Autosomal Dominant Polycystic Kidney Disease: Disease Progression
Overview of Cyst Initiation and Expansion in ADPKD

1. Genetic mutation of a PKD gene leads to abnormal intracellular signaling...

2. ...which results in the formation of fluid-filled cysts that destroy normal kidney tissue...

3. ...leading to enlarged cystic kidneys and associated complications.

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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.

Cyst Burden and Patient Complications in ADPKD: An Overview

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ADPKD, autosomal dominant polycystic kidney disease.
# 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>
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</tr>
</tbody>
</table>

- Indicates the best-validated markers

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

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Description¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Normal or high kidney function</td>
</tr>
<tr>
<td>2</td>
<td>60–89</td>
<td>Mildly reduced kidney function</td>
</tr>
<tr>
<td>3a</td>
<td>45–59</td>
<td>Mildly to moderately reduced kidney function</td>
</tr>
<tr>
<td>3b</td>
<td>30–44</td>
<td>Moderately to severely reduced kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>Severely reduced kidney function</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>Kidney failure (also called ESRD)</td>
</tr>
</tbody>
</table>

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 ADPKD²

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

The CRISP Study

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

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.

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.

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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.

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\(^\dagger\)

\*A subgroup of patients have more rapidly progressive disease.
\(^\dagger\)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.

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