Lessons from CRISP, HALT PKD, TEMPO, REPRISE and the PKD Outcomes Consortium: TKV and Other Biomarkers

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Disclosures

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  – Otsuka, Dept. of Defense, Kadmon, Sanofi

• Consultant:
  – Otsuka, Sanofi-Genzyme, Regulus, Palladiobio, GoldfinchBio, Vertex

• Speaker:
  – Otsuka Canada

• Section Editor UpToDate:
  – Renal Cystic Disease
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Hereditary systemic disorder
- Bilateral kidney cysts
- Progressive decline in GFR leading to kidney failure in ~50% of patients by 6th decade
- Extrarenal manifestations
  - Cysts
  - Extracellular matrix abnormalities
- All of the issues associated with CKD
  - Anemia, metabolic bone disease, nutrition, increased CV risk
ADPKD: Cysts Are The Disease

- Growth of cysts leads to enlargement of kidneys
- The total volume of both kidneys is the reflection of the growth of cysts
- TKV (Total kidney volume)
- Large kidneys lose function more quickly
- TKV is an outstanding early biomarker of disease progression
Interventions in Early Disease Are Difficult to Evaluate Due to Slow Decrease in GFR

Welcome to ADPKD Summit Participants ...

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Company</th>
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<tbody>
<tr>
<td>Francesco Emma</td>
<td>Bambino Gesù Children’s Hosp</td>
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<tr>
<td>Amy Porter</td>
<td>Critical Path Institute*</td>
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<td>Gary Lundstrom</td>
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<td>Kitty Bogy</td>
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<td>Dione Kobayashi</td>
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<td>James McArthur</td>
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<td>European Medicines Agency*</td>
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<td>Michelle Campbell</td>
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<td>Naomi Lowy</td>
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<td>Norman Stockbridge</td>
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<td>Shen Xiao</td>
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<td>Ken Gruchalla</td>
<td>Health Canada</td>
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<td>Bonnie Blazer-Yost</td>
<td>Indiana University</td>
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<td>Andrea Remuzzi</td>
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<td>Jerry R. Colca</td>
<td>Metabolic Solutions Development Co*</td>
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<td>Greg Germino</td>
<td>NIDDK</td>
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<td>Frank Czerwiec</td>
<td>Otsuka OPDC*</td>
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<td>Jaime Blais</td>
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<td>Lorenzo Pellegrini</td>
<td>Palladio Biosciences</td>
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<td>Tess Harris</td>
<td>PKD Charity*</td>
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<td>Alexis Denny</td>
<td>PKD Foundation</td>
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<td>David Baron</td>
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<td>John Grundy</td>
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<td>Alaa Hamed</td>
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<td>Vijay Modur</td>
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<td>Alan Yu</td>
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<td>Cynthia Beam</td>
<td>Vertex Pharmaceuticals*</td>
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<td>Dan Bowers</td>
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<td>Joe Mancini</td>
<td>Vertex Pharmaceuticals*</td>
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* ADPKD Planning Committee
Terminology

- Clinical Outcome
- Biomarker
- Surrogate Endpoint

*BEST (Biomarkers, EndpointS, and other Tools) Resource used as source for FDA definitions. The BEST Resource was developed by the FDA and NIH to address the need for harmonization of terms used in translational science and medical product development and specifically terms related to study endpoints and biomarkers.

Slides from ADPKD Summit;
Available at https://c-path.org/category/presentations/
• **Biomarker:** FDA and EMA definitions are similar; BEST definition shown below.

  – A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

  – Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives.
Types of Biomarkers

• **Prognostic Biomarker**: A biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest.

• **Predictive Biomarker**: A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.

• **Pharmacodynamic/Response Biomarker**: A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.
Clinical Factors Predictive of Worse Prognosis

- PKD1 gene
- Younger age at diagnosis
- Male gender
- Hypertension
- Increased left ventricular mass
- Hepatic cysts in women
- Three or more pregnancies
- Gross hematuria
- Urinary tract infections in men
- Renal size expressed as renal volume

Factors Associated with More Severe Disease

- Copeptin
- Proteinuria
- Monocyte chemotactic protein-1 (MCP-1)
- Urinary β2-microglobulin, KIM-1, H-FABP, and NGAL
- Inability to concentrate the urine
- OMICS
Association of MCP with TKV and eGFR

Grantham et al., *Nephrol Dial Transplant* (2016) 0: 1–7
Prognostic Biomarkers

• Multiple areas of evidence confirm that TKV is prognostic of future decline in GFR
  – CRISP
  – Mayo Imaging Classification
  – PKDOC

• Associated with earlier age of ESRD in populations
  – Genotype
  – PROPKD score
CRISP1: GFR declined 4.3 ml/min/1.73 m² only in those with TKV > 1500 ml

NEJM 354:2122-30, 2006
Correlations between baseline htkTKV and GFR during follow-up. Pearson correlation coefficients determined for baseline htkTKV and iothalamate GFR at baseline and five subsequent visits (n=114 with complete data) to year 8. The degree of correlation at each time point is shown. htkTKV, height-adjusted total kidney volume.
Ultrasound/MRI Kidney Length Predicts CKD3a

Kidney Volume Calculator based on Ellipsoid equation ($\frac{\pi}{6}xLxWxD$) from MRI or CT image

### Required Data Entry

**Right Kidney**
- Sagittal Length (mm)
- Coronal Length (mm)
- Width (mm)
- Depth (mm)

**Left Kidney**
- Sagittal Length (mm)
- Coronal Length (mm)
- Width (mm)
- Depth (mm)

### Calculated Results

**Right Kidney Volume (mL)**

**Left Kidney Volume (mL)**

**Total Kidney Volume (mL)**

[Calculate Volumes]

[Clear All]
Five subclasses (1A–1E) based on estimated kidney growth rates: yearly percentage increase of: 1.5% (subclass 1A), 1.5%–3% (1B), 3%–4.5% (1C), 4.5%–6% (1D), or 6% (1E)

Irazabal et al JASN, 2014
Irazabal et al JASN, 2014
Total Kidney Volume Is a Prognostic Biomarker of Renal Function Decline and Progression to End-Stage Renal Disease in Patients With Autosomal Dominant Polycystic Kidney Disease

Ronald D. Perrone¹, Mohamad-Samer Mouksassi², Klaus Romero³, Frank S. Czerwiec⁴, Arlene B. Chapman⁵, Berenice Y. Gitomer⁶, Vicente E. Torres⁷, Dana C. Miskulin¹, Steve Broadbent³ and Jean F. Marier²

A Drug Development Tool for Trial Enrichment in Patients With Autosomal Dominant Polycystic Kidney Disease

Ronald D. Perrone¹, Mohamad-Samer Mouksassi², Klaus Romero³, Frank S. Czerwiec⁴, Arlene B. Chapman⁵, Berenice Y. Gitomer⁶, Vicente E. Torres⁷, Dana C. Miskulin¹, Steve Broadbent³ and Jean F. Marier²
PKDOC Data Overview and Summary
Predicted Probability at Baseline of Avoiding a 30% Decline in eGFR: Effect of Baseline TKV
On October 22, 2015 the EMA released a final Qualification Opinion in support of Total Kidney Volume for use as a prognostic biomarker in clinical trials for patients with Polycystic Kidney Disease.
II. CONTEXT OF USE

A. Use Statement

This guidance provides qualification recommendations for the use of TKV, measured at baseline, as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in renal function (defined as a confirmed 30% decline in the patient’s estimated glomerular filtration rate (eGFR)) for inclusion in interventional clinical trials. This biomarker may be used in combination with the patient’s age and baseline eGFR as an enrichment factor in these trials.
Genotype Impact on Renal Survival

741 patients from 519 pedigrees; Cornec-Le Gall 2013 JASN

P < 0.0001
PROPKD Score

Point system based on risk of ESRD

• Male gender: 1 point
• HTN before age 35: 2 points
• First urologic event before age 35: 2 points
• PKD2 mutation: 0 points
• Non truncating PKD1 mutation: 2 points
• Truncating PKD1 mutation: 4 points

The PROPKD Score: A New Algorithm to Predict Renal Survival in Autosomal Dominant Polycystic Kidney Disease

Cornec-Le Gall JASN 2015
Figure 2. The PROPKD score enables stratification of risk of progression to ESRD in patients with ADPKD.
Mayo Imaging Classification is a Predictive Biomarker

• Prognostic enrichment demonstrated in HALT and TEMPO

• Limiting to Mayo classes 1C, D, E (TEMPO) or 1D and 1E (HALT) show highly significant effect of interventions

• Sample size requirements reduced
A Changes in Total Kidney Volume over Time

- **Standard blood pressure**
- **Low blood pressure**

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<th>Follow-up (mo)</th>
<th>Standard blood pressure</th>
<th>Low blood pressure</th>
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<tr>
<td>24</td>
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<tr>
<td>48</td>
<td>7.2</td>
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<tr>
<td>60</td>
<td>7.4</td>
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- Low blood pressure, 5.6%/yr
- Standard blood pressure, 6.6%/yr
- Difference, −1.0 percentage points/yr (95% CI, −1.6 to −0.2)
- P = 0.006

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<th>No. of Patients</th>
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*NEJM* Nov 15, 2014
Low chronic slope = -2.7 ml/min/yr
Standard chronic slope = -3.1 ml/min/yr
p=0.05

Low overall slope = -2.9 ml/min/yr
Standard overall slope = -3.0 ml/min/yr
p=0.55

**NEJM** Nov 15, 2014 (online)
Prognostic Enrichment in HALT PKD

• Merging Classes 1A and 2 (lowest severity), 1B and 1C (intermediate severity) and 1D and 1E (highest severity) detected stronger beneficial effects on TKV increase and eGFR decline in Class 1D and E with a smaller number of patients.

Irazabal et al; Nephrol Dial Transplant (2016) 0: 1–9
Primary Endpoint: Annual Percent Change in Kidney Volume

- TKV < 1500 mL
- TKV > 1500 mL
- eCrCl < 80 mL/min
- eCrCl > 80 mL/min
- Age < 35 Years
- Age ≥ 35 Years
- Hypertension
- Non-hypertension

TKV Slope Reduction (%/year)

- Male
- Female

Favors Tolvaptan

P<0.0001

NEJM Nov 3 2012 (online)
Prognostic Enrichment in TEMPO 3:4

• Restricting enrollment to classes 1C, 1D and 1E would have required 10.5% fewer patients

• In this smaller cohort:
  – Tolvaptan reduced TKV from 5.78% to 2.91% per year (P < 0.001)
  – Tolvaptan reduced eGFR slopes from 3.93 to 2.82 ml/min/1.73 m$^2$ per year (P < 0.001)
  – Tolvaptan reduced the risk of the composite endpoint (hazard ratio = 0.84, P = 0.003)

• TEMPO 3:4 already enriched (TKV>750 ml)
Interim Summary

• Increased TKV is associated with later renal function decline

• In intervention trials, treatment effects on TKV have not uniformly predicted treatment effects on the progressive loss of kidney function
  – TEMPO 3:4 is an exception; further confirmed by REPRISE

• How does this finding impact the regulatory perspective?
  
  We don’t know yet…….
One year change in eGFR (pre-treatment to post-treatment)

-2.34

-3.61

Difference: 1.27 mL/min/1.73m²
p-value: <0.0001

NEJM Nov 4, 2017 (online)
Favors tolvaptan  
Favors placebo  
Treatment Difference ± 95% CI (Tolvaptan vs Placebo) 
Estimated One-year eGFR slope

### Estimated One-Year eGFR slope (including all periods)

**SECONDARY EFFICACY ENDPOINT**

- **Tolvaptan**
  - Estimated One-Year eGFR slope: -3.16 mL/min/1.73m²
  - p-value: <0.0001
- **Placebo**
  - Estimated One-Year eGFR slope: -4.17 mL/min/1.73m²

**Category**

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<td>Non-US</td>
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**Difference:** 1.01 mL/min/1.73m²  
**p-value:** <0.0001

*NEJM* Nov 4, 2017 (online)
Regulatory Perspective

- Clinical Outcome
- Biomarker
- Surrogate Endpoint

*BEST (Biomarkers, EndpointS, and other Tools) Resource used as source for FDA definitions. The BEST Resource was developed by the FDA and NIH to address the need for harmonization of terms used in translational science and medical product development and specifically terms related to study endpoints and biomarkers.
**Terminology**

- **Clinical Outcome**: Significant overlap in definitions/concepts
  - **FDA (BEST Resource)**: An outcome that describes or reflects how an individual feels, functions or survives (*BEST Resource*). The FDA has also referred to an endpoint that describes how an individual feels, functions or survives as a “clinically meaningful endpoint.”
  - **EMA**: No single/set definition, but generally used to refer to an endpoint that measures **clinical benefit** (*based on ICH E8*). Clinical outcomes can range from “improvement of symptoms” to “delay of disease progression” or “prolonging survival”.
Terminology

- **Surrogate endpoint:** Again, overlapping definitions/concepts
  - **FDA (BEST Resource):** An endpoint that is used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather *is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.*

From a U.S. regulatory standpoint, surrogate endpoints and potential surrogate endpoints can be characterized by the level of clinical validation: validated surrogate endpoint, reasonably likely surrogate endpoint, candidate surrogate endpoint
• **Surrogate endpoint:**
  
  – **EMA:** An endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit.

Surrogate endpoints may be used as primary endpoints when appropriate (when the surrogate is reasonably likely or well known to predict clinical outcome) and validated (based on ICH E8 and E9).
Conclusions

• The ideal therapeutic agent would block formation and/or growth of cysts at an early stage of life
• Total kidney volume is well-established as a prognostic and predictive biomarker
• The US FDA considers TKV to be a reasonably likely surrogate for effects on PKD progression; EMA already accepted TKV/eGFR in TEMPO 3:4
• The evidence for other potential biomarkers for PKD progression in human clinical trials is sparse
• Development and validation of molecular biomarkers would facilitate even greater opportunities for early intervention and shorter clinical trials
Colleagues and Collaborators

- **PKD Foundation/SAC**
  V Gattone, J Grantham, T Steinman, Ben Cowley, T Watnick, A Chapman, L Guay-Woodford, L Rome, A Denny, D Baron, S Somlo, J Bissler, P Igarashi, M Mrug, D Wallace, J Calvet, V Torres, P Harris, R Sanford

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  **Mayo:** V Torres, M Irazabal
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  **U Colorado:** B Gitomer, R Schrier
  **Tufts:** J Castedo, D Miskulin
  **CRISP DCC:** J Bost, T Bae, D Landsittel
  **Pharma:** Amgen, Genzyme, Novartis, Otsuka, Pfizer, Roche
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  **FDA:** S Amur, J Lawrence, S-J Wang, J Hung, S Pendse, N Xu, A Thompson, N Stockbridge, D Marathe, J Florian, M Sahre, H Rogers, M Noone, D Krainak, J Delfino
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  - **CCF:** W Braun
  - **BIDMC:** T Steinman, P Czarnecki
  - **KUMC:** J Grantham, F Winklhofer, A Yu
  - **Tufts:** D Miskulin
  - **Emory:** F Rahbari-Oskoui, A Chapman
  - **NIDDK:** M Flessner

- **TEMPO 3:4/REPRISE:**
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  - **Emory/U Chicago:** A Chapman
  - **Brussels/Zurich:** O Devuyst
  - **UMC Groningen:** R Gansevoort
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