Prognostic Biomarker Qualification: Case Study: ADPKD and TKV

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Disclosures

• Research Support:
  – Boston Scientific

• Consultation
  – Otsuka, Kadmon, Sanofi-Genzyme
ADPKD

• 4th leading cause of ESRD
• No race/gender favored
• >3,000,000 worldwide
• Cysts
  — Kidneys
  — Liver
  — Pancreas
  — Spleen
  — Brain
• Begin in utero
• Develop in tubules
• Separate from tubules
• Isolated sacs

ADPKD Progression

Kidney function (%) vs. Age (years)

Concentrating defect, Hypertension, Proteinuria

Pain, Hematuria, Stones, Infections
ADPKD patients suffer renal complications prior to loss of kidney function

By age 30, over 50% have at least one complication

NIH CRISP Studies; Rahbari-Oskoui, *ASN Renal Week*, 2010.
Characteristics of ADPKD That Associate with ESRD

- **Genotype:** > 95% PKD1 individuals demonstrate renal cysts by age 30
- **Hypertension:** occurs in 60% with intact renal function by age 30
- **Proteinuria:** is not a common feature of this disease, but has important prognostic implications
- **Gross hematuria:** > 50% will have had an episode by age 40

All characteristics have now been shown to mediate their risk through kidney volume
Prospective longitudinal observational study with annual protocolized visits, MRIs and GFR measurements

Age 15-45 yrs

eGFR >70 ml/min

2/3 with hypertension <35 yrs or PrU >300 mg/d
Inter-observer variability: 2.1%
Intra-observer variability: 2.4%
Day-to-day variability: 2.4%
Increased Kidney Volume is Due to Increased Cyst Volume

Kidney growth is highly variable and each individual has their own growth curve

Measurement variability: Inter-observer 2.1%, Intra-observer 2.4%, Day-to-Day 2.4%
Grantham, NEJM CRISP 2006; Chapman Kidney Int 64; 1035–1045, 2003
Change in Kidney Volume Precedes Change in Kidney Function

p<0.05 for htTKV change from baseline; # p<0.05 for GFR change from baseline; htTKV=Height-adjusted total kidney volume; ¹ Percent Change Standardized to a common unit; NIH CRISP Studies; Chapman CJASN 7:479, 2012
<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cut-point</th>
<th>95% CI of AUC</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>htTKV</td>
<td>cc/m</td>
<td>0.84</td>
<td>0.74</td>
<td>0.7</td>
<td>600</td>
<td>(0.79, 0.90)</td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>mg/dL</td>
<td>0.75</td>
<td>0.58</td>
<td>0.81</td>
<td>1.1</td>
<td>(0.67, 0.82)</td>
<td>0.02</td>
</tr>
<tr>
<td>BUN</td>
<td>mg/dL</td>
<td>0.76</td>
<td>0.63</td>
<td>0.79</td>
<td>16</td>
<td>(0.70, 0.83)</td>
<td>0.04</td>
</tr>
<tr>
<td>Urine Albumin</td>
<td>mg/d</td>
<td>0.70</td>
<td>0.66</td>
<td>0.67</td>
<td>30</td>
<td>(0.61, 0.78)</td>
<td>0.002</td>
</tr>
<tr>
<td>MCP-1</td>
<td>pg/mg</td>
<td>0.75</td>
<td>0.80</td>
<td>0.62</td>
<td>410</td>
<td>(0.68, 0.83)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline age</td>
<td>y</td>
<td>0.66</td>
<td>0.60</td>
<td>0.65</td>
<td>35</td>
<td>(0.59, 0.74)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

AUROC = 0.84
95% CI = (0.79, 0.90)
Sensitivity = 74%
Specificity = 75%
Cut Point = 600 (cc/m)
QUALIFICATION OF TOTAL KIDNEY VOLUME AS A PROGNOSTIC BIOMARKER FOR USE IN CLINICAL TRIALS EVALUATING PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

RD Perrone, JF Marier, MS Mouksassi, F Czerwiec, K Romero, E Dennis, D Miskulin, A Chapman, B Gitomer, and VE Torres for the PKD Outcomes Consortium
Primary Research Objectives

- Determine the predictive value of TKV, baseline eGFR, baseline age and other prognostic factors (e.g., sex, PKD mutation, race) in estimating the risk of worsening of eGFR and ESRD to support the regulatory qualification of TKV as a prognostic biomarker for use in clinical trials.

- Develop a joint model that can simultaneously assess longitudinal TKV measurements and the probability of disease outcome. Use the above joint model as a drug development tool (DDT) for trial enrichment strategies.
Decision Tree for Use of Baseline TKV for Prognostic Clinical Trial Enrichment

Patient Selection for Clinical Trials

Goal:
Prevention of Early Outcomes

Goal:
Reduction of Complications

Goal:
Reduce Progression to ESRD

eGFR

Candidate Endpoint:
30% Worsening of eGFR

Candidate Endpoint:
57% Worsening of eGFR

Candidate Endpoint:
ESRD

Trial and Inclusion Criteria
Early Outcome Trial
W ml < TKV < X mL, age (range)

Trial and Inclusion Criteria
Disease Progression Trial
X ml < TKV < Y mL, age (range)

Trial and Inclusion Criteria
Late Stage Trial
TKV > Y mL, age (range)

Clinical Trial Impact:

• Fewer patients
• Shorter study duration
• Reduced clinical trial costs
• Reduced exposure to potential drug toxicities
• Improved success rate of clinical drug development
• Use to select patients for appropriate clinical trials
PKDOC Data Overview and Summary

Define Priority PKD Data

Emory Registry N=376

Mayo Registry N=1,010

Colorado Registry N=1,112

CRISP Observational Study N=241

ADPKD Common Data Elements

ADPKD Supplement to the SDTM User Guide

CDISC SDTM

Standardized PKD Data

Aggregated Common ADPKD Research Database N = 2,355

PKD Consortium Critical Path Institute
## Trial Enrichment Using TKV: Highest Risk of Progression

<table>
<thead>
<tr>
<th>Follow-Up Times (Years)</th>
<th>Probabilities of Avoiding 30% Worsening of eGFR</th>
<th>TKV &lt; 1 L</th>
<th>TKV ≥ 1 L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age: &lt; 40 years</td>
<td>Age: ≥ 40 years</td>
<td>Age: &lt; 40 years</td>
</tr>
<tr>
<td></td>
<td>eGFR ≥ 50 mL/min</td>
<td>eGFR &lt; 50 mL/min</td>
<td>eGFR ≥ 50 mL/min</td>
</tr>
<tr>
<td>1</td>
<td>0.991</td>
<td>0.992</td>
<td>0.992</td>
</tr>
<tr>
<td>2</td>
<td>0.980</td>
<td>0.980</td>
<td>0.981</td>
</tr>
<tr>
<td>3</td>
<td>0.950</td>
<td>0.949</td>
<td>0.951</td>
</tr>
<tr>
<td>4</td>
<td>0.917</td>
<td>0.916</td>
<td>0.918</td>
</tr>
<tr>
<td>5</td>
<td>0.887</td>
<td>0.888</td>
<td>0.889</td>
</tr>
</tbody>
</table>
Predicted Probability at Baseline of Avoiding a 30% Decline in eGFR: Effect of Baseline TKV
## Classification of ADPKD patients

### Pre-specified imaging findings

<table>
<thead>
<tr>
<th>Class</th>
<th>Sub class</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Typical ADPKD</td>
<td></td>
<td>Cyst distribution is bilateral and diffuse with relatively even contribution to TKV</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Unilateral</td>
<td>Normal contralateral kidney with ≤2 cysts</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Asymmetric</td>
<td>Mild involvement of contralateral kidney with 3-9 cysts and &lt;30% of TKV.</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Segmental</td>
<td>Involvement only one pole of one or both kidneys</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Lop-sided</td>
<td>Mild replacement of kidney tissue with ≤5 cysts accounting for ≥50% TKV.</td>
</tr>
<tr>
<td>2</td>
<td>Atypical ADPKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Bilateral presentation w/ acquired unilateral atrophy</td>
<td>Atrophy of contralateral kidney.</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Bilateral presentation w/ bilateral kidney atrophy</td>
<td>Length &lt; 14.5 cm, atrophy of parenchyma and SCr ≥ 1.5 mg/dL</td>
</tr>
</tbody>
</table>

TKVe correlates strongly with TKVs.
Classification by Estimated Rate of Growth (from age and starting HtTKV = 150 ml/m)

Patient Age (Years)

Subclass 1A
≤1.5%

Subclass 1B
1.5 – 3%

Subclass 1C
3 – 4.5%

Subclass 1D
4.5 – 6%

Subclass 1E
> 6%

Post-Hoc Analysis: HALT PKD Study A
Distribution of Patients by Class at Baseline

N = 551

Class 1: 94.6%
Class 2: 5.4%
Image Classification of HALT PKD Study A Patients

- Subclass 1E: > 6% per year
- Subclass 1D: 4.5 – 6% per year
- Subclass 1C: 3 – 4.5% per year
- Subclass 1B: 1.5 – 3% per year
- Subclass 1A: ≤1.5% per year
• Class severity associates with greater rates of TKV increase and eGFR decline
• Changes in TKV and eGFR are negatively correlated
• The treatment effect of low BP increases with class severity
• In the patients with the most severe disease (class D-E), low BP associates with slower eGFR decline after month 4 and overall
• Restriction of enrollment to class 1D-E patients would have detected a stronger low BP effect on TKV growth and EGFR decline, with a much lower number of patients (187 vs 551)
• These results stress the importance of optimal patient selection to reduce the cost and the chance of a type II error
Interventional trials designed based on disease natural history

**Trial Population**
Mid-Stage ADPKD

- Significant cystic burden for age
  \[ TKV \geq 750 \text{ ml} \text{ Age 18-50} \]
- Preserved kidney function
  \[ \text{CKD 1-3: } eCrCl > 60 \text{ ml/min} \]

**Endpoints: Disease Specific Modifiable Outcomes**

- Cyst Growth by TKV
- Kidney Function Decline
- Progression related events
Thanks for your attention!