

Cystic Fibrosis (Mucoviscidosis)

Molecular mechanism · organ pathology ·
clinicopathologic diagnosis

Pathology lecture

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

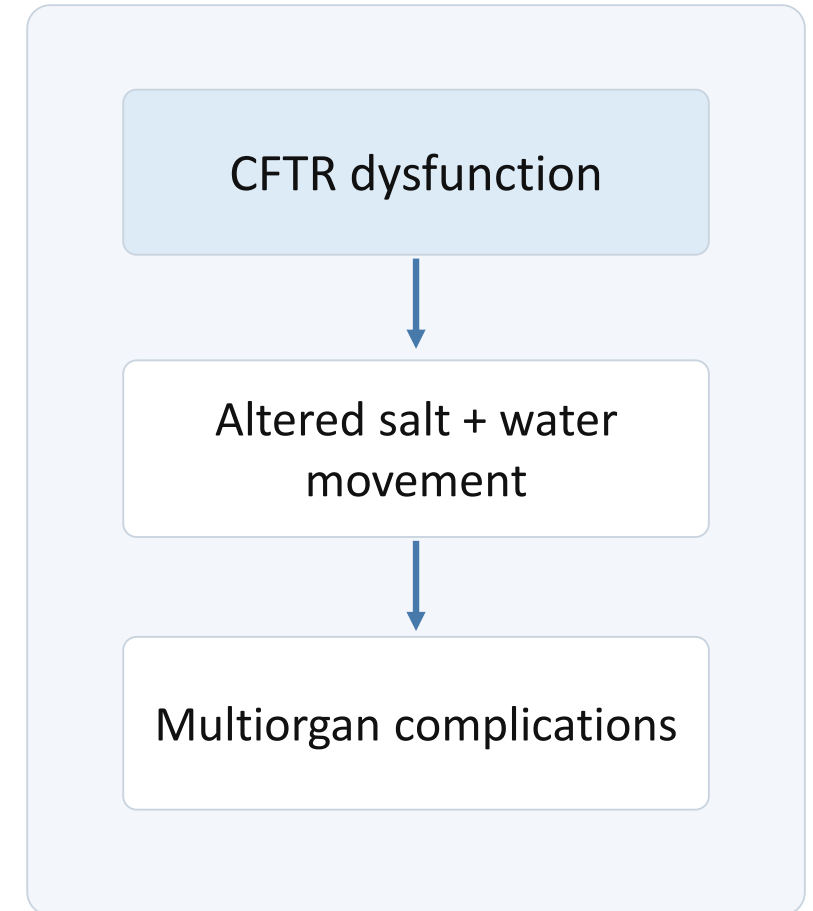
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Learning outcomes

- Explain how CFTR dysfunction alters epithelial ion and fluid transport.
- Relate viscous secretions to structural injury in lung, pancreas, intestine, and hepatobiliary tract.
- Recognize the clinical spectrum, diagnostic logic, and genotype-dependent variation.
- Distinguish supportive care from mechanistically targeted CFTR treatments.

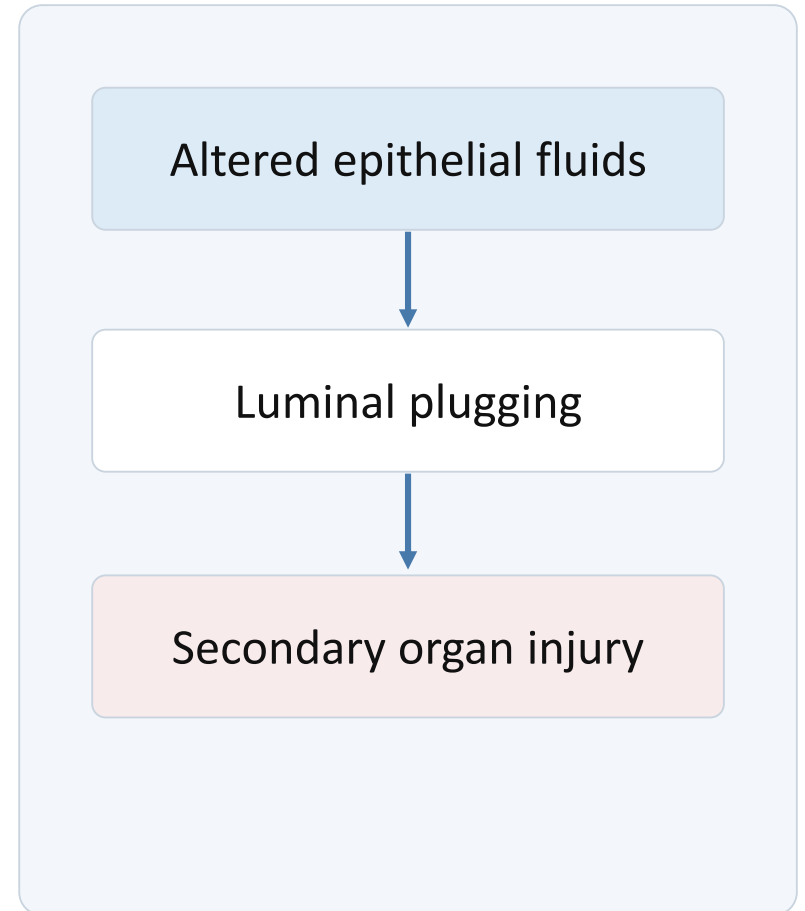
A single-gene disorder with multisystem consequences

- Autosomal recessive disorder of epithelial ion transport.
- Affects exocrine glands and respiratory, gastrointestinal, and reproductive epithelia.
- Thickened secretions obstruct ducts and airways.
- Clinical effects arise from obstruction, infection, inflammation, and impaired secretion.



Why “mucoviscidosis” describes the phenotype

- Viscous, poorly hydrated secretions accumulate within epithelial passages.
- Mechanical obstruction compromises secretion drainage.
- Retained secretions predispose to inflammation and secondary infection.
- Manifestations depend on which ductal system is affected.



Clinical expression is heterogeneous

- Onset ranges from prenatal or neonatal disease to childhood, adolescence, and adulthood.
- Some individuals present with classic multisystem disease.
- Others exhibit comparatively mild or organ-limited manifestations.
- Variation reflects CFTR alleles, tissue physiology, and modifier effects.

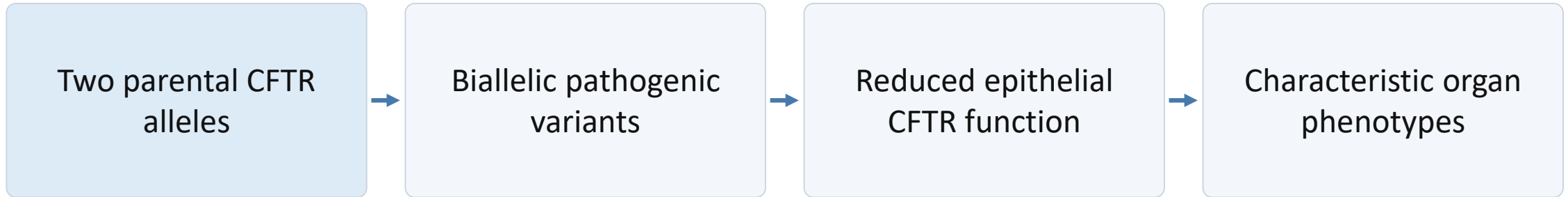
Classic CF

Pancreas-sufficient CF

Late-onset pulmonary
disease

Isolated reproductive
phenotype

Transmission follows an autosomal recessive pattern



- Affected individuals carry disease-causing variants in both alleles.
- Different variant combinations alter residual CFTR function and the clinical phenotype.

Historical epidemiologic context

- An incidence of approximately 1 in 2,500 live births among people of Northern European descent.
- The source reports a U.S. Carrier frequency of approximately 1 in 20 in that ancestry group.
- CFTR variants occur globally, with substantial population differences.
- These textbook figures are ancestry-specific historical estimates, not universal contemporary rates.

One molecular defect, different tissue responses

Respiratory / intestinal epithelium

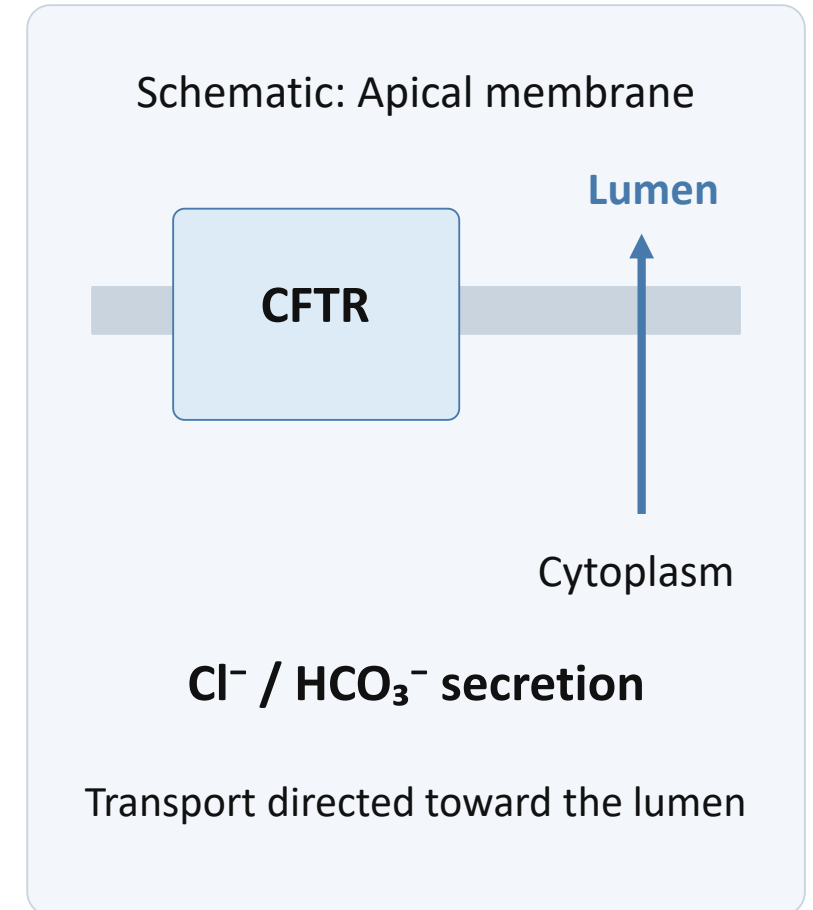
- Reduced anion secretion
- Dehydrated surface fluid
- Mucus stasis and obstruction

Sweat duct epithelium

- Reduced salt reabsorption
- Excess NaCl remains in sweat
- High sweat chloride

CFTR is an epithelial anion channel

- CFTR gene is located on chromosome 7q31.2.
- The encoded protein forms an apical membrane ion channel.
- Its primary relevant substrates are chloride and bicarbonate ions.
- It also regulates interacting ion channels and secretory processes.



The CFTR protein has modular architecture

Two membrane-spanning
domains



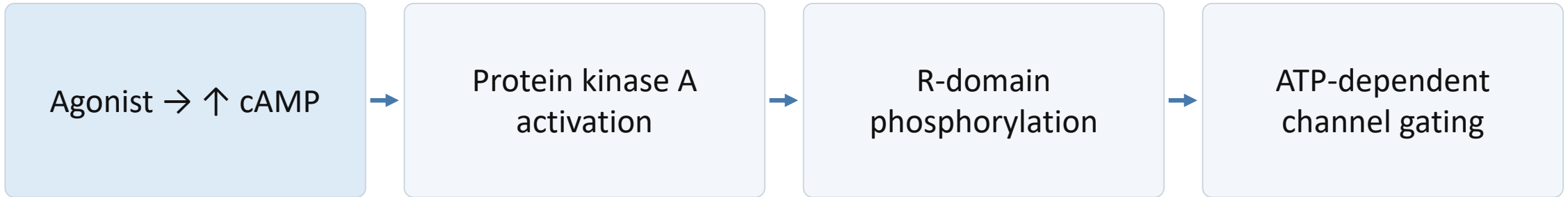
Two nucleotide-binding domains



Regulatory (R) domain

- The membrane domains form the ion-conducting pore.
- ATP handling at nucleotide-binding domains controls channel gating.
- Phosphorylation of the R domain promotes channel opening.

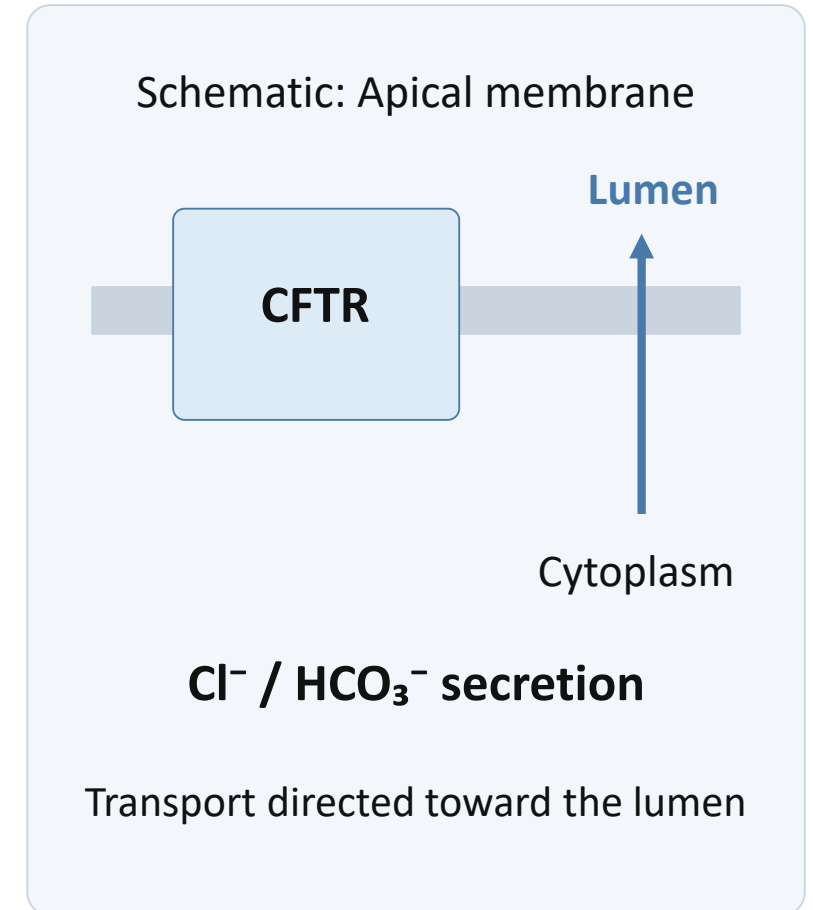
Cyclic AMP controls channel activation



- The channel is not a permanently open hole; Regulatory signals coordinate its operation.
- Disruptions in gating can cause disease even if the protein reaches the membrane.

Chloride transport is not the only CFTR function

- CFTR conducts HCO_3^- as well as Cl^- .
- It interacts with epithelial sodium channel (ENaC).
- CFTR-linked transport helps set the hydration and chemistry of surface secretions.
- Abnormal bicarbonate transport favors acidic, poorly soluble mucus.



Normal airway fluid supports mucociliary clearance

Apical anion secretion



Appropriate surface
water layer



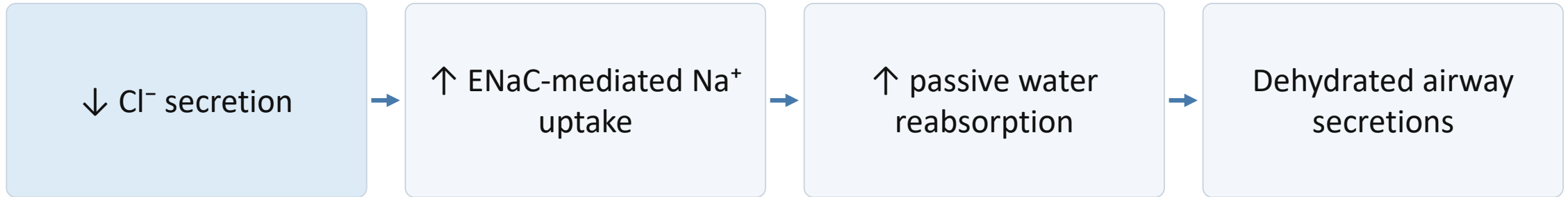
Cilia mobilize mucus



Microorganisms are
cleared

- Water content and ciliary movement cooperate to clear inhaled material.
- The airway surface fluid layer is physiologically important even when its salt concentration is unchanged.

CF airways lose surface-fluid volume

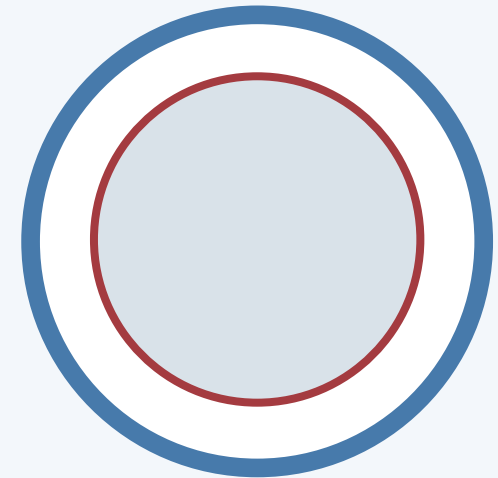


- An isotonic but low-volume airway surface layer.
- The dominant physiologic lesion is dehydration of mucus, not simply excessive airway salt concentration.

Airway mucus becomes difficult to clear

- Water loss concentrates airway mucus.
- Ciliary activity becomes ineffective against dense secretions.
- Mucus obstructs bronchi and bronchioles.
- Stagnant secretions facilitate bacterial persistence.

Schematic bronchial lumen



Inspissated mucus

Obstruction + infection

The sweat duct behaves in the opposite direction

- Normal sweat ducts reabsorb luminal chloride and associated sodium.
- CFTR dysfunction reduces ductal NaCl reclamation.
- Sweat therefore contains increased electrolyte concentrations.
- Sweat glands show no characteristic structural abnormality despite the transport defect.

Schematic: Sweat duct lumen

$\text{Na}^+ + \text{Cl}^-$ stay in lumen



Elevated sweat salt

Normal gland morphology

Bicarbonate defects promote ductal plugging



- CFTR interacts with SLC26-family anion exchangers.
- Some variants preserve chloride transport relatively well while markedly disrupting bicarbonate transport.

Salt elevation and mucus dehydration are not contradictions

Sweat duct

- Normal role: Electrolyte reabsorption
- CF: NaCl remains in the lumen
- Phenotype: Salty sweat

Airway / intestine

- Normal role: Luminal anion secretion
- CF: Water depleted from luminal fluid
- Phenotype: Thickened secretions

Different organs share a duct-obstruction mechanism

Defective epithelial
anion transport



Abnormal luminal
secretions



Ductal / airway
plugging



Atrophy, infection, or
fibrosis

- The final tissue response depends on local anatomy and function.
- Some tissues primarily develop destructive inflammation; Others lose secretory parenchyma.

More than one molecular mechanism causes CF

- Variants alter the amount, localization, gating, conductance, or stability of CFTR.
- The source describes six functional mutation classes.
- Different classes leave different amounts of residual channel activity.
- Functional classes explain disease mechanisms but do not fully predict severity in every organ.

Absent synthesis

Misfolding / trafficking

Gating failure

Reduced channel activity

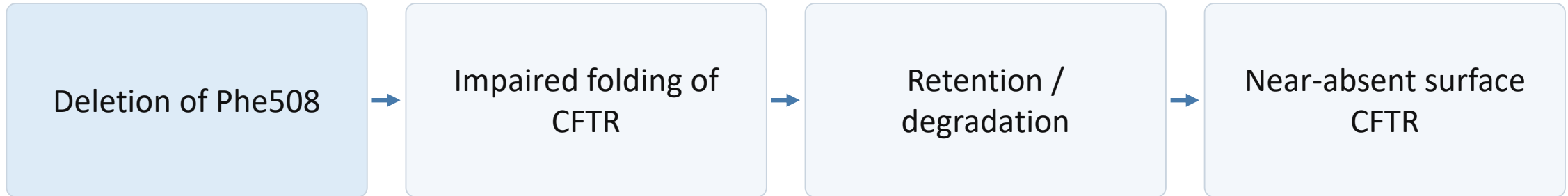
Classes I–III: Severe reduction in function

Class	Principal defect	Consequences
I	No protein synthesis	No apical CFTR
II	Misfolding / trafficking	Degradation before surface delivery
III	Defective gating	Membrane protein with poor opening

Classes IV–VI: Residual or unstable function

Class	Principal defect	Consequences
IV	Reduced conductance	Reduced ion flow through pore
V	Reduced production	Decreased amount of near-normal CFTR
VI	Membrane instability	Accelerated loss from surface

Phe508del illustrates defective processing



- Also historically written $\Delta F508$; It is a class II processing variant.
- Protein quantity at the membrane falls because of impaired maturation and trafficking.

Gating and conductance are distinct failures

Class III: Gating

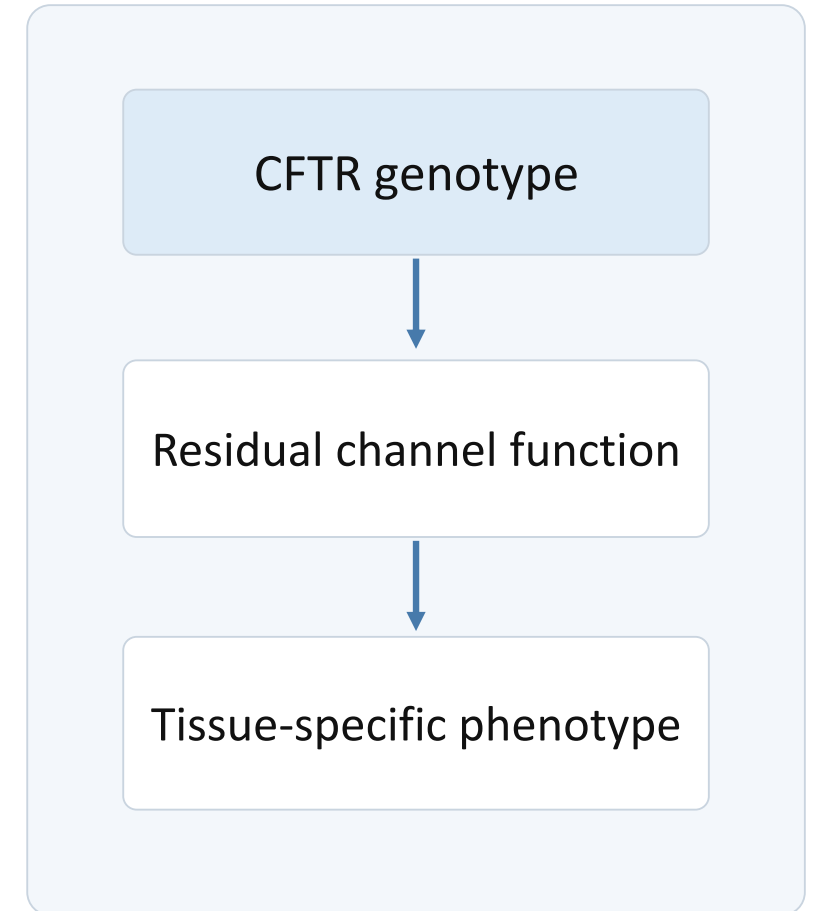
- Protein may reach apical surface
- Opening response is defective
- Example in source: Gly551Asp

Class IV: Conductance

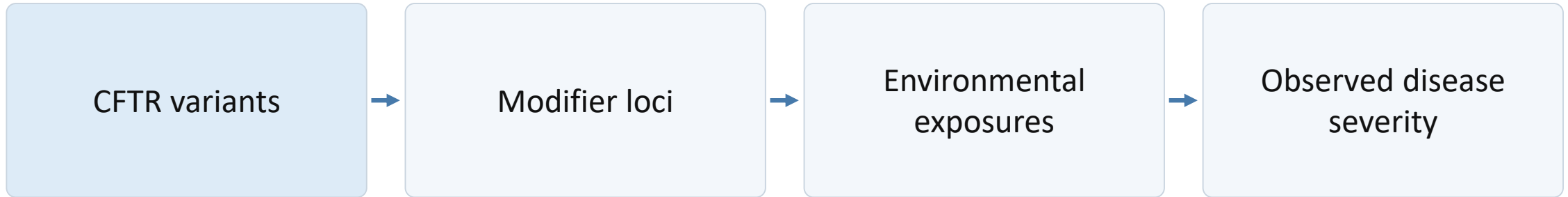
- Protein may reach apical surface
- Ion flux through open pore is reduced
- Example in source: Arg117His

Genotype predicts pancreatic disease better than lung disease

- Two severely impaired alleles commonly produce pancreatic-insufficient classic CF.
- One allele with residual function may preserve exocrine pancreatic output.
- Pulmonary severity depends more heavily on environmental and genetic modifiers.
- Identical CFTR genotypes need not produce identical pulmonary trajectories.

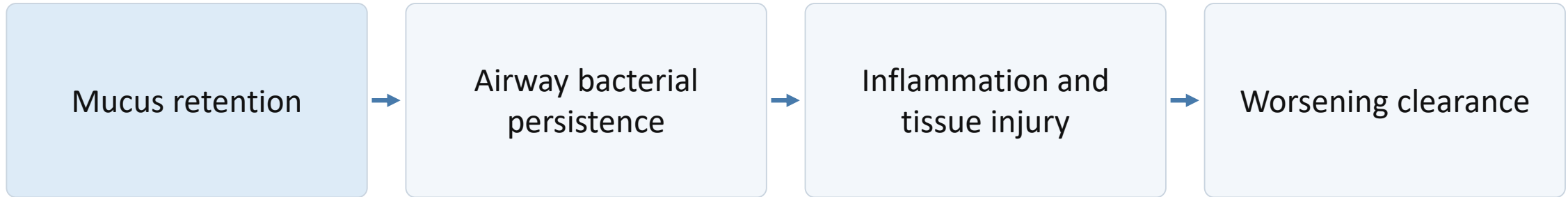


Modifier effects broaden the phenotype



- MBL2, TGFB1, and IFRD1 as example modifier loci.
- Intercurrent viral and chronic bacterial infections influence lung disease progression.

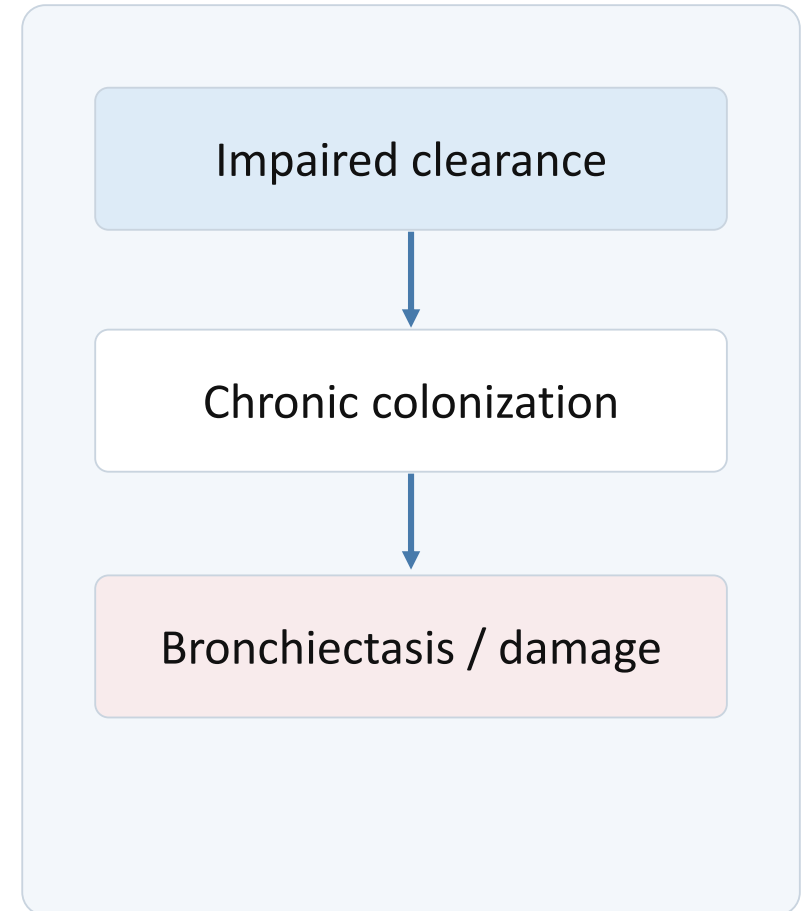
The lung develops a self-perpetuating injury cycle



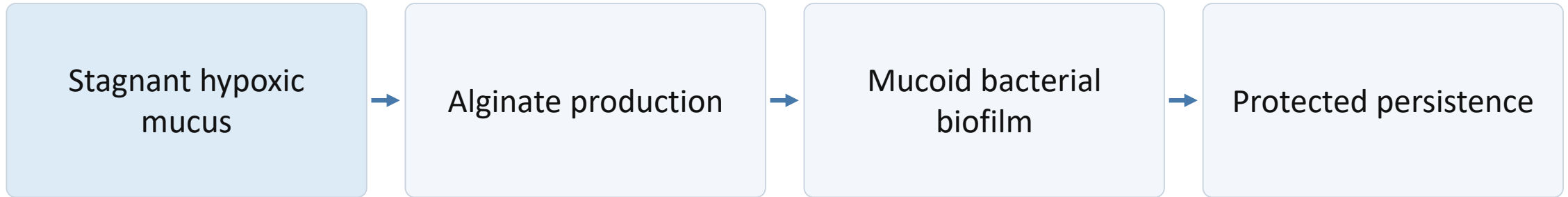
- Obstructed airways create conditions that favor further infection.
- Inflammatory damage can amplify obstruction and chronic structural lung disease.

Chronic infection is not just an acute exacerbation

- Impaired clearance permits intermittent and then chronic colonization.
- *Pseudomonas aeruginosa* is particularly important in progressive lung disease.
- Persistent organisms may establish biofilms that resist host defense.
- Recurrent infection and inflammation ultimately distort airway architecture.



Pseudomonas biofilm impedes clearance



- The alginate-rich phenotype is associated with chronic infection.
- Host antibody and cellular responses may add injury without eliminating embedded bacteria.

Airway pathogens have clinical significance

Organism	Pathologic significance
Staphylococcus aureus	Recurrent airway infection
Haemophilus influenzae	Recurrent airway infection
Pseudomonas aeruginosa	Mucoid chronic colonization; biofilm
Burkholderia cepacia complex	Potential severe progressive infection

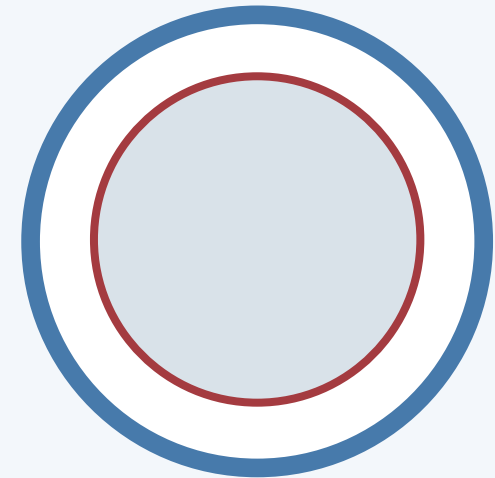
Other respiratory complications extend the differential

- Robbins also identifies *Stenotrophomonas maltophilia* and nontuberculous mycobacteria as opportunistic pathogens.
- Allergic bronchopulmonary aspergillosis occurs with increased frequency.
- *Burkholderia cenocepacia* may cause severe illness within the B. Cepacia complex.
- Microbiology must be interpreted with the chronic bronchiectatic setting in mind.

Early pulmonary morphology: Impacted bronchioles

- Thick mucus distends the bronchiolar lumen.
- Mucus-producing epithelial cells undergo hypertrophy and hyperplasia.
- Luminal obstruction impairs distal ventilation and clearance.
- Secondary infection intensifies epithelial and tissue injury.

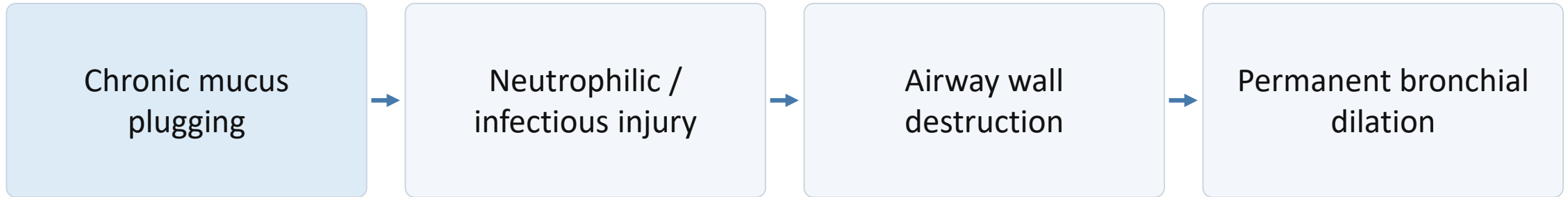
Schematic bronchial lumen



Inspissated mucus

Obstruction + infection

Advanced pulmonary morphology: Bronchiectasis



- The text describes chronic bronchitis, bronchiectasis, and sometimes lung abscesses.
- Anatomical damage becomes an independent obstacle to effective clearance.

Pulmonary findings connect mechanism to symptoms

Mechanism / lesion	Clinical association
Mucus plugging	Chronic cough, sputum, wheezing
Airway obstruction	Air trapping, hyperinflation
Bronchiectasis / infection	Persistent radiographic changes
Chronic pulmonary disease	Clubbing, cardiopulmonary complications

Sinus disease belongs to the CF phenotype

- Chronic sinonasal disease is a characteristic extrapulmonary airway manifestation.
- Nasal polyps are included among recognized clinical features.
- Persistent sinus abnormalities can coexist with bronchial disease.
- Organ-specific symptoms may precede recognition of multisystem CF.

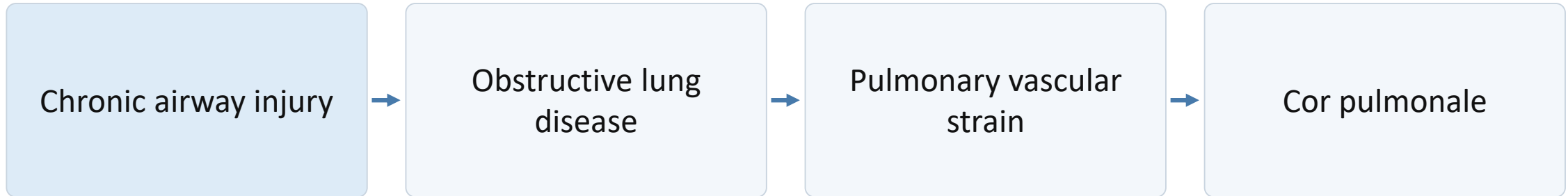
Chronic sinusitis

Nasal polyps

Bronchiectasis

Airway infections

Pulmonary disease drives major late complications

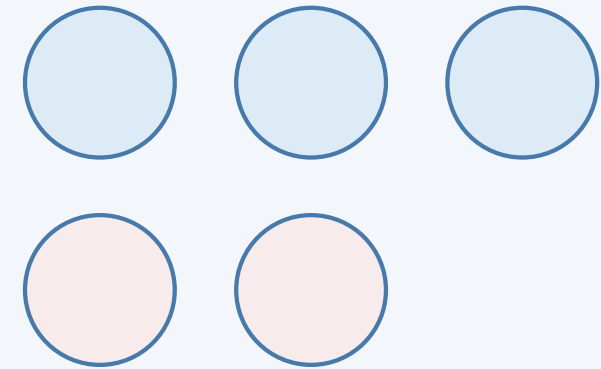


- The text identifies cardiorespiratory complications as a major cause of mortality.
- Lung disease severity is influenced by organisms, host inflammation, and modifiers.

The pancreas is frequently structurally involved

- Pancreatic lesions occur in most individuals with classic CF.
- Mild involvement may begin as mucus accumulation and duct dilation.
- Severe lesions show acinar destruction and progressive fibrosis.
- At an advanced stage, islets may persist within fibrofatty stroma.

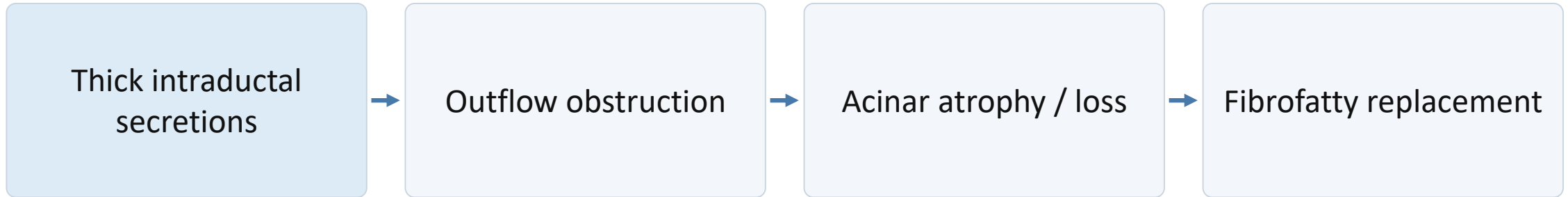
Schematic: Exocrine pancreas



Mucus-filled ducts → acinar loss

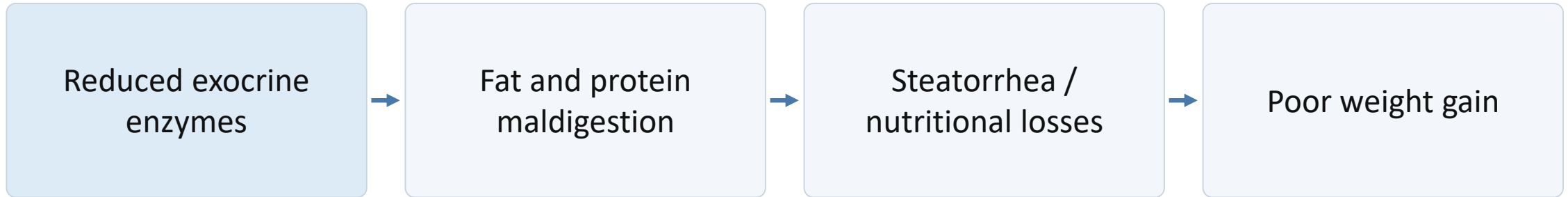
Fibrofatty replacement

How duct obstruction destroys the exocrine pancreas



- Impaired enzyme delivery contributes to malabsorption.
- Morphologic severity varies markedly across CFTR genotypes.

Pancreatic insufficiency impairs nutrient absorption



- Large, foul-smelling stools and abdominal distention may begin during infancy.
- Pancreatic disease explains much of the failure-to-thrive phenotype.

Fat-soluble vitamin deficiencies are predictable

Deficiency	Clinicopathologic significance
Vitamin A	Deficiency may contribute to epithelial changes
Vitamin D	Reduced fat-soluble vitamin availability
Vitamin E	Vitamin depletion with chronic malabsorption
Vitamin K	Vitamin depletion with chronic malabsorption

Not every patient requires pancreatic enzymes

Pancreatic-insufficient CF

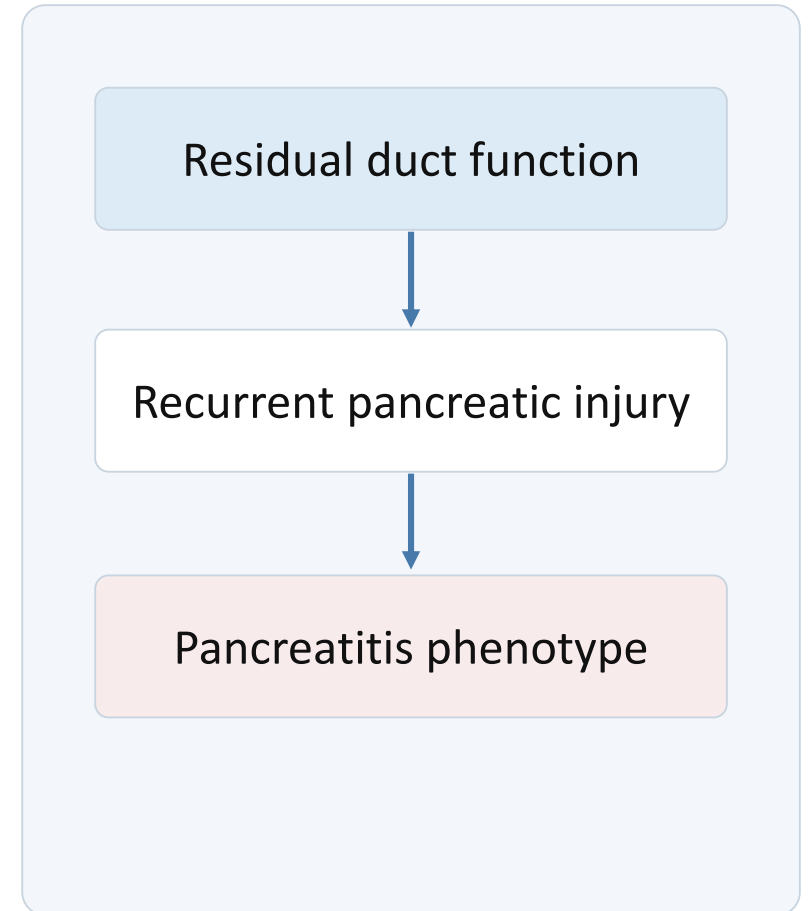
- Often two severe alleles
- Steatorrhea / failure to thrive
- Substantial acinar destruction

Pancreas-sufficient CF

- Residual CFTR activity may persist
- Better growth and absorption
- Pancreatitis may still occur

Pancreatitis can signal less complete CFTR loss

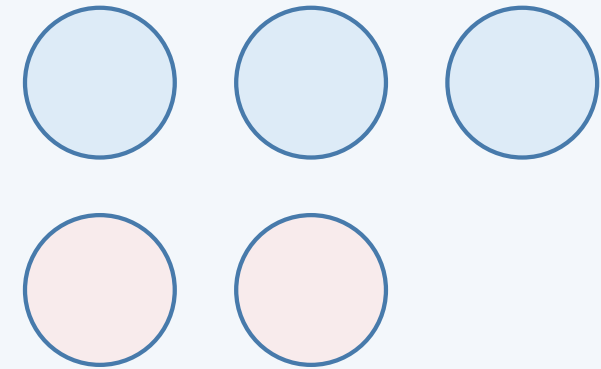
- Some pancreas-sufficient individuals develop recurrent pancreatitis.
- Recurrent episodes may manifest with acute abdominal pain.
- CFTR-associated chronic pancreatitis may occur without classic multisystem CF.
- Interpret isolated pancreatic disease in the context of genotype and physiology.



Pancreatic injury may also affect islet function

- Progressive parenchymal destruction can involve the endocrine pancreas.
- Cystic-fibrosis-related diabetes occurs in a subset of affected adults.
- Exocrine insufficiency and endocrine dysfunction are related but distinct consequences.
- The clinical presentation depends on extent and duration of pancreatic injury.

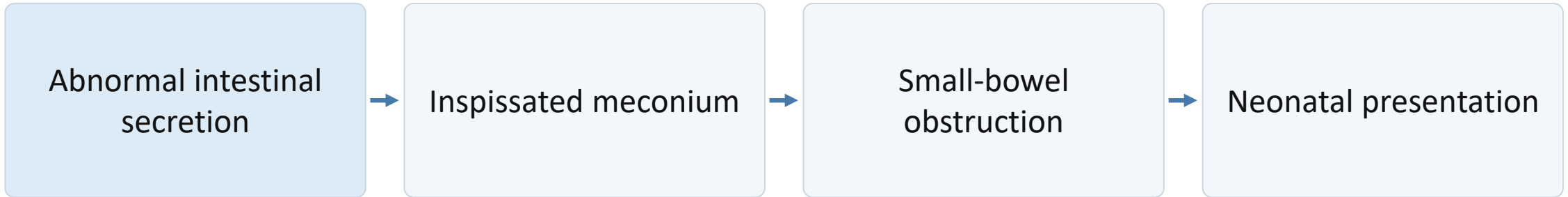
Schematic: Exocrine pancreas



Mucus-filled ducts → acinar loss

Fibrofatty replacement

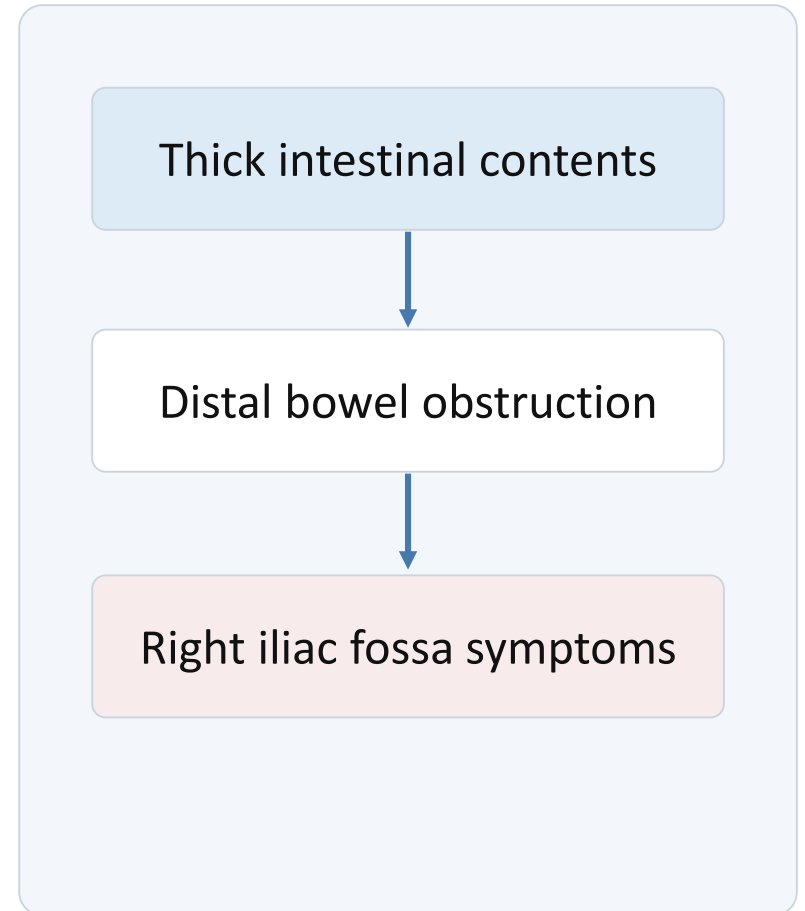
Meconium ileus is an early diagnostic clue



- Neonatal meconium ileus as an initial presentation in a minority of cases.
- The obstruction is a consequence of abnormal luminal secretions, not a primary muscle disorder.

Distal intestinal obstruction can recur later

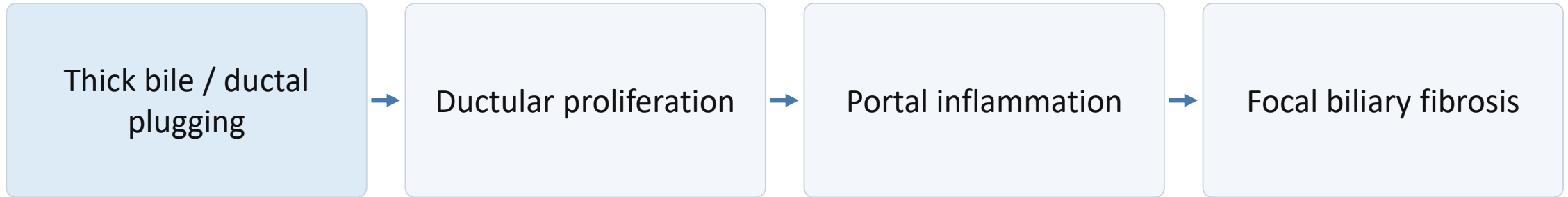
- Older patients may have episodes of distal intestinal obstruction syndrome.
- A typical syndrome includes right lower quadrant pain.
- A palpable meconium mass may be present in the right iliac fossa.
- Intussusception can occur in association with obstruction.



Additional gastrointestinal manifestations

- Persistent malabsorptive diarrhea may contribute to rectal prolapse.
- Loss of protein can cause marked hypoproteinemia and generalized edema.
- Intestinal phenotypes are most pronounced when pancreatic exocrine secretion is inadequate.
- Relatively pancreas-sufficient individuals often have better nutritional outcomes.

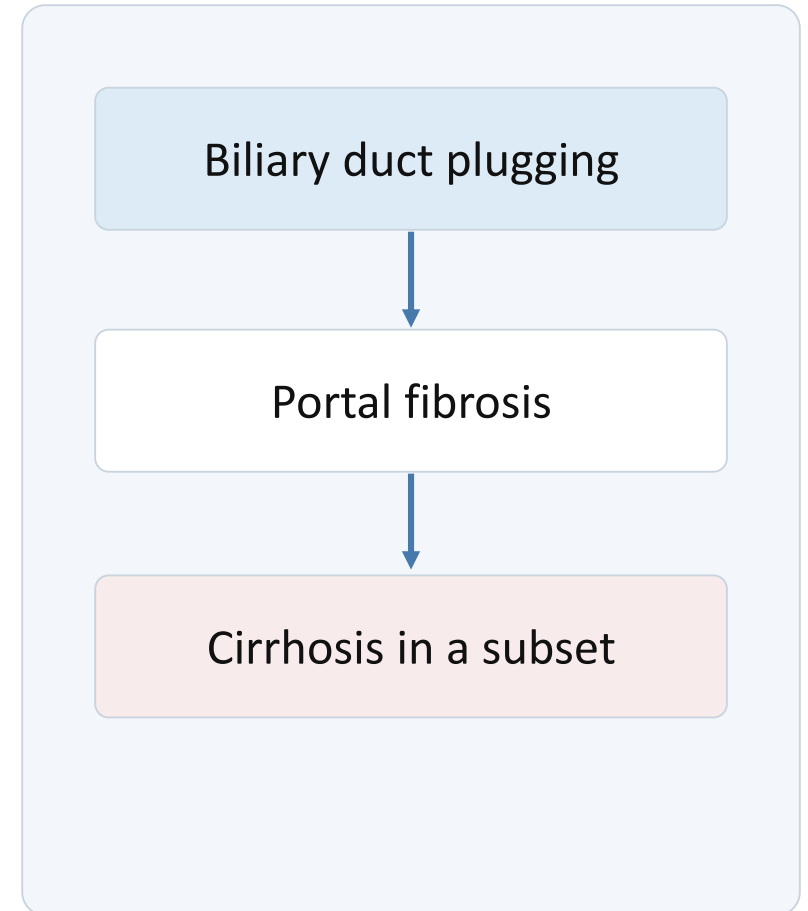
CF hepatobiliary disease begins with secretion obstruction



- Hepatic steatosis may coexist.
- A subset progresses to focal or diffuse biliary cirrhosis.

Cystic fibrosis liver disease is variable

- Focal biliary cirrhosis may arise after chronic biliary injury.
- Severe diffuse cirrhotic disease affects a minority of patients.
- Clinical or biochemical liver abnormalities may emerge later in life.
- Bile-duct sludge or stones can produce acute pain and jaundice.



Salivary gland changes resemble pancreatic changes

Ductal mucus retention



Duct dilation



Epithelial metaplasia

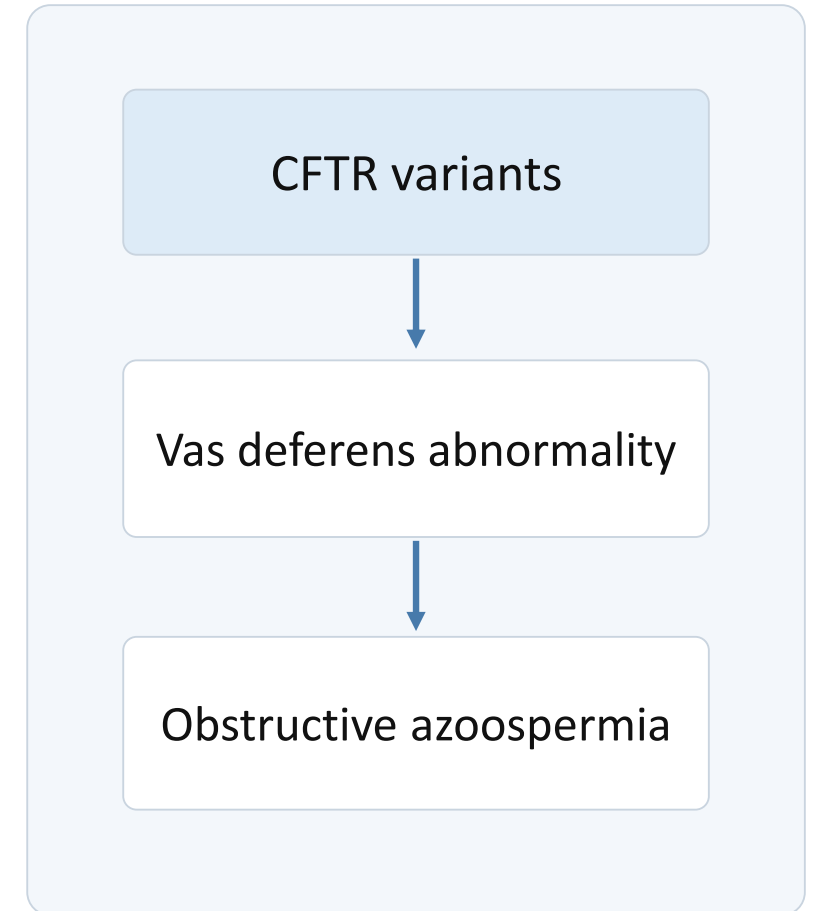


Gland atrophy and fibrosis

- Squamous metaplasia of ductal epithelial lining.
- Shared ductal anatomy explains similar injury responses in multiple exocrine glands.

Male reproductive findings can dominate presentation

- Congenital bilateral absence of the vas deferens is characteristic.
- Obstructive azoospermia causes infertility in most affected adult males.
- In some individuals this may be the only clinical indication of a CFTR-associated disorder.
- An otherwise limited reproductive phenotype does not exclude CFTR variants.



Classic versus nonclassic cystic fibrosis

Classic phenotype

- Sinopulmonary involvement
- Pancreatic insufficiency common
- Multiorgan features often coexist

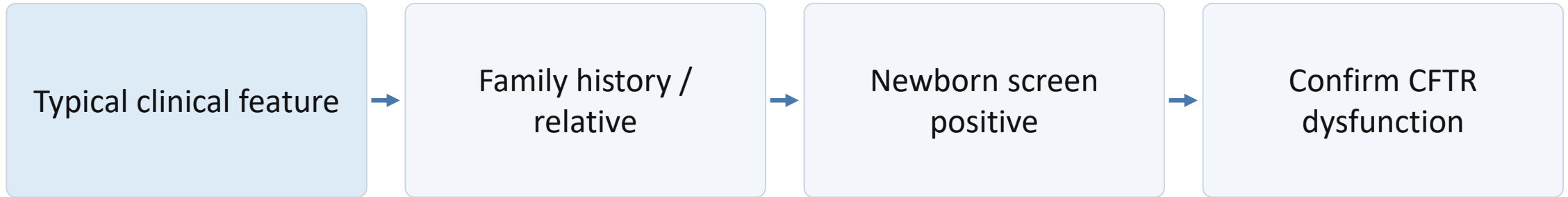
Nonclassic phenotype

- Later or limited presentation
- Residual CFTR function often present
- May involve pancreas, lung, or vas deferens

Common clinical feature clusters

System	Findings in Robbins
Airways	Chronic cough, sputum, infections, bronchiectasis
GI / nutrition	Meconium ileus, steatorrhea, poor growth
Hepatobiliary	Chronic liver disease or biliary cirrhosis
Sweat / salt	Elevated sweat chloride; salt depletion
Reproduction	Congenital bilateral absent vas deferens

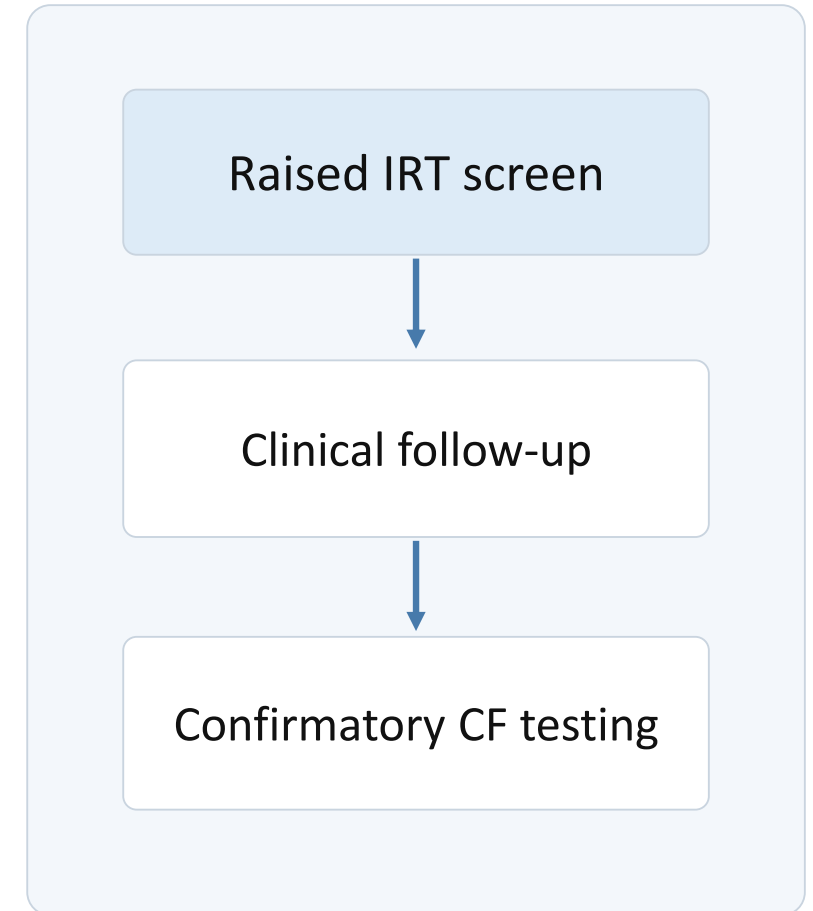
Clinical suspicion arises from phenotype or screening



- Characteristic multisystem findings raise pretest probability.
- A positive screen is an entry point for confirmation, not a final diagnosis.

Newborn screening measures pancreatic injury

- Immunoreactive trypsinogen in blood as a common screening analyte.
- Pancreatic injury may elevate the measured concentration.
- A positive result requires appropriate confirmatory testing.
- Screening assesses risk; It does not directly prove altered epithelial ion transport.



Sweat chloride reflects duct transport physiology

- Loss of CFTR-mediated salt reclamation raises sweat NaCl.
- The sweat test is grounded in a disease-specific transport defect.
- Textbook diagnostic criteria combine phenotype/screening with objective CFTR dysfunction.
- Atypical variants may yield borderline or near-normal sweat concentrations.

Schematic: Sweat duct lumen

$\text{Na}^+ + \text{Cl}^-$ stay in lumen



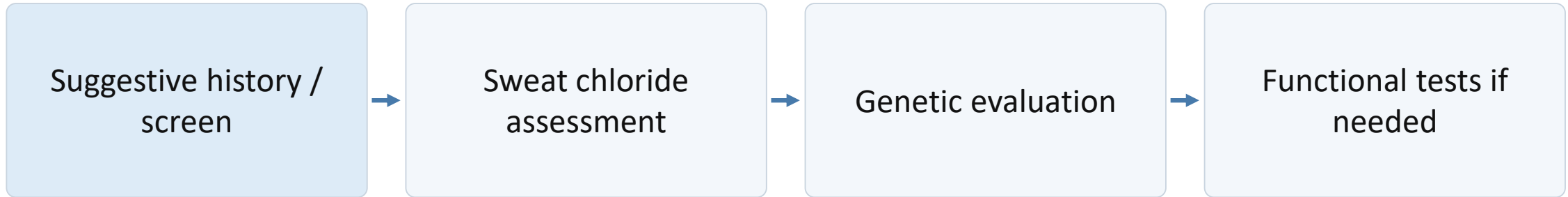
Elevated sweat salt

Normal gland morphology

Diagnostic evidence has complementary roles

Approach	What it contributes
Clinical phenotype / family	Raises suspicion or pretest probability
Immunoreactive trypsinogen	Newborn screening signal
Sweat chloride	Evidence of impaired sweat-duct ion transport
CFTR variant analysis	Identification of disease-causing variants
Functional electrophysiology	Nasal or intestinal CFTR functional evidence

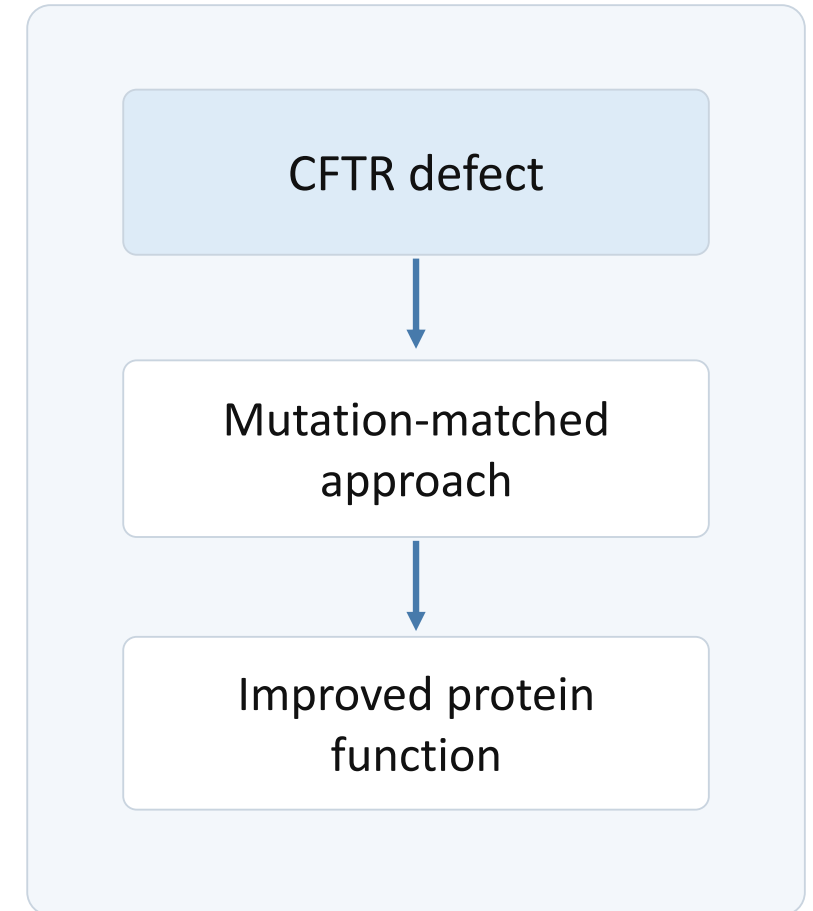
Interpret intermediate or discordant tests cautiously



- Robbins reproduces a diagnostic framework allowing complementary evidence.
- Do not assume that all CFTR sequence variants are disease-causing or that one normal test rules out atypical disease.

Molecular therapy targets the causal protein defect

- Conventional treatment addresses infection, nutrition, and organ complications.
- CFTR-directed therapies act on the protein itself.
- Eligibility depends on disease-causing variant and molecular behavior.
- Robbins groups CFTR agents into potentiators, correctors, and amplifiers.



Potentiators versus correctors

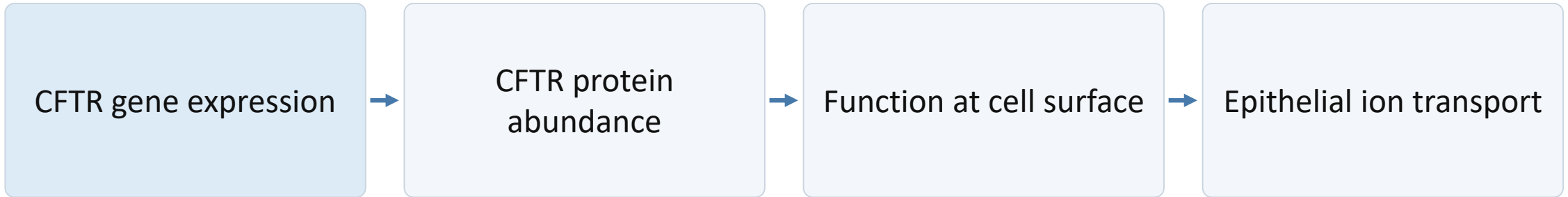
Potentiators

- Improve channel opening
- Especially relevant to gating defects
- Require surface-available CFTR

Correctors

- Support folding / processing
- Increase membrane CFTR delivery
- Relevant to processing defects

Amplifiers represent a different intervention point



- Amplifiers as agents intended to increase CFTR protein production.
- More protein alone may not repair a defective gating or trafficking mechanism.

Supportive treatment remains organ-directed

Clinical problem	Management strategy described
Recurrent airway infection	Antimicrobial therapy
Pancreatic insufficiency	Pancreatic enzyme replacement
Severe end-stage lung disease	Bilateral lung transplantation
Specific CFTR variants	Targeted modulator combination therapy

Integrated case: Neonatal obstruction

Clinical problem

- A newborn develops intestinal obstruction from unusually thick meconium.
- The family reports unusually salty sweat in an affected sibling.
- Consider how an epithelial transport defect could explain both findings.

Mechanistic interpretation

Meconium ileus suggests intestinal secretion abnormality; Defective sweat-duct salt reabsorption provides the parallel diagnostic clue.

Integrated case: Recurrent pulmonary infection

Clinical problem

- An adolescent has productive cough, recurrent infections, and bronchiectasis.
- Airway cultures repeatedly yield mucoid *Pseudomonas aeruginosa*.
- Explain how impaired CFTR function favors this chronic infection pattern.

Mechanistic interpretation

A dehydrated mucus layer impairs clearance; Stagnant hypoxic secretions favor alginate-rich biofilm and ongoing airway damage.

Integrated case: Pancreatic-sufficient phenotype

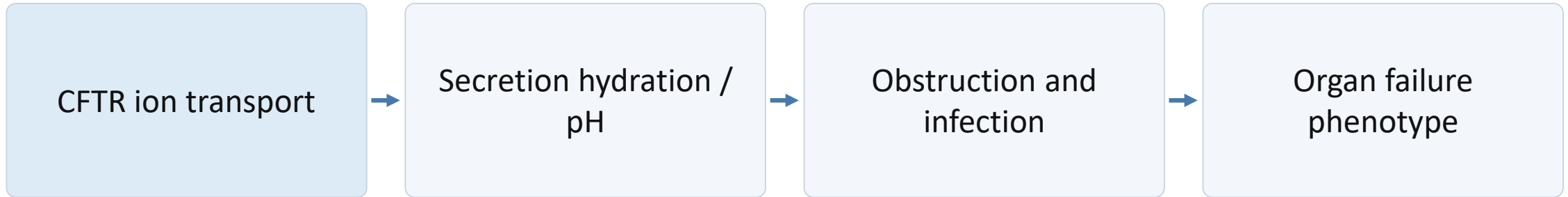
Clinical problem

- An adult has recurrent idiopathic pancreatitis and no prominent steatorrhea.
- CFTR-related disease is considered despite relatively preserved nutrition.
- Explain why a milder or organ-limited CFTR phenotype is plausible.

Mechanistic interpretation

Residual channel function may preserve exocrine output while permitting episodic ductal injury; Pulmonary and pancreatic severity need not parallel each other.

Four causal links explain the clinical syndrome



- The same mutation can produce contrasting sweat and airway electrolyte effects.
- Pulmonary, pancreatic, biliary, intestinal, and reproductive lesions follow tissue-specific consequences.

Pathology synthesis

- Respiratory tract: Mucus plugging, chronic infection, bronchiectasis, and pulmonary complications.
- Pancreas: Ductal obstruction, exocrine acinar loss, fibrosis, and malabsorption.
- Intestine and biliary tree: Thick secretions, obstruction, and possible progressive liver injury.
- Reproductive tract: Congenital bilateral absence of vas deferens and obstructive azoospermia.
- Sweat glands: Characteristic functional electrolyte defect without structural lesion.

Diagnostic synthesis and clinical reasoning

- Recognize a constellation of sinopulmonary disease, pancreatic or intestinal disease, and characteristic reproductive findings.
- Use newborn screening or phenotype to initiate—not conclude—diagnosis.
- Confirm CFTR dysfunction through complementary sweat, molecular, or epithelial functional evidence.
- Relate phenotype to residual CFTR function, tissue physiology, and modifier effects.

Source and scope

Principal textbook

Robbins, Cotran & Kumar: Pathologic Basis of Disease

11th edition (2026) · Diseases of Infancy and Childhood

Cystic Fibrosis and adjacent CFTR mechanism, morphology, and clinical-feature sections

The presentation uses original editable schematics. No textbook micrographs or scanned textbook figures are reproduced.