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Improving Awareness & Patient Outcomes

Autosomal Dominant Polycystic Kidney Disease (ADPKD): Disease Progression for Radiology

May 2022 US.NephU.D.22.00004

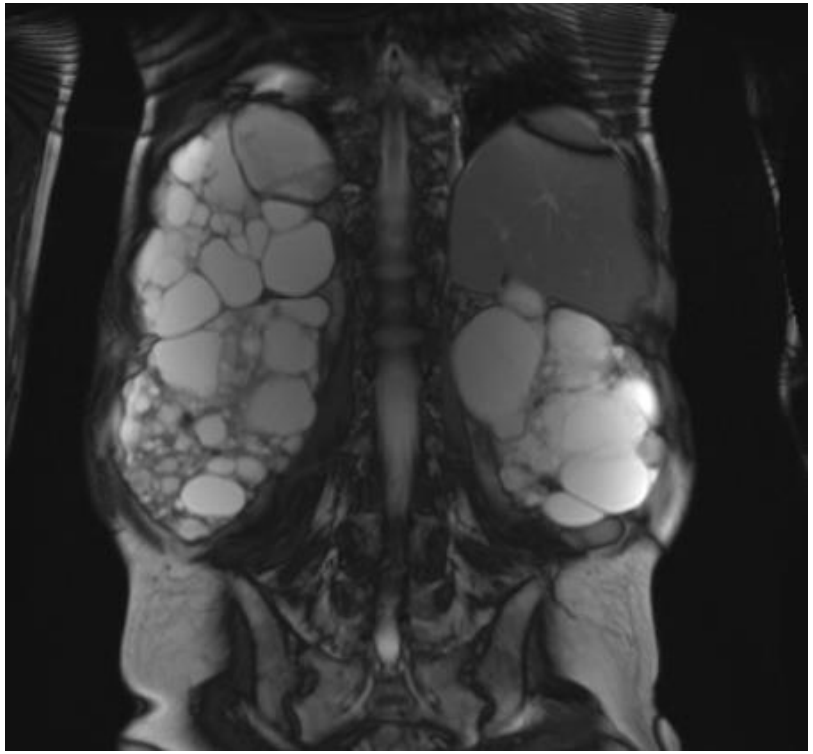
Section Outline

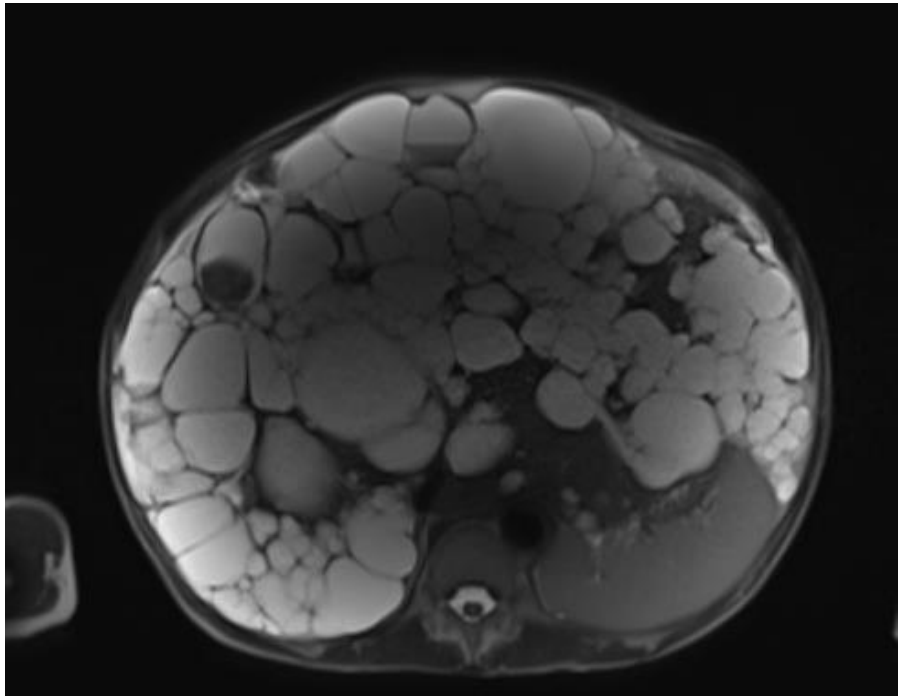
- ADPKD Overview
- Overview of Disease Progression and Total Kidney Volume
- ADPKD Classification

ADPKD OVERVIEW

A Dramatic Presentation of ADPKD

62 y/o woman with a Total kidney volume of 2760 cc (R 1700, L 1060) and Total liver volume of 8900 cc. Her creatinine is 1.8 mg/dL





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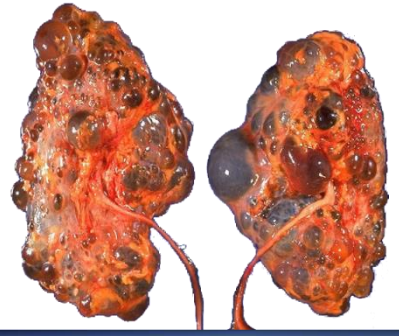
What Is PKD?

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.

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 1:2000 people worldwide are currently diagnosed with ADPKD,[4] and between 1:400 and 1:1000* people living today will be diagnosed with ADPKD in their lifetime[1]

*The higher prevalence value of 1:1000 is believed to be inaccurate because 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.

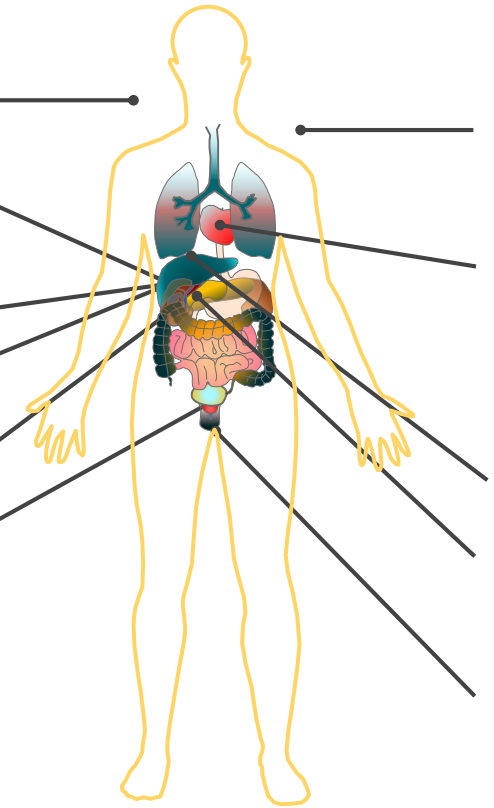
1. Torres VE, Harris PC. (2009). Kidney Int. 76(2):149-168. 2. United States Renal Data System. 2016 USRDS Annual Data Report Volume.
2. ESRD in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016 (accessed 14 February 2019).
3. Chebib FT, Torres VE. (2016). Am J Kidney Dis. 67(5):792-810.
4. Willey C. DRAFT: The Descriptive Epidemiology of ADPKD in the U.S. 2017.

ADPKD Is a Systemic Disease with Renal and Extrarenal Manifestations

Renal cysts are the first manifestation of ADPKD and precede changes in kidney function by many years[1–3]

Renal Manifestations

- Hypertension
- Renal cysts
- Hematuria
- Nocturia
- Palpable kidneys
- Kidney stones
- Abdominal/flank pain
- Renal artery/vein occlusions
- Recurrent UTIs



Extrarenal Manifestations

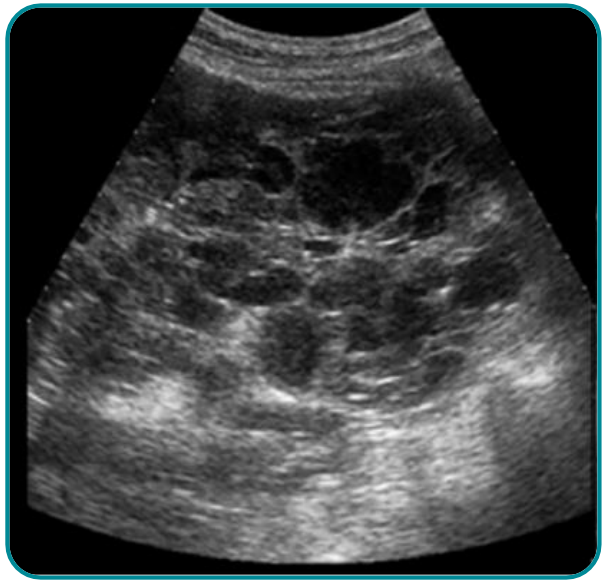
- Intracranial aneurysms
- Subarachnoid cysts
- Vascular dissections
- Valvular heart disease
- Pericardial effusion
- Diverticulosis
- Hepatic cysts
- Hernia
- Pancreatic cysts
- Seminal vesical cysts
- Male infertility

ADPKD=autosomal polycystic kidney disease.

1. Chebib FT, Torres VE. (2016). Am J Kidney Dis. 67(5): 792–810.
2. Halvorson CR et al. (2010). Int J Nephrol Renovasc Dis. 3: 69–83.
3. Ratnam S, Nauli SM. (2010). Int J Nephrol Urol. 2(2): 294–308.

Ultrasound (US) is the Most Commonly Used Imaging Modality for Diagnosis of ADPKD[1]

Figure reproduced with permission from Saedi et al.[3]



US of right kidney in a 55-year-old patient with ADPKD[3]

Unified US Criteria for Diagnosis in Patients With Positive Family History (Pei Criteria)[2]

Age (yr)	No. of cysts required for diagnosis
15–39	Total ≥3 Unilateral or bilateral
40–59	Total ≥4 ≥2 in each kidney
≥60	Total ≥8 ≥4 in each kidney

1. Pei Y et al. *J Am Soc Nephrol.* 2015;26(3):746-753.
2. Pei Y et al. *J Am Soc Nephrol.* 2009;20(1):205-212;
3. Saedi D et al. *Cases J.* 2009;2(1):66.

Differential Diagnosis of Multiple Renal Cysts

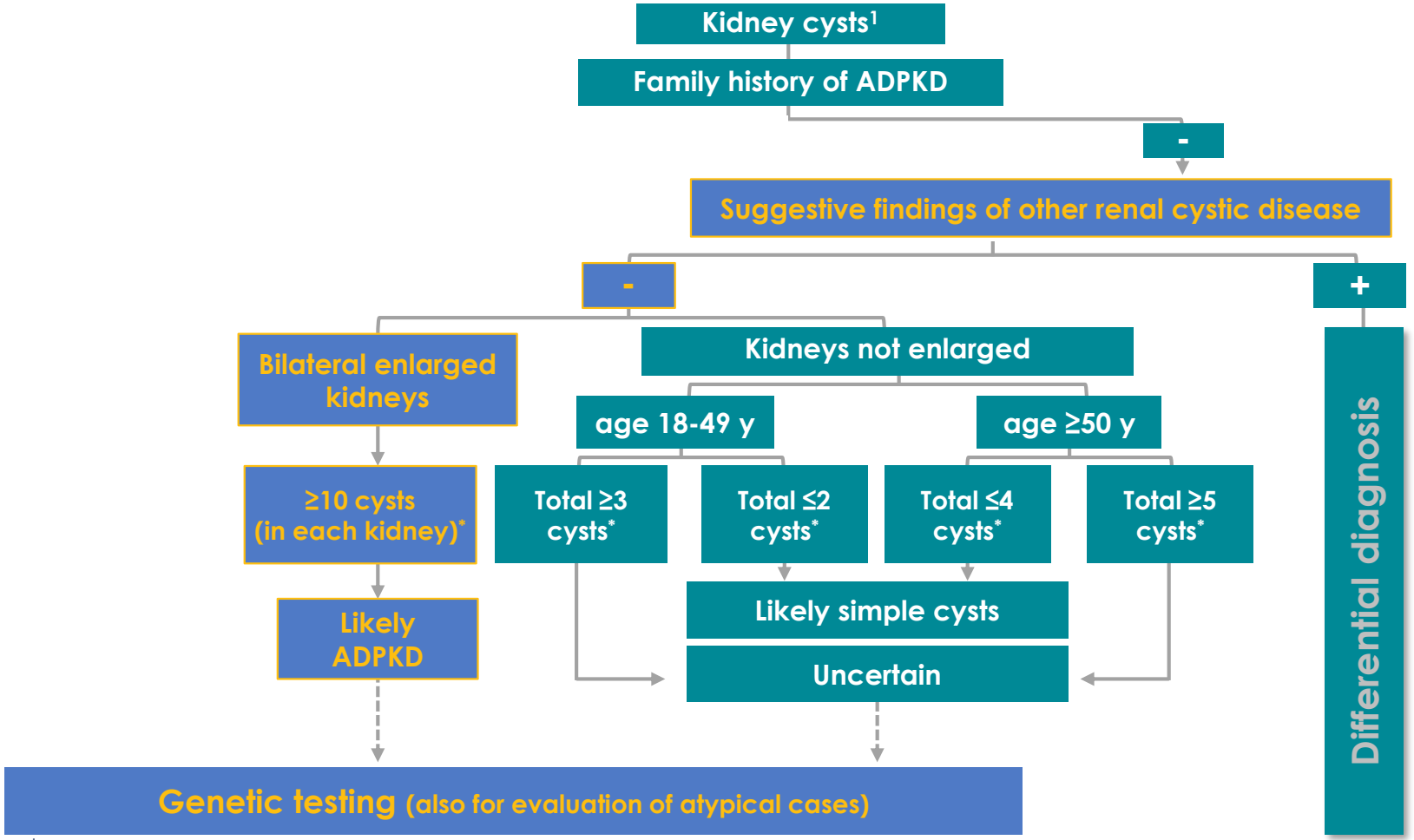
- Renal cysts can be a manifestation of both hereditary and acquired disorders other than ADPKD[1]

  - Acquired renal cystic disease[1]
  - Polycystic liver disease[1]
  - ARPKD[1]
  - Tuberous sclerosis[1]
  - von Hippel-Lindau syndrome[1]
  - Orofaciodigital syndrome I[1]
  - Medullary sponge kidney[1]
  - Renal cysts and diabetes syndrome[2]
  - Glomerulocystic disease[1]
  - Simple renal cysts[1]

ARPKD=autosomal recessive polycystic kidney disease

1. Pei Y, Watnick T. *Adv Chronic Kidney Dis.* 2010;17(2):140-152; 2. Chebib FT, Torres VE. *Am J Kidney Dis.* 2016;67(5):792-810.

Diagnostic Algorithm for ADPKD



*Finding on ultrasound.

ADPKD=autosomal dominant polycystic kidney disease; US=ultrasound.

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

Simple Renal Cysts in the General Population

Incidence of Simple Cysts on Ultrasound (N=729)[1]		
Age	**Unilateral Cyst (%)**	**Bilateral Cysts (%)**
15–29	0	0
30–49	1.7	1
50–70	11.5	4
>70	22.1	9

Incidence of Simple Cysts on Contrast-Enhanced CT[2]		
Age	**Age 18–49 yr N=1345 (%)**	**Age 50–75 yr N=603 (%)**
Any cyst ≥2 mm	39	63
Any cyst ≥5 mm	22	43
Bilateral cysts ≥5 mm	2.3	11
Ravine criteria for ADPKD*	0.3	0.8

CT=computed tomography.

*Ravine criteria for ADPKD are intended for assessing ultrasound cysts in first-degree relatives with ADPKD. Cyst thresholds are age 15–29 years, ≥2 cysts; 30–59 years, ≥2 cysts in each kidney; and 60 years and older, ≥4 cysts in each kidney.

1. Ravine D et al. *Am J Kidney Dis*. 1993;22(6):803-807;
2. Rule AD et al. *Am J Kidney Dis*. 2012;59(5):611-618.

OVERVIEW OF DISEASE PROGRESSION AND TOTAL KIDNEY VOLUME

Variability of ADPKD Disease Progression

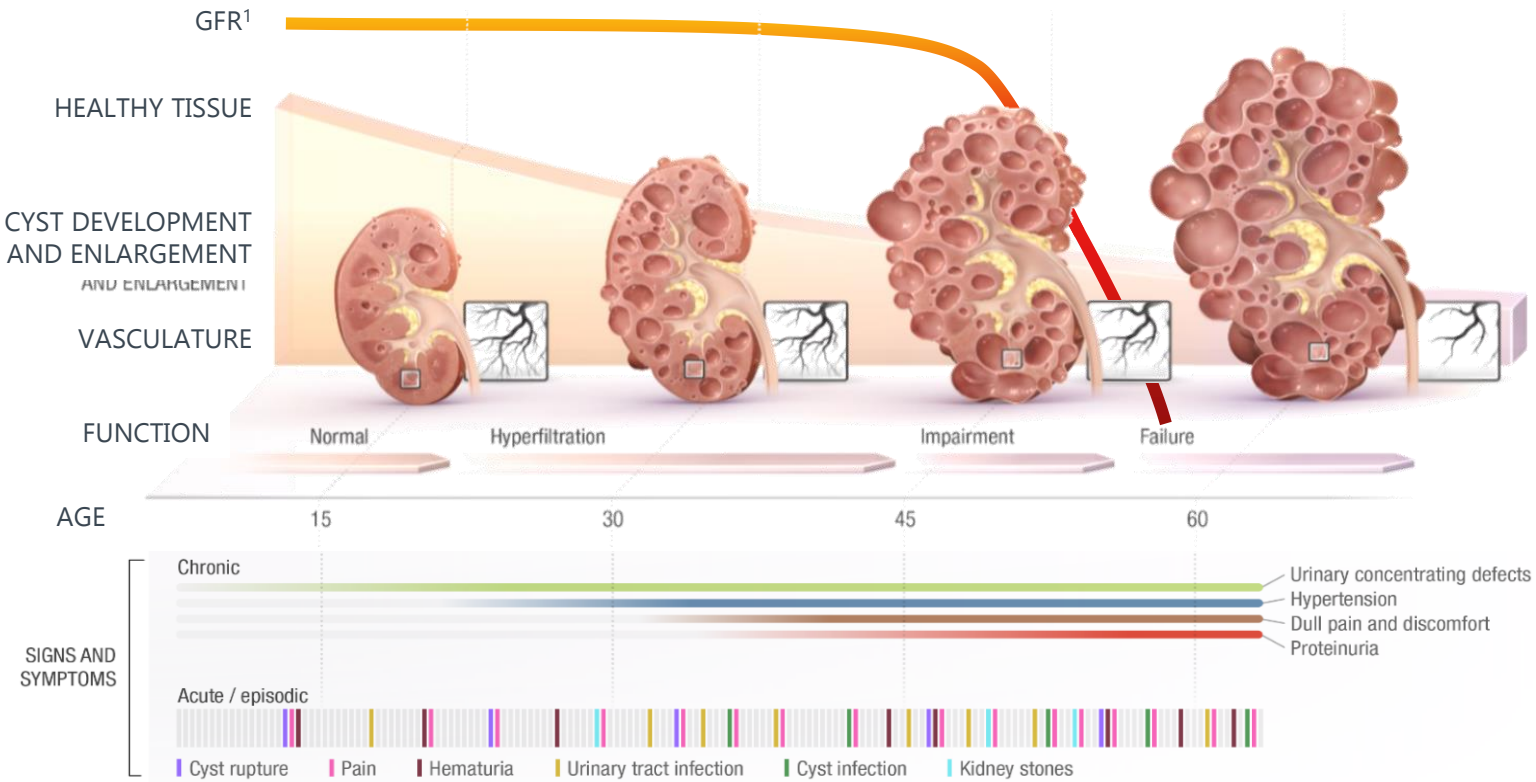
- The rate of disease progression could vary significantly among patients with ADPKD, even within the same family[1,2]
- Patients with rapidly progressing ADPKD reach ESRD at a younger age[3]
- Recent studies show that baseline clinical, genetic and imaging data can identify patients who are at risk for rapid progression[3]

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

1. Grantham JJ et al. (2006). *N Engl J Med.* 354: 2122–30.
2. Harris PC, Rossetti S. (2010). *Adv Chronic Kidney Dis.* 17(2): 131–9.
3. Gansevoort RT et al. (2016). *Nephrol Dial Transplant.* 31(3): 337–48

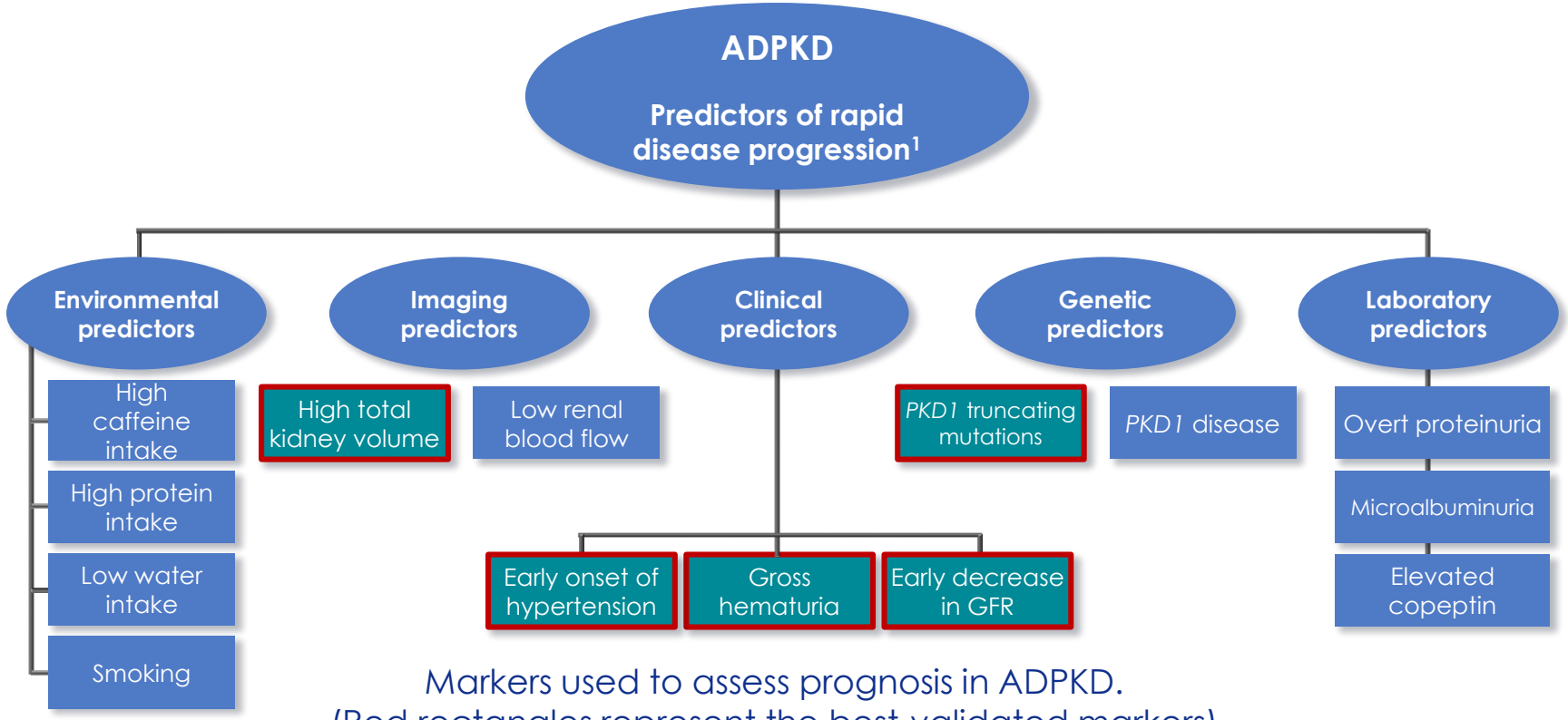
Cyst Burden and Patient Complications in ADPKD: An Overview

Kidney Disease Progression in ADPKD



1. ADPKD=autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate.
2. 1. Grantham JJ et al. (2011). Nat Rev Nephrol. 7(10):556-566.

Predictors of Rapid Disease Progression in ADPKD



Markers used to assess prognosis in ADPKD.
(Red rectangles represent the best-validated markers)

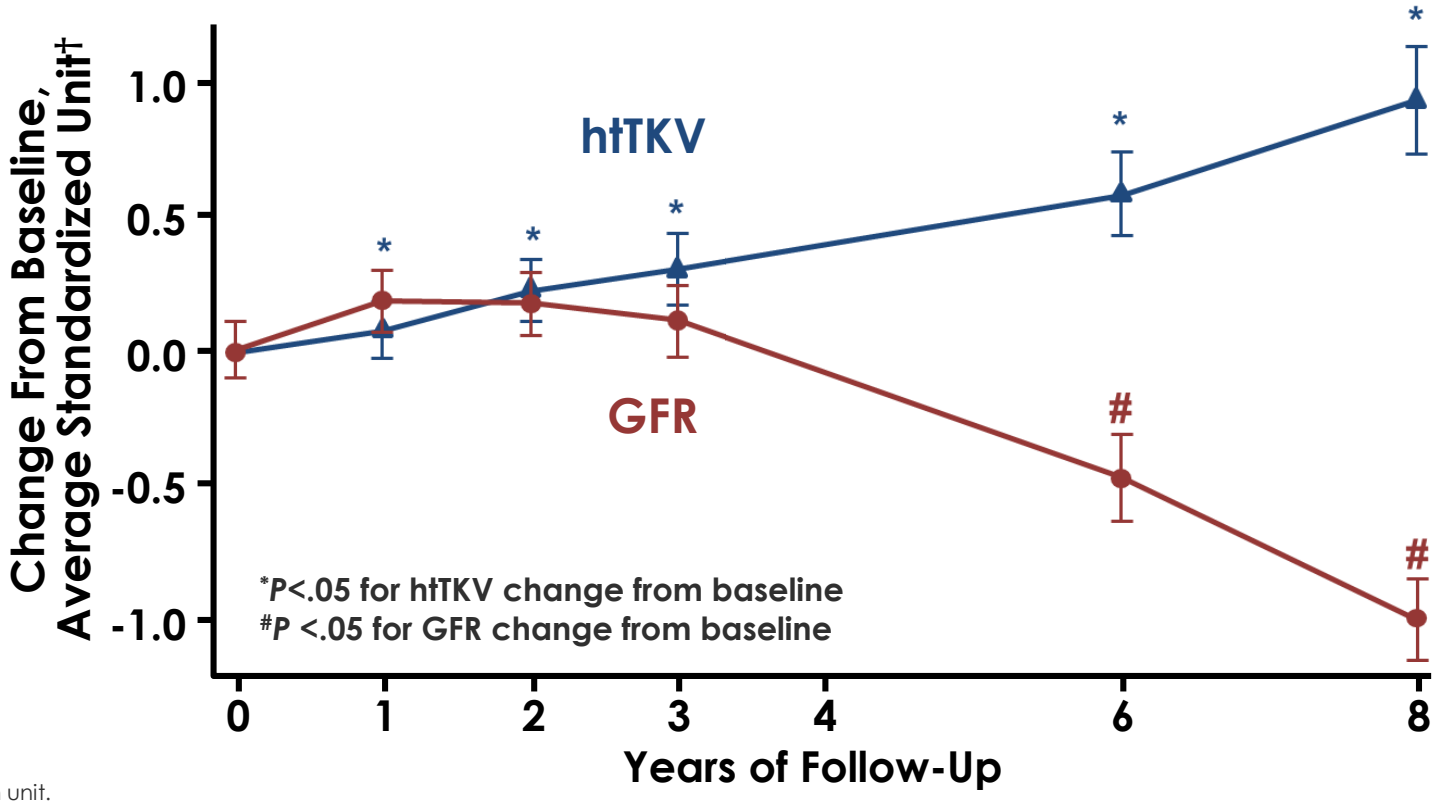
Additionally, male sex,[2] obesity,[3] and low HDL cholesterol[4] have also been identified as risk factors for ADPKD progression

ADPKD=autosomal dominant polycystic kidney disease; GFR=glomerular filtration rate; HDL=high-density lipoprotein; *PKD1*=polycystic kidney disease gene 1.

1. Figure adapted from Gansevoort RT et al. (2016). *Nephrol Dial Transplant.* 31(3):337-348.
2. Schrier RW et al. (2014). *J Am Soc Nephrol*. 25(11):2399-2418.
3. Nowak KL, et al. (2018). *J Am Soc Nephrol*. 29(2):571-578.
4. Torres VE, et al. (2011). *Clin J Am Soc Nephrol*. 6(3):640-647.

Change in Kidney Volume in ADPKD Precedes Changes in Renal Function

Kidney and cyst volume are determinants of renal outcome and precede changes in renal function by many years[1]

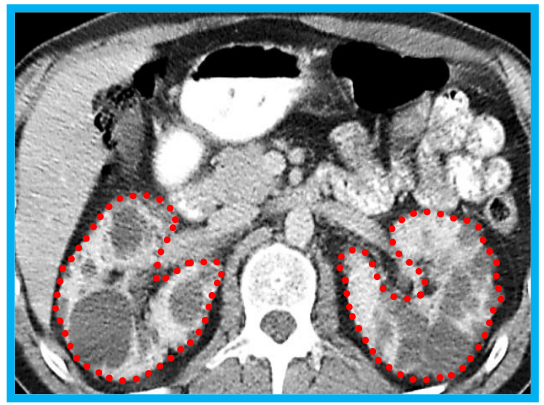


†% change standardized to common unit.
GFR=glomerular filtration rate; htTKV=height-adjusted total kidney volume.

1. Chapman AB et al. (2012). *Clin J Am Soc Nephrol*. 7(3): 479–86.

GFR and TKV in ADPKD Progression

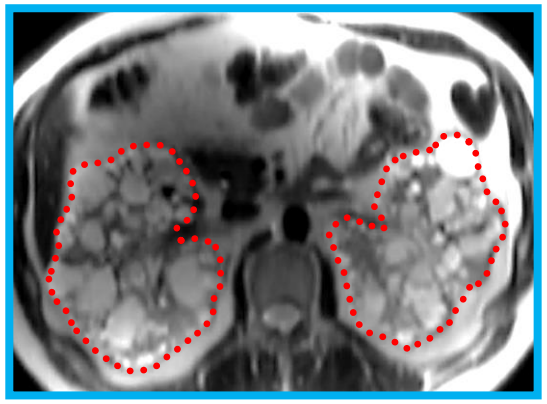
Over 13 years, TKV increased by 300%, with a 53% loss of kidney function[1]



Age 30

CKD Stage 1
GFR 93 mL/min

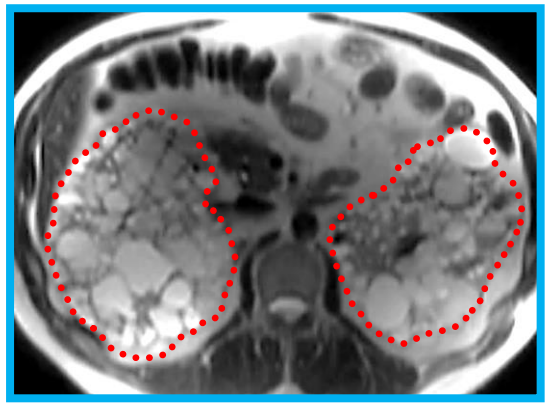
TKV 1,441 mL



Age 37

CKD Stage 2
GFR 61 mL/min

TKV 2,775 mL



Age 43

CKD Stage 3
GFR 44 mL/min

TKV 4,459 mL

1. FDA.http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM364583.pdf. (accessed 18 Nov 2014).

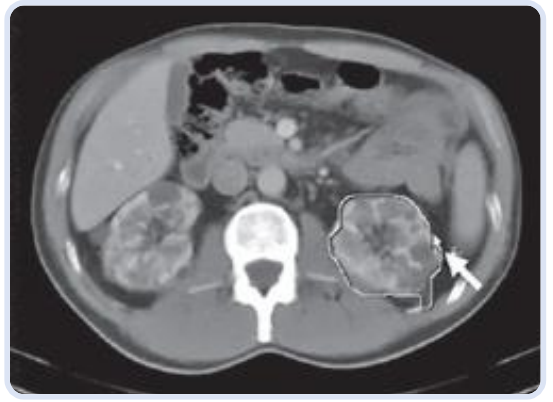
Increased Kidney Volume Is Associated With Renal Complications

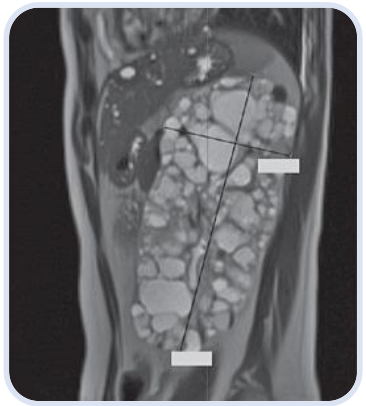
Analysis of Several Observational Studies[1]				
Renal Complication	Patients, n	Mean Volume/Kidney ± SD, mL		*P* Value
		Complication Present	Complication Absent	
Loss of GFR	220	598 ± 368	366 ± 168	<0.0001
Hypertension	241	628 ± 48	352 ± 33	<0.0001
Gross hematuria	191	820 ± 87	588 ± 52	<0.03
Proteinuria	270	1190 ± 93	578 ± 32	<0.0001

1. Grantham JJ et al. (2006). *Clin J Am Soc Nephrol*. 1(1): 148–57.

Methods of Calculating TKV

	Manual Segmentation	Ellipsoid Formula
Imaging modality	MRI and CT*	MRI, CT,* and US
Analysis time	40 minutes	5 minutes
Accuracy	100%	87% with MRI or CT; 21% with US†
Directions	• Trace kidney outline onto cross-sectional images • Multiply all traced areas by slice thickness • Combine slice volumes	• Measure length, width, and depth for both kidneys • Calculate volume using ellipsoid formula





CT=computed tomography; MRI=magnetic resonance imaging; TKV=total kidney volume; US=ultrasound. *CT-related data were not available, but by approximation can be considered close to MRI methodology. †Measurement accuracy according to Mayo Clinic model classification.

1. Figures reproduced with permission from Magistroni R et al. *Am J Nephrol*. 2018;48(1):67-78.

Planimetry for Determining Total Kidney Volume

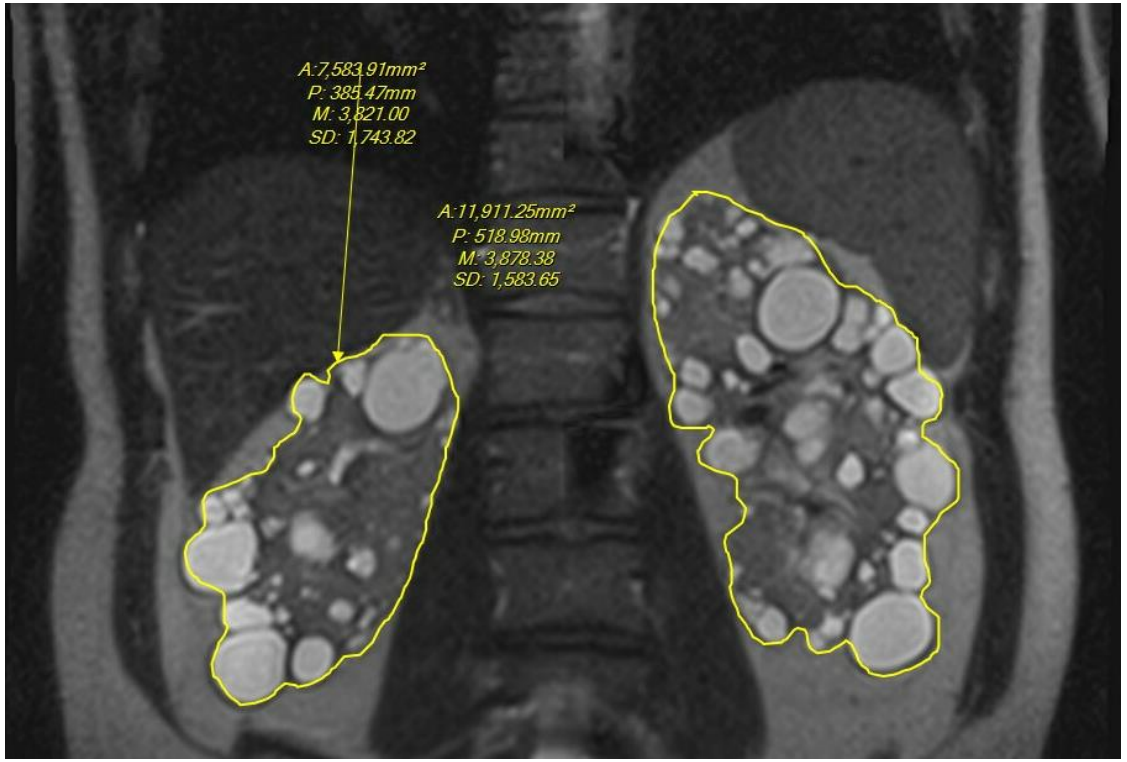


Image used with permission from Dr. Neera Dahl.

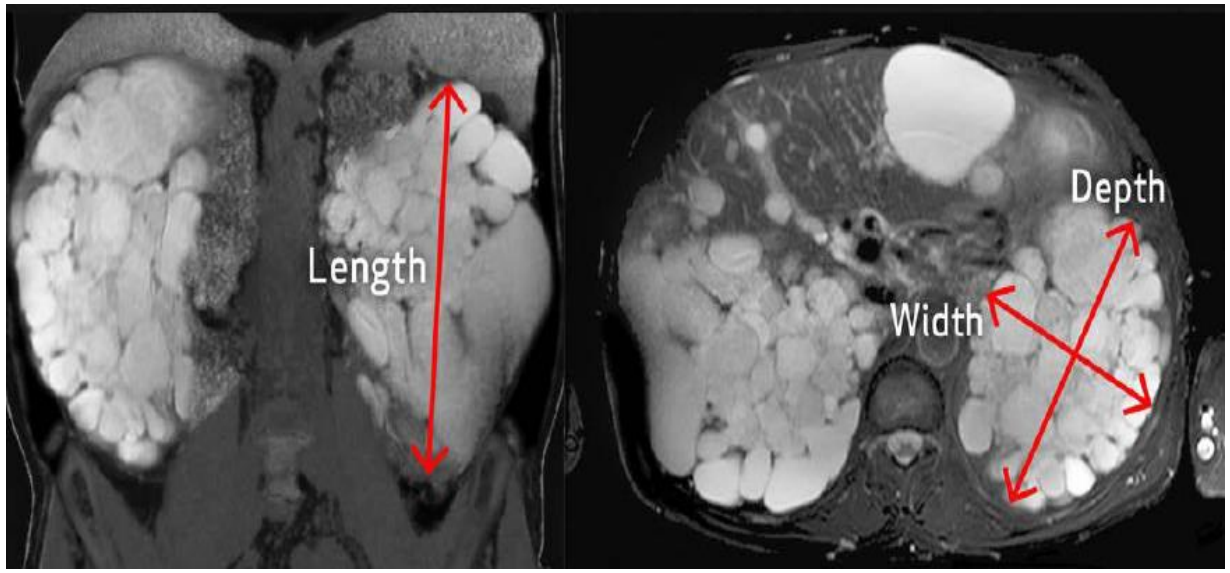
Planimetry with manual segmentation:

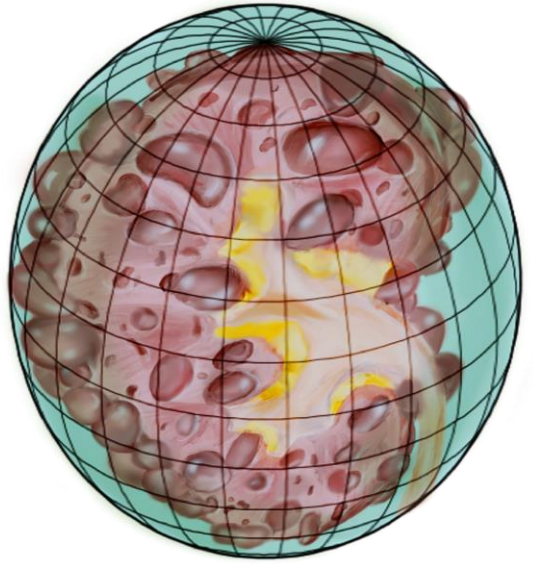
Accuracy: 100%

Radiologist's time: 40 min

Value to nephrologist: **Priceless**

Calculating Total Kidney Volume (TKV) Using the Ellipsoid Formula[1,2]





Please consider giving dimensions (sagittal length, coronal length, width, depth) if unable to perform planimetry

Ellipsoid formula based on the ellipsoid shape
π/6 x (LxWxD)

1. Irazabal MV et al. *J Am Soc Nephrol*. 2015;26(1):160-172;
2. Mayo Foundation and Medical Education and Research. https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754. Accessed January 7, 2020.

Imaging Modalities for TKV: Strengths and Limitations1

Image Modality	Measurement Accuracy	Strengths	Limitations
MRI	Can detect cysts ≥2 mm in diameter	• Can reliably measure kidney volume over short periods of time with minimal bias and low inter- and intraoperator variability • Allows segmentation of individual cysts, providing quantitative assessment of disease	• Cost • Lack of availability
CT	Can detect cysts ≥2 mm in diameter	Provides accurate and reliable measurement of TKV and cyst volume in ADPKD	• Potentially nephrotoxic contrast medium (contrast not needed for TKV) • Exposure to radiation (low-dose protocols in some centers)[2]
Ultra-sound	Can detect cysts >1 cm in diameter	• Does not require radiation • Widely available • Low cost	• Lacks precision and accuracy for detecting short-term changes in kidney volume • Highly operator-dependent

TKV can be calculated based on a single image without a requirement for serial procedures

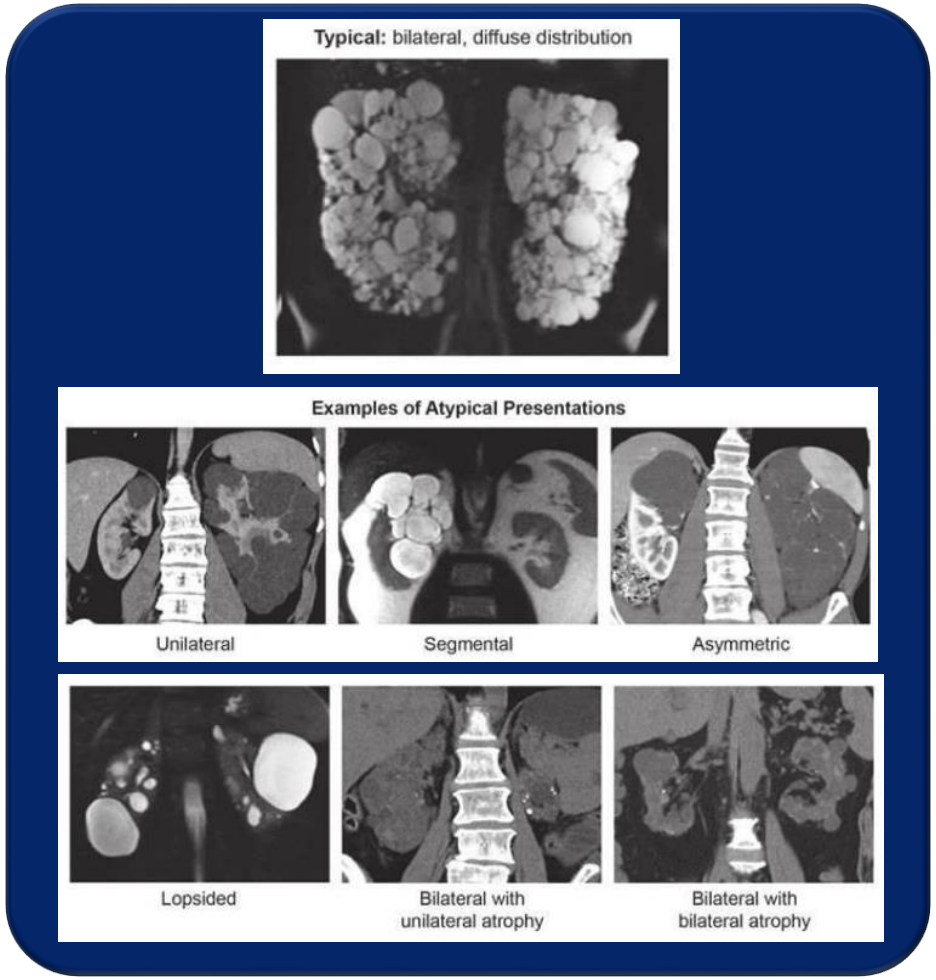
CT=computed tomography; MRI=magnetic resonance imaging; TKV=total kidney volume.

1. Magistroni R et al. *Am J Nephrol.* 2018;48(1):67-78;. 2. Bevilacqua MU et al. *Radiology.* 2019;291(3):660-667.

ADPKD CLASSIFICATION

ADPKD Imaging Classification: Typical vs Atypical Renal Presentation

- Patients were classified as Typical (Class I) or Atypical (Class II) based on cyst presentation[1]
- Typical (n=538) patients were sub-classifed according to htTKV and age[1]
- Atypical patients (n=52) were excluded from the study since baseline TKV in these patients was found to be a poor predictor of future loss of renal function

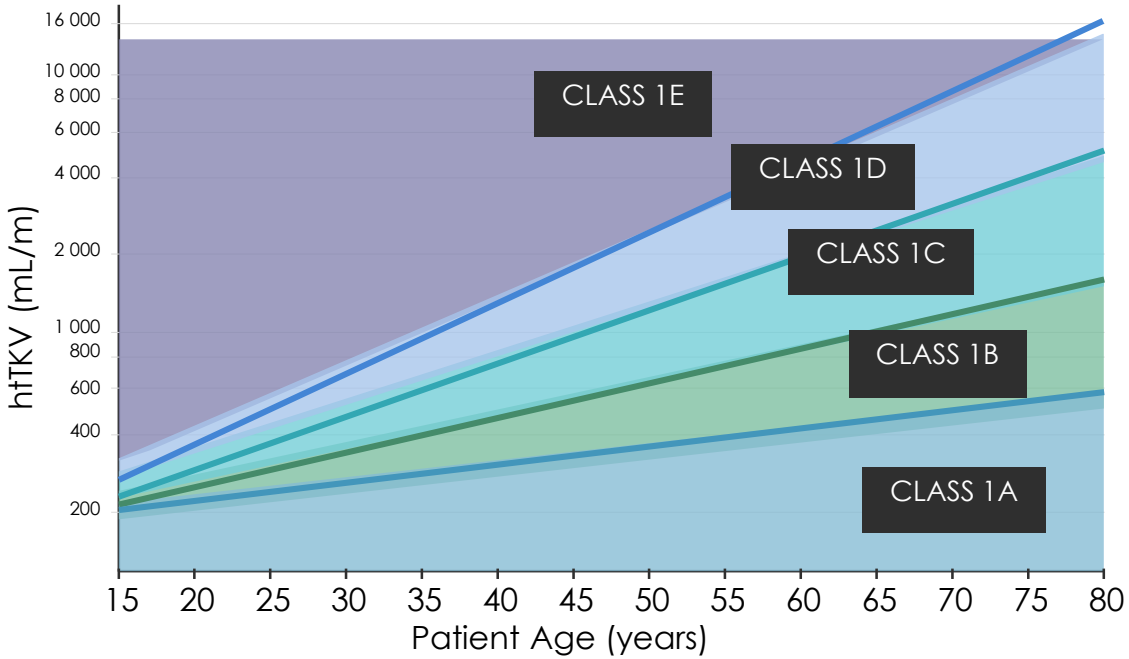


Adapted from Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.

1. Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.

TKV-Based Classification of ADPKD

Age and htTKV predicts decline in eGFR over time in patients with a typical* presentation of ADPKD

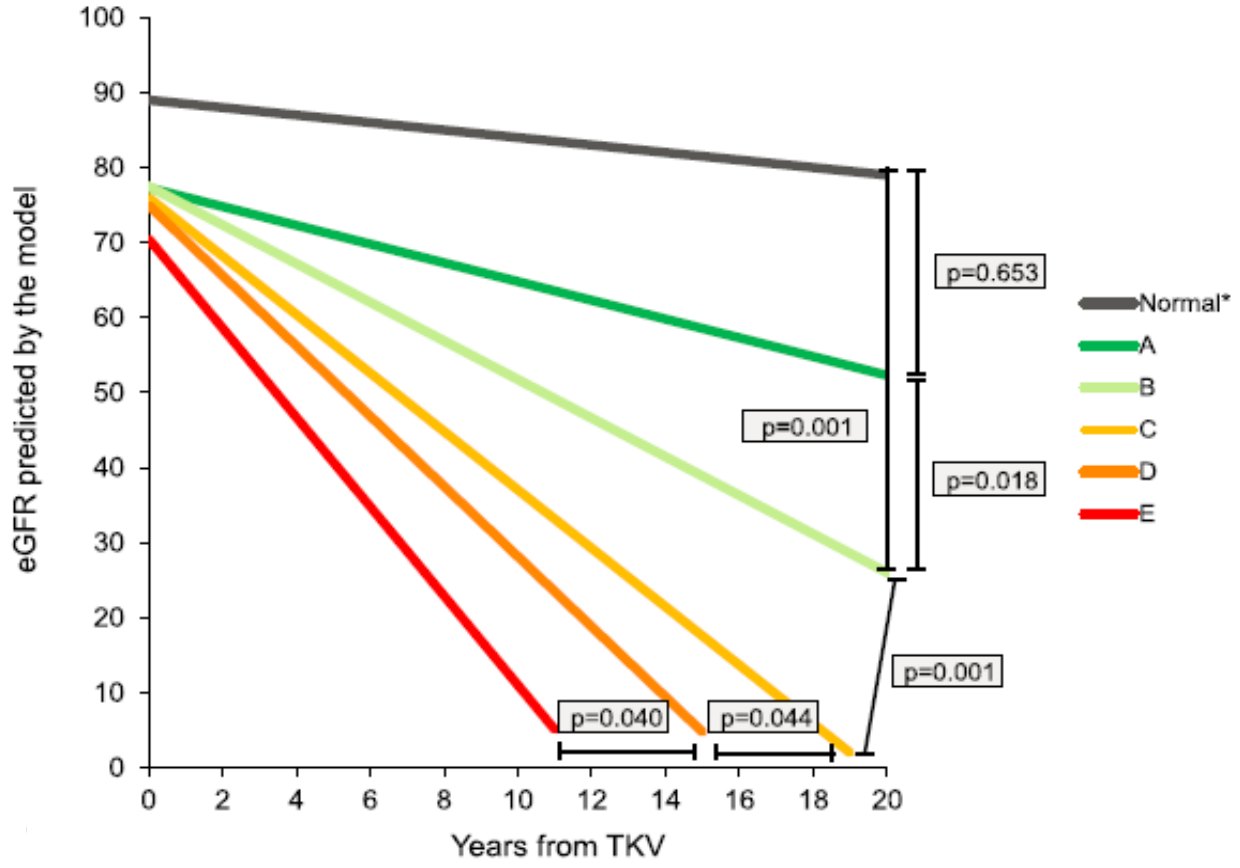


Class	Estimated kidney growth rate: yearly percentage increase	Risk for eGFR decline
1E	>6.0%	High risk
1D	4.5 – 6.0%	High risk
1C	3.0 – 4.5%	High risk
1B	1.5 - 3.0%	Intermediate risk
1A	<1.5%	Low risk

*Typical presentation refers to patients with a bilateral and diffuse cyst distribution in both kidneys with mild to severe replacement of kidney tissue by cysts, with all cysts contributing similarly to TKV.
ADPKD=autosomal dominant polycystic kidney disease; eGFR=estimated glomerular filtration rate; htTKV=height-adjusted TKV; TKV=total kidney volume.

1. Irazabal MV et al. (2015). J Am Soc Nephrol. 26:160-172.

ADPKD Classification Defines Patients With Different Risks for Decline in eGFR

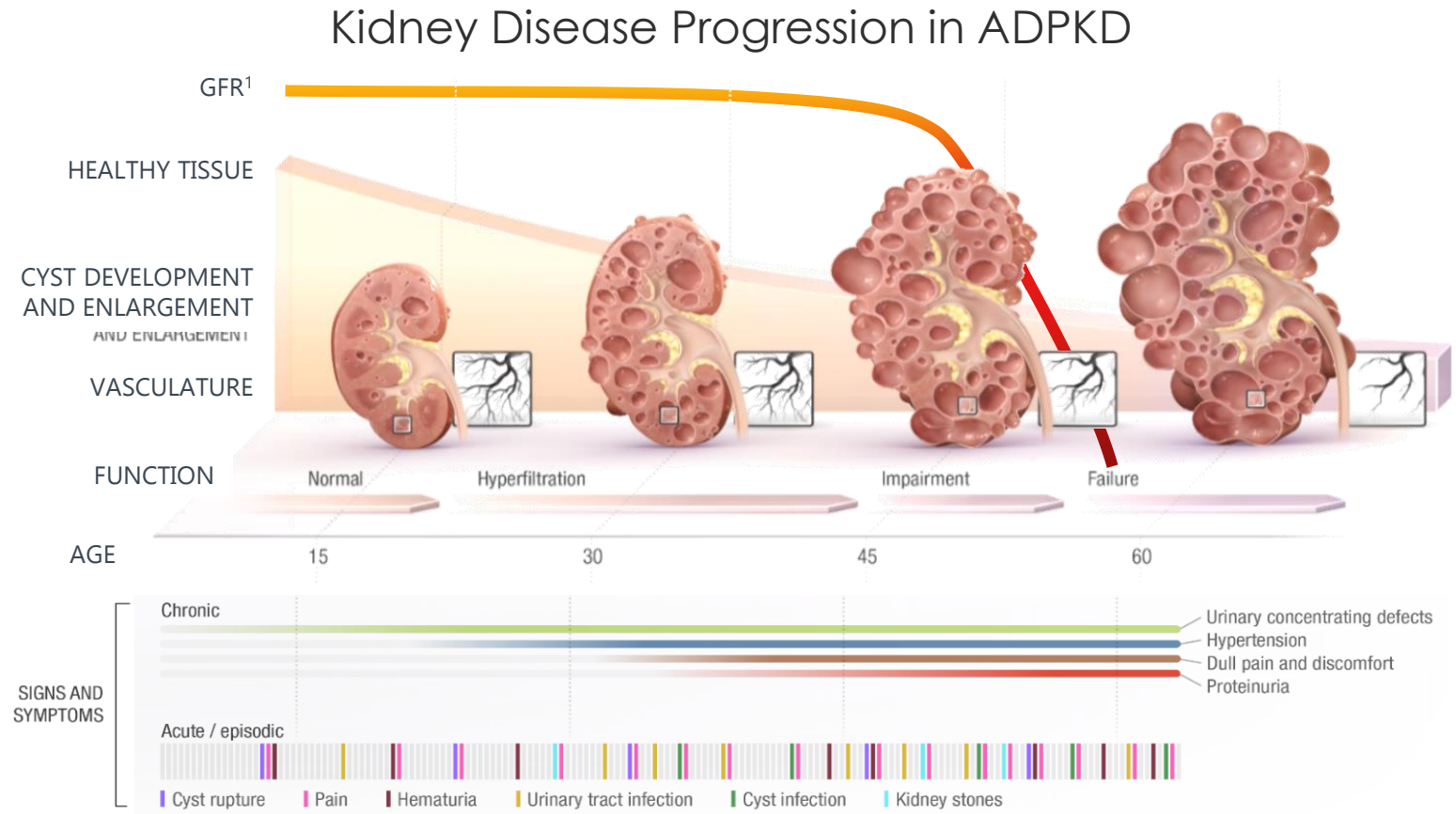


Estimated slope (ml/min per 1.73 m2 per year) by subclass (A–E)

Subclass	Men	Women
A	-0.23	0.03
B	-1.33	-1.13
C	-2.63	-2.43
D	-3.48	-3.29
E	-4.78	-4.58

1. Irazabal MV et al. (2015). *J Am Soc Nephrol*. 26(1): 160–72.

Cyst Burden and Patient Complications in ADPKD: An Overview



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

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

A High Risk ADPKD Patient

- 25 y/o man with ADPKD diagnosed as a young child. He has had hypertension for 2 years.
- His father had ADPKD and subsequently underwent a renal transplant in his mid-50s.
- He has no flank or back pain, and no hematuria
- PE: WD/WN in NAD, BMI 25, 160/122, 70
- Normal exam, no palpable cysts or edema
- Creatinine 88.4 µmol/L (1.0 mg/dL)
- Kidney volumes: Right 530 ml, Left 594 ml.
- Height adjusted TKV is 661 ml/m

Total Kidney Volume helps us to identify him prior to loss of kidney function

- Mayo Class 1E
- Assuming a truncating PKD1 mutation his PROPKD score is 9.

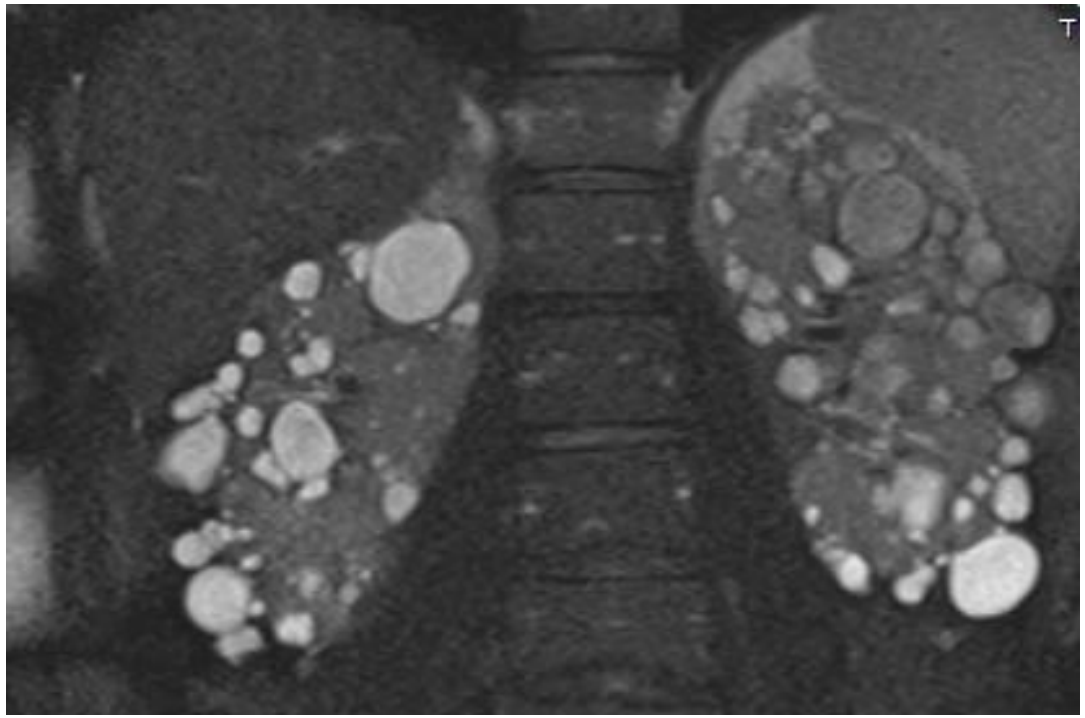


Image used with permission from Dr. Neera Dahl.

Summary

- The rate of disease progression could vary significantly among patients with ADPKD, even within the same family[1,2]
- The CRISP study demonstrated that baseline htTKV (measured by stereology MRI) is an independent predictor of future GFR decline in ADPKD patients[3]
- Ideally every abdominal imaging report of an ADPKD patient will contain the following:
  - A comment on whether the cyst distribution is typical or atypical
  - Kidney measurements or the kidney volume of each kidney

1. Grantham JJ et al. (2006). *N Engl J Med.* 354: 2122–30. 2. Harris PC, Rossetti S. (2010). *Adv Chronic Kidney Dis.* 17(2): 131–9 . 3. Chapman AB et al. (2012). *Clin J Am Soc Nephrol*. 7(3): 479–86