ARPKD: IN THE KIDNEY

Erum Aftab Hartung, MD, MTR
Assistant Professor of Pediatrics
Division of Nephrology, CHOP
Perelman School of Medicine at the University of Pennsylvania

ARPKD-CHF Conference: Empowering the Patient
Saturday November 3, 2018

Children's Hospital of Philadelphia℠

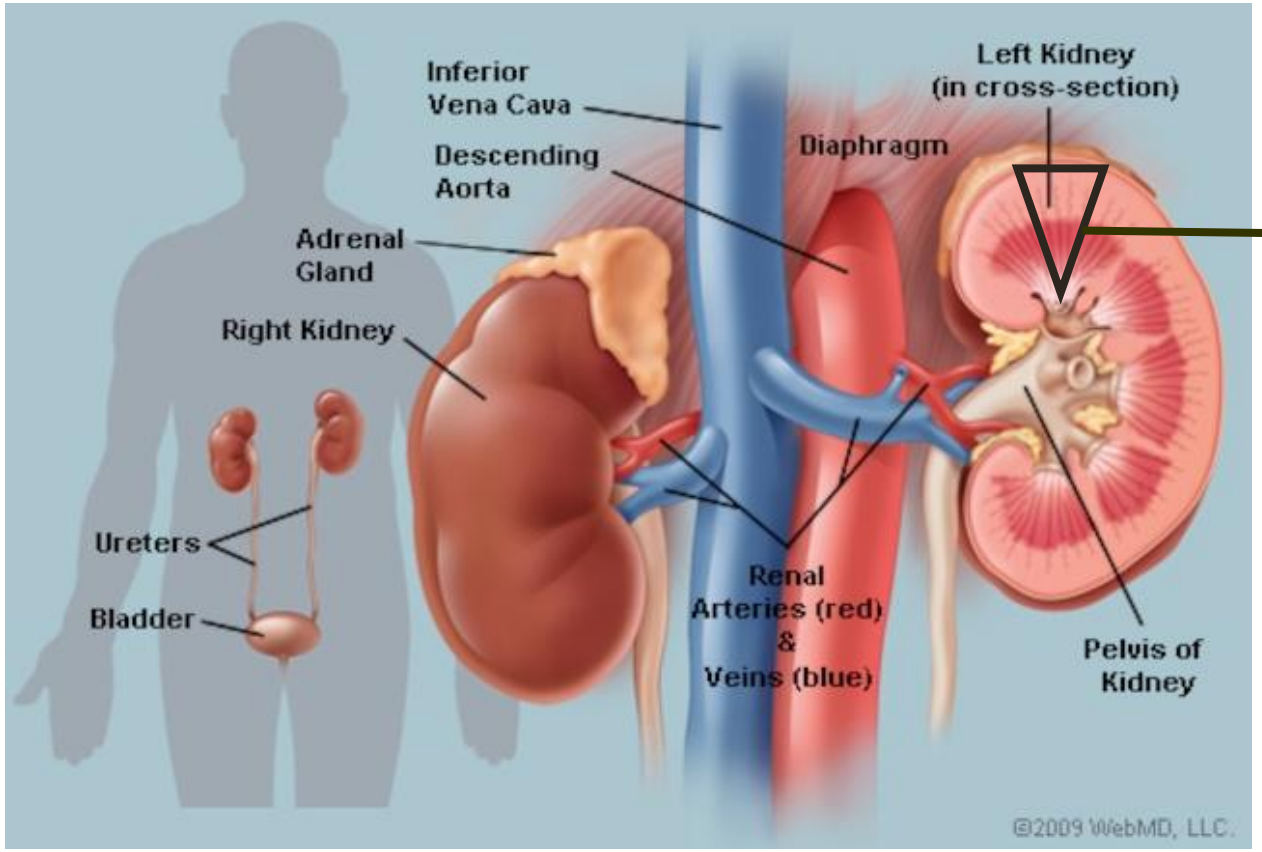
BACKGROUND & DISCLOSURES

- Attending Physician in CHOP Division of Nephrology
- Co-Director of Combined Kidney-Liver Program (with Dr. Jessica Wen)
- Member of Scientific Advisory Committee and PKD in Children Council of the PKD Foundation
- Research funding: NIH/NIDDK and Kadmon Corporation (clinical trial)

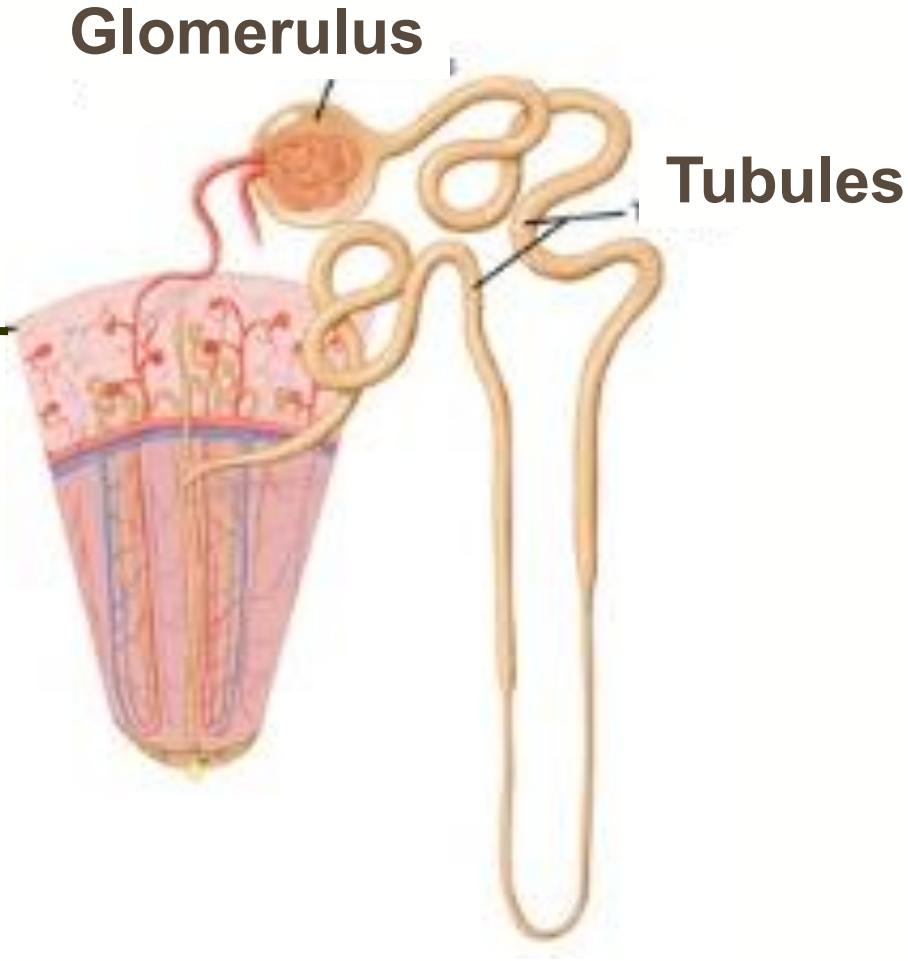
MY GOALS FOR TODAY

- To review:
  - what the kidneys do
  - how kidney cysts form and grow
  - differences and similarities between ARPKD and ADPKD
  - clinical features of ARPKD
  - long-term kidney outcomes in ARPKD

KIDNEYS 101



Nephron



https://www.webmd.com/kidney-stones/picture-of-the-kidneys#1
https://my.clevelandclinic.org/health/diseases/15096-kidney-disease-chronic-kidney-disease

WHAT DO THE KIDNEYS DO?

- Get rid of **waste products** from the body
- Control the body's **fluid balance**
- Regulate levels of the body's **electrolytes** (chemicals such as sodium, potassium, and bicarbonate)
- Regulate **blood pressure**
- Make a hormone called **erythropoietin ("EPO")** that tells the body to make red blood cells
- Activate **vitamin D**, which is important for bone health

WHAT IS CHRONIC KIDNEY DISEASE (CKD)?

- CKD means that the kidneys are not fully able to perform all their normal functions
- CKD can be caused by many different diseases, including ARPKD
- Kidney function is measured using **glomerular filtration rate (GFR)**
  - calculated based on blood creatinine (± cystatin C) levels
  - Can be thought of as “percent” kidney function (is actually measured in mL/min/1.73m^2)

CKD STAGES

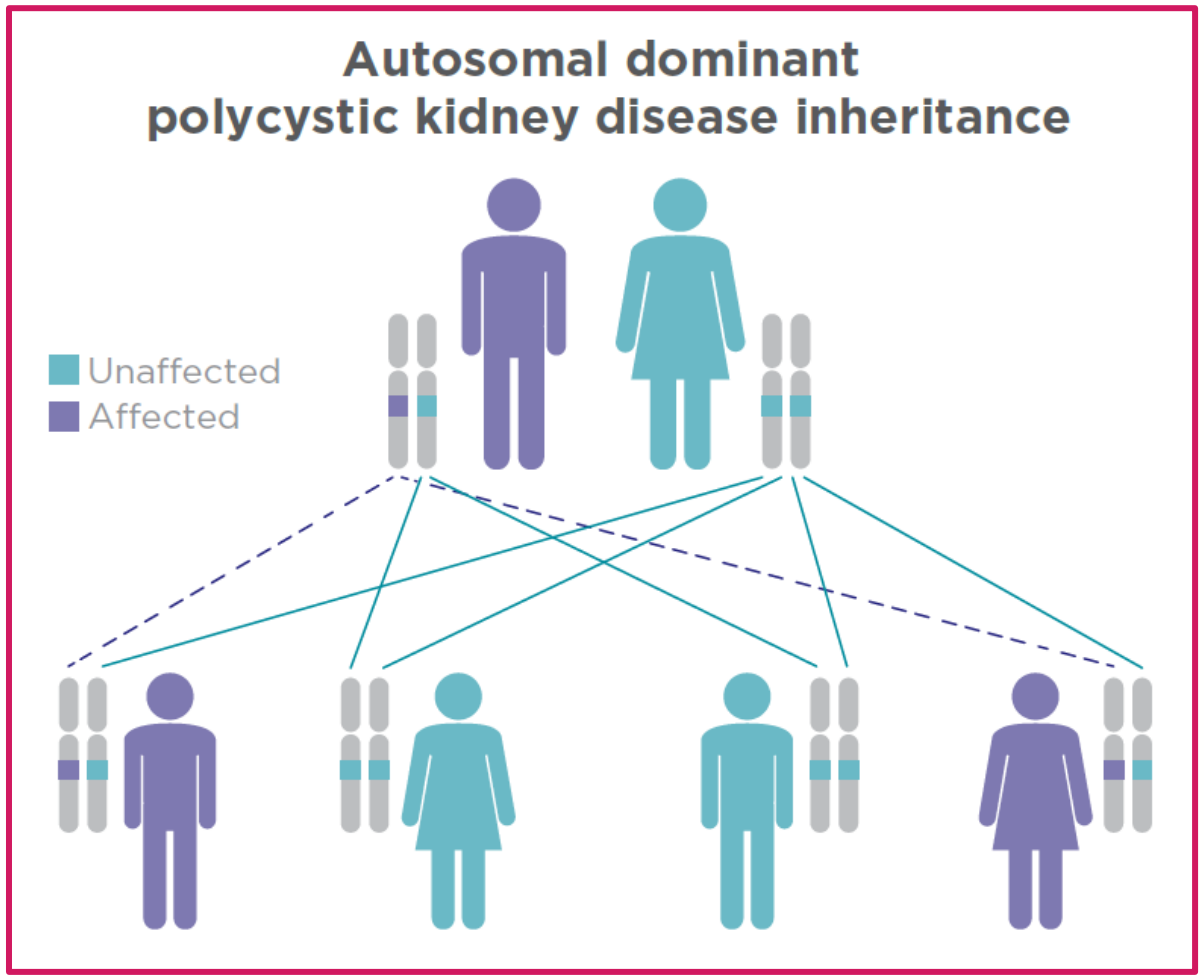
CKD Stage	Description	GFR
1	Mild, normal GFR	≥90
2	Mild	60-89
3	Moderate	30-59
4	Severe	15-29
5	Severe (end-stage kidney disease, ESRD/ESKD)	<15

WHAT IS A CYST?

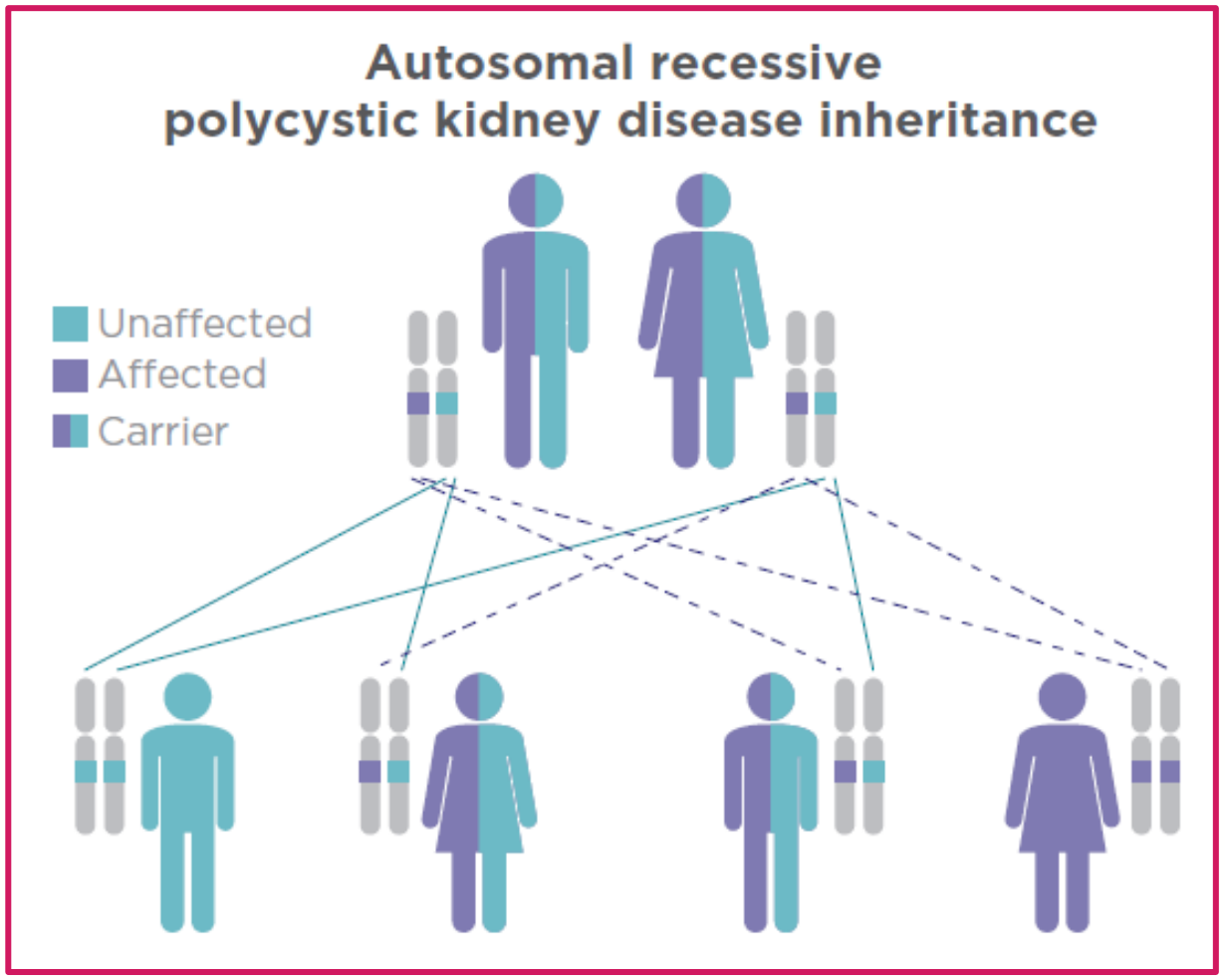
- A fluid-filled structure – like a water balloon
- Why do cysts form and grow?
  - The cells lining the “walls” of the cyst multiply and grow
  - More fluid fills the cysts

ADPKD VS. ARPKD

ADPKD VS. ARPKD: INHERITANCE



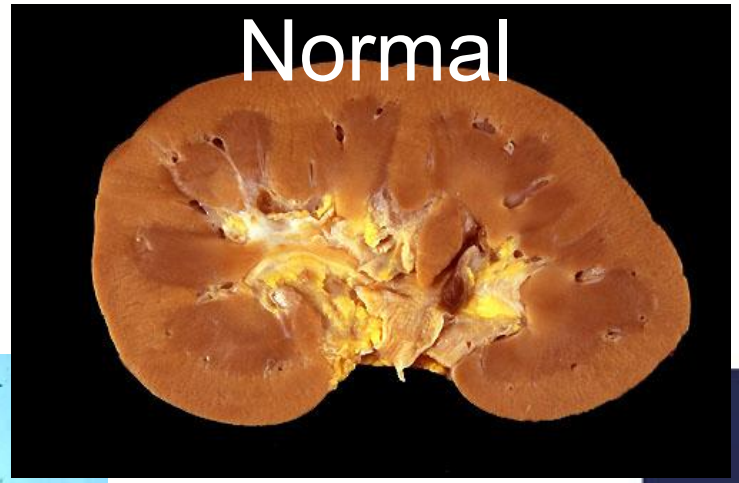
Genes: *PKD1* or *PKD2*



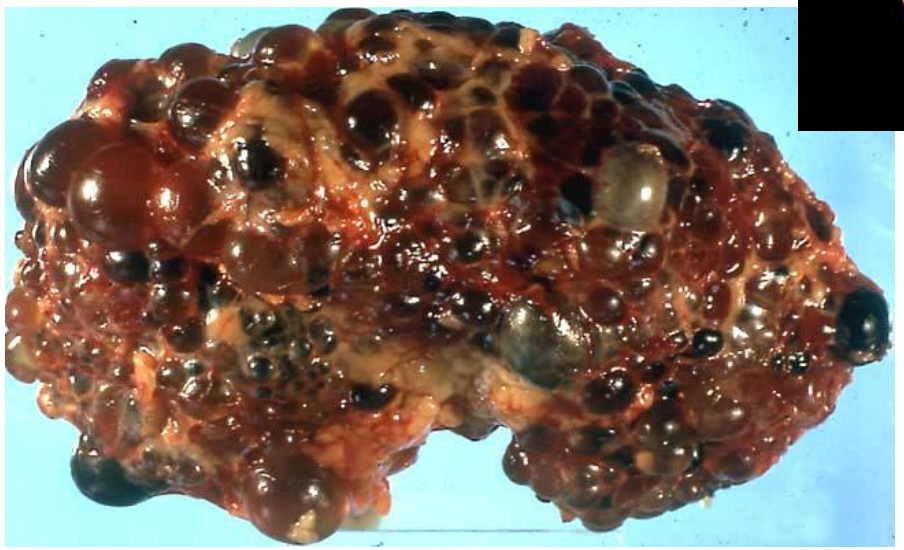
Gene: *PKHD1*

PKD Patient Handbook & ARPKD Patient Handbook; PKD Foundation, www.pkdcure.org

KIDNEY CYSTS: ADPKD VS. ARPKD

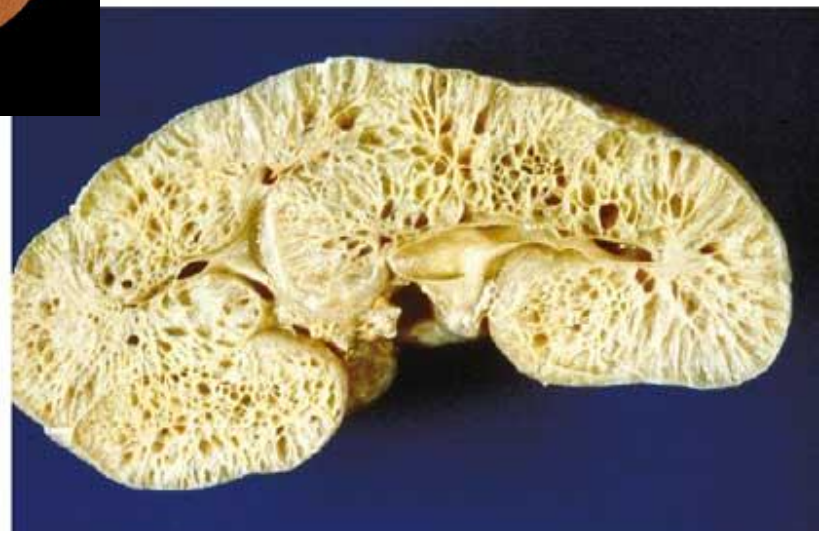


ADPKD



Larger bubble-like cysts throughout the kidney

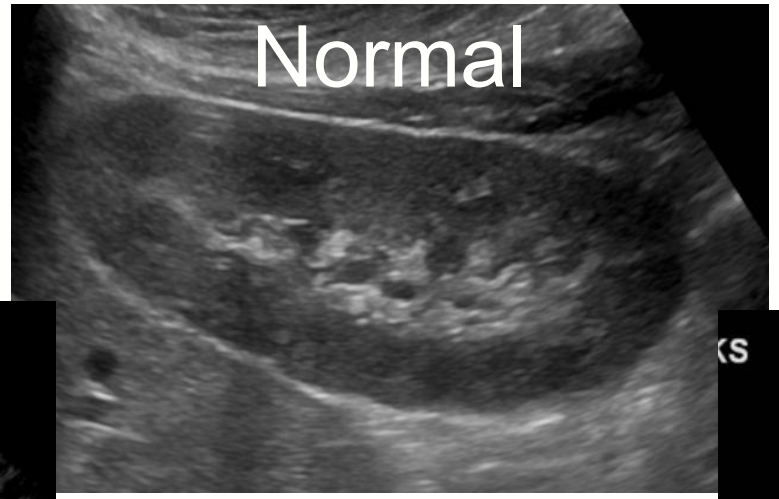
ARPKD



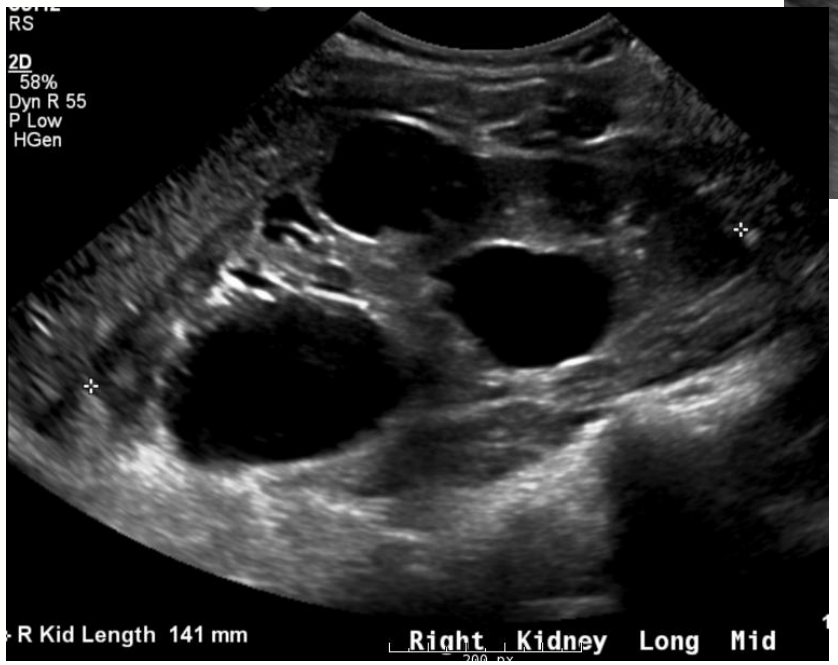
Tiny, tubular cysts, often more in the central part of the kidney (medulla)

ULTRASOUND: ADPKD VS. ARPKD

Normal

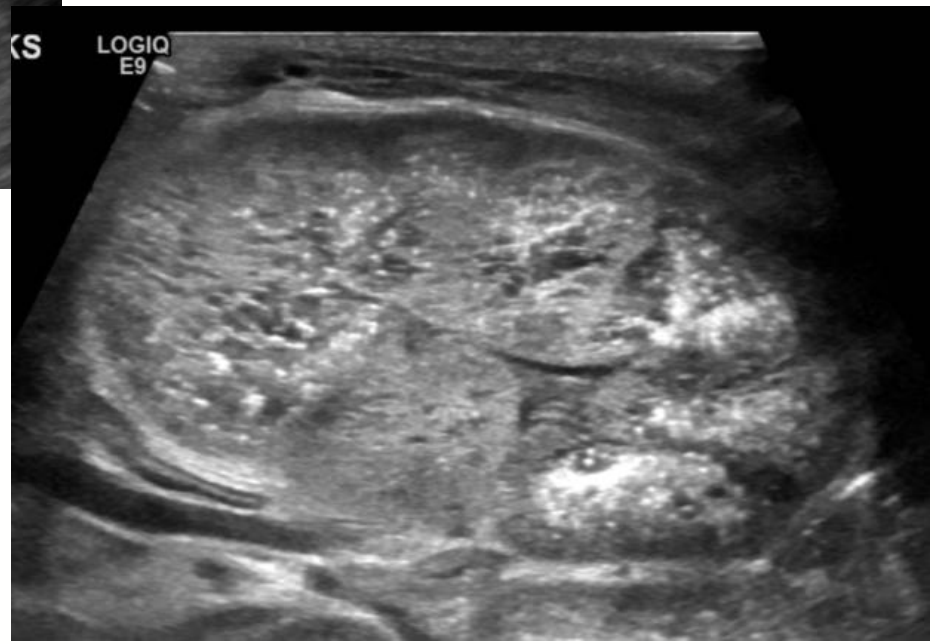


ADPKD



Larger bubble-like cysts, often in the cortex (outer part)

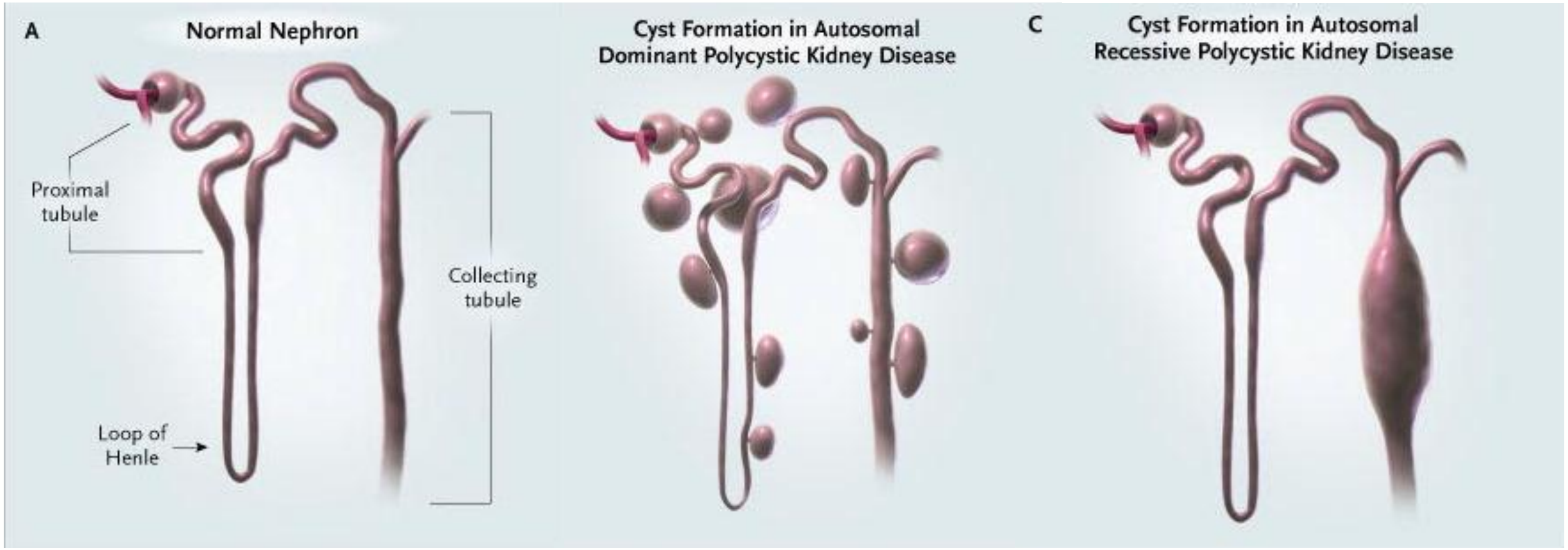
ARPKD



Few or no visible cysts, kidneys “echogenic” = bright

HOW DO KIDNEY CYSTS FORM?

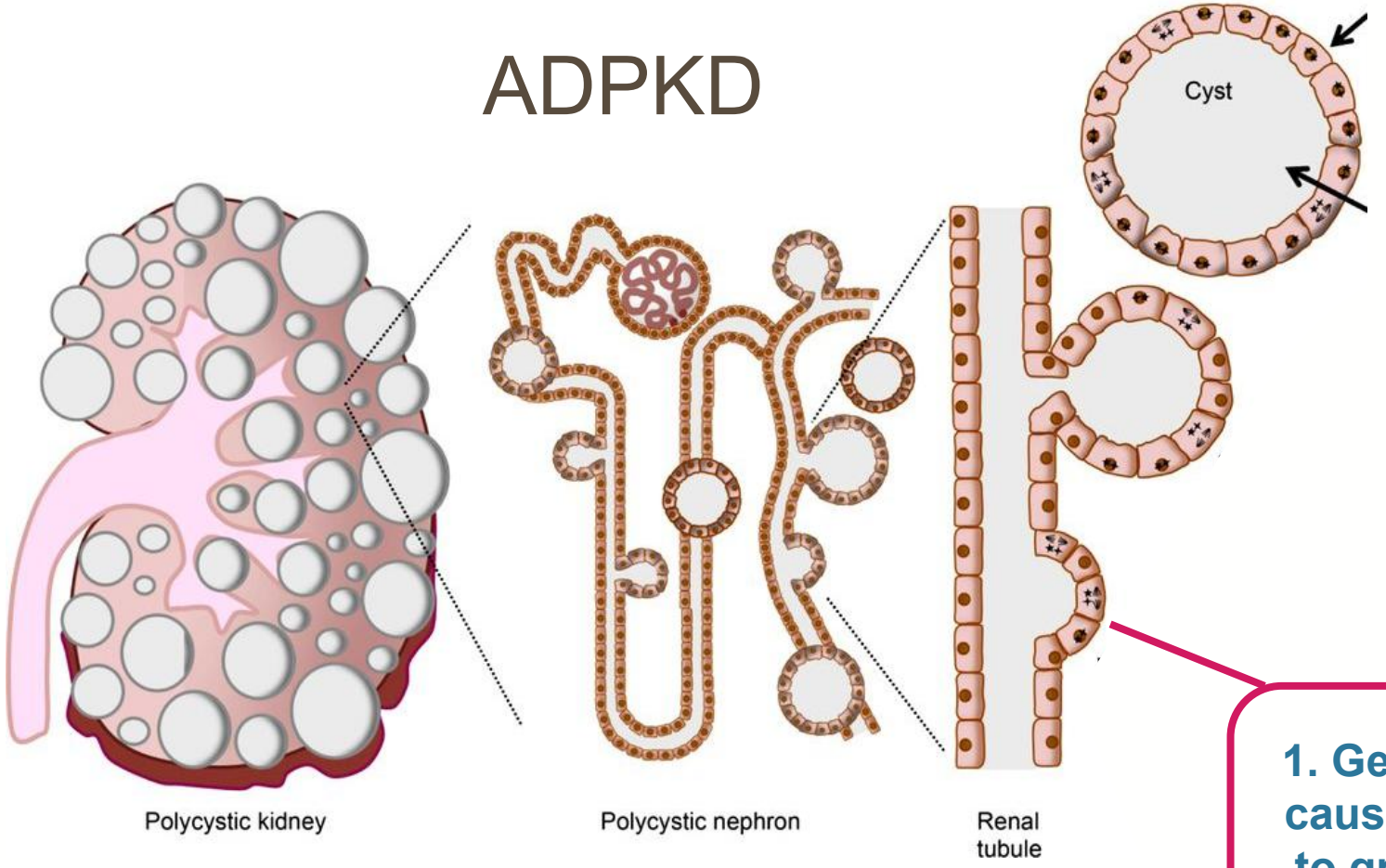
Normal ADPKD ARPKD



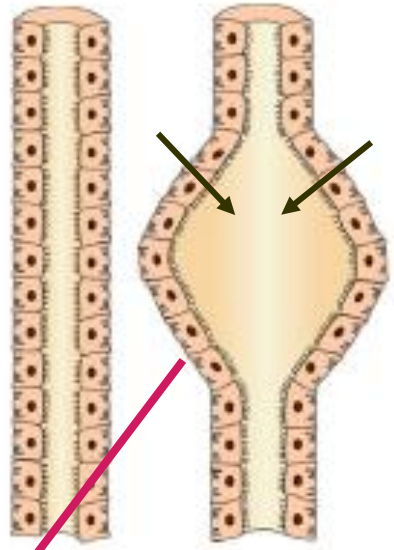
Wilson PD. N Engl J Med 2004;350:151-164.

HOW DO CYSTS FORM AND GROW?

ADPKD



ARPKD



2. Excess fluid secreted into cysts and tubule cells keep multiplying

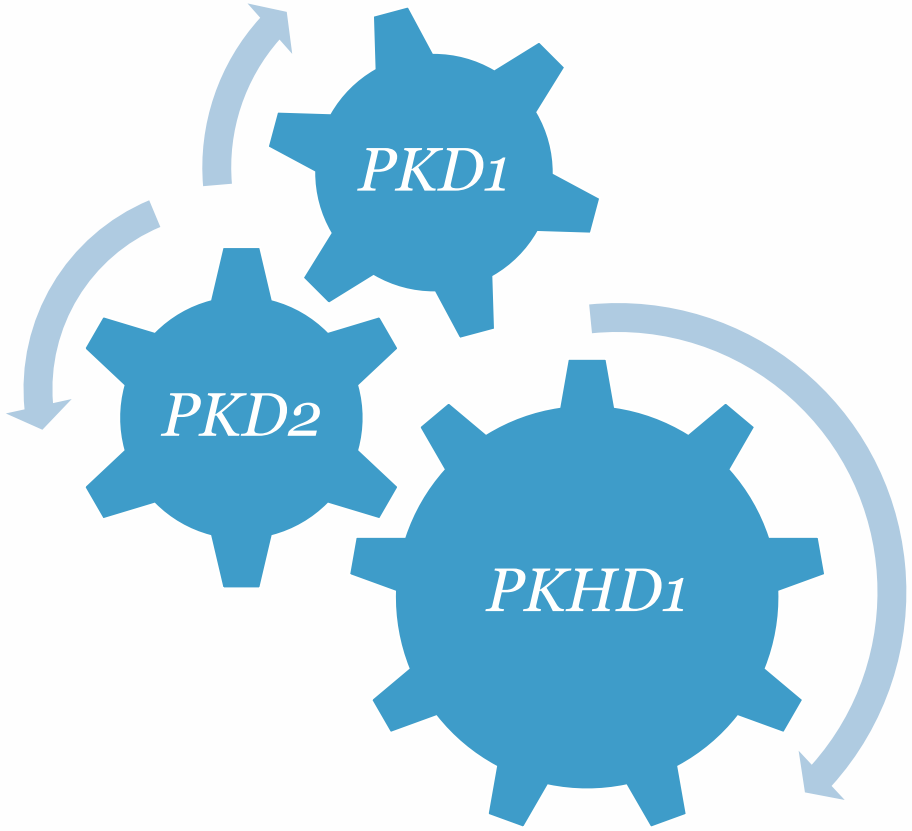
(influenced by vasopressin, cAMP, EGF, Src)

1. Genetic mutation causes tubule cells to grow & multiply abnormally

Blanco G & Wallace DP. Am J Physiol 2013; Staruschenko A. Compr Physiol 2012

ADPKD VS. ARPKD

- Even though ADPKD and ARPKD are different diseases caused by different genes, similar mechanisms cause cysts in both diseases
- Research in ADPKD and ARPKD often goes hand-in-hand, and discoveries in one disease help us learn about the other



ADPKD vs. ARPKD

	ADPKD	ARPKD
Gene(s)	*PKD1* (85%), *PKD2* (15%)	*PKHD1*
Incidence	~1 in 1000 people	~1 in 20,000 people
Cyst type	Large, bubble-like cysts	Small tubular cysts
Imaging (US)	Large kidneys with visible round cysts	Large, echogenic (bright) kidneys, no/few visible cysts
Age at ESRD	Late adulthood (50s-70s)	Childhood - young adulthood
Associated problems	Liver cysts, brain aneurysms	Congenital hepatic (liver) fibrosis, portal hypertension

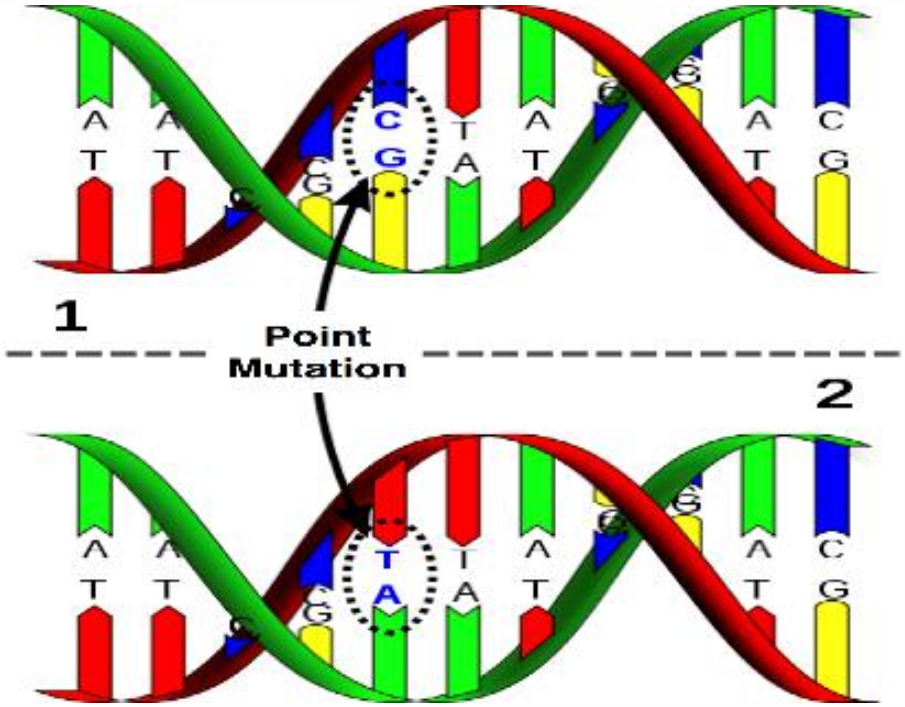
ARPKD: CLINICAL FEATURES

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPKD)

- Previously called infantile polycystic kidney disease
- Incidence ~1 in 10,000-40,000 births
- Carrier rate ~1 in 70-100 people

GENETICS OF ARPKD

- *PKHD1* gene, which makes a protein called fibrocystin/polyductin
- There are many different mutations described, so most families have “private mutations”



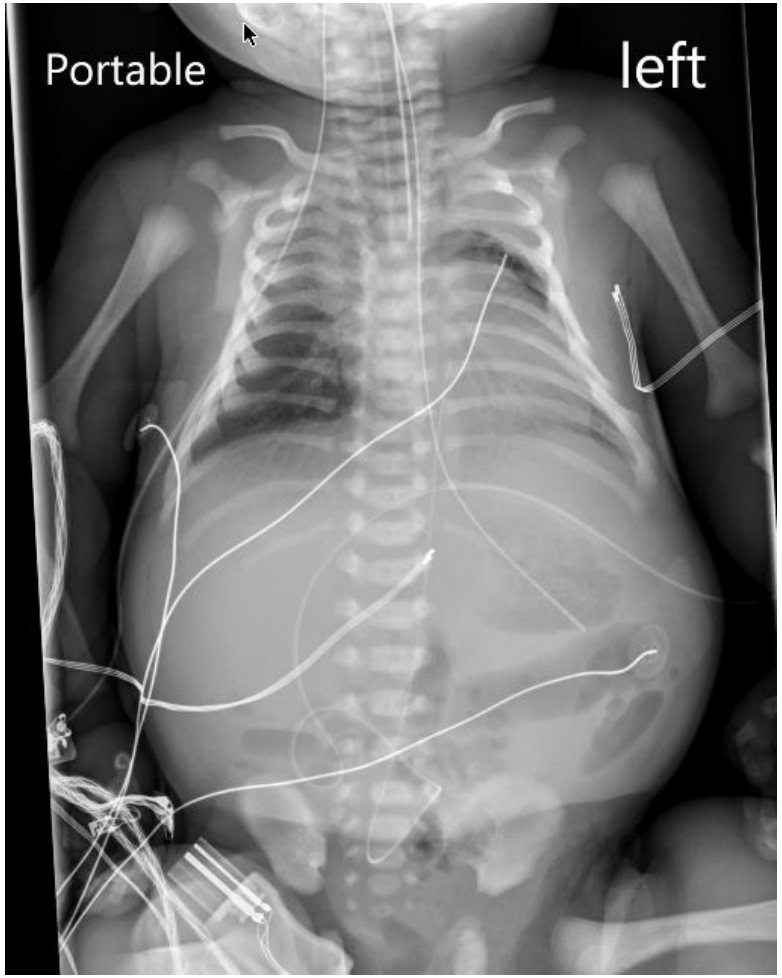
ARPKD: CLINICAL FEATURES

- Highly variable presentation:
  - ~1/3 of patients
    - “classic” neonatal (newborn) presentation:
      - low amniotic fluid (oligohydramnios)
      - very enlarged kidneys
      - underdeveloped lungs (pulmonary hypoplasia)
      - even with modern medical care, unfortunately ~30% of babies die
  - ~2/3 of patients
    - present in later childhood / adulthood, sometimes with liver-predominant disease

Adeva M. et al. Medicine 2006[20]

NEWBORNS WITH ARPKD

- **Breathing (respiratory) problems:**
  - main cause of illness and death
  - underdeveloped lungs (due to low amniotic fluid) + very enlarged kidneys making it difficult to expand lungs properly
  - ~40% of babies require ventilator[1]
  - pneumothorax (collapsed lung) relatively common
- **Feeding difficulties** due to massively enlarged kidneys
  - often require NG or G-tube feeding



[1]Guay-Woodford LM & Desmond RA, Pediatrics 2003

NEWBORNS WITH ARPKD

- **Surgery to remove kidney(s) (nephrectomy)**
  - Sometimes surgical removal of one or both kidneys is done to try to improve breathing and feeding (to make more room in the abdomen)
  - Best approach is unclear
  - Significant surgical risks + earlier need for dialysis need to be balanced with any possible benefits

Hartung EA & Guay-Woodford LM, Pediatrics 2014

ARPKD: OTHER CLINICAL FEATURES

- **Hypertension (high blood pressure)**
  - to be discussed by Dr. Meyers
- **Congenital hepatic fibrosis & portal hypertension**
  - to be discussed by Drs. Wehrman, Loomes, and Wen
- **Growth problems**
  - well-known complication in children with CKD from any cause
  - observed in ~30% of children in North American ARPKD study[1]
  - some early studies suggested that children with ARPKD have growth problems out of proportion to CKD severity
  - In CKiD cohort study, growth impairment was similar in children with ARPKD compared to those with other congenital causes of CKD[2]

[1]Guay-Woodford LM. Pediatrics 2003; [2]Hartung EA. Front Pediatr 2016

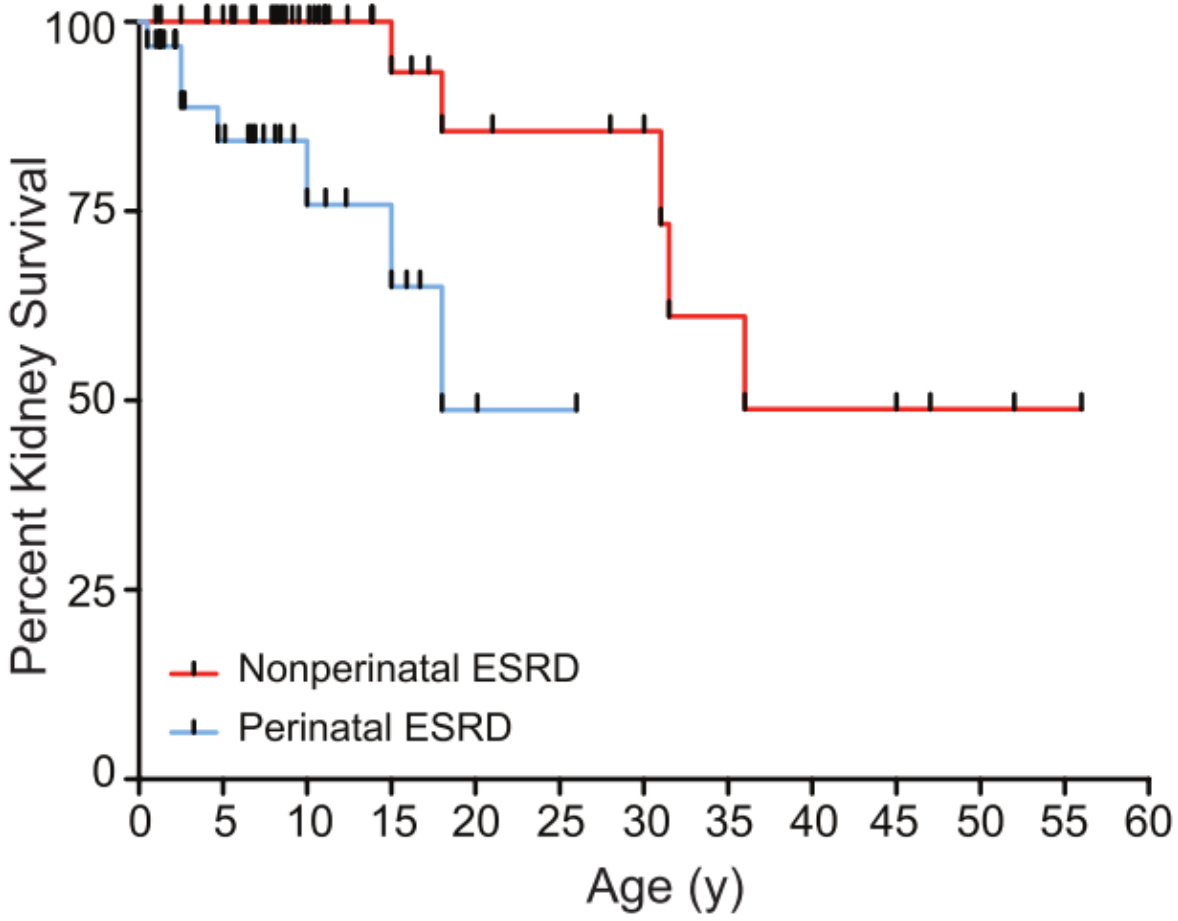
ARPKD: OTHER CLINICAL FEATURES

- **Learning difficulties**
  - Children with CKD from any cause are at risk for learning problems
  - In CKiD cohort study, neurocognitive abilities in children with ARPKD were similar to those with other congenital causes of CKD[1] (scores slightly below average compared to healthy children)

[1] Hartung EA, Pediatr Nephrol 2014

ARPKD: KIDNEY OUTCOMES

- **Chronic kidney disease**: age at progression to end stage kidney disease (ESKD) depends on age at presentation. In NIH cohort (n=73)[1]:
  - Neonatal presenters: 25% ESKD by age 11 years
  - Later presenters: 25% ESKD by age 32 years



[1]Gunay-Aygun M. et al, CJASN 2010

ARPKD: END STAGE KIDNEY DISEASE

- **Dialysis:** replaces some functions of the kidneys after they fail (removing waste products and extra water, balancing electrolytes)
  - **Peritoneal dialysis**
    - Catheter surgically placed in abdomen
    - Fluid is put in and drained out for multiple cycles nightly using a PD cycler machine at home
    - Native kidneys may need to be removed to allow PD
  - **Hemodialysis (blood dialysis)**
    - Catheter or fistula surgically placed in large vein
    - Child comes to dialysis center at hospital/clinic 3-4 times per week for ~4 hours
- **Kidney Transplant**
  - Will be discussed in detail by Dr. Meyers

ARPKD Patient Handbook; PKD Foundation, www.pkdcure.org

ARPKD: OTHER KIDNEY MANIFESTATIONS

- **Acidosis:** low serum bicarbonate or CO_2 levels due to inability to get rid of acid in the urine
  - may need bicarbonate or citrate supplements
- **Low sodium levels (hyponatremia)** in newborn period; ~25% of patients[1]
  - ? due to inability to properly dilute urine (not excess sodium loss)
  - Fluid restriction (e.g. concentrating feeds) or furosemide usually preferred over sodium supplementation (can worsen HTN)

[1]Guay-Woodford LM. Pediatrics 2003

ARPKD: OTHER KIDNEY MANIFESTATIONS

- **Urine concentrating defect**: may make larger amounts of urine than normal
  - may cause bedwetting
  - risk for dehydration
- **Risk of urinary tract infections (UTI)**
  - **UTIs** reported in 20-50% of patients[1]
  - May be due to poor urine flow in cystic tubules

[1]Hartung EA & Guay-Woodford LM. *Pediatrics* 2014

KEY TAKE-HOME POINTS

- ADPKD and ARPKD are different diseases, but mechanisms causing cyst growth are similar - research in one disease may benefit the other
- The clinical features and kidney outcomes of ARPKD can be highly variable, and depend on the age at presentation

QUESTIONS?

ADDITIONAL READING

- Hartung EA, Guay-Woodford LM. Autosomal Recessive Polycystic Kidney Disease: A Hepatorenal Fibrocystic Disorder With Pleiotropic Effects. *Pediatrics*. 2014;134(3):e833-845
- Guay-Woodford LM, Bissler JJ, Braun MC, et al. Consensus Expert Recommendations for the Diagnosis and Management of Autosomal Recessive Polycystic Kidney Disease: Report of an International Conference. *J Pediatr*. July 2014