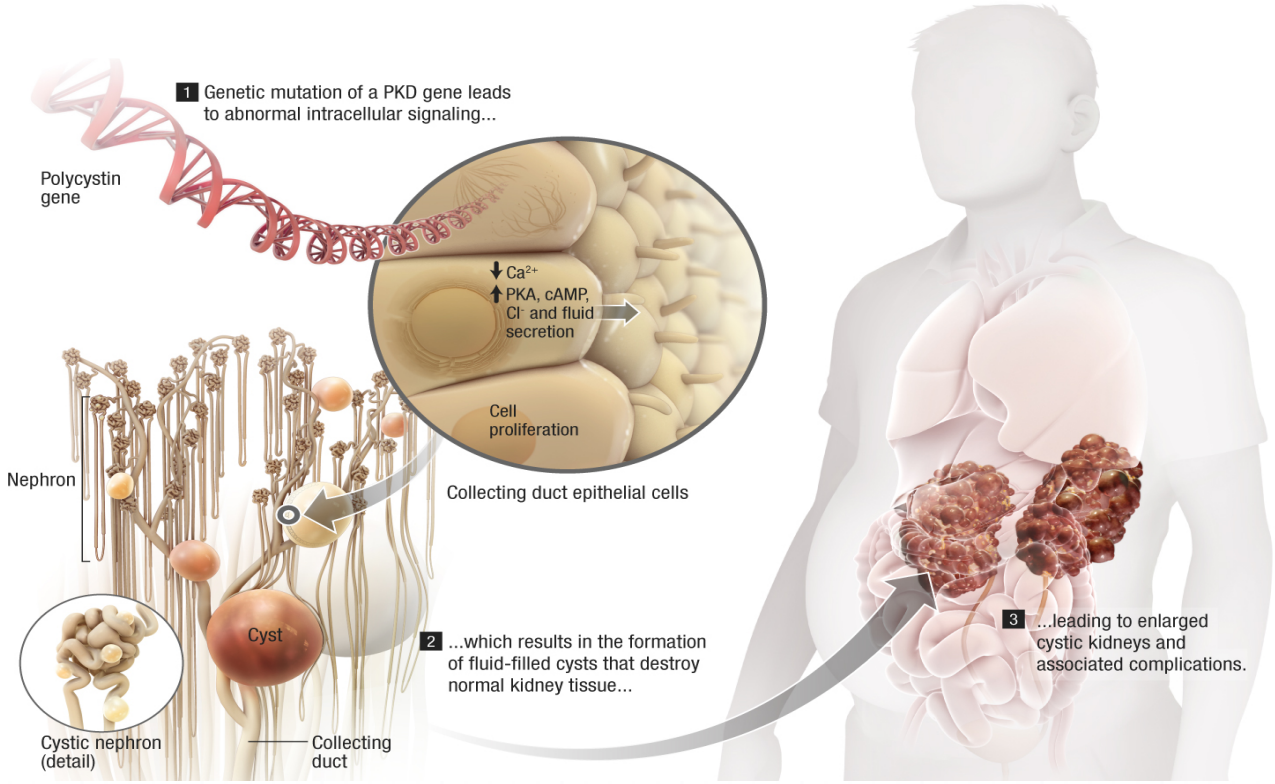
ADPKDsim

Autosomal Dominant Polycystic Kidney Disease:

Disease Progression

January 2019 MRC2.CORP.D.00397

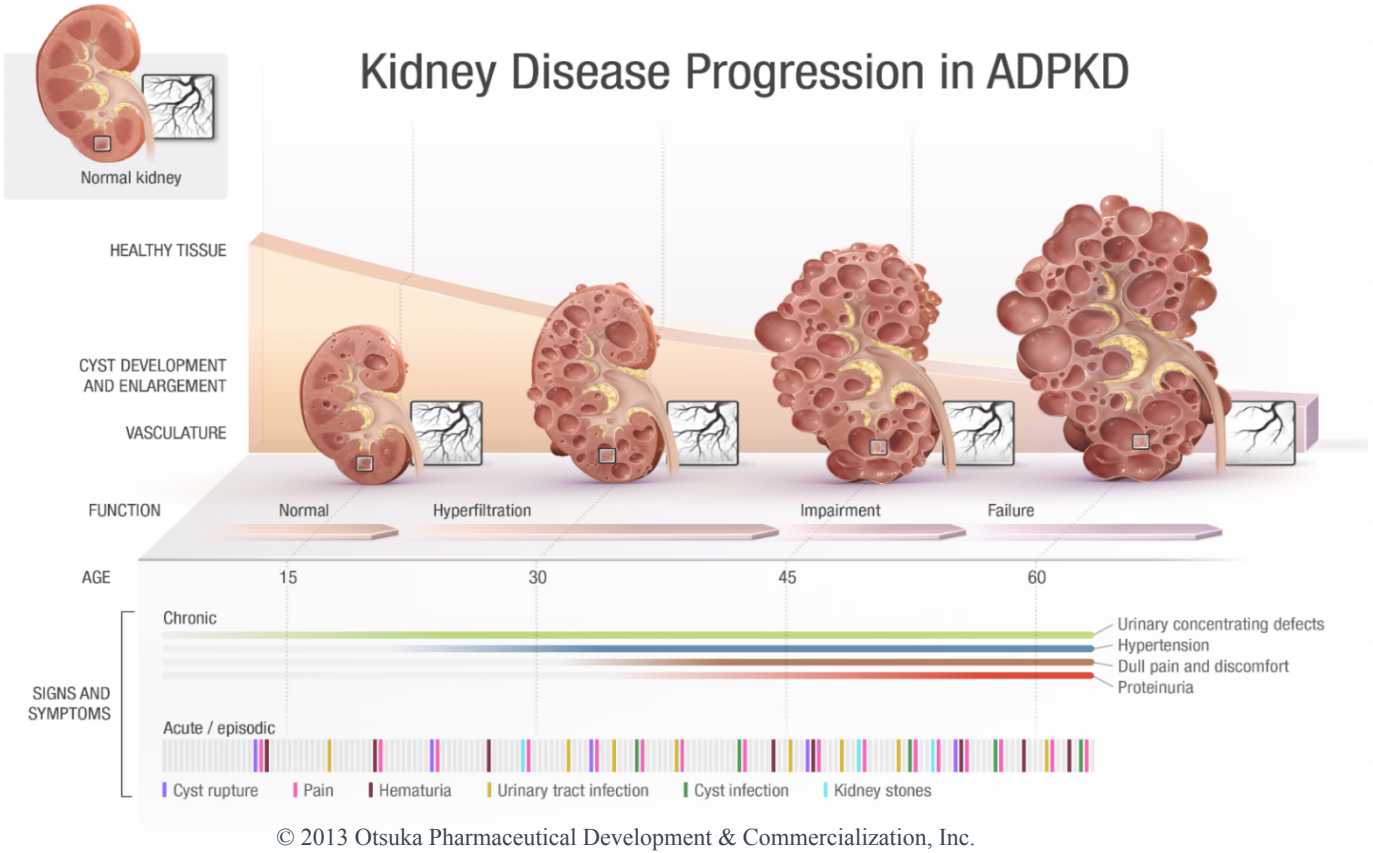
Overview of Cyst Initiation and Expansion in ADPKD[1–6]



ADPKD, autosomal dominant polycystic kidney disease; Ca^{2+}, calcium ion; cAMP, cyclic adenosine monophosphate; Cl^-, chloride ion; PKA, protein kinase A; PKD polycystic kidney disease.

1. Hateboer N et al. *Lancet*. 1999;353(9147): 103–7.
2. Chapin HC et al. *J Cell Biol*. 2010;191(4): 701–10.
3. Yamaguchi T et al. *Am J Kidney Dis*. 1997;30(5): 703–9.
4. Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10): 556–66.
5. Wallace DP. *Biochim Biophys Acta*. 2011;1812(10): 1291–300.
6. Grantham JJ et al. *N Engl J Med*. 2006;354(20): 2122–30.

Cyst Burden and Patient Complications in ADPKD: An Overview



ADPKD, autosomal dominant polycystic kidney disease.

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.

The CRISP Study

- NIH funded, 12-year, observational study (N=241) of adult ADPKD patients[1]
- Baseline TKV 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.

Future Decline in Renal Function Predicted by Baseline Kidney Volume
CRISP Study

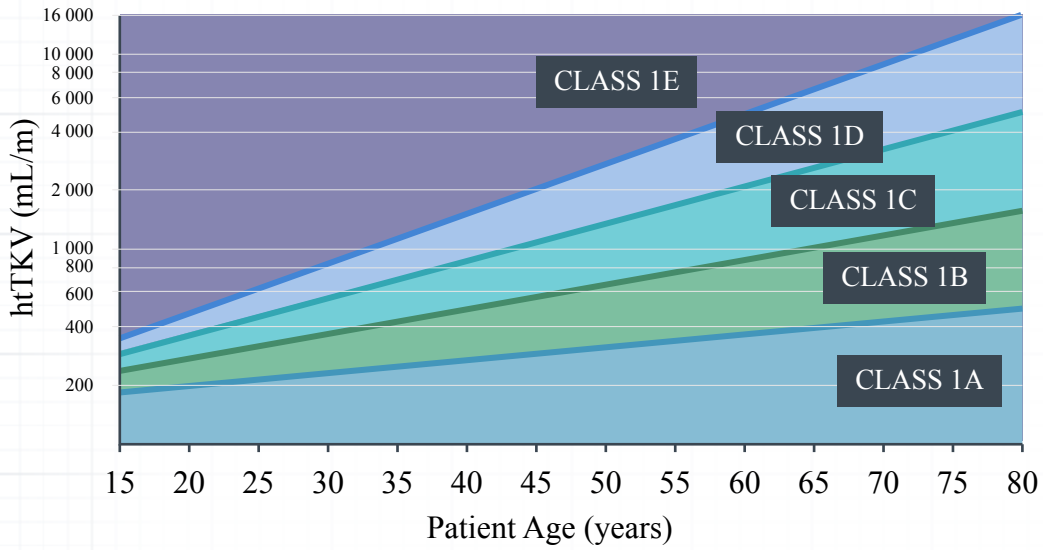
- **Primary goal of CRISP**: to determine the extent to which TKV forecasts the development of renal insufficiency in ADPKD
- **Assessment**: Correlations between baseline htTKV and GFR during follow-up were assessed
  - Pearson correlation coefficients were determined for baseline htTKV and iothalamate 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.

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.

Ultrasound for Measurement of Kidney Length

MRI is the recommended imaging modality for the measurement of kidney volume[1]

…However

Ultrasound-derived kidney length has been proposed as a surrogate for MRI-measured TKV and for predicting the development of CKD stage 3[2]

- In a study comparing US and MRI in predicting ADPKD worsening, investigators of an analysis of 241 patients from the CRISP study reported best cut points for predicting development of stage 3 CKD[2]
  - Kidney length >16.5 cm by US
  - Height-adjusted TKV > 650 mL/m by US
  - The authors concluded that "kidney length alone is sufficient to stratify the risk of progression to renal insufficiency early in ADPKD using either US or MRI"[2]
  - Limitation: In this study, US kidney length was not normalized for height[1]
    - Height is considered an important variable in the measurement and interpretation of kidney volume
    - This may be an important limitation of the US-based kidney length prediction threshold of >16.5 cm

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; MRI, magnetic resonance imaging; TKV, total kidney volume; US, ultrasound.

1. Gansevoort RT et al. *Nephrol Dial Transplant.* 2016; 31(3): 337–48.
2. Bhutani H et al. *Kidney Int.* 2015; 88(1): 146–51.

ADPKD Disease Progression: Summary

ADPKD is a progressive kidney disease[1,2]

Cyst growth precedes decline in kidney function; patients with ADPKD may remain asymptomatic for years while the disease progresses[3]

Nearly 50% of patients with ADPKD reach ESRD by age 60[4]

Rate of progression is variable from patient to patient, even within the same family[1*]

Predictors of rapid disease progression include radiographic parameters (e.g., total kidney volume), genetics, family history, clinical indicators and laboratory biomarkers[5]

Prognostic tools such as the TKV-based Classification of ADPKD[6] may help identify patients at risk for rapid disease progression before it occurs[†]

*A subgroup of patients have more rapidly progressive disease.
†Note: This tool has been used in research but has not been clinically validated.
ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; TKV, total kidney volume.

1. Grantham JJ, et al. *N Engl J Med*. 2006;354(20):2122–30.
2. Grantham JJ and Torres VE. *Nat Rev Nephrol.* 2016;12(11): 667–77.
3. Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10): 556–66.
4. Chebib FT and Torres VE. *Am J Kidney Dis.* 2016;67(5): 792–810.
5. Gansevoort RT et al. *Nephrol Dial Transplant.* 2016;31(3): 337–48.
6. Irazabal MV et al. *J Am Soc Neph*rol 2015;26(1):160-172.

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