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Improving Awareness & Patient Outcomes

Understanding the ADPKD Patient Journey: From Primary to Specialty Care

September 16, 2024

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Presenters

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Family Practice Physician

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Moderators

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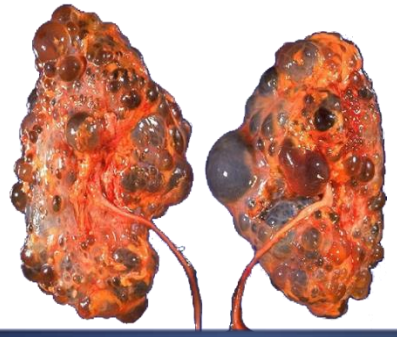
Nephrology Medical Science Liaison
Otsuka Pharmaceutical Development and Commercialization, Inc.

What Is PKD?

Polycystic kidney disease (PKD) is a group of monogenic disorders characterized by the propensity to develop numerous renal cysts[1]



Syndromic forms[1,2] → **Rare, recessively inherited**

Autosomal dominant (ADPKD)[3,4] → ***PKD1/PKD2* (~91%)**; ***NMD**** (~9%)

Autosomal recessive (ARPKD)[1] → ***PKHD1***

***The "no mutation detected" (NMD) group may contain those patients with mutations in other genes impacting cystic development, such as GANAB.[5]**

ADPKD=autosomal dominant PKD; ARPKD=autosomal recessive PKD; GANAB=gene encoding glucosidase II subunit-a; NMD=no mutation detected; PKD=polycystic kidney disease; PKHD1=polycystic kidney and hepatic disease

1. Harris PC and Torres VE. (2009). Annu Rev Med. 60:321-337.
2. Jauregui AR et al. (2005). Exp Cell Res. 305(2):333-342.
3. Heyer CM et al. (2016). J Am Soc Nephrol. 27(9):2872-2884.
4. Irazabal MV et al. (2017). Nephrol Dial Transplant. 32(11):1857-1865.
5. Lanktree MB, Chapman AB. (2017). Nat Rev Nephrol. 13(12):750-768.

ADPKD Is the Most Common Life-threatening Inherited Renal Disease

ADPKD does not discriminate on gender, race, ethnicity, or geography[1,2]

- ADPKD affects both sexes equally, and occurs in all ethnicities[3]
- ADPKD is the most common life-threatening inherited renal disease and accounts for up to ~5% of all patients with ESRD[2]
- ADPKD is the fourth leading cause of ESRD in the United States after diabetes, hypertension and glomerulonephritis[2]
- As many as 1:2,000 people worldwide are currently diagnosed with ADPKD,[3] and between 1:400 and 1:1,000* people living today will be diagnosed with ADPKD in their lifetime[1]

*The higher prevalence value of 1:1,000 is believed to be inaccurate as the data are based on a postmortem study and therefore report lifetime morbid risk rather than point prevalence.

ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease.

1. Torres VE, Harris PC. (2009). Kidney Int. 76(2): 149–68.
2. United States Renal Data System. 2016 USRDS Annual Data Report Volume 2: ESRD in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016 (accessed 8 Aug 2017).
3. Willey C. DRAFT: The Descriptive Epidemiology of ADPKD in the U.S. 2017.

ADPKD Is Inherited as an Autosomal Dominant Trait

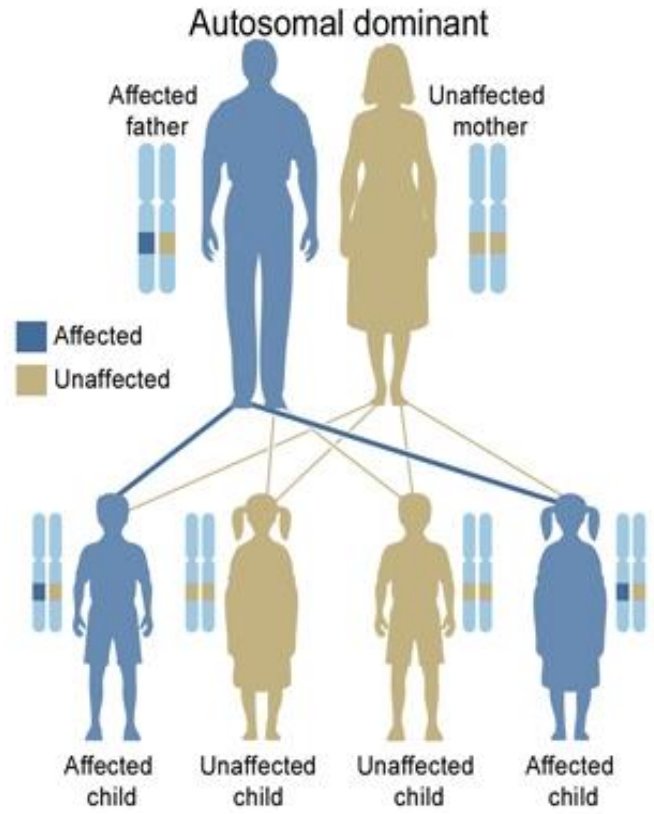


Figure adapted from U.S. National Library of Medicine

Inheritance pattern of autosomal dominant disease[5]

- ADPKD is an autosomal dominant disease with a high degree of penetrance[1]
- A child of an affected parent has a 50% chance of inheriting ADPKD[1]
- In 5% to 10% of cases, ADPKD is caused by a de novo mutation[2,3]
  - In ~10% of newly diagnosed cases, patients report a negative family history[3]
- Disease progression can be highly variable, even among family members with the same mutation[3]
  - Variability suggests a "two-hit" model for ADPKD, in which germ-line and somatic inactivation of both copies of a PKD gene lead to cystogenesis[4]

ADPKD=autosomal dominant polycystic kidney disease.

1. Harris PC, Rossetti S. (2010). Nat Rev Nephrol. 6(4):197-206.
2. Grantham JJ. (2009). Ann Transplant. 14:86-90.
3. Reed B et al. (2008). Am J Kidney Dis. 52(6):1042-1050.
4. Pei Y et al. (1999). J Am Soc Nephrol. 10(7):1524-1529.
5. ADPKD. PKD International. http://www.pkdinternational.org/what-is-pkd/ (accessed 13 February 2019).

ADPKD Presenting Symptoms

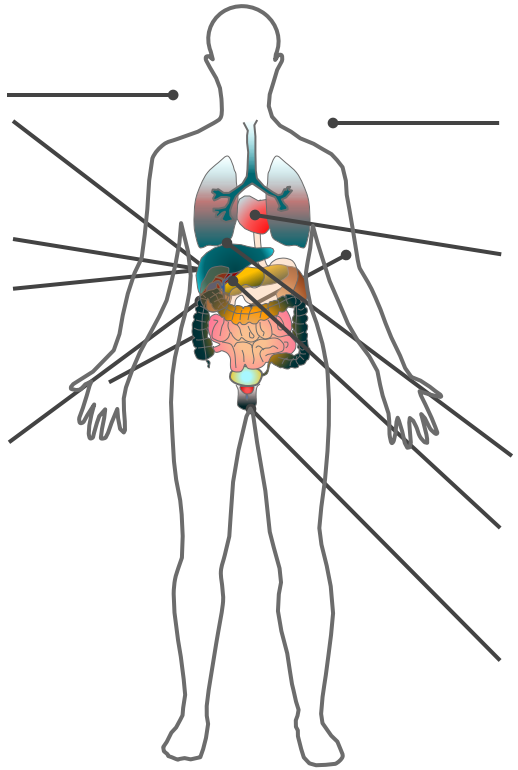
ADPKD=autosomal dominant polycystic kidney disease.

ADPKD Is a Systemic Disease

Renal cysts are the first manifestation of ADPKD and precede changes in kidney function by many years[1–8]

Renal Manifestations

- Hypertension
- Renal cysts
- Hematuria
- Nocturia
- Palpable kidneys
- Kidney stones
- Abdominal/flank pain
- Renal artery/vein occlusions
- Urinary tract infection



Extrarenal Manifestations

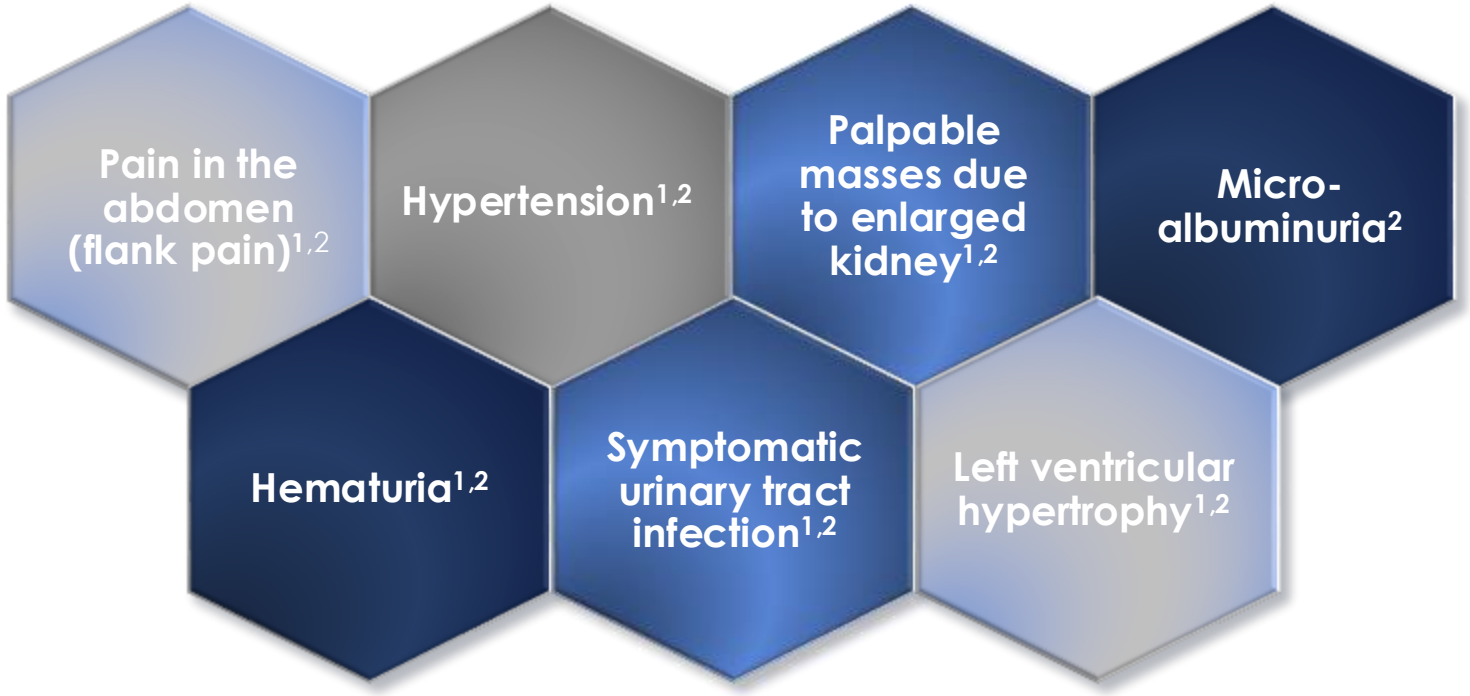
- Intracranial aneurysms
- Vascular dissections
- Cardiac valve abnormalities
- Pericardial effusion
- Diverticulosis†
- Hepatic cysts
- Hernia
- Pancreatic cysts
- Seminal vesicle cysts*
- Male infertility*

*In male patients. †Most common in patients with end-stage renal disease.

ADPKD=autosomal dominant polycystic kidney disease.

1. Halvorson CR et al. (2010). Int J Nephrol Renovasc Dis. 3:69-83.
2. Torres VE, and Harris PC. (2009). Kidney Int. 76(2):149-168.
3. Chebib FT and Torres VE. (2016). Am J Kidney Dis. 67(5):792-810.
4. Patient Platform. http://www.patient.co.uk/doctor/autosomal-dominant-polycystic-kidney-disease (accessed 13 February 2019).
5. Luciano RL and Dahl NK. (2014). Nephrol Dial Transplant. 29(2):247-254.
6. Mikolajczyk AE, et al. (2017). Clin Gastroenterol Hepatol. 15(1):17-24.
7. Chapman AB and Rahbari-Oskui FF. Renal Cystic Disorders. In: Wilcox CS et al. eds. Therapy in Nephrology & Hypertension. 3rd ed. Philadelphia, PA: Saunders; 2008.
8. Chauveau D et al. (1994) Kidney Int. 45:1140-1146.

Presenting Symptoms



- Patients may be asymptomatic and only have a family history of the disease

ADPKD=autosomal dominant polycystic kidney disease.

1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis*. 3: 69-83.
2. Patient Platform. http://www.patient.co.uk/doctor/autosomal-dominant-polycystic-kidney-disease (accessed 13 Sept 2017).

Hypertension in ADPKD

- Approximately 70% of individuals with ADPKD have HTN[1]
  - Approximately 20% to 30% of children[2]
- Higher prevalence of HTN in patients with ADPKD vs the general US population* in men and women <45 years of age[3]
  - Differences between patients with ADPKD and the general US population are most dramatic in the 20- to 34-year age group
- Significantly more males with ADPKD develop HTN than females[3]
  - Greatest gender differences occur between ages 20–44 years
- Generally occurs before decrease in GFR[2]
- Earlier onset than HTN in the general population[3]
- Associated with left ventricular hypertrophy[1]

*As reported in a National Health and Nutrition Examination Survey (NHANES) IV, 1999–2000.

ADPKD=autosomal dominant polycystic kidney disease; GFR=glomerular filtration rate; HTN=hypertension.

1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis*. 3:69-83.
2. Ecder T and Schrier RW. (2001). *J Am Soc Nephrol*. 12(1):194-200.
3. Kelleher CL et al. (2004). *Am J Hypertens*. 17(11):1029-1034.

Discussion:

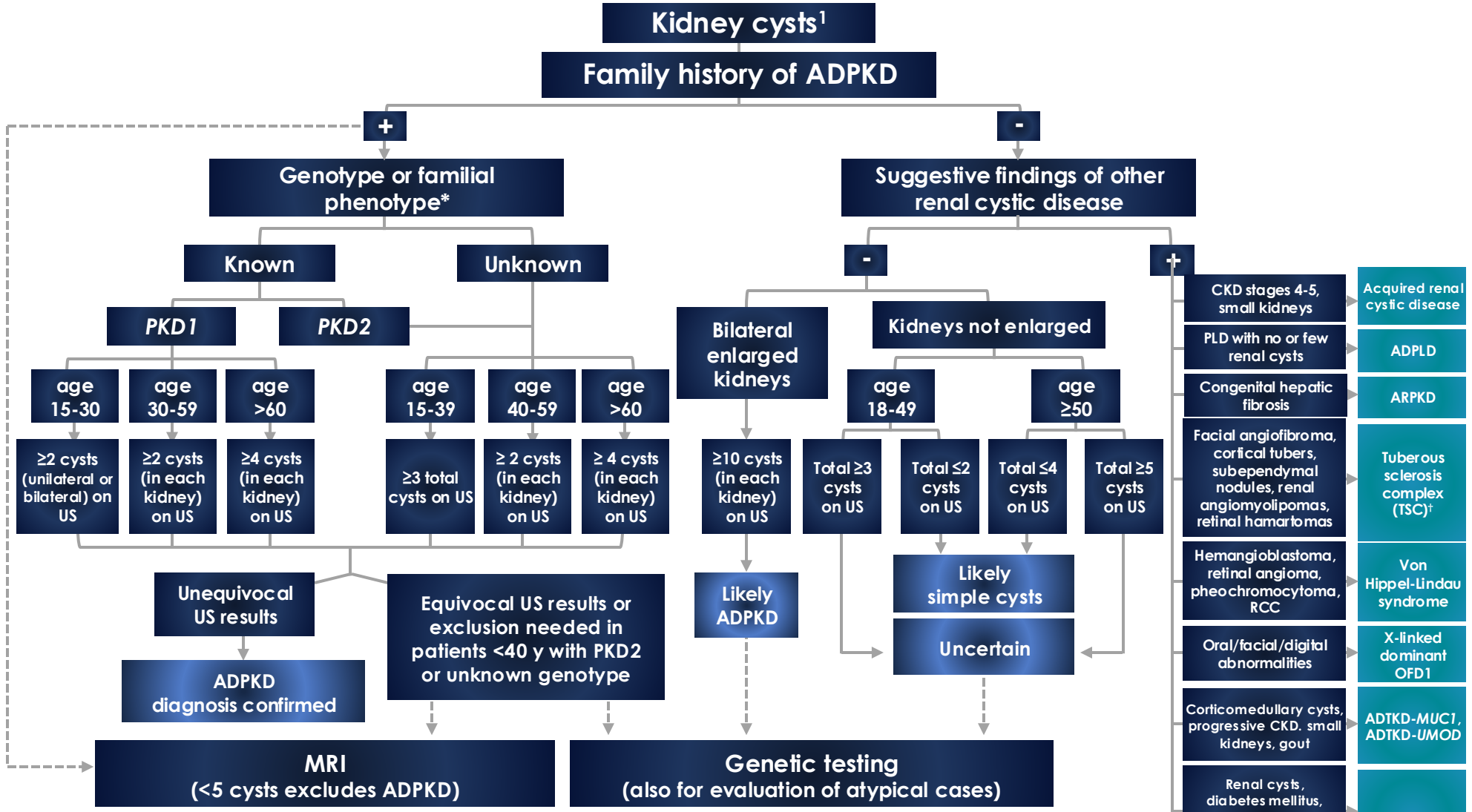
- Do you think there is enough awareness of ADPKD and presenting symptoms in primary care? Subspecialties?

- What are some challenges providers might face in diagnosing ADPKD outside of nephrology?

ADPKD Diagnosis

ADPKD=autosomal dominant polycystic kidney disease.

Diagnostic Algorithm for ADPKD



ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease; MRI=magnetic resonance imaging; *PKD1*=polycystic kidney disease gene 1; *PKD2*=polycystic kidney disease gene 2; RCC=renal cell carcinoma; US=ultrasound.

1. Figure adapted from Chebib FT, Torres VE. (2016). *Am J Kidney Dis.* 67(5): 792–810.

Expansion Destroys Normal Tissue and Causes Loss of Renal Function

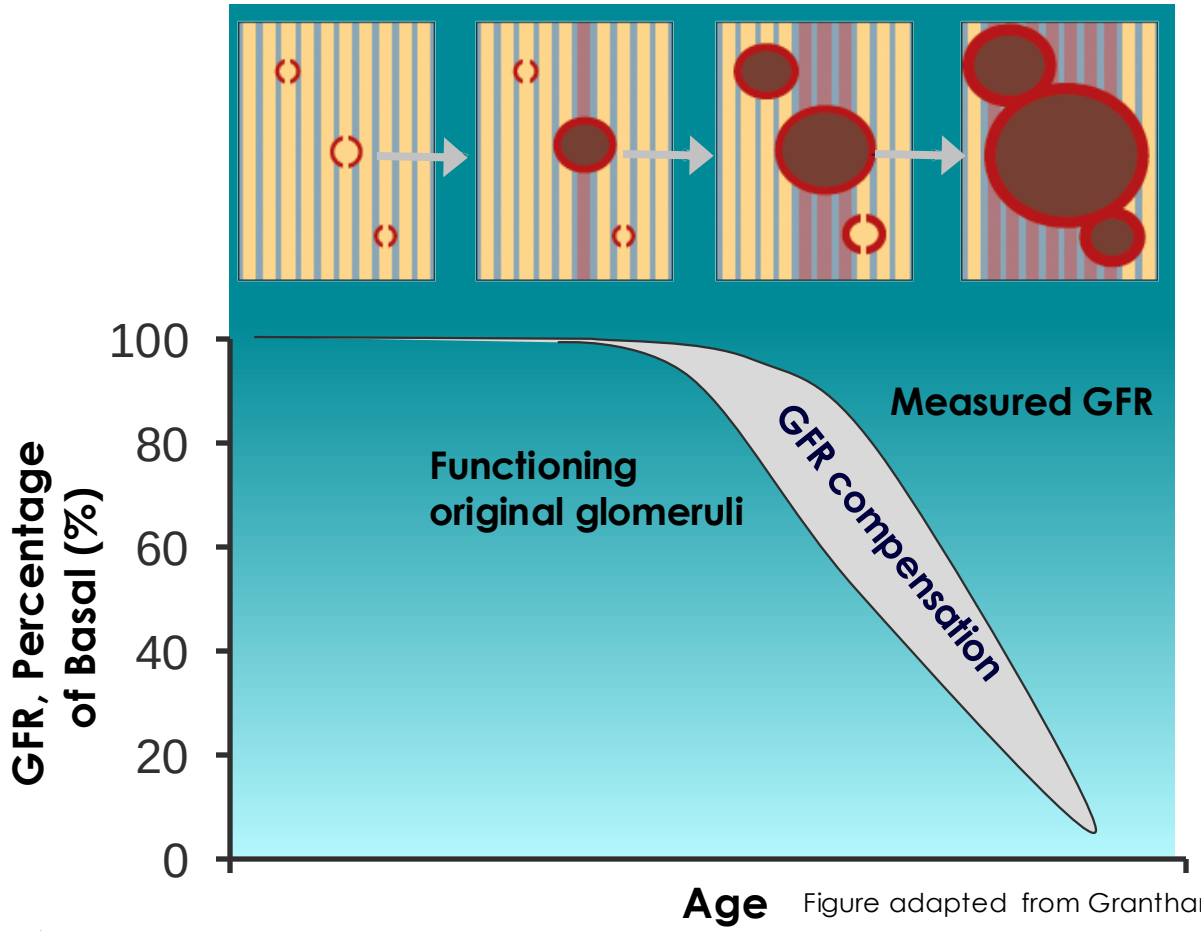


Figure adapted from Grantham et al[1]

- Renal function remains steady until kidney volume increases 4–6 times normal size[2]
- Irreversible damage occurs by the time GFR declines[3]
- Disease progression is variable from patient-to-patient[4]

GFR=glomerular filtration rate.

1. Grantham JJ et al. (2011). *Nat Rev Nephrol*. 7(10): 556–66.
2. Braun WE. (2009). *Cleve Clin J Med*. 76(2): 97–104.
3. Grantham JJ et al. (2006). *N Engl J Med*. 354(20): 2122–30.
4. Milutinovic J et al. *Am J Kidney Dis*. 1992;19(5):465–72.

Predictors of Rapid Disease Progression in ADPKD[1]

Markers used to assess prognosis in ADPKD

Environmental Predictors	Imaging Predictors	Clinical Predictors	Genetic Predictors	Laboratory Predictors
High protein intake	High total kidney volume	Early onset of hypertension	PKD1 truncating mutations	Overt proteinuria
Low water intake	Low renal blood flow	Gross hematuria	PKD1 disease	Microalbuminuria
Smoking		Early decrease in GFR		Elevated copeptin

Indicates the best-validated markers

ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; PKD1, polycystic kidney disease gene

1. Gansevoort RT et al. Nephrol Dial Transplant. 2016; 31(3):337–48.

Discussion:

- When are patients with ADPKD typically referred to nephrology? Do you feel that this timeline is ideal?

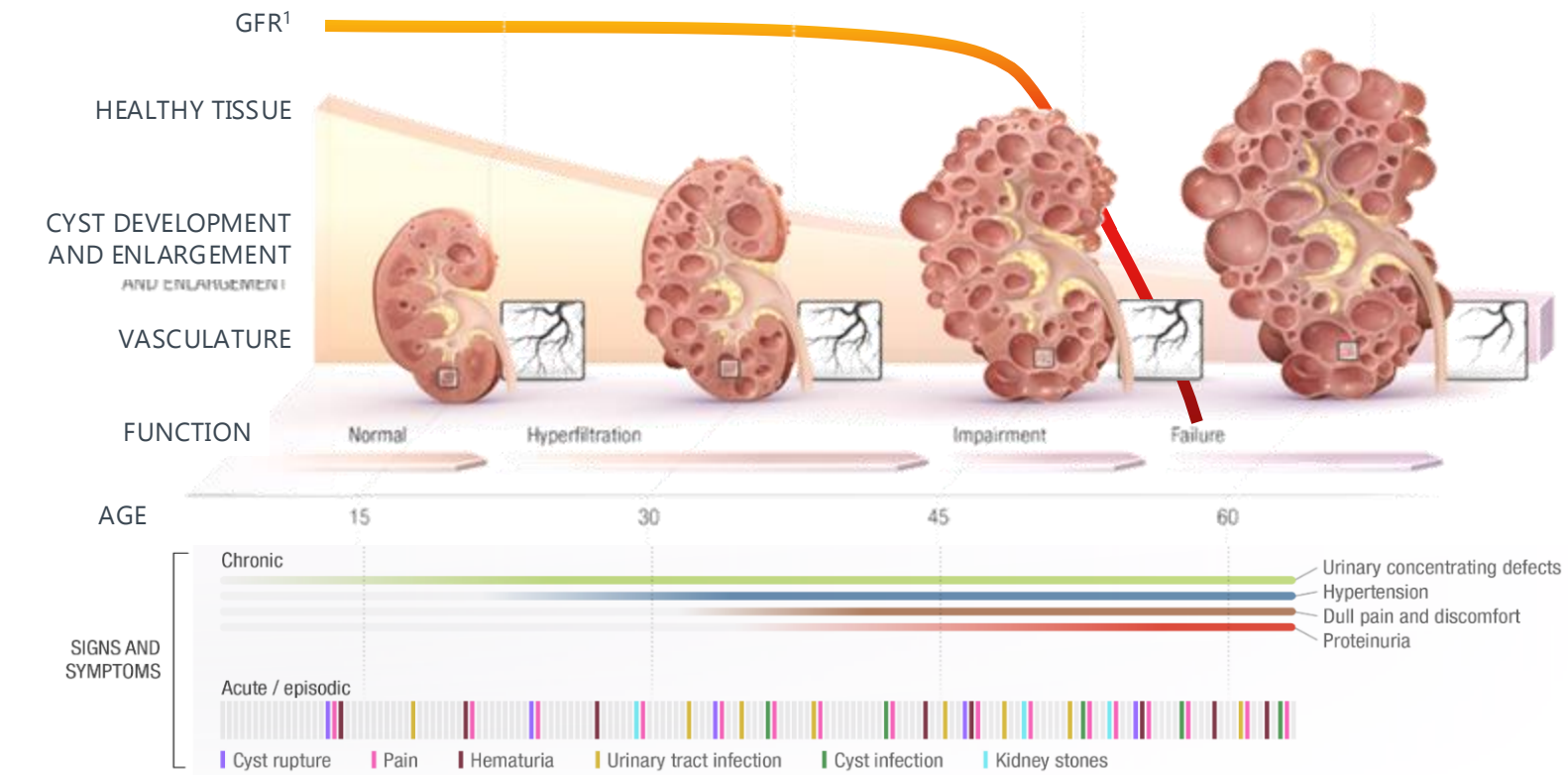
- Are there additional tests that could be ordered by the referring provider that would help ease the transition to nephrology?

ADPKD Complications

ADPKD=autosomal dominant polycystic kidney disease.

Cyst Burden and Patient Complications in ADPKD: An Overview[1]

Kidney Disease Progression in ADPKD

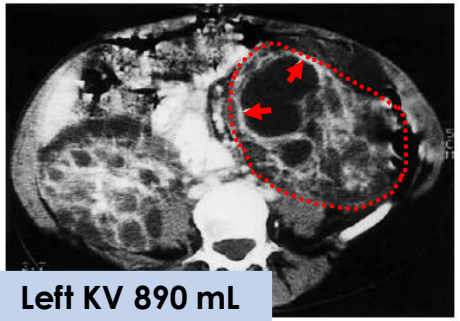


ADPKD=autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate.

1. Grantham JJ et al. (2011). Nat Rev Nephrol. 7(10):556-566.

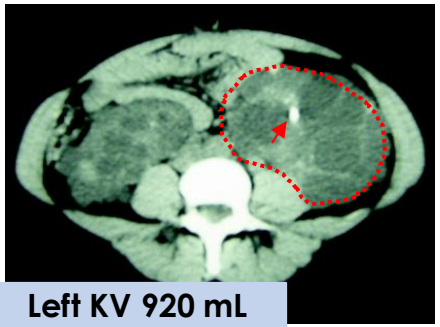
Renal Events That Contribute to Pain in ADPKD[1]

Cyst Infection



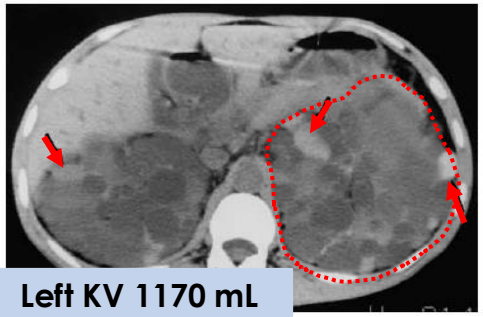
- 20-year-old
- Acute left flank pain
- eGFR: 106 mL/min per 1.73 m^2

Nephrolithiasis



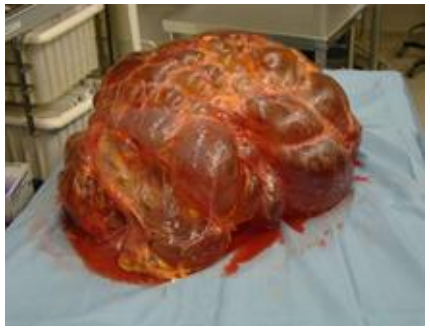
- 35-year-old
- Acute left flank pain

Cyst Hemorrhage



- 32-year-old
- Acute left flank pain
- eGFR: 80 mL/min per 1.73 m^2

Pain



- 52-year-old
- Chronic pain
- Kidney weight: 21.5 kg

Normal single KV: ~150 mL; normal weight of 1 kidney: ~0.15 kg.
ADPKD=autosomal dominant polycystic kidney disease; eGFR=estimated glomerular filtration rate; KV=kidney volume.

1. FDA Cardiovascular and Renal Drugs Advisory Committee, August 5, 2013.

Discussion:

- Do you feel there is enough awareness of ADPKD and potential complications in urology and other subspecialties?

- Who primarily manages these complications in ADPKD?

Final Thoughts

- Do you have any final thoughts you would like to leave with the NephU community today?

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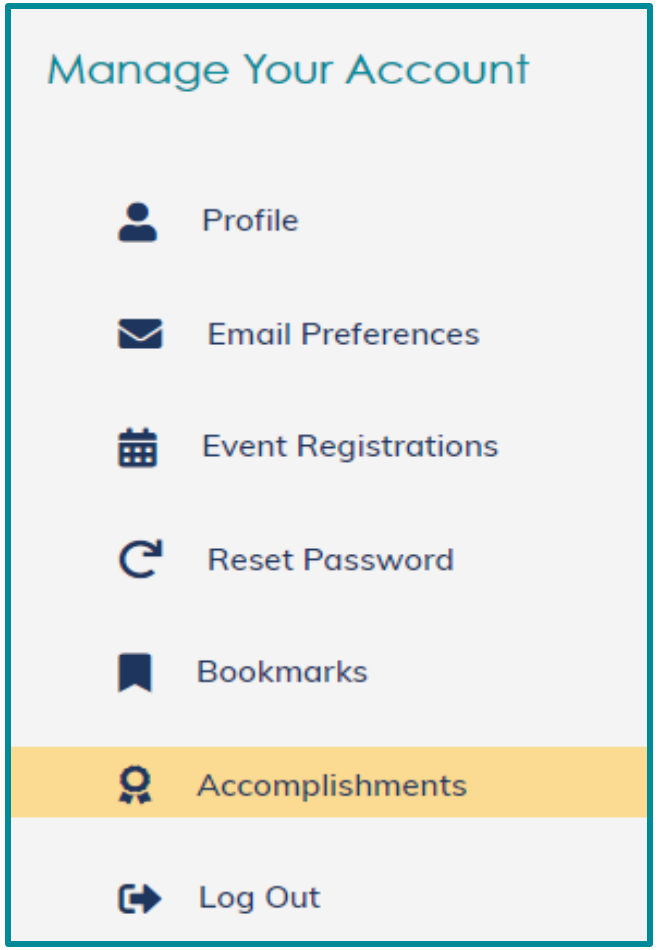

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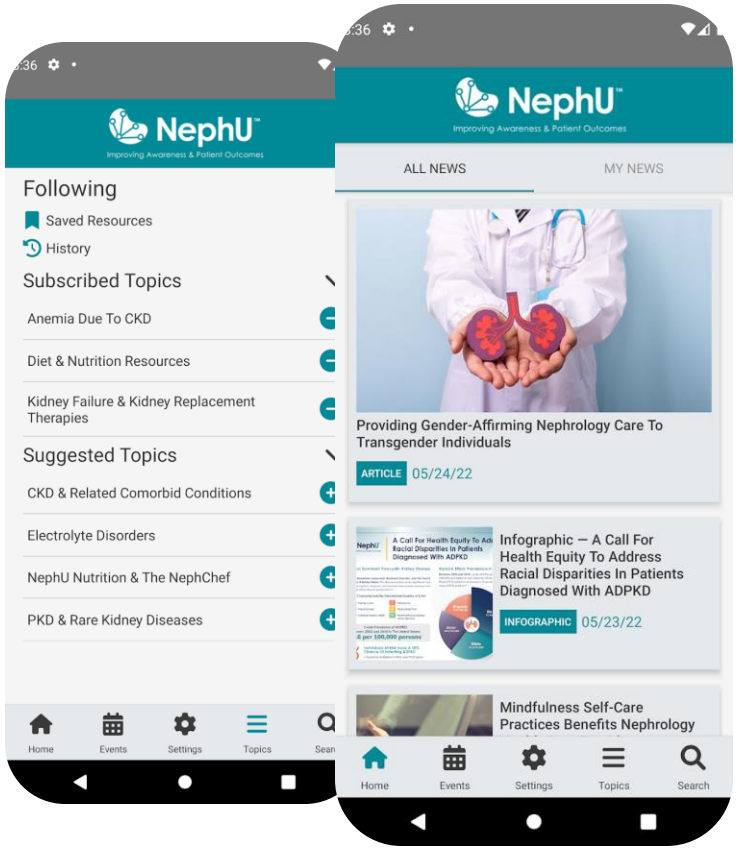

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