ARPKD: IMAGING RESEARCH AND CLINICAL TRIALS

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ARPKD-CHF Conference: Empowering the Patient
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Children's Hospital of Philadelphia℠

OBJECTIVES

- To review current research studies in ARPKD
  - ARPKD database: UAB Hepatorenal Fibrocystic Disease Core
  - CHOP Research studies
    - Novel Imaging in ARPKD
    - Clinical trial - tesevatinib

ARPKD DATABASE

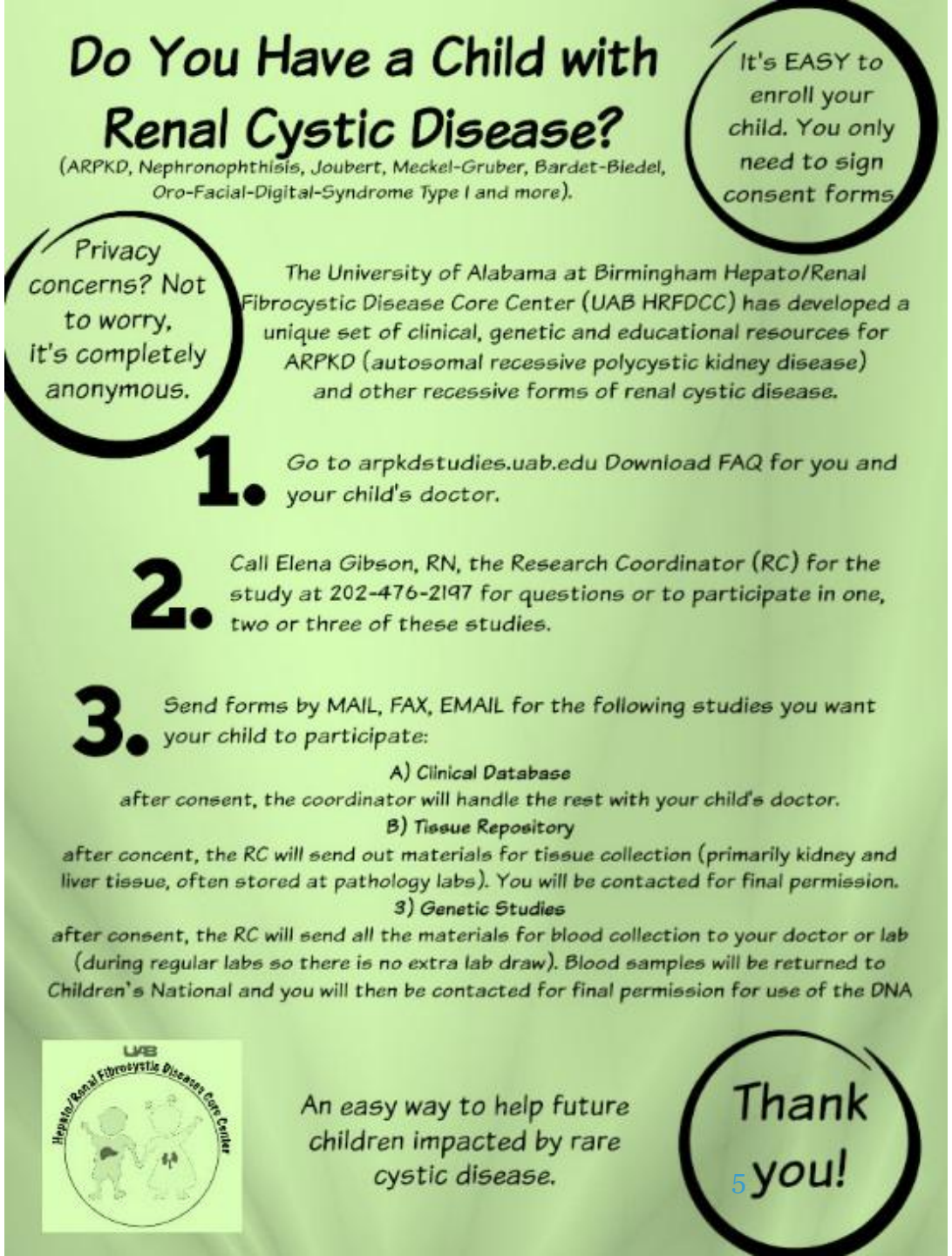
- **University of Alabama at Birmingham (UAB) Hepatorenal Fibrocystic Diseases (HRFD) Core Center**
  - Led by Dr. Lisa Guay-Woodford (Children's National Medical Center) and UAB colleagues
  - Funded by NIH/NIDDK
  - Focused on understanding causes of cystic kidney diseases (ARPKD + other genetic kidney-liver diseases) and the development of new therapeutic strategies

ARPKD DATABASE: UAB HRFD CORE CENTER

- Anonymous
- No study visits needed - just sign consent forms and UAB team coordinates obtaining medical records/samples
- Three components:
  1. **Clinical database**
     - Info from patient's medical records is entered into database
  2. **Tissue repository**
     - Kits are sent to request existing tissue samples (e.g. kidney/liver) from pathology labs
  3. **Genetic studies**
     - Kits are sent to obtain a blood sample during a regular lab draw

ARPKD DATABASE: UAB HRFD CORE CENTER

- Contact: Elena Gibson, RN
  - 202-476-2197
  - egibson@childrensnational.org



ARPKD STUDIES UNDERWAY AT CHOP

- **ARPKD Novel imaging biomarkers in ARPKD**
  - Funded by NIH/NIDDK grant (K23-DK109203)
- **A Phase 1, Safety, Pharmacokinetic, Single Ascending Dose Study of Tesevatinib in Pediatric Subjects With ARPKD** (NCT03096080)
  - Funded by Kadmon Corporation, LLC

NOVEL IMAGING BIOMARKERS IN ARPKD STUDY

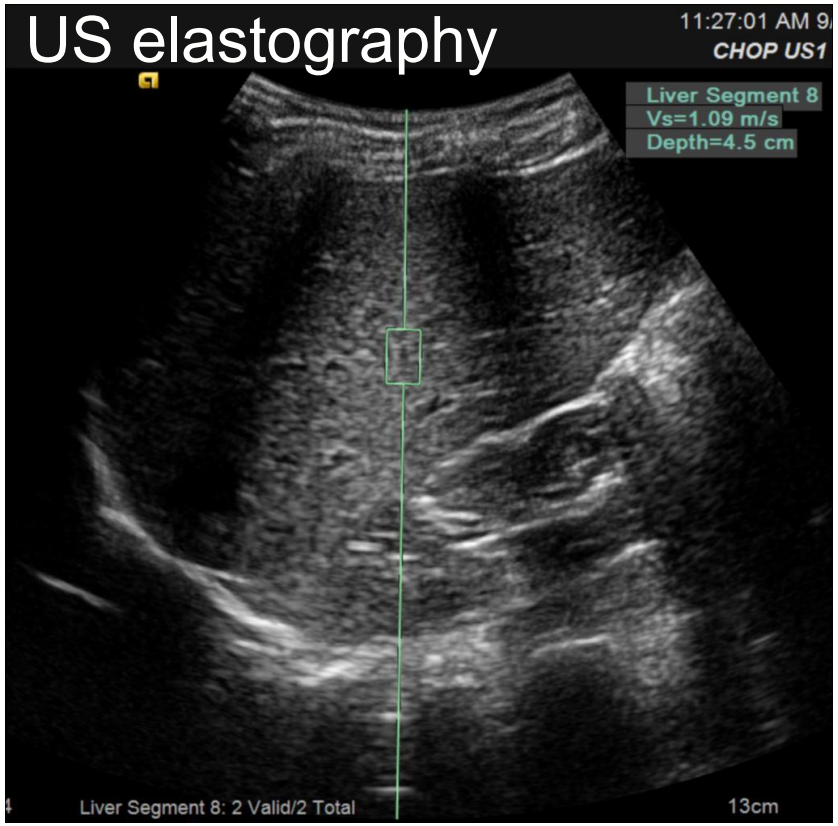
- **Goal**: To develop new, non-invasive imaging methods to measure progression of kidney and liver disease in ARPKD
- **Why?**
  - A major barrier to performing clinical trials of potential new drugs in ARPKD patients is the lack of accurate ways to measure disease progression within a realistic time frame (2-3 years)
  - Current methods (blood tests, standard ultrasound or MRI) are not accurate enough to detect changes in the short term

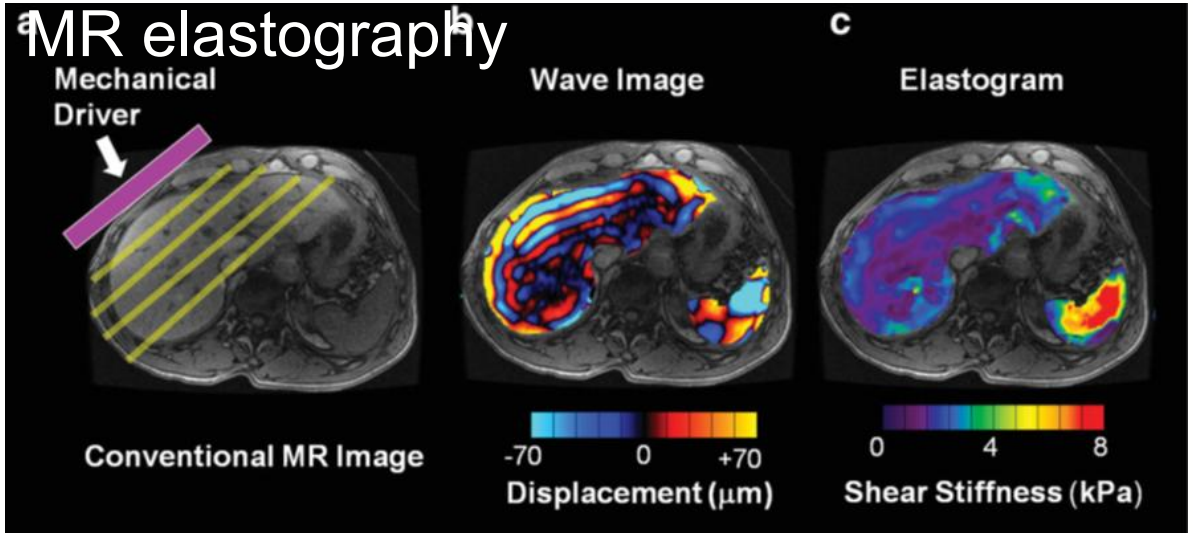
NOVEL IMAGING BIOMARKERS IN ARPKD STUDY

- **Who?**
  - Patients with a diagnosis of ARPKD, from birth to 21 years old
  - Healthy children for comparison
- **What is involved?**
  - One study visit each year for up to 4 years (CHOP Main campus), with:
    - Interviews & physical exam
    - Blood and urine tests
    - Ultrasound of the liver, spleen, and kidneys
    - MRI of the liver, spleen, and kidneys (only in children old enough to lie still for up to 1 hour, usually at least 7 y/o)

NOVEL IMAGING BIOMARKERS IN ARPKD STUDY

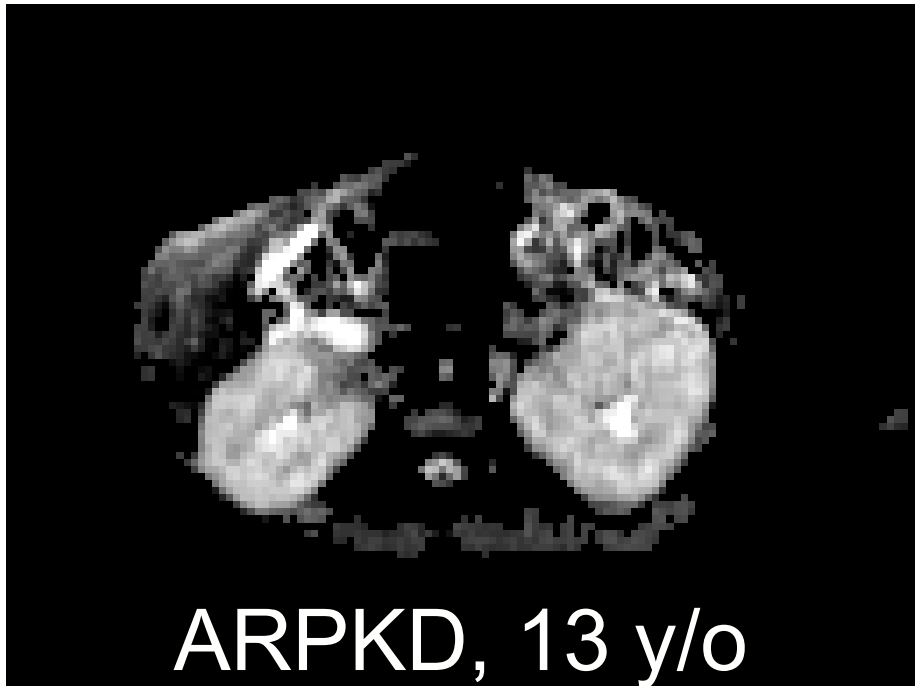
- **What are the imaging methods?**
  - Liver and spleen: measurements of tissue stiffness to quantify liver fibrosis and portal hypertension
    - Ultrasound (US) elastography
    - Magnetic resonance (MR) elastography





NOVEL IMAGING BIOMARKERS IN ARPKD STUDY

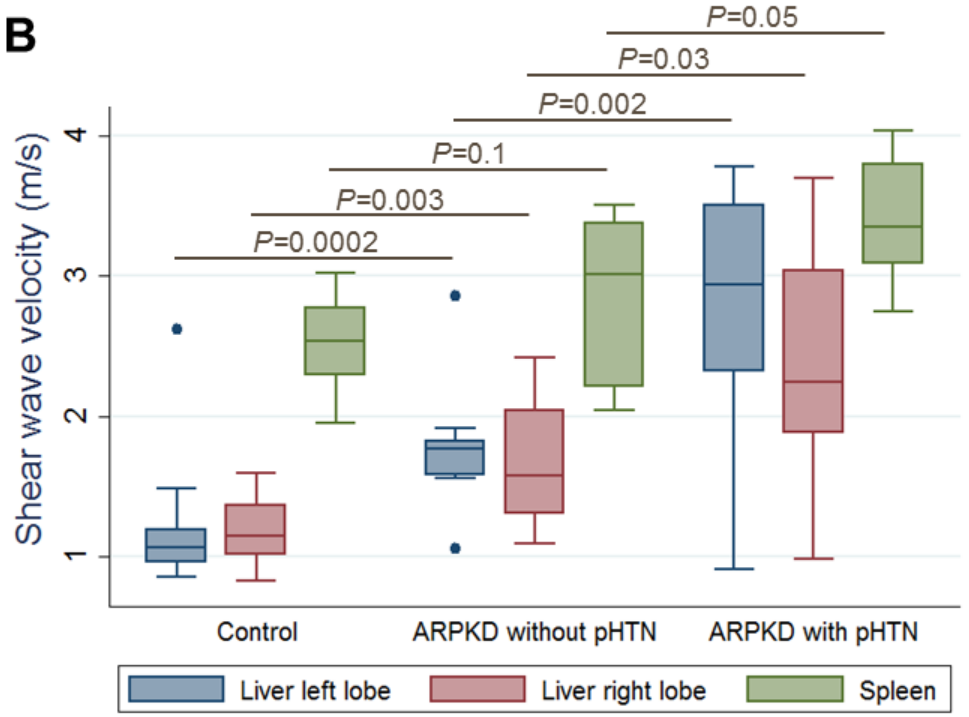
- **What are the imaging methods?**
  - Kidneys: measurements of tissue stiffness and cyst burden
    - US elastography
    - Multiple MRI sequences (quantitative T2 mapping, diffusion)



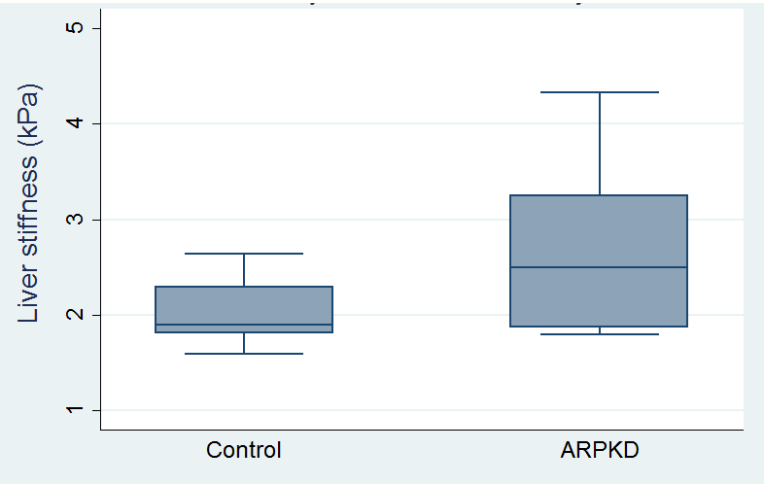
NOVEL IMAGING BIOMARKERS IN ARPKD STUDY

- 27 ARPKD patients and 24 healthy children have participated thus far
- **Findings to date**:
  - **US elastography** of the liver appears to be helpful in detecting liver fibrosis and portal hypertension in children with ARPKD
  - **MR elastography** also appears promising to detect liver fibrosis

US elastography



MR elastography

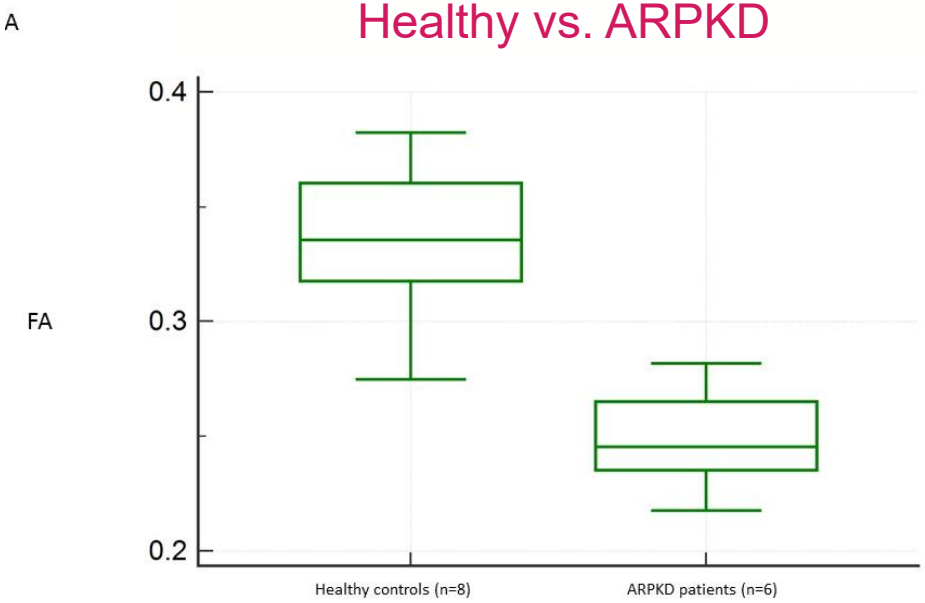


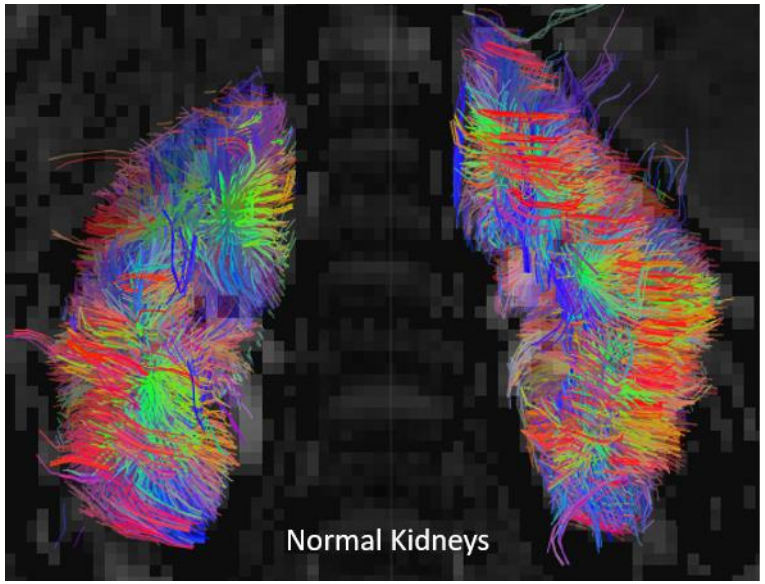
Hartung EA et al., manuscript under review;
Sharma S et al., ASN abstract 2017

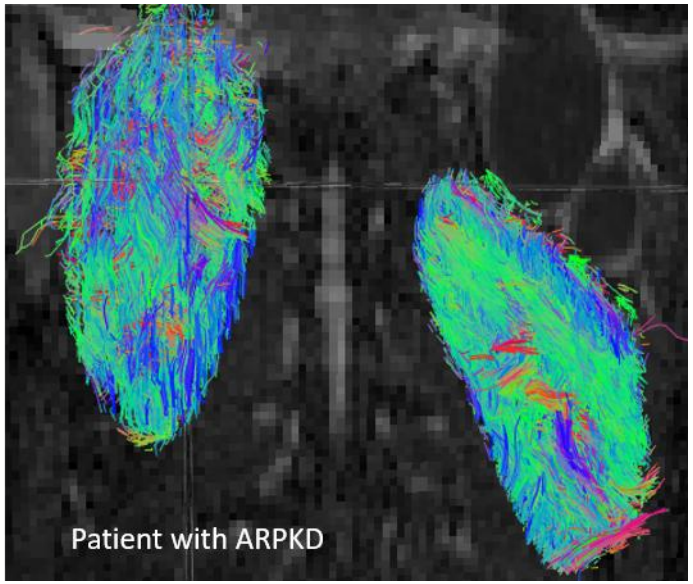
NOVEL IMAGING BIOMARKERS IN ARPKD STUDY

- **Findings to date:**
  - **Diffusion tensor MRI** shows significant kidney tissue disorganization (lower fractional anisotropy, FA) in ARPKD patients compared to healthy controls

FA measured by DTI-MRI
Healthy vs. ARPKD







TESEVATINIB CLINICAL TRIAL

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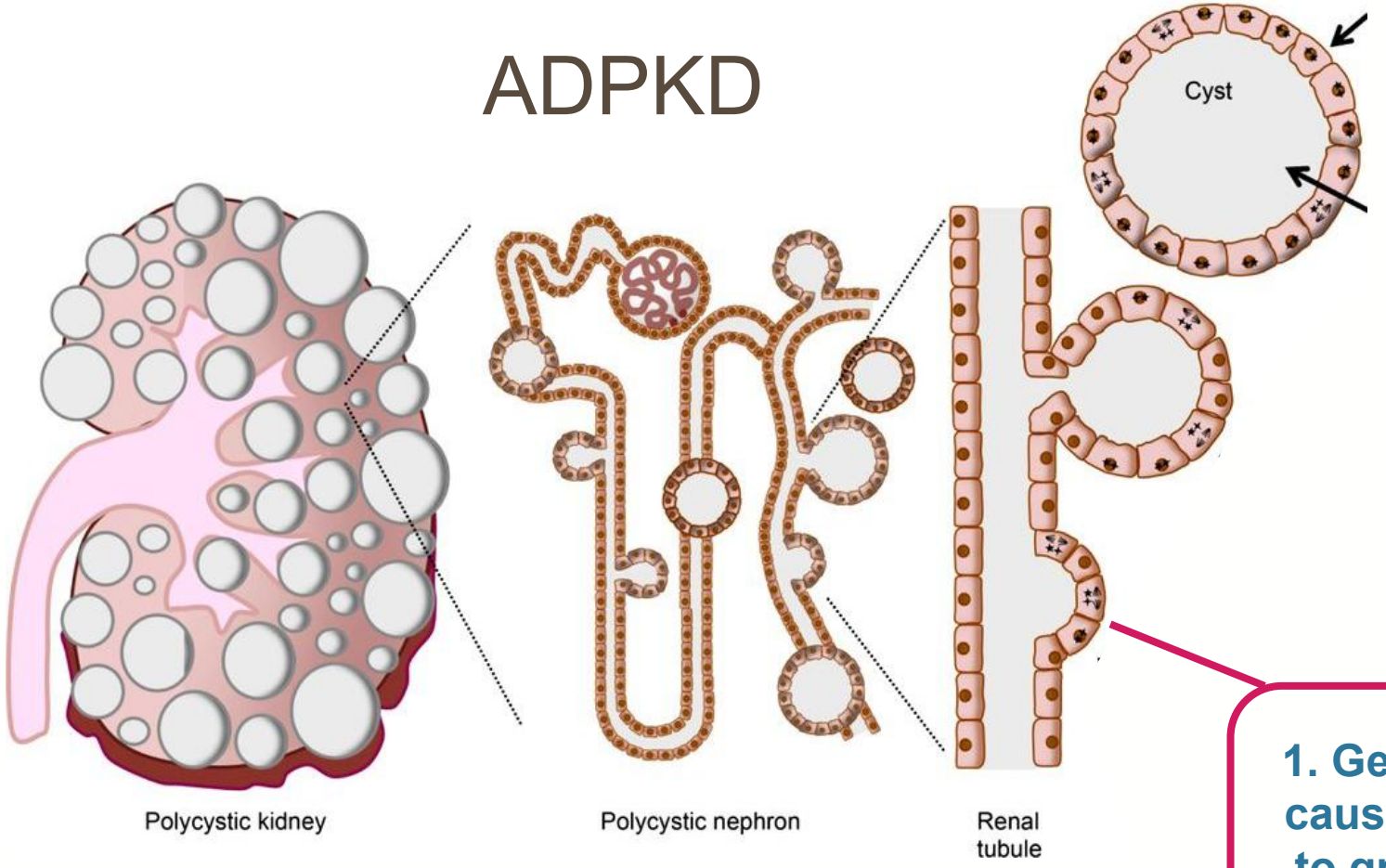
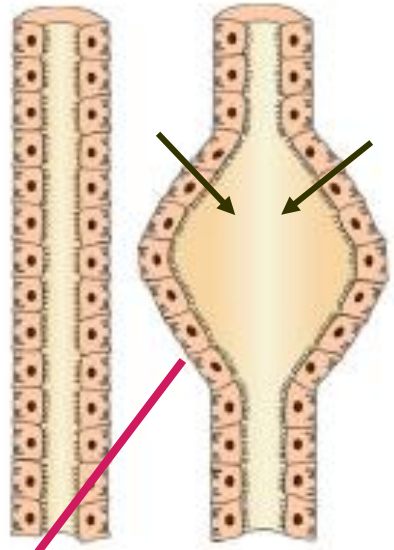
HOW DO CYSTS FORM AND GROW?

ADPKD



ARPKD



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

(influenced by vasopressin, cAMP, EGF, Src)

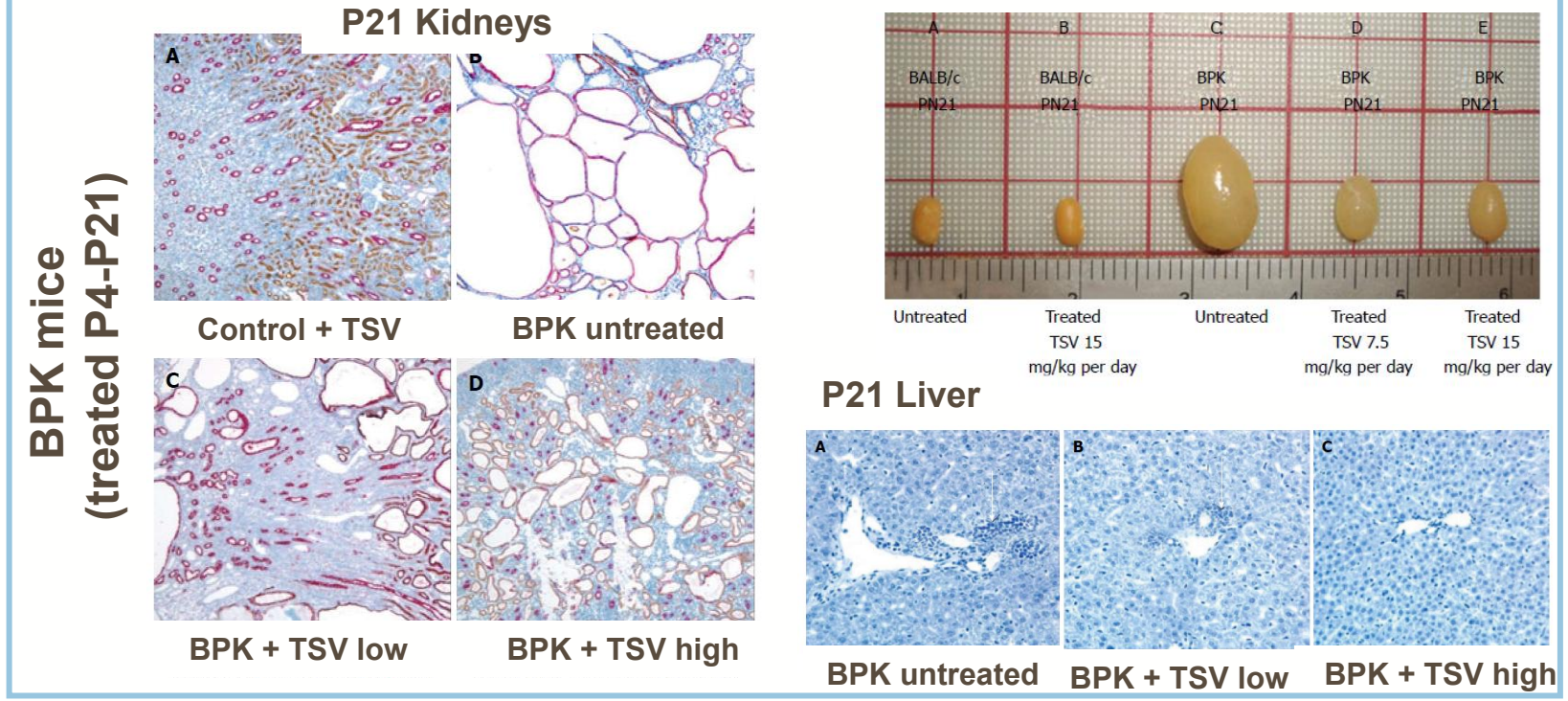
1. Genetic mutation causes tubule cells to grow & multiply abnormally

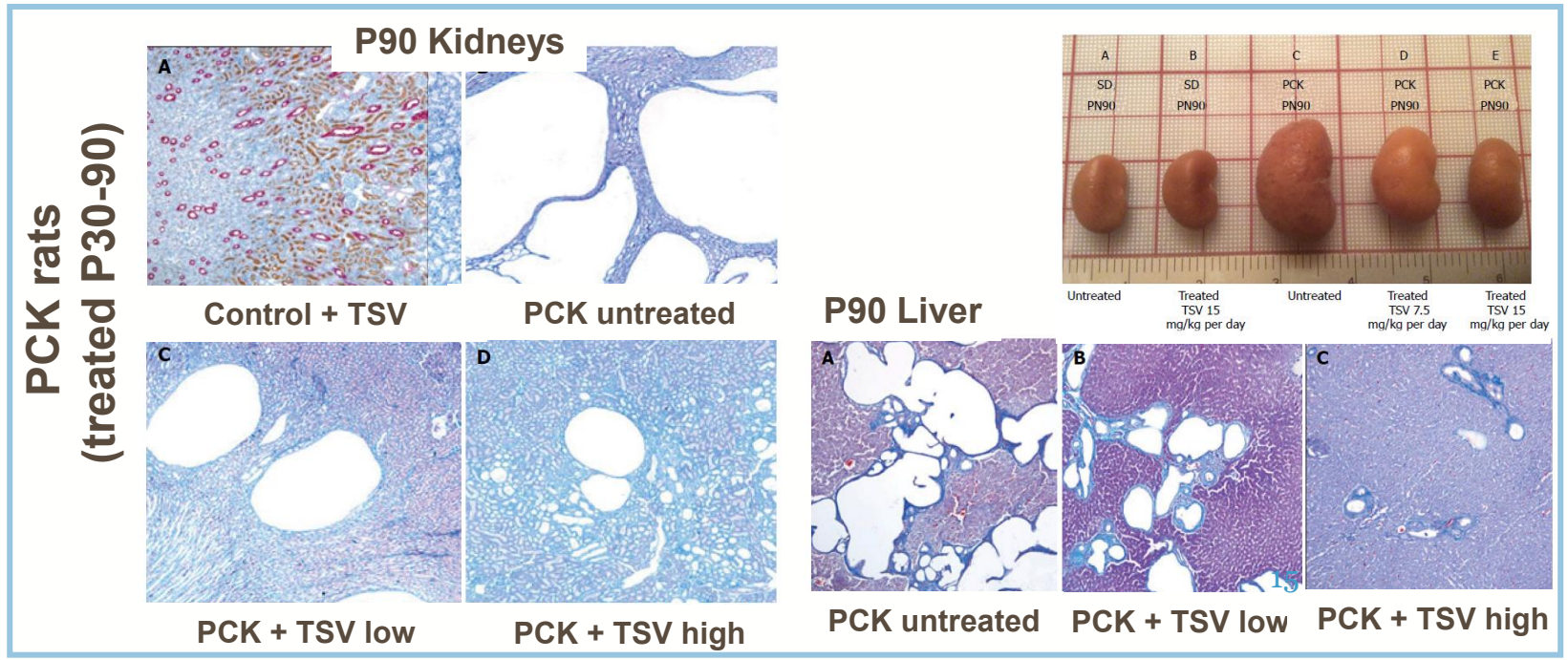
Blanco G & Wallace DP. Am J Physiol 2013; Staruschenko A. Compr Physiol 2012

ARPKD: DRUG TRIALS

- **Tesevatinib**
  - multi-kinase inhibitor (EGF, Src, cAMP)
- Improved kidney & liver disease in 2 different animal models of ARPKD (BPK mice and PCK rats)[1]

[1]Sweeney WE et al. World J Nephrol 2017





ARPKD TESEVATINIB STUDY

- **A Phase 1, Safety, Pharmacokinetic, Single Ascending Dose Study of Tesevatinib in Pediatric Subjects With ARPKD** (www.ClinicalTrials.gov, NCT03096080)
- **Goal:** To study the pharmacokinetics (how the drug is processed in the body) and safety of a single dose of tesevatinib in children with ARPKD
- **Why?**
  - Phase 1 clinical trial (earliest phase) to find out the best dose and ensure safety before moving to a multiple-dose trial
- **Who?**
  - Children with ARPKD aged 5-12 years old
  - GFR ≥ 50, plus other eligibility criteria

ARPKD TESEVATINIB STUDY

- **What is involved?**
  - 6 total visits over ~6 weeks
  - A single dose of tesevatinib by mouth, at one of 3 dose levels
    - 6 patients have completed dose level 1, currently recruiting for dose level 2
  - Study procedures include vision and hearing tests, ECG, echocardiogram, ultrasound, IV placement, urine and blood testing, and physical exam

ARPKD STUDIES AT CHOP

- Informational flyers for all research studies are in the back
- Interested in participating? Please contact me or my study coordinator:
- Mohini Dutt
  - 267-425-3933
  - duttm2@email.chop.edu
- Erum A. Hartung, MD, MTR
  - 215-590-2449
  - hartunge@email.chop.edu

KEY TAKE-HOME POINTS

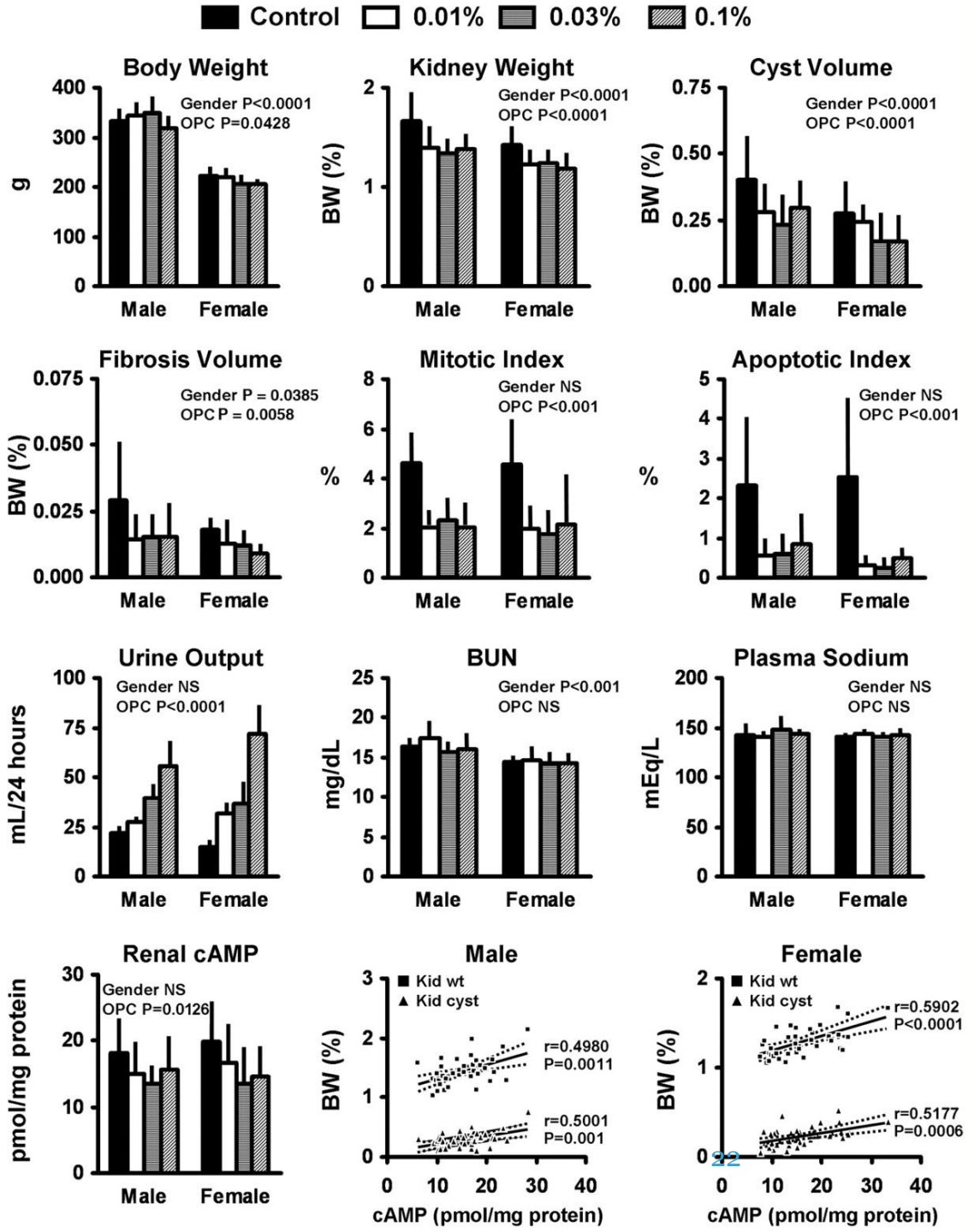
- Every day brings hope for new research advances in ARPKD
- There are many opportunities to get involved!

QUESTIONS?

SUPPLEMENTAL SLIDES: POTENTIAL FUTURE DRUG TRIALS

ARPKD: DRUG TRIALS

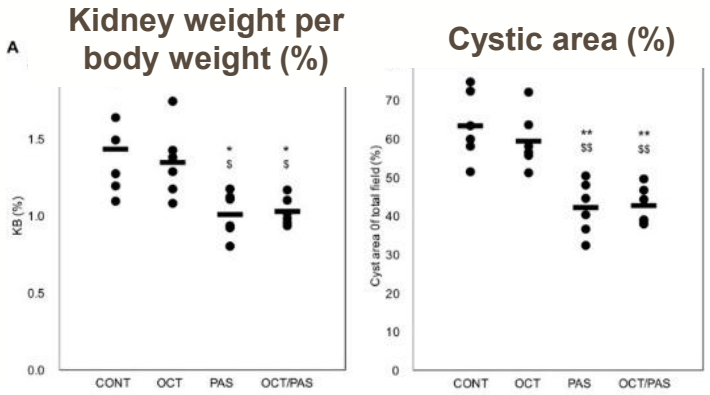
- **Tolvaptan**
  - Vasopressin receptor (V2R) antagonist
  - Pre-clinical trials in PCK rat showed some improvements in cyst & kidney volume and fibrosis with tolvaptan
  - No pediatric trials yet in ARPKD

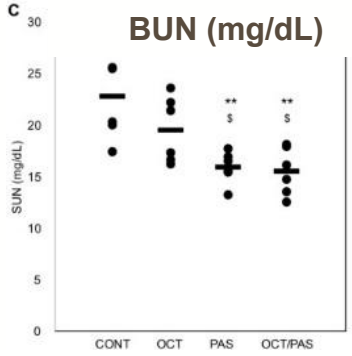


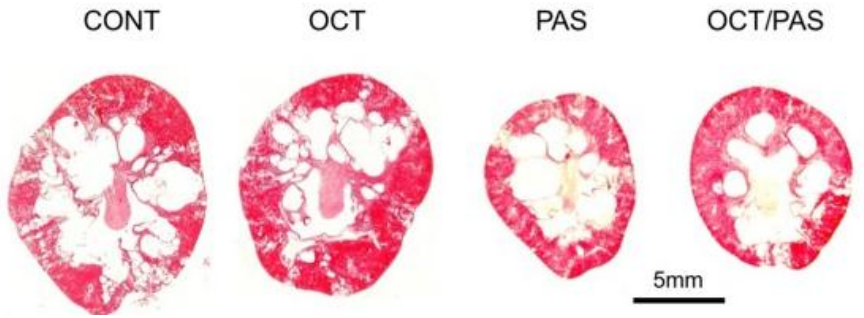
[1]Wang X et al. JASN 2005

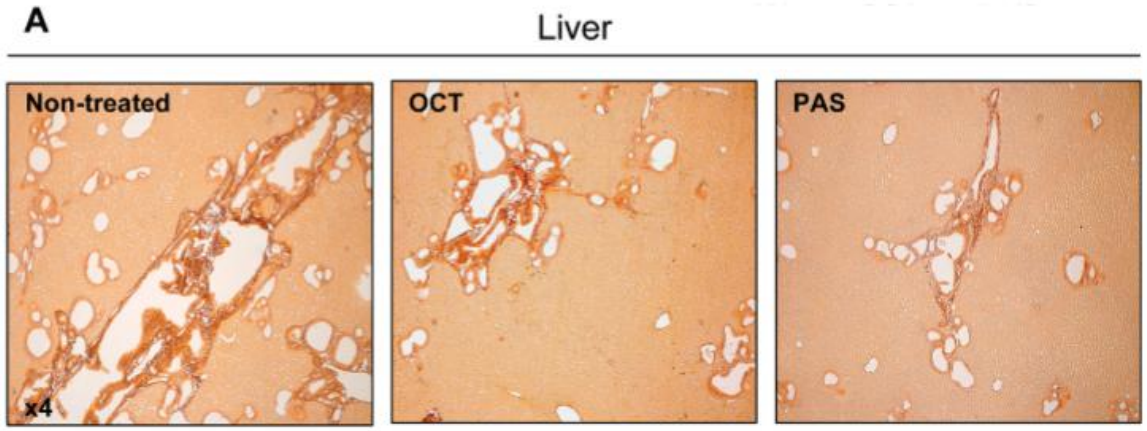
ARPKD: DRUG TRIALS

- **Octreotide / pasireotide**
  - Somatostatin analogs → decrease cAMP activity
  - Appear effective for kidney[1] and liver[2] disease in PCK rat model
  - No pediatric trials yet in ARPKD









[1]Kugita M et al. PLoS One 2017;
[2]Masyuk et al. Hepatology 2013