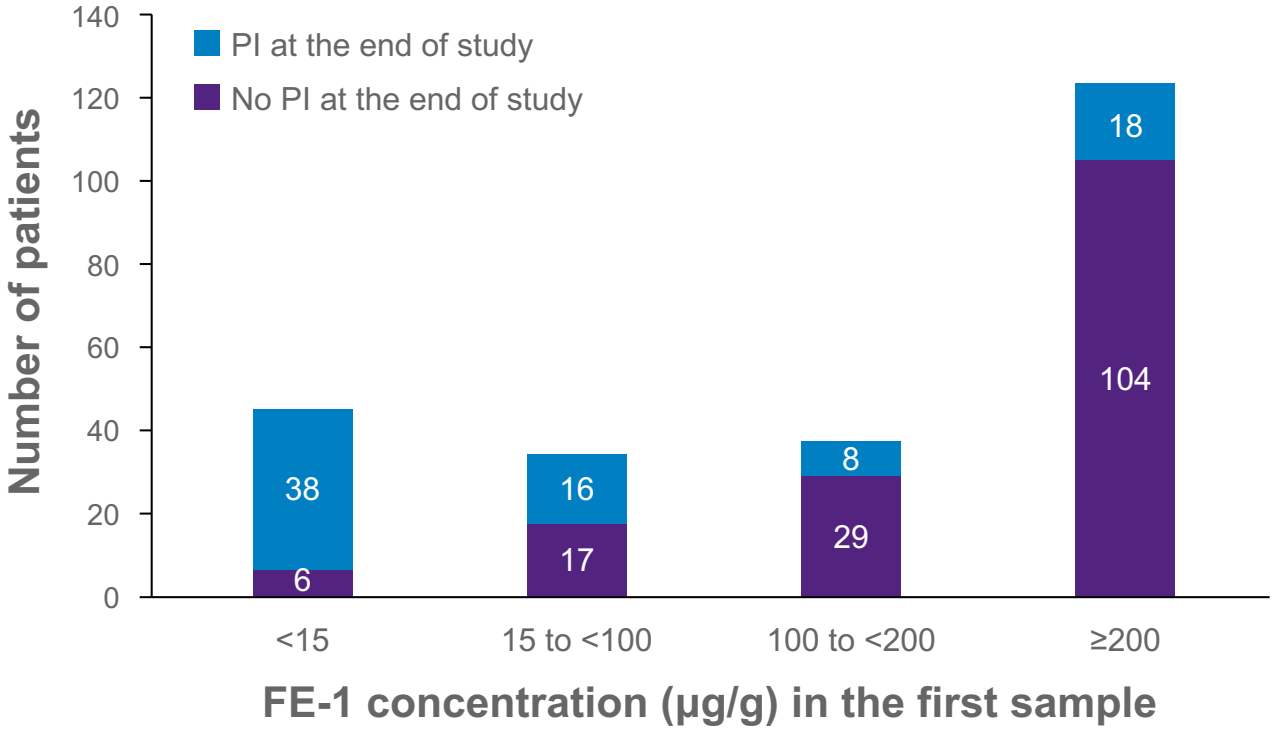
Variability in FE-1 Values Over the First Year of Life



- In the first year of life, 4/48 infants with FE-1 measures <200 µg/g at age <3.5 months had measures >200 µg/g at age >9 months
- Most (44/48) infants with CF whose first FE-1 measures were <200 µg/g finished the first year <200 µg/g
- Some infants may progress from PS to PI in the first year of life, but also some infants with an initial low FE-1 may have values consistent with PS later in the first year of life

FE-1, fecal elastase-1. Dotted line indicates accepted cut-off value for pancreatic insufficiency.
Figures adapted with permission from O'Sullivan BP, et al. 2013. O'Sullivan BP, et al. *J Pediatr*. 2013;162:808-812.

Evolution of Pancreatic Function During the First 2 Years of Life



Evolution of pancreatic function within the first 2 years of life in 236 infants with CF according to FE-1 concentration in a first sample obtained at Day 104

Maturation of pancreatic function may be delayed and occur throughout the first 2 years of life

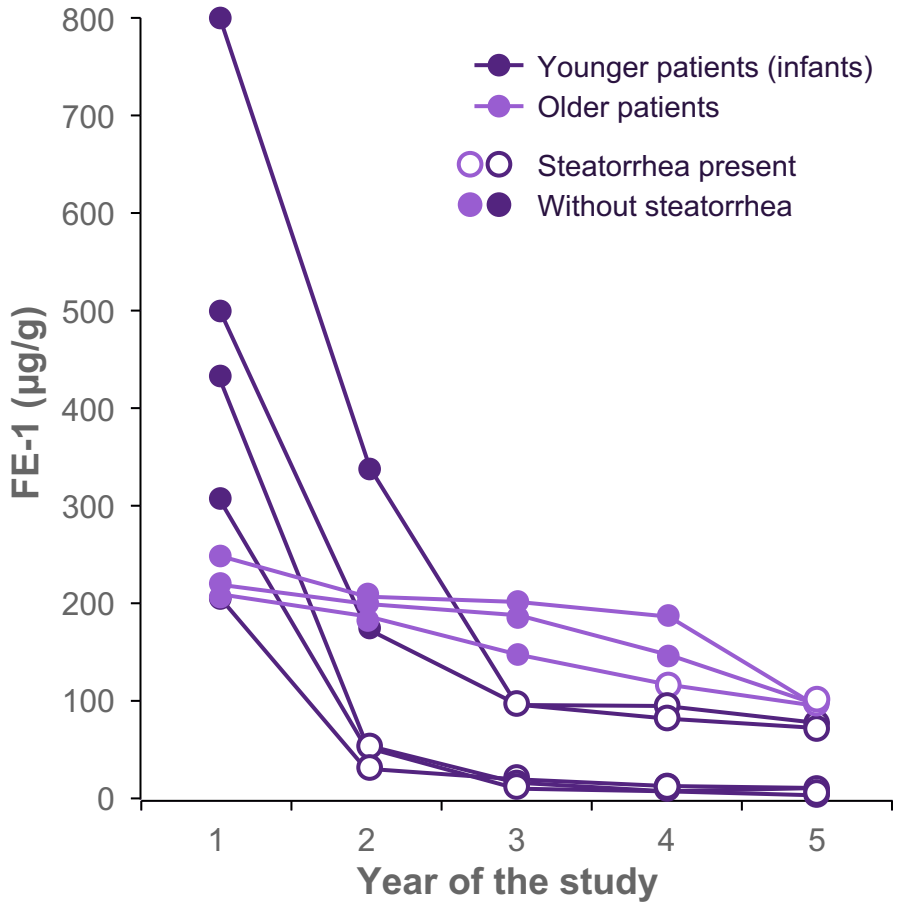
FE-1, fecal elastase-1; PI, pancreatic insufficient.

Figure reproduced with permission from Benahmed NA, et al. 2008. Benahmed NA, et al. *Ann Biol Clin (Paris)*. 2008;66:549-552.

Progression of Pancreatic Dysfunction After 2 Years of Age

- If a patient is PS after infancy, they are likely to remain PS
  - From a cohort of 630 patients with CF, only 20 PS patients became PI, at an average duration of 5.6 years from diagnosis (range 0.6 to 20.6)[1]
- In patients who progress to PI, decreases in FE-1 precede maldigestion and appearance of steatorrhea[2]
- The FE-1 test is a helpful screening tool for longitudinal assessment of declining exocrine pancreatic function in PS patients with CF[2]

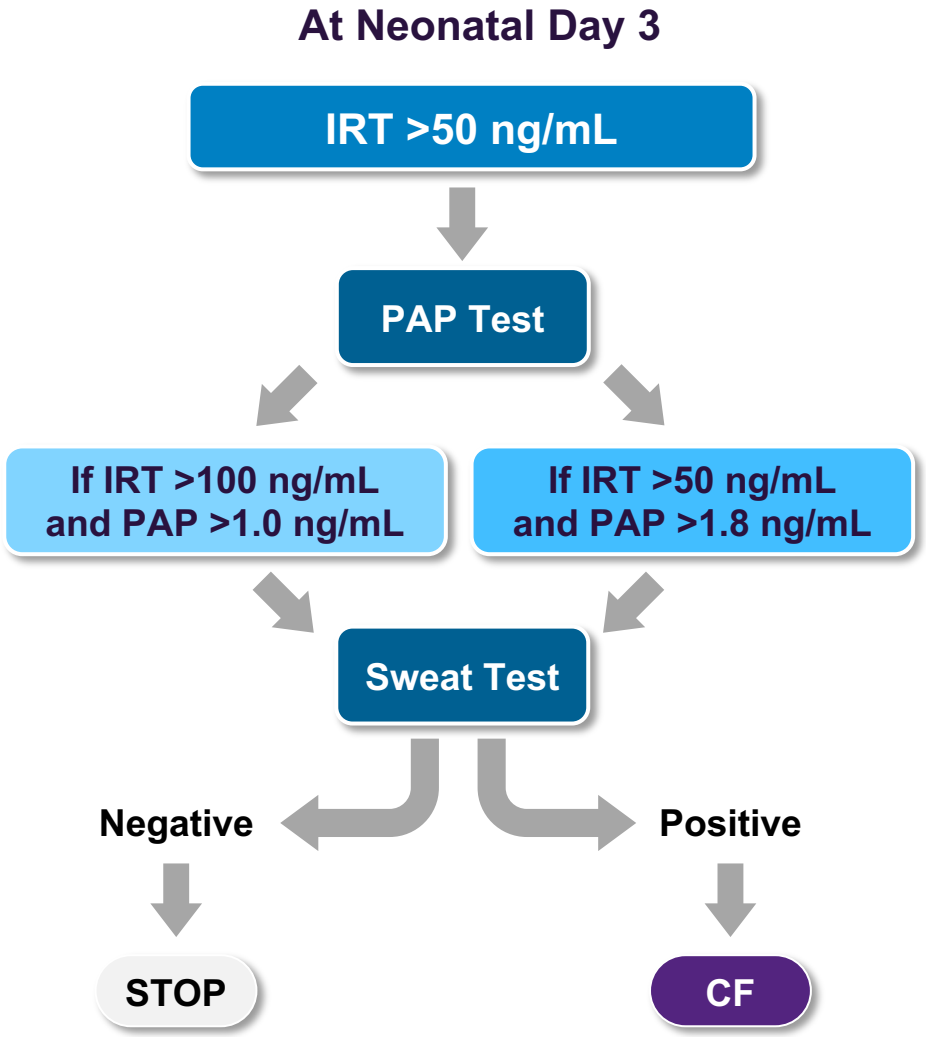
Decline of exocrine pancreatic function in initially PS patients with CF[2]



FE-1, fecal elastase-1; PI, pancreatic insufficient; PS, pancreatic sufficient. Figure adapted with permission from Walkowiak J, et al. 2003.

1. Couper RTL, et al. *Pediatr Res*. 1992;32:179-182. 2. Walkowiak J, et al. *J Pediatr Gastroenterol Nutr*. 2003;36:474-478.

Pancreatitis Associated Protein (PAP) Test



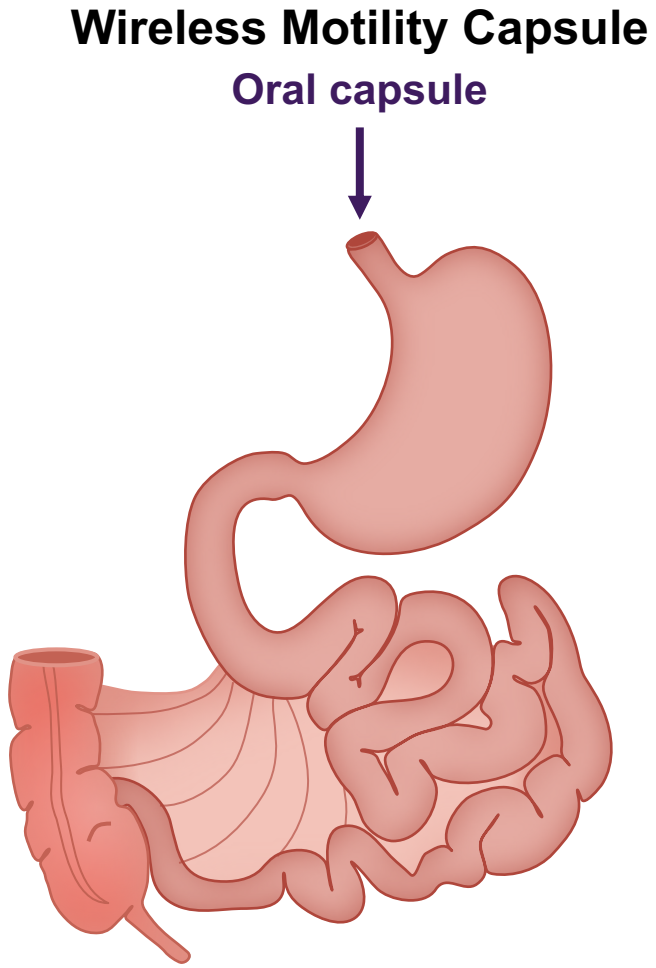
- PAP is a secretory protein that is absent from the healthy pancreas and synthesized in high amounts after sustained pancreatic stress[1]
- PAP has been reported to be elevated in newborn infants with CF[1]
- PAP is detected from blood spots collected from neonates using ELISA[2]
- The PAP test is proposed as an alternative screening tool for CF after initial elevated IRT results[2]

ELISA, enzyme-linked immunosorbent assay; IRT, immunoreactive trypsinogen; PAP, pancreatitis associated protein.

1. Sarles J, et al. *Arch Dis Child Fetal Neonatal Ed*. 1999;80:F118-F122. 2. Sarles J, et al. *J Pediatr*. 2005;147:302-305.

Measuring Intestinal pH Profile in CF

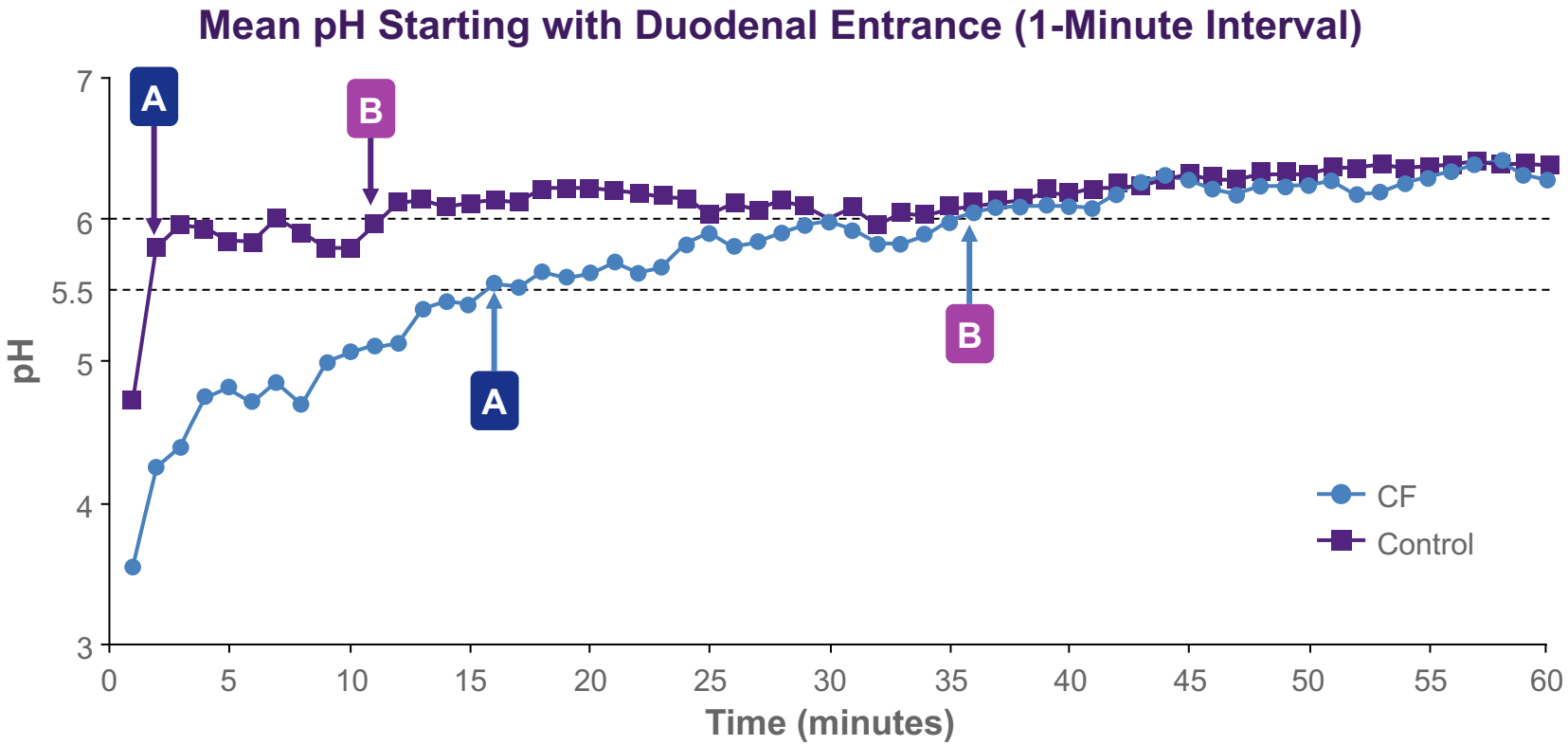
- CFTR is essential for adequate pancreatic and duodenal bicarbonate secretion[1,2]
- In patients with CF, bicarbonate secretion is insufficient to neutralize gastric acid load[1,2]
- On average, duodenal pH is 1 to 2 units lower (more acidic) in patients with CF compared with healthy controls[2]
- A wireless motility capsule can be used to measure pH during intestinal transit[2,3]



CFTR, cystic fibrosis transmembrane conductance regulator.

1. Wilschanski M, et al. *Gut*. 2007;56:1153-1163. 2. Bodewes FA, et al. *J Cyst Fibros*. 2015;14:169-177. 3. Gelfond D, et al. *Dig Dis Sci*. 2013;58:2275-2281.

Wireless Motility Capsules Detected Deficient Capacity for Neutralization of Gastric Acid in Patients with CF



- Gastrointestinal pH assessment reveals likely inadequate bicarbonate secretion in CF
- Significant differences between groups in time to reach and maintain pH >5.5 [A] and pH >6.0 [B] (P<0.001)
- Inadequate acid neutralization likely contributes to the nutritional deficiencies and various gastrointestinal symptoms prevalent in patients with CF

Figure adapted with permission from Gelfond D, et al. 2013. Gelfond D, et al. *Dig Dis Sci*. 2013;58:2275-2281.

Coefficient of Fat Absorption (CFA) Test

Considered the ‘gold standard’ indirect test[1–3]

Based on calculation of the CFA

- Ratio of ingested to excreted fat (CFA) of <93% indicates pancreatic insufficiency[1–3]
- In infants <6 months of age, a CFA of ≥85% is considered normal[3]

Methodology[1]

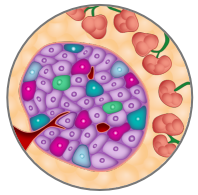
- Three days of a high-fat diet (food diary needs to be accurate)
- Stool collection between the beginning and end of the high-fat diet
- Fecal fat analysis

Seldom performed in patients with CF because of the following potential limitations[4]

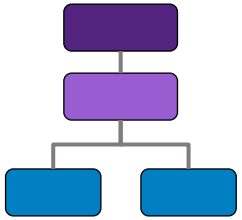
- Time-consuming, cumbersome
- Fails to determine the underlying cause of steatorrhea
- Prone to inaccuracy caused by errors in stool collection and recording of nutrient intake

1. Borowitz D, et al. *J Pediatr Gastroenterol Nutr*. 2007;44:219-223. 2. Weintraub A, et al. *J Pediatr Gastroenterol Nutr*. 2009;48:306-310. 3. Borowitz D, et al. *J Pediatr*. 2009;155(6 Suppl 4):S73-S93. 4. Beharry S, et al. *J Pediatr*. 2002;141:84-90.

Exocrine Pancreatic Disease in CF



Structure and Function



Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

Exocrine Pancreatic Insufficiency Manifestations in CF

Patients in the U.S. with mutations typically associated with little-to-no CFTR function are more likely to be prescribed PERT (96.7%)[1]

Nutritional and growth outcomes are often not fully corrected with optimal PERT[2]

Steatorrhea, an indicator of PI, occurs when lipase secretion from the exocrine pancreas is <4% of the lowest levels seen in subjects with normal pancreatic function[3]

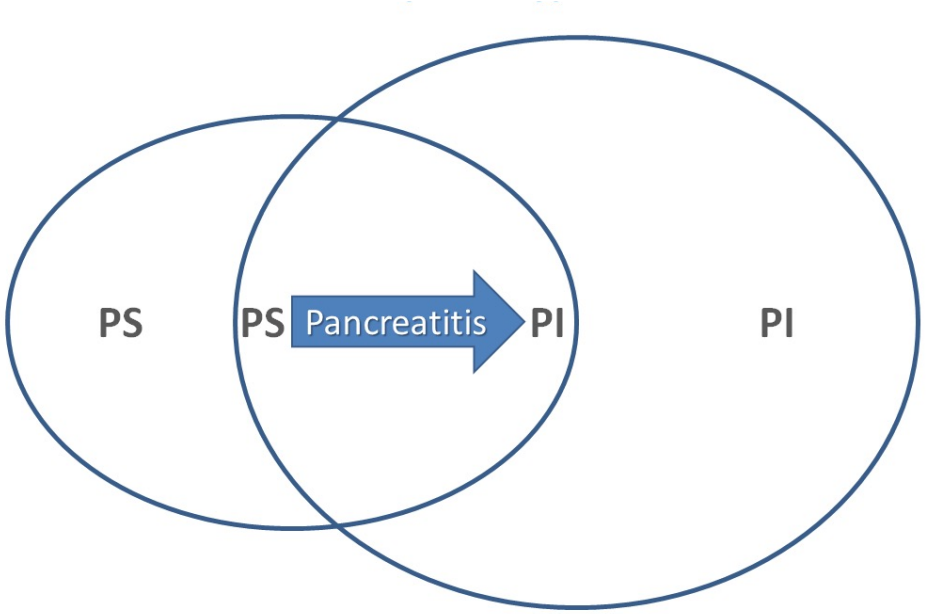
Poor nutritional status in CF is highly correlated with lung function deterioration and is a strong predictor of mortality[4]

CFTR, cystic fibrosis transmembrane conductance regulator; PERT, pancreatic enzyme replacement therapy; PI, pancreatic insufficiency.

1. Cystic Fibrosis Foundation (CFF) Patient Registry 2019 Annual Data Report. Bethesda, Maryland ©2020 CFF. 2, Borowitz D, et al. *J Pediatr Gastroenterol Nutr*. 2005;41:273-285. 3. Gaskin KJ, et al. *Gastroenterology*. 1984;86:1-7. 4. De Lisle RC, et al. *Cold Spring Harb Perspect Med*. 2013;3:a009753.

Pancreatitis May Occur in Patients Who Are Pancreatic Sufficient

Pancreatic phenotypes in CF[1]



Functioning acinar tissue is required to develop pancreatitis, and is reported in up to 20% of patients with CF who are PS[1–3]

Patients with CF who are PS can become PI later in life with or without a history of pancreatitis[2,3]

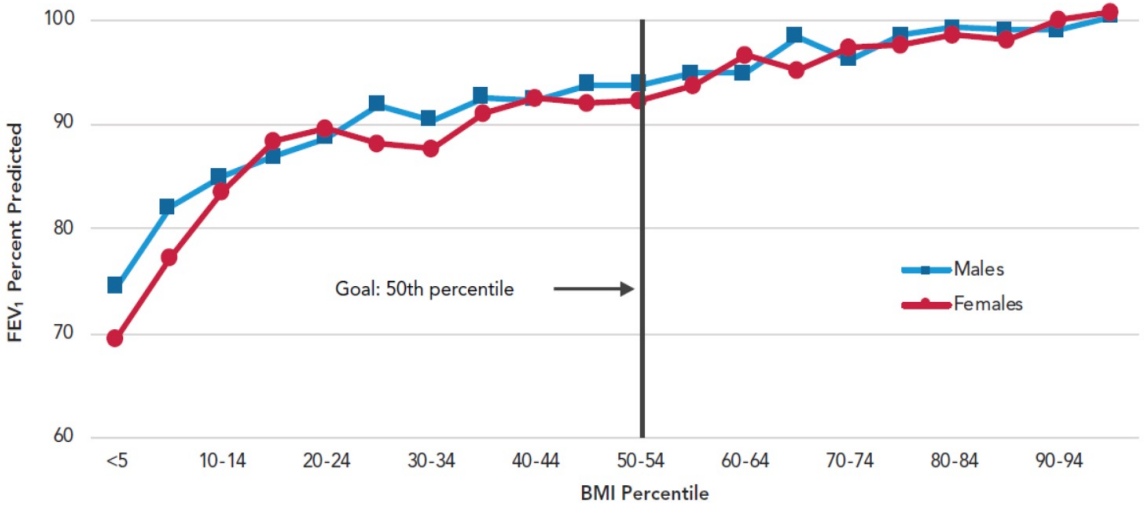
Patients with CF who are PS and also have a history of pancreatitis are more likely to develop PI than those without a history of pancreatitis (OR: 5.5 [range: 1.3–23])[2]

OR, odds ratio; PI, pancreatic insufficient; PS, pancreatic sufficient. Sizes of the ovals representing the PS and PI populations are not drawn to scale.

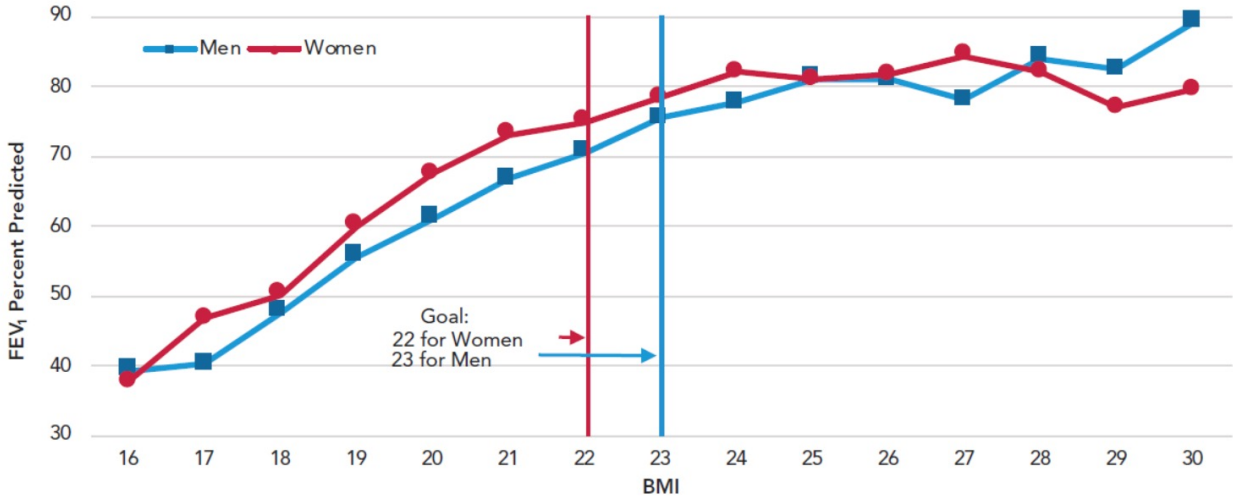
Figure adapted with permission from Augarten A, et al. 2008. 1. Augarten A, et al. *Eur J Gastroenterol Hepatol*. 2008;20:164-168. 2. Ooi CY, et al. *Gastroenterology*. 2011;140:153-161. 3. Durno C, et al. *Gastroenterology*. 2002;123:1857-1856.

Growth and Nutritional Status are Associated with Pulmonary Function in U.S. Patients with CF

$ppFEV_1$ vs BMI Percentile for Children Aged 6–19 Years (2019 Data)



$ppFEV_1$ vs BMI Value for Adults Aged 20–40 Years (2019 Data)

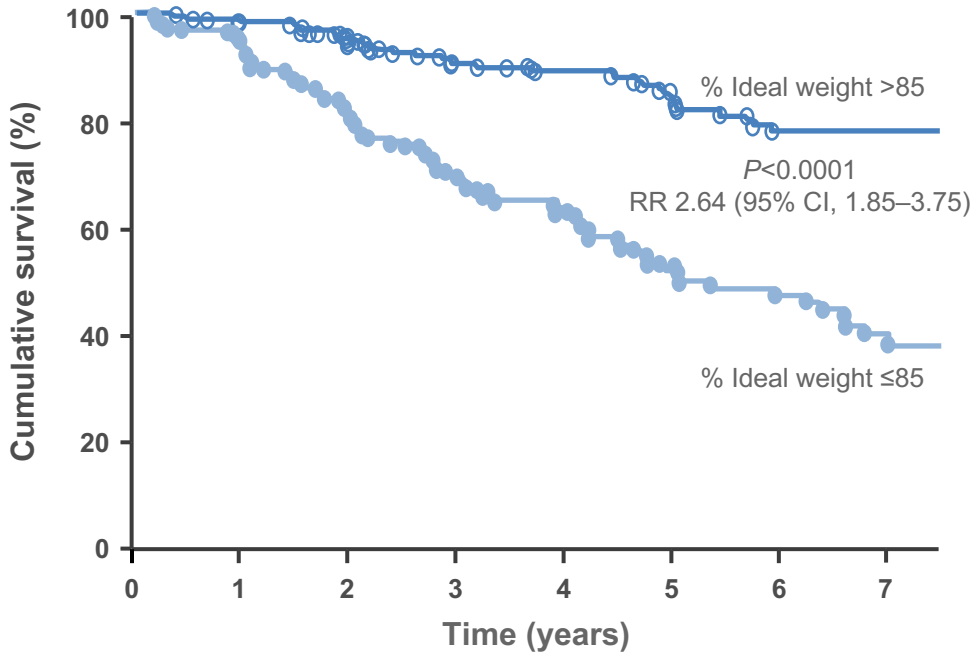


BMI, body mass index; $ppFEV_1$, percent predicted forced expiratory volume in one second.

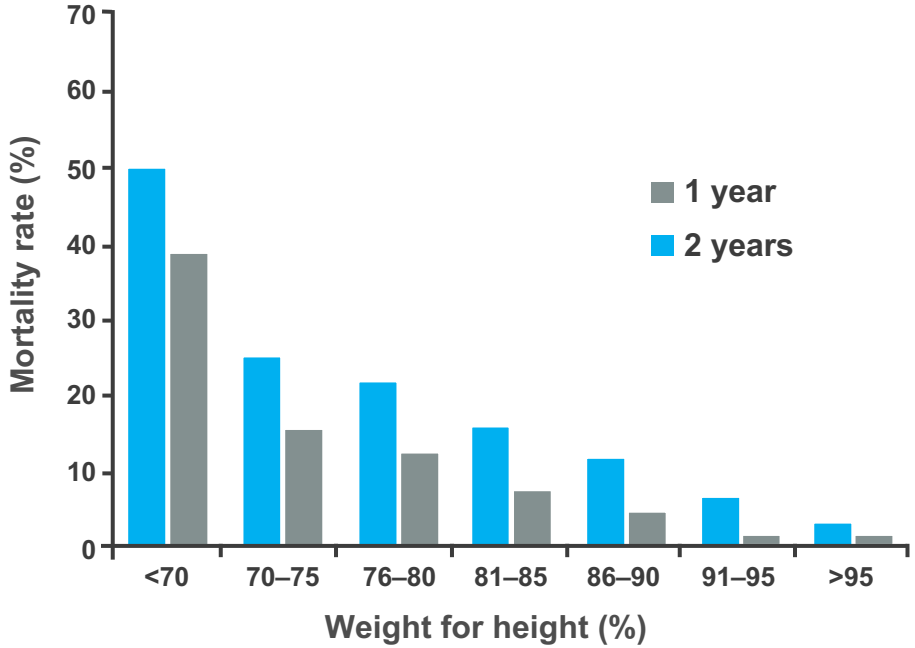
Cystic Fibrosis Foundation (CFF) Patient Registry 2019 Annual Data Report. Bethesda, Maryland ©2020 CFF.

Reduced Growth is a Significant and Independent Risk Factor for Mortality in Patients with CF

Survival by Percentage of Ideal Weight[1]



Greater Weight-for-Height Percentage is Associated with Improved Survival in CF[2]

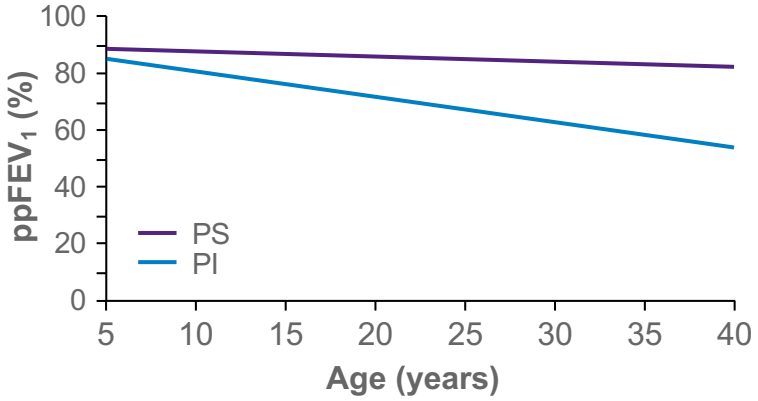


RR, risk ratio. Left-hand figure adapted with permission from Sharma R, et al, 2001. Right-hand figure adapted with permission from Kerem E, et al. 1992.

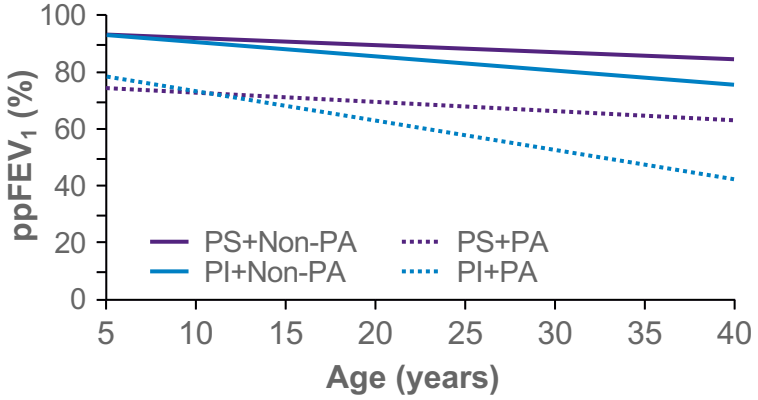
1. Sharma R, et al. *Thorax*. 2001;56:746-750. 2. Kerem E, et al. *N Engl J Med*. 1992;362:1187-1191.

Deterioration of Lung Function in PI and PS Patients

Mixed model regression lines of $ppFEV_1$ vs age in years for CF patients with PS and PI



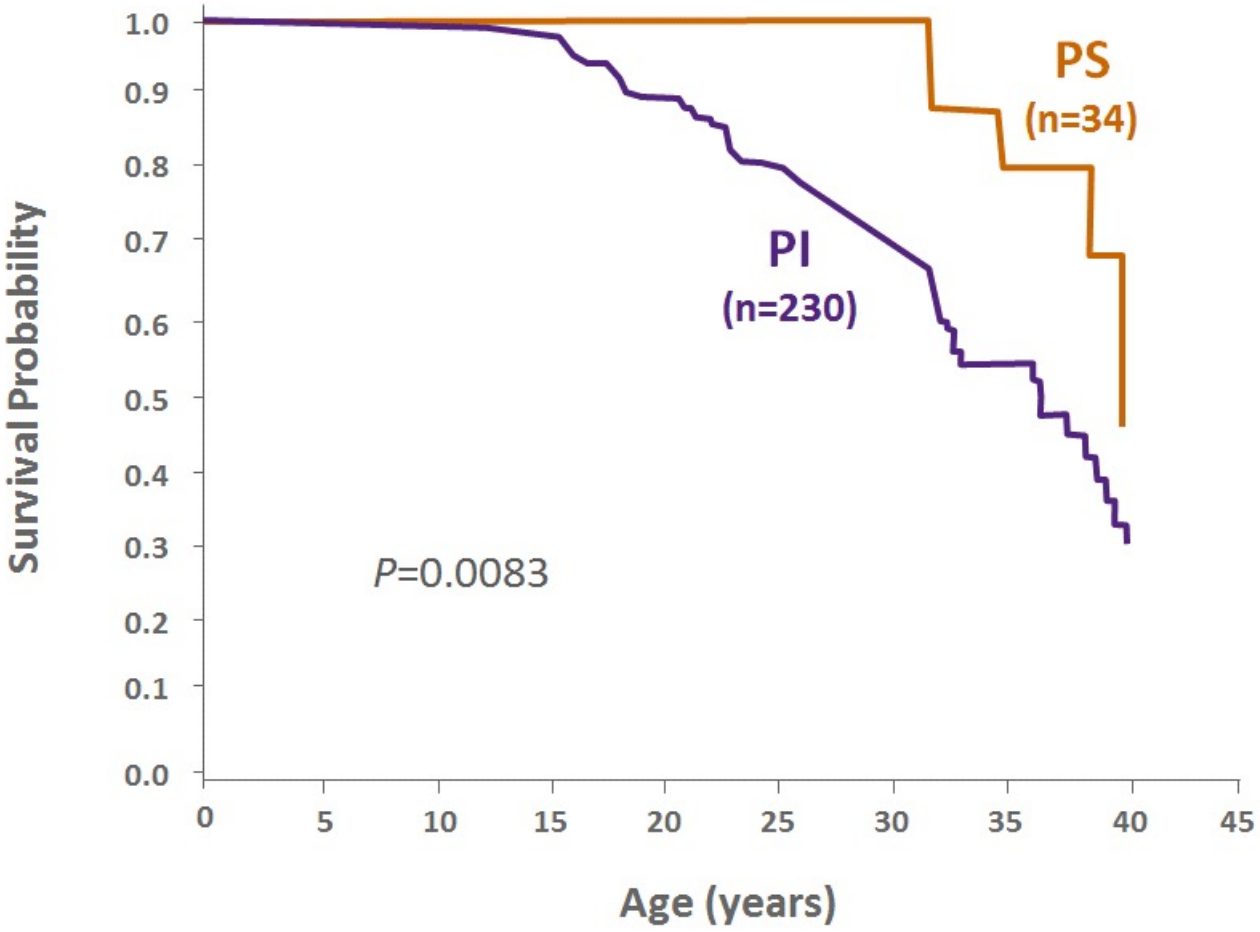
Mixed model regression lines of $ppFEV_1$ vs age in years for patients with PS and PI with or without chronic *P. aeruginosa* colonization



- PI patients showed a steeper annual rate of deterioration of $ppFEV_1$ than PS patients
- PS patients had a lower rate of *P. aeruginosa* colonization compared with PI patients
- Faster deterioration in $ppFEV_1$ was found in PI patients with *P. aeruginosa* infection

PA, *P. aeruginosa*; PI, pancreatic insufficient; $ppFEV_1$, percent predicted forced expiratory volume in one second; PS, pancreatic sufficient.
Figures adapted with permission from Schaedel C, et al. 2002. Schaedel C, et al. *Pediatr Pulmonol*. 2002;33:483-491.

Patients with *CFTR* Alleles Associated with Pancreatic Sufficiency had Significantly Better Survival



Kaplan-Meier survival curves for patients with CF who are PS (orange line) and patients with CF who are PI (purple line)*

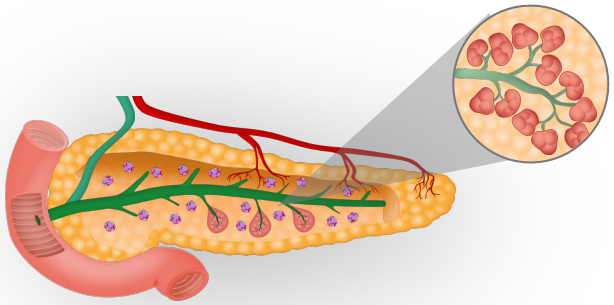
PI, pancreatic insufficient; PS, pancreatic sufficient.

*Pancreatic status was based on genotype: *F508del* homozygous = PI; mutations associated with 'mild' status = PS.

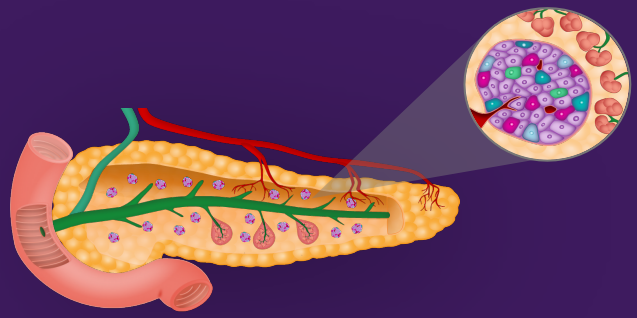
Davis PB, et al. *Pediatr Pulmonol*. 2004;38:204-209.

Pancreatic Disease in CF

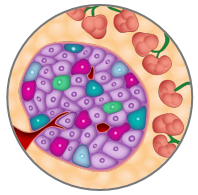
Exocrine



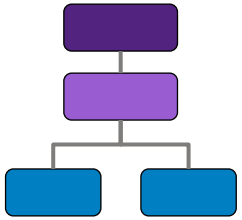
Endocrine



Endocrine Pancreatic Disease in CF



Structure and Function



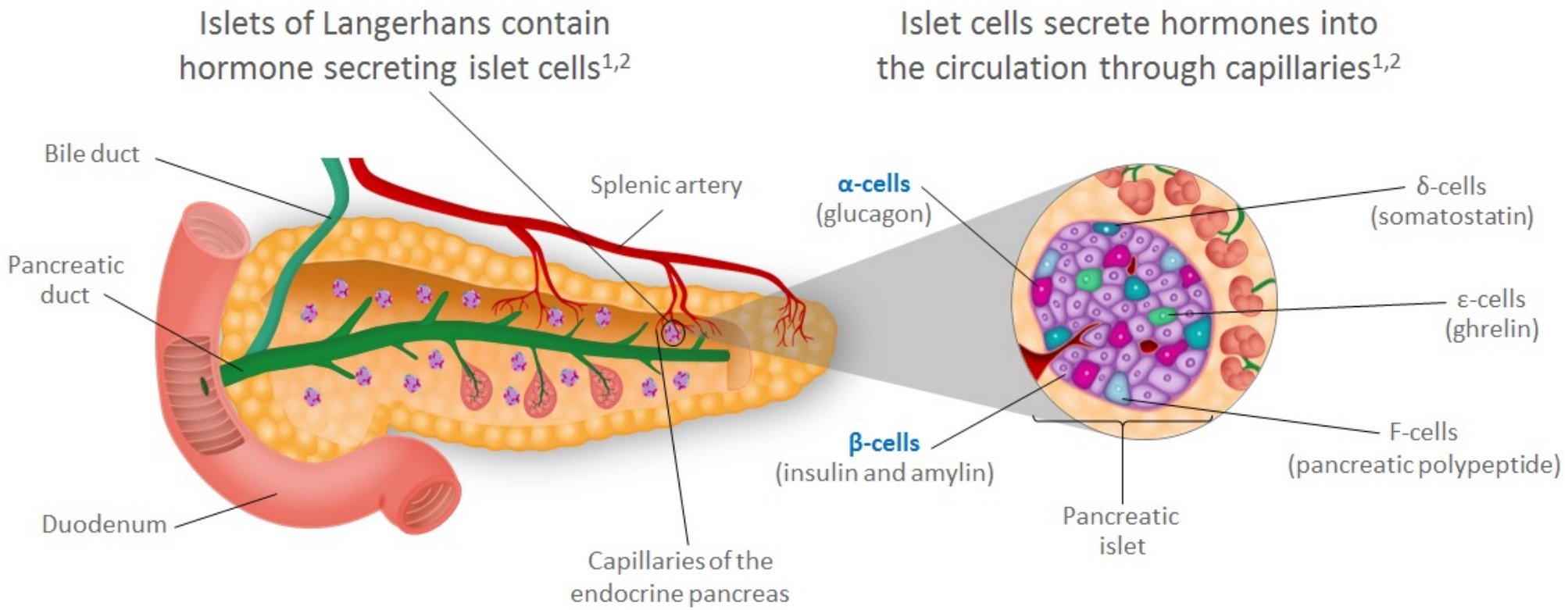
Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

Endocrine Pancreas: Structure and Function

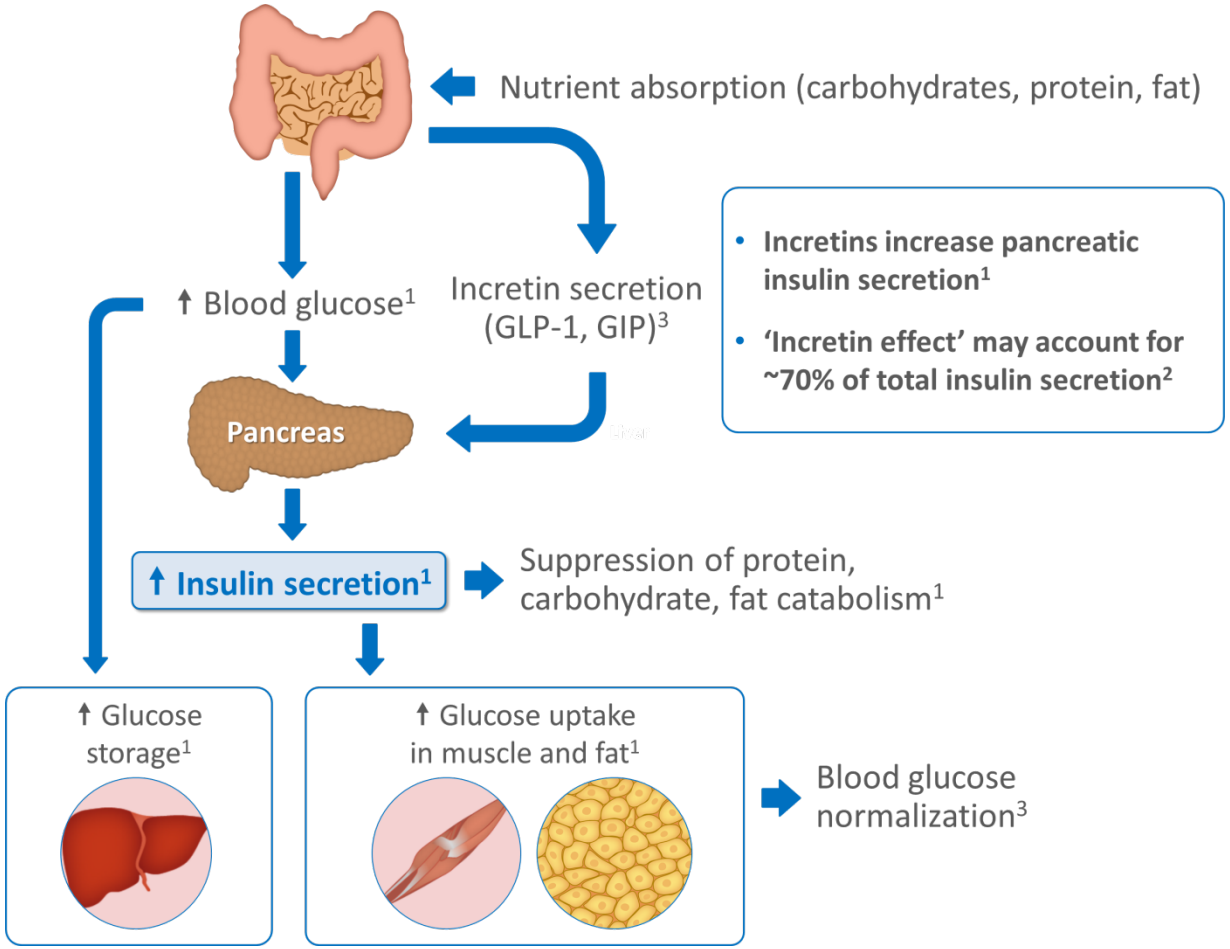
- The endocrine function of the pancreas is to produce and secrete hormones (e.g. insulin, glucagon, etc.) into the bloodstream[1,2]
- Endocrine islet cells comprise 1% to 2% of pancreatic mass[1]



1. Begg DP, et al. *Adv Physiol Educ*. 2013;37:53-60. 2. Pandol SJ. *The Exocrine Pancreas*. San Rafael (CA): Morgan & Claypool Life Sciences; 2010.

Role of the Pancreas in Glucose Metabolism in Healthy Non-CF Individuals

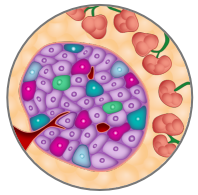
Glucose concentrations are tightly regulated in healthy individuals[1–3]



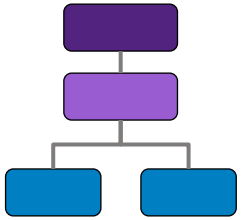
GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1.

1. Nussey S, et al. Chapter 2. *The Endocrine Pancreas*. In: Endocrinology: An Integrated Approach. Oxford: BIOS Scientific Publishers; 2001. 2. Nauck M, et al. *Diabetologia*. 1986;29:46-52. 3. Aronoff SL, et al. *Diabetes Spectrum*. 2004;17:183-190.

Endocrine Pancreatic Disease in CF



Structure and Function

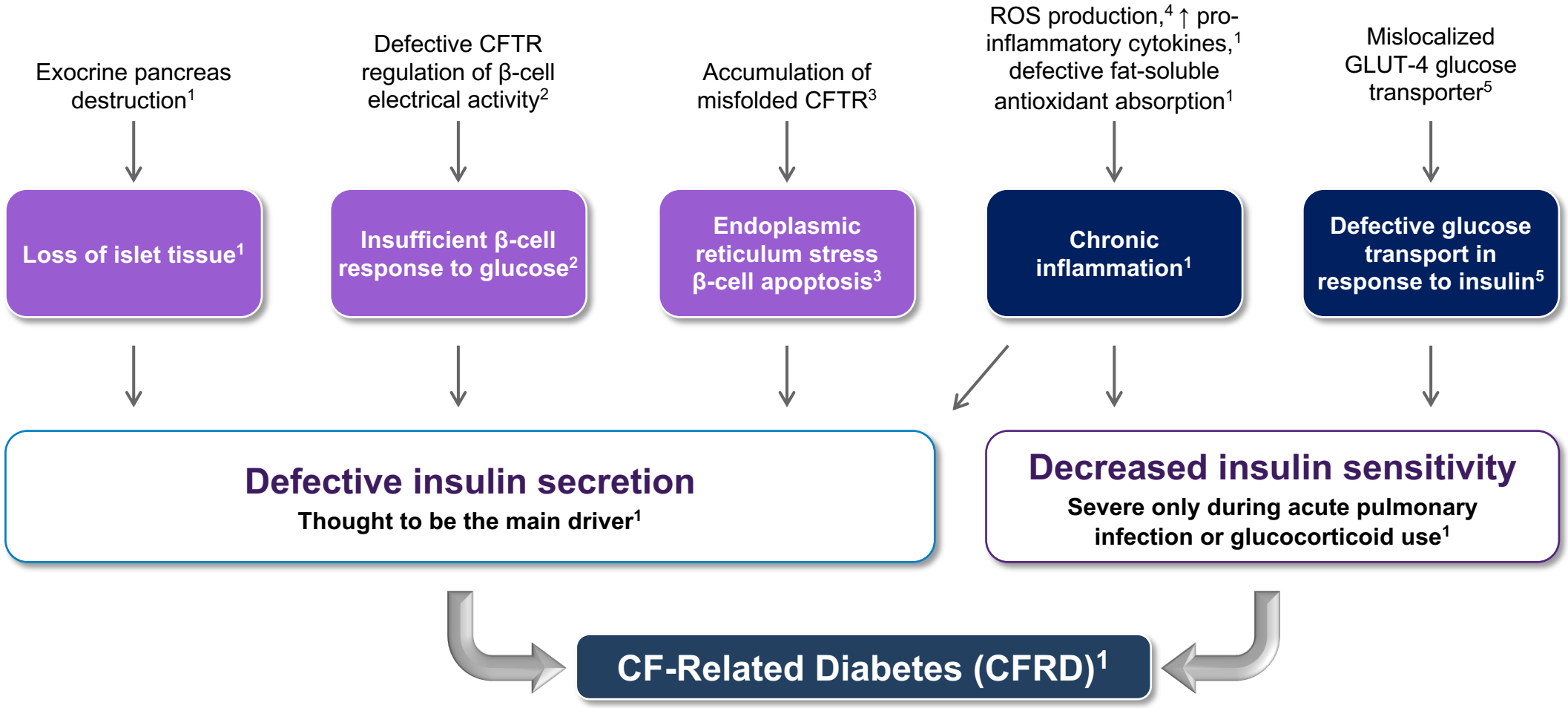


Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

Potential Mechanisms of Endocrine Pancreas Pathophysiology in CF



GLUT-4, glucose transporter-4; ROS, reactive oxygen species.

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

Comparison of CFRD with Type 1 and Type 2 Diabetes

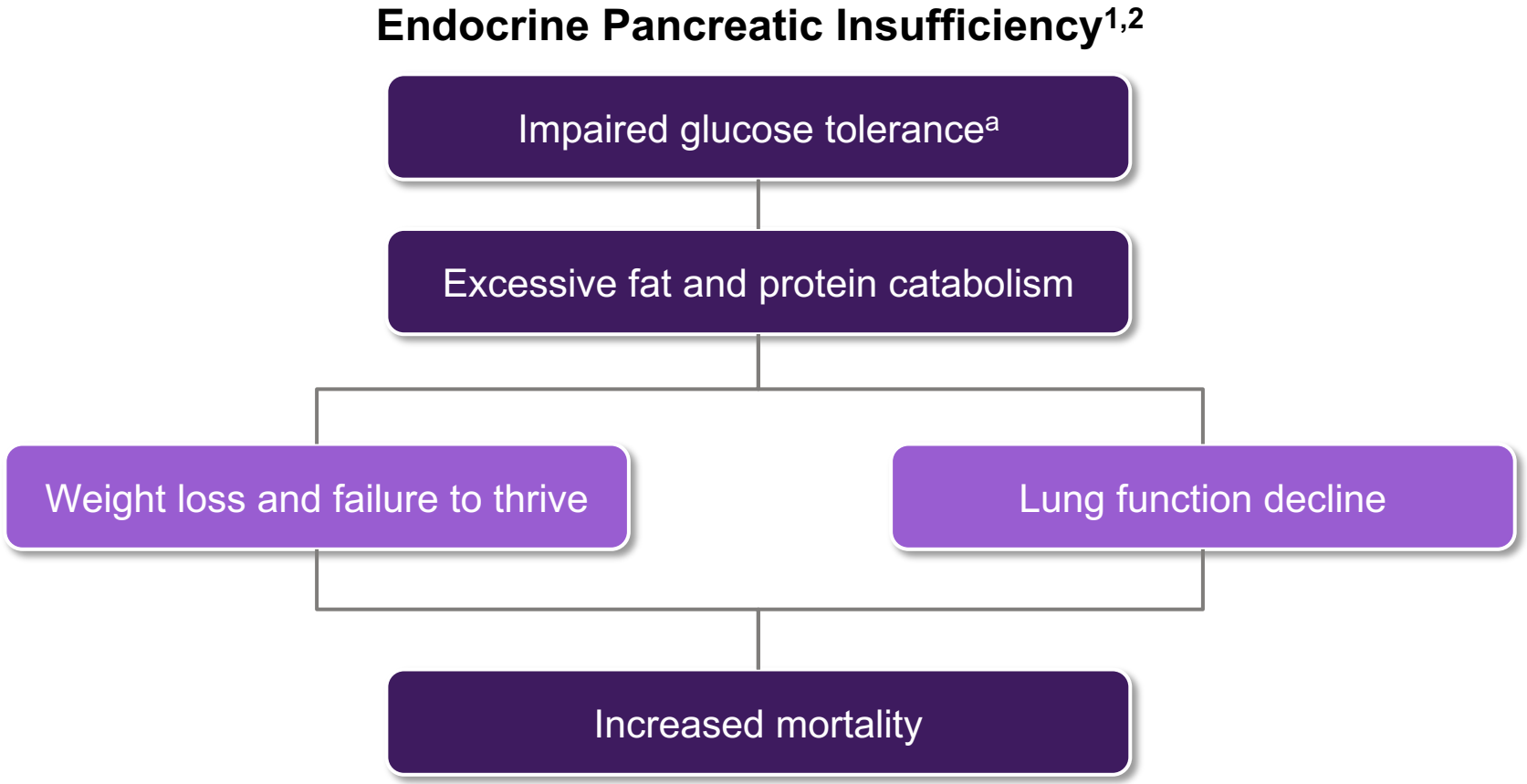
Despite some shared features with type 1 and type 2 diabetes mellitus, CFRD is a distinct clinical entity

Parameter	CFRD	Type 1 Diabetes	Type 2 Diabetes
Prevalence in population	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
Macrovascular complications	No	Yes	Yes
Metabolic syndrome	No	No	Yes
Major cause of death	Pulmonary	Cardiovascular	Cardiovascular

CFRD, CF-related diabetes.

Table adapted with permission from Moran A, et al. 2018. Moran A, et al. *Pediatr Diabetes*. 2018;19(Suppl 27):64-74.

CF-Related Endocrine Pancreatic Manifestations are Multifactorial and Contribute to Disease Progression

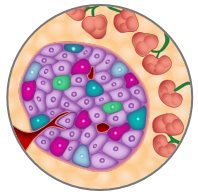


Pancreatic manifestations may vary in individual patients

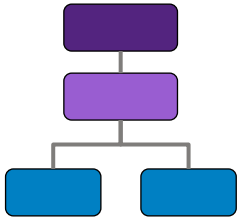
CFRD, cystic fibrosis-related diabetes. [a]CF-related diabetes is part of a continuum of glucose tolerance abnormalities, ranging from impaired glucose tolerance, to CFRD without fasting hyperglycemia, to CFRD with fasting hyperglycemia.[2]

1. Moran A, et al. *Diabetes Care*. 2010;33:2697-2708. 2. Moran A, et al. *Diabetes Care*. 2010;33:2677-2683.

Endocrine Pancreatic Disease in CF



Structure and Function



Pathophysiology

Monitoring and Screening Tests

Prevalence and Clinical Sequelae

Self-Monitoring Blood Glucose (SMBG) – If Elevated, Confirm by Central Laboratory Glucose Measurement

Oral Glucose Tolerance Test (OGTT)[1]

- At present, a standard 2-hour OGTT is the recommended screening test for CFRD
- Four glucose tolerance categories in CF (based a standard OGTT) are:
  1. Normal glucose tolerance (NGT)
  2. Indeterminate glycemia (INDET)
  3. Impaired glucose tolerance (IGT)
  4. CFRD
- INDET occurs in patients with normal fasting and 2-hour OGTT but who have 1-hour OGTT >200 mg/dL
  - Commonly seen in children with CF and is associated with worse clinical outcomes in CF

Fasting Plasma Glucose (FPG)[1]

- FPG can be used, but may lead to missed diagnoses because nearly two-thirds of patients with CFRD do not have fasting hyperglycemia[1]

Hemoglobin A_{1c} (HbA_{1c})

- HbA_{1c} as a screening test for CFRD is not recommended as HbA_{1c} is often spuriously low in CF[1]
  - Recent findings suggest that HbA_{1c} might be a viable assay in CF due to improvements in variability of commercially available assays[2]

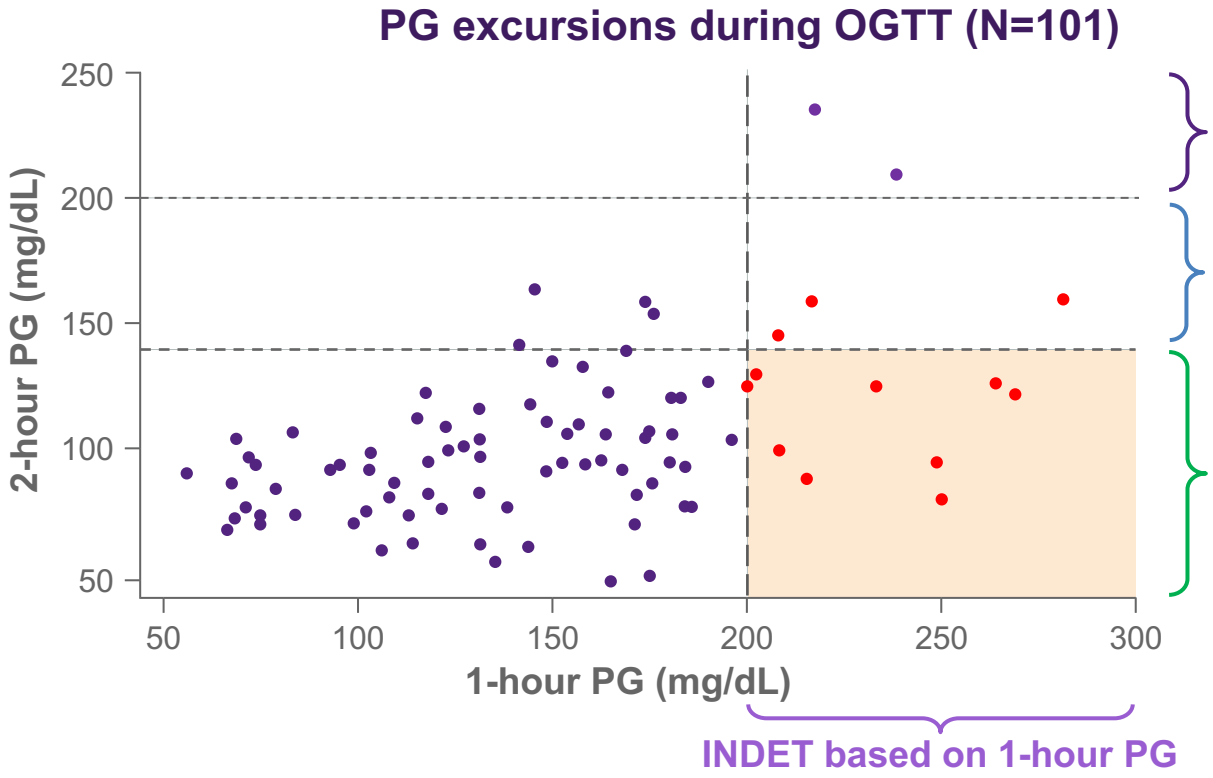
The current ISPAD,[1] ECFS,[3] and CFF/ADA/PES[4] best practice guidelines all recommend annual screening for CFRD starting at 10 years of age in all patients with CF

Some US CF centers are now choosing to start screening at 6 years of age[1]

ADA, American Diabetes Association; CFF, Cystic Fibrosis Foundation; CFRD, cystic fibrosis-related diabetes; ECFS: European Cystic Fibrosis Society; INDET, indeterminate glycemia; ISPAD, International Society for Pediatric and Adolescent Diabetes ; PES, Pediatric Endocrine Society; PG, plasma glucose.

1. Moran A, et al. *Pediatr Diabetes*. 2018;19(Suppl 27):64-74. 2. Lam GY, et al. *J Cyst Fibros*. 2019;18:e14-e15. 3. Castellani C, et al. *J Cyst Fibros*. 2018;17:153-178. 4. Moran A, et al. *Diabetes Care*. 2010;33:2697-2708.

Abnormal Glucose Tolerance is Often Missed in Patients with CF and Normal 2-Hour OGTT

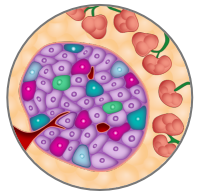


- Clinically important PG elevations may be missed if OGTT omits evaluation of 1-hour PG
- 1-hour PG elevations are negatively associated with $ppFEV_1$
- Optimal therapy may require additional focus on normalizing 1-hour PG

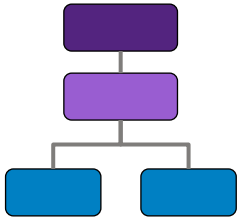
CFRD, cystic fibrosis-related diabetes; IGT, impaired glucose tolerance; INDET, indeterminate glycemia; NGT, normal glucose tolerance; OGTT, oral glucose tolerance testing; PG, plasma glucose; $ppFEV_1$, percent predicted forced expiratory volume in one second.

Figure adapted with permission from Brodsky J, et al. 2011. Brodsky J, et al. *Diabetes Care*. 2011;34:292-295.

Endocrine Pancreatic Disease in CF



Structure and Function



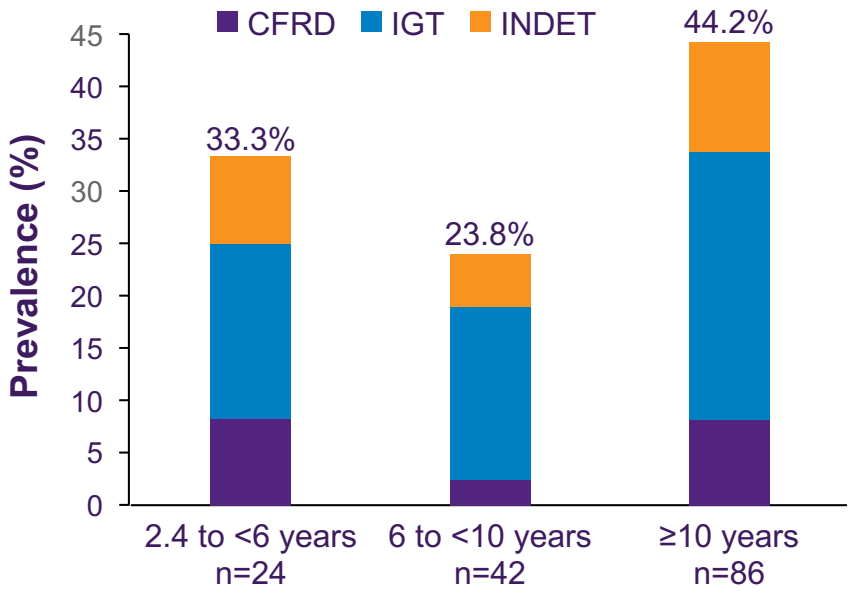
Pathophysiology

Monitoring and Screening Tests

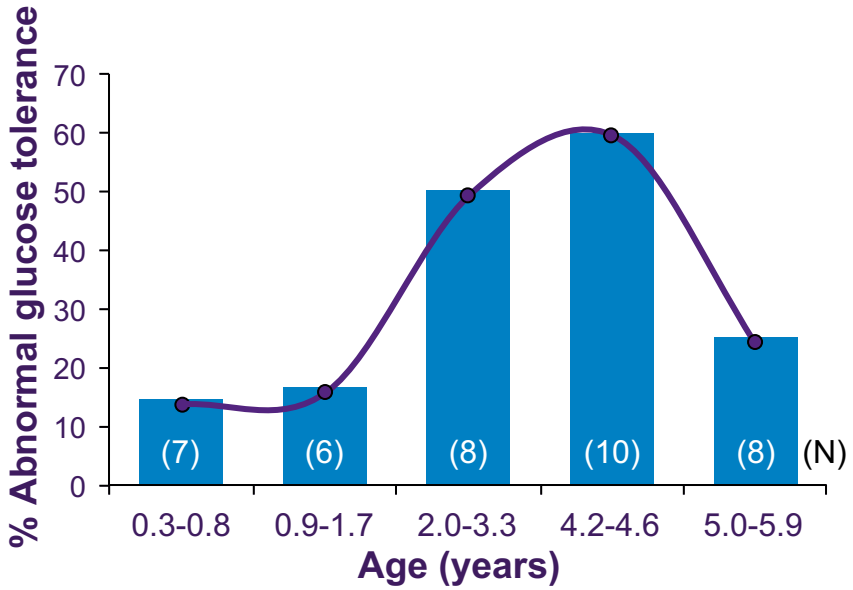
Prevalence and Clinical Sequelae

Abnormal Glucose Tolerance Occurs in Young Children with CF

Prevalence of Abnormal Glucose Tolerance in Children with CF According to Age Group[1]



Frequency of Abnormal Glucose Tolerance in Children with CF Separated by Age Quintiles[2]



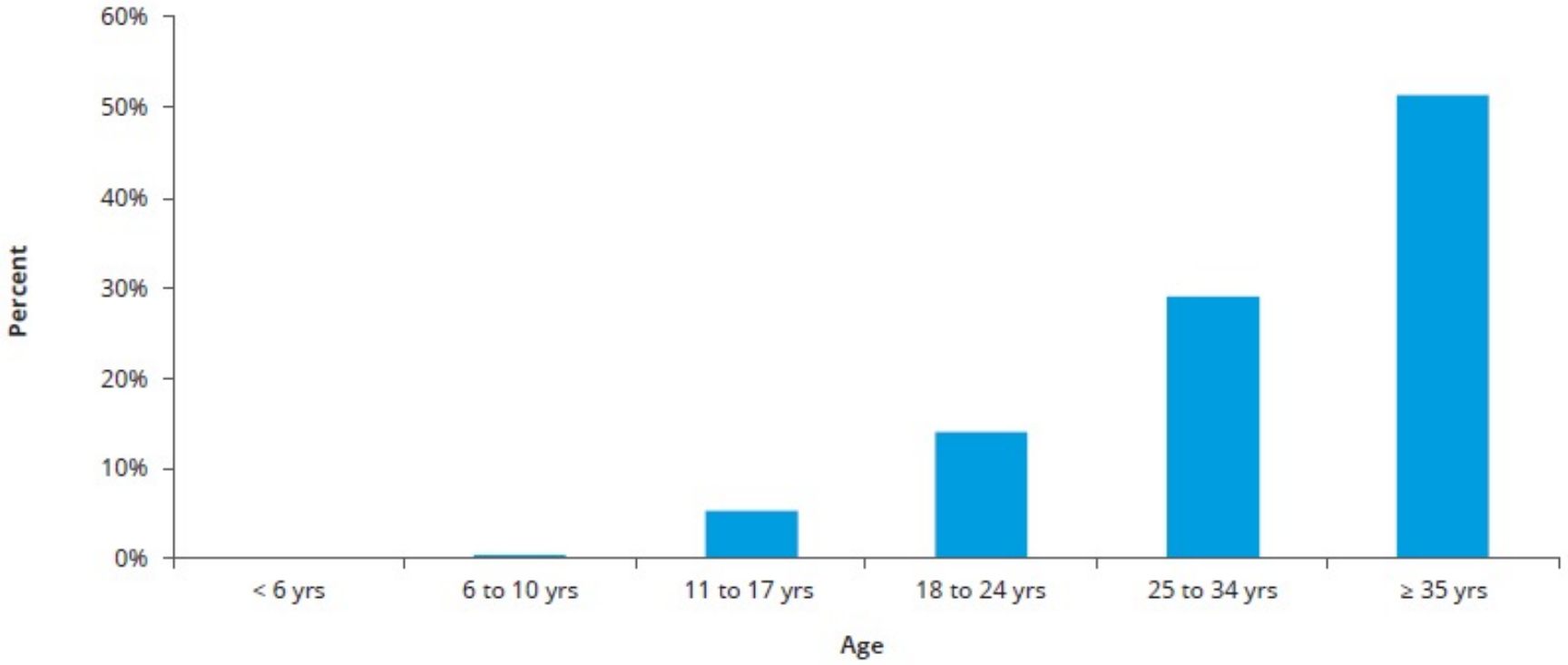
- Abnormal glucose tolerance was detected at the first visit in 39% (9/23) of children with CF (aged 3 months to 6 years) vs 0/9 control children (*P*=0.03)[2]
- Abnormal glucose tolerance occurred in all age groups in children with CF[1,2]

Right figure adapted with permission from Yi Y, et al. 2016.
CFRD, cystic fibrosis-related diabetes; IGT, impaired glucose tolerance; INDET, indeterminate glycemia.

1. Mozzillo E, et al. *Diabetes Care*. 2012;35:e78. 2. Yi Y, et al. *Am J Respir Crit Care Med*. 2016;194:974-980.

Prevalence of CFRD Increases with Age in Canada

Percentage of CF individuals with CFRD by age (N = 957), 2019

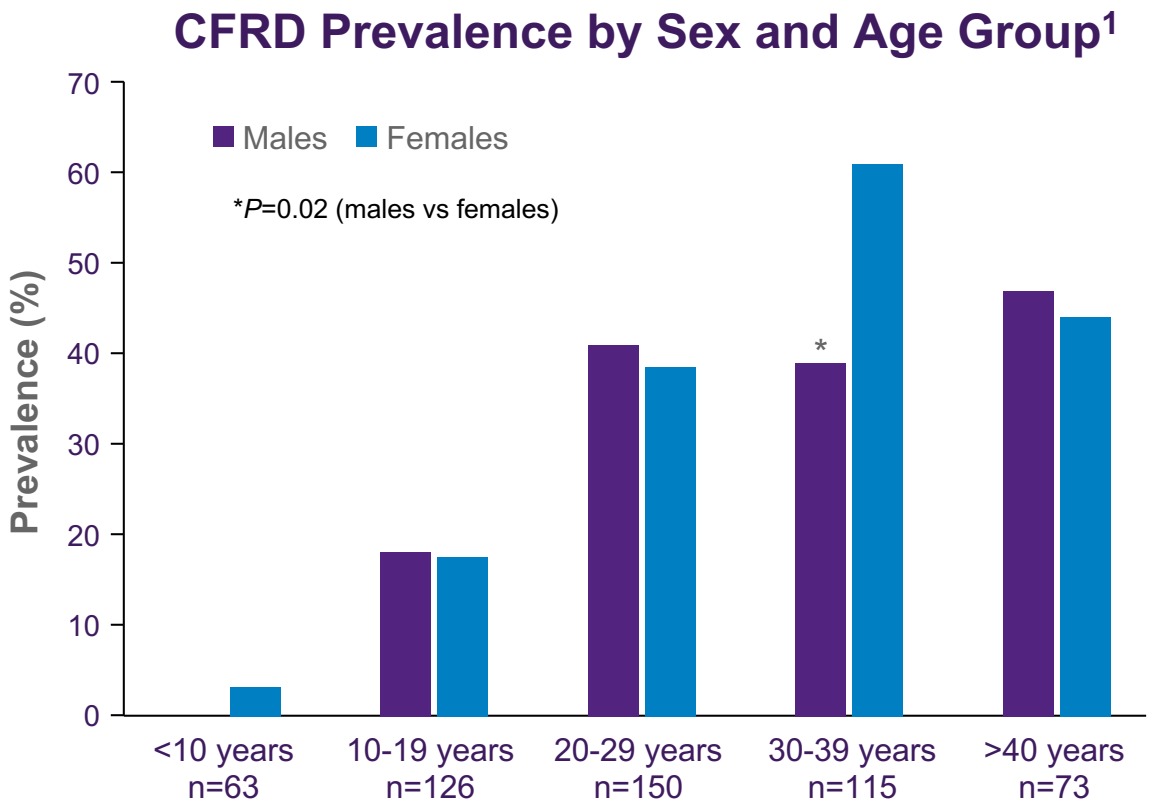


There is increasing prevalence of CFRD in the adult population

- CFRD was reported in 957(22.0%) individuals with CF in Canada:
  - 54 (3.3%) children
  - 903 (33.5%) adults
- Of these individuals with CFRD:
  - 49.8% were female
  - 23.7% have received a transplant
  - 51.2% were 35 years of age or older

CFRD, cystic fibrosis-related diabetes. Image adapted from “Canadian Cystic Fibrosis Registry, 2019 Annual Report.
* Cystic Fibrosis Canada. (2020). *The Canadian Cystic Fibrosis Registry 2019 Annual Data Report*. Toronto, Canada: Cystic Fibrosis Canada.

Prevalence of CFRD Increases with Age (U.S.)



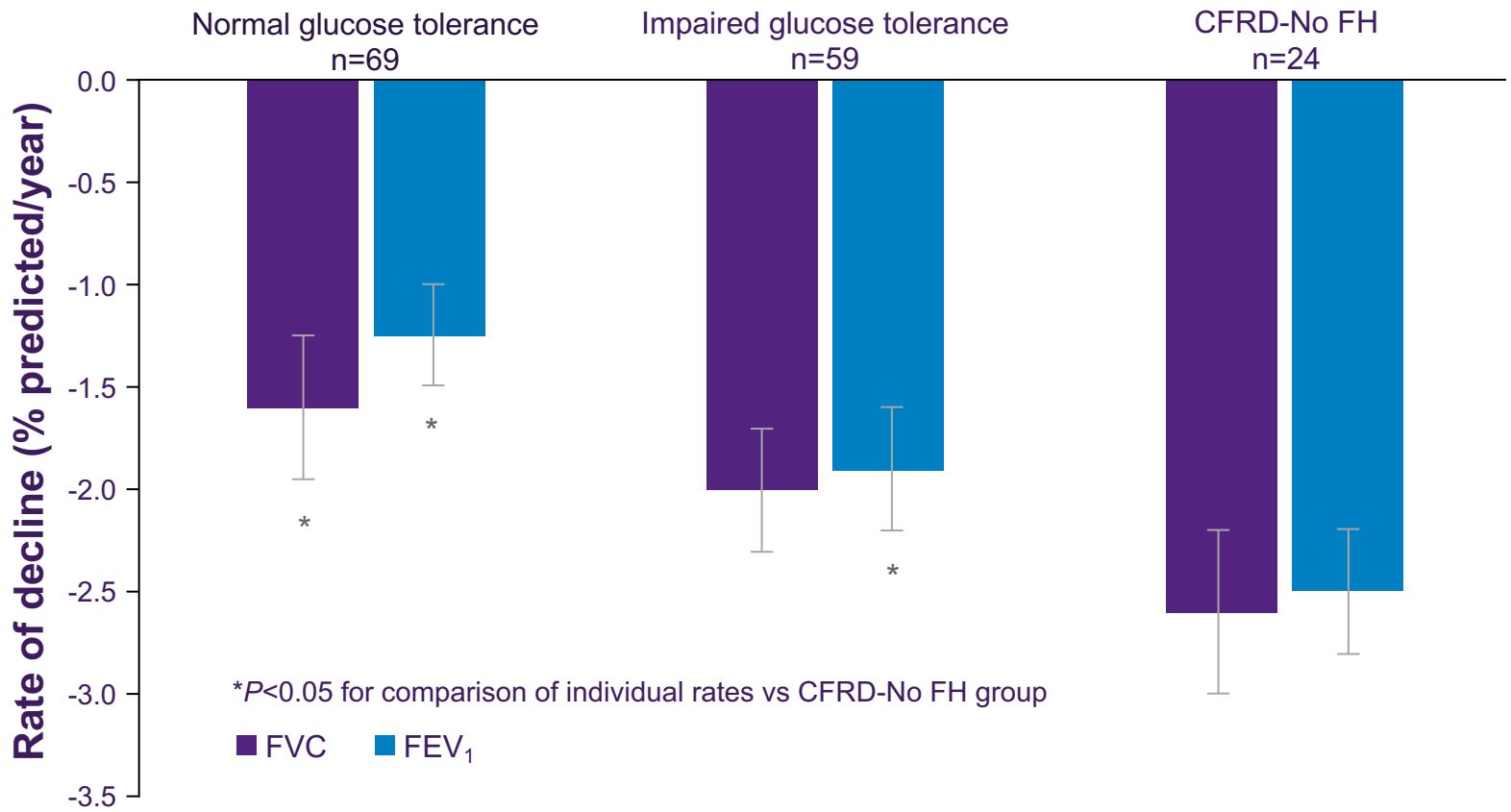
- CFRD occurs in about 15% of adolescents and 50% of adults with CF[2]
- Among the US population overall, estimates for 2018 were:[3]
  - 8.2% of the US population had diagnosed diabetes
  - 0.06% of children and adolescents ≤20 years of age had diagnosed diabetes

CFRD, cystic fibrosis-related diabetes. Figure adapted with permission from Moran A, et al. 2009.

1. Moran A, et al. *Diabetes Care*. 2009;32:1626-1631. 2. Ode KL, et al. *Lancet Diabetes Endocrinol*. 2013;1:52-58. 3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (last accessed November 2020).

CFRD is Associated with More Rapid Decline in Lung Function

Adjusted Rates of Decline (±SE) in FEV_1 and FVC by OGTT Category[a]

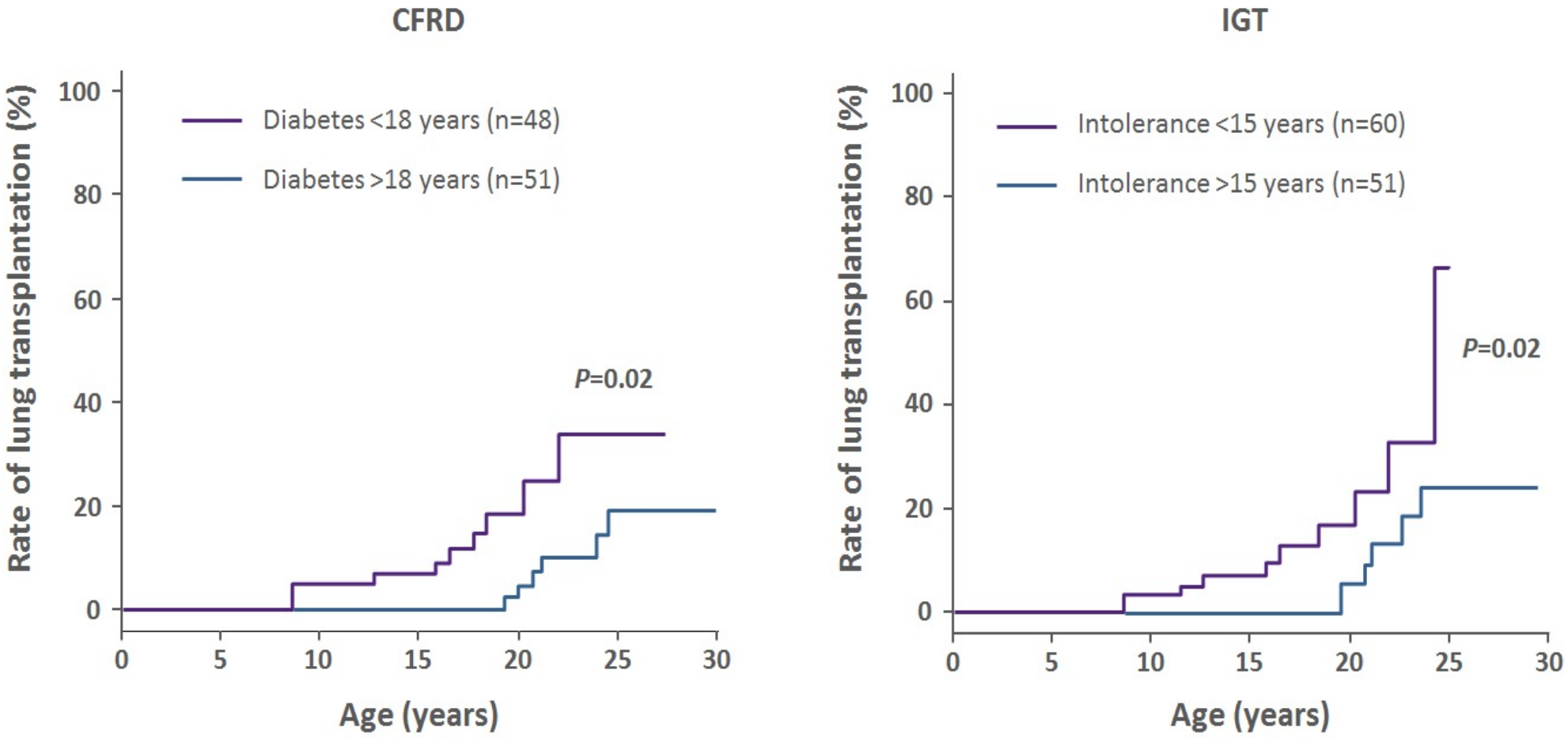


CFRD, cystic fibrosis-related diabetes; CFRD-No FH, cystic fibrosis-related diabetes without fasting hyperglycemia; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; OGTT, oral glucose tolerance testing; SE, standard error.

[a]Rates were adjusted for sex and baseline age, body mass index, microbiology, use of corticosteroids, and FEV_1 level.

Figure adapted with permission from Milla CE, et al. 2000. Milla CE, et al. *Am J Respir Crit Care Med*. 2000;162(3 Pt 1):891-895.

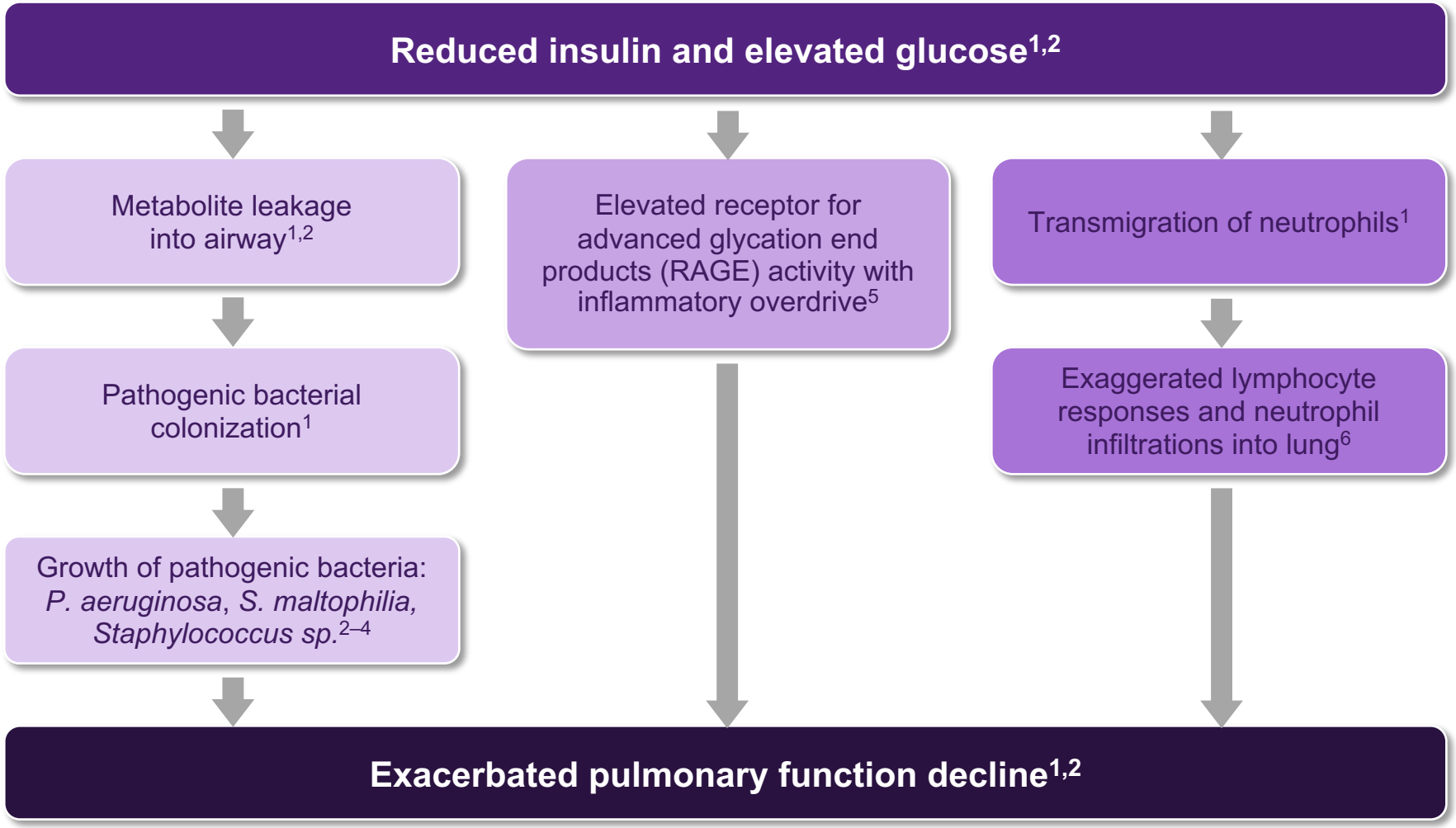
Early Onset of CFRD or IGT is Associated with Higher Rates of Lung Transplantation at a Younger Age



CFRD, cystic fibrosis-related diabetes; IGT, impaired glucose tolerance.

Bismuth E, et al. *J Pediatr*. 2008;152:540-545.

Potential Links Between Defects in Glucose Metabolism and Lung Function

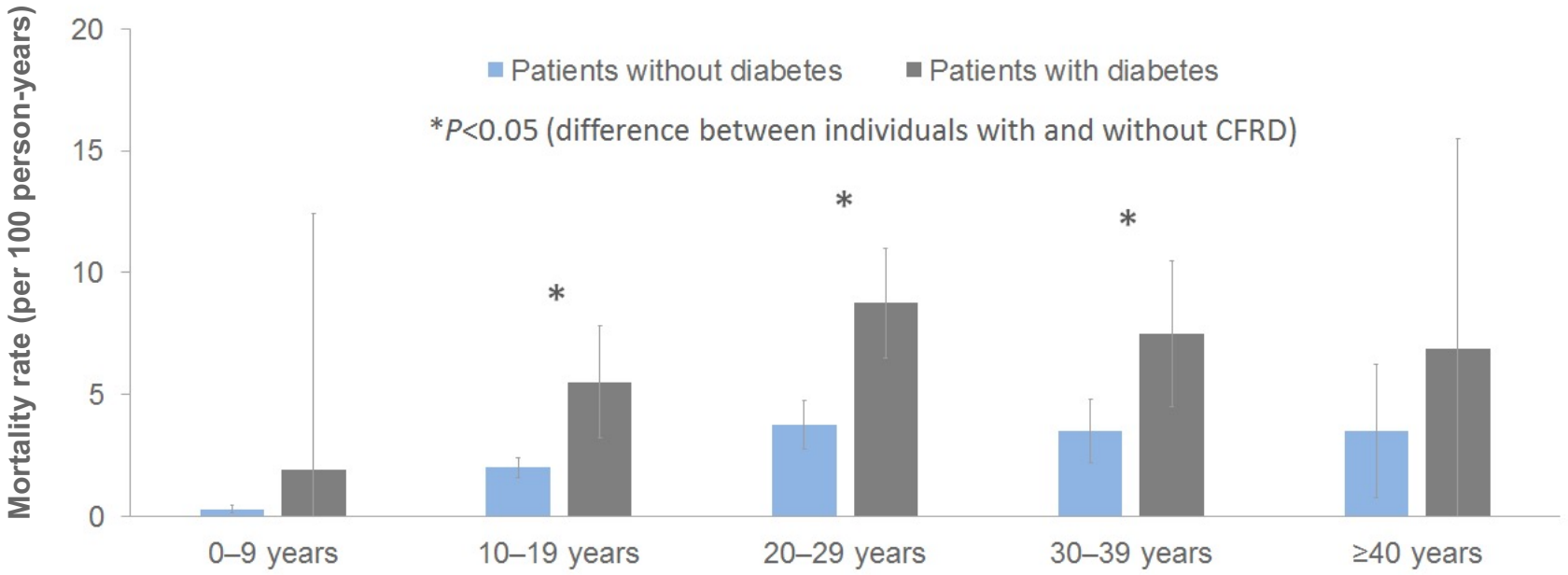


Not all manifestations of CF in the pancreas fall along a continuum, and clinical manifestations may vary in individual patients

1. Molina SA, et al. *Pediatr Pulmonol*. 2015;50(S41):246. Abstract 150. 2. Hameed S, et al. *Curr Opin Pediatr*. 2015;27:525-533. 3. Fothergill JL, et al. *J Cyst Fibros*. 2015;14(Suppl 1):S53. Abstract ePS06.1. 4. Garnett JP, et al. *PLoS One*. 2013;8:e76283. 5. Mulrennan S, et al. *Sci Rep*. 2015;5:8931. 6. Ziai S, et al. *Diabetes Res Clin Pract*. 2014;105:22-29.

CFRD is Associated with Higher Mortality in CF

Mortality Rates (95% CI) by Age and Diabetes in Patients with CF[1]



Mortality Rates per Person and per 100 Person-Years for Adults Aged ≥20 Years (by CFRD Status)[2]

	Patients (n)	Person-Years	Deaths (n)	Mortality Rate per Person (%)	*P* value	Mortality Rate per 100 Person-Years (95% CI)	*P* value
No CFRD (all)	241	831	9	4	0.0001	1.0 (0.4 to 2)	0.001
CFRD (all)	221	809	30	14		4.8 (3 to 8)	

CFRD, cystic fibrosis-related diabetes; CI, confidence interval. Figure adapted with permission from Chamnan P, et al. 2010.

1. Chamnan P, et al. *Diabetes Care*. 2010;33:311-316. 2. Lewis C, et al. *Am J Respir Crit Care Med*. 2015;191:194-200.

CFRD with Fasting Hyperglycemia is Associated with Microvascular Complications

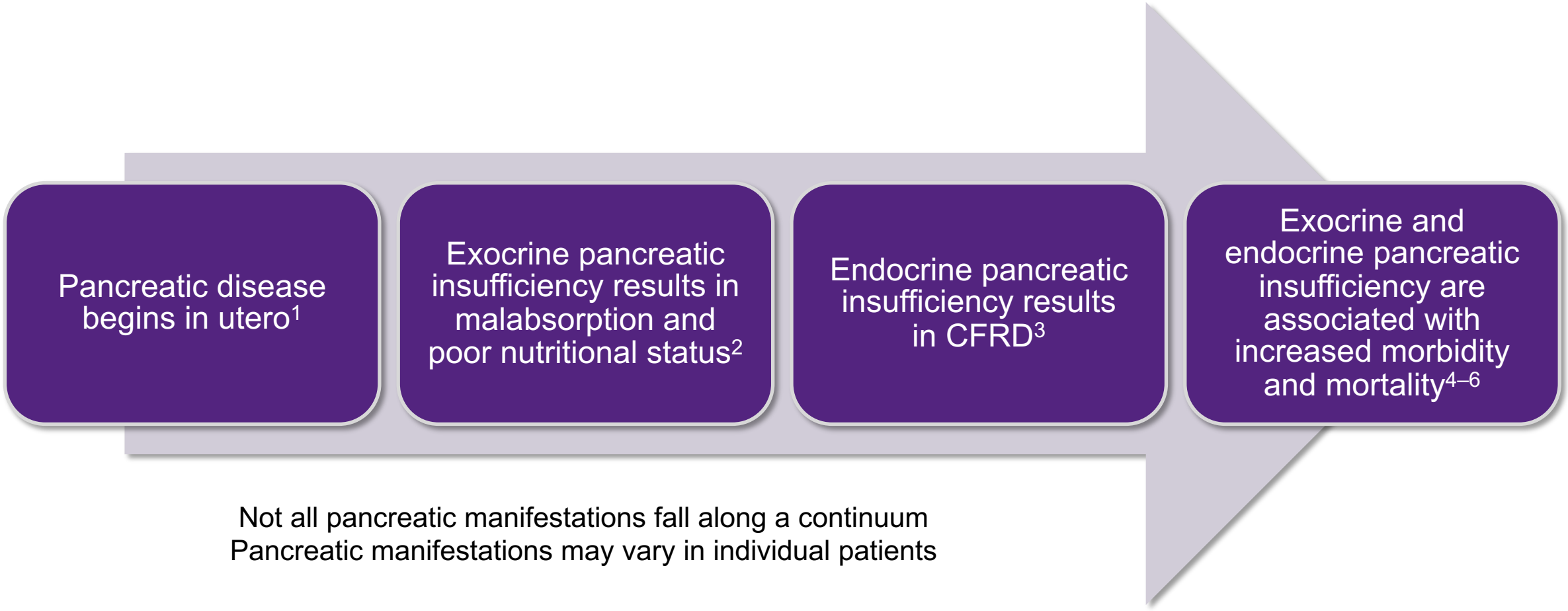
	Duration of Diabetes (years)			
	<5	5–10	>10	All
No fasting hyperglycemia				
% with ↑ $U_{alb:cr}$ (n tested)	0 (36)	0 (23)	0 (20)	0 (79)
% with retinopathy (n tested)	0 (23)	0 (18)	0 (16)	0 (57)
With fasting hyperglycemia				
% with ↑ $U_{alb:cr}$ (n tested)	0 (22)	4 (25)	14 (36)[a]	7 (83)[a]
% with retinopathy (n tested)	0 (20)	0 (28)	16 (37)[a]	7 (84)[a]

$U_{alb:cr}$, annual spot urine microalbumin-to-creatinine ratio; [a]P<0.05 (fasting vs no fasting hyperglycemia); Microalbuminuria = 30–299 µg/mg creatinine.

- Microvascular complications are common in individuals with type 1 and type 2 diabetes and represent a significant source of morbidity and mortality
- A significant percentage of patients with CFRD with fasting hyperglycemia showed signs of microvascular complications compared with those without fasting hyperglycemia

Schwarzenberg SJ, et al. *Diabetes Care*. 2007;30:1056-1061.

Summary



Not all pancreatic manifestations fall along a continuum
Pancreatic manifestations may vary in individual patients

CFRD, cystic fibrosis-related diabetes.

1. Imrie JR, et al. *Am J Pathol*. 1979;95:697-708. 2. De Lisle RC, et al. *Cold Spring Harb Perspect Med*. 2013;3:a009753,. 3. Barrio R. *Eur J Endocrinol*. 2015;172:R131-R141.
4. Davis PB, et al. *Pediatr Pulmonol*. 2004;38:204-209. 5. Moran A, et al. *Diabetes Care*. 2010;33:2697-2708. 6. Moran A, et al. *Diabetes Care*. 2010;33:2677-2683.