A Rapid Progression Assessment Tool:

PROPKD Score
Predicting Renal Outcomes in ADPKD
# Predictors of Rapid Disease Progression in ADPKD

## Markers used to assess prognosis in ADPKD

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

Indicates the best-validated markers

ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; PKD1, polycystic kidney disease gene 1.
**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

<table>
<thead>
<tr>
<th>Population</th>
<th>Median age of onset of ESRD or death (years), [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PKD1</strong></td>
<td>53.0 [51.2-54.8]†</td>
</tr>
<tr>
<td><strong>PKD2</strong></td>
<td>69.1 [66.9-71.3]</td>
</tr>
<tr>
<td>Unaffected controls</td>
<td>78.0 [73.8-82.2]‡</td>
</tr>
</tbody>
</table>

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

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*Control population was comprised of spouses and unaffected siblings. †PKD1 vs PKD2, p<0.0001. ‡PKD2 vs controls, p=0.0001.
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.
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.

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.

The PROPKD Score

PROPKD Score\(^1\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Being male</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension before 35 years of age</td>
<td>2</td>
</tr>
<tr>
<td>First urologic event* before 35 years of age†</td>
<td>2</td>
</tr>
<tr>
<td>Mutation</td>
<td></td>
</tr>
<tr>
<td>(PKD2) mutation</td>
<td>0</td>
</tr>
<tr>
<td>Non truncating (PKD1) mutation</td>
<td>2</td>
</tr>
<tr>
<td>Truncating (PKD1) mutation</td>
<td>4</td>
</tr>
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\[\text{PROPKD Score} = \sum\]

- 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.

PROPKD Score

PROPKD Score

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:

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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

*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. ‡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.

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

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