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Diagnostic Imaging and Total Kidney Volume:

A Nephrologist and Radiologist Discuss Breaking Down Barriers

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This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc.

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Objectives

- Understand the importance of obtaining a height-adjusted Total Kidney Volume (htTKV) in Autosomal Dominant Polycystic Kidney Disease (ADPKD) patients
- Review the strengths and limitations of different imaging modalities Nephrologists can order to obtain a TKV
- Review different methods Radiologists have available to calculate TKV
- Discuss methods to break down communication barriers between the Nephrologist and Radiologist

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]	Autosomal dominant (ADPKD)[3,4]		Autosomal recessive (ARPKD)[1]
Rare, recessively inherited	***PKD1/PKD2* (~91%)**	***NMD** (~9%)**	***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]

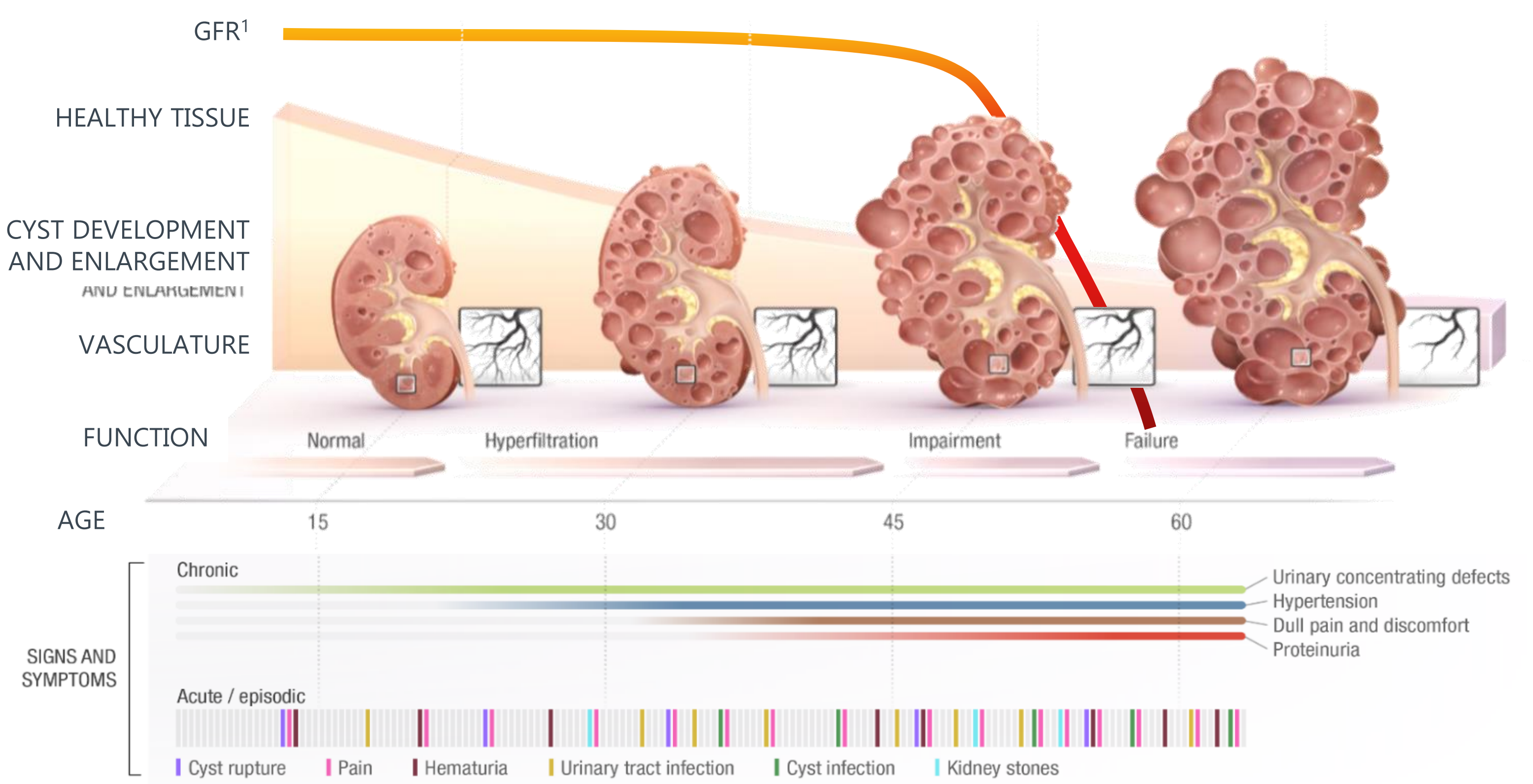
- ADPKD affects both sexes equally, and occurs in all ethnicities[3]
- ADPKD is the most common life-threatening inherited renal disease and accounts for up to ~5% of all patients with ESRD[2]
- ADPKD is the fourth leading cause of ESRD in the United States after diabetes, hypertension, and glomerulonephritis[2]
- As many as 1:2000 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.

Cyst Burden and Patient Complications in ADPKD: An Overview

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.

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

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]

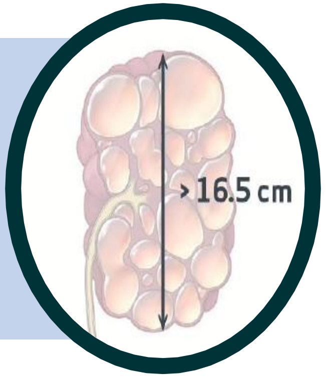
Age (yr)	No. of cysts required for diagnosis
15–39	Total ≥3 Unilateral or bilateral
40–59	Total ≥4 ≥2 in each kidney
≥60	Total ≥8 ≥4 in each kidney

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

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.

Ultrasound for the Measurement of Kidney Length

US-measured predictor of rapid progression†
KL > 16.5 cm
in patients < 45 years old[1,2]



Limitations of US-KL in identifying rapid progression

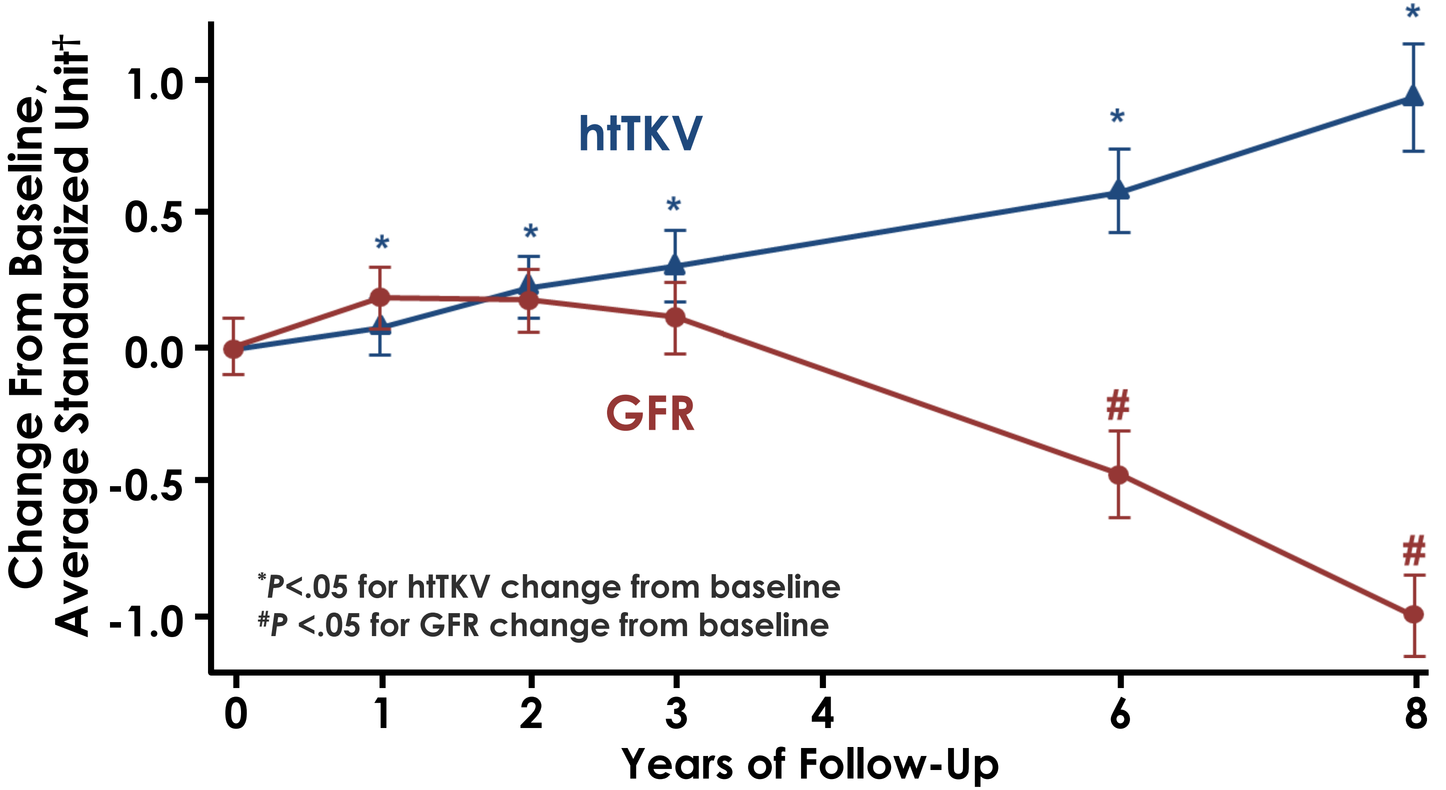
- In data analysis, KL was not normalized for height, which is an important variable*[2]
- Young patients with lengths < 16.5 cm may still have rapidly progressing disease[3]
- Atypical patients with slow progression may have lengths > 16.5 cm[3]
- US-measured KL is less accurate with larger kidneys[1]
- US measurements are operator-dependent and lack precision and accuracy for detecting short-term changes in kidney volume and increase the risk of misclassifying ADPKD progression[1,3,4]

*Based on data analysis comparing US and MRI KL measurements from CRISP.[1] † When rapid progression is defined as CKD 3 development within 8 years.[1,2]
ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; htTKV, height-adjusted TKV; KL, kidney length; MRI, magnetic resonance imaging; TKV, total kidney volume; US, ultrasound.

1. .Bhutani H et al. *Kidney Int.* 2015; 88:146-151.
2. Gansevoort RT et al. *Nephrol Dial Transplat.* 2016; 31:337-348.
3. Chebib FT et al. *J Am Soc Nephrol.* 2018; 29(10):2458-2470. 4
4. Magistroni R et al. *Am J Nephrol.* 2018; 48:67-78.

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]



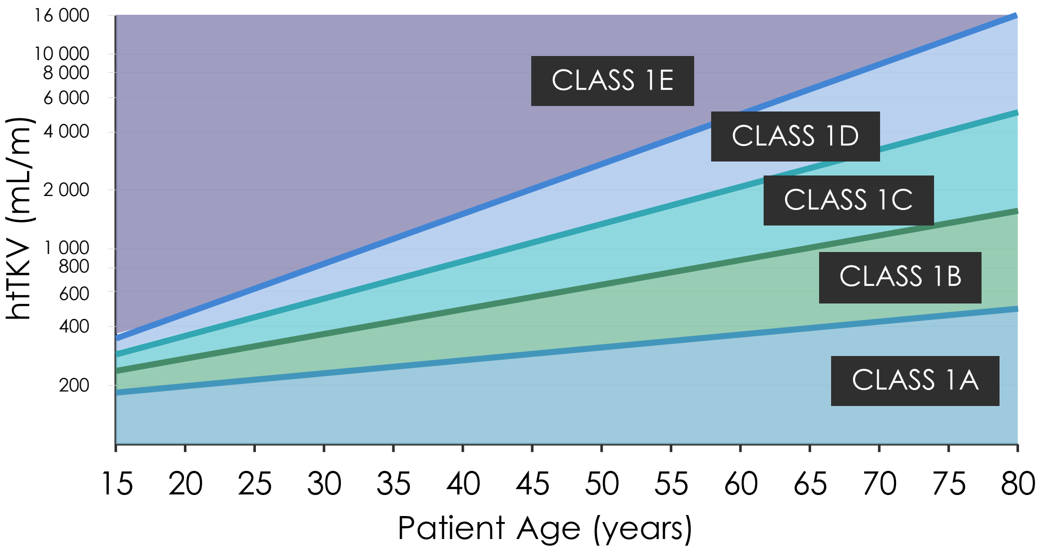
†% change standardized to common unit.

GFR=glomerular filtration rate; htTKV=height-adjusted total kidney volume.

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

TKV-Based Classification of ADPKD

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



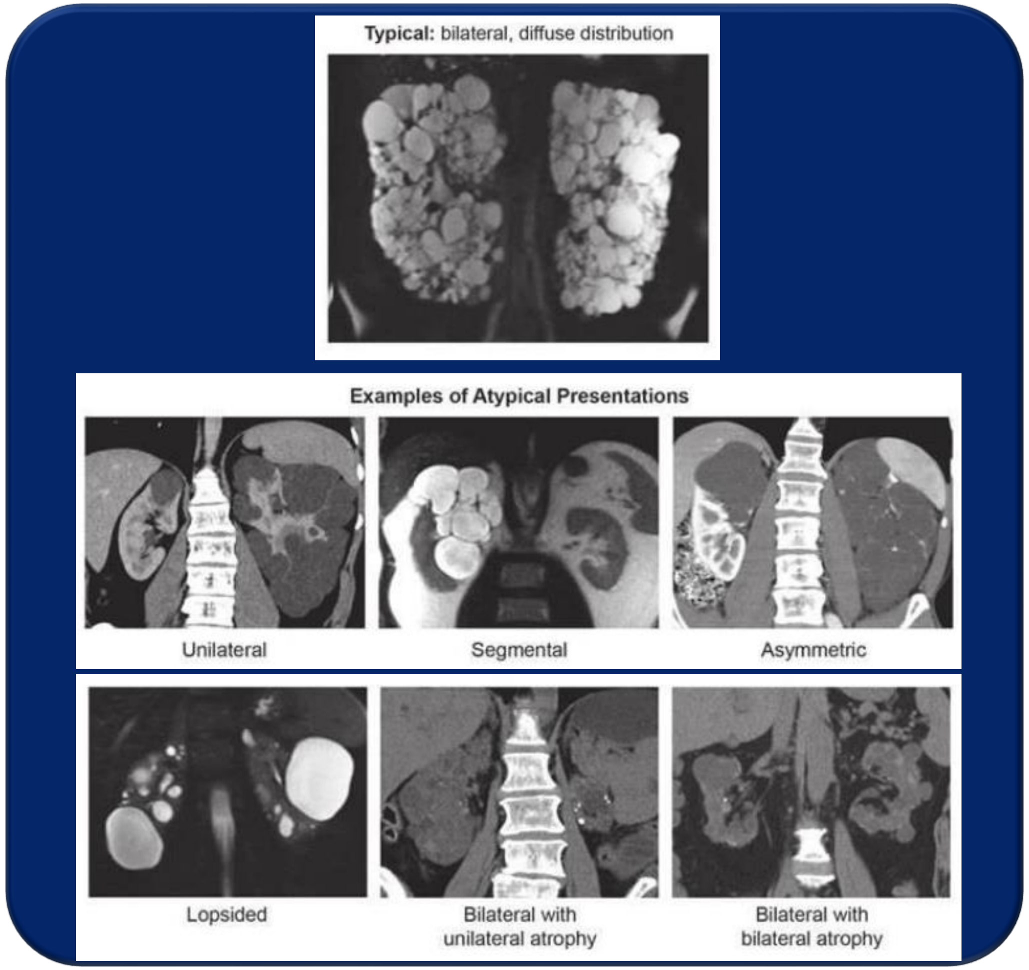
Class	Estimated kidney growth rate: yearly percentage increase	Risk for eGFR decline
1E	>6.0%	High risk
1D	4.5 – 6.0%	High risk
1C	3.0 – 4.5%	High risk
1B	1.5 - 3.0%	Intermediate risk
1A	<1.5%	Low risk

*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 Imaging Classification: Typical vs Atypical Renal Presentation

- Typical (Class I) cases refer to patients with bilateral and diffuse cyst distribution in both kidneys. All cysts contribute similarly to TKV[1]
- Atypical (Class 2) cases refer to patients who do not fulfil the criteria for typical disease and represent 5%-10% of ADPKD patients. In these patients TKV does not predict eGFR decline[1]



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.

Imaging Modalities for TKV: Strengths and Limitations[1]

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

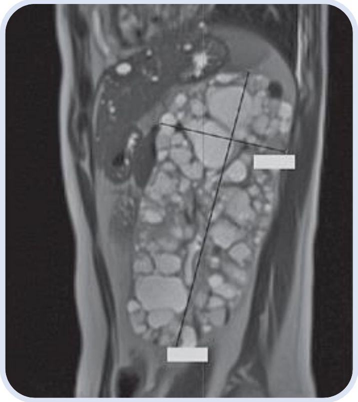
TKV can be calculated based on a single image without a requirement for serial procedures

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.

Methods of Calculating TKV

	Manual Segmentation	Ellipsoid Formula	3D	Semiautomated and Automated
Imaging modality	MRI and CT*	MRI, CT*, and US	US	MRI and CT*
Analysis time	40 minutes	5 minutes	5 minutes	Semiautomated 2 minutes, Automated N/A
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	• An electromagnetic tracker is attached to the US probe; Use of AI	• Use of AI; several techniques available with quality check by radiologist



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.

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

Planimetry for Determining Total Kidney Volume

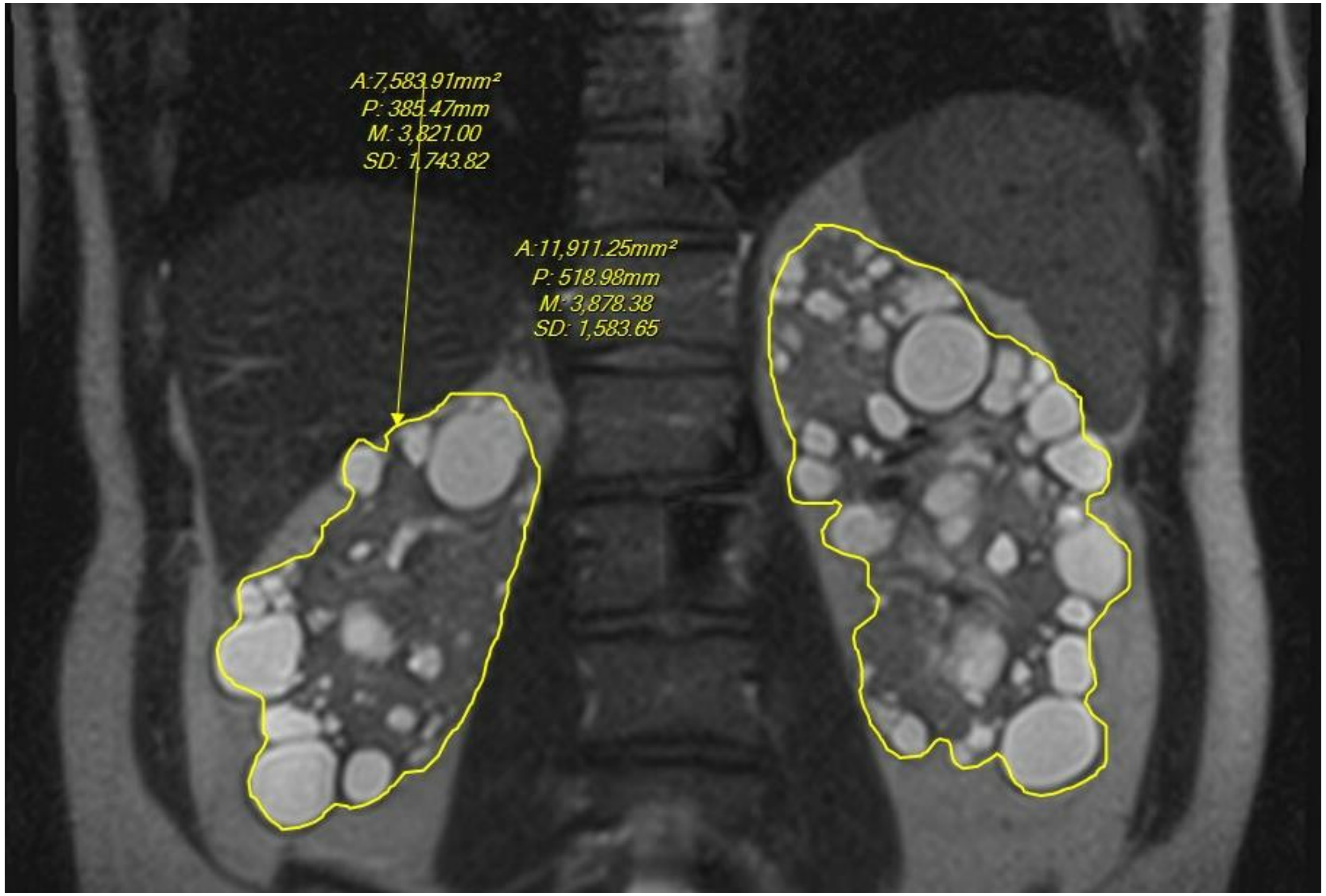
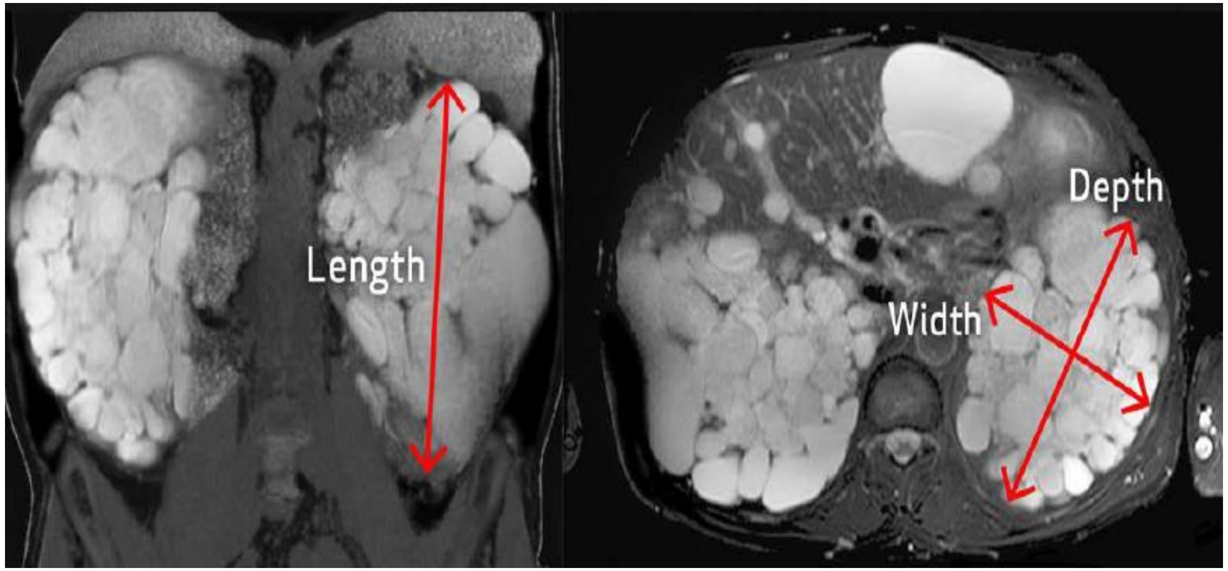
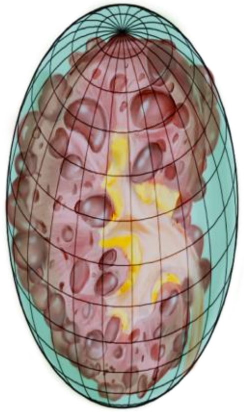


Image used with permission from Dr. Neera Dahl.

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





Ellipsoid Formula
(if typical PKD)

Left Kidney		Right Kidney	
$\frac{\pi}{6}$ x (LxWxD)	+	$\frac{\pi}{6}$ x (LxWxD)	= TKV

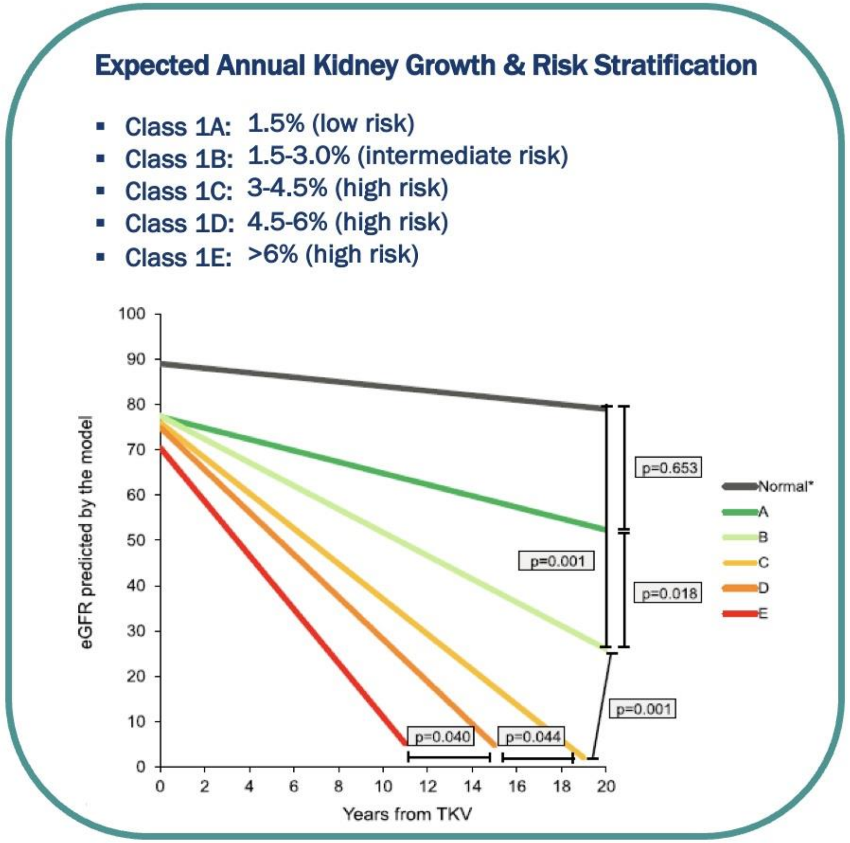
Units for kidney dimensions are in mm. To get kidney volume in mL, multiply by 0.001. The length should be the average of the sagittal and coronal lengths.

Note: Convert the TKV to a height-adjusted TKV by dividing TKV by height in meters

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 Compared to MRI Manual Segmentation

Image Modality	TKV underestimation (mean % difference)[1]	MCIC misclassification[1]	Prediction for high-risk MCIC (1C-1E)[1]	
MRI Ellipsoid	-3.2%	11%	• PPV 96% • NPV 90%	• Sensitivity 94% • Specificity 96%
3D Ultrasound	-9.1%	21%	• PPV 95% • NPV 88%	• Sensitivity 88% • Specificity 96%
Ultrasound Ellipsoid	-11%	22%	• PPV 98% • NPV 95%	• Sensitivity 85% • Specificity 99%



Republished with permission of The American Society of Nephrology, from Irazabal MV et al. *J Am Soc Nephrol*. 2015: 26(1): 160–72

TKV measurements in ADPKD by 3D US and US ellipsoid displayed similar bias, variability, and are less accurate than MRI ellipsoid

1. Pedram A et al. (2022). *CJASN*. 17(6):827-834

Sample Radiology Request Form

RADIOLOGY REQUEST FORM: TOTAL KIDNEY VOLUME (TKV)

Patient Name:

Sex:

Height:

Weight:

Phone Number:

Referring Doctor:

□MRI □CT □US

□Non-contrast □Contrast*

Left Kidney dimensions (mm):	Right Kidney dimensions (mm):
Maximal kidney length on the sagittal plane: _____	Maximal kidney length on the sagittal plane: _____
Maximal kidney length on the coronal plane: _____	Maximal kidney length on the coronal plane: _____
Maximal kidney width on the transverse (axial) plane: _____	Maximal kidney width on the transverse (axial) plane: ____
Maximal kidney depth on the transverse (axial) plane: _____	Maximal kidney depth on the transverse (axial) plane: ____

TKV (mL): ____________ htTKV (mL): _____________

T_2-weighted imaging is preferred for better visualization of cysts.[1]

*Contrast is not needed for the sole purpose of using the image to estimate TKV.

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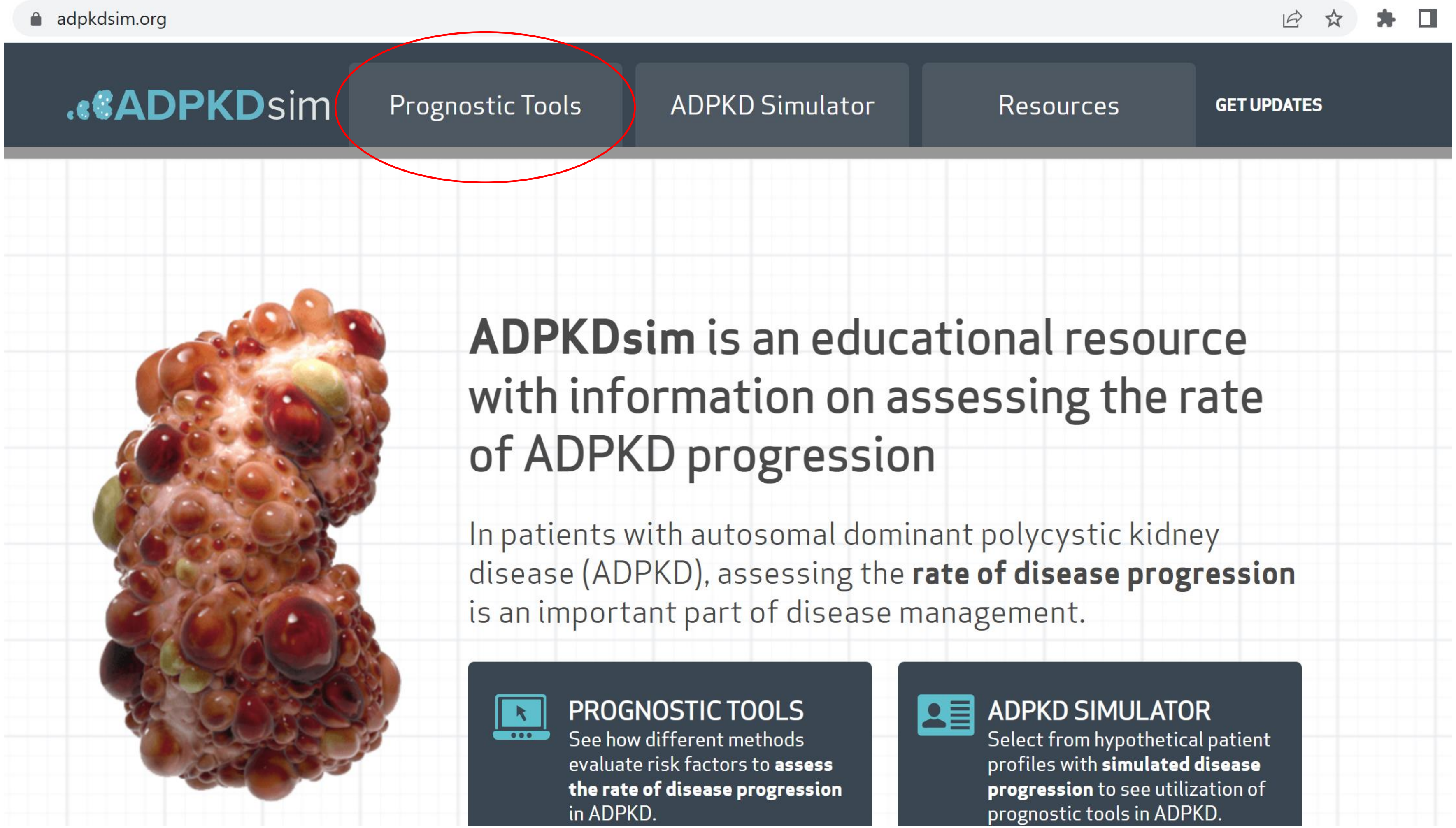
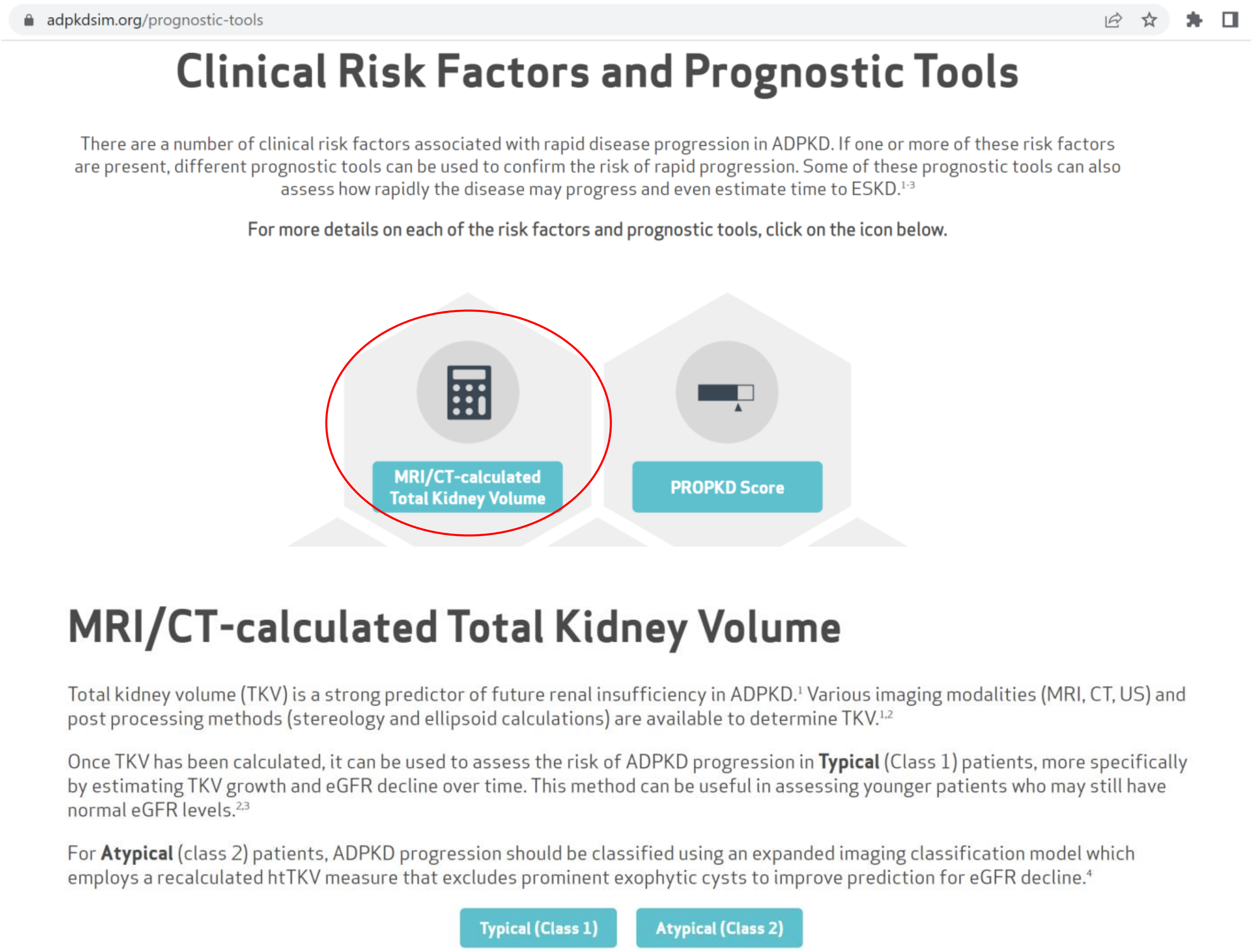
Resources for TKV Calculation: ADPKDsim.org



Resources for TKV Calculation: ADPKDsim.org



adpkdsim.org/prognostic-tools

Clinical Risk Factors and Prognostic Tools

There are a number of clinical risk factors associated with rapid disease progression in ADPKD. If one or more of these risk factors are present, different prognostic tools can be used to confirm the risk of rapid progression. Some of these prognostic tools can also assess how rapidly the disease may progress and even estimate time to ESKD.[1-3]

For more details on each of the risk factors and prognostic tools, click on the icon below.

MRI/CT-calculated Total Kidney Volume

PROPKD Score

MRI/CT-calculated Total Kidney Volume

Total kidney volume (TKV) is a strong predictor of future renal insufficiency in ADPKD.[1] Various imaging modalities (MRI, CT, US) and post processing methods (stereology and ellipsoid calculations) are available to determine TKV.[1,2]

Once TKV has been calculated, it can be used to assess the risk of ADPKD progression in **Typical** (Class 1) patients, more specifically by estimating TKV growth and eGFR decline over time. This method can be useful in assessing younger patients who may still have normal eGFR levels.[2,3]

For **Atypical** (class 2) patients, ADPKD progression should be classified using an expanded imaging classification model which employs a recalculated htTKV measure that excludes prominent exophytic cysts to improve prediction for eGFR decline.[4]

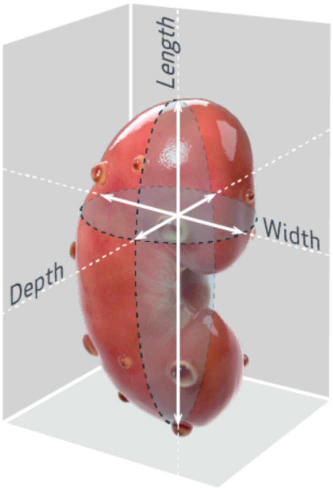
Typical (Class 1)   Atypical (Class 2)

Resources for TKV Calculation: ADPKDsim.org

1 **Order an MRI or CT:** Request length (L), width (W), and depth (D) dimensions for both kidneys.

Patient A's kidney dimensions:

Left Kidney		Right Kidney
189	Length* (mm)	185
93	Width† (mm)	98
79	Depth† (mm)	81



***Length.** The length can be obtained by averaging the maximum longitudinal diameters taken from coronal and sagittal images. Alternatively, a single, longitudinal diameter measurement can be obtained from a tilted coronal image.[3,4]

†Width and depth. Use the width and depth of the kidney obtained from transverse images at the maximum transverse diameter.[3]

Resources for TKV Calculation: ADPKDsim.org

2 **Calculate TKV:** Use the ellipsoid volume (V) formula $\frac{\pi}{6} \cdot (L \times W \times D) = V$.[5,6]

	Left Kidney		Right Kidney	
Start with the basic formula:	$\frac{\pi}{6} \cdot (L_L \times W_L \times D_L)$	+	$\frac{\pi}{6} \cdot (L_R \times W_R \times D_R)$	= TKV
Insert the kidney values:	$\frac{\pi}{6} \cdot$ (189 mm x 93 mm x 79 mm)	+	$\frac{\pi}{6} \cdot$ (185 mm x 98 mm x 81 mm)	= TKV
Do the math:	727,060 mm^3	+	768,921 mm^3	= TKV
Convert to mL for final volume:*	Left Kidney Volume 727.1 mL	+	Right Kidney Volume 768.9 mL	= TKV 1,496 mL

*Unit conversion: 1,000 mm^3 = 1 mL

Resources for TKV Calculation: ADPKDsim.org

3 **Calculate htTKV:** Use the TKV and height to calculate the htTKV.[5]

Start with the basic formula:

$$\frac{\text{TKV}}{\text{height}} = \text{htTKV}$$

Enter height and calculate:

$$\frac{1{,}496 \text{ mL}}{1.85 \text{ m}} = $$

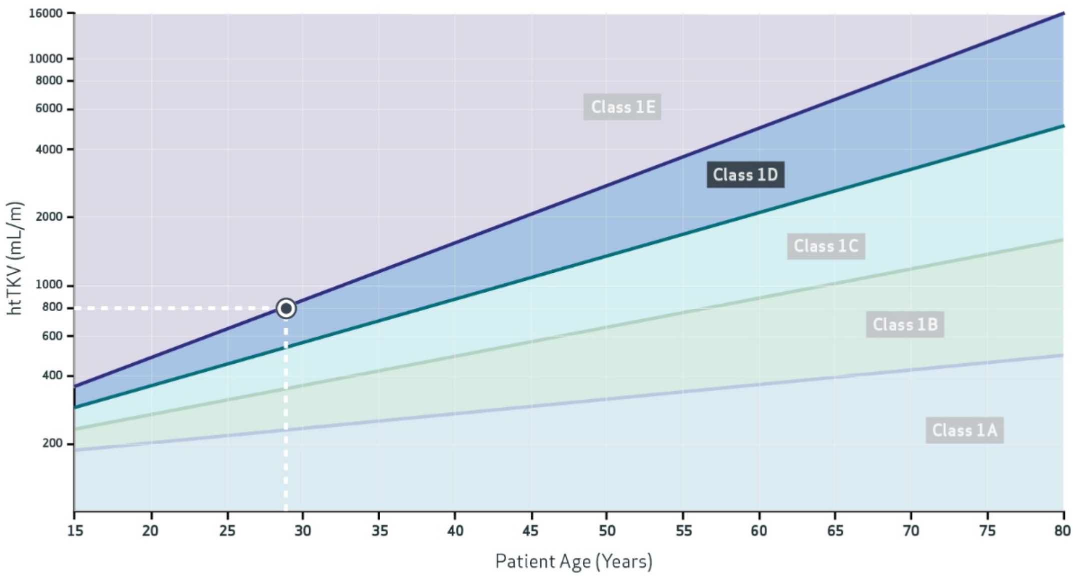
htTKV

808.6 mL/m

Resources for TKV Calculation: ADPKDsim.org

4 **Determine ADPKD Imaging Classification:** Plot htTKV by age on the graph below.[3]

ADPKD Imaging Classification by htTKV and Age*



Patient Classifications*

CLASS	ESTIMATED KIDNEY GROWTH RATE YEARLY % INCREASE	RISK FOR eGFR DECLINE
1E	>6%	High Risk
1D	4.5% - 6%	High Risk
1C	3% - 4.5%	High Risk
1B	1.5% - 3%	Intermediate Risk
1A	<1.5%	Low Risk

Adapted with permission of The American Society of Nephrology, from Irazabal MV, et al. Imaging classification of autosomal polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol.* 2015;26(1):160-172.

Patient A is likely at high risk for rapid progression.

Progression of TKV ordering over time in a single PKD patient

	2018	2019	2020	2022
Imaging Modality	Ultrasound	MRI	MRI	MRI
TKV requested by nephrologist in order comments		✓	✓	✓
Each Kidney Length	✓		✓	✓
Each Kidney Width			✓	✓
Each Kidney Depth			✓	✓
Volume of Each Kidney		✓	✓	✓
Total Kidney Volume			✓	✓
Height-adjusted Total Kidney Volume				✓

Sample used with permission from Drs. Shirazian and Makkar

Summary

- htTKV is a validated prognostic biomarker for ADPKD1
- TKV by MRI and Manual Segmentation is considered the gold standard2
- When manual segmentation is not an option the ellipsoid formula can be used and there are online calculators such as ADPKDsim3,4
- 3-dimensional ultrasound (3D US) and US ellipsoid are shown to have similar bias and variability to one another, and both are less accurate than MRI-ellipsoid or manual segmentation5
- Creating a htTKV radiology order form could be useful
- Communication is key!

1. Chapman AB et al. (2012). *Clin J Am Soc Nephrol*. 7(3): 479–86.
2. Bhutani H et al. *Kidney Int.* 2015; 88:146-151
3. Irazabal MV et al. *J Am Soc Nephrol*. 2015;26(1):160-172; 2.
4. Mayo Foundation and Medical Education and Research. https://www.mayo.edu/research/documents/pkd-center-adpkd-classification/doc-20094754. Accessed January 7, 2020. adpkdsim.org
5. Pedram A et al. (2022). *CJASN*. 17(6):827-834

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