

Cystic Fibrosis Gene

Mutational Spectrum and Genotype–Phenotype Correlation

Molecular mechanisms · Organ-specific consequences

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Learning objectives

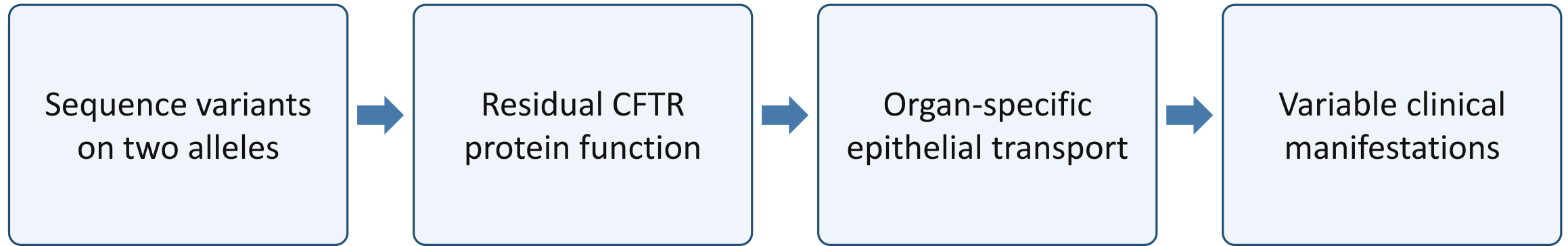
Identify the molecular consequences of CFTR variants

Distinguish six functional mutation classes

Explain why pancreatic and pulmonary phenotypes differ in predictability

Recognize classic and nonclassic presentations

From CFTR genotype to clinical phenotype



Molecular effects precede organ-specific clinical expression.

CFTR is an epithelial anion channel

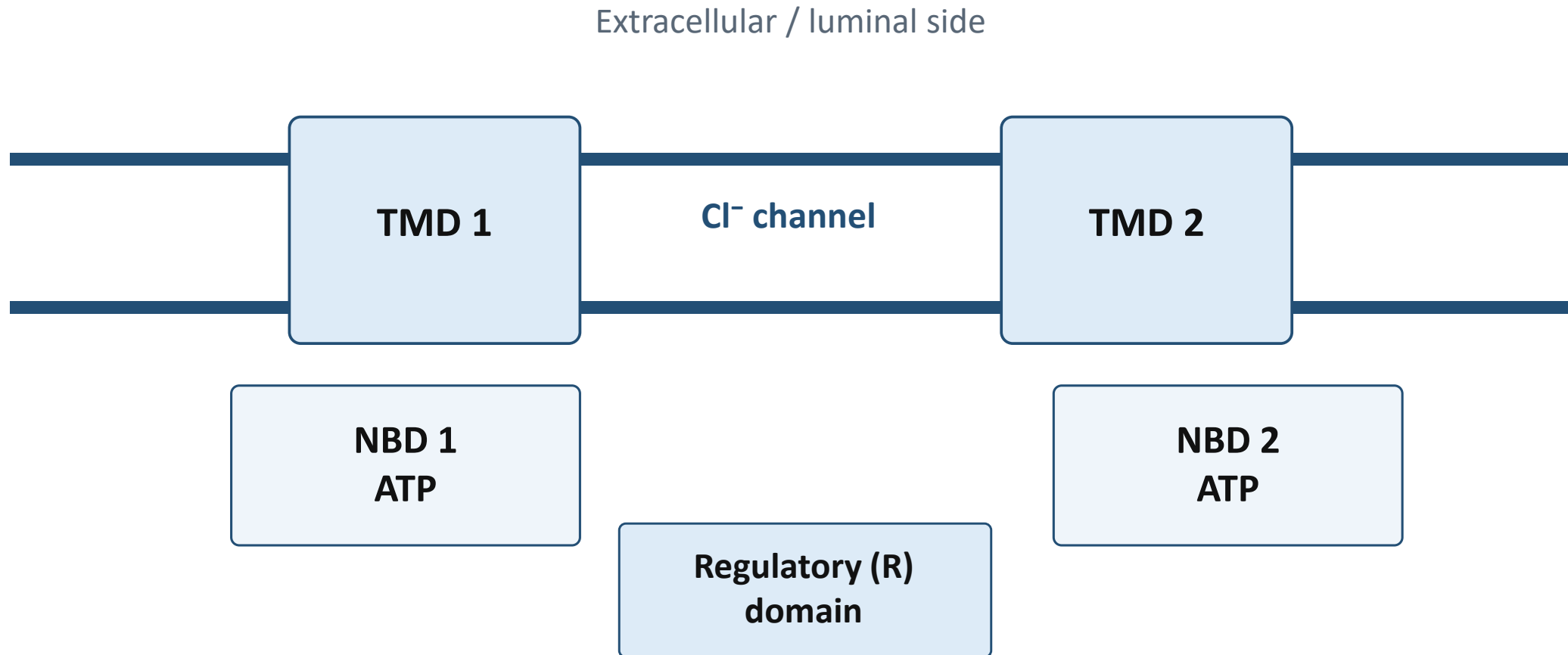
CFTR is present at the apical membrane of many epithelial cells

Its channel permits chloride transport and participates in bicarbonate transport

Effects of dysfunction depend strongly on the epithelial tissue

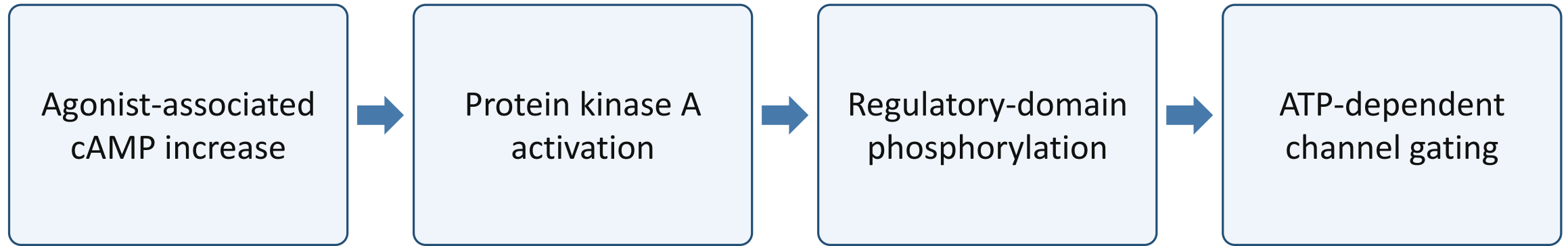
A DNA variant is clinically relevant through its effect on protein function

Five functional regions organize CFTR activity



TMDs form the pore; ATP-linked NBDs and the phosphorylated R domain regulate opening.

How a normal CFTR channel opens



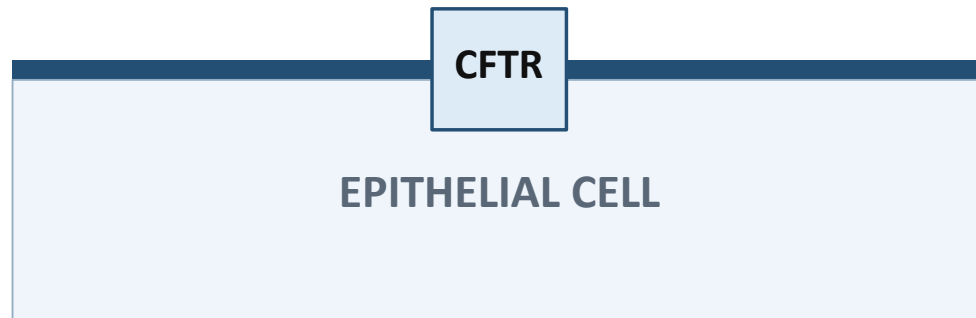
ATP-linked gating occurs after regulatory-domain phosphorylation.

Airway epithelium: Reduced secretion changes surface fluid

NORMAL

LUMINAL COMPARTMENT

Cl^- secretion maintains surface fluid



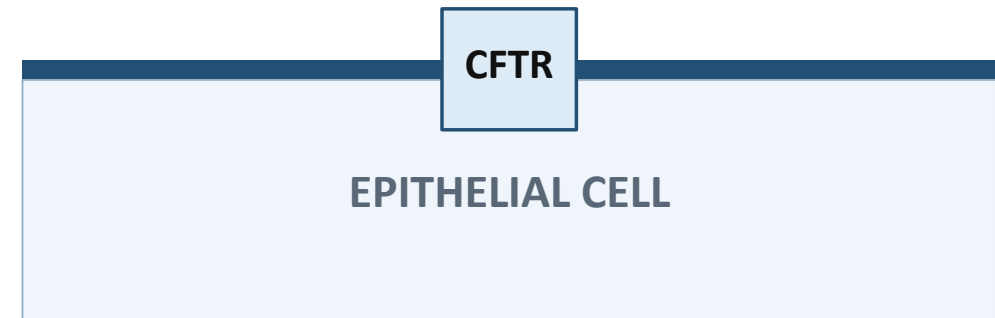
EPITHELIAL CELL

Hydrated mucus supports clearance

CFTR DYSFUNCTION

LUMINAL COMPARTMENT

Reduced Cl^- secretion; $\uparrow \text{Na}^+$ uptake



EPITHELIAL CELL

Less surface water $\rightarrow$ viscid mucus

Sweat duct: Defective reabsorption produces salty sweat

NORMAL

LUMINAL COMPARTMENT

CFTR and ENaC reabsorb ductal salt

CFTR

EPITHELIAL CELL

Lower salt content of final sweat

CFTR DYSFUNCTION

LUMINAL COMPARTMENT

NaCl reabsorption is impaired

CFTR

EPITHELIAL CELL

Salt-rich final sweat

Bicarbonate transport is part of the phenotype

CFTR directly transports bicarbonate and interacts with SLC26 exchangers

Some variants disproportionately impair bicarbonate handling

More acidic luminal secretions promote mucin precipitation and duct plugging

Pancreatic pathology cannot be inferred from chloride conductance alone

A single CFTR defect has tissue-dependent effects

Tissue	Normal CFTR role	Consequence of dysfunction
Airways	Chloride secretion and surface hydration	Dehydrated mucus, impaired clearance
Sweat duct	Chloride and sodium reabsorption	Elevated sweat salt
Pancreatic ducts	Alkaline ductal secretion	Viscid plugs and injury

CFTR sequence variation is highly heterogeneous

More than 2,000 disease-associated variants

Missense variants predominate, but frameshift, splice-site and nonsense changes also occur

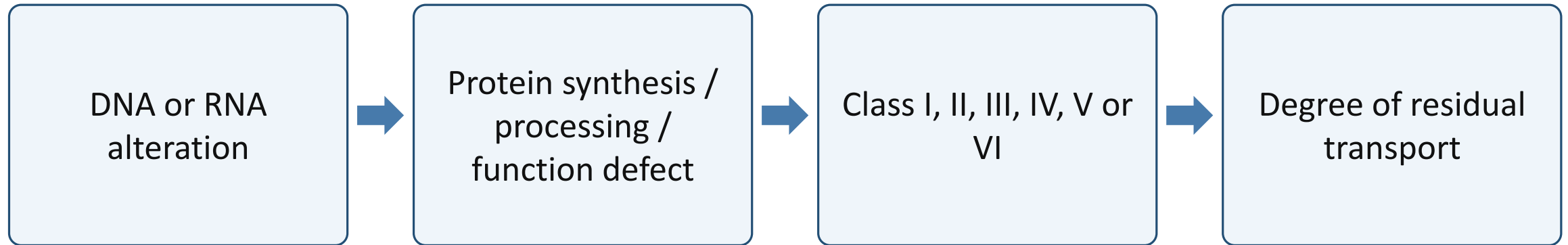
Only a small number of disease-causing variants are individually common

Different variants can converge on the same functional defect

Molecular change is not the same as functional class

Variant type	Primary sequence-level change	Potential protein consequence
Missense	Amino-acid substitution	Defective gating or conductance
Nonsense / frameshift	Premature termination	Absent or truncated protein
Splice-site / promoter	Altered RNA processing or expression	Reduced normal protein abundance

The six-class framework groups mechanisms



Six classes are defined by the principal failure point

Class	Defining mechanism	Apical membrane implication
I	Protein synthesis failure	Essentially absent CFTR
II	Folding and processing failure	Nearly absent CFTR
III	Defective channel gating	Protein present but fails to open
IV	Decreased pore conductance	Protein present, reduced flow
V	Reduced protein production	Fewer normal channels
VI	Reduced membrane stability	Shortened surface residence

Severe and milder labels describe broad tendencies

Classes I–III

Often produce very low residual CFTR activity

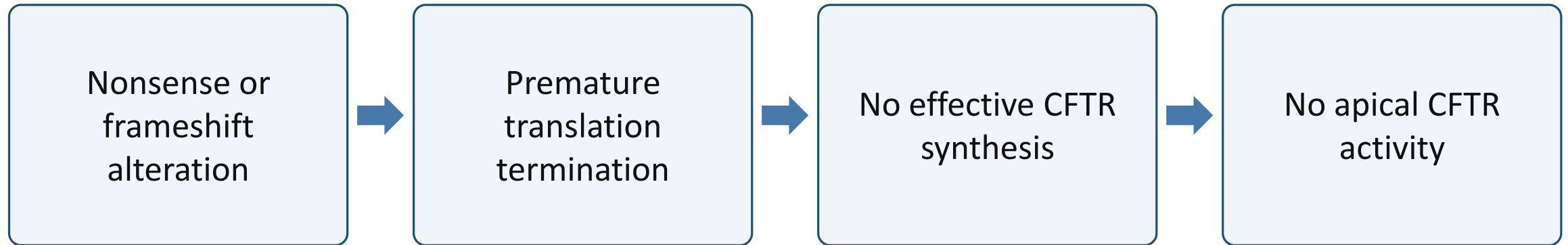
Classically associated with more severe organ disease

Classes IV–VI

Often permit more residual activity

The functional grouping does not fully predict every organ phenotype

Class I: Premature termination prevents synthesis



Class I is fundamentally a protein-quantity defect

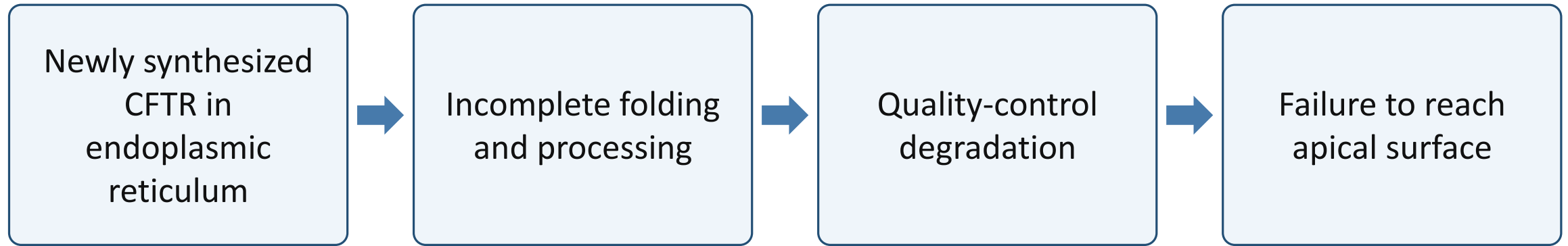
The source describes class I as a null mutation class

Apical epithelial surfaces lack functional CFTR protein

Enhancing gating of a channel that is not present cannot restore activity by itself

The mechanistic distinction is absence rather than a closed pore

Class II: Misfolding interrupts trafficking



Loss of mature apical protein is caused by intracellular disposal.

Phe508del is the canonical processing variant

Deletion of three nucleotides removes phenylalanine at residue 508

The textbook denotes the variant $\Delta F508$; Current protein-style notation is p.Phe508del

It is a class II variant, not a premature-stop mutation

The principal result is defective folding, processing and transport

Class II differs from class I despite a similar endpoint

Class I: Translation failure

Little or no protein is produced

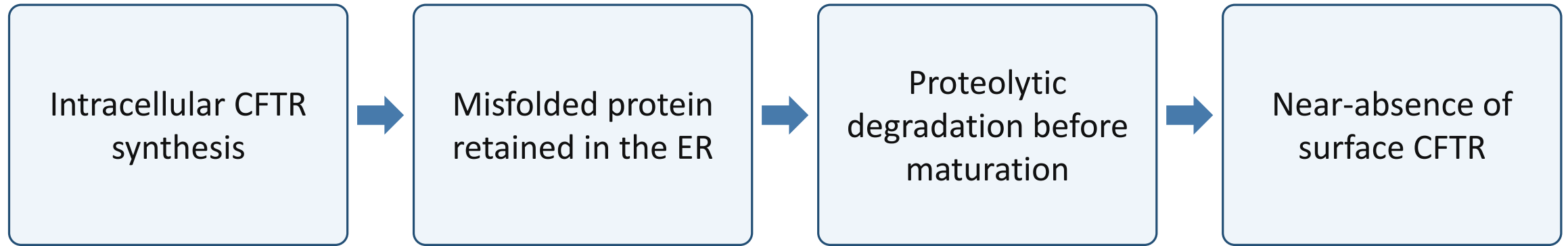
Premature termination is the key failure

Class II: Processing failure

Protein is produced but misfolded

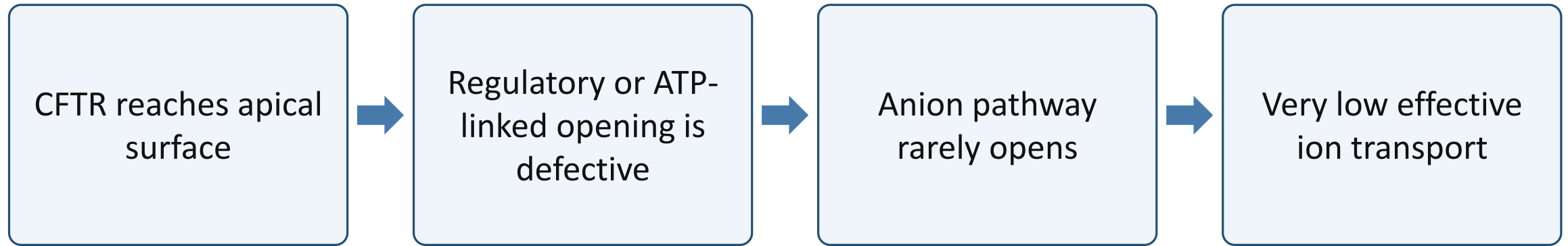
Endoplasmic-reticulum disposal
prevents surface delivery

Why Class II produces little membrane channel



Processing failure precedes the defect at the apical membrane.

Class III: Gating failure prevents channel opening



Membrane abundance and transport activity are not equivalent.

Class III is a functional defect of a present protein

Membrane expression may be relatively preserved

The primary problem is channel activation or gating

This class with Gly551Asp (G551D)

Membrane abundance alone does not prove useful CFTR activity

Gating defect versus processing defect

Class II

Surface CFTR is scarce because the protein is misprocessed

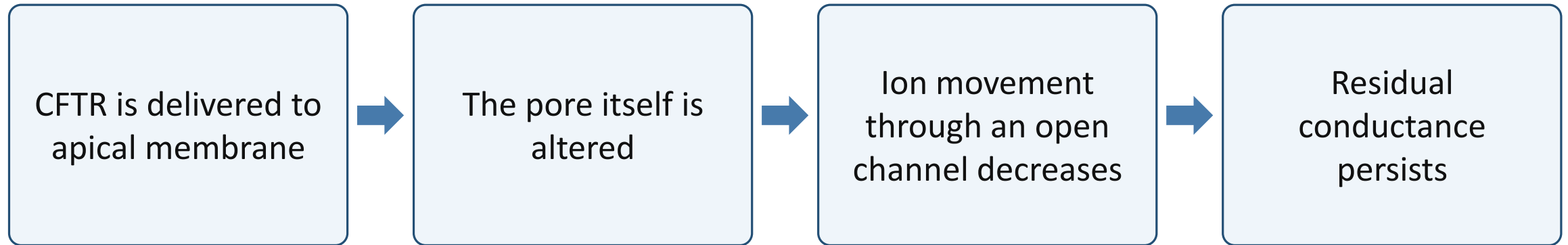
Principal deficit: Channel delivery

Class III

CFTR can be present at the surface but has defective opening

Principal deficit: Activation of existing channels

Class IV: The pore conducts less anion



An open but poorly conducting channel retains partial function.

Class IV mutations affect channel conductance

The transmembrane portion forms the anion permeation pathway

The protein can be present in normal amounts at the membrane

The textbook figure uses Arg117His (R117H) as an example

Reduced transport is not identical to inability to open

Class III versus Class IV: What limits flux?

Class III — gating

Channel opening is defective

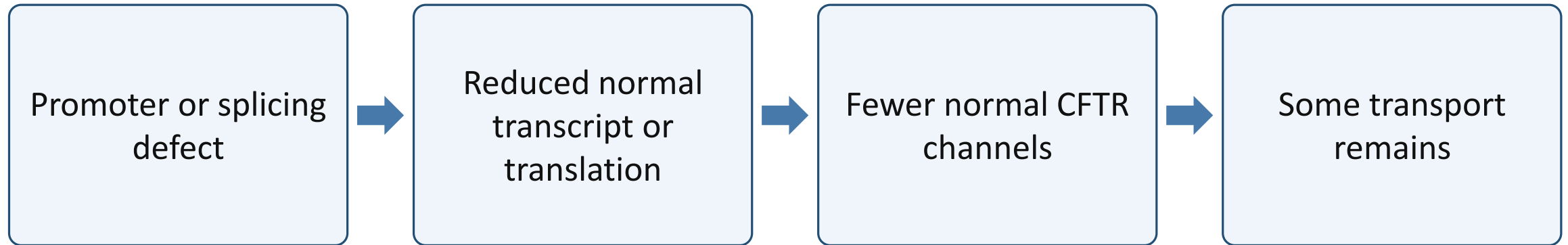
An available pore does not reliably enter
a conducting state

Class IV — conductance

Channel is present but ion transfer is
reduced

An open channel carries less anion

Class V: Less normal CFTR is produced



Class V retains a quantity of normal channels

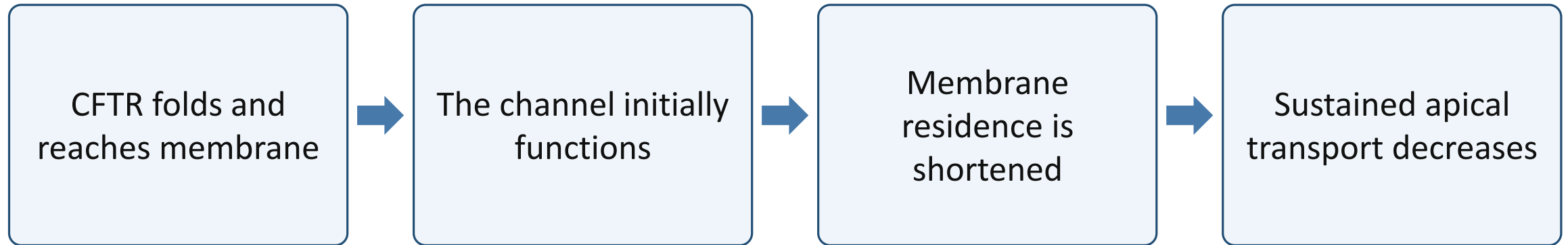
The principal abnormality is reduced production rather than a defective pore

Altered splicing may reduce the correctly processed transcript

The normal protein that is made can function

Residual production helps explain milder manifestations

Class VI: Surface channels are unstable



Early functionality does not ensure persistent membrane transport.

Class V versus Class VI: Fewer channels for different reasons

Class V — reduced supply

Less normal CFTR is made

Limited delivery lowers membrane abundance

Class VI — poor persistence

Functional CFTR reaches the membrane

Accelerated loss reduces its sustained abundance

Three routes to too little CFTR at the surface

Class	Site of defect	Mechanistic result
I	Translation	No protein synthesized
II	ER folding / trafficking	Protein degraded before delivery
V	RNA processing / promoter	Too little normal protein produced
VI	Plasma membrane	Delivered protein is unstable

Three mechanisms can compromise a membrane channel

Class	Protein reaches membrane?	Primary deficit
III	Yes	Poor opening or gating
IV	Yes	Reduced ion passage
VI	Yes, initially	Reduced stability and residence

Functional classes are explanatory, not fully predictive

A variant's molecular effect matters more than a label alone

CFTR activity can vary quantitatively rather than in six completely separate states

The six classes are a mechanistic teaching framework

Clinical phenotype also depends on the second allele and other modifiers

Genotype–phenotype analysis begins with two alleles

Maternal CFTR allele

Paternal CFTR allele

Combined residual CFTR
function



Tissue-specific clinical
manifestations

Cystic fibrosis follows autosomal recessive inheritance

Affected individuals usually harbor pathogenic CFTR variants on both alleles

Two alleles may carry the same variant or different variants

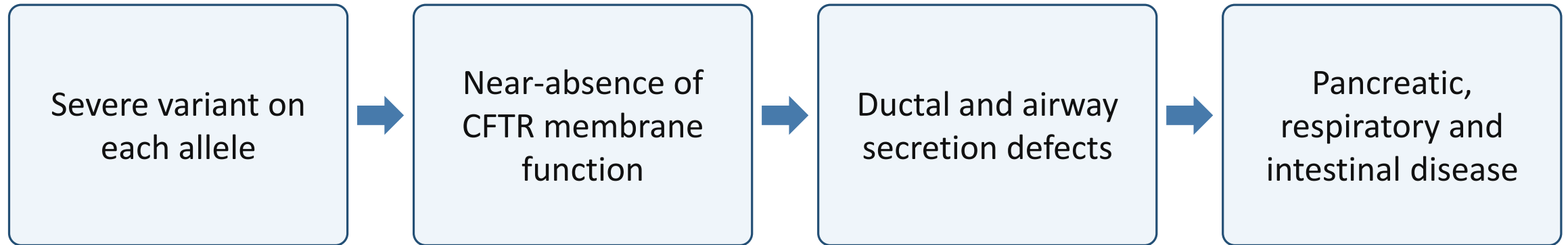
Allelic combination influences overall residual function

Molecular findings must be related to organ-specific phenotype

Allelic combinations form a conceptual severity spectrum

Allele pair	Expected residual activity	Broad phenotype trend
Severe + severe	Very low	Typical classic phenotype
Severe + milder	Some activity	Frequently attenuated organ involvement
Milder + milder	More residual function possible	Variable / nonclassic features

Two severe alleles favor the classic phenotype



The classic multisystem pattern is recognizable

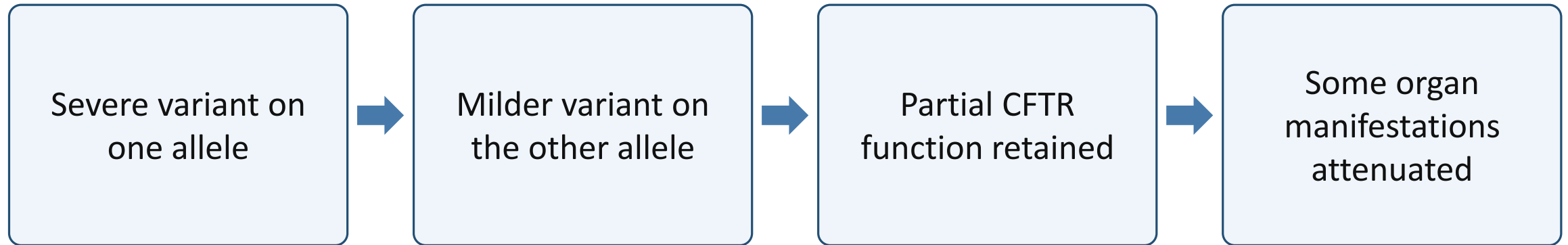
Pancreatic insufficiency can impair digestive function

Sinopulmonary infections reflect dysfunctional airway clearance

Gastrointestinal manifestations arise from abnormal secretions

The constellation is more informative than any isolated symptom

One milder allele can preserve essential function



Pancreatic status is particularly genotype-dependent

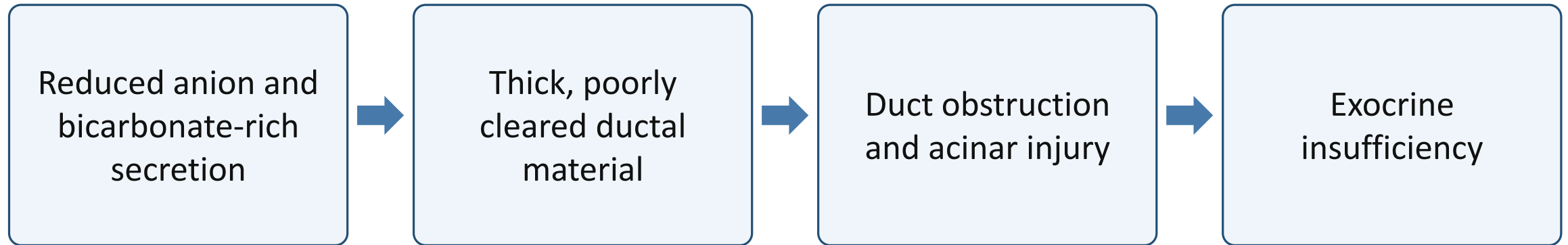
The strongest genotype–phenotype agreement is pancreatic

Two severe alleles commonly lead to pancreatic insufficiency

A single milder allele with residual function can preserve pancreatic sufficiency

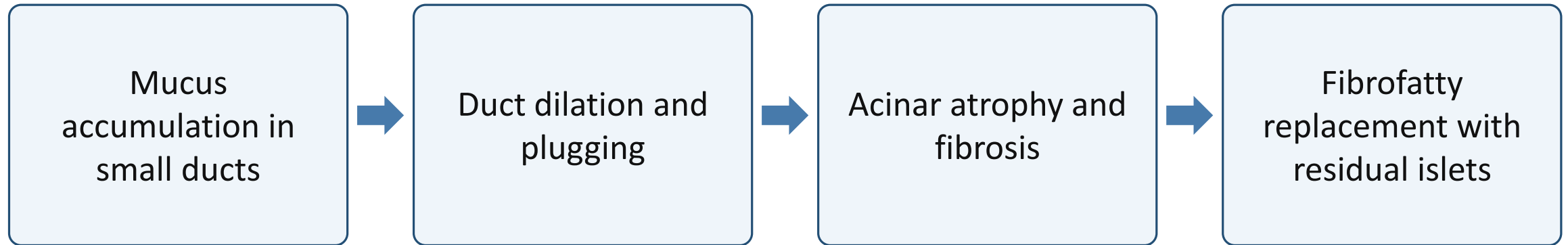
This principle is a tendency, not a patient-specific certainty

Pancreatic duct dysfunction explains exocrine failure



The structural consequence is duct obstruction followed by acinar loss.

Progressive pancreatic morphology follows obstruction



Pancreatic sufficiency and insufficiency represent different effects

Pancreatic sufficiency

Enough residual secretion to preserve exocrine function

More consistent with at least one milder allele

Pancreatic insufficiency

Severe duct plugging, atrophy and reduced enzyme delivery

Strongly associated with very low CFTR activity

The pancreas does not stand in for the lung

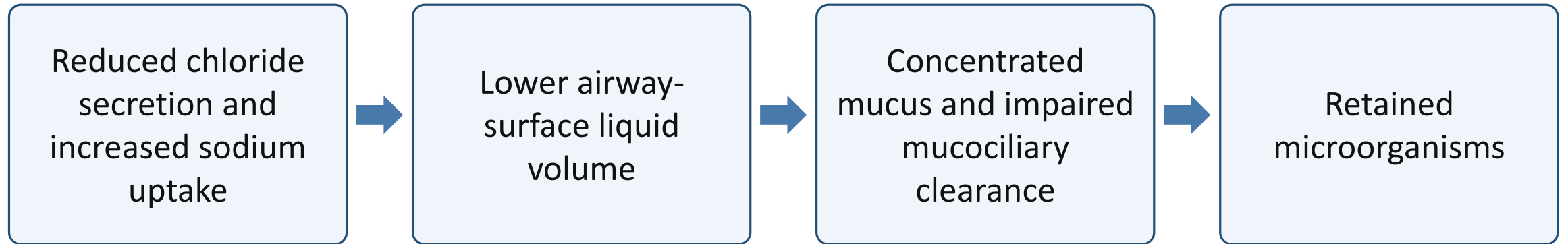
Pancreatic phenotype may correlate reasonably well with mutation severity

Patients with similar alleles may still have very different pulmonary courses

The pulmonary environment adds exposures and feedback loops

A pancreatic prediction must not be translated mechanically to lung prognosis

Airway dehydration initiates pulmonary vulnerability



Why lung function is less predictable from genotype

The pulmonary disease course reflects host–microbe interactions

Secondary genes influence infection and inflammatory responses

Environmental exposure and intercurrent infections matter

Identical CFTR genotypes do not ensure identical lung severity

Modifier genes alter the clinical expression of CFTR disease

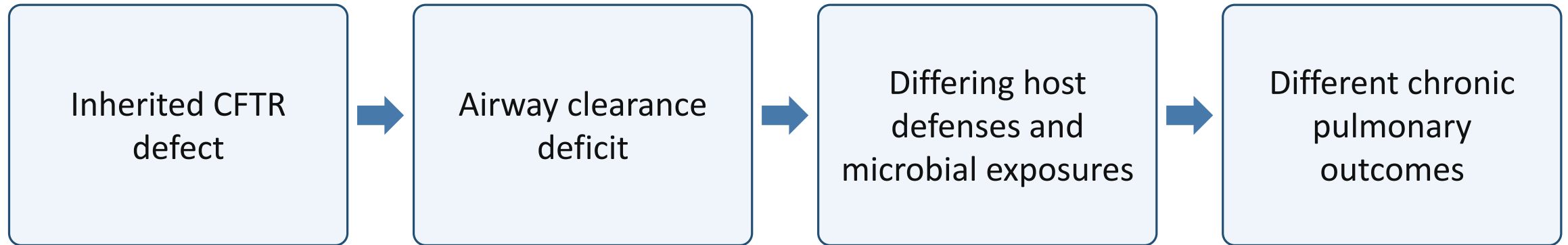
MBL2, TGFB1 and IFRD1 as examples

Their products influence responses to infection or inflammation

These loci do not replace CFTR as the causal disease gene

Modifier effects are particularly relevant to lung manifestations

One mutation can generate divergent lung trajectories



Environmental contributions complicate prediction

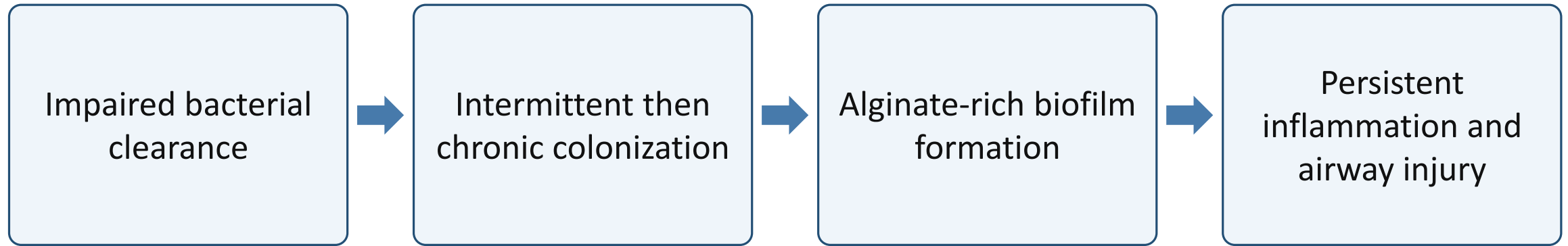
Concurrent viral respiratory illness can promote bacterial colonization

Opportunities for repeated exposure vary between individuals

Microbial persistence and host responses amplify airway injury

The inherited channel defect alone cannot explain all variability

Pseudomonas colonization illustrates a feedback loop



Persistent organisms and inflammatory injury reinforce one another.

Alginate biofilm promotes persistence

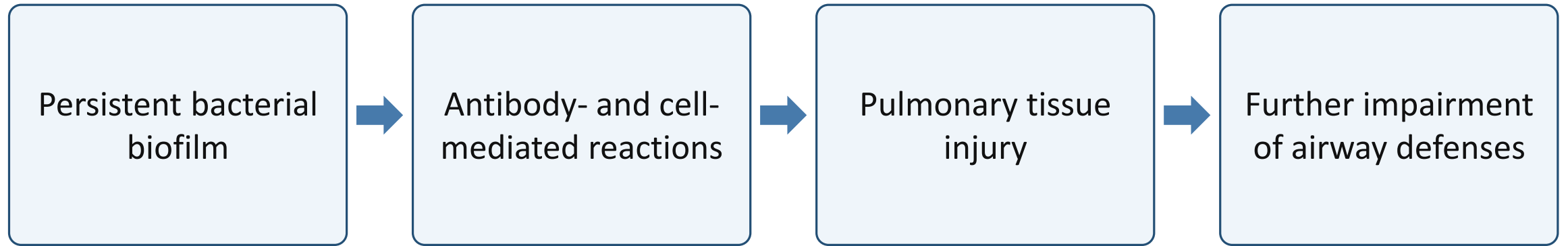
Hypoxic conditions arise within stagnant airway secretions

Colonizing *Pseudomonas* can produce alginate, a mucoid polysaccharide

Biofilm formation reduces effective microbial clearance

Chronic infection drives destructive pulmonary disease

Immune injury further amplifies lung disease



The same CFTR genotype may not mean the same prognosis

Shared variants

Similar primary molecular defect

Comparable inherited baseline
dysfunction

Different modifiers

Different infection and inflammatory
histories

Potentially divergent pulmonary
morbidity

Organ manifestations differ in functional thresholds

Organ system	Important manifestation	Strength of genotype inference
Pancreas	Exocrine insufficiency / sufficiency	Relatively strong
Lung	Bronchiectasis and infection severity	Relatively weak
Sweat glands	Altered salt reabsorption	Reflects CFTR transport loss
Male reproductive tract	Absent vas deferens	May be prominent in nonclassic disease

Residual CFTR function gives a graded phenotype

The source figure links greater CFTR function to generally milder disease

Different tissues cross clinically relevant thresholds at different functional levels

A single threshold does not predict all organ outcomes

Severity ranges from classic multisystem disease to localized manifestations

Sweat phenotype cannot be equated with lung severity

Sweat-duct CFTR normally supports salt reabsorption

Loss of function produces increased sodium chloride in sweat

The same protein participates in secretion in the airway

Organ-specific transport explains different observed consequences

Classic and nonclassic phenotypes form a spectrum

Very low residual CFTR function



Classic multisystem phenotype

Partial residual CFTR function



Variable nonclassic manifestations

Nonclassic disease may be discovered later

Some patients have CFTR-related features without the full classic childhood picture

Genetic testing can reveal bi-allelic CFTR variants in unusual presentations

The textbook terms these cases nonclassic or atypical cystic fibrosis

Clinical recognition matters for evaluation and counseling

Chronic pancreatitis can reveal nonclassic CFTR disease

Idiopathic chronic pancreatitis is among the examples listed by Robbins

The pancreatic phenotype may occur without classic sinopulmonary manifestations

Bicarbonate-related duct physiology provides mechanistic context

A pancreatic presentation alone does not establish the full classic syndrome

Late-onset pulmonary disease is another presentation

Some people first manifest chronic respiratory disease later in life

Residual CFTR activity may moderate the childhood phenotype

The source includes late-onset chronic pulmonary disease among atypical presentations

Pulmonary severity still depends on genetic and environmental modifiers

Bronchiectasis may prompt CFTR evaluation

Idiopathic bronchiectasis appears among the CFTR-associated presentations

Abnormal airway hydration and recurrent infection provide mechanistic context

Other classic manifestations may be absent

A single organ presentation should not be dismissed solely because childhood history is atypical

Absent vas deferens links CFTR to male infertility

The source lists bilateral absence of the vas deferens with obstructive azoospermia

This phenotype may appear without severe pancreatic or pulmonary disease

It illustrates the organ dependence of CFTR dysfunction

Recognition has implications for reproductive genetic counseling

Classic versus nonclassic presentations

Dimension	Classic pattern	Nonclassic pattern
Clinical distribution	Multisystem involvement	Restricted or atypical organs
Pancreatic disease	Often exocrine insufficiency	Can be preserved or variably affected
Pulmonary disease	Sinopulmonary infections common	May be later or isolated
Interpretation	Very low residual function common	Residual function and modifiers relevant

Avoid deterministic interpretation of a CFTR genotype

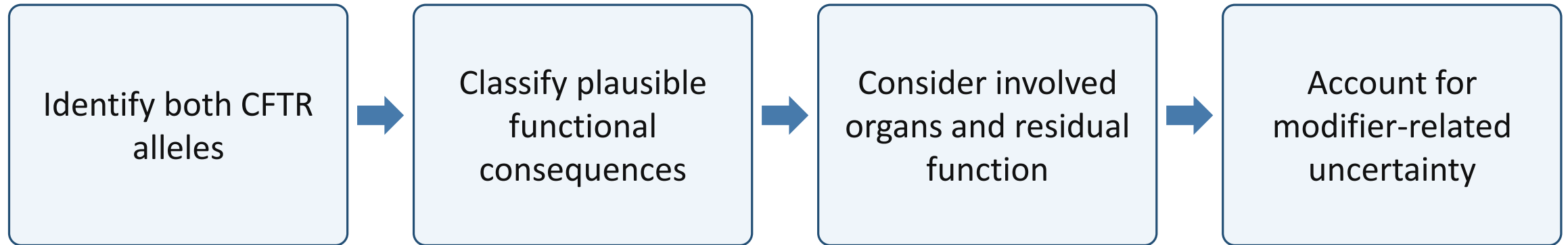
Mutation class predicts a mechanism, not an exact clinical outcome

Two-allele combinations matter more than a single mutation label

Pancreatic status is more predictable than future lung disease

Organ manifestations and clinical context remain essential

Clinical interpretation should integrate several levels



Predict tissue-level tendencies; Avoid patient-level determinism.

Genetic counseling requires phenotype awareness

Inherited CFTR variants have reproductive implications in families

Nonclassic cases can be missed when only classic symptoms are considered

Bi-allelic variants can accompany limited-organ disease

Avoid promising a specific pulmonary course from mutation class

Application case: Two processing variants

A child has CFTR variants on both alleles, each predicted to impair folding and trafficking

Both variants are functionally class II

Which organ phenotype is most strongly expected from this genotype?

Why would lung severity remain less precisely predictable?

Case interpretation: Severe alleles and organs

Two class II variants strongly suggest low membrane CFTR activity

Pancreatic insufficiency is a major expected manifestation

Airway vulnerability is biologically plausible, but exact trajectory is uncertain

Infections and modifier genes may change pulmonary severity

Application case: Isolated adult manifestations

An adult has idiopathic bronchiectasis and bilateral CFTR variants with residual activity

The patient has no typical childhood pancreatic history

Does the absence of the classic pattern exclude CFTR-associated disease?

Which distinction should the clinician make?

Case interpretation: Recognize nonclassic disease

Such organ-limited presentations as nonclassic or atypical CF

Residual protein activity can preserve some organ functions

Clinical and genetic assessment should remain integrated

The finding is relevant to counseling even without classic childhood disease

Functional classification: Concise review

Class	Primary deficit	Useful distinction
I / II	Synthesis / processing	Little apical protein
III / IV	Gating / conductance	Protein present but flux impaired
V / VI	Production / stability	Partial, reduced surface abundance

High-yield synthesis

The six classes localize the primary molecular failure point

Two-allele residual function underlies broad disease severity

Pancreatic genotype–phenotype correlation is stronger than pulmonary prediction

Nonclassic disease can present as isolated pancreatic, pulmonary or reproductive abnormalities

Selected source and figure context

Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026)

Chapter 10: Diseases of Infancy and Childhood, pages 425–428

Primary subsection: CFTR mutational spectrum and genotype–phenotype correlation

Context: CFTR function, modifiers and organ manifestations