Glomerular Filtration Rate vs Total Kidney Volume (TKV):
Predictive Markers of Disease Progression and Why TKV is Important
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.
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 identified as being at high risk of rapid disease progression are those likely to reach ESRD at an earlier age than expected\(^5\)

Patients with ADPKD may remain asymptomatic for years while the disease progresses,\(^3\) likely due to compensatory hyperfiltration\(^4\)

Nearly 50% of patients with ADPKD will reach ESRD by age 60\(^6\)

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


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# 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

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


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As cysts expand, they engage increasing amounts of normal parenchyma

In the early stages of ADPKD, compensatory hyperfiltration and tubule hypertrophy camouflage the decrease in functioning parenchyma

Renal function remains steady until kidney volume increases 4–6 times normal size

Irreversible damage occurs by the time GFR declines

Disease progression is variable from patient to patient

GFR, glomerular filtration rate.

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.

GFR and TKV in ADPKD Progression

htTKV: 2662.0 mL/m

eGFR: 6.3 mL/min/1.73m²

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.

Increased Kidney Volume is Associated with Renal Complications

<table>
<thead>
<tr>
<th>Renal Complication</th>
<th>Patients, n</th>
<th>Mean Volume/Kidney ± SD, mL</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complication Present</td>
<td>Complication Absent</td>
</tr>
<tr>
<td>Loss of GFR</td>
<td>220</td>
<td>598 ± 368</td>
<td>366 ± 168</td>
</tr>
<tr>
<td>Hypertension</td>
<td>241</td>
<td>628 ± 48</td>
<td>352 ± 33</td>
</tr>
<tr>
<td>Gross hematuria</td>
<td>191</td>
<td>820 ± 87</td>
<td>588 ± 52</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>270</td>
<td>1190 ± 93</td>
<td>578 ± 32</td>
</tr>
</tbody>
</table>

Why TKV is Important
The CRISP Study

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

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.
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.
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%)\(^1\)

• 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.

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.

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.
TKV-based Classification of ADPKD

Age and htTKV predicts decline in eGFR over time in patients with typical* presentation of ADPKD

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.

# Tying it all together: eGFR vs. TKV

**Example:**

- A 35 year old male with an eGFR of 89 ml/min/1.73m² and a height-adjusted TKV of 1202 mL/m²

- Based on his ADPKD Imaging classification, he has a >6% estimated yearly percentage increase in kidney growth

### Baseline Assessment

<table>
<thead>
<tr>
<th>Baseline Assessment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
</tr>
<tr>
<td>Height (ft &amp; in)</td>
<td>5'11&quot;</td>
</tr>
<tr>
<td>Weight (lbs)</td>
<td>210</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>M</td>
</tr>
<tr>
<td>Race (AA/O)</td>
<td>0</td>
</tr>
<tr>
<td>Mutations</td>
<td>Truncating PKD1</td>
</tr>
<tr>
<td>Ultrasound Kidney Length (cm)</td>
<td>Not available</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>1.15</td>
</tr>
<tr>
<td>htTKV (mL/m²)</td>
<td>1389</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>82</td>
</tr>
<tr>
<td>Patient &amp; Family History</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypertension before 35</td>
<td>Yes</td>
</tr>
<tr>
<td>Urological event before 35</td>
<td>No</td>
</tr>
<tr>
<td>Family members with ESRD</td>
<td>No</td>
</tr>
<tr>
<td>PROPKD Score</td>
<td>9 - HIGH Risk of Progression to ESRD</td>
</tr>
<tr>
<td>ADPKD Imaging Classification</td>
<td>Class 1E: &gt;5% estimated yearly percentage increase in kidney growth</td>
</tr>
</tbody>
</table>

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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.

Glomerular Filtration Rate vs Total Kidney Volume (TKV):

Predictive Markers of Disease Progression and Why TKV is Important