Anomalies and cystic diseases of the kidney

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Introduction

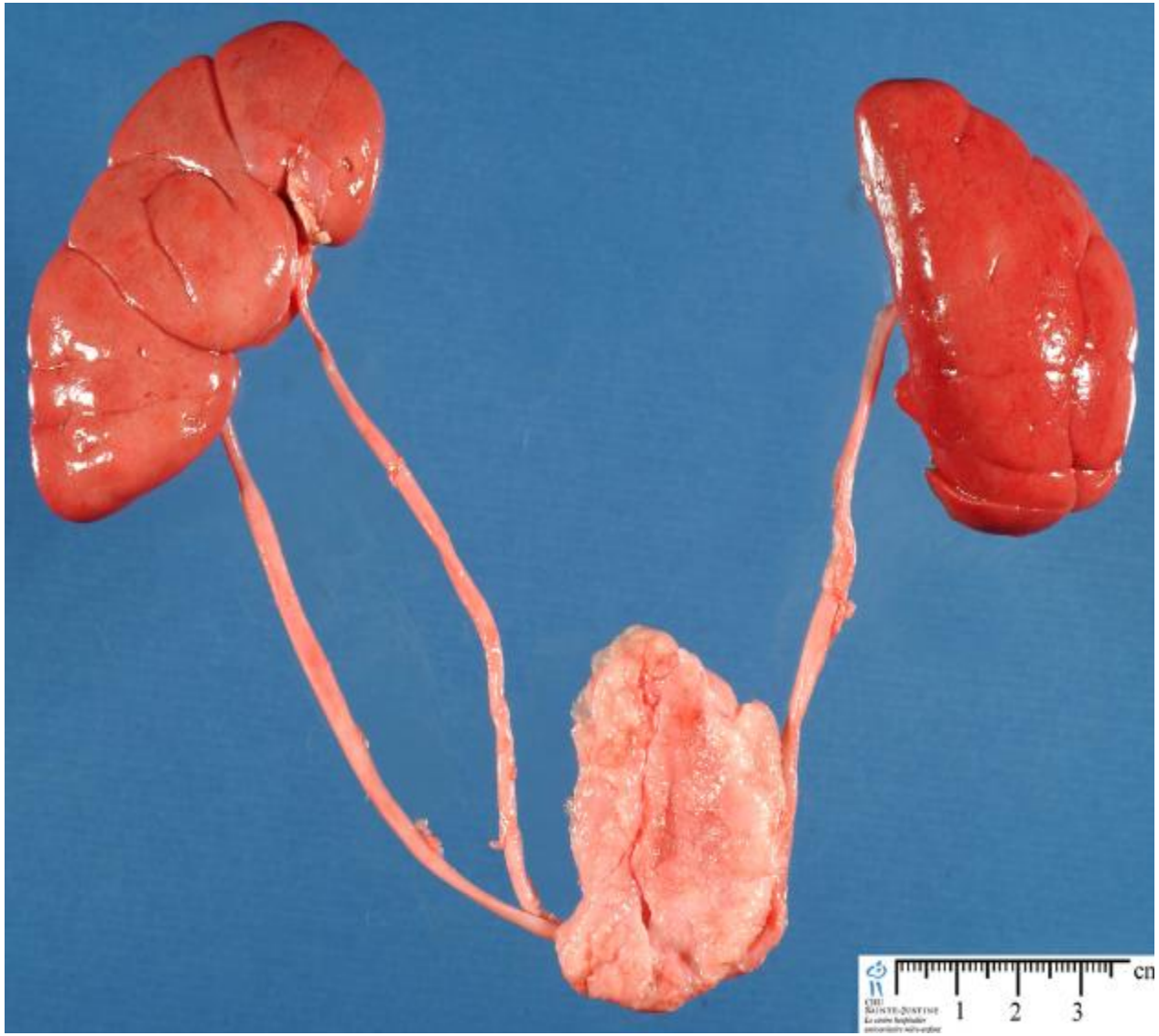
- 10% of individuals have urinary tract malformations, although many are asymptomatic
- 15% of congenital urogenital anomalies are secondary to an underlying chromosomal disorder
- In children, 20% of chronic renal failure is due to renal dysplasia or hypoplasia
- In adults, 10% of chronic renal failure is due to adult polycystic kidney disease

Agenesis

- Complete absence of renal tissue; unilateral or bilateral
- Bilateral agenesis: incompatible with life; associated with large adrenal glands; leads to Potter (oligohydramnios) sequence; possible causes include maternal insulin dependent diabetes mellitus and male sex of fetus but usually no specific etiology
- Unilateral agenesis: not fatal

Duplication of ureters

- Usually asymptomatic; may be associated with obstruction

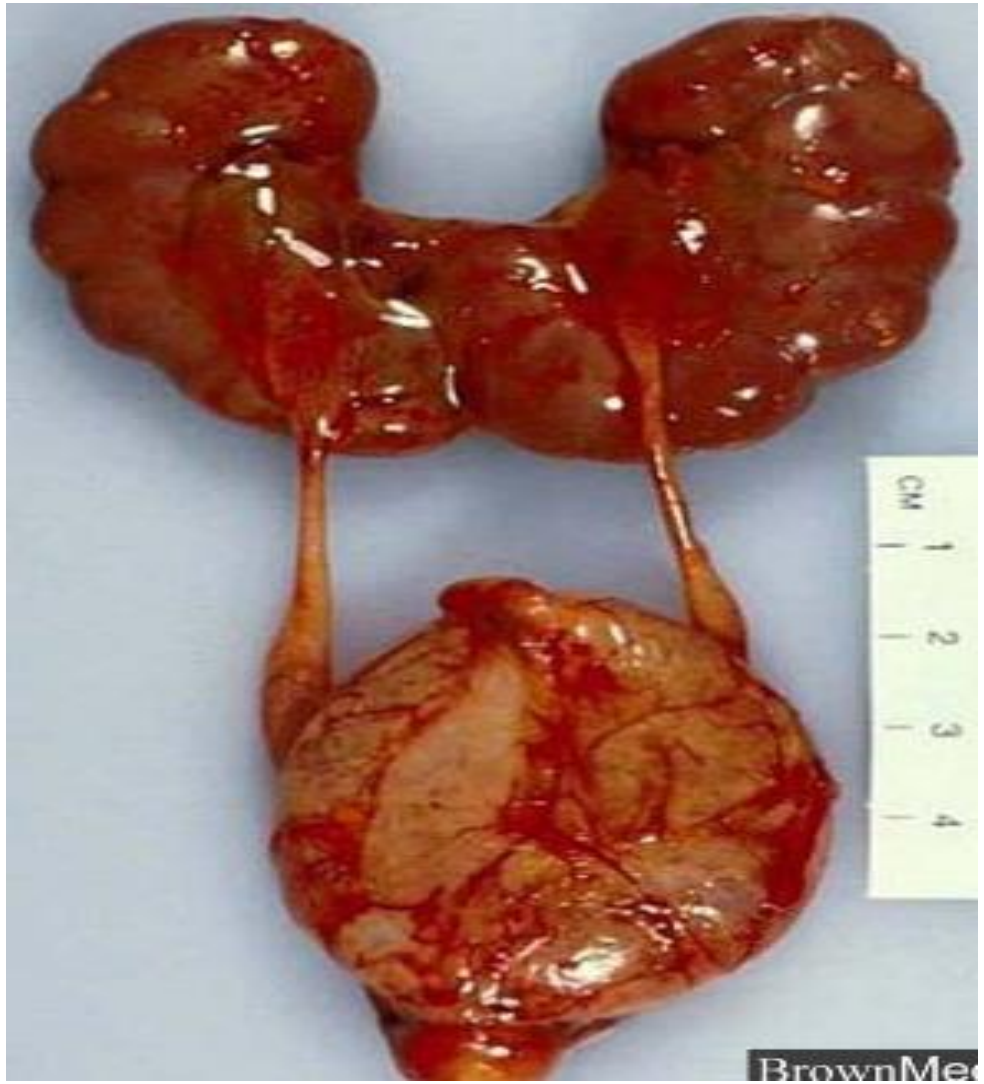


Ectopic (displaced) kidneys

- Usually at pelvic brim, may have kinking of ureters

Horseshoe kidney

- Most common congenital kidney anomaly
- 90% are fused at lower pole
- Associated with obstruction, anomalous superior vena cava
- Complete fusion of the kidneys produces a formless mass in the pelvis (pancake kidney)

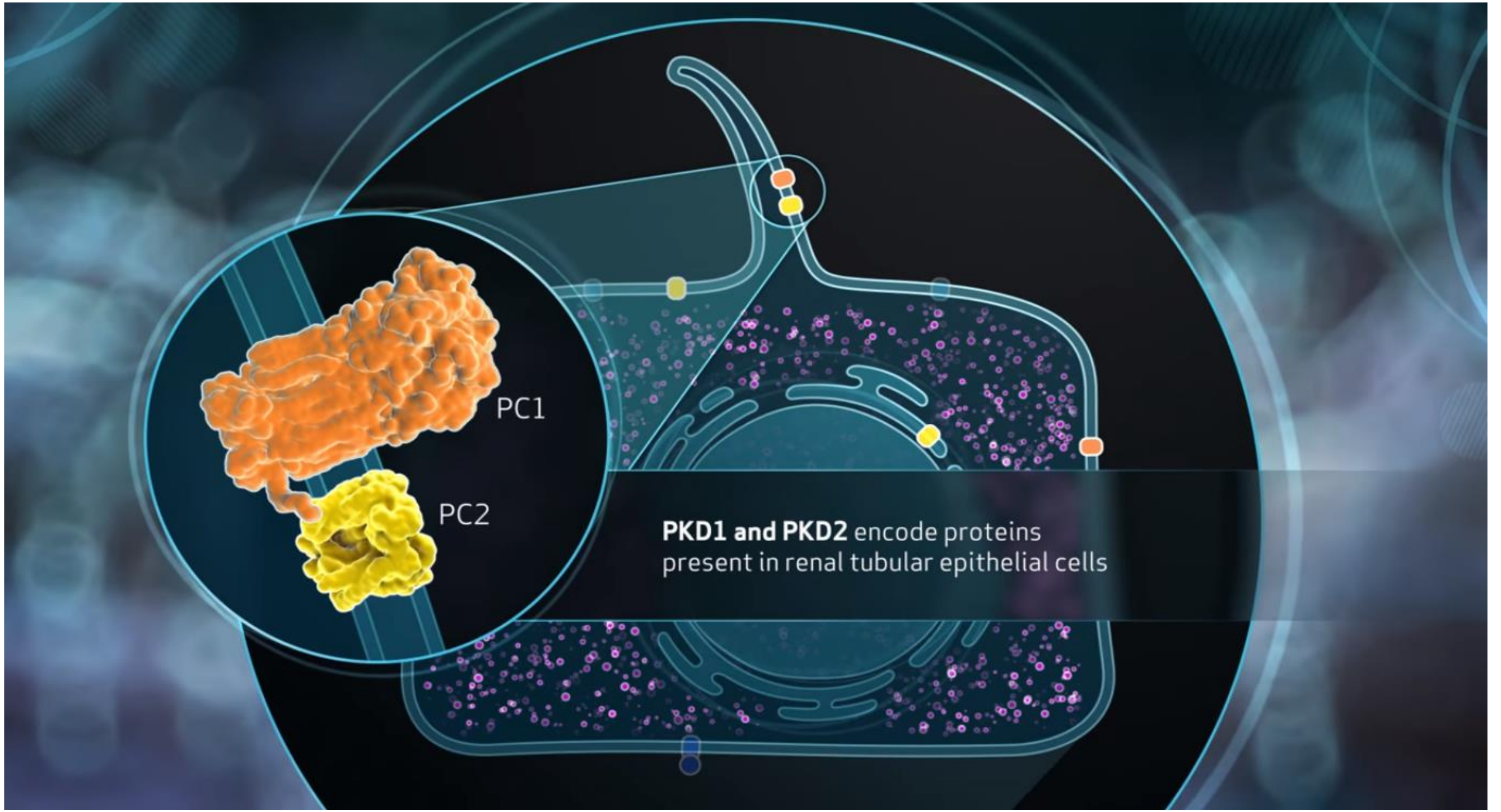


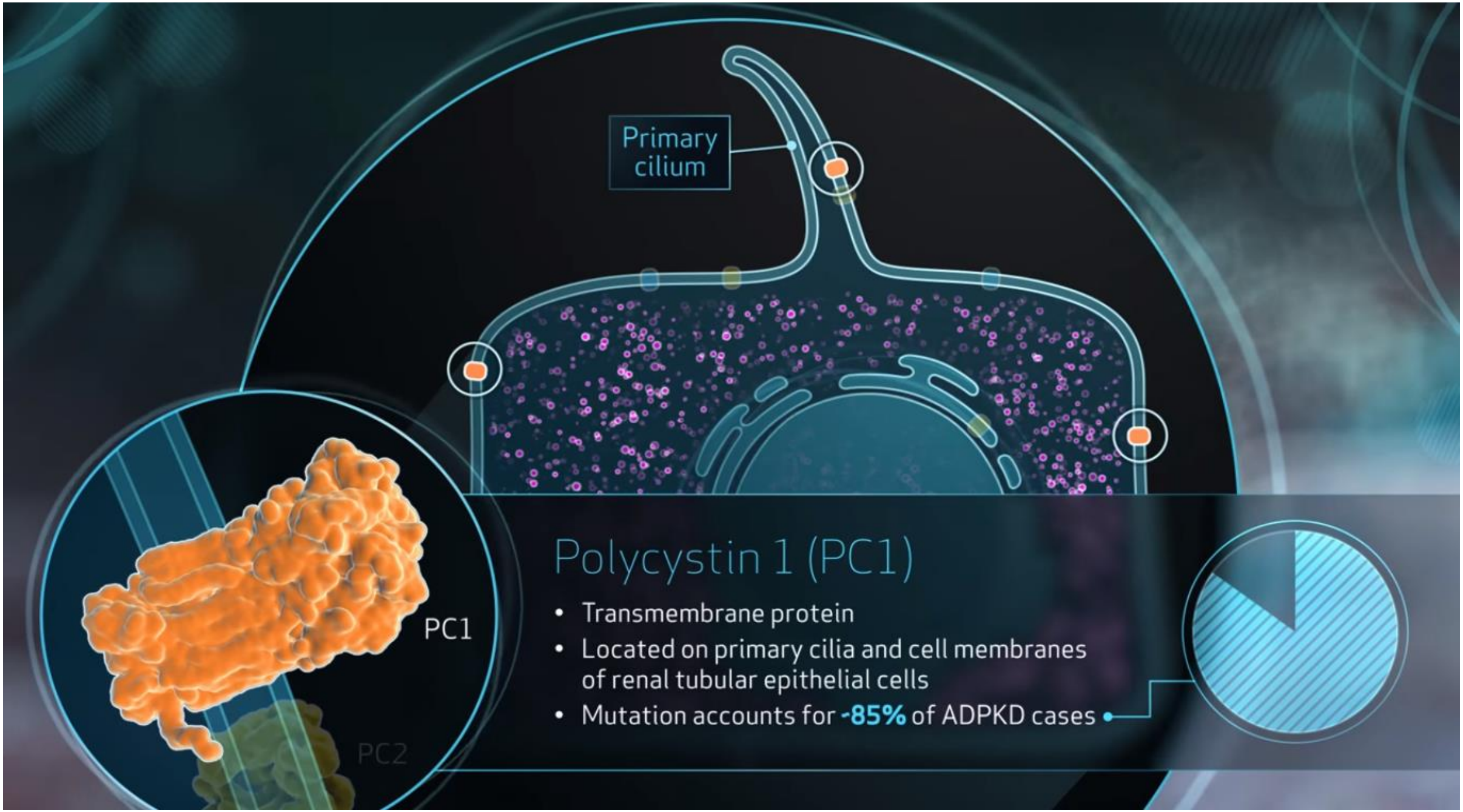
Hypoplasia

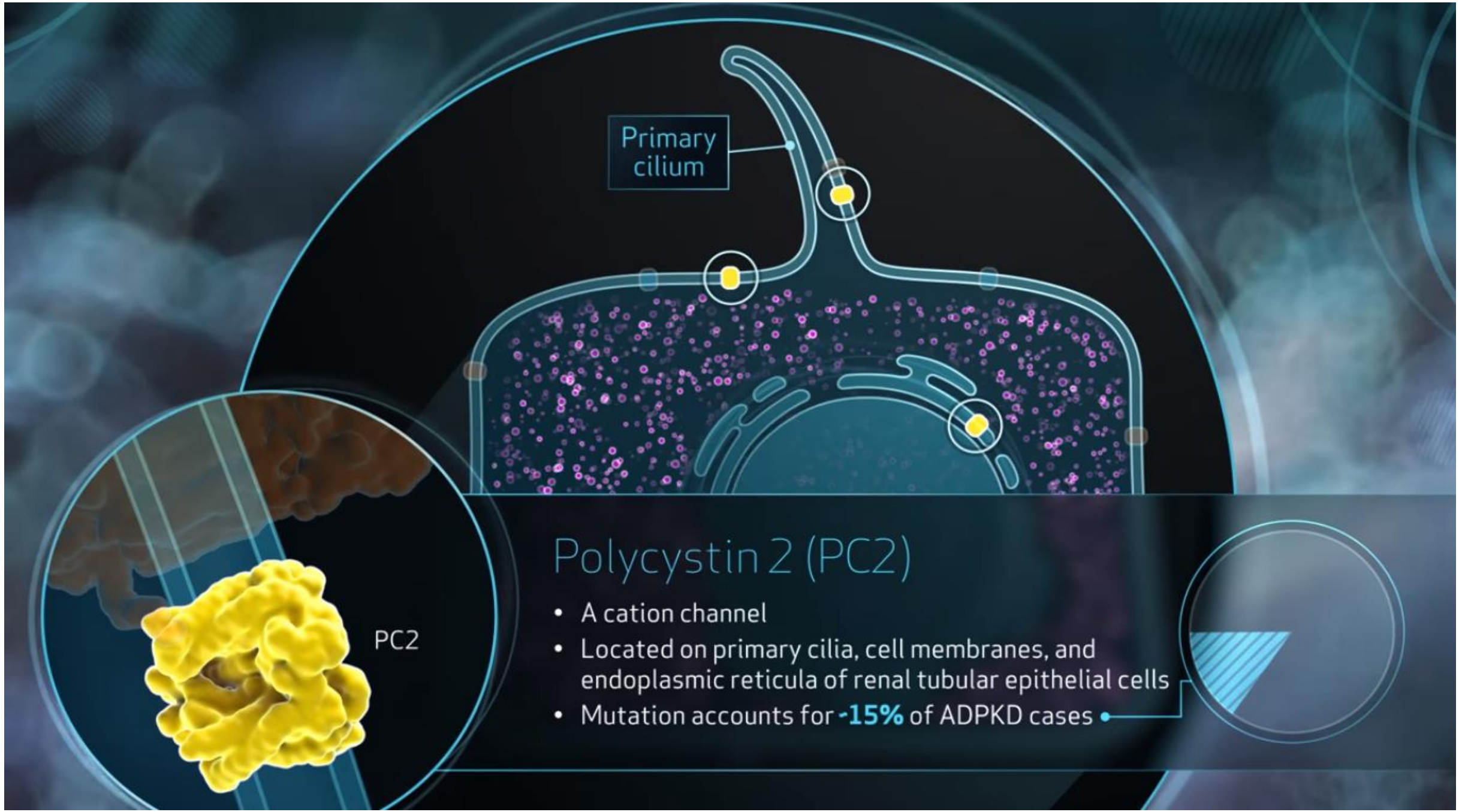
- Rare; failure of kidney to develop to normal size without scarring
- Usually unilateral with a reduced number of nephrons and pyramids (6 or less) but otherwise normal architecture
- Associated with *PAX2* mutations
- **Oligomeganephronia:** type of hypoplasia with small kidney but hypertrophied nephrons due to compensatory hypertrophy caused by reduced number of nephrons

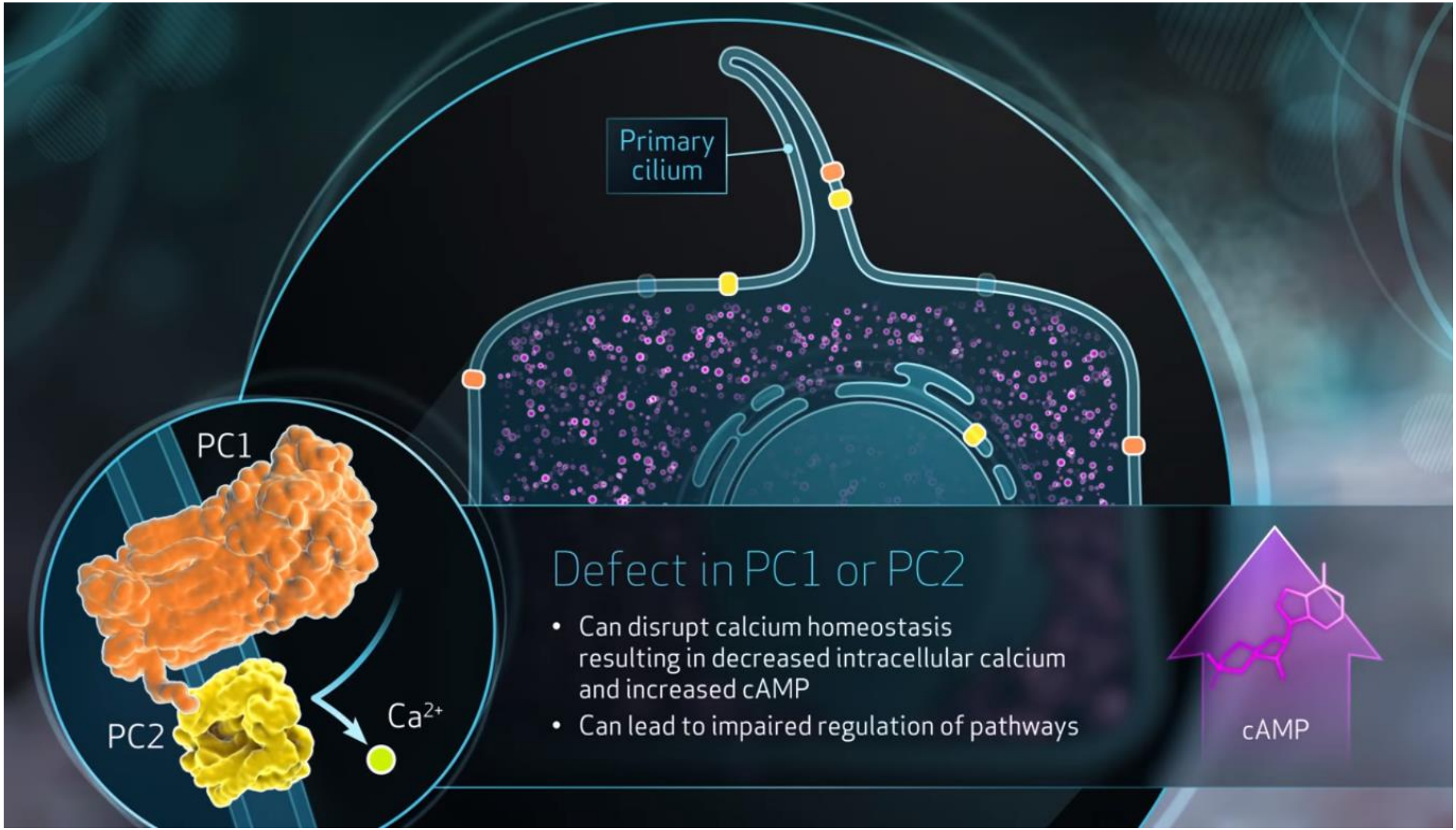
Autosomal dominant polycystic kidney disease

- Autosomal dominant renal cystic disorder due to mutations in genes coding for polycystin 1 (*PKD1*, chromosome 16p, most common) and polycystin 2 (*PDK2*, chromosome 4q)
- Also associated with *TSC2 / PKD1* contiguous gene syndrome
- Usually inherited; new mutations without a family history occur in approximately 10%
- 1 - 2 / 1,000 births
- M = F


PC1
PC2
PKD1 and PKD2 encode proteins
present in renal tubular epithelial cells


Primary cilium
PC1
PC2
Polycystin 1 (PC1)
• Transmembrane protein
• Located on primary cilia and cell membranes of renal tubular epithelial cells
• Mutation accounts for ~85% of ADPKD cases


Primary cilium
PC2
Polycystin 2 (PC2)
• A cation channel
• Located on primary cilia, cell membranes, and endoplasmic reticula of renal tubular epithelial cells
• Mutation accounts for ~15% of ADPKD cases

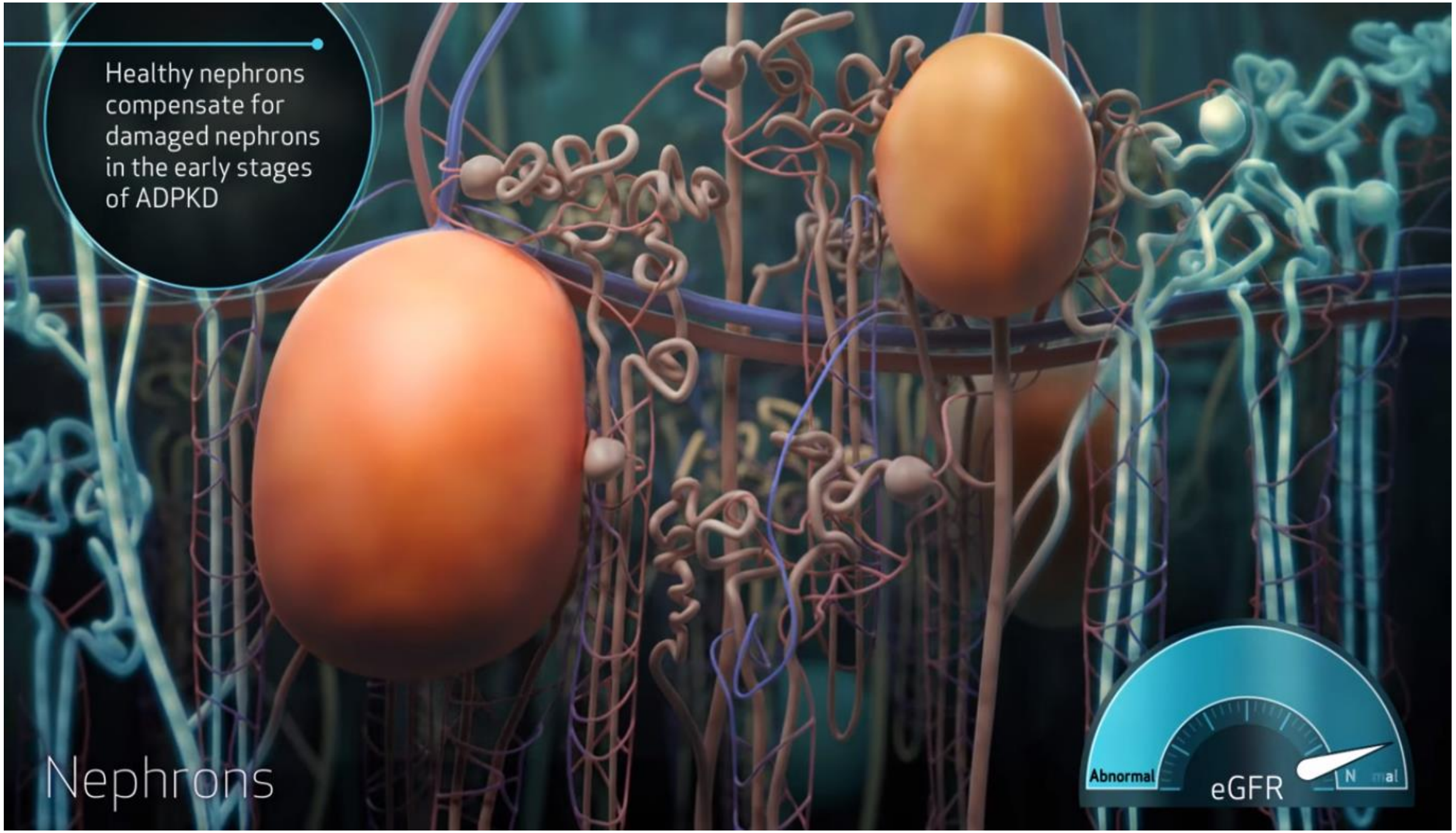

Primary cilium
PC1
PC2
Ca^{2+}
Defect in PC1 or PC2
• Can disrupt calcium homeostasis resulting in decreased intracellular calcium and increased cAMP
• Can lead to impaired regulation of pathways
cAMP

Pathophysiology

- Mutated proteins are involved in cell differentiation, polarization, proliferation and membrane transport
- The exact mechanism of cyst formation is not yet understood
- Cysts form in all regions of the nephron, enlarging and expanding throughout life
- Normal renal function is maintained until mid adulthood in most patients

Clinical features

- Third most common cause of end stage renal disease
- Patients present with hematuria, abdominal pain, hypertension, urinary tract infection or urolithiasis
- Associated with von Meyenburg complexes in liver; hepatic cysts (40% - 88%); berry aneurysms (10% - 30%); mitral valve prolapse (20%); cysts in pancreas, lung, spleen, pineal gland and seminal vesicles; aortic aneurysms; hepatic fibrosis and intestinal diverticula
- 25% die from infection, 40% from hypertension and heart disease and 15% from berry aneurysms or stroke

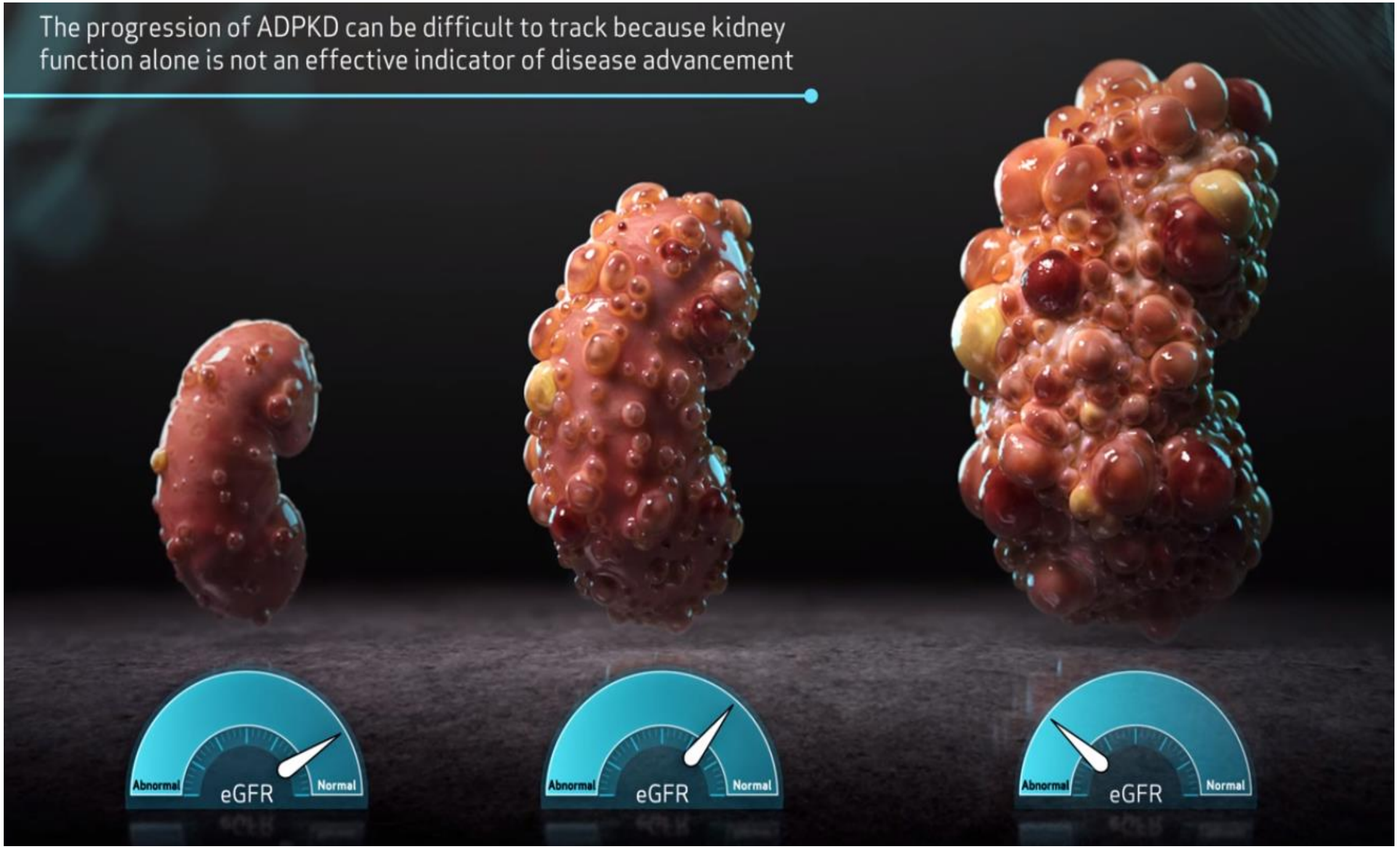

Healthy nephrons compensate for damaged nephrons in the early stages of ADPKD
Nephrons
Abnormal
eGFR
Normal

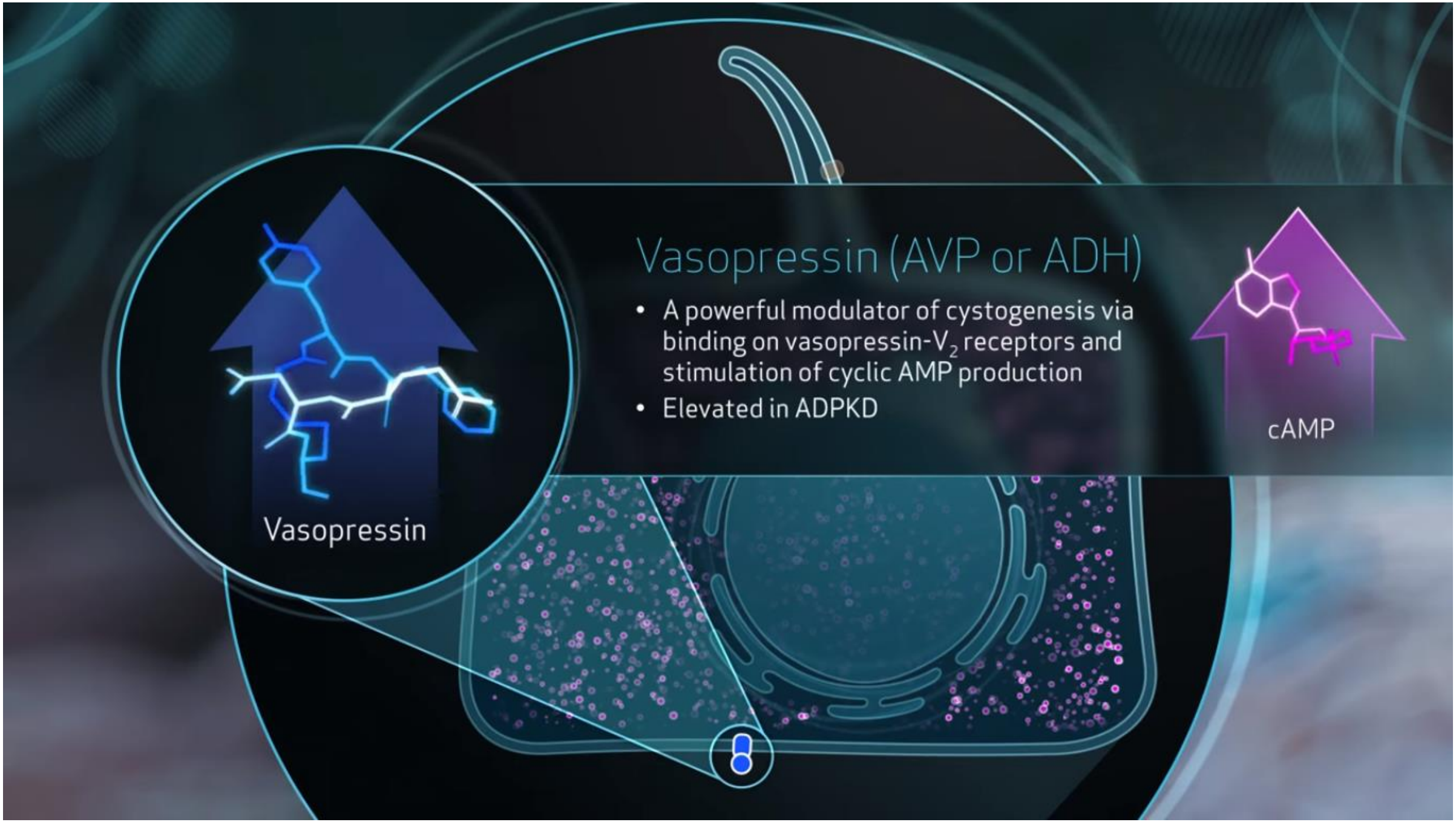

Nephrons
Abnormal
eGFR
Normal

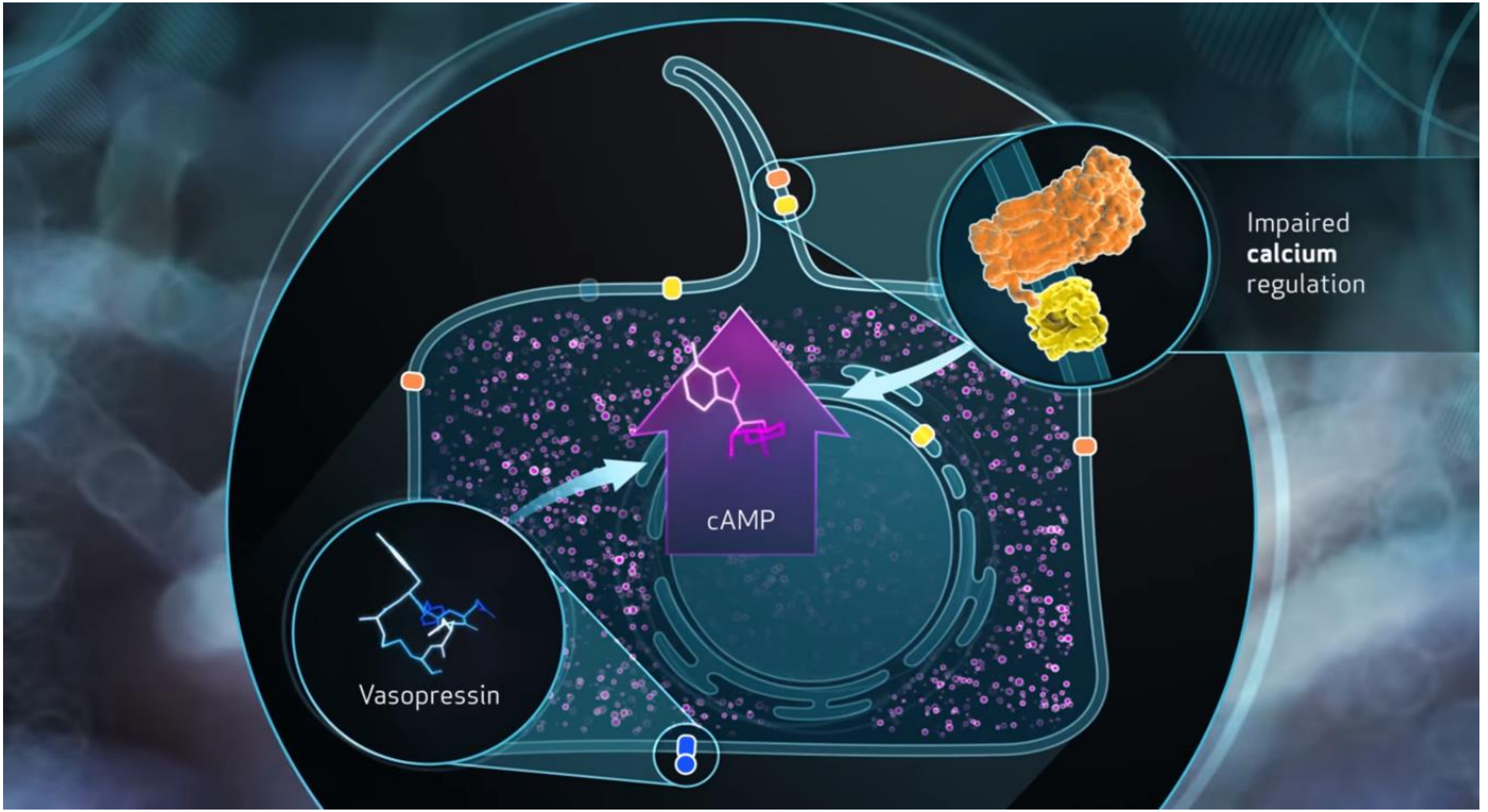
Prognostic factors

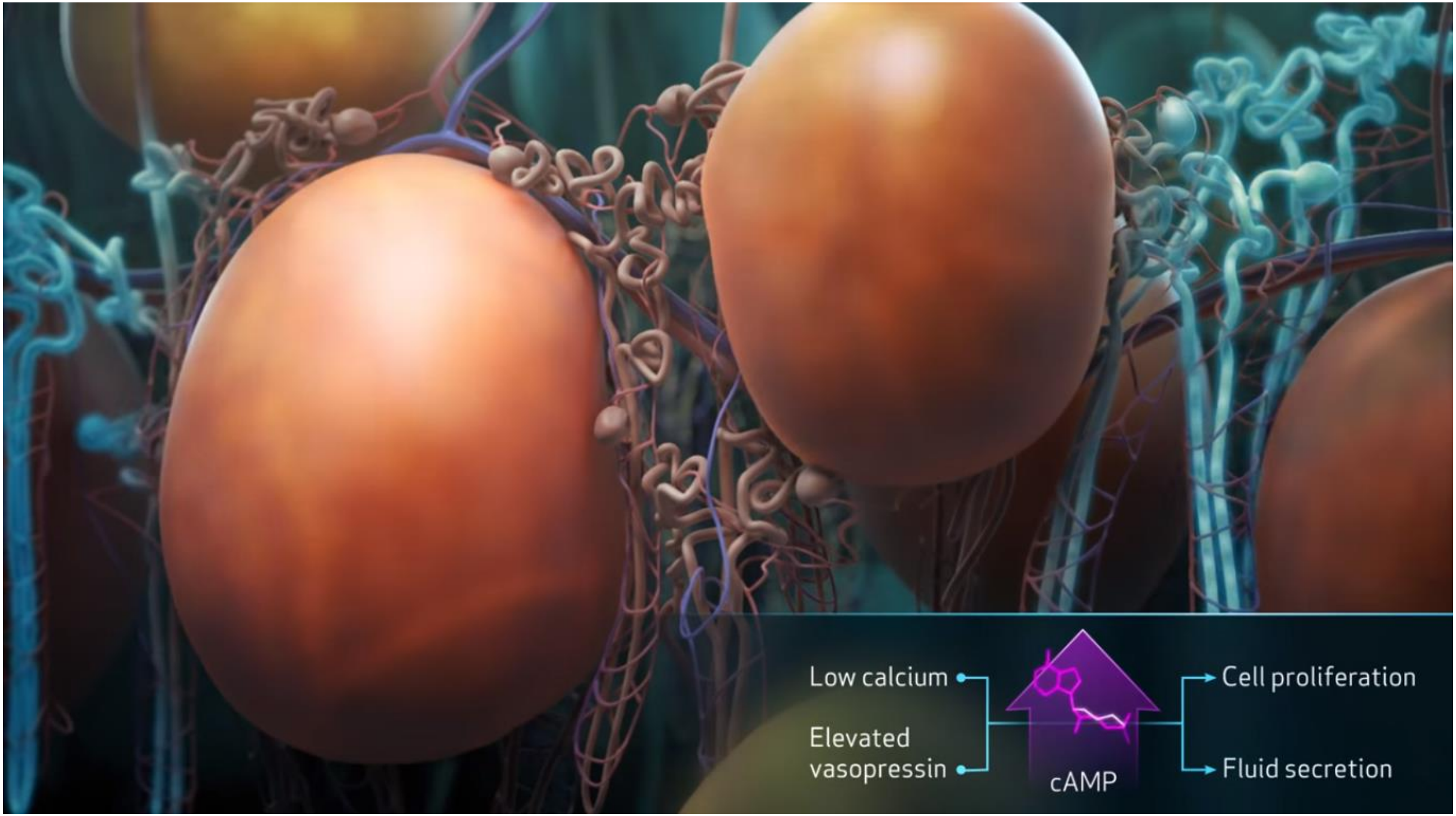
- Poor prognostic factors: sickle cell trait, male sex, early disease onset, early hypertension onset and proteinuria

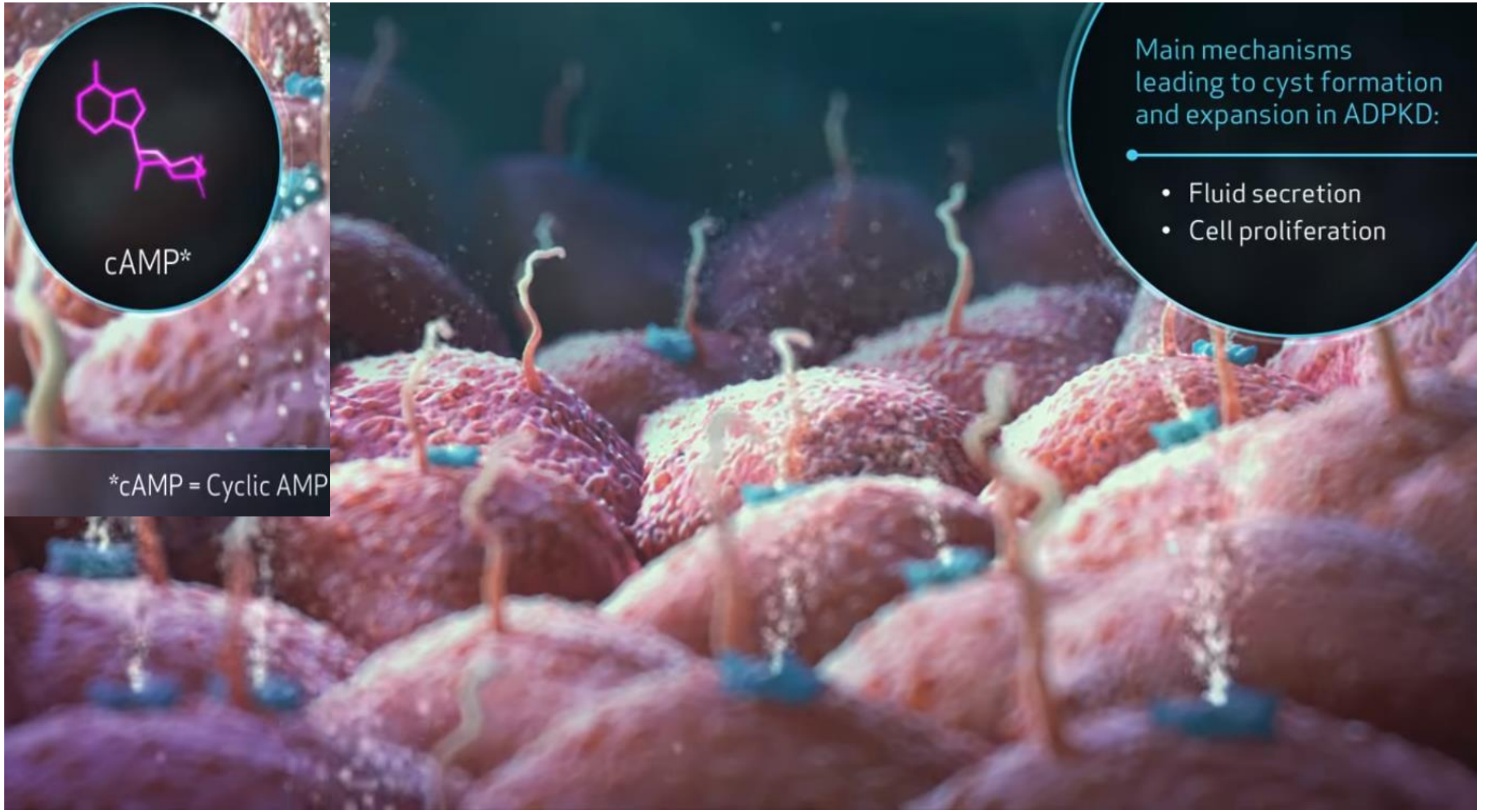
- **Treatment:** Laparoscopic nephrectomy, transplant


The progression of ADPKD can be difficult to track because kidney function alone is not an effective indicator of disease advancement
Abnormal
eGFR
Normal
Abnormal
eGFR
Normal
Abnormal
eGFR
Normal


Vasopressin (AVP or ADH)
• A powerful modulator of cystogenesis via binding on vasopressin-V_2 receptors and stimulation of cyclic AMP production
• Elevated in ADPKD
Vasopressin
cAMP


Impaired
calcium
regulation
cAMP
Vasopressin


Low calcium
Elevated vasopressin
cAMP
Cell proliferation
Fluid secretion

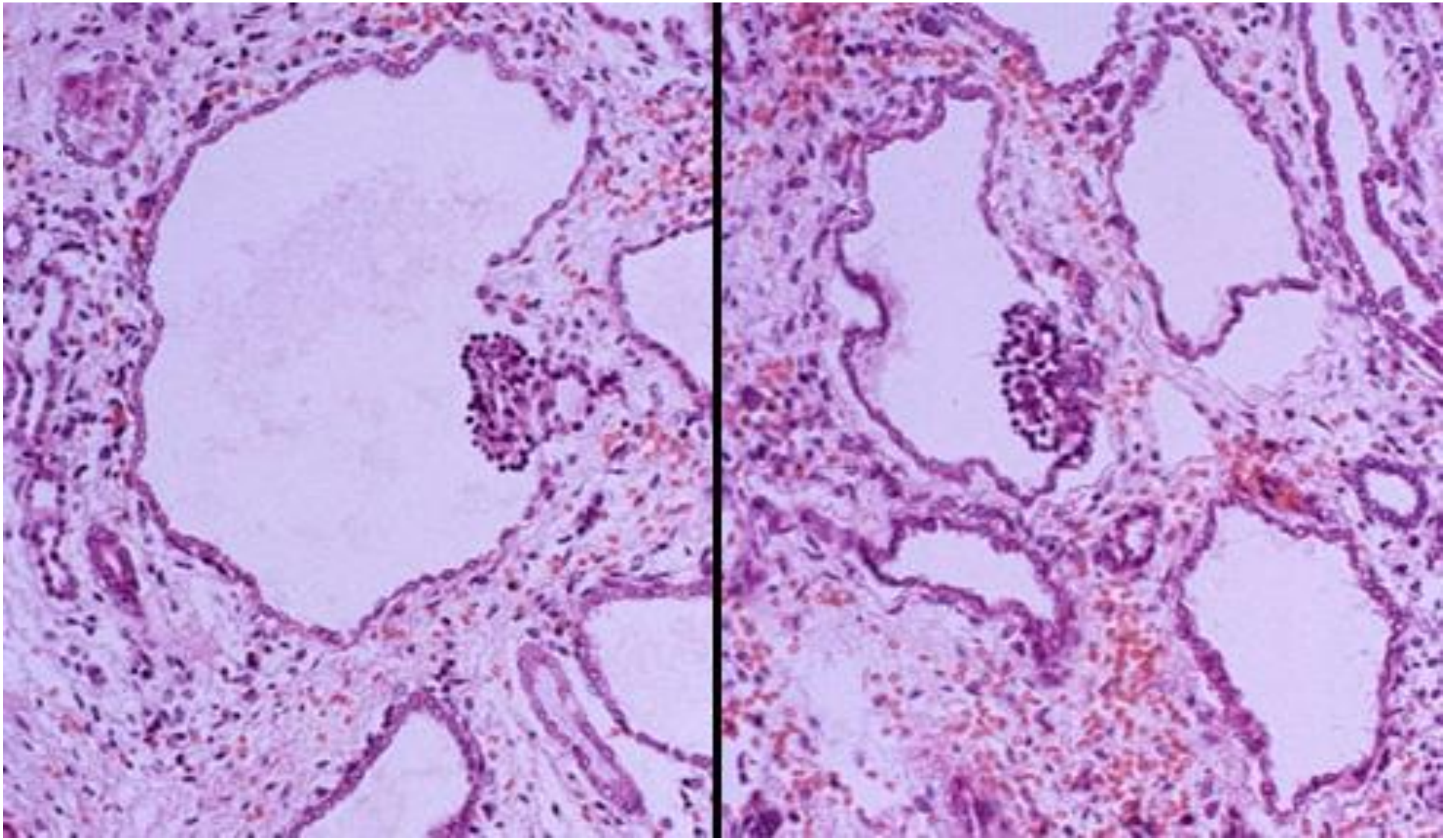

cAMP*
*cAMP = Cyclic AMP
Main mechanisms leading to cyst formation and expansion in ADPKD:
• Fluid secretion
• Cell proliferation

Gross description

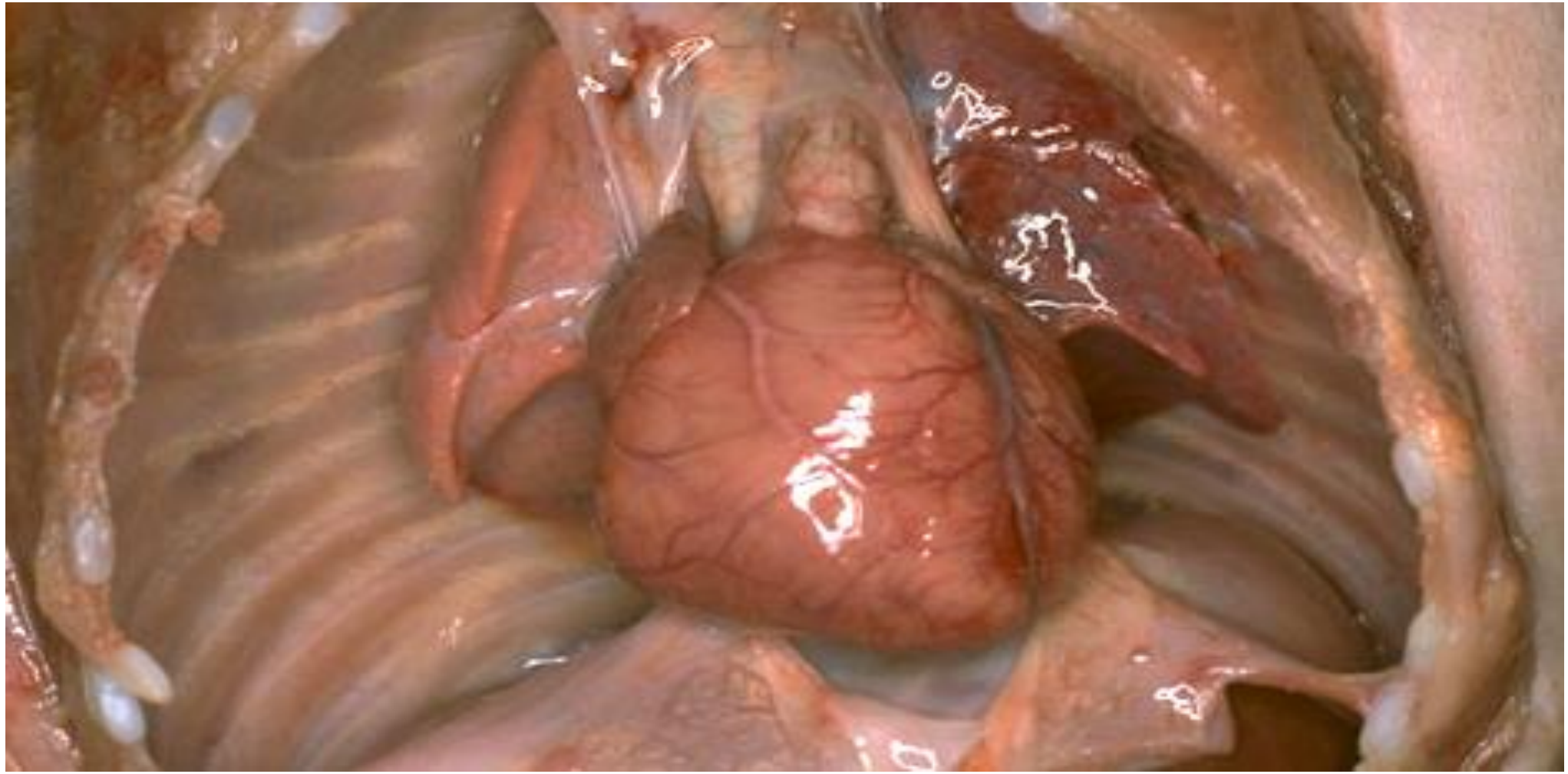
- Markedly enlarged kidneys (up to 8 kg) composed of sub-capsular cysts up to 4 cm
- Cysts contain clear to brown fluid

Microscopic (histologic) description

- Cysts are lined by cuboidal or flattened epithelium, may have papillary projections or polyps
- Functional nephrons exist between cysts with areas of global sclerosis, tubular atrophy, interstitial fibrosis and chronic inflammation
- Infants may show primarily cystic dilatation of Bowman's space
- 20% have renal adenomas



Pulmonary hypoplasia



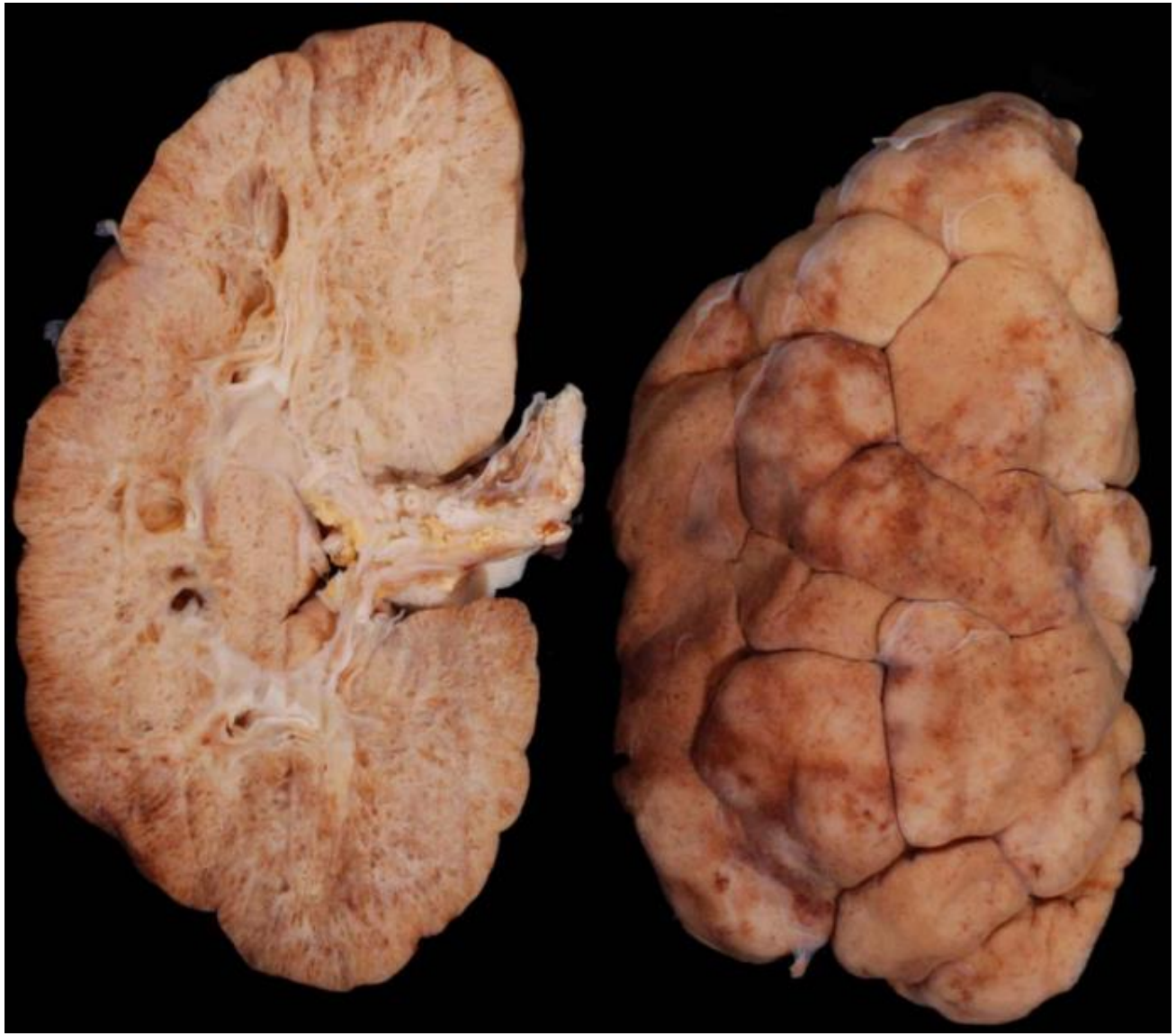
Autosomal recessive polycystic kidney disease

- Usually presenting with bilateral renal cystic disease at birth
- 1 per 20,000 live births
- Patients present prior to or at birth with frequent complications due to limited urine output including oligohydramnios, Potter sequence, joint deformities and pulmonary hypoplasia
- Early mortality is most common, usually due to pulmonary complications
- Perinatal mortality 30 - 50%; 5 year survival is 80 - 95% if survive first month of life
- In surviving cases with pulmonary hypoplasia, kidneys must be removed to allow for growth of lungs

- Usually no cysts other than kidney and liver but liver is always affected (every portal triad, every case) with herring duct cysts (ductal plate malformation) and congenital hepatic fibrosis
- Patients later develop hypertension, renal insufficiency, portal hypertension with splenomegaly or cholangitis
- May also include older patients presenting with hepatosplenomegaly, hypersplenism, variceal bleeding and cholangitis

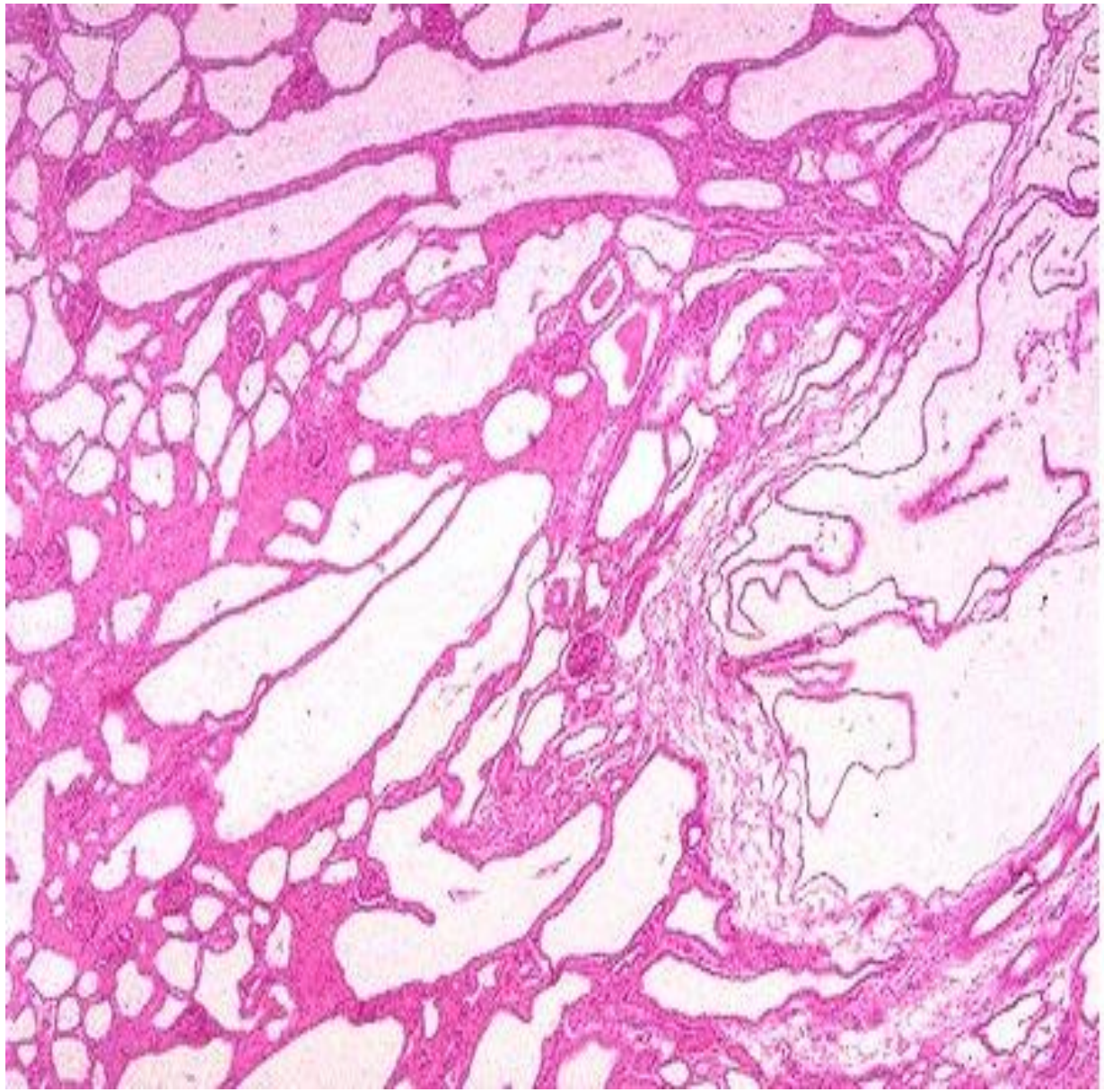
Gross description

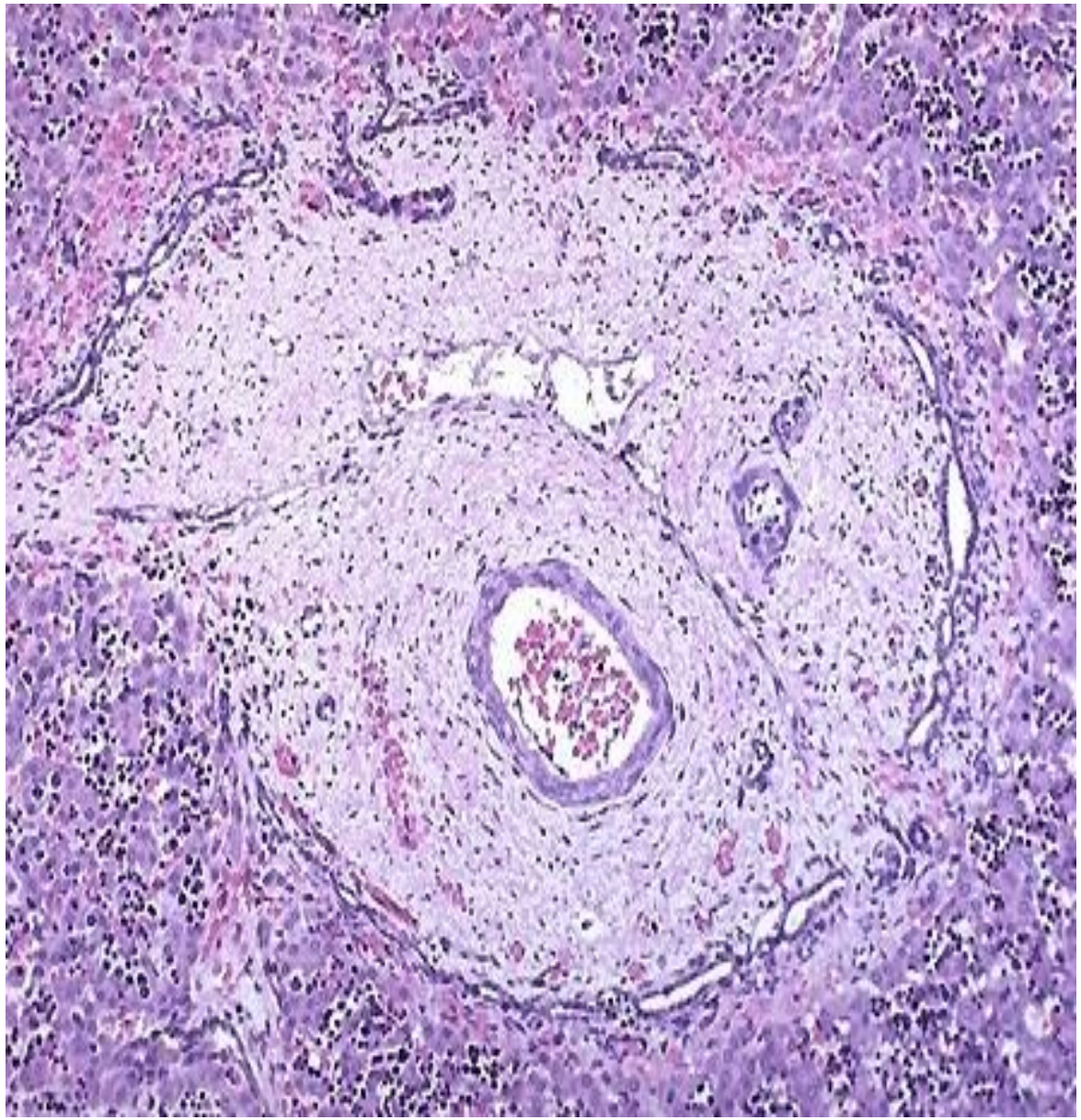
- Markedly enlarged kidneys with smooth surface
- Small cysts in cortex and medulla (collecting ducts)
- Dilated channels are perpendicular to cortical surface



Microscopic (histologic) description

- Radially arranged, elongated cysts that form as dilations of all collecting tubules with fluid accumulation
- Cysts lined by cuboidal or flattened cells from collecting tubules
- Normal nephrons without cystic change / interstitial fibrosis are present in between the cysts
- The liver shows portal fibrosis with complex bile ductular profiles





Molecular / cytogenetics description

- Mutations in PKHD1 gene (Polycystic Kidney and Hepatic Disease 1, produces fibrocystin / polyductin) at 6p12, expressed in kidney, pancreas and liver.

Acquired cystic kidney disease

- Three or more cysts per kidney in patients on longstanding hemo- or peritoneal dialysis for end stage renal disease (unrelated to underlying renal pathology)
- Occurs in 10% - 20% of patients within the first three years of dialysis, 50% within the first five years and 90% after ten years
- Also occurs in patients with long term uremia prior to dialysis
- Males > females during first ten years of dialysis
- Not restricted to adults; occurs in children and young adults on dialysis

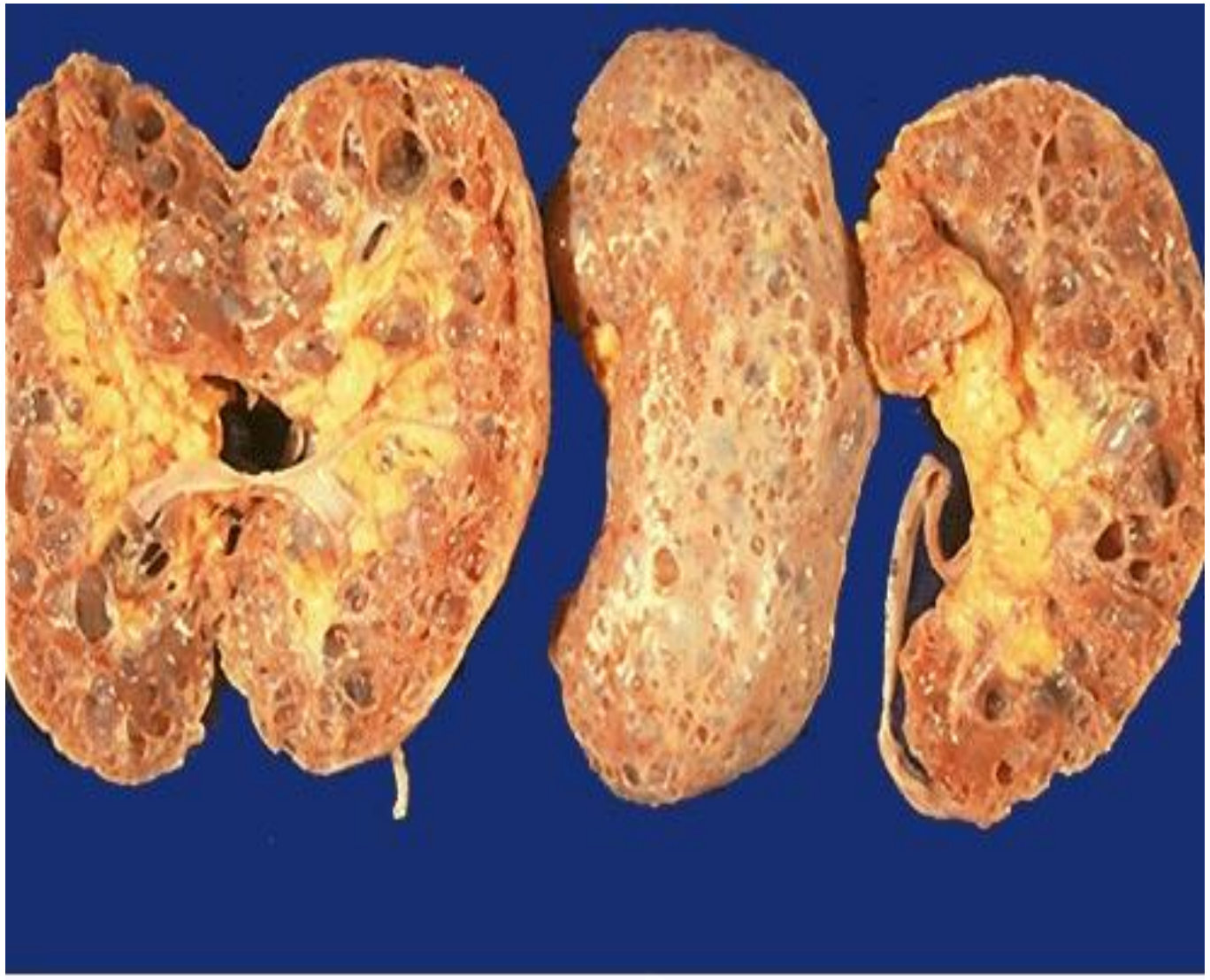
Increased (7 - 50x) risk of renal cell carcinoma (7% at 10 years), but death is rare

Gross description

- Moderately enlarged kidneys (usually < 800 g) with cortical and medullary cysts containing clear fluid
- > 40% replacement of kidney with cysts

Microscopic (histologic) description

- Cysts lined by flattened or cuboidal epithelium that may show focal pseudo-papillae with nuclear enlargement and loss of polarity
- Cysts may contain oxalate crystals
- Surrounding parenchyma shows global glomerulosclerosis, interstitial fibrosis and tubular atrophy



These adult kidneys are about normal in size but have a few scattered **small cysts**, none of which is over 2 cm in size. This is cystic change associated with chronic renal dialysis.

Medullary sponge kidney

- Sporadic cystic disease characterized by bilateral cystic dilations of medullary collecting ducts; normal cortex
- **Epidemiology**

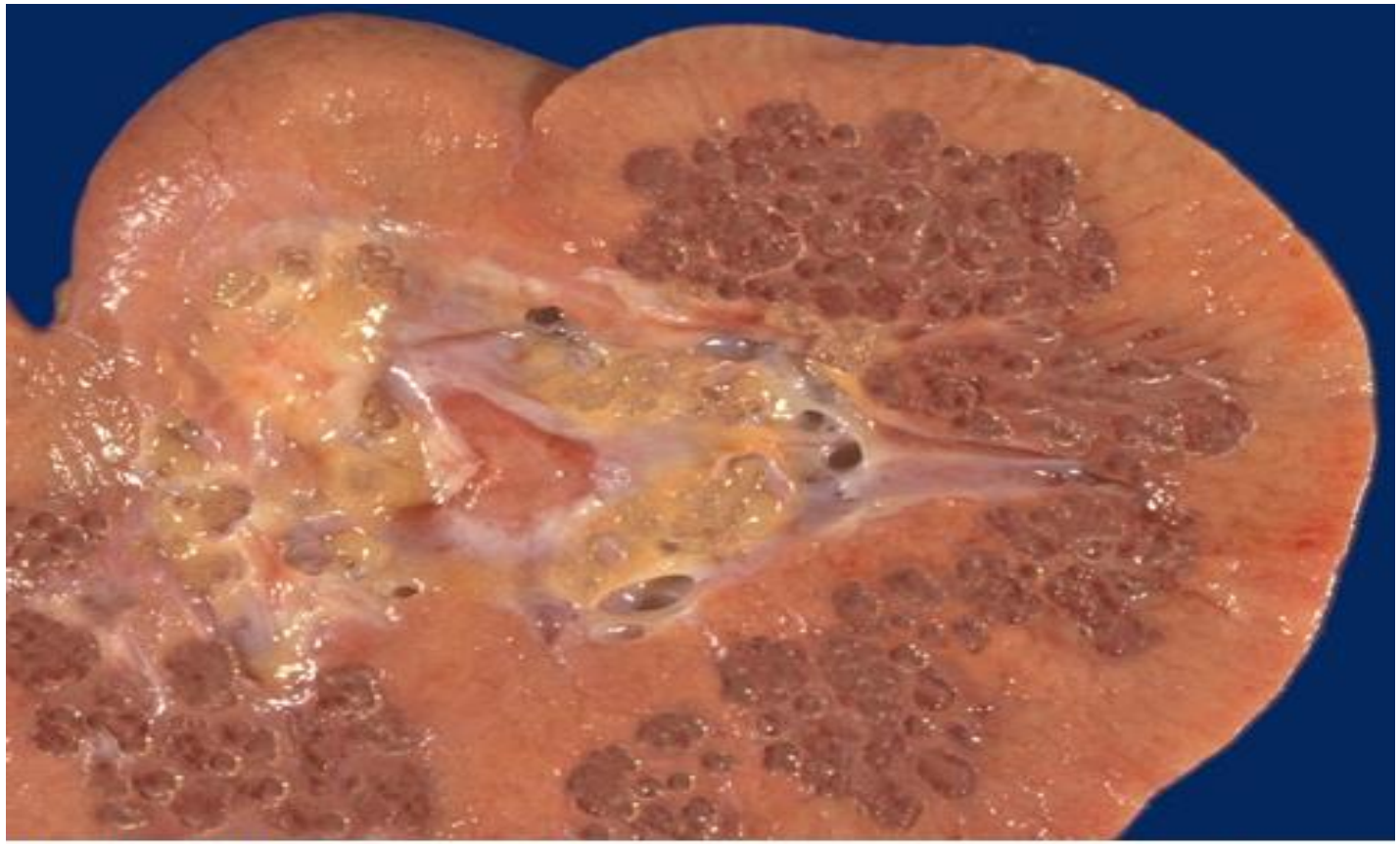
1 per 5000 births; no gender preference; not familial

Associated with hemihypertrophy of body (25% of cases), Marfan's, Caroli's and Ehlers-Danlos syndrome

- Usually presents in adulthood
- Patients are usually asymptomatic with normal renal function
- Calcifications on X-ray, stones, hematuria and infection at age 30+ years
- Does not progress to end stage renal disease
- Diagnosed with intravenous pyelography

Gross description

- Normal sized kidneys with multiple, small cysts in medullary pyramids and papillae, giving medulla a sponge-like appearance
- Most often bilateral



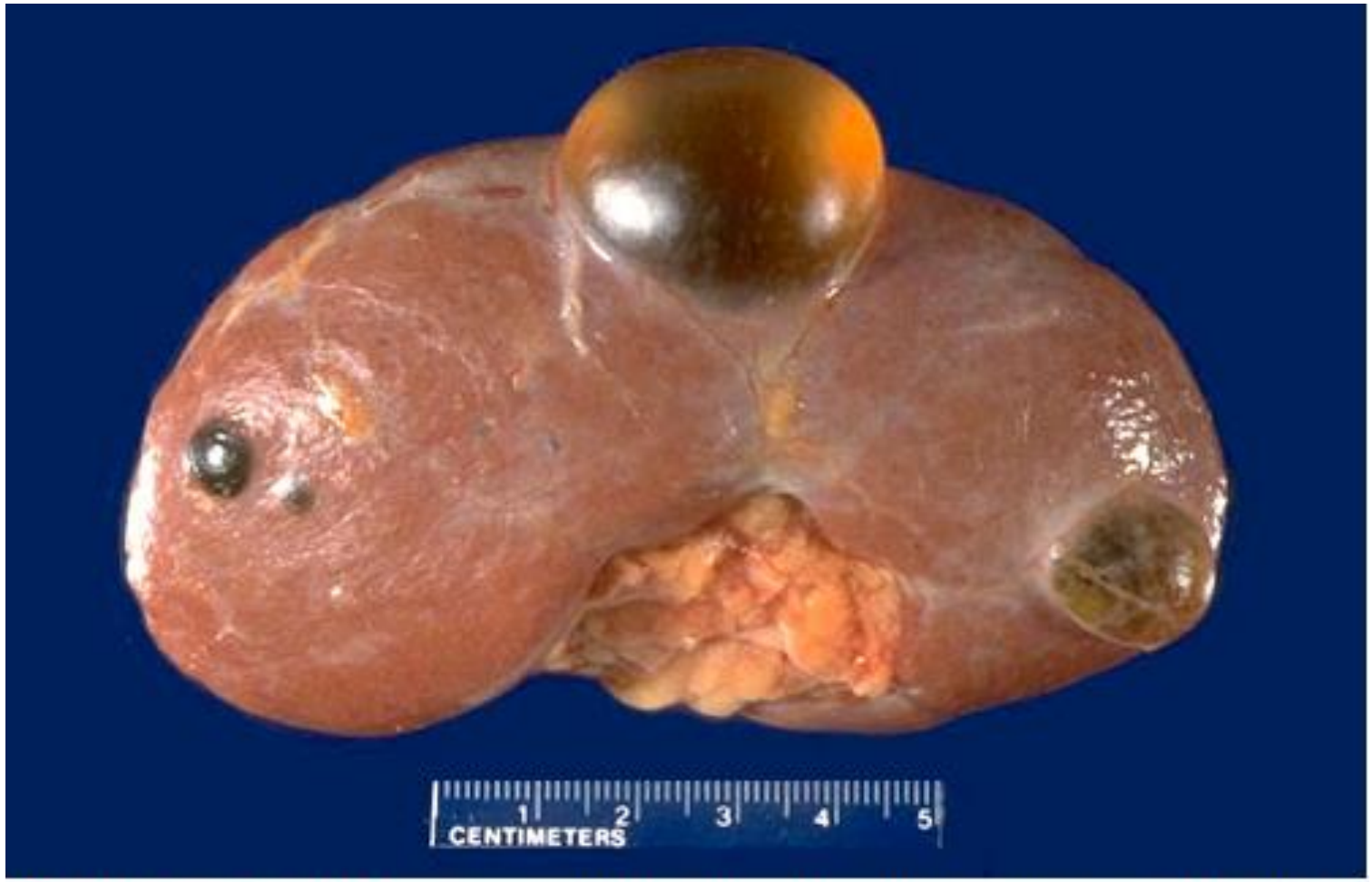
Note the **0.1 to 0.5 cm cysts** involving the inner medullary and papillary regions in this kidney. Note that the cortex appears normal. This is medullary sponge kidney (MSK), which is congenital, but most often occurs sporadically without a defined inheritance pattern. It is often bilateral, but incidental and found only on radiologic imaging studies, with an incidence of 0.5 to 1% in adults. MSK may become symptomatic in young adults, with onset of recurrent hematuria and/or urinary tract infection as a consequence of formation of calculi, which develop in 60% of cases. Renal failure is unlikely to occur, but may result from severe pyelonephritis.

Microscopic (histologic) description

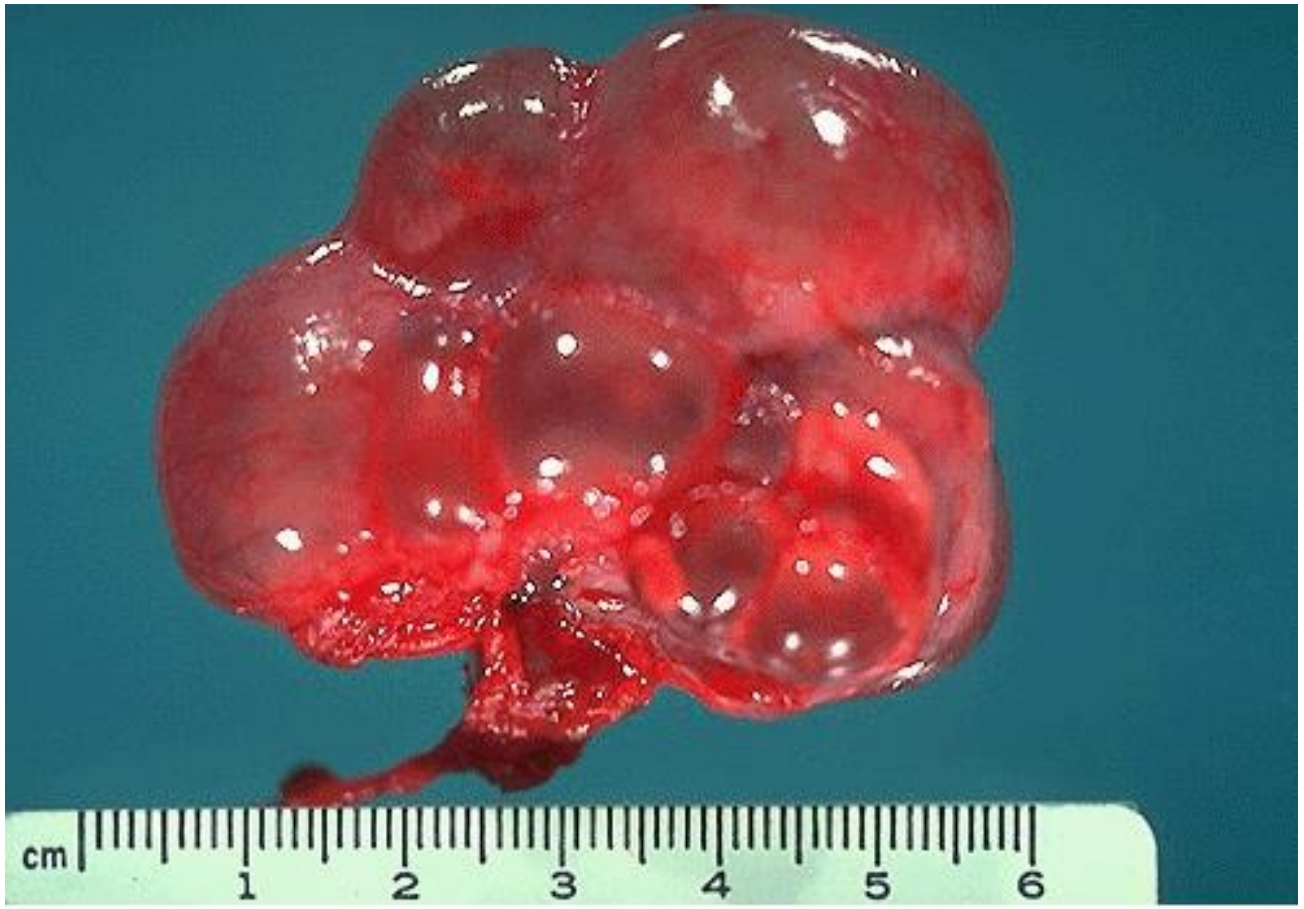
- Medullary cysts lined by cuboidal epithelium or urothelium
- May have concretions adherent to cyst wall
- Often severe inflammation and scarring in interstitium, often with tubular atrophy near papillary tips

Management

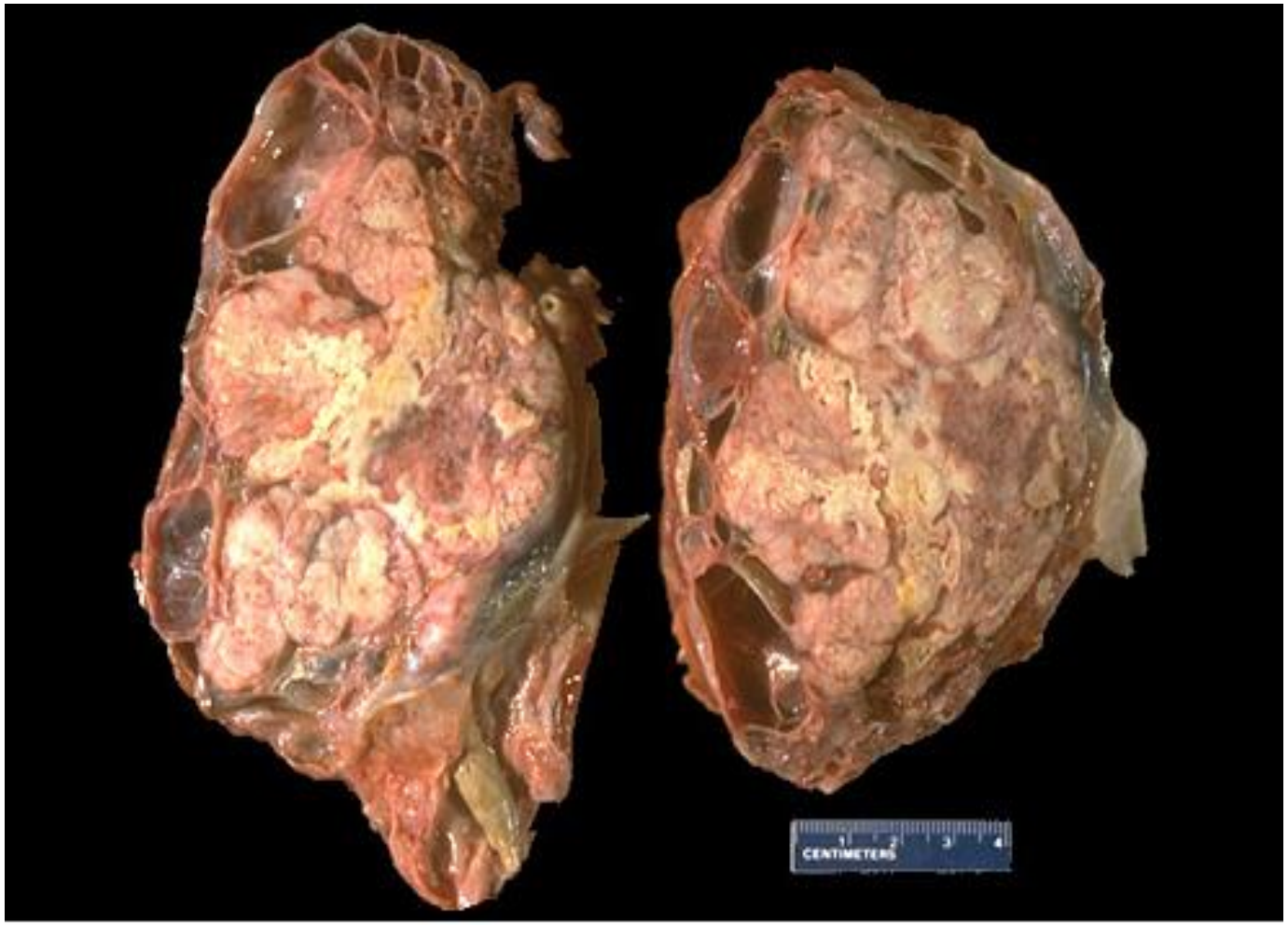
- Cranberry juice to maintain urinary acidity
- Nephrectomy is NOT recommended



Simple renal cysts, as seen here, have thin walls and are fluid filled. They can be multiple, but they are never as numerous as with polycystic change, and they do not predispose to chronic renal failure or to neoplasia. Such simple cysts become more common as persons become older.



This is a multicystic dysplastic kidney. This condition must be distinguished from ARPKD because it occurs only sporadically and not with a defined inheritance pattern, though it is more common than ARPKD. The cysts of multicystic renal dysplasia are larger and more variably sized than those of ARPKD. Often, multicystic renal dysplasia is unilateral. If bilateral, it is often asymmetric. If bilateral, oligohydramnios and its complications can ensue, just as with ARPKD.



Cystic change resulting from long-term renal dialysis may rarely give rise to renal cell carcinoma. A large irregular tan variegated **mass** is seen here on sectioning of a kidney that has large **cysts** arranged around the mass.