A Rapid Progression Assessment Tool:

PROPKD Score
Predicting Renal Outcomes in ADPKD

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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.

PKD1 Mutations are Associated with Increased ADPKD Disease Severity

- The European PKD1-PKD2 Study Group examined the survival and clinical expression of *PKD1* and *PKD2*
  - The study enrolled individuals from 31 families with *PKD1* mutations(333 affected individuals), 31 families with *PKD2* mutations (291 affected individuals), and 398 unaffected controls*
  - The cumulative probability of survival was less for patients with PKD1 than those with PKD2, compared to controls

Population	Median age of onset of ESRD or death (years), [95% CI]
PKD1	53.0 [51.2-54.8]†
PKD2	69.1 [66.9-71.3]
Unaffected controls	78.0 [73.8-82.2]‡

  - Patients with *PKD2* mutations were less likely to have hypertension, UTI, or gross hematuria than those with *PKD1* mutations

*Control population was comprised of spouses and unaffected siblings. †*PKD1* vs *PKD2,* p<0.0001. ‡ *PKD2* vs controls, p=0.0001.
ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; *PKD1/2*, polycystic kidney disease gene 1/2; UTI, urinary tract infection.
Hateboer N et al. *Lancet.* 1999; 353(9147): 103–7.

PROPKD Study: Objectives

- As new targeted therapies for ADPKD emerge, there is a need for accurate prognostic tools that can predict renal outcomes to:
  - Enable optimal selection of patients in clinical trials
  - Provide reassurance to patients about the course of their disease
- Objective: Stratify the risk of progression to ESRD in patients with ADPKD according to genetic and clinical data
  - Enriched for older/ESRD patients*
- Genkyst cohort
  - Registry involving ~70 nephrologists and 1,341 patients from Brittany, France

*Compared to Mayo Classification patient cohort.
ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; PROPKD, Predicting Renal Outcomes in ADPKD.
Cornec-Le Gall E et al. *J Am Soc Nephrol.* 2016; 27(3): 942–51.

Effect of Gender and Type of Mutation on Disease Progression

- The cross-sectional PROPKD study developed a prognostic model to predict renal outcomes in patients with ADPKD (N=1341) on the basis of genetic and clinical data
- Patients with truncating *PKD1* mutations were more likely to develop ESRD earlier than patients with non-truncating *PKD1* mutations or *PKD2* mutations (median ages for ESRD onset 55.1, 65.8, and 77.8 years, respectively)
- Renal outcomes were significantly worse in men with truncating *PKD1* mutations
- Sex was not identified as an influence in patients with non-truncating *PKD1* mutations or in patients with *PKD2* mutations

ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; *PKD1/2*, polycystic kidney disease gene 1/2; PROPKD, Predicting Renal Outcomes in ADPKD.

Cornec-Le Gall E et al. *J Am Soc Nephrol.* 2016; 27(3): 942–51.

Early-onset Hypertension and Urological Events are Predictors of Rapid Progression

- Hypertension is a common symptom seen early in the course of ADPKD[1,2]
  - Recognized as an independent risk factor for progression to ESRD[3]
  - Patients with ADPKD who develop HTN before 35 years of age are at higher risk for rapid disease progression[4]
- Early urological events (macroscopic hematuria, flank pain, or cyst infection) are also associated with rapid progression of ADPKD[5]

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

1. Chapman AB et al. *Adv Chronic Kidney Dis*. 2010; 17(2): 153–63.
2. Ecder T, Schrier RW. *Nat Rev Nephrol.* 2009; 5(4): 221–8.
3. Masoumi A et al. *Ther Clin Risk Manag.* 2008; 4(2): 393–407.
4. Cornec-Le Gall E et al. *J Am Soc Nephrol.* 2016; 27(3): 942–51.
5. Gansevoort RT et al. *Nephrol Dial Transplant.* 2016; 31(3): 337–48.

The PROPKD Score

PROPKD Score[1]

Variable	Points
Being male	1
Hypertension before 35 years of age	2
First urologic event* before 35 years of age†	2
Mutation	
PKD2 mutation	0
Non truncating *PKD1* mutation	2
Truncating *PKD1* mutation	4
PROPKD Score	SUM

- A score of ≤3 excludes progression to ESRD before the age of 60 years with a negative predictive value of 81.4%[2]
- A score of >6 predicts rapid disease progression with ESRD onset before the age of 60 years with a positive predictive value of 90.9%[2]
- For those with an intermediate score (4–6 points), the prognosis is unclear[2]

ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; *PKD1/2*, polycystic kidney disease gene 1/2; PROPKD, Predicting Renal Outcomes in autosomal dominant polycystic kidney disease.

1. Cornec-Le Gall E et al. *J Am Soc Nephrol*. 2016; 27(3): 942–51.
2. Gansevoort RT et al. *Nephrol Dial Transplant*. 2016; 31(3): 337–48.

PROPKD Score

PROPKD Score[1]

Multivariate survival analysis identified four variables that were significantly associated with age at ESRD onset, and scoring system from 0 to 9 was developed as follows:

PROPKD Calculator	
Variable	Points
Being male	1
Hypertension before 35 years of age	2
First urologic event* before 35 years of age†	2
Mutation	
PKD2 mutation	0
Non truncating *PKD1* mutation	2
Truncating *PKD1* mutation	4
PROPKD Score =	SUM

Sample PROPKD Score Calculation

ADPKD patient info: 29 year old male with hypertension and a truncating *PKD1* mutation

1 point for being male
2 points for hypertension before 35 years of age
\+ 4 points for a truncating *PKD1* mutation

PROPKD Score = 7 points

HIGH Risk of Progression to ESRD

PROPKD Score	1	2	3	4	5	6	7	8	9
Risk of Progression to ESRD	**LOW** **70.6 median age for ESRD onset** • Eliminates evolution to ESRD before age 60‡			**INTERMEDIATE** **56.9 median age for ESRD onset**			**HIGH** **49 median age for ESRD onset** • Forecasts ESRD onset before age 60§		

*Previous urological events defined as gross hematuria, cyst infections, and flank pain related to cysts. †PROPKD score may not be helpful identifying rapid progression in patients < 35 years old unless they are already hypertensive and have experienced urological complications.[2] ‡Negative predictive value of 81.4%. §Positive predictive value of 90.9%.
ADPKD, autosomal dominant polycystic kidney disease; ESRD, end-stage renal disease; *PKD1/2*, polycystic kidney disease gene 1/2; PROPKD, Predicting Renal Outcomes in autosomal dominant polycystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease.

1. Cornec-Le Gall E et al. *J Am Soc Nephrol.* 2016; 27(3): 942–51.
2. Chebib FT et al. *J Am Soc Nephrol*. 2018; 29(10):2458-2470.

Limitations of the PROPKD Score

- **PROPKD Score Limitations:**[1,2]
  - Requires genetic testing for PKD mutations
  - May not be useful in patients younger than 35 unless they have already experienced urological events or hypertension
  - Inapplicable to the subset of patients that are negative for *PKD1* or *PKD2* mutations
  - Genetic analysis may be expensive

PROPKD, Predicting Renal Outcomes in autosomal dominant polycystic kidney disease; PKD, Polycystic Kidney Disease; *PKD1/2,* polycystic kidney disease gene 1/2.

1. Cornec-Le Gall E et al. *J Am Soc Nephrol.* 2016; 27(3): 942–51.
2. Chebib FT, et al. *J Am Soc Nephrol.* 2018; 29: 2458–2470.

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