Stanford MEDICINE

Cystic Fibrosis

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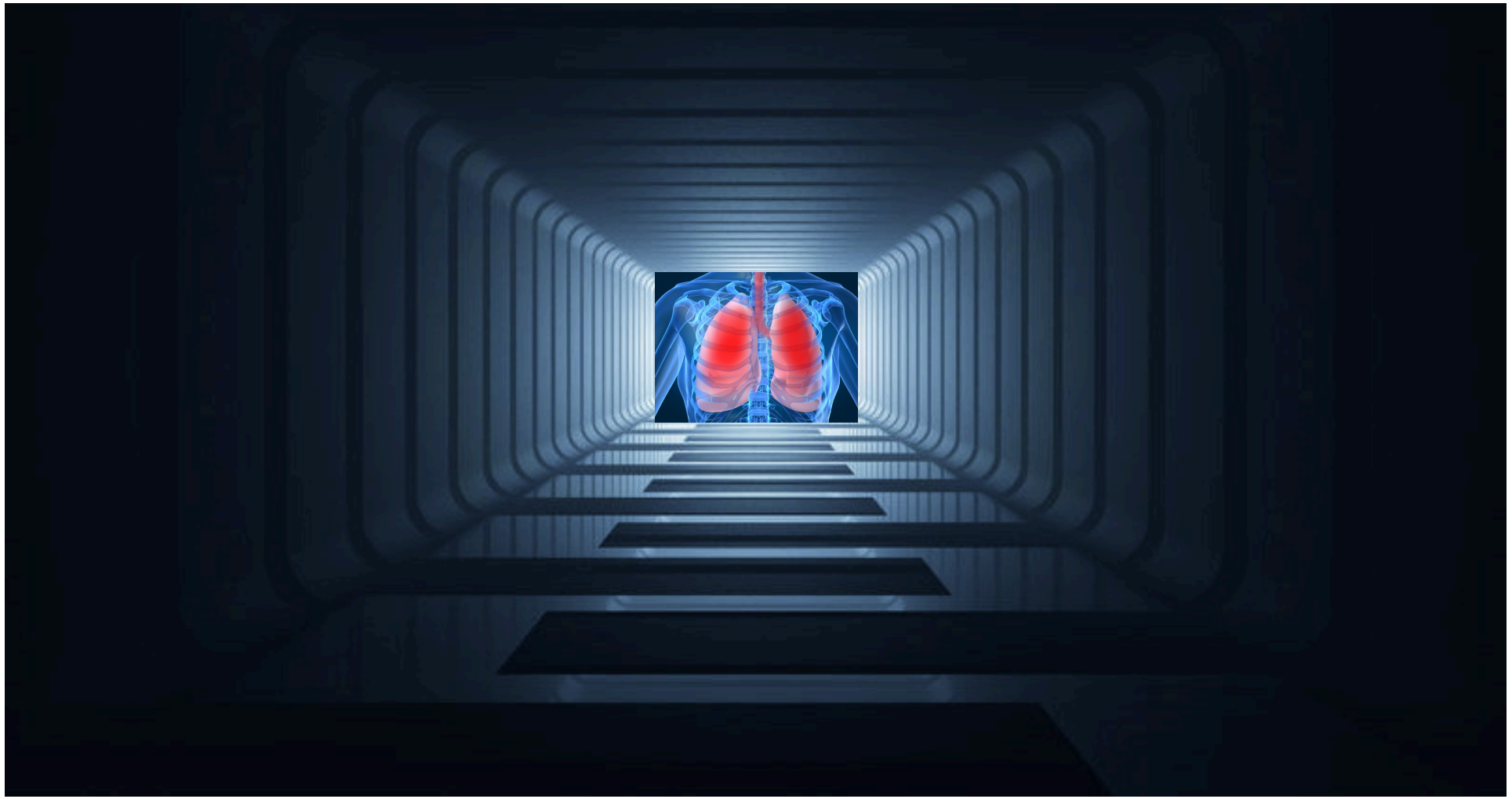
Disclosures

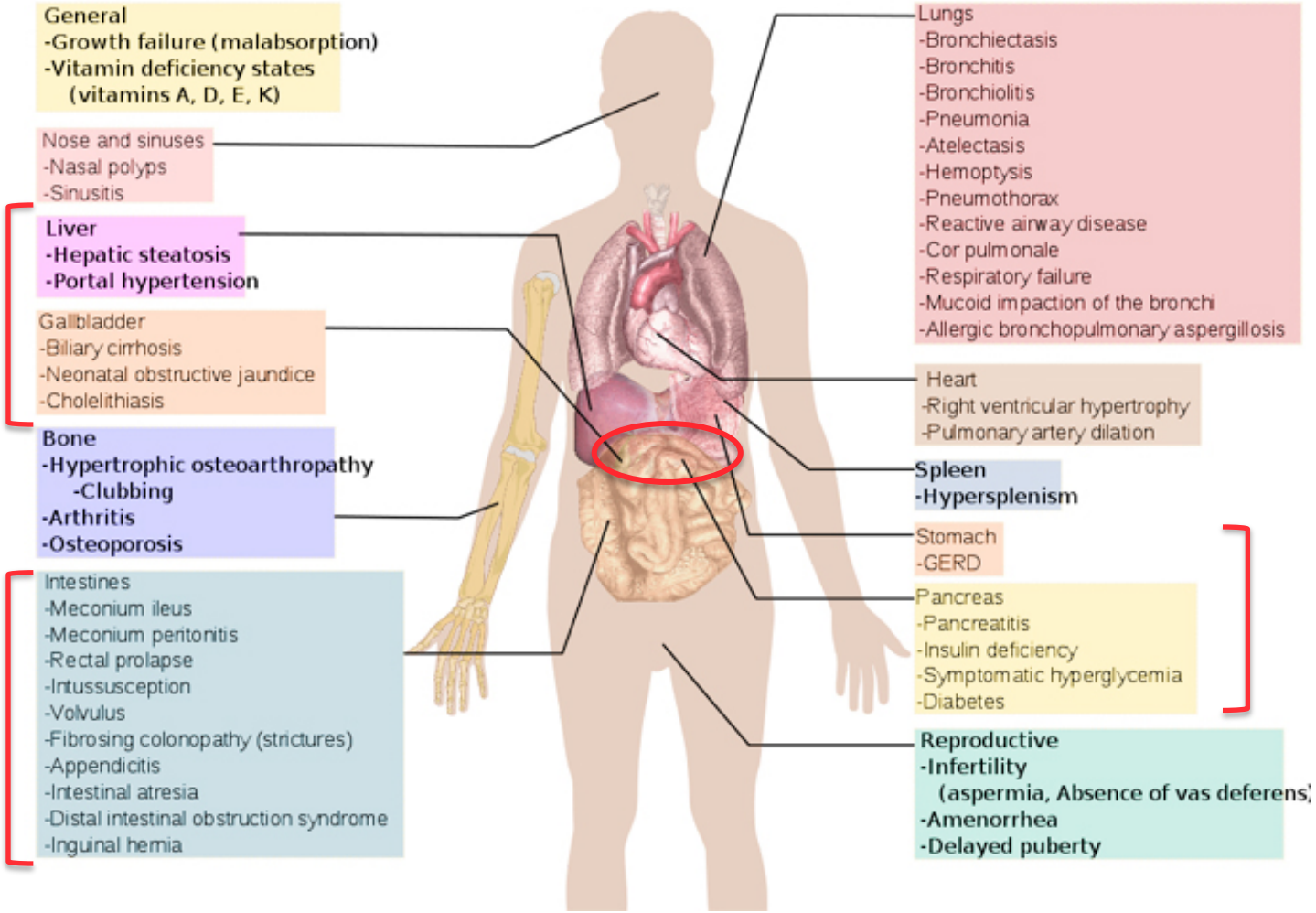
- I have no financial relationships to disclose.

Cystic Fibrosis – Often Viewed as a Lung Disease



Manifestations of Cystic Fibrosis

CF is a whole body disease!



Progress in Pediatrics

CYSTIC FIBROSIS OF THE PANCREAS AND ITS RELATION TO CELIAC DISEASE

A CLINICAL AND PATHOLOGIC STUDY

DOROTHY H. ANDERSEN, M.D.

Am J Dis Child. 1938; 56:344-99

- Described 49 cases of children with diagnosis of celiac disease, but with abnormal pancreas on autopsy
- 3 groups of children:
  1. <1 week old: died from inspissated mucus causing intestinal obstruction
  2. 1 week – 6 months old: FTT, malnutrition, large abdomen, diarrhea, steatorrhea, Vitamin A deficiency, chronic respiratory infections
  3. 6 months – 14 years old: malnutrition, underdevelopment, bronchiectasis

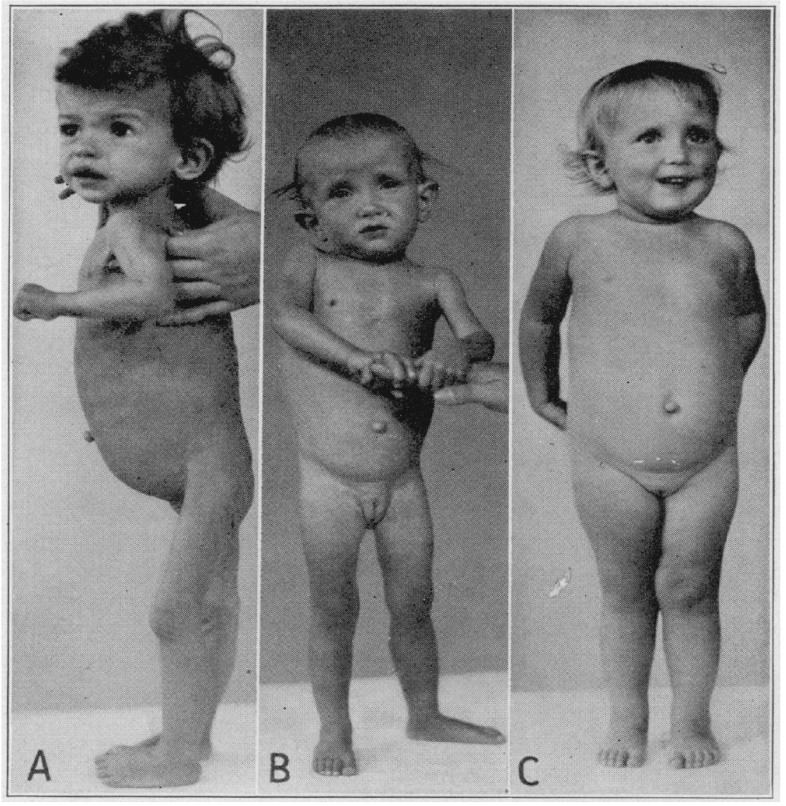


Fig. 2.—*A*, C. H. (case 37 [XVIII]) at the age of 1 year; *B*, M. D. (case 44 [XX]) at the time of admission to the hospital at the age of 22 months, and *C*, M. D. at the age of 3 years.

Cystic Fibrosis

- Incidence: ~30,000 in U.S. and ~100,000 worldwide
  - Varies based on racial/ethnic background
- Caused by gene mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) ion channel
  - Gene identified in 1989

News & Comment

The Cystic Fibrosis Gene Is Found

Researchers have identified the major gene defect that causes cystic fibrosis. The discovery should lead to better diagnosis and perhaps improved therapies for the now fatal disease

THE RACE TO FIND the cystic fibrosis gene is over. In three papers to be published in the 8 September issue of *Science*, researchers from Toronto and Ann Arbor report that they have cloned the gene and pinpointed the gene defect that causes most cystic fibrosis cases. "The data are virtually irrefutable that they have the right gene," says Louis Kunkel of Children's Hospital Medical Center in Boston, a cloning expert who led the successful search for the gene causing Duchenne muscular dystrophy.

Cystic fibrosis researchers have known. The cystic fibrosis gene did not carry any such convenient tag, unfortunately.

In 1985, however, 2 years before Tsui and his colleagues joined forces with Collins and his team, the Toronto group had provided a big boost to efforts to find the gene when they mapped it to chromosome 7. Williamson and Ray White of the Howard Hughes Medical Institute at the University of Utah in Salt Lake City further narrowed its location by identifying two "markers," the *met* oncogene and a DNA sequence designated

Gene sleuths. *Lap-Chee Tsui (left), Francis Collins, and their colleagues tracked down the cystic fibrosis gene.*

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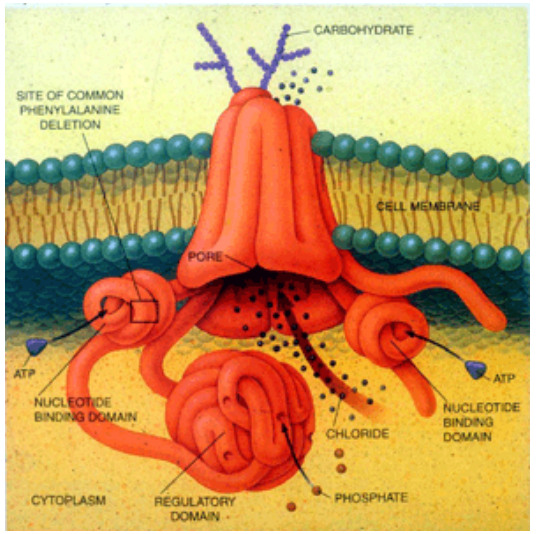
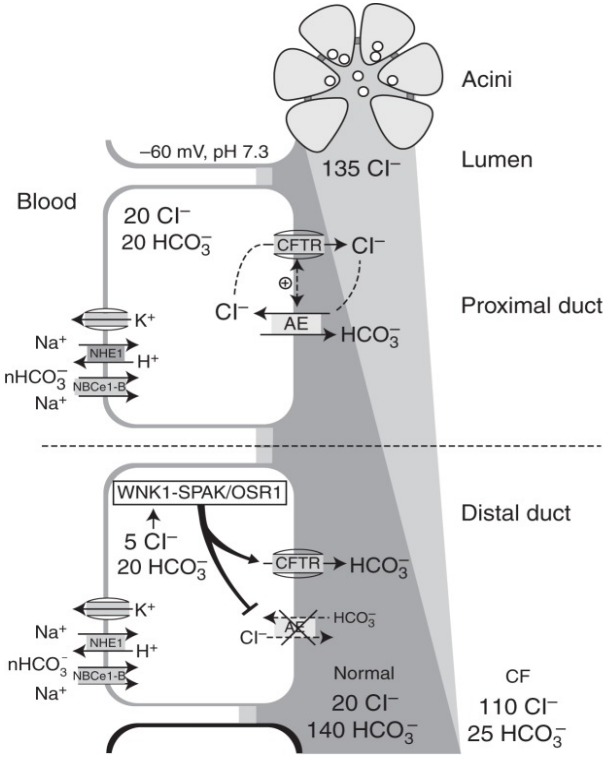
Science. 1989; Sep 1: 923.

CFTR

- Present in epithelial and non-epithelial tissues
- Membrane spanning anion channel
- Regulated by phosphorylation of R domain
- Permeable to Cl^- and HCO_3^-

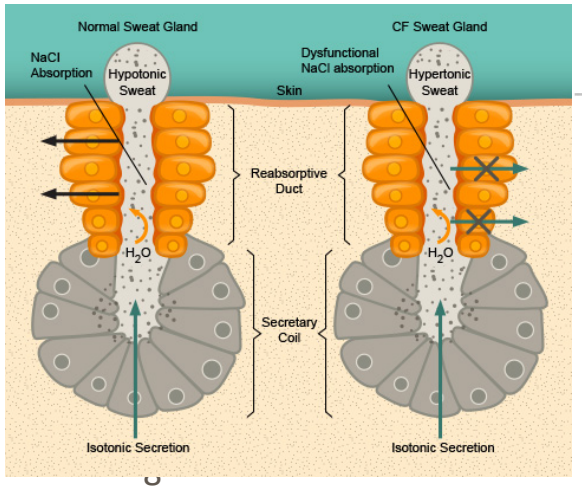




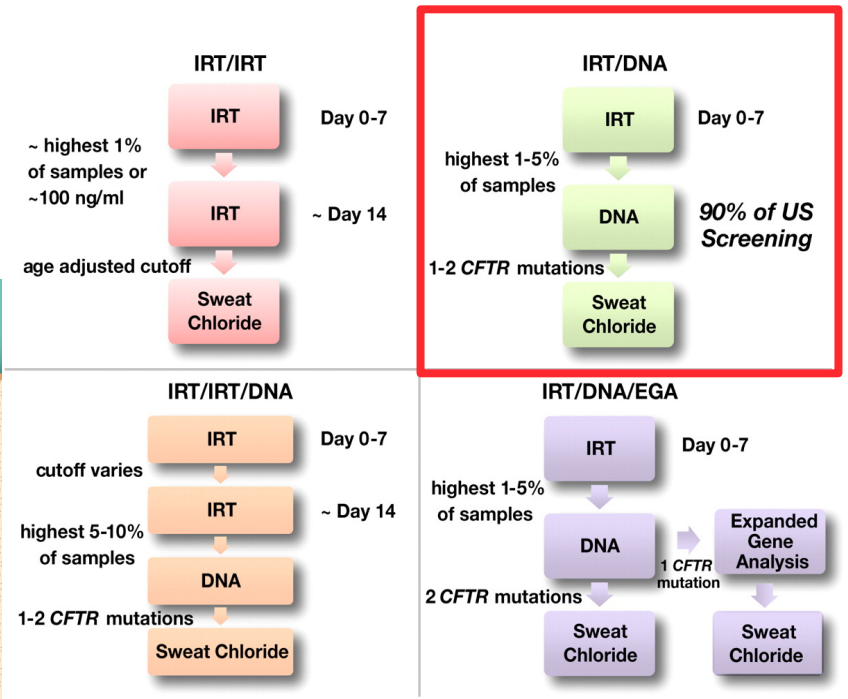
Welsh, M.J., Smith A.E. 1995. Scientific American, 52-59.
Scand J Gastroenterol. 1994; 29(10):889-96

Making the Diagnosis

- Newborn Screening (NBS)
  - Colorado was first state to include CF in NBS in 1982
  - All 50 states included CF in NBS since 2010
- Genetic testing
- Sweat testing: first introduced in 1959 and remains the gold standard
  - >60 mmol/L: CF
  - 30-59 mmol/L : Indeterminate
  - <30 mmol/L : Normal



NBS Algorithms



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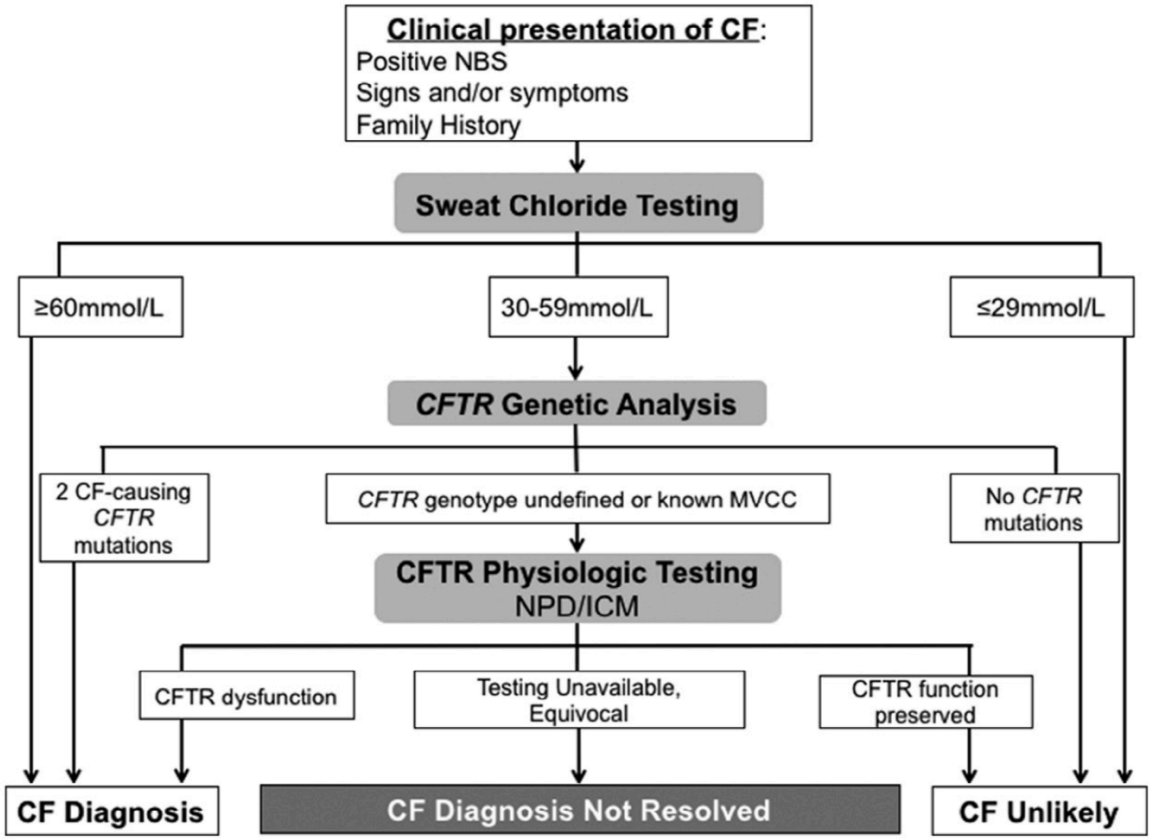
Lab Med. 2011; 42(10): 595-601.

Quinton P. Physiology (Bethesda) 2007;22:212–25

Making the Diagnosis

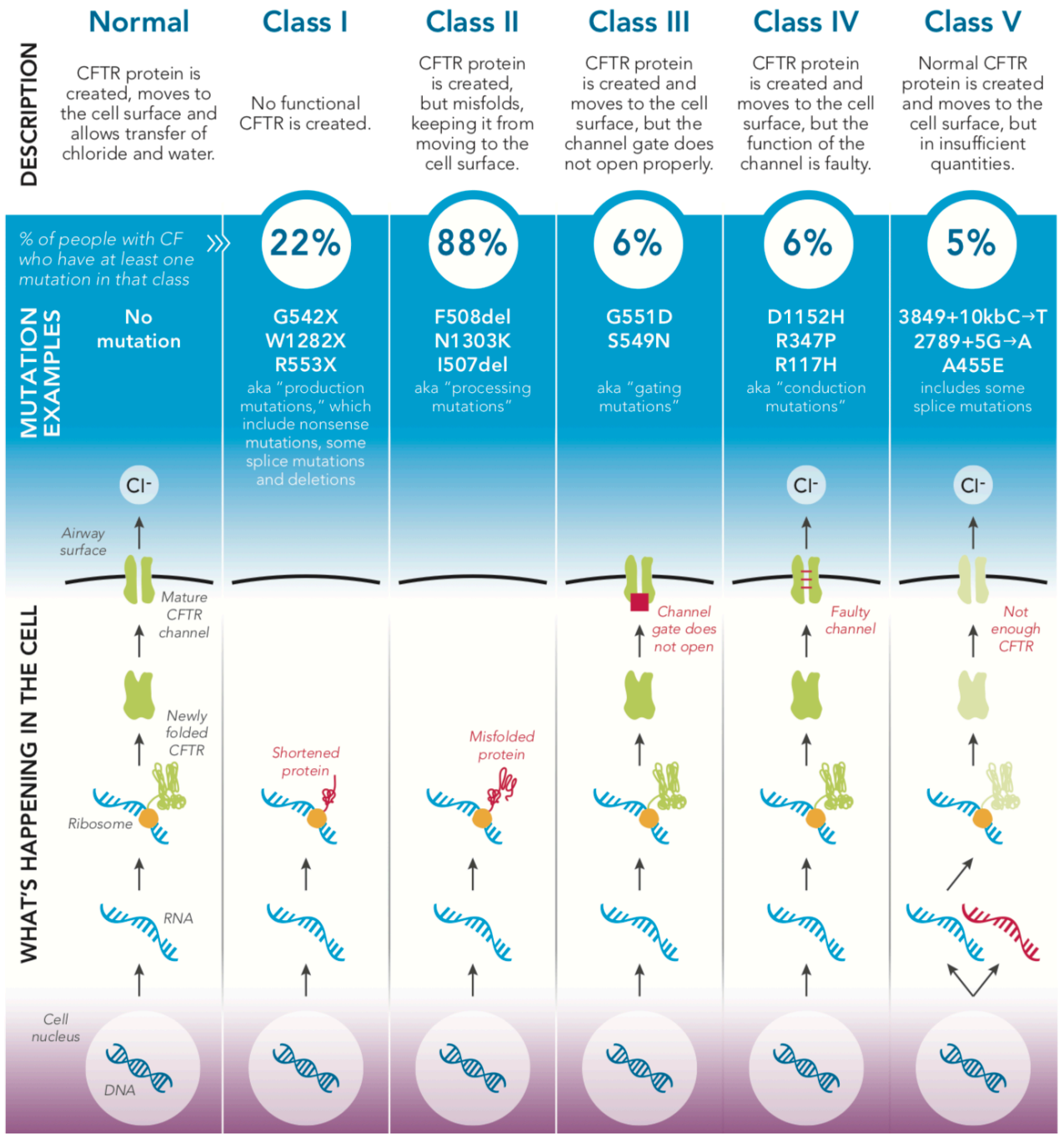
2017 CF Foundation Guidelines



J Pediatr 2017;181S:S4-15

CFTR Gene Mutations

- >1,700 mutations identified
- Resources for information on effects of CFTR mutations:
  - www.cftr2.org
  - www.genet.sickkids.on.ca
- New therapies are mutation-specific, so important to know genetics



www.cff.org

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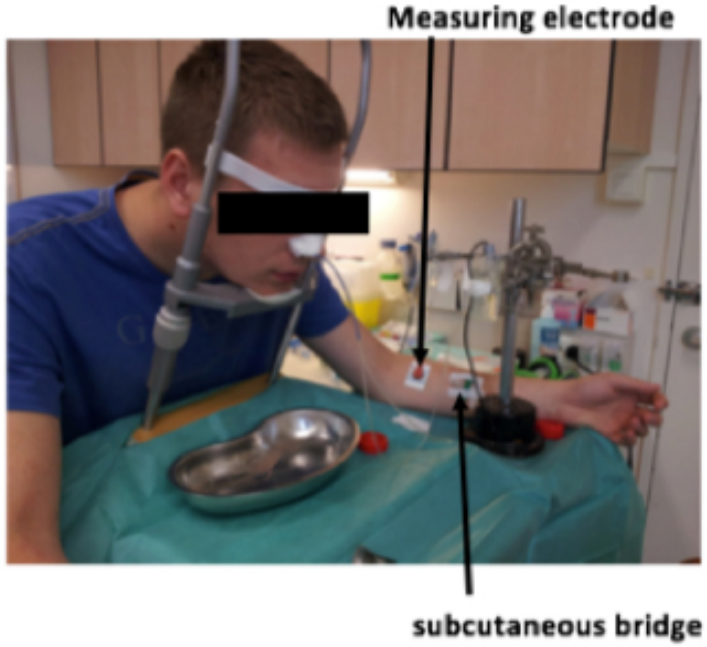
Cystic Fibrosis CRMS CFTR-related Disorder

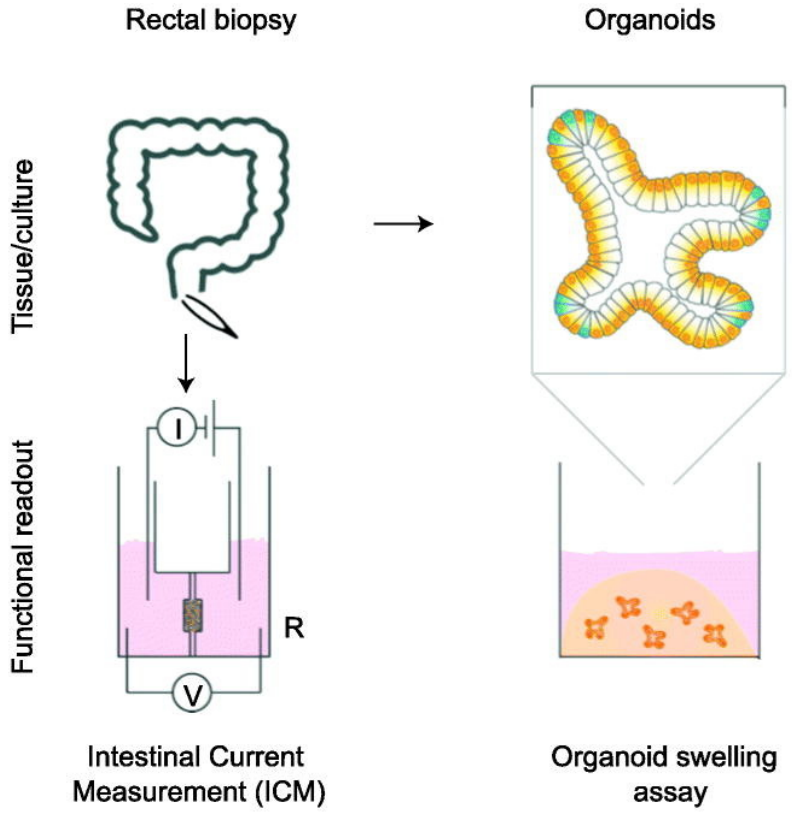
- Definition of CRMS (CFTR-related metabolic syndrome):
  - Sweat Cl <30 mmol/L + 2 CFTR mutations (one is not disease-causing)
  - Sweat Cl 30-59 mmol/L + 1 or no disease-causing CFTR mutations
- Definition of CFTR-Related Disorder:
  - A clinical entity associated with CFTR dysfunction that does not fulfill diagnostic criteria for CF (e.g. chronic pancreatitis, congenital bilateral absence of vas deferens)

J Pediatr. 2009; 155(6 Suppl):S106-16
J Cyst Fibros. 2011; 10(S2): pS86-S102

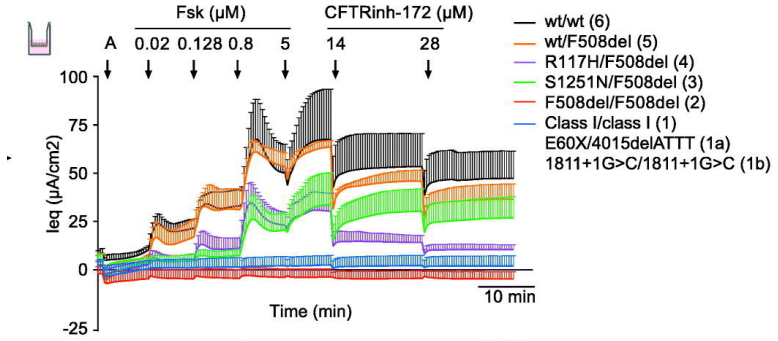
Making the Diagnosis – Functional Testing

Nasal Potential Difference

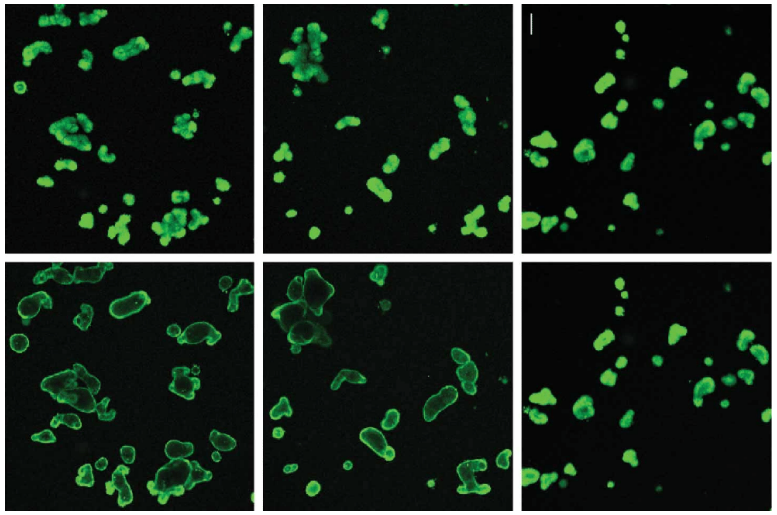




Intestinal Current Measurement

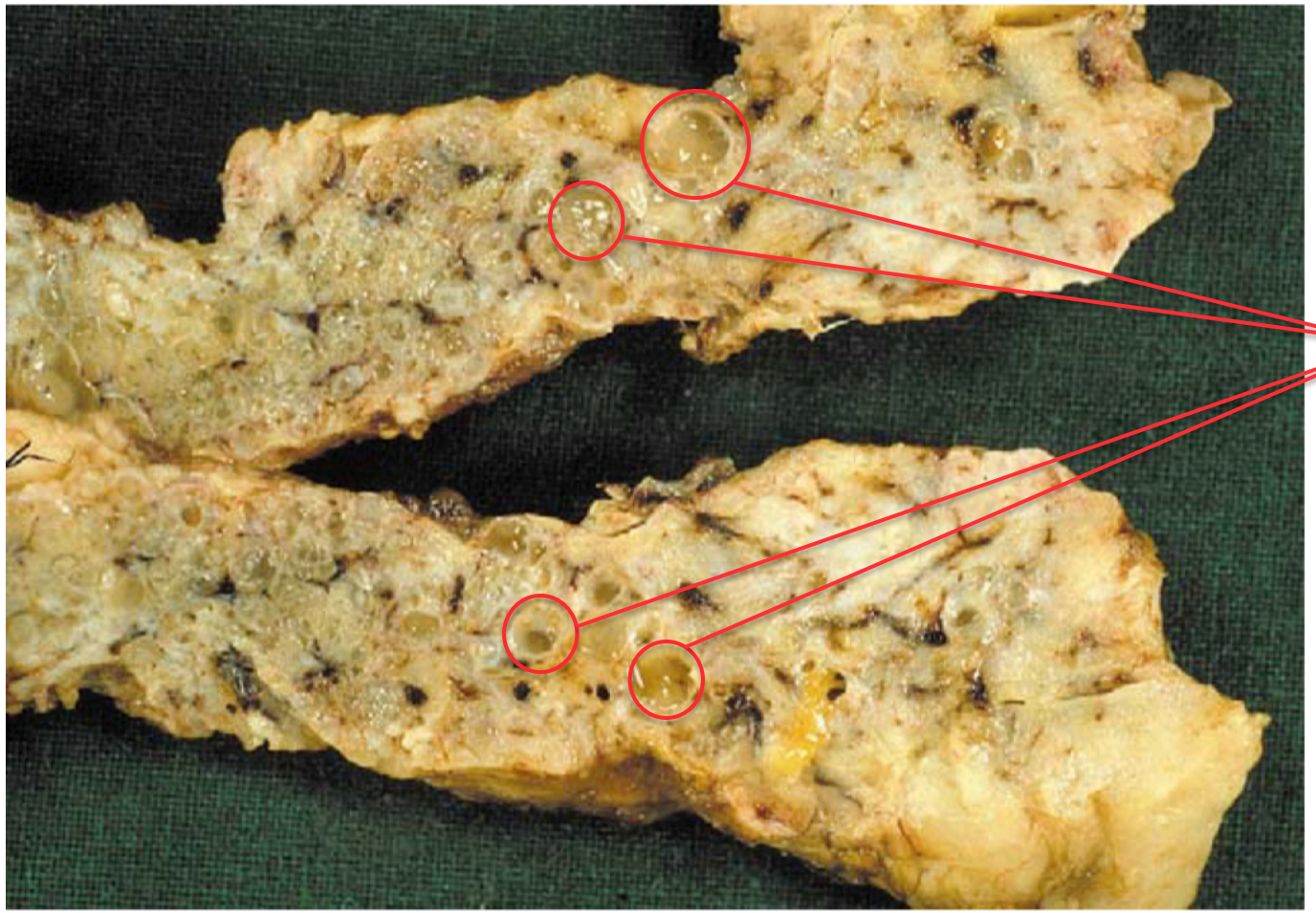


Forskolin-Induced Swelling



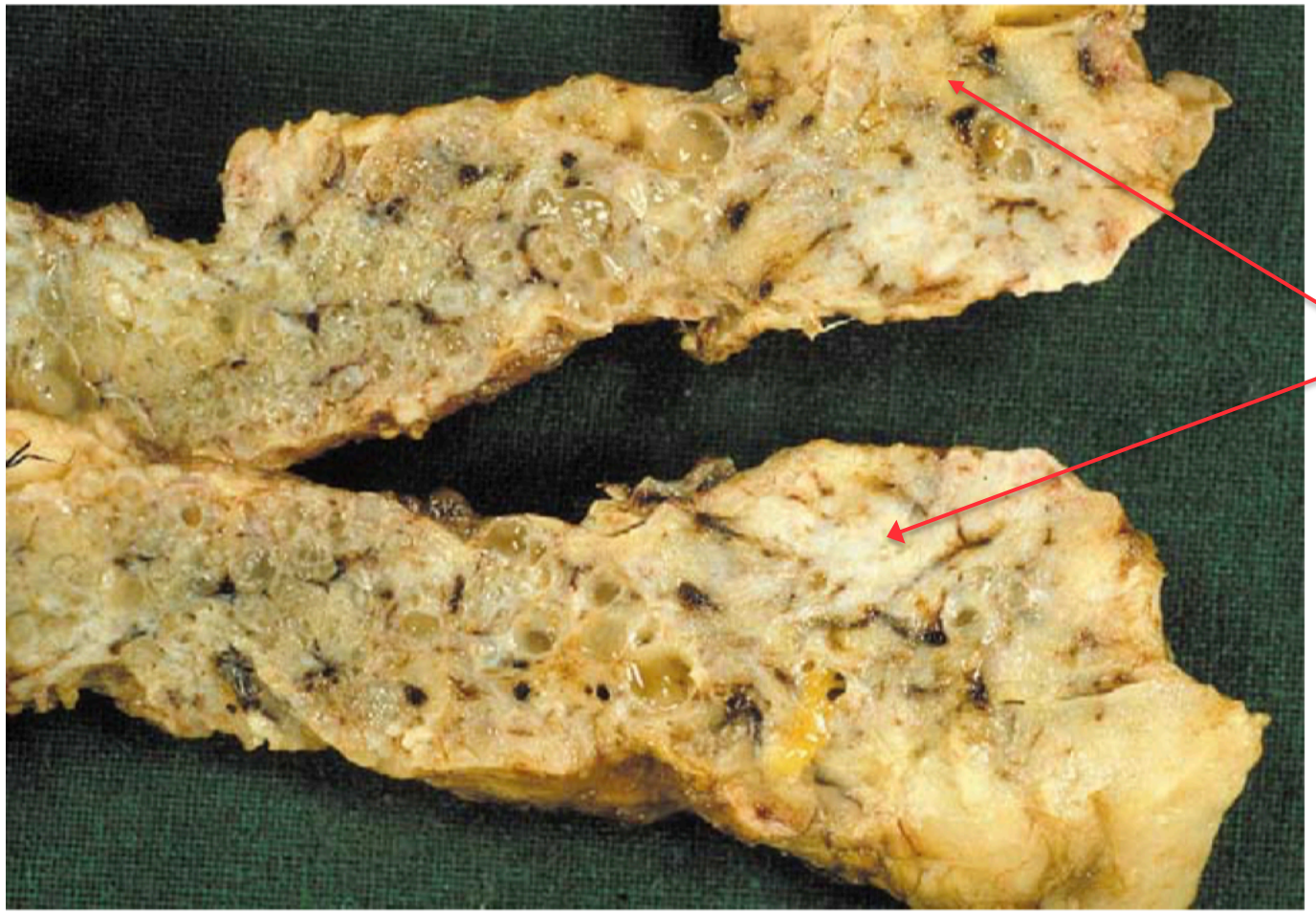
J Vis. Exp. 2018; 139: e57006, doi:10.3791/57006.
J Cyst Fibros. 2018; 17(3): 316-24.

Classic Gross Abnormalities in the Pancreas



Current Diagnostic Pathology. 2002; 8: 50-59

Classic Gross Abnormalities in the Pancreas

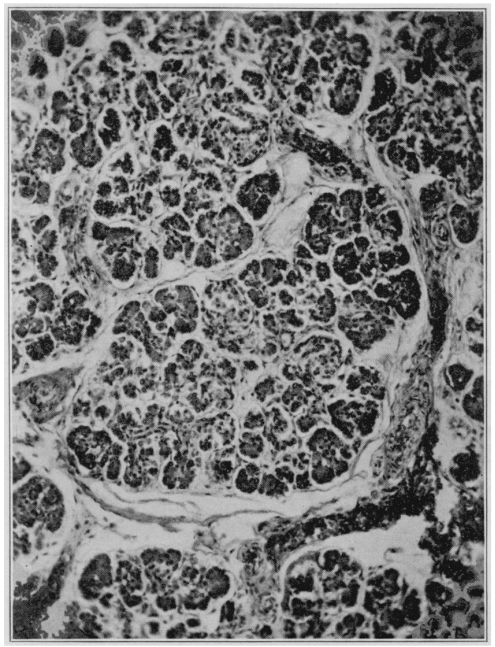


Fibrosis and fatty replacement

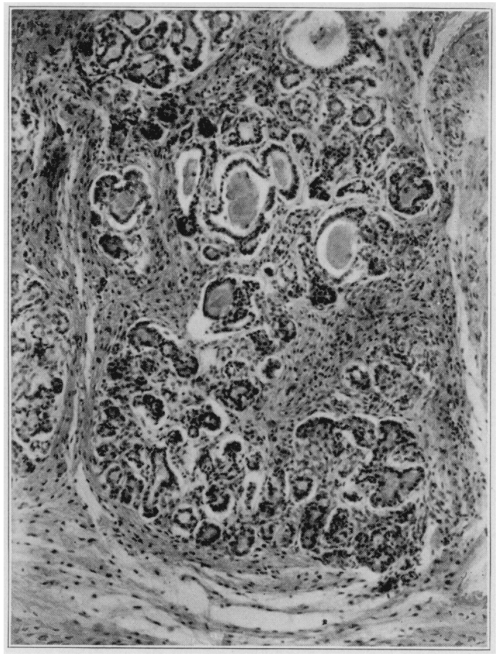
Current Diagnostic Pathology. 2002; 8: 50-59

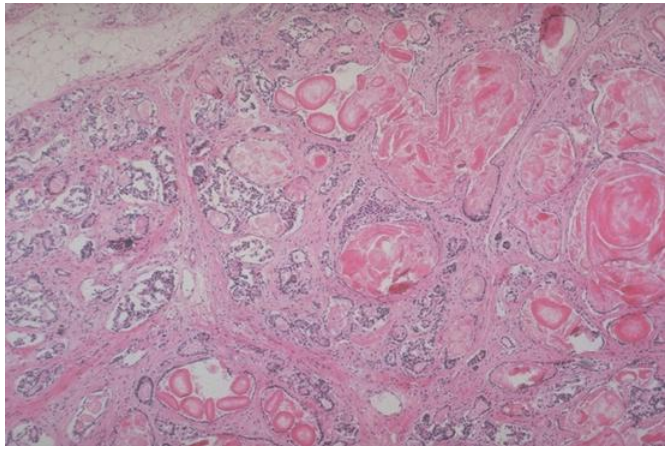
Classic Microscopic Findings

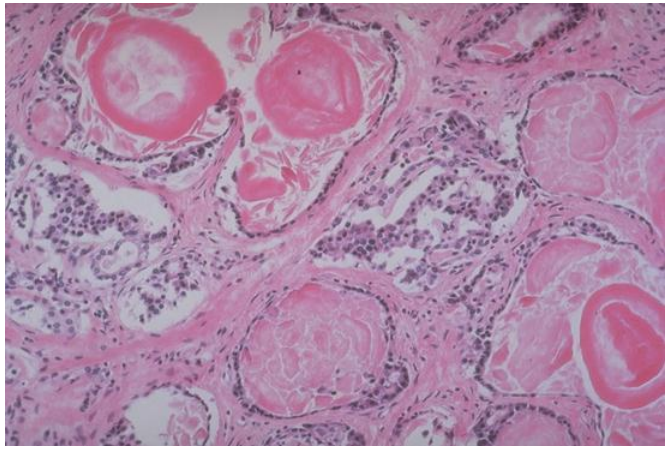
Normal
(3 days old)



CF
(6 days old)





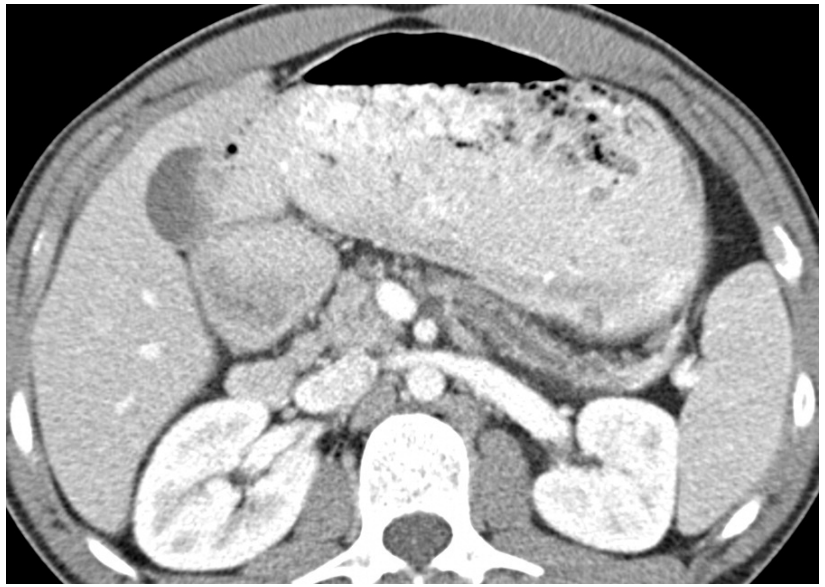


Obstructed and distended pancreatic ducts with increased eosinophils

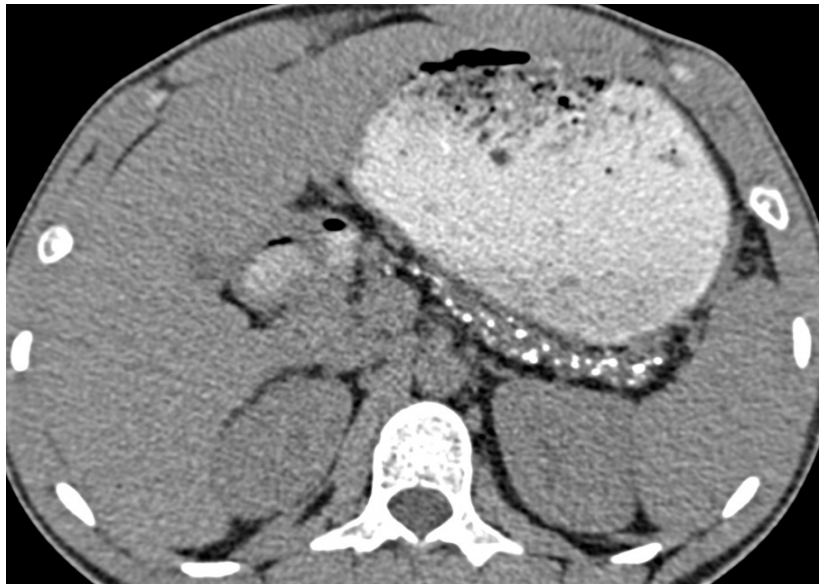
Am J Dis Child. 1938;56:344-99
Cystic fibrosis. PathologyOutlines.com website. https://www.pathologyoutlines.com/topic/pancreascysticfibrosis.html.

Classic Imaging Findings

- Fatty replacement, atrophy, sometimes calcifications



Axial portal venous phase CT scan
in a 29 year-old with CF



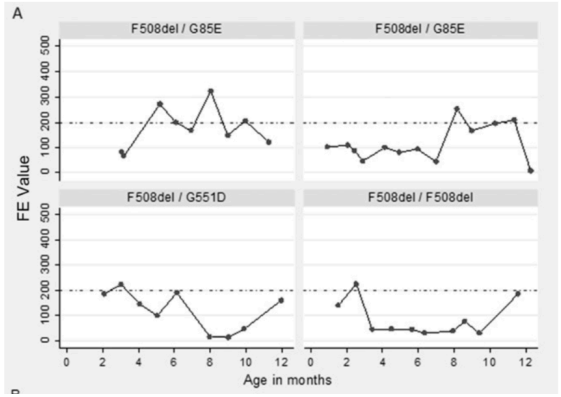
Axial non-enhanced CT scan
in a 28 year-old with CF

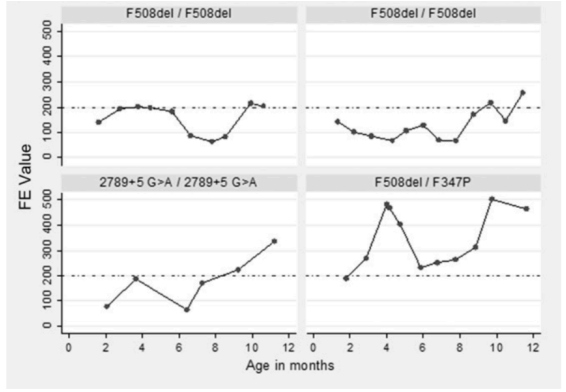
RadioGraphics 2015; 35(3): https://doi.org/10.1148/rg2015140110

Pancreatic Complications in CF

Exocrine Pancreatic Insufficiency

- Incidence: ~85% of CF children have EPI (may be less for adults)
- Diagnosis:
  - Practice: **fecal elastase**, endoscopic pancreatic function testing
  - Research: quantification of secretin-MRCP, secretin-stimulated transabdominal US or endoscopic US
- Treatment:
  - Pancreatic enzymes (~1,000-2,500 lipase units/kg/meal)
    - Work with your CF dietician!
  - Concomitant gastric acid suppression?



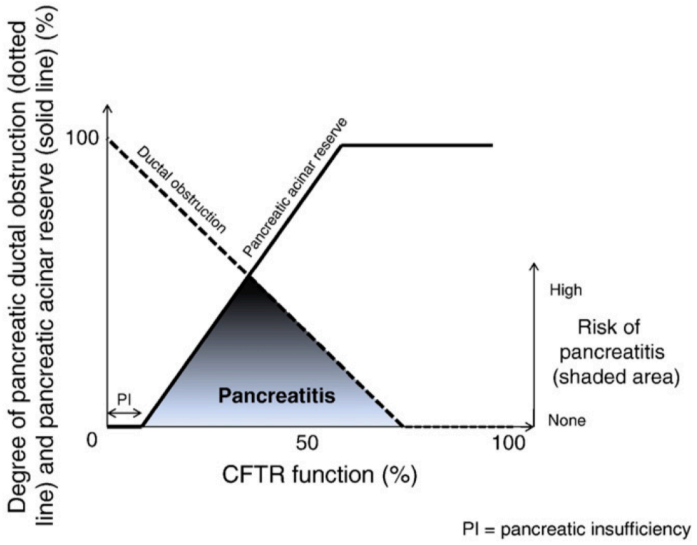


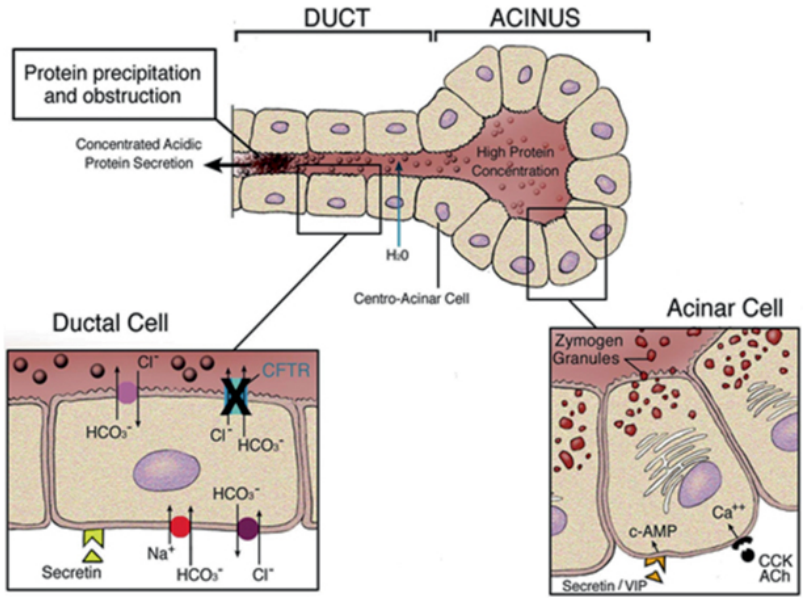
J Pediatr. 2013; 162:808-12

Pancreatic Complications in CF

Pancreatitis

- Incidence: ~10% of CF-PS patients will develop pancreatitis
- Pathophysiology: Pancreatic ductal flow becomes blocked → premature enzyme activation → inflammation and damage
- Caused by altered CFTR-dependent ion transport in pancreas
  - Degree of CFTR dysfunction determines risk





J Cyst Fibros. 2017; 16:S79-86
Wilschanski M., Uc A. 2016. Cystic Fibrosis. In: Textbook of Pediatric Gastroenterology, Hepatology and Nutrition.

Pancreatic Complications in CF

Pancreatic Cystosis

- Pancreatic parenchyma is replaced by multiple cysts of various sizes
  - Occurs in ~8% of CF patients
  - Usually identified incidentally

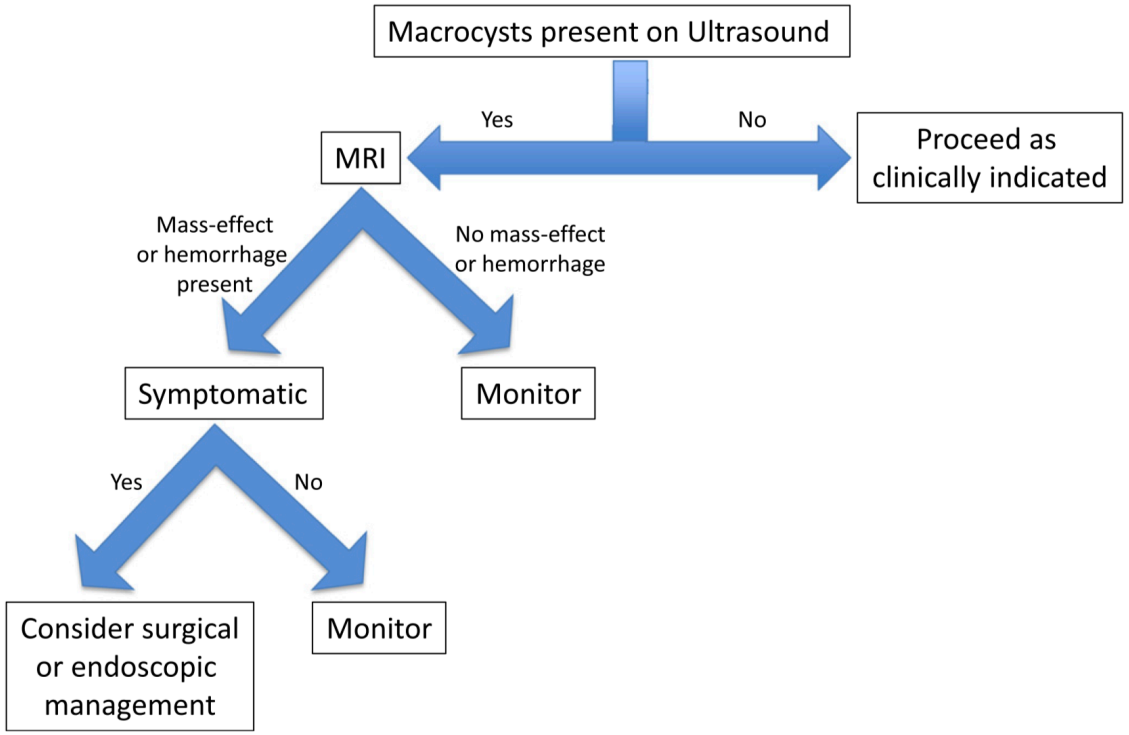
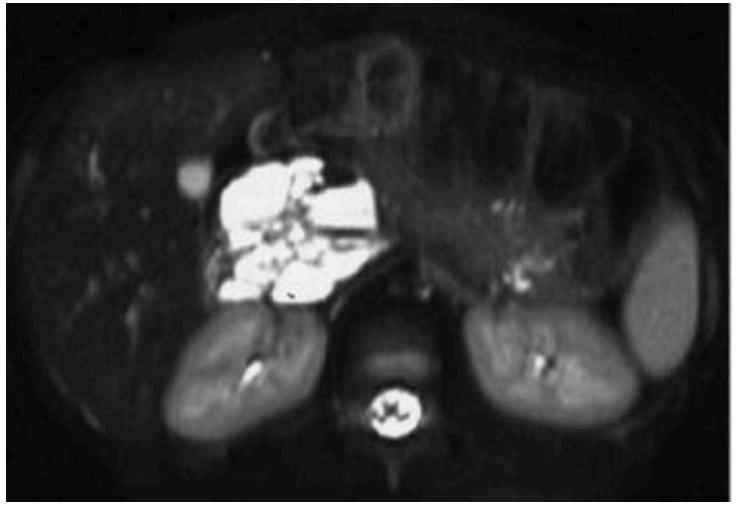
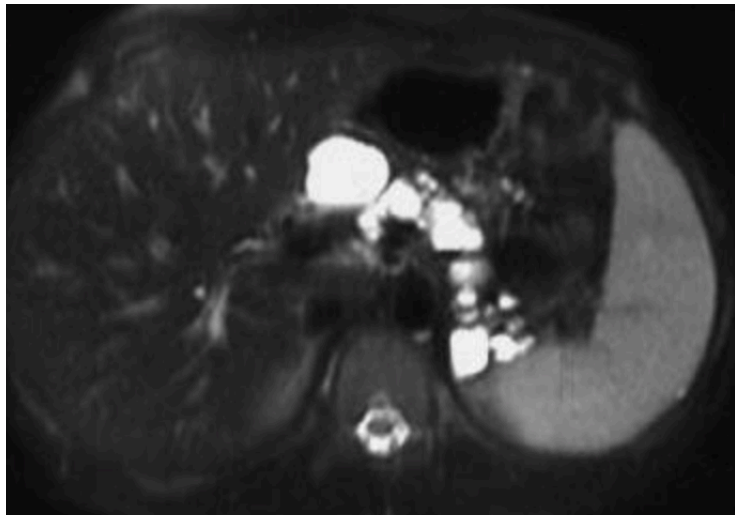


Fig. 4. Proposed decision making algorithm for pancreatic cystosis.

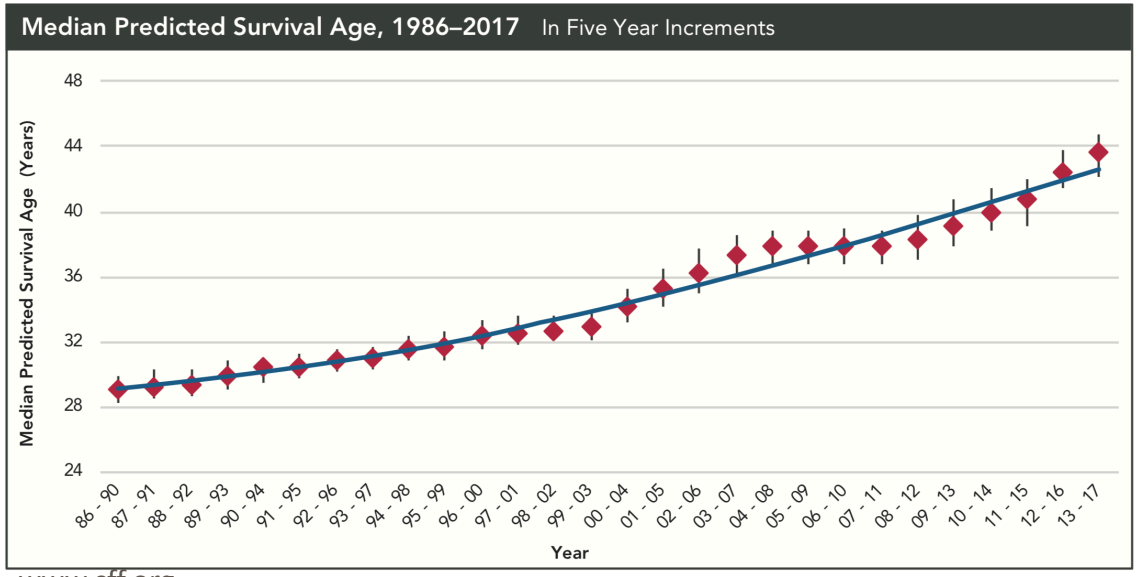




J Cyst Fibros. 2017; 16:S79-86
Case Rep Pediatr. 2016; 2016: 5321785.

Future for CF is bright

- CFTR Modulators:
  - Ivacaftor (Kalydeco) – FDA approved in 2012
  - Lumacaftor/Ivacaftor (Orkambi) - 2015
  - Tezacaftor/Lumacaftor/Ivacaftor (Elexacaftor) – July 22, 2019 application submitted
  - Other modulators in development



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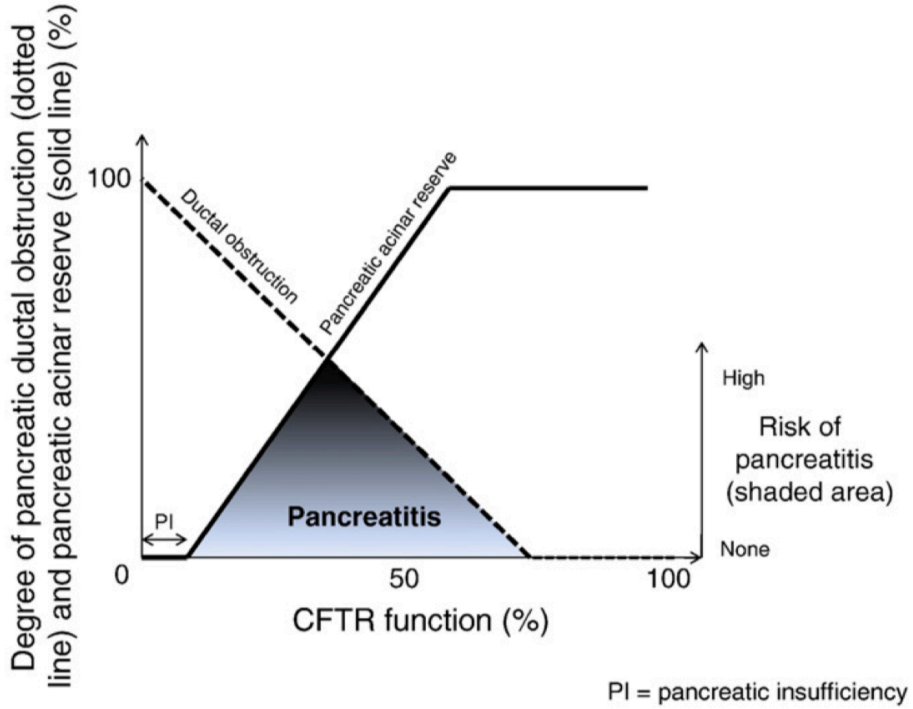
- Increasing incidence of CFTR-related disorders (e.g., pancreatitis)?



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