

Cystic Fibrosis

Malabsorption and gastrointestinal pathology

An epithelial ion-transport disorder with pancreatic, intestinal and hepatobiliary consequences

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

www.abusuraihsakhri.com

Learning objectives

Mechanism

Explain how defective CFTR alters epithelial electrolyte and water movement.

Morphology

Recognize the sequence from ductal concretions to pancreatic fibrosis.

Function

Relate loss of digestive enzymes to steatorrhea and deficiencies.

Application

Differentiate intestinal obstruction and pancreatic phenotypes.

Scope: Gastrointestinal consequences of cystic fibrosis

The gastrointestinal chapter treats cystic fibrosis principally as a cause of malabsorption.

Pulmonary disease is central to systemic cystic fibrosis, but is background in this lecture.

Pancreatic duct obstruction connects the genetic defect to defective intraluminal digestion.

Where cystic fibrosis disrupts nutrient absorption

Intraluminal digestion

Pancreatic enzymes degrade nutrients; This is the principal CF-related defect.

Terminal digestion

Brush-border hydrolases complete carbohydrate and peptide digestion.

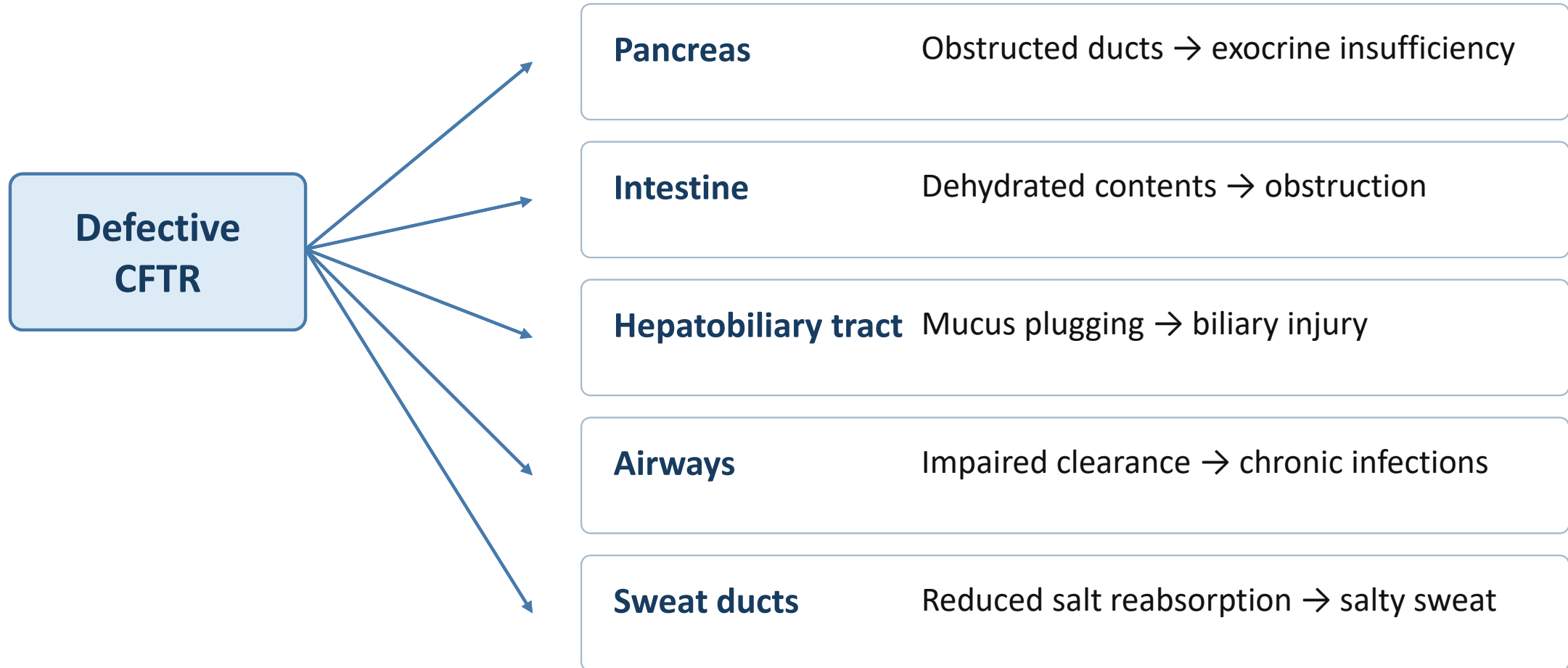
Transepithelial transport

Absorbed molecules cross intestinal epithelial cells.

Lymphatic transport

Absorbed lipids are transported away from the mucosa.

A single inherited defect affects multiple organs



CFTR is an epithelial anion channel

CFTR: Cystic fibrosis transmembrane conductance regulator.

The encoding gene lies on chromosome 7q31.2.

CFTR mediates chloride transport and contributes to bicarbonate transport.

The effect of CFTR dysfunction depends on epithelial tissue type.

CFTR architecture supports regulated channel opening

Transmembrane domains

Two membrane-spanning domains form the anion-conducting pore.

Nucleotide-binding domains

ATP binding and hydrolysis regulate gating.

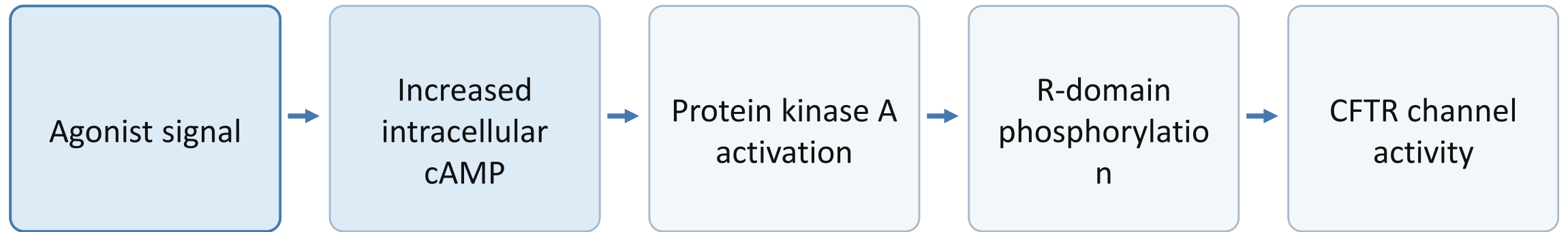
Regulatory domain

Protein kinase A phosphorylation facilitates channel opening.

Functional consequence

A defect can affect abundance, trafficking, gating or conductance.

How a normally functioning CFTR channel opens



Healthy intestinal epithelial surface fluid

Normal epithelium

SCHEMATIC: LUMEN

Fluid secretion



CFTR

m

CFTR supports chloride secretion; Luminal surface fluid remains hydrated.

Cystic fibrosis

SCHEMATIC: LUMEN

Reduced fluid

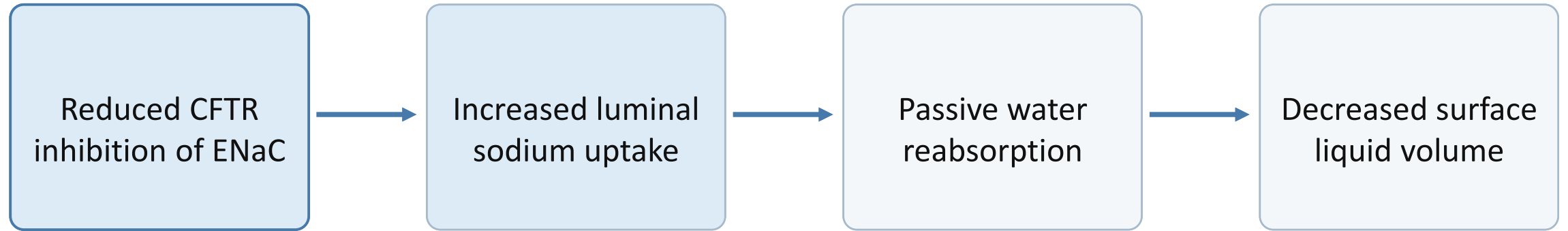


CFTR

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Reduced anion secretion and altered sodium handling reduce luminal water.

Epithelial sodium transport amplifies water loss



Bicarbonate transport is especially important in ducts

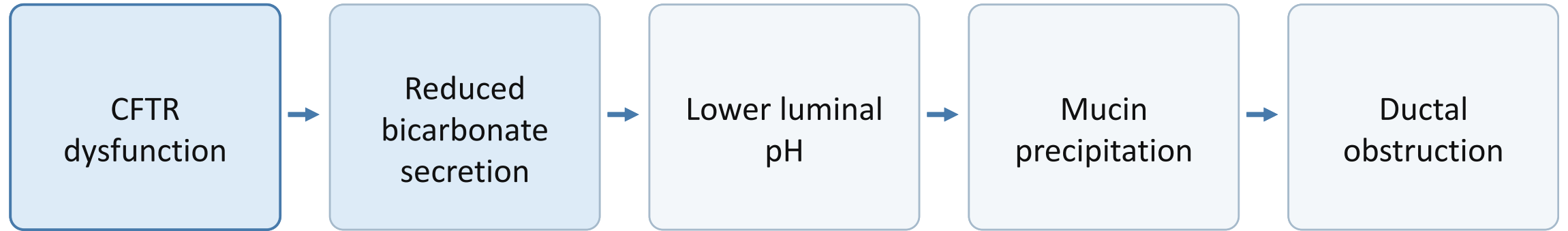
CFTR conducts bicarbonate as well as chloride.

CFTR also interacts with SLC26-family apical anion exchangers.

Reduced bicarbonate delivery results in abnormally acidic secretions.

Acidic fluid favors mucin precipitation and duct plugging.

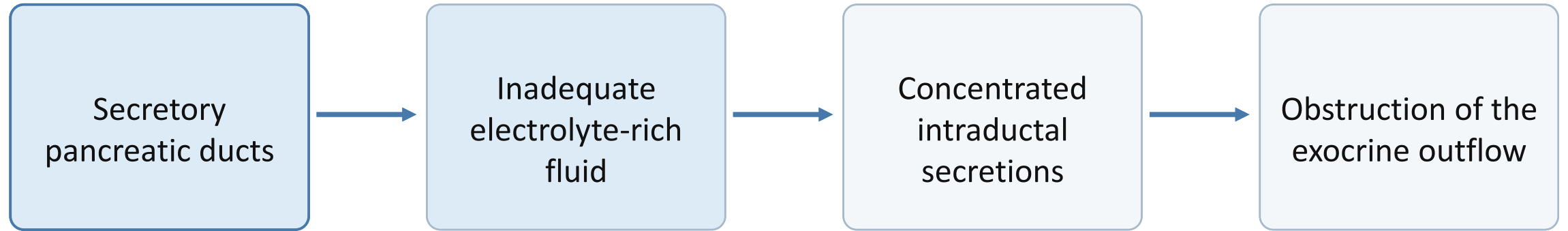
The biochemical route to mucus precipitation



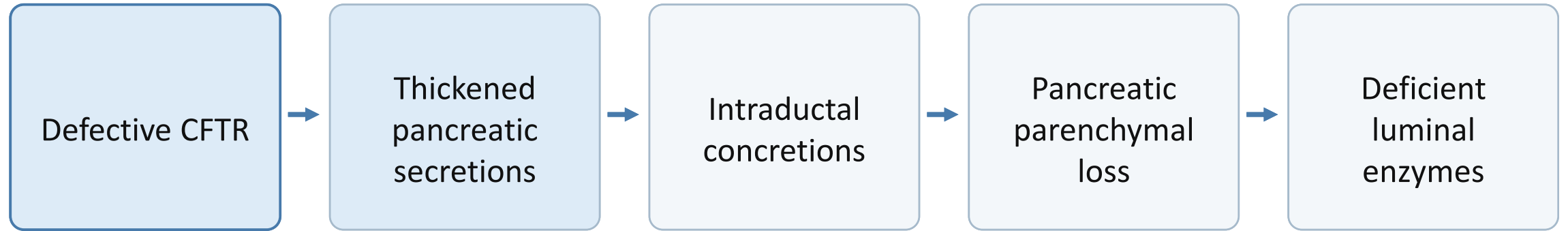
Chloride and bicarbonate defects have related effects

Transport defect	Pancreatic/GI consequence
Reduced chloride secretion	Less water maintained in the epithelial lumen
Reduced bicarbonate secretion	Acidic secretion and increased mucin precipitation
Combined ductal effect	Low-volume, poorly flowing, viscous secretions

Why the pancreas is a vulnerable target

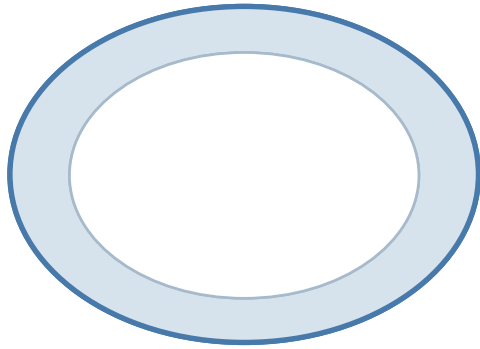


From CFTR dysfunction to malabsorption



Normal pancreatic outflow versus obstructed ducts

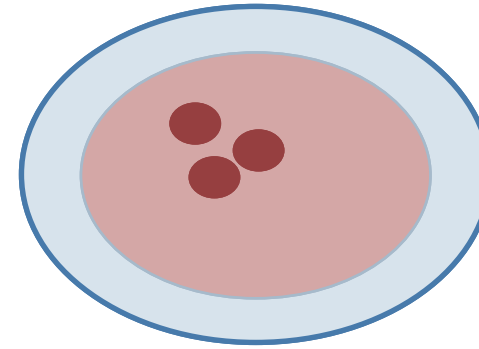
Patent duct



Schematic — simplified lumen

Aqueous pancreatic fluid carries enzymes into the intestine.

Obstructed duct



Schematic — simplified lumen

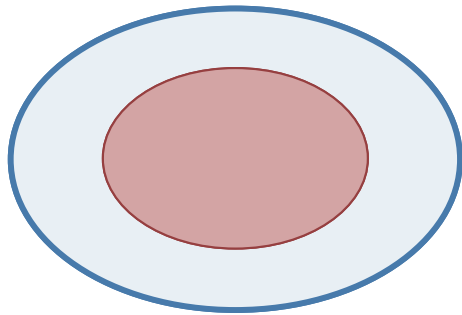
Viscous concretions impede flow and injure exocrine tissue.

Pancreatic lesions may begin in utero

Intraductal concretions can start forming during fetal development.
Luminal obstruction may therefore predate postnatal symptoms.
Pancreatic damage accumulates before clinically apparent malabsorption.

Initial pancreatic morphology: Retained mucus

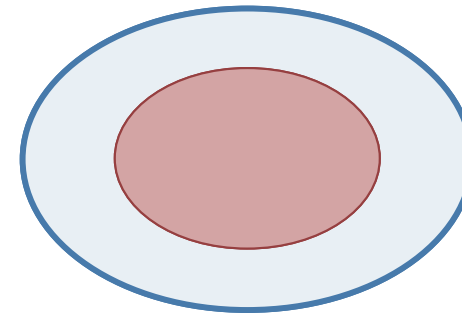
Milder disease



Schematic — duct / surrounding tissue

Mucus accumulates in small ducts with variable gland dilation.

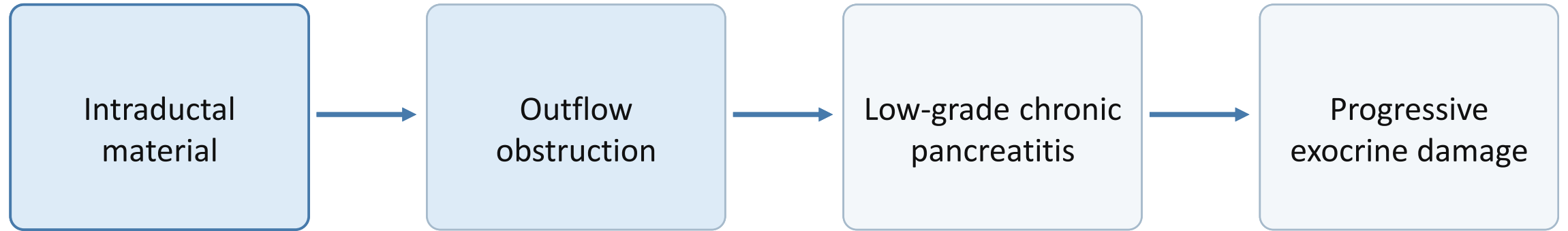
Progressive disease



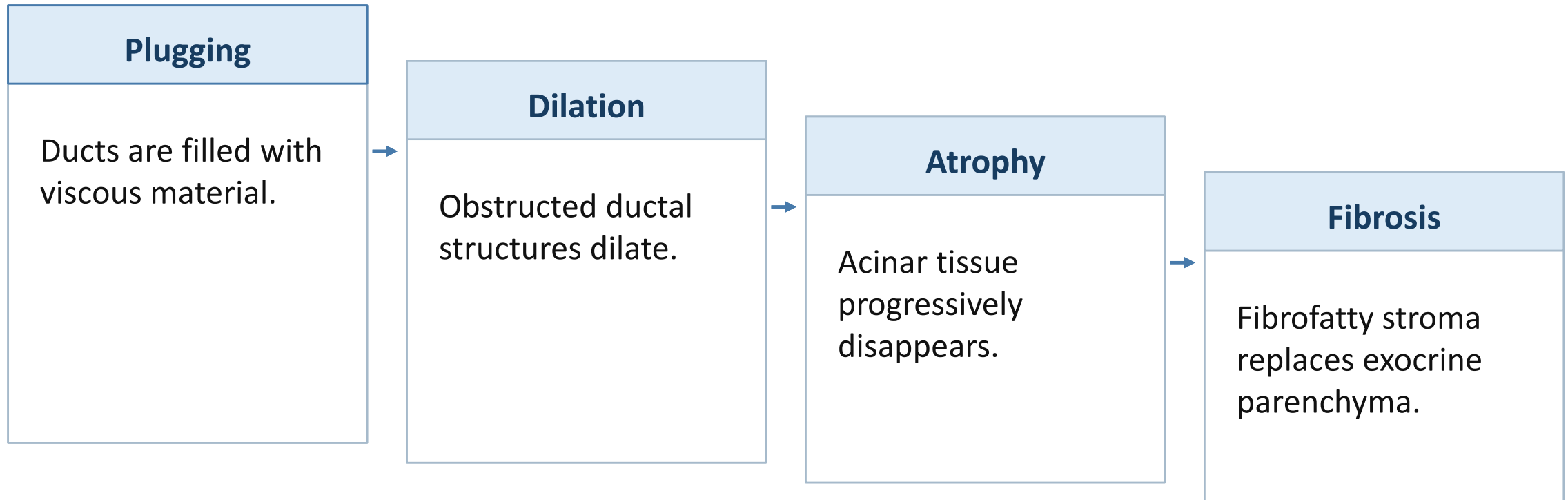
Schematic — duct / surrounding tissue

Marked intraductal plugging leads to obstructive tissue injury.

Duct obstruction produces chronic pancreatic injury



Advanced pancreatic pathology

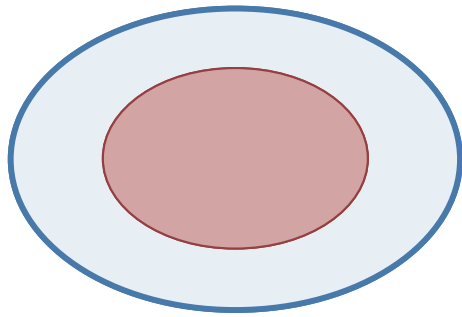


End-stage pancreas: Acini lost, islets relatively retained

Feature	Interpretation
Exocrine compartment	Widespread acinar destruction and fibrosis
Ductal compartment	Dilatation and persistent obstruction
Endocrine compartment	Islets can remain within fibrofatty stroma

Microscopic pattern: An obstructive fibroatrophic process

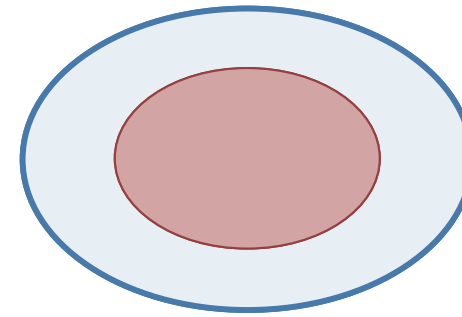
Early pattern



Schematic — duct / surrounding tissue

Luminal mucus with duct dilation and residual acini.

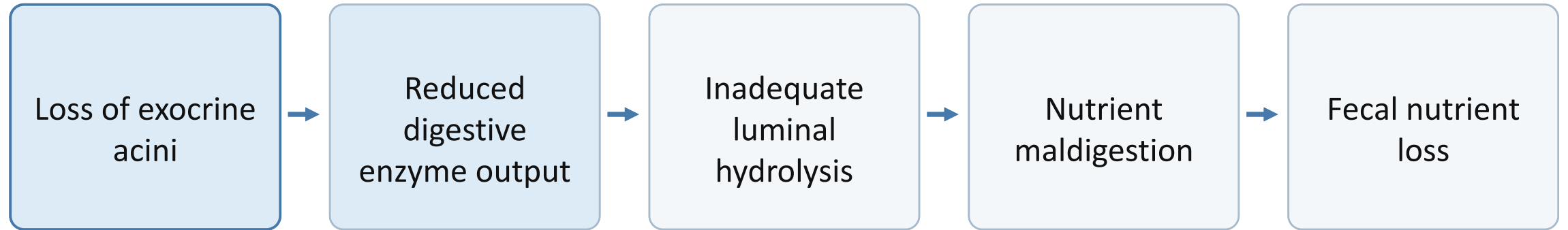
Late pattern



Schematic — duct / surrounding tissue

Marked loss of exocrine parenchyma with fibrous replacement.

How exocrine pancreatic insufficiency develops



Pancreatic insufficiency is common in classic CF

The gastrointestinal section reports exocrine pancreatic insufficiency in more than 80% of patients.

The systemic CF chapter describes pancreatic insufficiency in about 85%–90%.

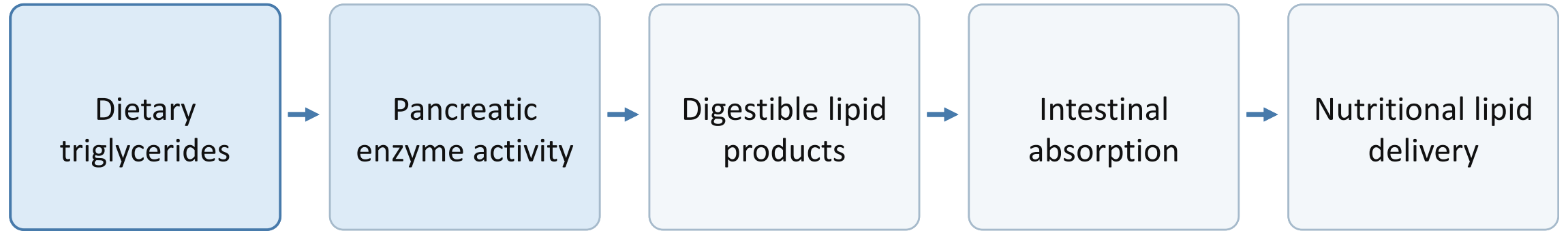
A pancreatic-sufficient phenotype also occurs.

Severity reflects the functional consequences of the CFTR alleles.

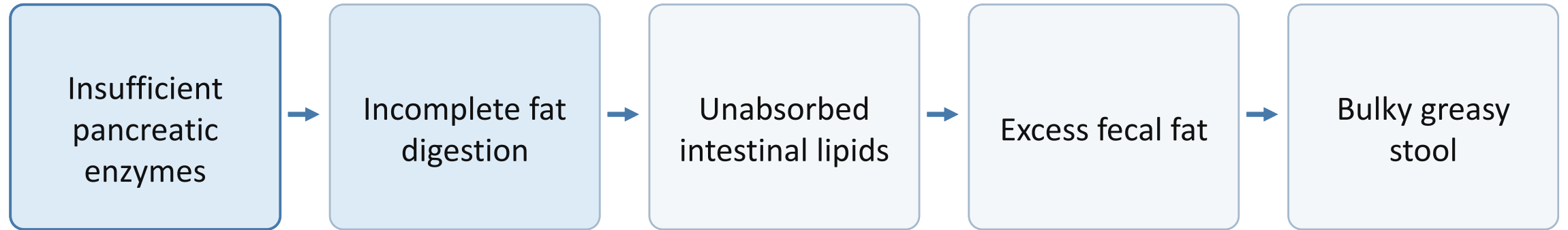
Defective intraluminal digestion is not a villous lesion

Disorder	Predominant mechanistic location
Cystic fibrosis	Pancreatic enzyme deficiency; Predominantly intraluminal digestion failure
Celiac disease	Intestinal mucosal disease with absorptive and digestive defects
Disaccharidase deficiency	Brush-border terminal digestion defect

Normal fat handling requires pancreatic digestion



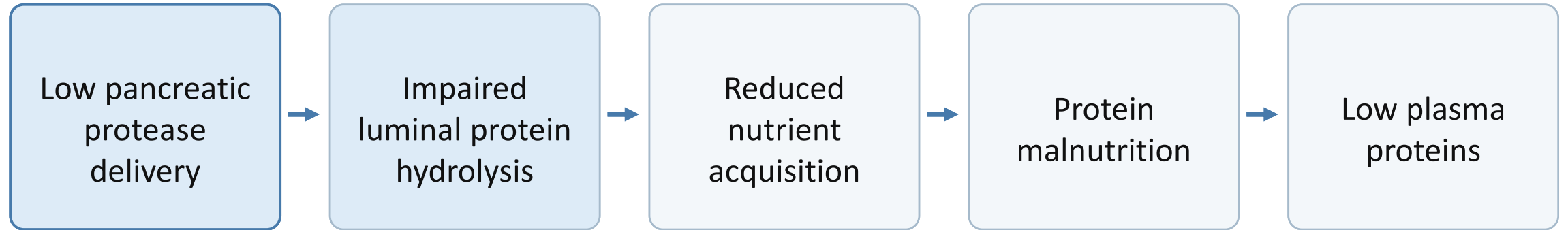
Why steatorrhea develops in CF



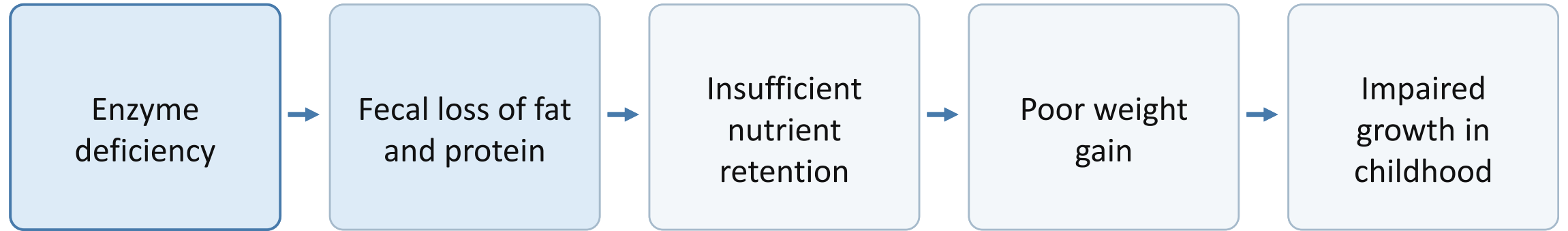
Recognizing malabsorptive stools

Bulky and foul-smelling stools are characteristic of CF-associated malabsorption. Stool may be greasy or frothy because of excessive fecal fat. Abdominal distension and chronic diarrhea can accompany steatorrhea. These findings indicate maldigestion; They are not individually specific for CF.

Protein maldigestion adds nutritional loss



Malabsorption links pancreas to impaired growth



Fat-soluble vitamins are vulnerable

Vitamin A

Deficiency may affect epithelial integrity;
Pancreatic duct metaplasia.

Vitamin D

Deficiency can contribute to osteopenia and
disordered mineral homeostasis.

Vitamin E

Vitamin E belongs to the fat-soluble group at risk
in malabsorption.

Vitamin K

Deficiency can lead to a bleeding tendency.

Vitamin A: Duct epithelial consequences

Loss of exocrine secretion impairs absorption of fat-soluble nutrients.

Vitamin A deficiency may contribute to squamous metaplasia of pancreatic duct epithelium.

Duct lining cells already sustain damage from inspissated secretions.

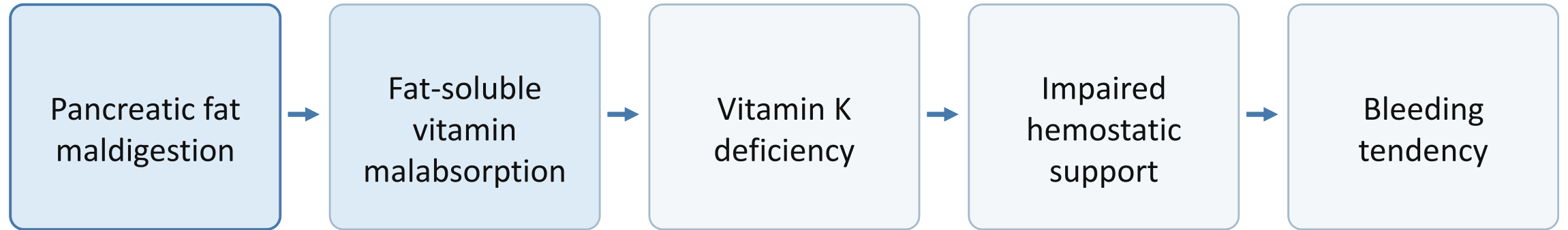
Vitamin D: Skeletal consequences of malabsorption

Chronic malabsorption can reduce absorption of vitamin D and minerals.

The Robbins malabsorption section associates these deficiencies with osteopenia and tetany.

Poor growth may coexist with skeletal and mineral consequences.

Vitamin K deficiency can manifest as bleeding



Clinical phenotype: Nutritional and GI manifestations

Stool

Large, greasy, foul-smelling stools; Persistent diarrhea.

Abdomen

Distension, flatus, discomfort and sometimes obstruction.

Growth

Poor weight gain, wasting and failure to thrive.

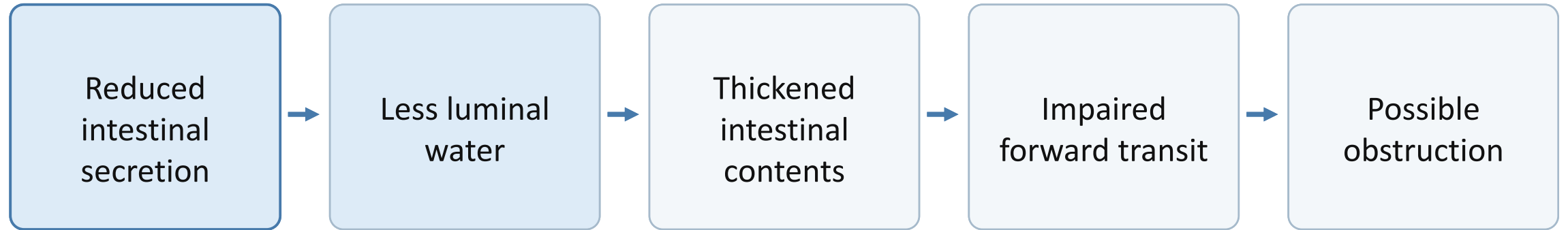
Systemic

Vitamin deficiency and, when severe, hypoproteinemic edema.

Pancreatic and intestinal luminal problems are distinct

Site	Principal consequence
Pancreas	Obstructed ducts → parenchymal destruction → enzyme deficiency
Intestine	Viscous luminal contents → bowel obstruction in some patients
Clinical difference	Malabsorption predominates for pancreas; Obstruction is a separate intestinal event

Viscous intestinal contents predispose to blockage

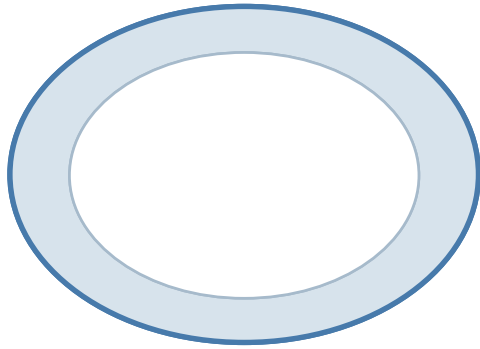


Meconium ileus: Neonatal obstruction

Thick, viscid meconium may obstruct the small intestine in affected newborns. The systemic chapter reports presentation with meconium ileus in approximately 5%–10% of cases. This can bring cystic fibrosis to clinical attention at or shortly after birth.

Meconium ileus: Mechanism and anatomic pattern

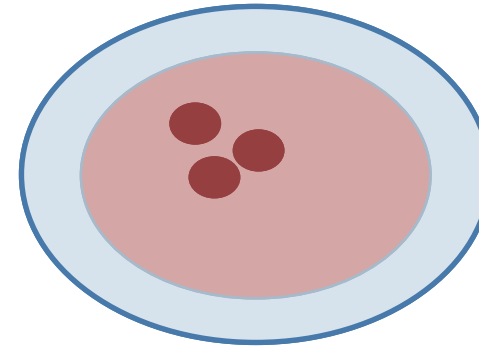
Normal neonatal bowel



Schematic — simplified lumen

Meconium traverses an unobstructed intestinal lumen.

Cystic fibrosis



Schematic — simplified lumen

Inspissated meconium forms an obstructive luminal plug.

Clinical exercise: Neonatal intestinal obstruction

Clinical reasoning exercise

A neonate develops early signs of intestinal obstruction.
The obstructing material is unusually thick meconium.
What inherited epithelial transport disease links this presentation to pancreatic insufficiency?

Case reasoning: Meconium ileus points toward CF

CFTR dysfunction reduces epithelial fluid secretion into the intestine.

Inspissated meconium can obstruct the small bowel.

The same channel defect also drives pancreatic duct plugging and malabsorption.

Distal intestinal obstruction syndrome in older patients

Distal intestinal obstruction may occur after infancy.

Recurrent right lower quadrant pain.

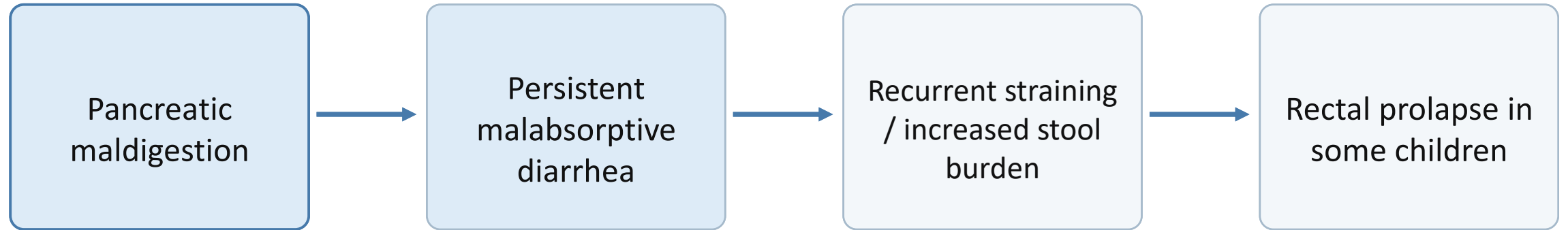
A palpable meconium-containing mass may occur in the right iliac fossa.

Intussusception may or may not accompany the episode.

Meconium ileus versus distal intestinal obstruction

Feature	Meconium ileus	Distal intestinal obstruction
Typical period	Newborn / soon after birth	Older children or other individuals
Dominant problem	Early small-bowel obstruction	Recurrent distal intestinal obstruction
Clinical clues	Thick neonatal meconium	Right lower quadrant pain ± palpable mass

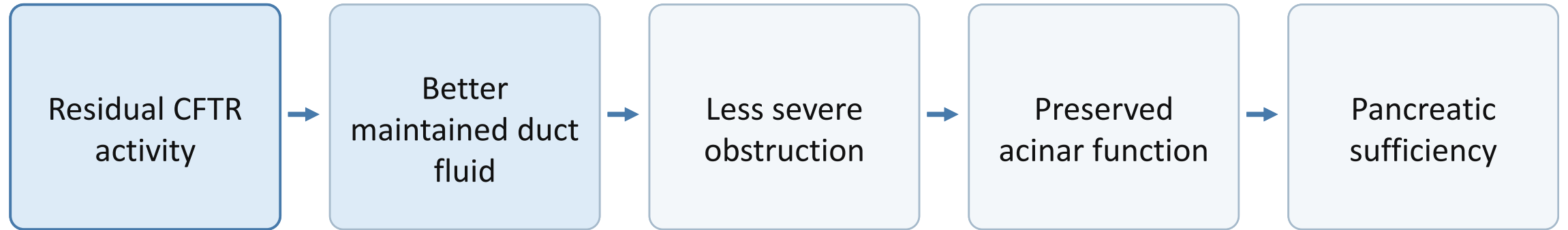
Rectal prolapse may complicate chronic diarrhea



Pancreatic sufficiency is a real CF phenotype

Phenotype	Exocrine consequence
Pancreatic insufficient	Defective enzyme delivery → malabsorption and enzyme-replacement need
Pancreatic sufficient	Enough residual exocrine function to avoid routine enzyme replacement

Why some mutations spare pancreatic function



Pancreatic-sufficient CF can present with pancreatitis

Some pancreas-sufficient patients have recurrent acute pancreatitis. Episodes can include acute abdominal pain and severe complications. Late-onset apparently idiopathic pancreatitis may reveal CFTR-related disease. Thus pancreatic sufficiency and pancreatic inflammation can coexist.

CFTR-associated pancreatitis can appear outside classic CF

Some idiopathic chronic pancreatitis to biallelic CFTR variants.

Other classic organ-system findings may be absent.

The pancreatic chapter also discusses CFTR-related pancreatitis susceptibility in heterozygous carriers.

Variant interpretation and broader clinical context therefore matter.

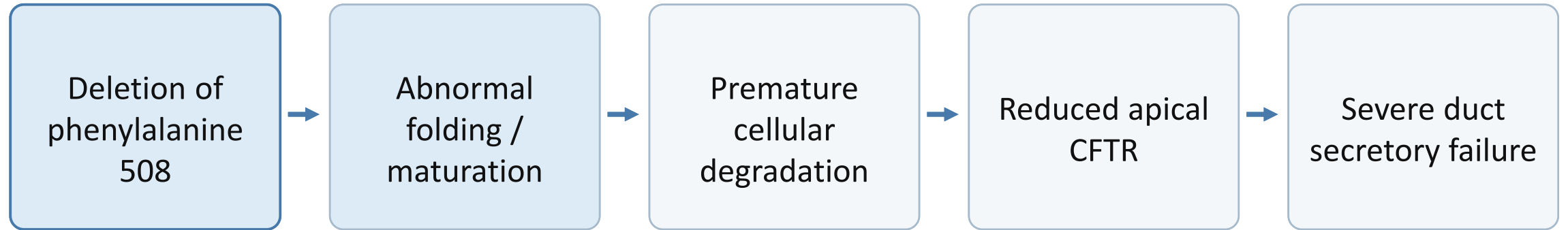
Genotype–phenotype correlation is strongest in pancreas

Organ system	Predictability
Pancreas	Residual CFTR function predicts pancreatic sufficiency comparatively well.
Lung	Infection and modifier genes produce less consistent genotype prediction.
Clinical implication	Do not extrapolate pancreatic severity to all other organs.

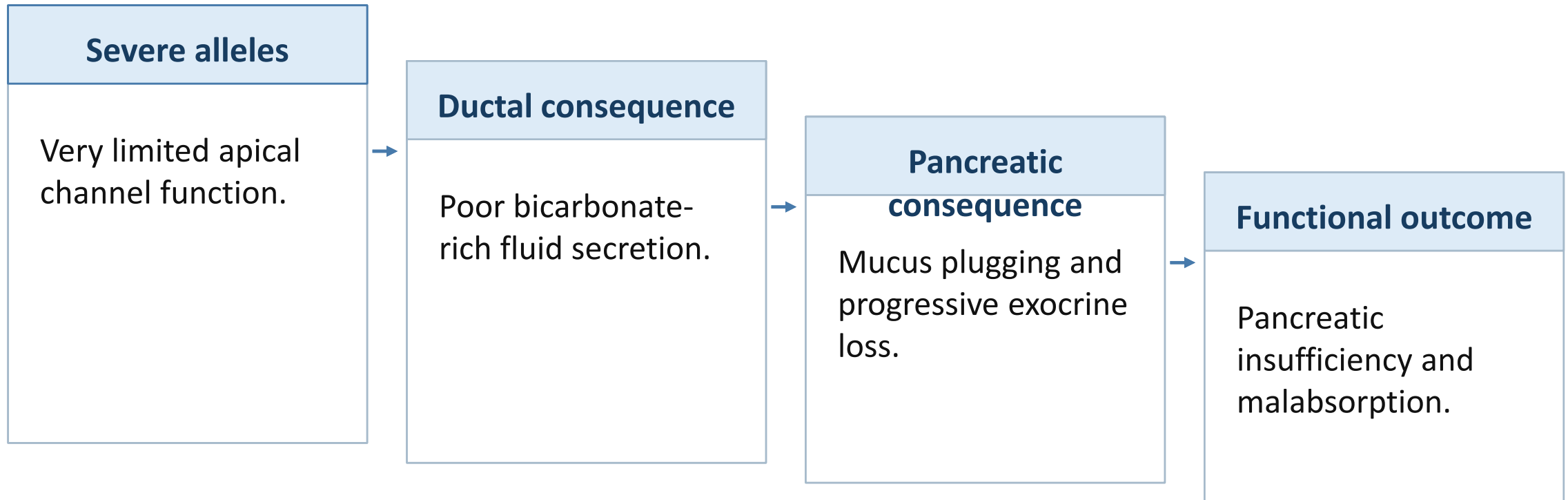
Six broad mechanisms of CFTR protein dysfunction

Class	Molecular mechanism	Functional result
I	Defective protein synthesis	Little or no functional channel
II	Folding / trafficking abnormality	Protein fails to reach surface
III	Defective gating	Surface channel fails to open properly
IV	Reduced ionic conductance	Ion movement through channel impaired
V	Reduced protein abundance	Less otherwise functional channel
VI	Reduced surface stability	Shorter lifetime of membrane CFTR

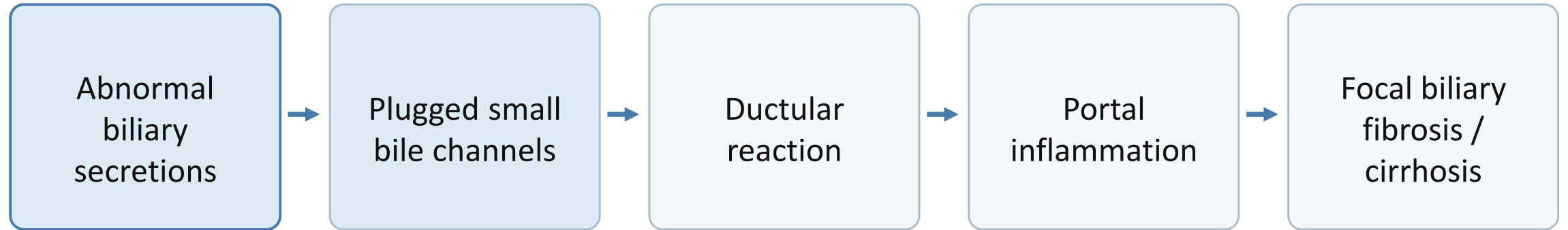
Phe508del exemplifies defective CFTR processing



Pancreatic severity reflects remaining CFTR function



Hepatobiliary changes use the same obstructive logic



Histologic liver pattern in cystic fibrosis

Biliary mucus accumulation and plugging are described.

Ductular proliferation accompanies portal inflammation.

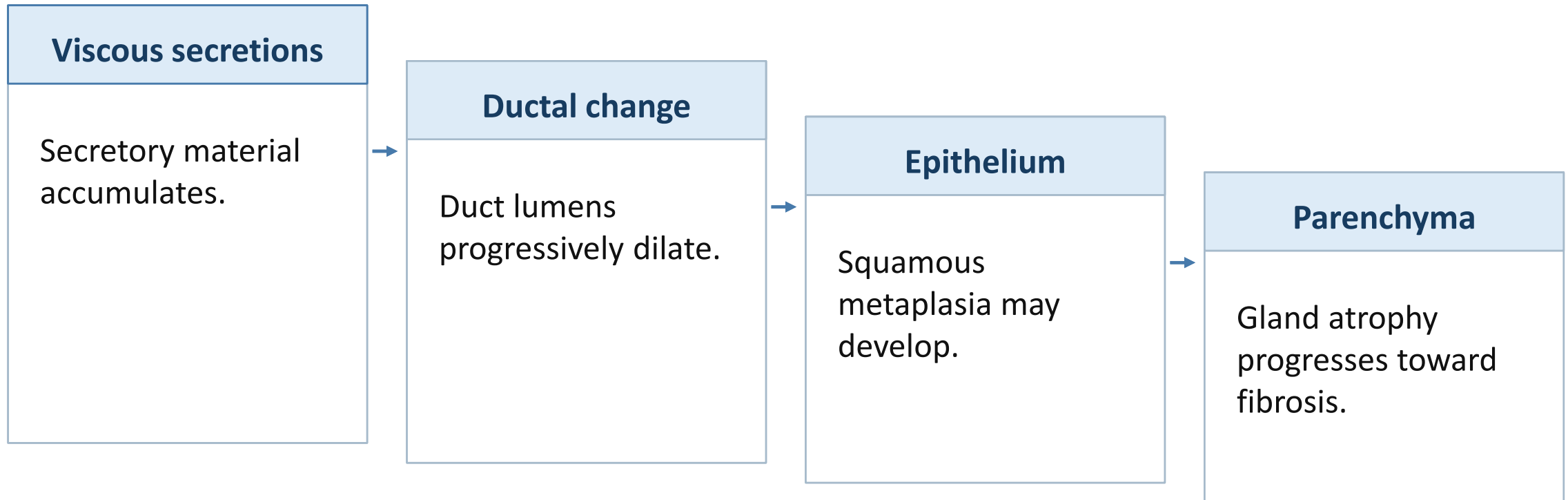
Steatosis may also occur.

Progressive involvement can produce focal biliary cirrhosis and, rarely, diffuse nodularity.

Clinical liver disease may emerge later

Hepatobiliary disease becomes increasingly relevant with longer survival.
Symptomatic or biochemical involvement often around puberty.
Common bile duct sludge or stones can cause pain with acute jaundice.
Diffuse biliary cirrhosis is reported in fewer than 10% of affected individuals.

Salivary ducts demonstrate the shared exocrine pattern



Sweat and intestinal epithelia behave differently

Epithelial site	Effect of CFTR dysfunction
Sweat gland duct	Reduced NaCl reabsorption → elevated sweat electrolyte concentration
Intestinal and airway epithelium	Reduced luminal anion secretion → depleted surface fluid
Lesson	CFTR loss affects ion transport differently by tissue

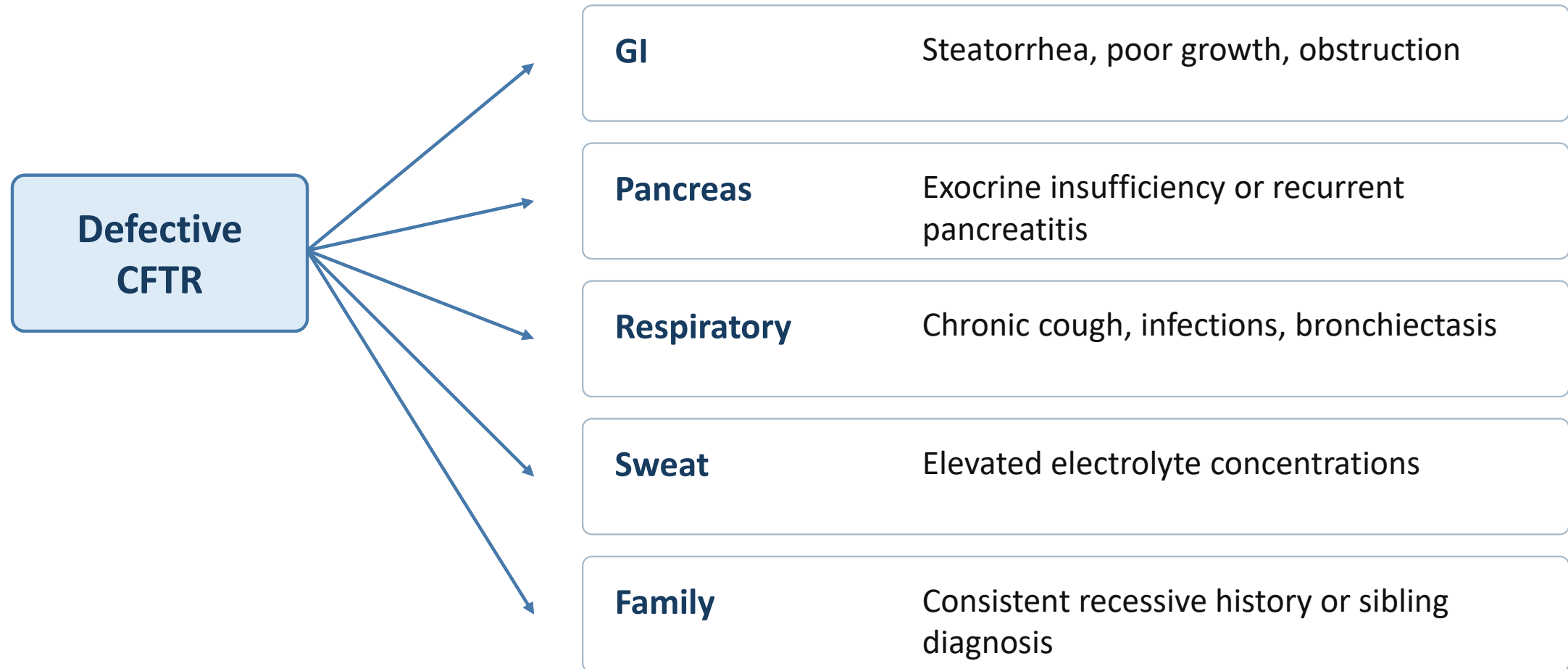
Malabsorptive diarrhea versus other diarrhea types

Pattern	Mechanism	Distinguishing observation
Malabsorptive	Impaired nutrient absorption, often steatorrhea	Common with pancreatic insufficiency
Osmotic	Unabsorbed solutes retain luminal fluid	Classically improves with fasting
Secretory	Ongoing epithelial fluid secretion	Often persists during fasting
Exudative	Inflammatory mucosal injury	May include purulent or bloody stool

GI differential: Pancreatic failure versus mucosal disease

Candidate process	Where dysfunction arises
CF-associated pancreatic insufficiency	Reduced luminal enzyme delivery to the gut
Celiac disease	Gluten-triggered immune-mediated small-intestinal pathology
Crohn disease	Chronic inflammatory disease can produce malabsorption

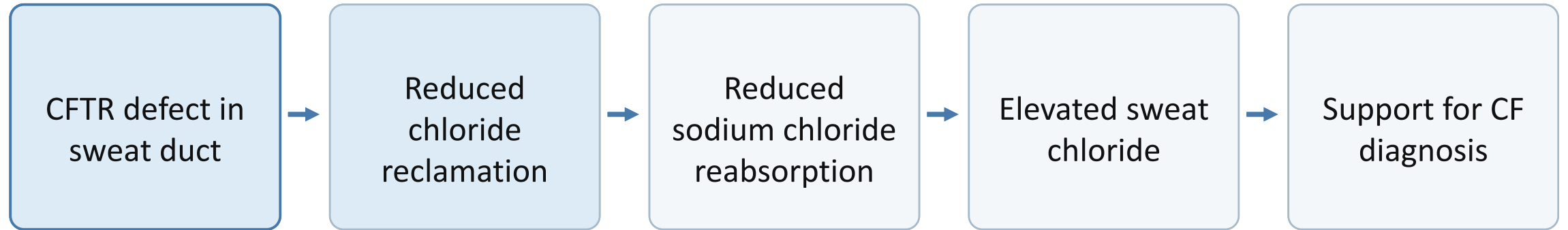
The diagnostic clue is a multisystem pattern



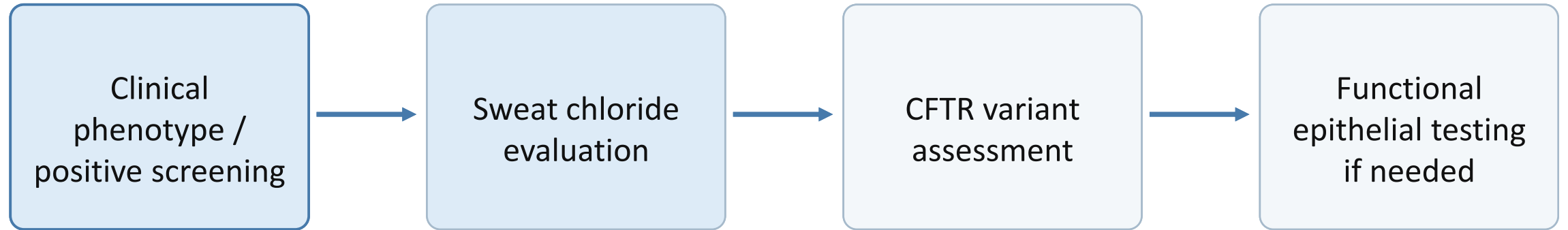
Newborn screening is a starting point, not final diagnosis

A common newborn screening approach measures immunoreactive trypsinogen.
Elevated levels reflect pancreatic injury.
A positive newborn screen requires appropriate confirmatory evaluation.
Pancreatic manifestations may provide the first clinical evidence of CF.

Sweat testing exploits tissue-specific CFTR physiology



Clinical features must be integrated with CFTR evidence



Diagnostic interpretation requires caution

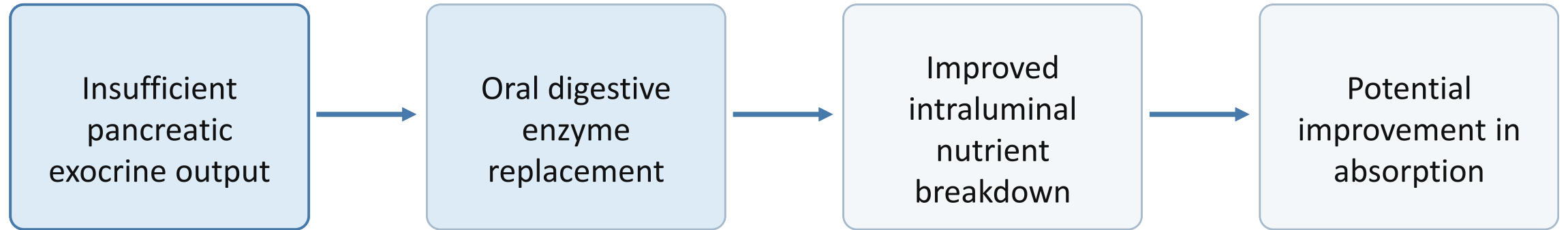
Classic cystic fibrosis has characteristic manifestations and demonstrable CFTR dysfunction.

Milder alleles may be associated with less typical clinical presentations.

Sweat results may be normal or near-normal in a minority of atypical cases.

Physiological testing and genetic interpretation can be complementary.

Pancreatic enzyme replacement targets the failed step



Mutation-directed therapies target upstream CFTR biology

Potentiators

Improve channel opening and function of suitable CFTR variants.

Correctors

Improve folding and trafficking of some defective CFTR proteins.

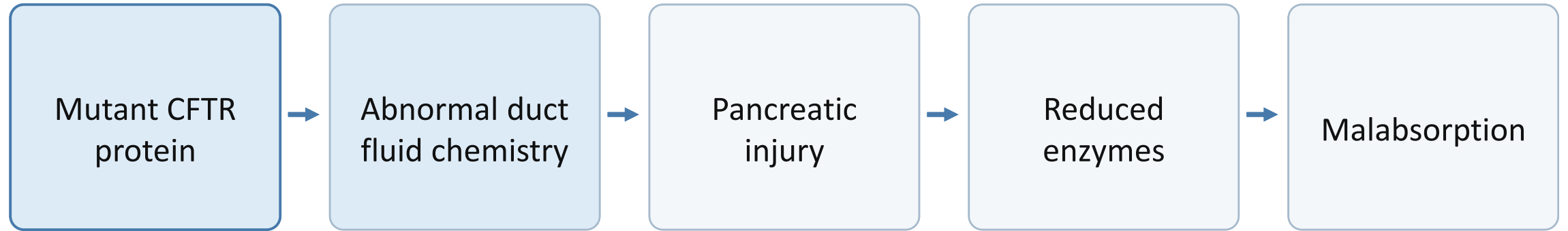
Amplifiers

Increase CFTR protein production; Discussed as a mechanistic class.

Enzyme therapy

Replaces downstream digestive function rather than correcting CFTR.

Therapeutic targets lie at different points in the cascade



Application: Interpreting a malabsorptive phenotype

Clinical reasoning exercise

A child has large greasy stools, poor weight gain and recurrent respiratory symptoms.

Pancreatic exocrine function is markedly reduced.

Which of the four phases of nutrient absorption is primarily disrupted?

Case reasoning: Failure occurs before mucosal uptake

CFTR dysfunction causes pancreatic ductal concretions and injury.

Loss of pancreatic exocrine tissue lowers enzyme delivery.

Intraluminal digestion fails; Unprocessed nutrients remain in stool.

A primary enterocyte transport defect is not required to explain this presentation.

Application: Pancreatitis without obvious steatorrhea

Clinical reasoning exercise

An individual with CFTR-related disease has repeated episodes of pancreatitis. Growth is preserved and enzyme replacement is not needed. Why can pancreatitis coexist with preserved exocrine output?

Case reasoning: Residual function can preserve digestion

Residual CFTR function may protect much of the exocrine pancreas.

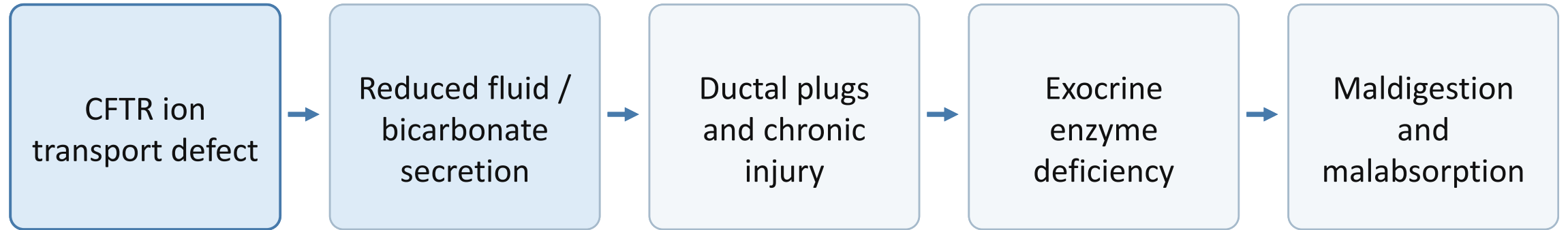
Duct secretion can still be abnormal enough to predispose to pancreatitis.

Pancreatic sufficiency therefore does not exclude CFTR-related pancreatic disease.

Common conceptual errors in cystic fibrosis malabsorption

Incorrect inference	Correct interpretation
“All CF causes pancreatic insufficiency.”	A pancreatic-sufficient phenotype is documented.
“The intestinal villi are the primary lesion.”	The principal CF malabsorptive defect is intraluminal digestion.
“Salty sweat means all lumens are hypertonic.”	Sweat ducts and intestinal epithelia have different CFTR roles.
“Enzyme therapy fixes the gene defect.”	Enzymes replace digestive function downstream of CFTR.

Integrated pathological mechanism



Core findings to retain

Primary lesion

Defective CFTR-mediated epithelial ion transport.

Pancreatic morphology

Ductal concretions, exocrine atrophy and fibrosis.

GI physiology

Impaired intraluminal digestion with steatorrhea.

Clinicopathology

Malnutrition; Possible meconium ileus, distal obstruction and biliary disease.

Primary textbook references

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026).
The Gastrointestinal Tract — Malabsorption and Diarrhea: Cystic Fibrosis.
Diseases of Infancy and Childhood — Cystic Fibrosis (Mucoviscidosis).
The Pancreas — sections discussing CFTR-associated pancreatic injury.