ARPKD: KIDNEY ISSUES & RESEARCH OVERVIEW

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ARPKD-CHF Web Conference

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Children's Hospital of Philadelphia℠

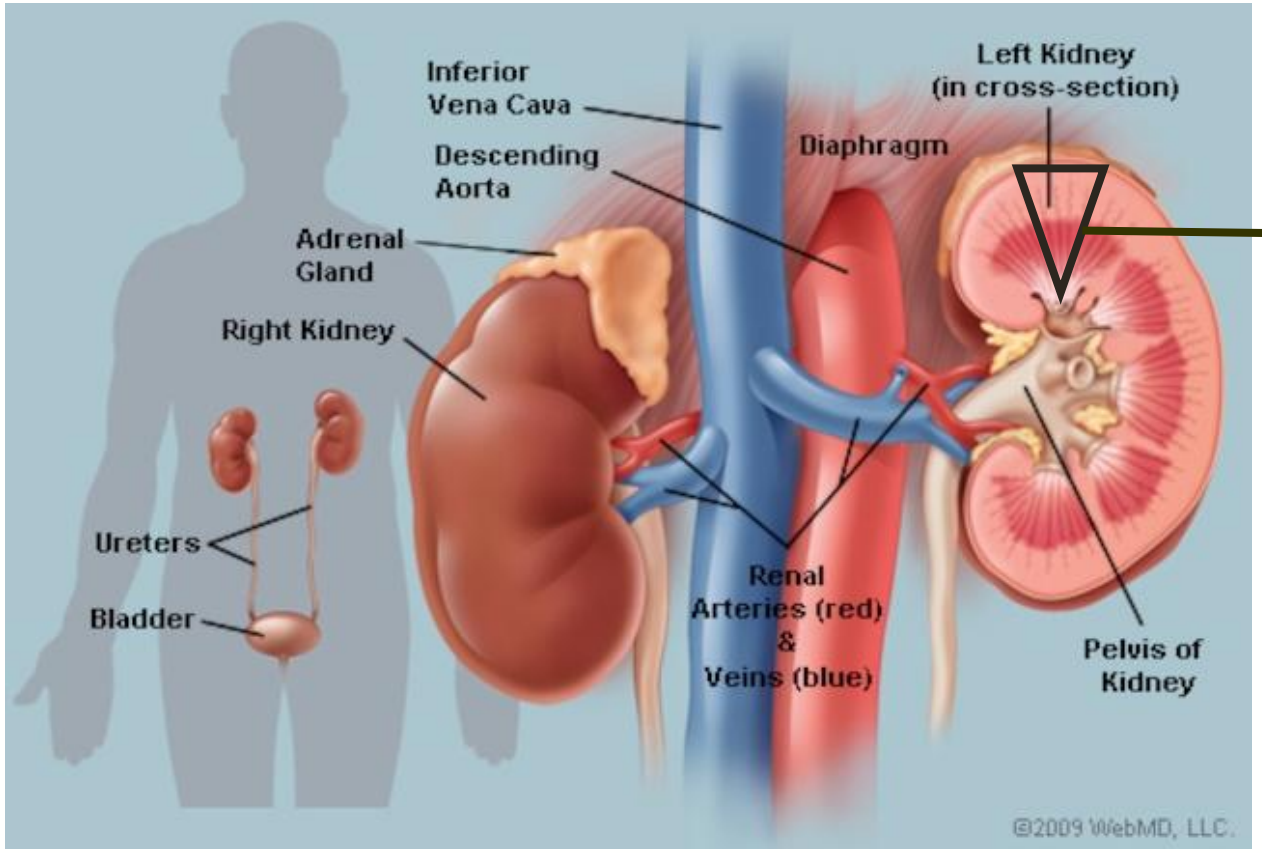
BACKGROUND & DISCLOSURES

- 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, Penn, and CHOP

MY GOALS FOR TODAY

- To review kidney-related issues in ARPKD:
  - 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
- To briefly summarize ARPKD research efforts at CHOP

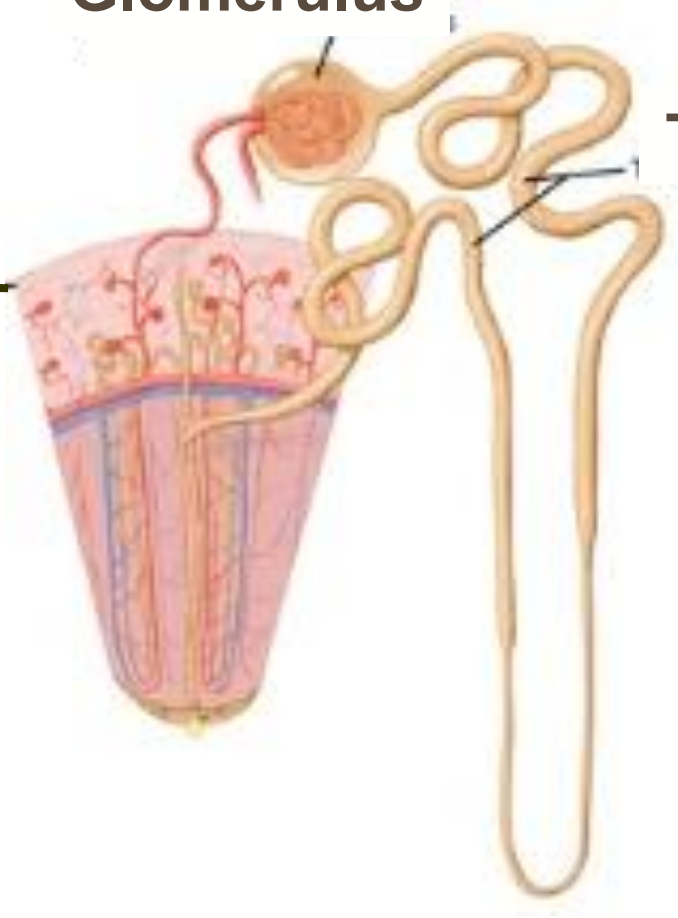
KIDNEYS 101



Nephron

Glomerulus

Tubules

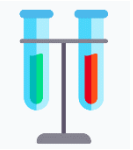


https://www.webmd.com/kidney-stones/picture-of-the-kidneys#1
https://my.clevelandclinic.org/health/diseases/15096-kidney-disease-chronic-kidney-disease

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

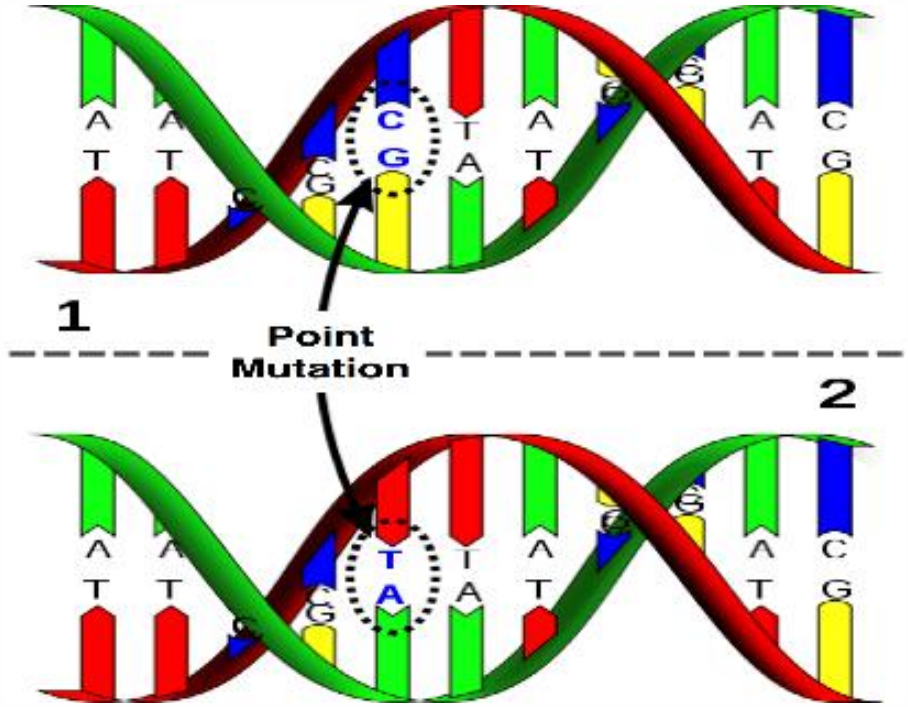
CKD Stage	Description	GFR
1	Mild, normal GFR	≥90
2	Mild	60-89
3	Moderate	30-59
4	Severe	15-29
5	Severe (kidney failure/end-stage kidney disease, ESKD)	<15

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

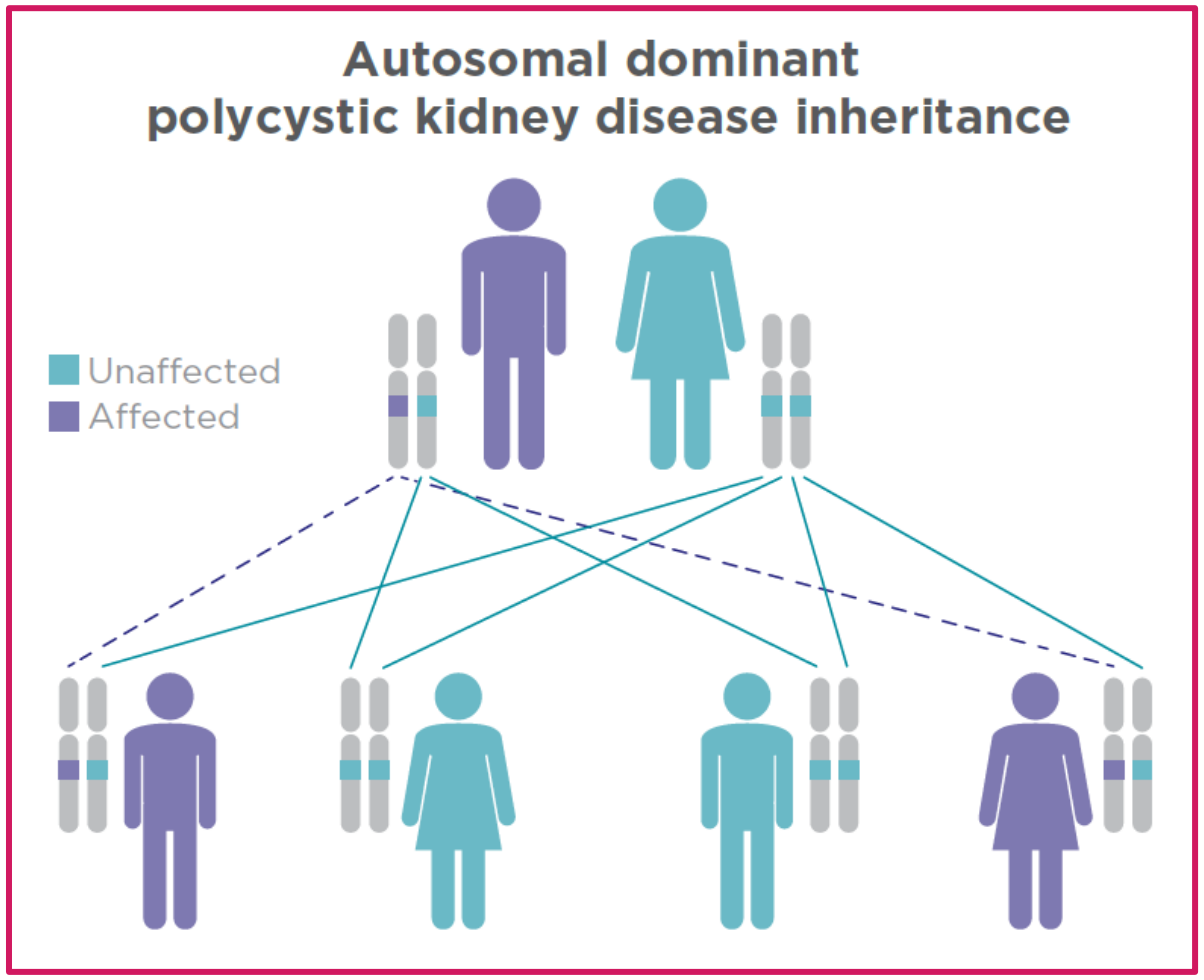
- Caused by mutations (variations) in the ***PKHD1*** gene, which makes a protein called fibrocystin/polyductin
- There are many different mutations described, so most families have “private mutations”



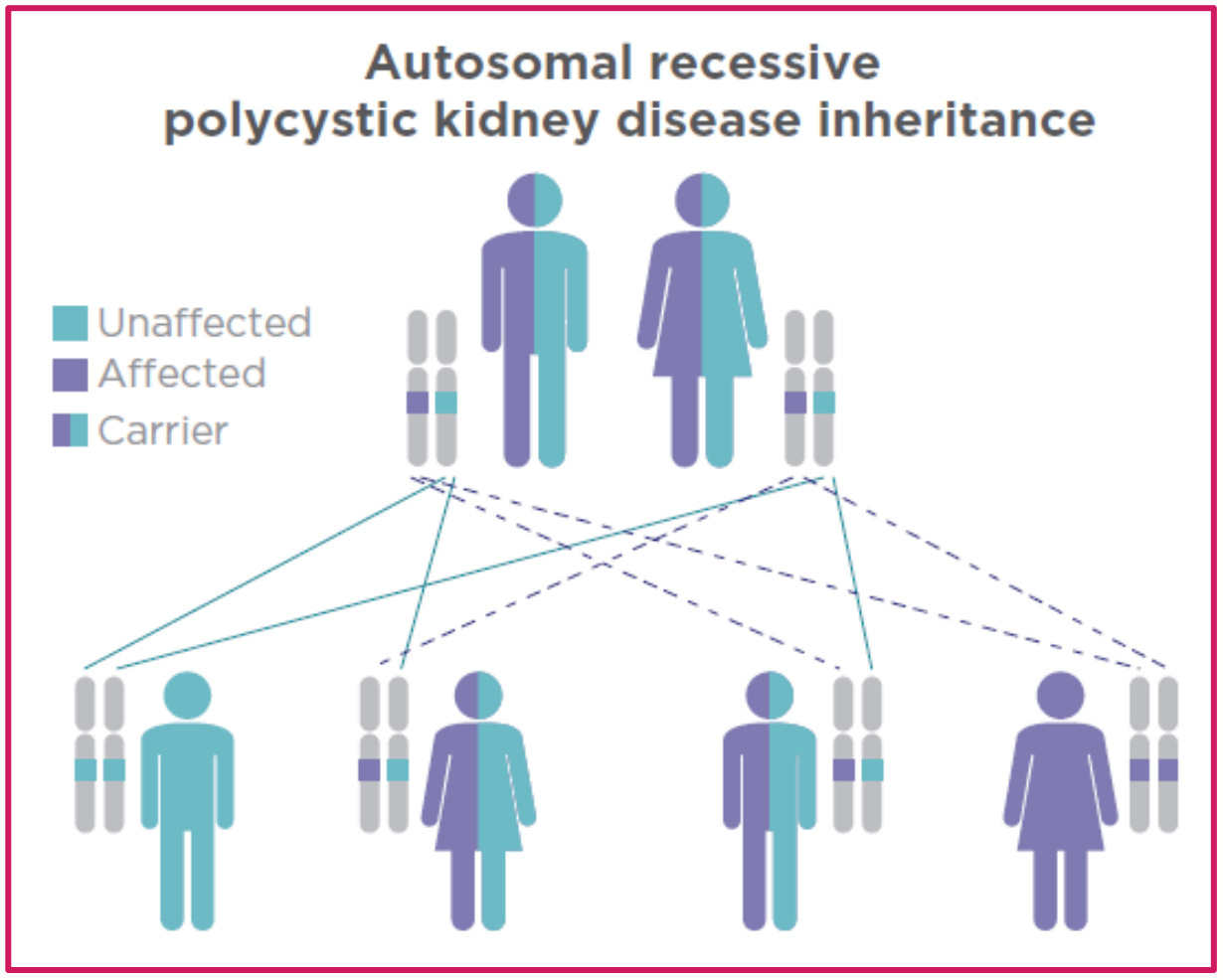
ADPKD (AUTOSOMAL DOMINANT PKD)
VS.
ARPKD (AUTOSOMAL RECESSIVE PKD)

10

ADPKD VS. ARPKD: INHERITANCE



Genes: *PKD1* or *PKD2*



Gene: *PKHD1*

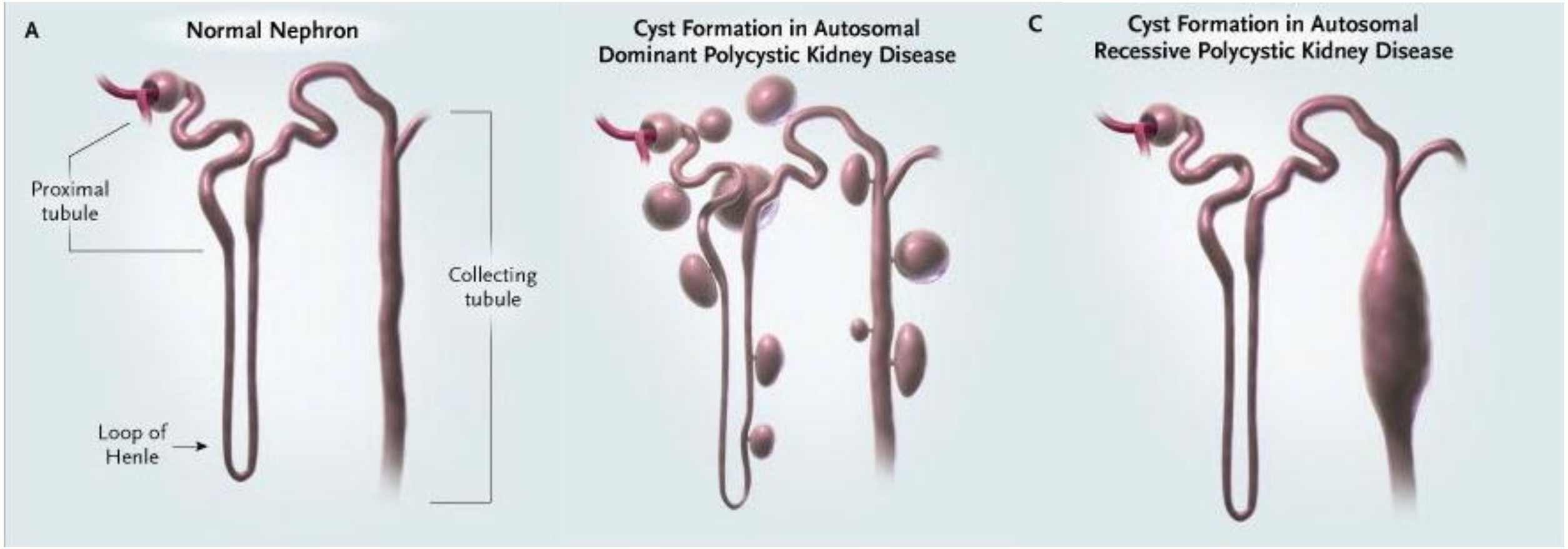
PKD Patient Handbook & ARPKD Patient Handbook; PKD Foundation, www.pkdcure.org

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

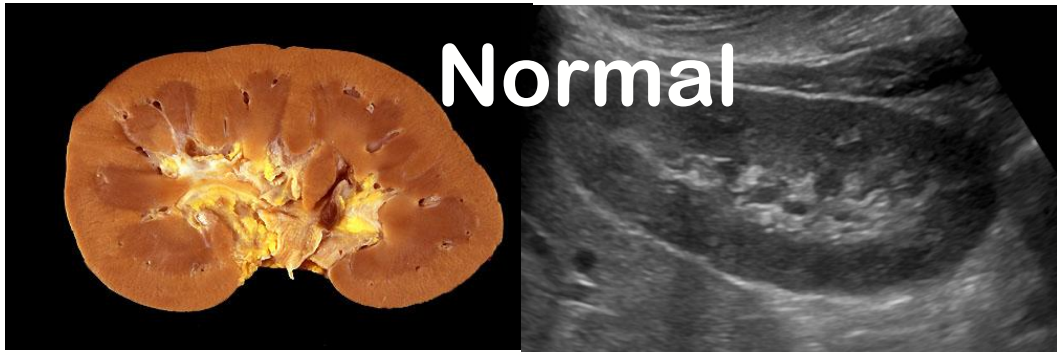
HOW DO KIDNEY CYSTS FORM?

Normal ADPKD ARPKD

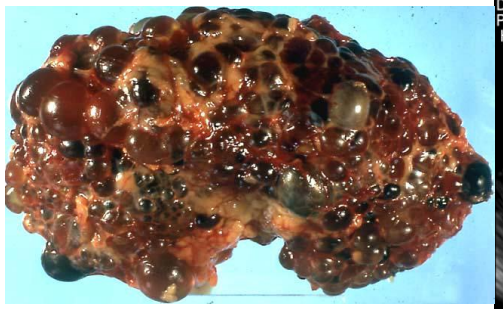


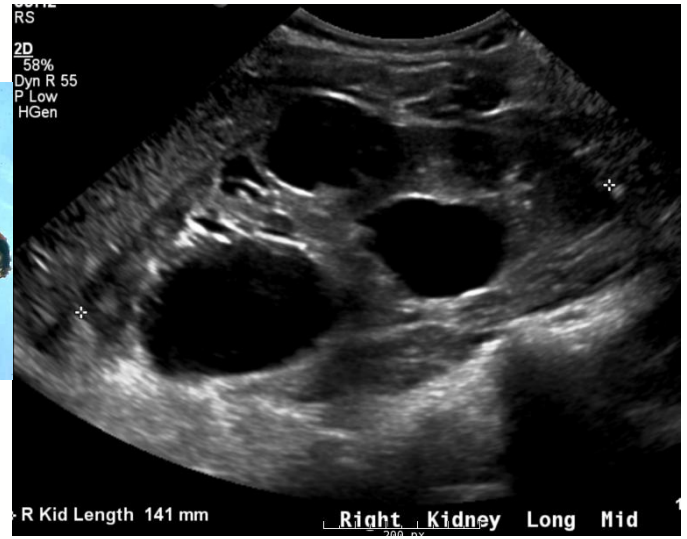
Wilson PD. N Engl J Med 2004;350:151-164.

KIDNEY CYSTS: ADPKD VS. ARPKD



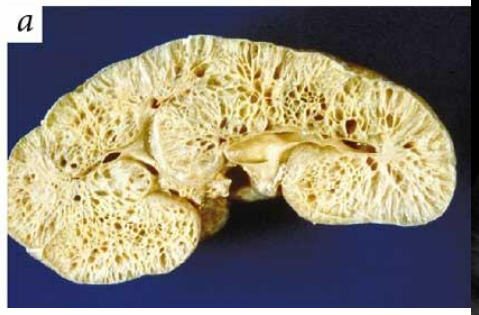
ADPKD

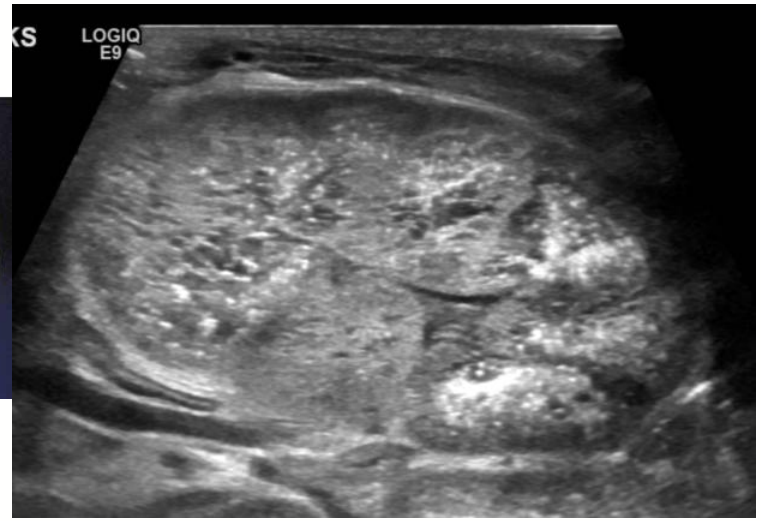




Larger bubble-like cysts, often in outer part (cortex) of kidney

ARPKD

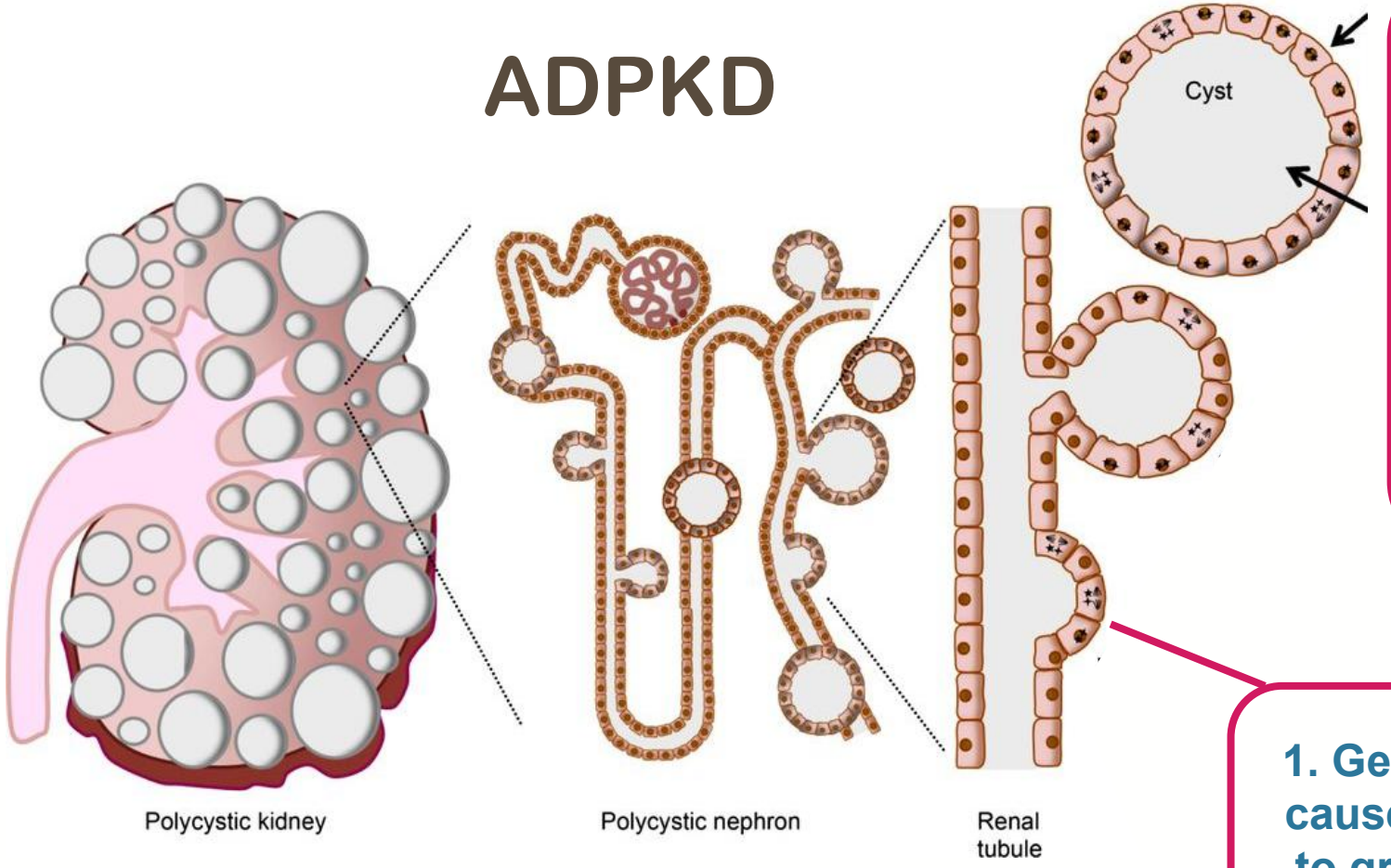




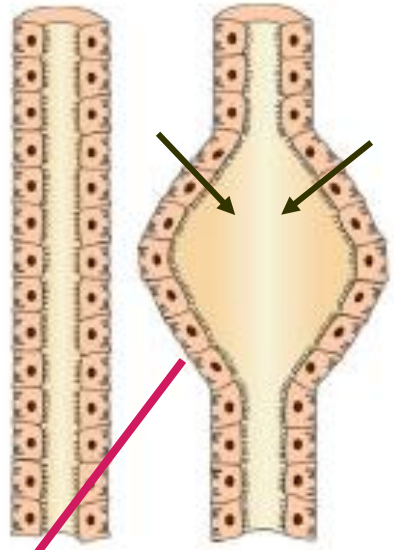
Tiny, tubular cysts, often more in the central part of the kidney (medulla). On US, few or no visible cysts, kidneys “echogenic” = bright

HOW DO CYSTS FORM AND GROW?

ADPKD



ARPKD



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

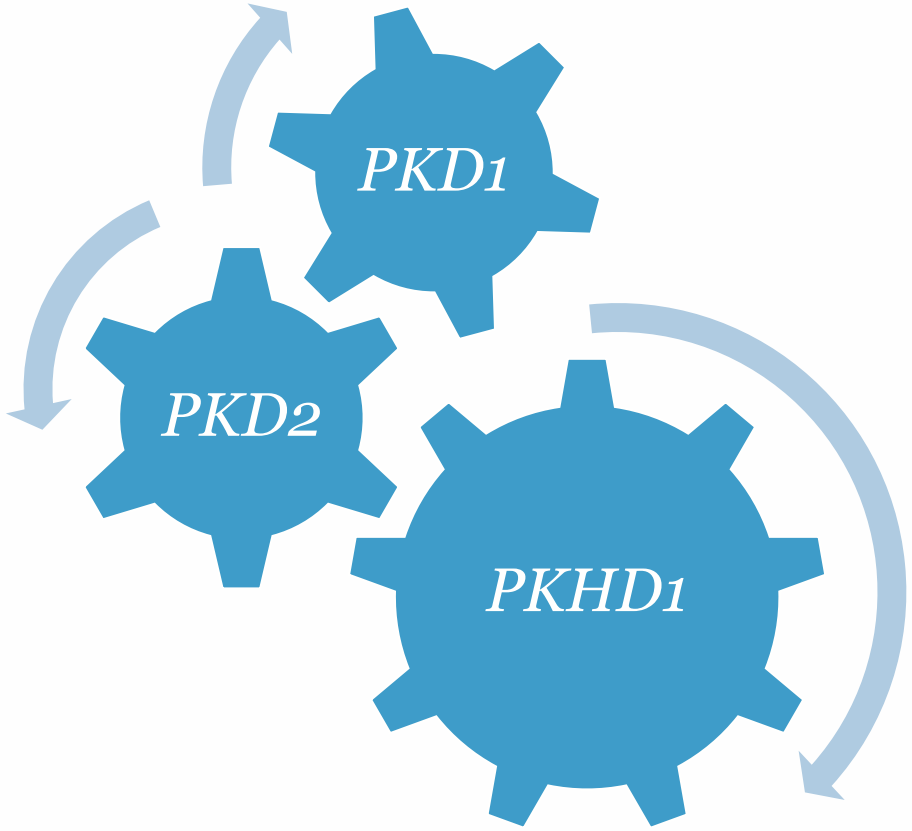
(influenced by vasopressin, cAMP, EGF, Src)

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

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

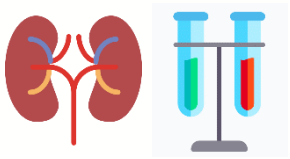
ADPKD VS. ARPKD

- 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



LIVING WITH ARPKD

Infancy & childhood



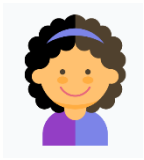
Kidney function and electrolytes

Blood pressure

Cardiovascular issues

Anemia

Bone health



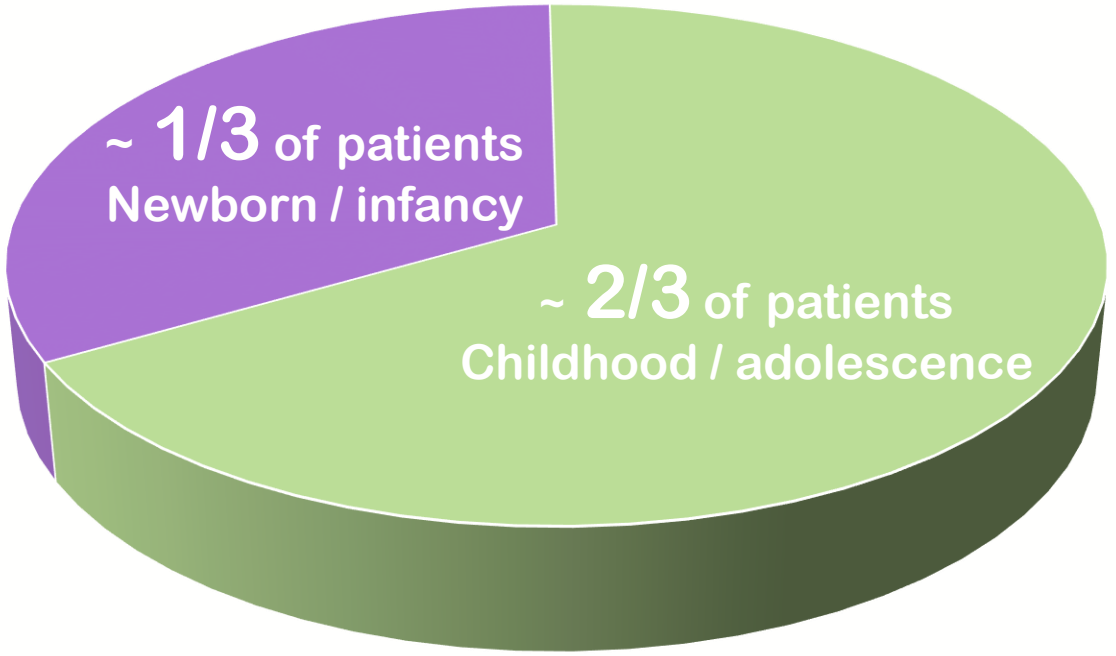
Growth and development

Infections

ARPKD: VARIABILITY

"Classic" newborn presentation

- low amniotic fluid (oligohydramnios)
- very enlarged kidneys
- underdeveloped lungs (pulmonary hypoplasia)
- even with modern medical care, unfortunately ~30% of babies die

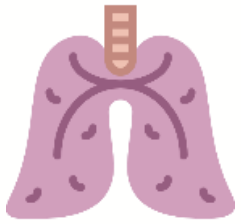


Later childhood or adolescent presentation

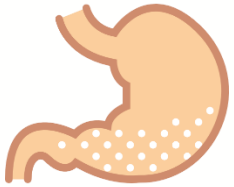
- generally milder disease progression
- May have liver-predominant disease

Adeva M. et al. Medicine 2006

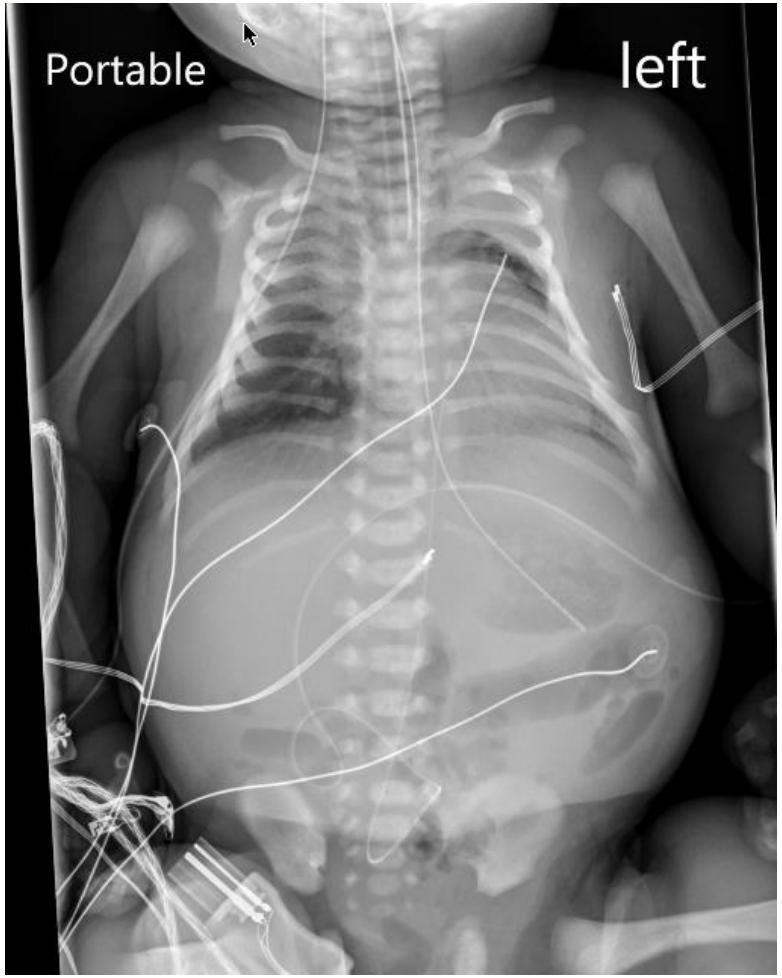
ARPKD: INFANCY



- **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

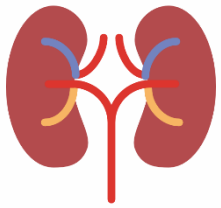


- **Feeding difficulties** due to massively enlarged kidneys
  - often require NG or G-tube feeding



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

ARPKD: INFANCY

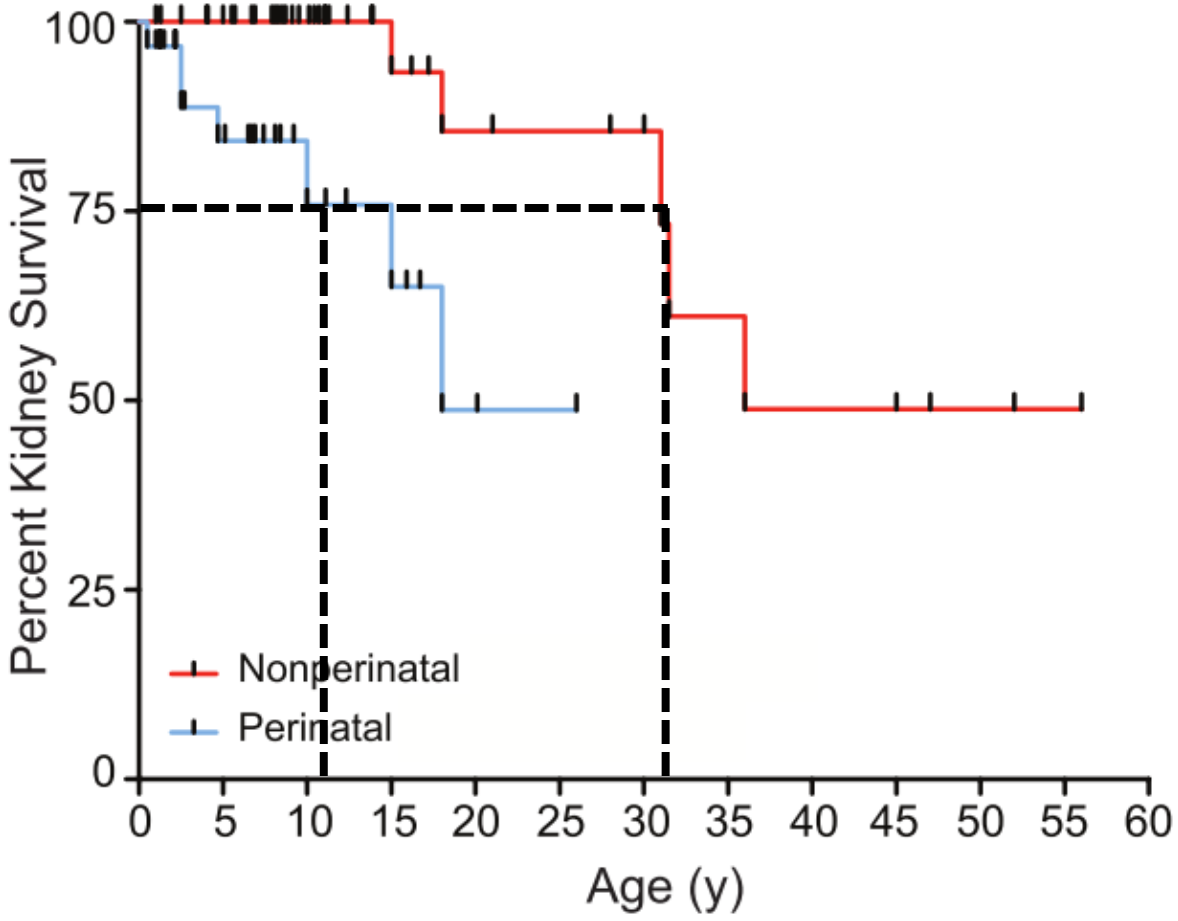


- **Surgery to remove kidney(s) (nephrectomy)**
  - Sometimes surgical removal of one or both kidneys is done to try to improve breathing and feeding (to make more room in the abdomen)
  - Best approach is unclear
  - Significant surgical risks + earlier need for dialysis need to be balanced with any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

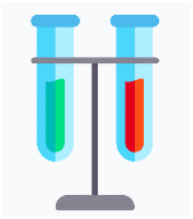
Hartung EA & Guay-Woodford LM, Pediatrics 2014

ARPKD: KIDNEY FUNCTION

- **Chronic kidney disease**: age when kidney failure develops depends on age when symptoms develop.
- In NIH study (73 patients)[1]:
  - "Perinatal" presenters (symptoms at <30 days old): 75% kidney survival at age 11 years
  - "Nonperinatal" presenters: 75% kidney survival at age 32 years



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

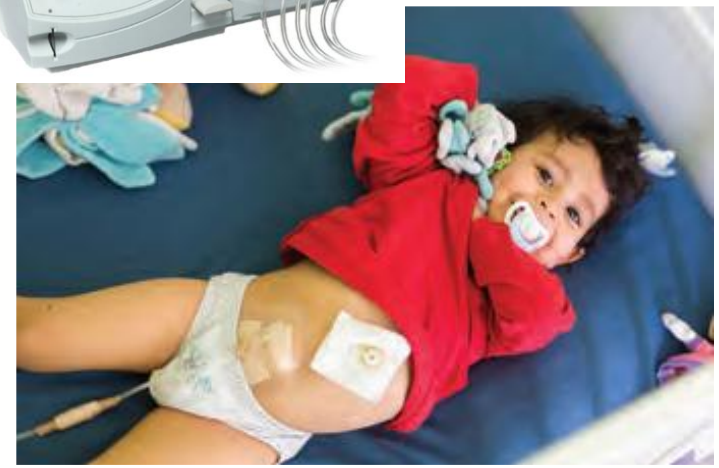


ARPKD: ELECTROLYTES & WATER

- **Acidosis**: low serum bicarbonate or CO_2 levels due to inability to get rid of acid in the urine
  - may need bicarbonate or citrate (e.g. Bicitra) supplements
- **Low sodium levels (hyponatremia)** in ~25% of infants[1]
  - ? due to inability to properly dilute urine (not sodium loss)
  - Fluid restriction (e.g. concentrating feeds) or furosemide (Lasix) usually preferred over sodium supplementation (can worsen blood pressure)
- **Urine concentrating defect**: may make larger amounts of urine than normal
  - may cause bedwetting
  - risk for dehydration

[1]Guay-Woodford LM. Pediatrics 2003

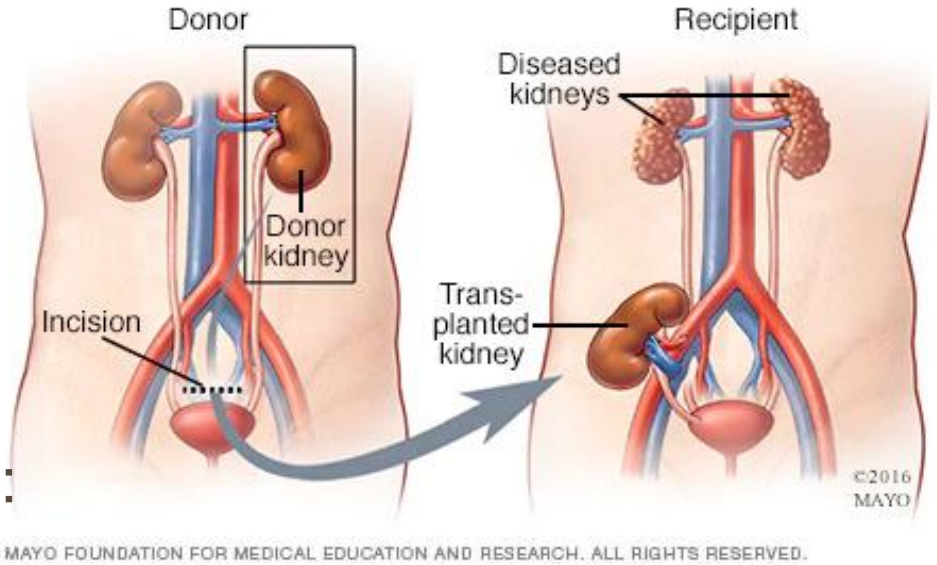
DIALYSIS



- 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
    - 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

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

KIDNEY TRANSPLANT



- Kidney from a **living or deceased donor** is surgically placed into the **recipient**
- **Extensive testing of donor & recipient** to ensure:
  - blood & tissue types are compatible
  - risks to living donor are minimized
  - risks of complications (e.g. infection) for recipient are minimized
- Children with PKD **may need kidney(s) removed** to make room in the belly
- **Lifelong medications** to prevent rejection
- With good medical care, a transplanted kidney can last for 10-20 years or more
- Most children who get a kidney transplant in childhood will eventually need another transplant, or may need dialysis while waiting for another transplant

ARPKD: BLOOD PRESSURE

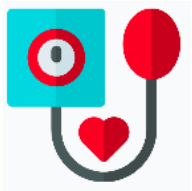
- **Hypertension (high blood pressure)**
  - Defined as BP > 95th percentile based on age, gender, and height

TABLE 5 BP Levels for Girls by Age and Height Percentile

Age (y)	BP Percentile	SBP (mm Hg)						
		Height Percentile or Measured Height						
		5%	10%	25%	50%	75%	90%	95%
1	Height (in)	29.7	30.2	30.9	31.8	32.7	33.4	33.9
	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1
	50th	84	85	86	86	87	88	88
	90th	98	99	99	100	101	102	102
	95th	101	102	102	103	104	105	105
	95th + 12 mm Hg	113	114	114	115	116	117	117

  - Symptoms: may be silent; can have irritability or headache if severe

[1]Flynn J. Pediatrics 2017

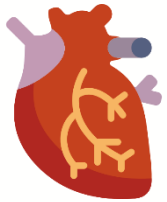


ARPKD: BLOOD PRESSURE

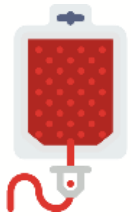
- **Hypertension (high blood pressure)**
  - can develop even when kidney function is normal
  - is very common: most children (>85%) with ARPKD need BP meds[1]
  - can be difficult to control: ~1/3 of children with ARPKD need 3 or more BP meds[1]
  - Medications:
    - ACE inhibitors (e.g. lisinopril, enalapril) or ARBs (e.g. losartan) often preferred (if potassium levels OK)
    - often need other meds too (e.g. amlodipine, labetalol, clonidine)

[1]Dell KM. J Pediatr 2016

ARPKD: CARDIOVASCULAR ISSUES



- **Heart**:
  - Good blood pressure control is important for heart health (and protects the kidneys)
  - **Echocardiograms** can look for problems such as **left ventricular hypertrophy** (thickening of heart walls)
- **Blood vessels**:
  - Unlike ADPKD, ARPKD is not usually thought to be associated with intracranial (brain) aneurysms or other vascular problems
  - Rare cases have been reported: 6 patients with brain aneurysms, 2 with aneurysms in other parts of the body
  - We will be starting a research study to look at risk for aneurysms and other blood vessel problems in children with ARPKD



ARPKD: ANEMIA

- Low hemoglobin or red blood cells
- Is common in children with any form of CKD:
  - low iron → may need iron supplements
  - low erythropoietin (“Epo”) → may need injections (Epogen, Darbepoetin [Aranesp])
- Children with ARPKD liver disease (congenital hepatic fibrosis and portal hypertension) can also develop anemia due to:
  - enlarged spleen trapping red blood cells (“hypersplenism”)
  - bleeding from esophageal varices

ARPKD: BONE HEALTH

- The kidneys activate **vitamin D**, which is important for bone health
- Healthy bones need appropriate levels of:
  - calcium
  - phosphorus
  - vitamin D
  - intact parathyroid hormone (iPTH)

Common problems in children with CKD	Possible treatments
high phosphorus levels	phosphorus binders (e.g. calcium carbonate, sevelamer)
low calcium levels	calcium supplements
low vitamin D levels	vitamin D supplements (cholecalciferol and/or calcitriol)
high iPTH levels	calcitriol

ARPKD: GROWTH AND DEVELOPMENT

- **Growth problems**
  - well-known complication in children with CKD from any cause
  - Our 2016 study showed that growth impairment was similar in children with ARPKD compared to those with other congenital causes of CKD[1]
- **Learning difficulties**
  - Children with CKD from any cause are at risk for learning problems
  - Our 2014 study showed that neurocognitive abilities in children with ARPKD were similar to those with other congenital causes of CKD[2]
    - scores slightly below average compared to healthy children

[1] Hartung EA, Frontiers in Pediatrics 2016; ; [2]Hartung EA, Pediatric Nephrology 2014

ARPKD: INFECTIONS

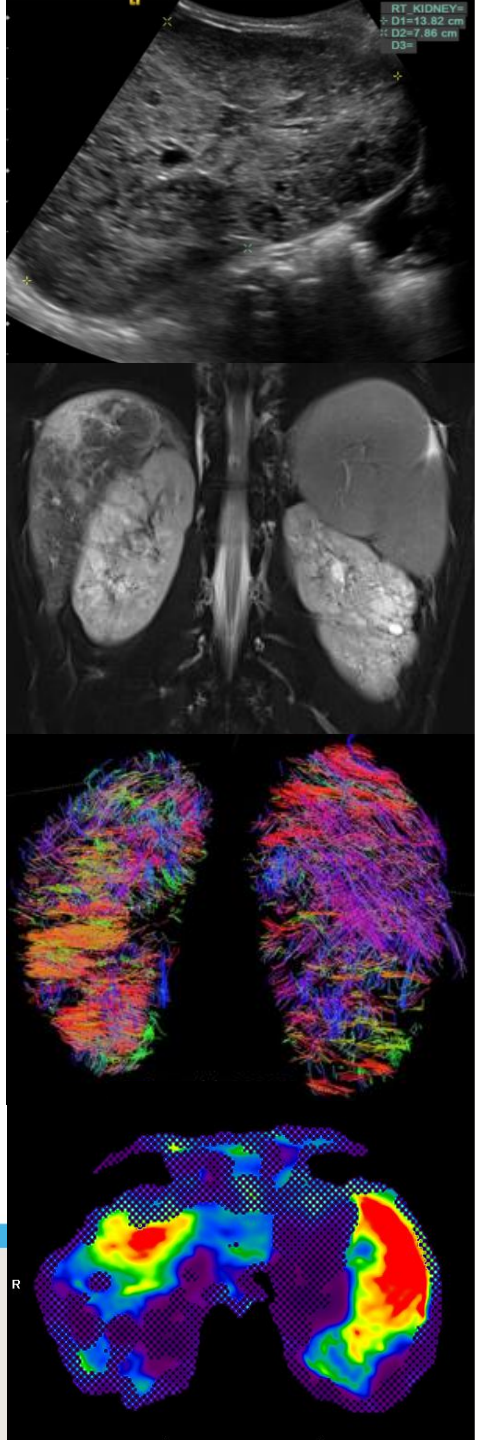
- Risk of urinary tract infections (UTI)
  - **UTIs** reported in 20-50% of patients[1]
  - May be due to poor urine flow in cystic tubules
- Risk of bile duct infections (cholangitis) – to be discussed by another speaker
- Other infections
  - Children with CKD from any cause are at higher risk of infections
  - Recommend:
    - Complete childhood vaccination schedule
    - Flu shot every year
    - Pneumococcal vaccine (Pneumovax) in children with reduced kidney function or liver disease

[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

RESEARCH OVERVIEW

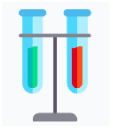


How do observational studies help us to develop treatments?

Observational studies

Understand disease course in humans

Develop disease measurements



Clinical trials

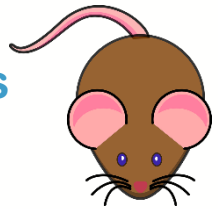
Test drugs in humans

Lab research

Understand PKD biology

Discover candidate drugs

Test drugs in animals



OUR GOAL:

Treatment for ARPKD/CHF

PHASES of a CLINICAL TRIAL

Preclinical
LABORATORY STUDIES

Duration: Several years

- ✓ Provide information on dosing and toxicity levels

Phase 1
SAFETY

Duration: Several months

- ✓ Evaluate safety
- ✓ Gather information about how a drug interacts with the human body

Phase 2
SAFETY AND DOSING

Duration: Several months

- ✓ Further evaluate safety
- ✓ Monitor side effects
- ✓ Check which dose works best
- ✓ Check effectiveness

Phase 3
SAFETY AND EFFICACY

Duration: Several years

- ✓ Confirm effectiveness
- ✓ Monitor safety

FDA APPROVAL

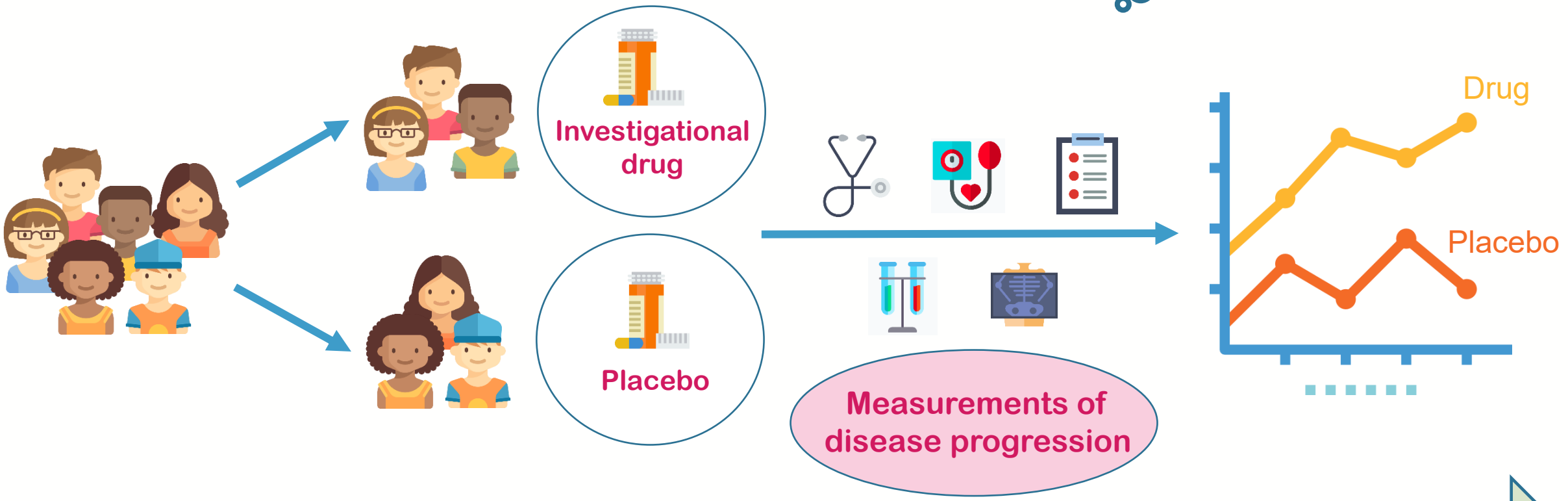
Phase 4
POST MARKETING SAFETY AND EFFICACY

- ✓ Gather information on the drug's effect in various populations and any side effects associated with long-term use

https://www.slhn.org/cancer/clinical-trials

PHASE 3 CLINICAL TRIAL: DOES THIS DRUG WORK?

How do observational studies help us to develop treatments?



Eligible participants → Randomization → Treatment phase (~1-4 years) → Results – did it work?

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ARPKD STUDIES AT CHOP

- **Ongoing observational studies:**
  - **Novel imaging biomarkers in ARPKD**
    - **Goal:** to develop new ultrasound & MRI-based imaging methods to measure liver and kidney disease progression in ARPKD/CHF
  - **PKDnet**
    - **Goal**: to develop a computable algorithm to find patients with ARPKD in PEDSnet, a large multicenter database of anonymized medical record data

ARPKD STUDIES AT CHOP

- **Ongoing observational studies:**
  - **ARPKD/HRFD database**
    - PI: Lisa Guay-Woodford (Children's National Medical Center, Washington, DC)
    - **Goal:** to create a national database of clinical and genetic data on patients with ARPKD and other hepatorenal fibrocystic disorders
- **Completed clinical trial:**
  - **Phase 1 clinical trial of Tesevatinib in children with ARPKD**
    - Funded by Kadmon Corporation, LLC
    - **Goal**: to find out how a single dose of tesevatinib is processed in the body and determine if it is safe

ARPKD STUDIES AT CHOP

- **Future studies:**
  - **Multi-parametric MRI of ARPKD Liver disease**
    - **Goal:** To use new MRI methods to measure ARPKD liver disease progression
  - **Intracranial aneurysms and vascular abnormalities in ARPKD**
    - **Goal:** To determine how common brain aneurysms and blood vessel abnormalities are in individuals with ARPKD, and to study potential risk factors for these problems

ARPKD STUDIES AT CHOP

- Interested in participating? Please contact me or my study coordinator:
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THANK YOU!

QUESTIONS?