ADPKDsim

Glomerular Filtration Rate vs Total Kidney Volume (TKV):

Predictive Markers of Disease Progression and Why TKV is Important

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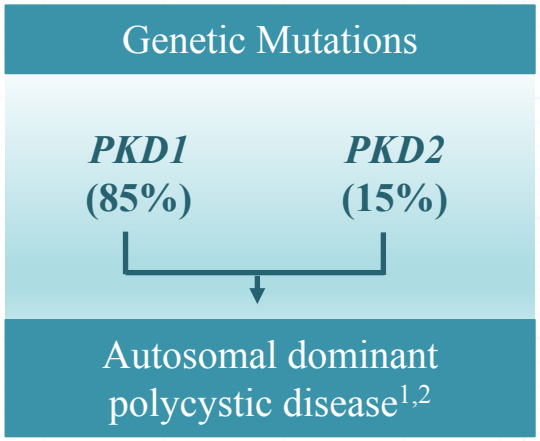
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- ADPKD is:
  - An inherited disease characterized by the development and progressive enlargement of fluid-filled cysts within the kidneys[1,2]
  - Autosomal dominant – a parent with ADPKD has a 50% chance of passing the disease on to each of his or her children[3]
- Continuous cyst growth in both kidneys increases the total kidney volume and eventually leads to end-stage renal disease[4]



PKD1/2, polycystic kidney disease gene 1/2.

1. Torres VE, Harris PC, Pirson Y. *Lancet*. 2007;369:1287-301.
2. Rossetti S et al. *J Am Soc Nephrol*. 2007;18:2143-60.
3. Harris PC, Rossetti S. *Nat Rev Nephrol*. 2010;6(4):197-206.
4. Grantham JJ, Torres VE. *Nat Rev Nephrol*. 2016;12(11):667-77.

ADPKD is a Progressive Disease With High Interpatient Variability

ADPKD **progresses** at **variable rates**, with some patients progressing more rapidly than others, even within the same family[1,2]

Patients with ADPKD may remain asymptomatic for years while the disease progresses,[3] likely due to compensatory hyperfiltration[4]

Patients identified as being at high risk of rapid disease progression are those likely to reach ESRD at an earlier age than expected[5]

Nearly 50% of patients with ADPKD will reach ESRD by age 60[6]

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

1. Grantham JJ et al. *N Engl J Med*. 2006;354(20):2122–30.
2. Schrier RW et al. *J Am Soc Nephrol*. 2014;25(11):2399–418.
3. Lanktree MB, Chapman AB. *Nat Rev Nephrol*. 2017;13(12):750–68.
4. Meijer E et al. *Clin J Am Soc Nephrol*. 2010;5(6):1091-98.
5. Gansevoort RT et al. *Nephrol Dial Transplant*. 2016;31(3): 337–48.
6. Chebib FT and Torres VE. *Am J Kidney Dis*. 2016;67(5): 792–810.

Predictors of Rapid Disease Progression in ADPKD

Markers used to assess prognosis in ADPKD

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

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.

Chronic Kidney Disease is Subdivided Into Five Stages According to GFR Category

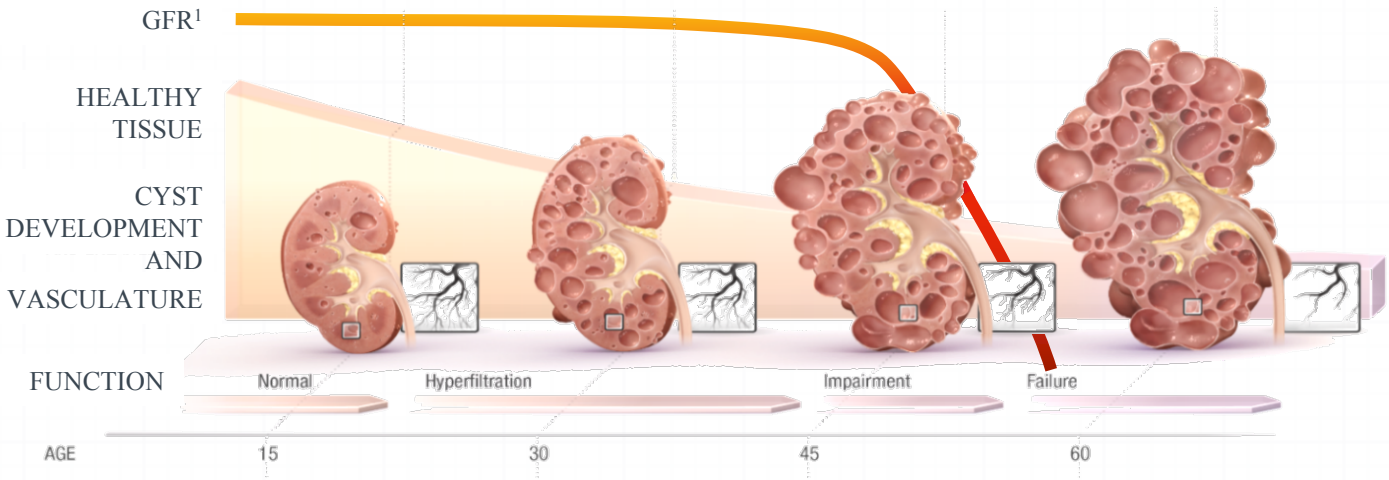
CKD Stage	GFR (mL/min/1.73 m^2)	Description[1]
1	≥90	Normal or high kidney function
2	60–89	Mildly reduced kidney function
3a	45–59	Mildly to moderately reduced kidney function
3b	30–44	Moderately to severely reduced kidney function
4	15–29	Severely reduced kidney function
5	<15	Kidney failure (also called ESRD)

In ADPKD, progression from Stage 3 CKD to ESRD can take more than 15 years, with GFR remaining normal for 3 to 5 decades, highlighting the limited use of these criteria in ADPKD[2]

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Inter Suppl*. 2013; 3(1): 1–150.
2. Chapman AB et al. *Clin J Am Soc Nephrol*. 2012; 7(3): 479–86.

Cyst Expansion Destroys Normal Tissue and Causes Loss of Renal Function



- As cysts expand, they engage increasing amounts of normal parenchyma[1]
- In the early stages of ADPKD, compensatory hyperfiltration and tubule hypertrophy camouflage the decrease in functioning parenchyma[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. *Nat Rev Nephrol*. 2011;7(10): 556–66.
2. Braun WE. *Cleve Clin J Med*. 2009;76(2): 97–104.
3. Grantham JJ et al. *N Engl J Med*. 2006;354(20): 2122–30.
4. Milutinovic J et al. *Am J Kidney Dis*. 1992;19(5): 465–72.

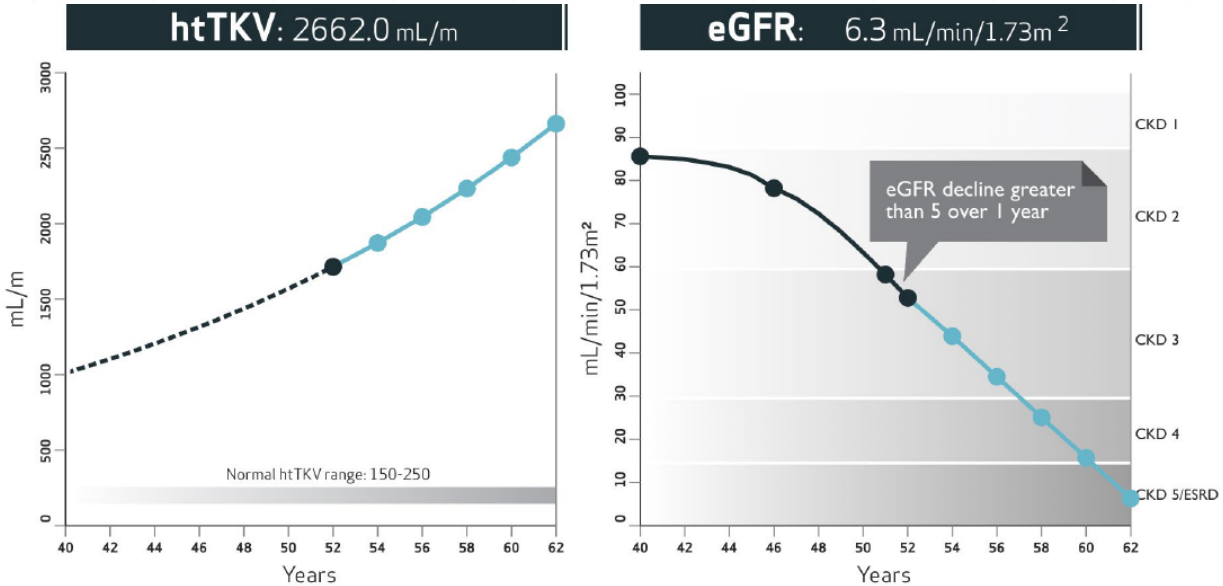
Limitations of Utilizing GFR in Assessing ADPKD Progression

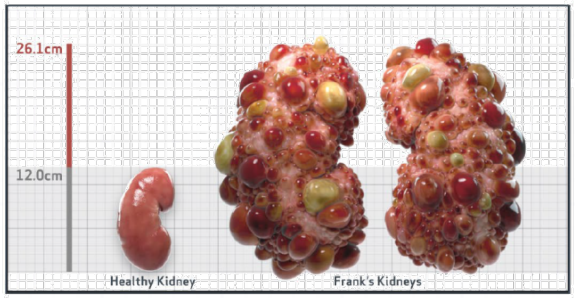
- GFR is the best index of kidney function but cannot be measured directly[1]
- eGFR utilizes sCr levels to assess filtration rates (equations: Cockcroft-Gault, MDRD, CKD-EPI)[1]
- Doubling of sCr level (57% observed reduction in GFR) is highly predictive of reaching ESRD[2]
- Caveats to using sCr level as the sole endpoint for ADPKD[2]:
  - Generally late event
  - Only captures marked loss of renal function
  - Uncertainty regarding association of lesser GFR declines with subsequent development of renal failure

ADPKD, autosomal dominant polycystic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated GFR; ESRD, end-stage renal disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; sCr, serum creatinine.

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Inter Suppl*. 2013;3(1): 1–150.
2. Gansevoort RT et al. *Nephrol Dial Transplant*. 2016;31(3): 337–48.

GFR and TKV in ADPKD Progression[1-6]





----- = Estimated historical values
● = Recorded values
● = Projected values

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated GFR; ESRD, end-stage renal disease; GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume.

1. Imagining classification of ADPKD: a simple model for selecting patients for clinical trials. http://www.mayo.edu/research/documents/pdk-center-adpkd-classification/doc-20094754. Accessed: December 18, 2018.
2. Irazabal MV, et al. *J Am Soc Nephrol*. 2015;26:160-172.
3. Gansevoort RT, et al. *Nephrol Dial Transplant*. 2016;31:337-348.
4. Wetzels JFM, et al. *Kidney Int*. 2007;72:632-637.
5. Levey AS, et al. *Kidney Int*. 2005;67:2089-2100.
6. Cheong B, et al. *Clin J Am Soc Nephrol*. 2007;2:38-45.

Increased Kidney Volume is Associated with Renal Complications

Analysis of Several Observational Studies				
		Mean Volume/Kidney ± SD, mL		
Renal Complication	Patients, n	Complication Present	Complication Absent	P Value
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

GFR, glomerular filtration rate; SD, standard deviation.
Grantham JJ et al. *Clin J Am Soc Nephrol*. 2006;1(1): 148–57.

Why TKV is Important

The CRISP Study

- NIH funded, 12-year, observational study (N=241) of adult ADPKD patients[1]
- Baseline TKV was measured by MRI and GFR by iothalamate clearance[1]
- Results showed that baseline TKV, renal blood flow[2], copeptin[3], serum HDL-cholesterol, urinary sodium excretion, and 24-hour urine osmolality[1] were predictors of progression
- Provided the foundation for future groundbreaking evaluations (i.e., Mayo classification, PROPKD score)[4,5]
- Based on CRISP and other studies, the FDA approved TKV as a prognostic biomarker for ADPKD in 2016[6]

ADPKD, autosomal dominant polycystic kidney disease; CRISP, Consortium for Radiological Imaging Studies of PKD; FDA, Food and Drug Administration; GFR, glomerular filtration rate; HDL, high-density lipoprotein; MRI, magnetic resonance imaging; NIH, National Institutes of Health; PKD, polycystic kidney disease; PROPKD, Predicting Renal Outcomes in ADPKD; TKV, total kidney volume.

1. Torres VE et al. *Clin J Am Soc Nephrol*. 2011; 6: 640–7.
2. Torres VE et al. *Lancet*. 2007; 369: 1287–301.
3. Boertien WE et al. *Am J Kidney Dis*. 2013; 61: 420–9.
4. Irazabal MV et al. *J Am Soc Nephrol*. 2015; 26(1): 160–72.
5. Cornec-Le Gall E et al. *J Am Soc Nephrol*. 2016; 27(3): 942–51.
6. FDA Center for Drug Evaluation and Research. Guidance for Industry: Qualification of Biomarker - Total Kidney Volume in Studies for Treatment of Autosomal Dominant Polycystic Kidney Disease. Published September 15, 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458483.pdf. Accessed December 18, 2018.

The CRISP Study

- **Primary goal of CRISP**: to determine the extent to which TKV forecasts the development of renal insufficiency in ADPKD
- **Assessment**: Correlations between baseline htTKV and GFR during follow-up were assessed
  - Pearson correlation coefficients were determined for baseline htTKV and iothalamate GFR at baseline and five subsequent visits over 7.9 years
- **Findings**: There was a significant negative correlation between baseline htTKV and GFR at each subsequent visit
  - Increased from baseline (r =-0.22, P=0.02) to year 8 (r =-0.65, P<0.001)
  - The relationship between renal function (as determined by GFR) and TKV improved significantly with longer follow-up
- **Conclusion**: Study results suggest that baseline htTKV predicts the development of renal insufficiency within 8 years
  - A single determination of htTKV in an adult patient could be used to determine the probability of developing significant renal insufficiency

ADPKD, autosomal dominant polycystic kidney disease; CRISP, Consortium for Radiological Imaging Studies of PKD; GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume; TKV, total kidney volume.

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

Future Decline in Renal Function is Predicted by Baseline Kidney Volume

CRISP Study

TKV is more predictive of future renal function decline than age, gender, or genotype

In the CRISP study:

- Baseline htTKV was negatively correlated with GFR at each visit, which increased from baseline (-0.22 at baseline through to -0.65 at year 8)
- Results indicated that for each 100-cc increment of htTKV at baseline, the odds of reaching a stage 3 chronic kidney disease endpoint within 7.9 years increase 1.48-fold
- These findings suggest that a single determination of htTKV in an adult patient could be used to determine the probability of developing significant renal insufficiency

*GFR by iothalamate clearance.
GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume; TKV, total kidney volume.
Chapman AB et al. *Clin J Am Soc Nephrol*. 2012; 7(3): 479–86.

Change in Kidney Volume in ADPKD Precedes Change in Renal Function

- The results of the CRISP study showed:
  - htTKV increased significantly from baseline each year, reaching a mean increase of 55% after 7.9 years of follow up[1]
  - GFR decline began in year 6 (-10.6%), and continued until year 8 (22.3%)[1]

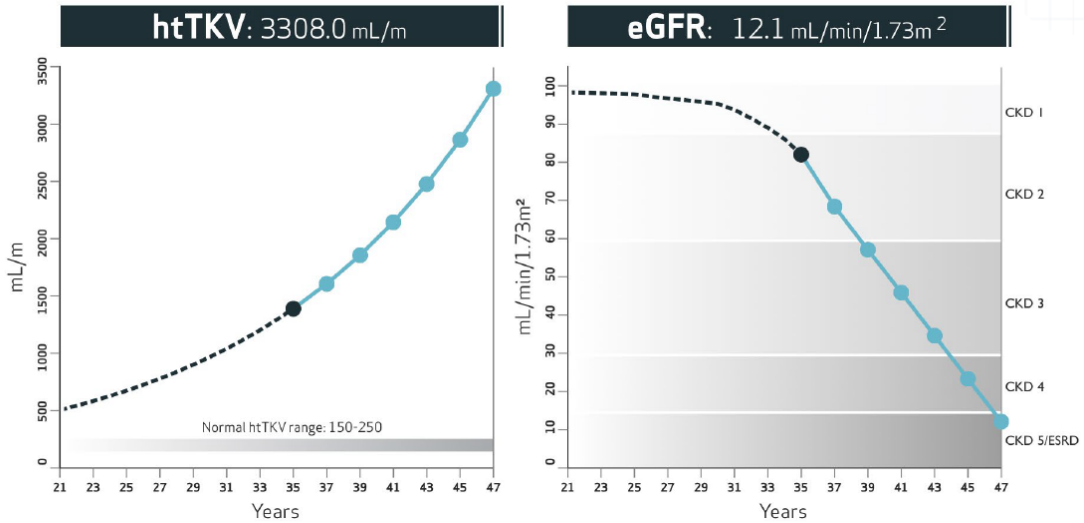


Image based on references 3-8

- Among patients in the early stages of ADPKD, compensatory hyperfiltration adjusts for the loss of nephron function and ensures that GFR is maintained within normal levels until the fourth or fifth decade of life[2]

ADPKD, autosomal dominant polycystic kidney disease; CRISP, Consortium for Radiological Imaging Studies of Polycystic Kidney Disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; eGFR, estimated GFR; GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume.

1. Chapman AB et al. *Clin J Am Soc Nephrol*. 2012; 7(3): 479–86.
2. Grantham JJ et al. *Clin J Am Soc Nephrol*. 2006; 1(1): 148–57.
3. Imagining classification of ADPKD: a simple model for selecting patients for clinical trials. http://www.mayo.edu/research/documents/pdk-center-adpkd-classification/doc-20094754. Accessed: December 18, 2018.
4. Irazabal MV, et al. *J Am Soc Nephrol*. 2015;26:160-172.
5. Gansevoort RT, et al. *Nephrol Dial Transplant*. 2016;31:337-348.
6. Wetzels JFM, et al. *Kidney Int*. 2007;72:632-637.
7. Levey AS, et al. *Kidney Int*. 2005;67:2089-2100.
8. Cheong B, et al. *Clin J Am Soc Nephrol*. 2007;2:38-45.

Change in Total Kidney Volume Predicts ADPKD Progression

- Renal cysts in polycystic kidney disease are mostly formed *in utero* and progressively enlarge throughout life
- Kidney volume represents an important guide for predicting the risk of a patient to develop the renal complications associated with ADPKD, such as pain, hypertension, gross hematuria and azotemia
- By comparing individual measurements of kidney volume in adults at any age with available data, a physician might be able to estimate future kidney enlargement
- Data from CRISP demonstrated that patients experiencing relatively rapid increases in TKV were at an increased risk of declining renal function

ADPKD, autosomal dominant polycystic kidney disease; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; TKV, total kidney volume.
Bae KT, Grantham JJ. *Nat Rev Nephrol*. 2010; 6(2): 96–106.

Development of the Current Imaging Classification System for ADPKD

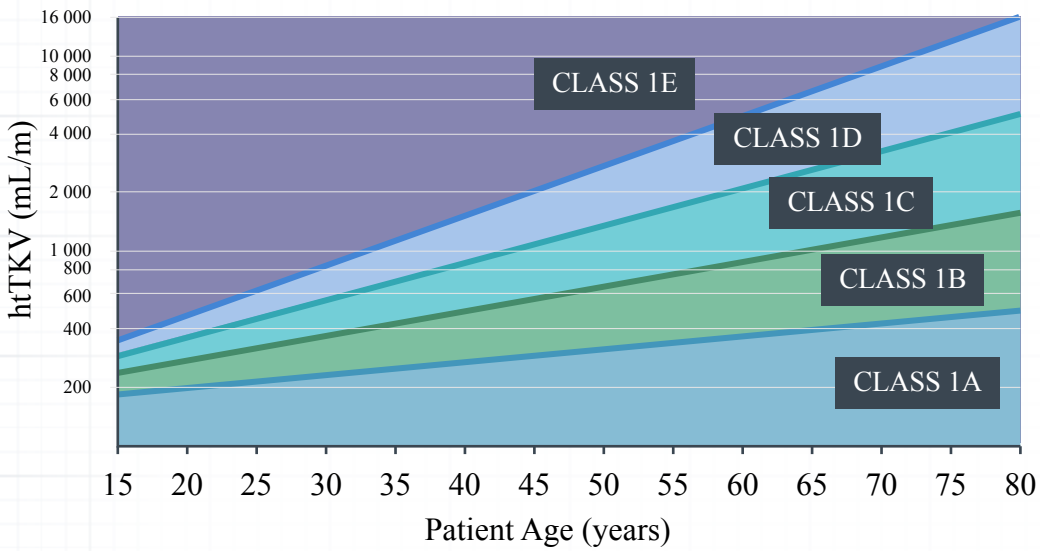
- TKV predicts the risk of developing renal insufficiency in ADPKD; however, there are limitations to its use:
  - Measurement requires high precision and is laborious
  - Kidney volume does not always predict change in renal function
- An imaging classification system was developed to facilitate the selection of patients with ADPKD who are suitable candidates for clinical trials or likely to benefit from an effective therapy
  - The system utilizes the ellipsoid equation for estimation of htTKV and patient age to define groups of patients with different risks of eGFR decline
  - The system has been validated and predicts the decline of GFR and renal survival in patients with typical ADPKD over a broad range of CKD stages, even in early stages of the disease

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated GFR; GFR, glomerular filtration rate; htTKV, height-adjusted TKV; TKV, total kidney volume..

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

TKV-based Classification of ADPKD

Age and htTKV predicts decline in eGFR over time in patients with 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.
Irazabal MV et al. *J Am Soc Nephrol.* 2015; 26: 160-172.

Tying it all together: eGFR vs. TKV

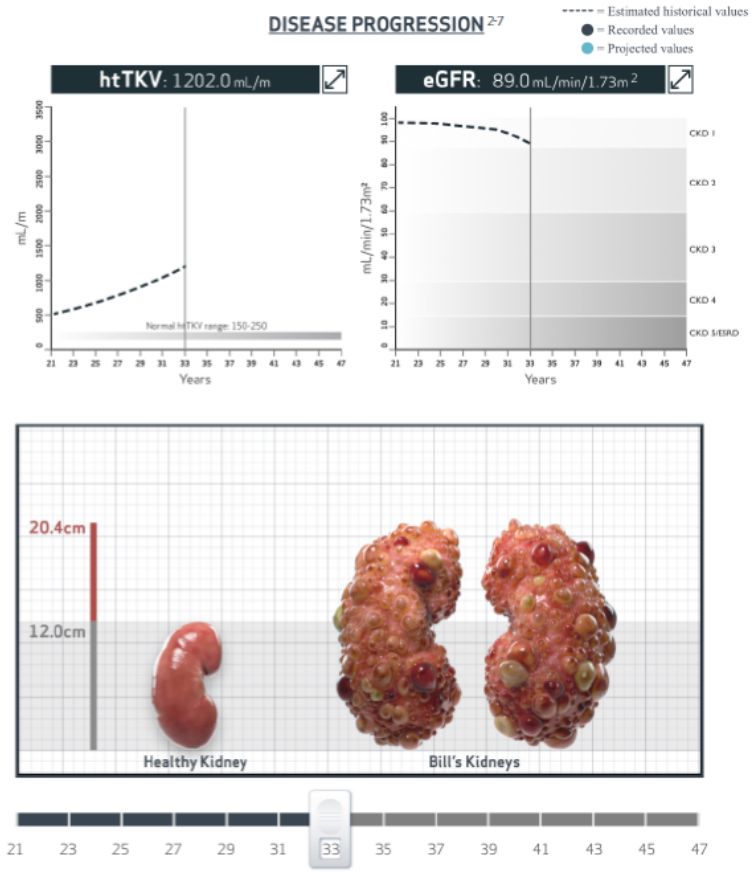
BASELINE ASSESSMENT [1-3]

Age:	35
Height (ft & in):	5'11"
Weight (lbs):	210
Sex (M/F):	M
Race (AA/O):	0
Mutations:	truncating *PKD1*
Ultrasound Kidney Length (cm):	not available
Serum creatinine (mg/dL):	1.15
htTKV (mL/m):	1389
eGFR (mL/min/1.73m^2):	82
Patient & Family History	
Hypertension before 35:	Yes
Urological event before 35:	Yes
Family members with ESRD:	No

PROPKD Score:
9 - HIGH Risk of Progression to ESRD

ADPKD Imaging Classification:
Class 1E: >6% estimated yearly percentage increase in kidney growth

DISEASE PROGRESSION [2-7]



Example:

- A 35 year old male with an eGFR of 89 ml/min/1.73m^2 and a height-adjusted TKV of 1202 mL/m
- Based on his ADPKD Imaging classification, he has a >6% estimated yearly percentage increase in kidney growth

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; htTKV, height-adjusted TKV; PROPKD, Predicting Renal Outcomes in ADPKD; TKV, total kidney volume.

1. Cornec-Le Gall E, et al. *J Am Soc Nephrol*. 2016;27(3):942-951.
2. Imagining classification of ADPKD: a simple model for selecting patients for clinical trials. http://www.mayo.edu/research/documents/pdk-center-adpkd-classification/doc-20094754. Accessed: December 18, 2018.
3. Irazabal MV, et al. *J Am Soc Nephrol*. 2015;26:160-172.
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6. Levey AS, et al. *Kidney Int*. 2005;67:2089-2100.
7. Cheong B, et al. *Clin J Am Soc Nephrol*. 2007;2:38-45.

Summary

- The rate of disease progression could vary significantly among patients with ADPKD, even within the same family[1,2]
- Limitations exist with solely relying on GFR as a marker of disease progression[3]
- The CRISP study demonstrated that baseline htTKV (measured by stereology MRI) is an independent predictor of future GFR decline in ADPKD patients[4]
- An imaging classification system validated CRISP study findings and showed:[5]
  - The ellipsoid calculation of htTKV has the same predictive power as that calculated by stereology
  - htTKV is a predictor of risk of early ESRD in Typical ADPKD patients (Class 1) and not atypical presentations of renal cysts

ADPKD, autosomal dominant polycystic kidney disease; CRISP, Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume; MRI, magnetic resonance imaging.

1. Grantham JJ et al. *N Engl J Med*. 2006;354: 2122–30.
2. Harris PC, Rossetti S. *Adv Chronic Kidney Dis*. 2010;17(2): 131–9.
3. Gansevoort RT et al. *Nephrol Dial Transplant*. 2016;31(3): 337–48.
4. Chapman AB et al. *Clin J Am Soc Nephrol*. 2012;7(3): 479–86;
5. Irazabal MV et al. *J Am Soc Nephrol*. 2015;26(1): 160–72.

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