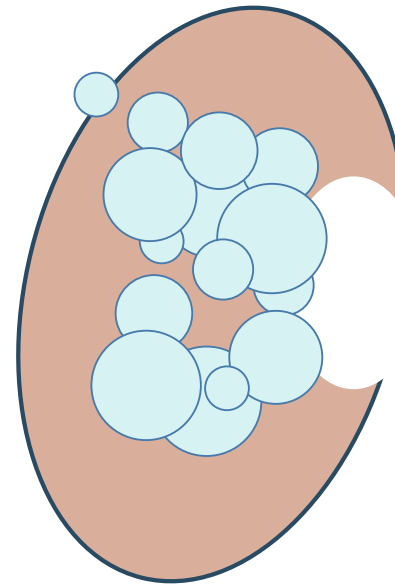
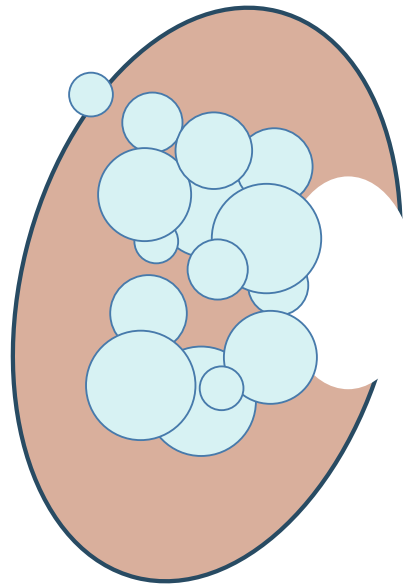


Autosomal Dominant (Adult) Polycystic Kidney Disease



Dr Abu Suraih Sakhri

Inheritance • Ciliary pathogenesis • Morphology • Clinicopathologic correlations

MBBS, MD (Pathology)
www.abusurairsakhri.com

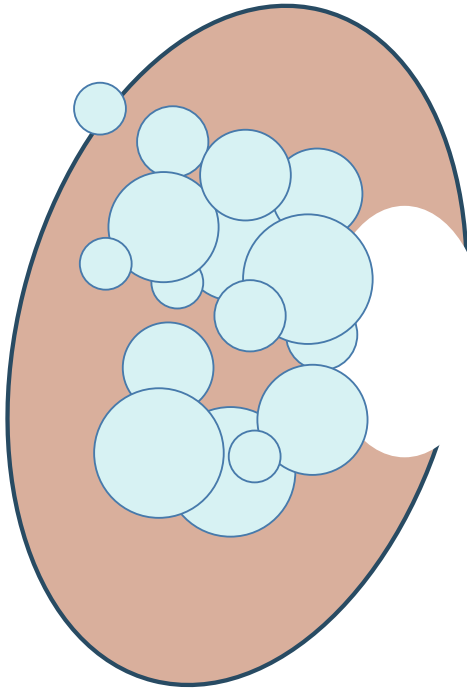
Learning objectives

- Explain the inherited susceptibility and focal cyst formation in ADPKD.
- Relate polycystin/ciliary dysfunction to tubular growth and secretion.
- Recognize gross, microscopic, renal and extrarenal manifestations.
- Apply distinguishing features to cystic-kidney differentials.

Defining lesion: Bilateral progressive renal cysts

- Inherited disorder with numerous cysts expanding in both kidneys.
- Cyst expansion progressively compresses and replaces renal parenchyma.
- Functional nephron loss ultimately causes chronic kidney disease and renal failure.

Bilateral distribution is characteristic



- Both kidneys enlarge as many individual cysts grow.
- The gross lesion is not a solitary focal cyst.
- Apparent unilateral “ADPKD” warrants consideration of another diagnosis.

Schematic — not a specimen

Why renal cystic disorders matter

- Heterogeneous family: Hereditary, developmental and acquired disorders.
- Some are important causes of chronic kidney disease.
- Cystic lesions can complicate imaging and occasionally resemble malignancy.
- Mechanism and distribution help interpret renal morphology.

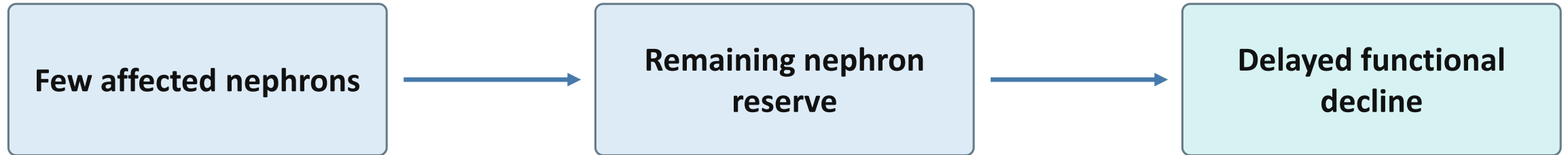
Selected cystic diseases: Context

Condition	Genetic context	Morphologic clue
ADPKD	Autosomal dominant	Large bilateral multicystic kidneys
Childhood PKD	Autosomal recessive	Enlarged cystic kidneys at birth
Nephronophthisis	Often autosomal recessive	Small kidneys; corticomedullary cysts
Acquired cystic disease	Nonhereditary	Cysts in end-stage kidneys

Frequency and renal burden: Textbook estimates

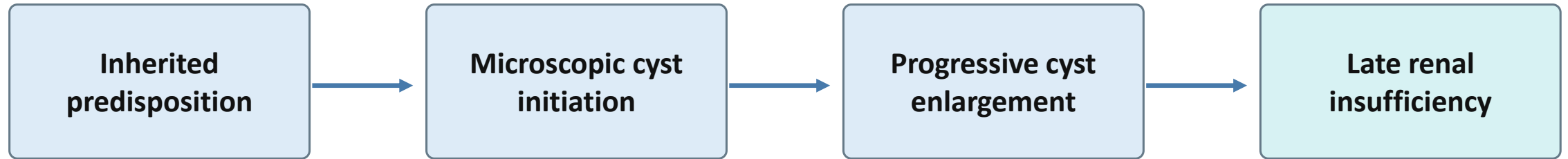
- ADPKD affects roughly 1 in 400–1,000 live births.
- Accounts for about 5%–10% of ESKD treated with dialysis or transplantation.
- Population proportions depend on ascertainment and clinical context.

Preserved function despite early cyst formation



- Cysts initially involve only a minority of nephrons.
- Clinical renal insufficiency commonly develops after decades of progression.

Natural history: Cyst burden precedes organ failure



- Symptoms can remain absent while the structural abnormality expands.
- Renal function often remains adequate until the fourth or fifth decade.
- Age at onset varies by genotype and additional modifiers.

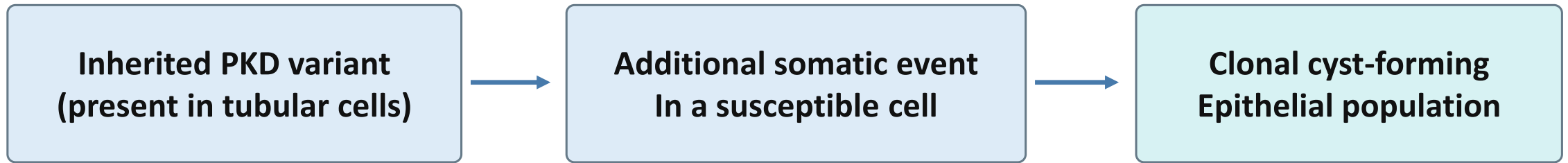
One disease, several clinical trajectories

- Age at symptom onset and progression is variable.
- PKD1-related disease is generally more severe than PKD2-related disease.
- Hypertension, sex and other inherited/environmental factors modify course.

Autosomal dominance describes inherited risk

- An affected parent may transmit one pathogenic allele to offspring.
- The genotype confers susceptibility to multiple independent renal cysts.
- Focal cyst initiation is modeled as requiring additional loss of normal polycystin activity.

Focal cyst initiation: A two-hit model

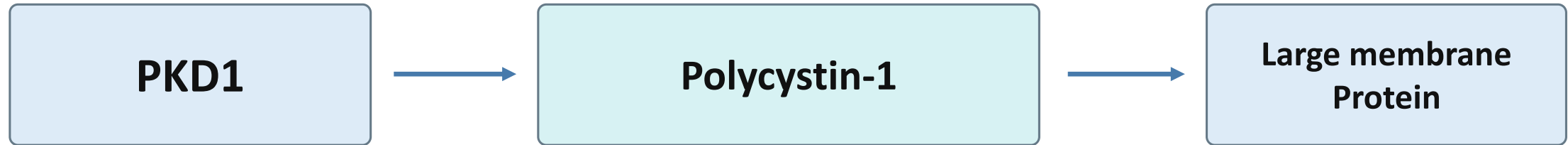


- The second-hit model explains why cysts arise focally despite a constitutional mutation.
- Cysts are regarded as clonal; The model should not be read as a universal account of every lesion.

Two major ADPKD genes

- The predominant genes are PKD1 and PKD2.
- Their protein products are polycystin-1 and polycystin-2.
- Both proteins are associated with signaling at the primary cilium.

PKD1 encodes polycystin-1



- Large extracellular domain with multiple transmembrane segments and short cytoplasmic tail.
- Expressed in tubular epithelial cells, particularly those of the distal nephron.
- Contains domains associated with cell–cell and cell–matrix interactions.

PKD2 encodes polycystin-2



- Integral membrane protein present throughout renal tubules and in extrarenal tissues.
- An ion-channel function links it to intracellular calcium signaling.
- PKD2-associated disease is generally less severe than PKD1-associated disease.

Polycystins: Complementary features

Polycystin-1 (PKD1)

Large membrane protein

Cell interaction–related domains

Highly expressed in distal nephron

More severe renal phenotype

Polycystin-2 (PKD2)

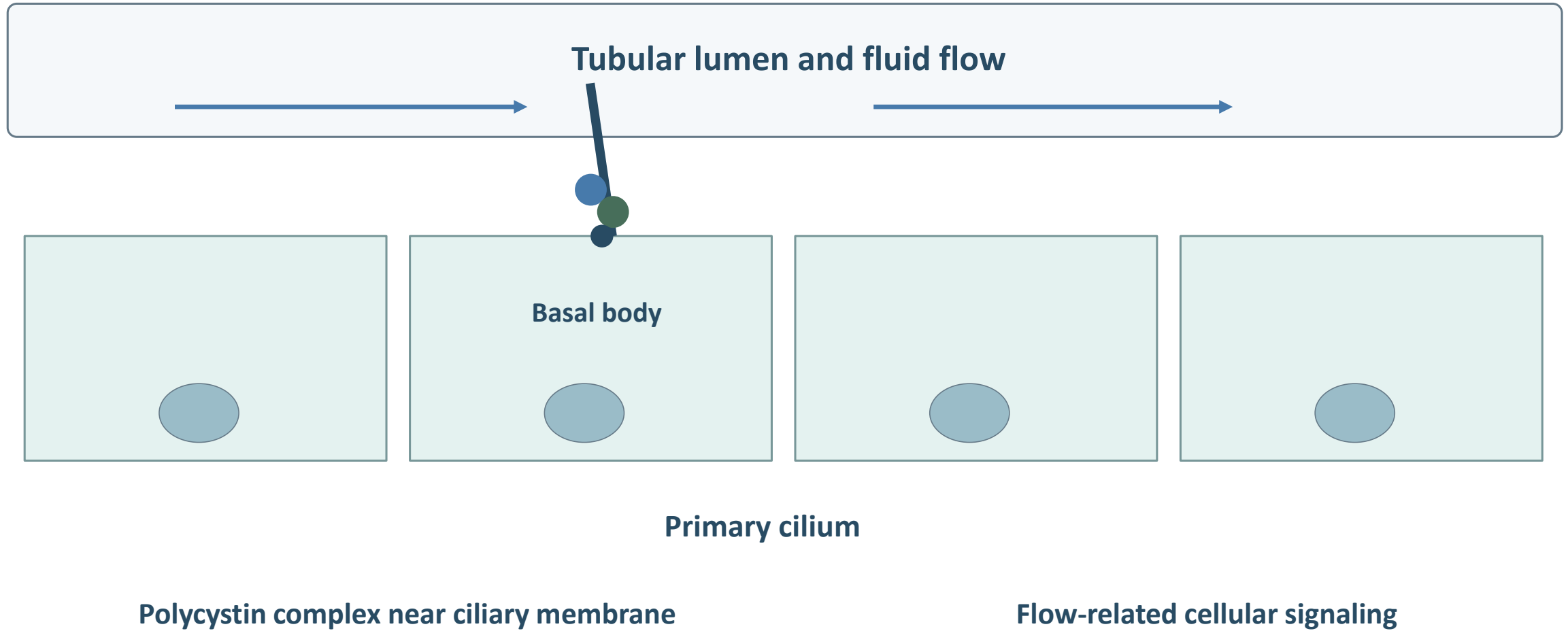
Calcium-permeable channel

Renal and extrarenal expression

Expressed in all nephron segments

Later renal decline on average

Primary cilium: A tubular sensory apparatus

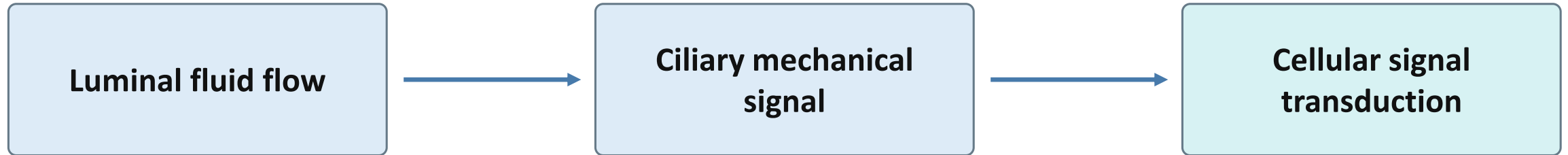


Single nonmotile organelle · Projects from apical epithelial surface · Microtubule-based

Primary cilium and basal body

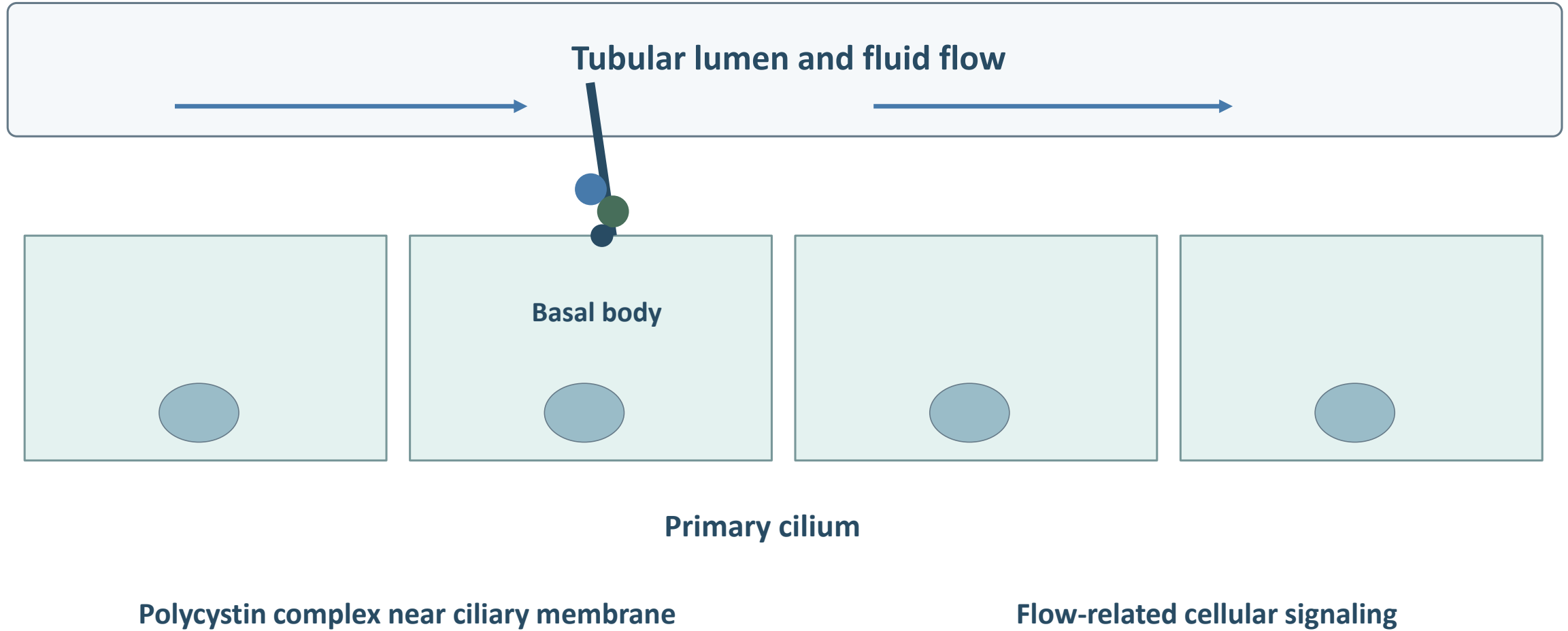
- The cilium projects into the tubular lumen from the apical surface.
- It arises from a centriole-derived basal body.
- Primary cilia are part of the cell's response to its local physical environment.

Mechanosensory hypothesis: Proposed sequence



- Tubular epithelial cells experience fluid flow and shear stress.
- Cilia, junctional complexes and cell–matrix adhesions contribute to mechanical sensing.

The polycystin complex localizes to cilia

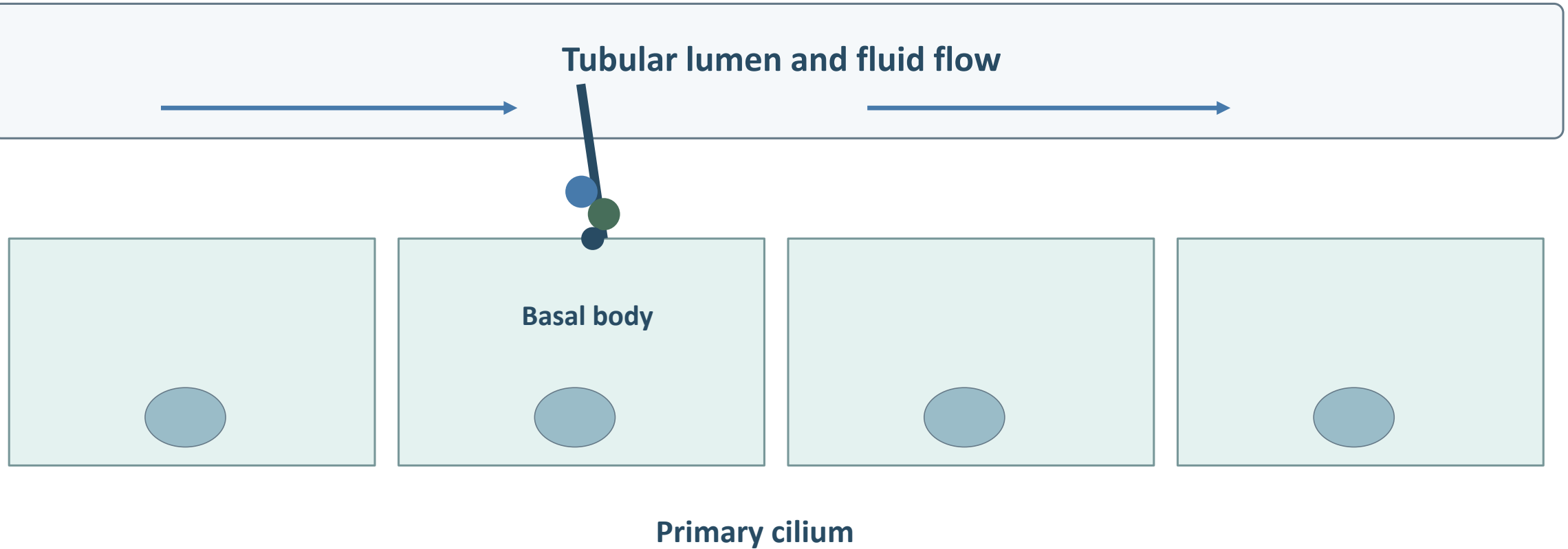


Polycystin-1 and polycystin-2 · Primary ciliary membrane · Calcium-linked cellular response

Evidence supporting ciliary involvement

- Polycystin-1 and polycystin-2 localize to primary cilia.
- Proteins mutated in other cystic disorders also localize to cilia/basal bodies.
- Experimental PKD1 loss affects ciliary signaling and, in model systems, cyst development.

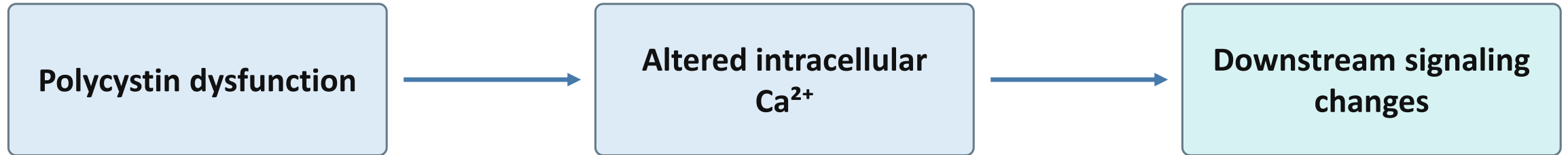
Abnormal ciliary response in PKD-related cells



Disrupted polycystin-dependent signaling

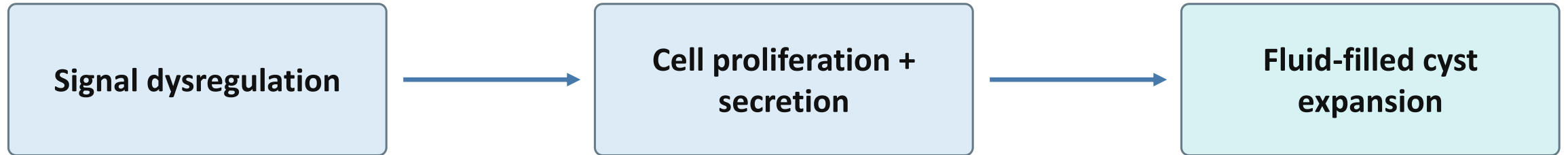
An intact-looking cilium can have impaired flow-dependent signaling. · Structural presence does not demonstrate normal ciliary function.

Altered calcium handling links gene to phenotype



- Calcium-dependent signaling can influence epithelial growth and secretion.
- The direction and detailed regulation of signaling are not fully resolved in the supplied mechanistic account.

Epithelial responses contribute to cyst growth

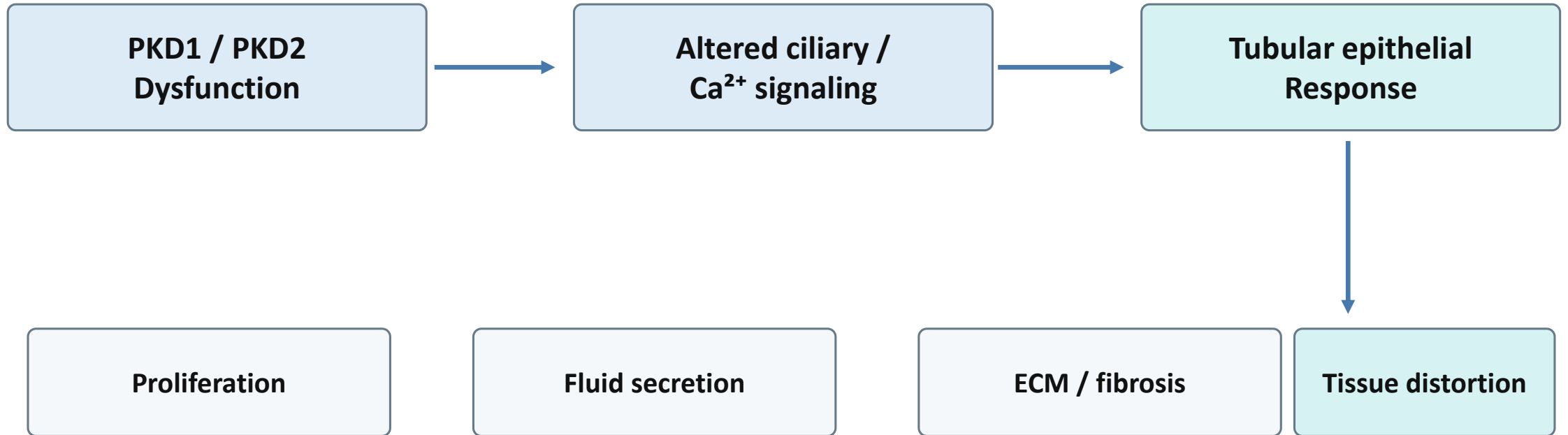


- Epithelial cell growth increases the cyst wall's cellular mass.
- Fluid secretion expands the cyst lumen and increases local compressive effects.

Matrix abnormalities contribute to disease

- Polycystin-related signaling interacts with cell–matrix adhesion mechanisms.
- Abnormal extracellular-matrix interactions may reinforce cyst evolution.
- Interstitial fibrosis accompanies progressive destruction of renal tissue.

Integrated mechanism: Native vector concept map

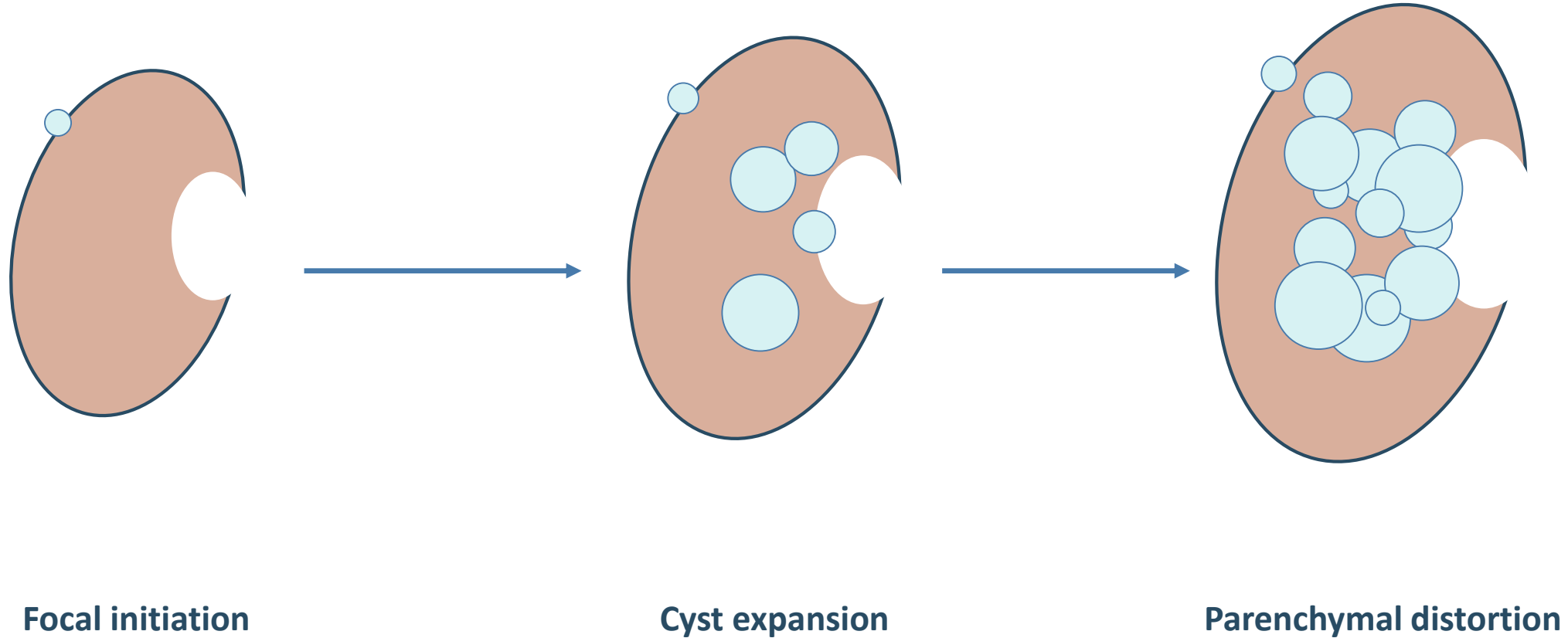


Schematic: Relationships, not measured kinetics

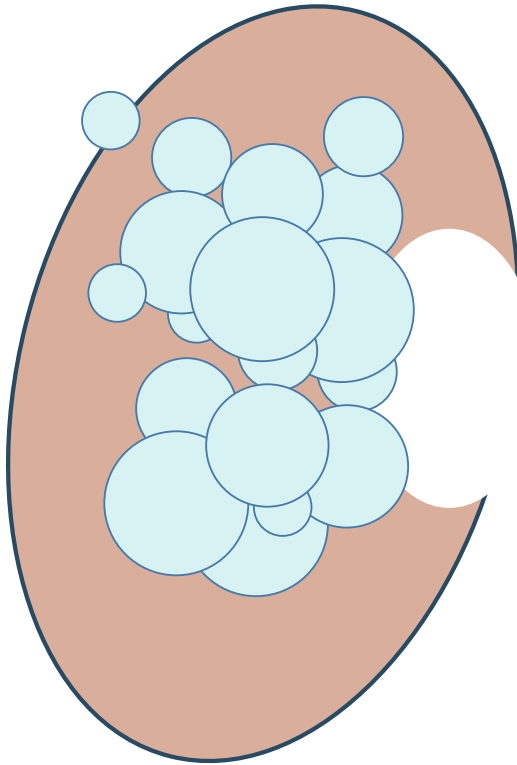
Why expanding cysts progressively damage the kidney

- Tubular dilation produces increasing volume within the renal parenchyma.
- Cysts displace surrounding nephrons, vessels and interstitial tissue.
- Secondary tissue injury and fibrosis reduce functioning nephron mass.

From discrete cysts to an enlarged kidney



Gross pathology: Massive bilateral enlargement



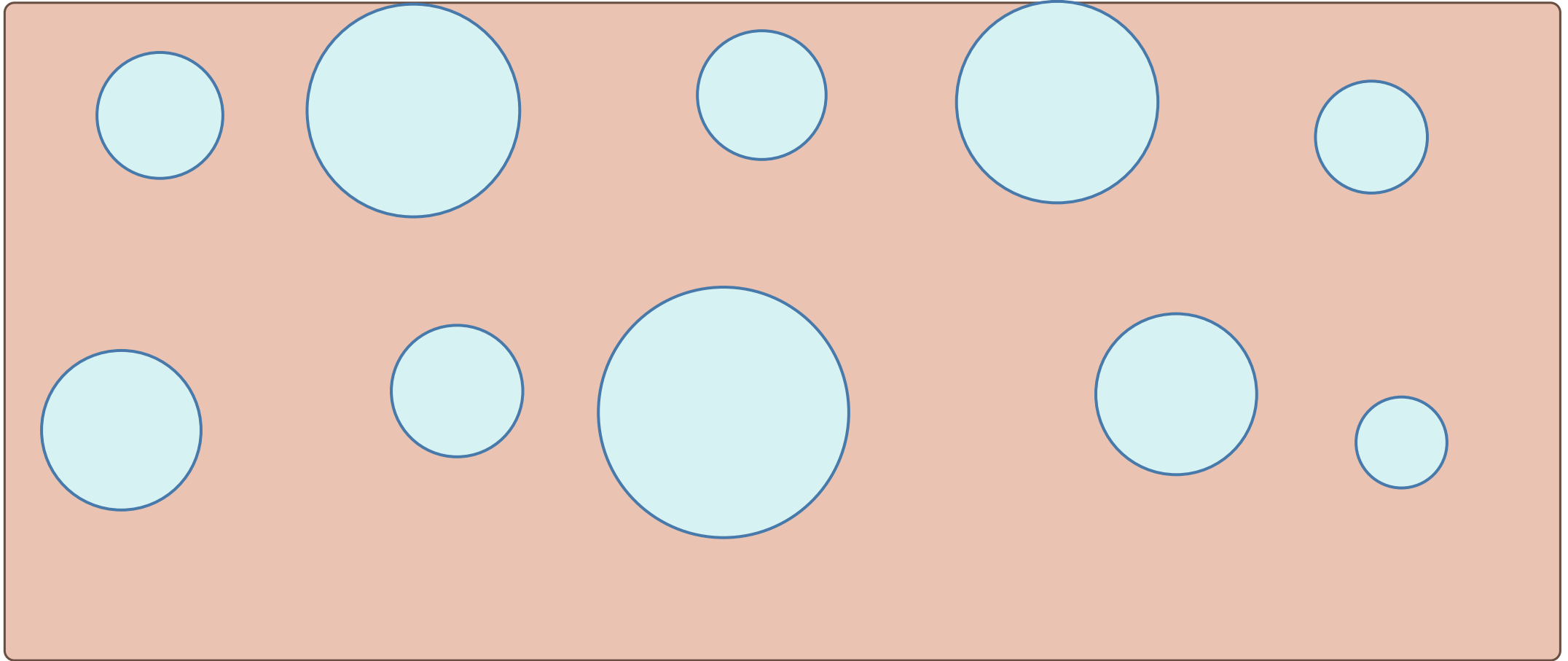
Schematic — not a specimen

- The kidneys can become greatly enlarged and irregularly cystic.
- Exceptional kidney weights reaching 4 kg each.
- The external surface may be dominated by cysts with little visible tissue between them.

Gross cysts vary in size and distribution

- Cysts may measure up to 3–4 cm in diameter in the Robbins description.
- They are distributed across the renal parenchyma rather than confined to a single zone.
- The combined cyst burden distorts the native renal outline.

A cut-surface schematic: Residual tissue between cysts

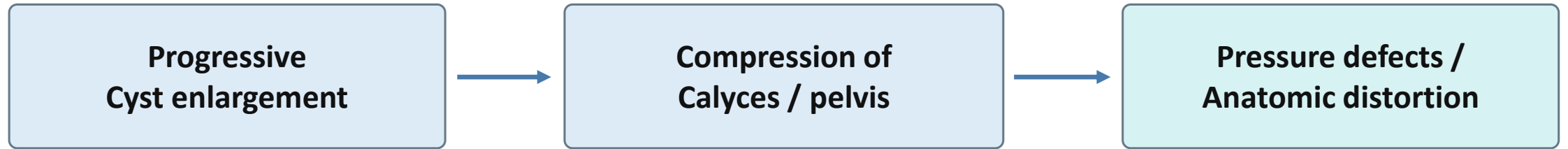


Schematic cross-section, not H&E / gross photograph

Cyst contents can be serous or hemorrhagic

- Cyst lumina may contain clear, serous fluid.
- Turbid or red–brown contents may indicate hemorrhagic material.
- Bleeding into cysts helps account for some episodes of flank pain and hematuria.

Why the collecting system is displaced

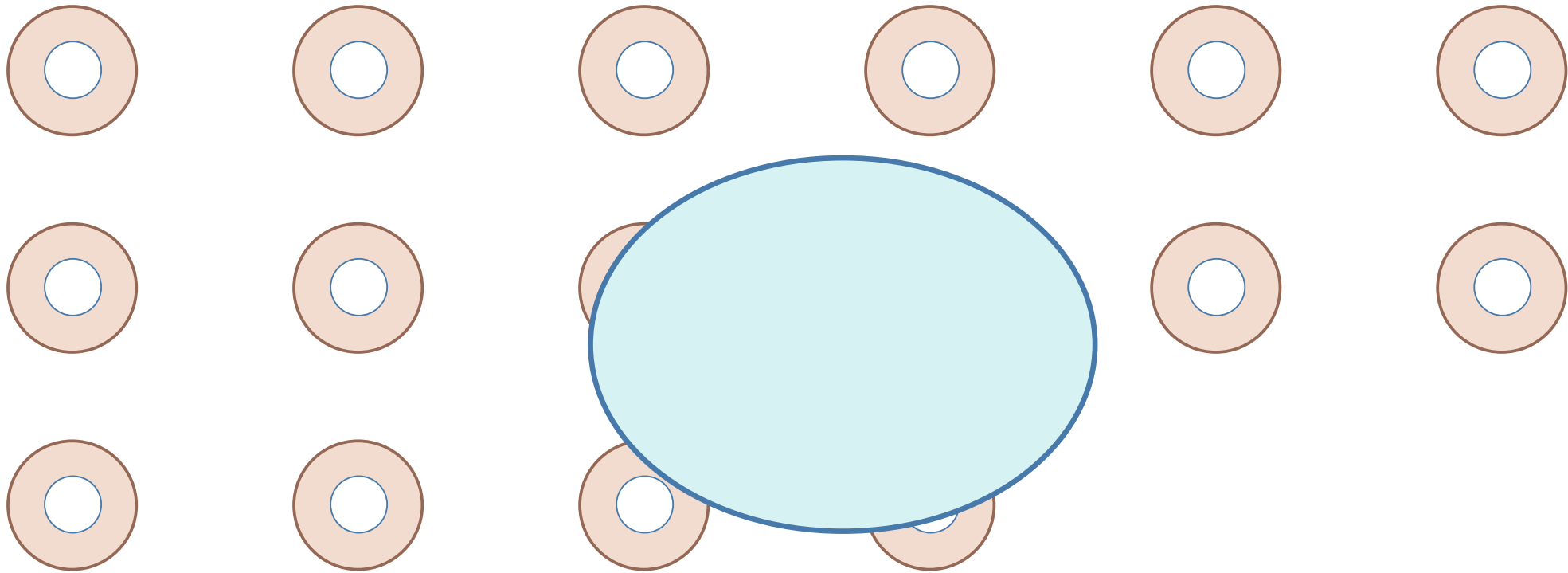


- An expanding cyst produces a mass effect, even when it is not an obstructing stone.
- Gross cyst burden and renal collecting-system distortion are related but distinct observations.

Residual functioning nephrons remain early

- Even severely cystic kidneys retain functioning nephrons between cavities.
- This explains the disparity between striking gross morphology and preserved early function.
- Progressive tissue replacement reduces the capacity of surviving nephrons.

Microscopic schematic: Cysts and residual tubules



Dilated cystic profile

Schematic microscopic architecture; Not a specimen

Variable epithelial lining reflects nephron origin

- Cysts arise from different portions of the tubular nephron.
- The epithelial lining is therefore variable rather than uniform.
- Occasional epithelial papillary formations or polyps may protrude into the lumen.

Why gross and microscopic impressions differ

- A gross cut surface can appear almost completely cystic.
- Microscopy may reveal islands of remaining viable nephron tissue.
- Residual nephrons explain slowly progressive azotemia in some patients.

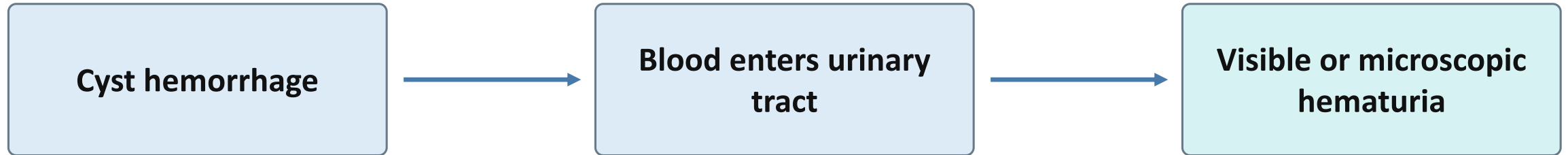
Clinical detection: Asymptomatic until dysfunction

- Many patients remain well while cysts enlarge slowly.
- Initial recognition may occur because of renal insufficiency or complications.
- A family history may trigger investigation before symptoms.

Flank pain: Two source-supported mechanisms

- Hemorrhage into a cyst can produce acute pain.
- Gradual cyst dilation and increasing kidney size can cause chronic discomfort.
- A dragging sensation reflects mass effect from enlarged kidneys.

Hematuria may follow cyst hemorrhage



- Hematuria may be an early clinical manifestation.
- Blood-clot passage can generate a separate episode of renal colic.

Blood clots can produce renal colic

- Clots passing through the collecting system cause episodic severe pain.
- This mechanism differs from chronic discomfort due to kidney enlargement.
- Stone disease is another source-supported cause of urinary pain.

Infection and stones complicate cystic kidneys

- Urinary tract infection is a recognized complication.
- Renal stones occur in affected individuals.
- Both complications can coexist with pain, hematuria and altered renal function.

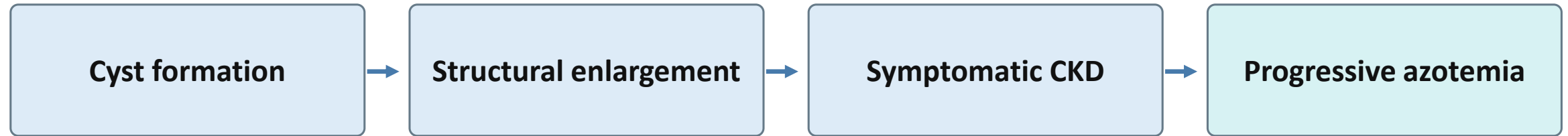
Hypertension is both manifestation and modifier

- Hypertension is a common clinical feature of ADPKD.
- It coexists with progressive renal structural injury.
- Hypertension as a factor that accelerates disease progression.

Urinary abnormalities during progression

- Proteinuria may occur but is rarely greater than 2 g/day account.
- Polyuria can accompany progressive chronic kidney disease.
- Azotemia may progress slowly over years before uremia develops.

Kidney dysfunction develops over a prolonged interval



- Progression is typically gradual rather than uniformly abrupt.
- Renal failure arising commonly in adulthood, around ages 40–60.
- The sequence varies markedly among individuals and genotypes.

PKD1: Reported age-related renal failure

Age	Renal failure estimate	Important interpretation
40 y	Less than 5%	Cumulative figure, textbook account
50 y	More than 35%	Cumulative figure, textbook account
60 y	More than 70%	Cumulative figure, textbook account
70 y	More than 95%	Cumulative figure, textbook account

Threshold inequalities are intentional; Values are not exact point estimates.

PKD2: Reported age-related renal failure

Age	Renal failure estimate	Important interpretation
50 y	Less than 5%	Cumulative figure, textbook account
60 y	15%	Cumulative figure, textbook account
70 y	45%	Cumulative figure, textbook account

The source describes a later and less severe trajectory than PKD1 on average.

Genotype–phenotype: Renal outcome

PKD1

Accounts for ~85% of textbook cases

Generally earlier progression

More severe renal trajectory

Age estimates describe groups

PKD2

Most of the remaining cases

Generally later progression

Less severe renal trajectory

Genotype alone does not predict a person

Modifiers of clinical severity

- The source identifies male sex and hypertension as adverse factors.
- It also notes faster progression in people of African descent, especially with sickle cell trait.
- Genetic and environmental influences make individual prognosis heterogeneous.

Extrarenal disease: Organ-system map

Liver

Biliary epithelial cysts

Cerebral vessels

Berry aneurysms

Heart valves

Prolapse / other anomalies

Other organs

Less frequent cysts

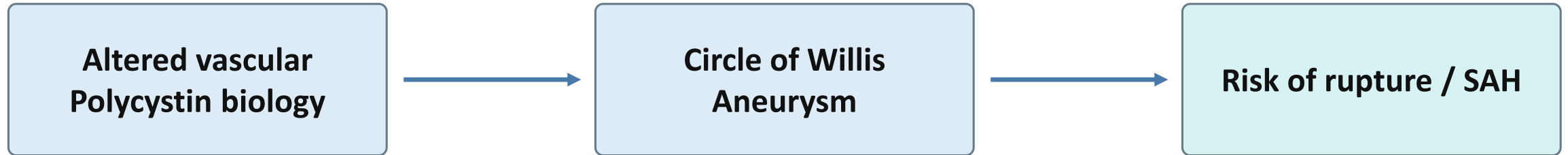
Hepatic cysts are a frequent association

- Liver cysts in about 40% of affected individuals.
- Hepatic cysts arise from biliary epithelium.
- They are usually asymptomatic despite being a conspicuous extrarenal feature.

Cysts may occur outside kidney and liver

- Cysts occur less often in the spleen, pancreas and lungs.
- Distribution outside the kidney supports a multisystem disease concept.
- Extrarenal cysts do not themselves establish the degree of renal impairment.

Intracranial berry aneurysm: Vascular hazard



- Aneurysms are important because rupture can be catastrophic.
- The source attributes a proportion of deaths to subarachnoid hemorrhage.

The aneurysm–hemorrhage connection

- Intracranial berry aneurysms occur in vessels of the circle of Willis.
- Rupture may produce subarachnoid hemorrhage.
- SAH-related death in 4%–10% of affected individuals.

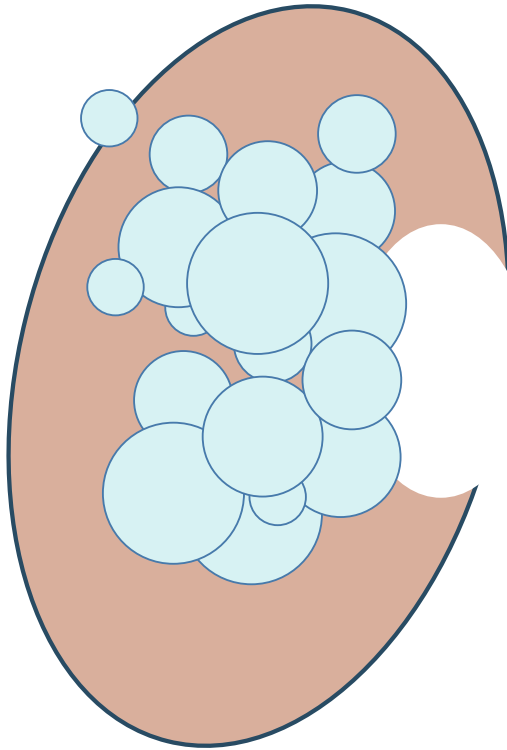
Cardiac-valve associations

- Mitral valve prolapse and other valve abnormalities are described.
- Abnormalities in approximately 20%–25% of patients.
- Most affected individuals with these abnormalities are asymptomatic.

Diagnosis: The source emphasizes imaging

- Radiologic imaging is the primary diagnostic method.
- Bilateral kidney enlargement with numerous cysts is the characteristic structural pattern.
- Interpret the pattern with family and clinical context rather than cyst count alone.

Imaging target: Bilateral multicystic architecture



Schematic — not a specimen

- Map both kidneys rather than evaluating an isolated cyst.
- Assess the burden and distribution of cysts and parenchymal distortion.
- This is a conceptual teaching image—not ultrasound, CT or MRI.

Adult versus childhood polycystic kidney disease

ADPKD

Autosomal dominant inheritance

Typically adult renal decline

Numerous large cysts, giant kidneys

Liver cysts; Vascular aneurysms

Autosomal recessive childhood PKD

Autosomal recessive inheritance

Renal disease present at or near birth

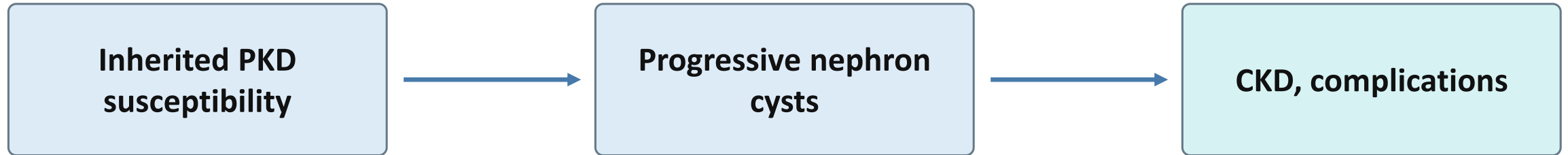
Enlarged cystic kidneys early in life

Congenital hepatic fibrosis

Important alternatives to ADPKD

Pattern	Useful distinguishing clue
Simple renal cysts	One/few cysts with otherwise normal-sized kidney
Acquired cystic disease	Cysts in end-stage renal disease / dialysis context
Nephronophthisis	Corticomedullary cysts; small kidneys
Multicystic renal dysplasia	Abnormal developmental kidney; often unilateral

Integrated renal disease sequence



- Genotype determines susceptibility and influences expected severity.
- Cyst expansion, interstitial damage and hypertension interact with renal outcome.

Teaching vignette: Cystic kidneys and hematuria

A 45-year-old with enlarged bilateral kidneys develops episodic flank pain and visible hematuria. Imaging demonstrates numerous cysts.

Which morphologic feature best explains bilateral enlargement?

Give two plausible mechanisms of pain.

Name one important extrarenal association.

Hypothetical teaching vignette

Teaching vignette: Mechanism-based answer

Case interpretation: A structural disease involving many enlarging tubular cysts, with superimposed symptoms.

Bilateral expansion and distortion of renal parenchyma.

Cyst hemorrhage or gradual dilation; Blood-clot passage may cause colic.

Hepatic cysts, berry aneurysms or mitral-valve abnormalities.

Hypothetical teaching vignette

Teaching vignette: Genotype and age

Two adults with ADPKD have similar imaging patterns. One has a PKD1-associated genotype; The other has PKD2-associated disease.

Which genotype has the more severe average renal course?

Why can prediction still be uncertain for an individual?

What non-genetic factor in the Robbins text accelerates progression?

Hypothetical teaching vignette

Teaching vignette: Interpretation

The genotype comparison concerns average clinical trajectories, not a deterministic outcome for either person.

PKD1 generally progresses earlier than PKD2.

Cyst initiation and environmental/genetic modifiers influence severity.

Hypertension is a source-supported accelerant.

Hypothetical teaching vignette

Mechanistic synthesis: Three connected levels

- Gene: PKD1 and PKD2 variants impair polycystin-dependent activity.
- Cell: Altered ciliary/calcium signaling affects proliferation and secretion.
- Organ: Expanding cysts distort parenchyma and cause fibrosis and nephron loss.

Clinicopathologic synthesis

- Recognize the bilateral, enlarged, multicystic phenotype.
- Connect hemorrhage, dilation, stones and infection to symptoms.
- Monitor the extrarenal disease concept: Liver, cerebral vessels and heart valves.
- Distinguish inherited adult disease from pediatric and acquired cystic patterns.

Primary reading and source boundaries

- Primary reference: Robbins, Cotran & Kumar, Pathologic Basis of Disease.
- Relevant textbook section: Autosomal Dominant (Adult) Polycystic Kidney Disease.
- Source-based mechanism diagrams are simplified conceptual models, not original textbook figures.
- Specific modern diagnostic cutoffs and treatment algorithms are beyond this source-based lecture.