CRITICAL PATH INSTITUTE

NORD®
National Organization for Rare Disorders

Rare Disease Cures Accelerator-Data and Analytics Platform
Virtual Workshop 2020

Up Next: *Case Study 1: Role of integrated data and advanced analytics to accelerate medical product development. A Case Study in Polycystic Kidney Disease*

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Role of integrated data and advanced analytics to accelerate medical product development:

A Case Study in Polycystic Kidney Disease

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PKD POLYCYSTIC KIDNEY DISEASE OUTCOMES CONSORTIUM

CRITICAL PATH INSTITUTE 15 YEARS

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Disclaimer

The opinions presented herein are those of the presenters, and are not necessarily the opinions of the presenters' employers, or any affiliates of their employers, or of any collaborating companies.

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Agenda

- ADPKD: Unmet Medical Need
- PKD Consortium: A Catalyst to ADPKD drug development
- Impact and Importance of Public-Private Partnership to Galvanize ADPKD Drug Development

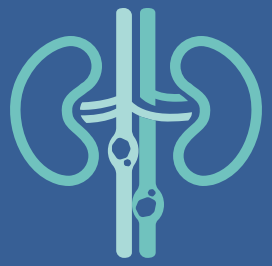
Prevalence and Impact of ADPKD in the United States

The **most common** inherited renal disease[1]

~140,000 patients currently diagnosed

Estimated prevalence is 4.3 per 10,000[2,*]

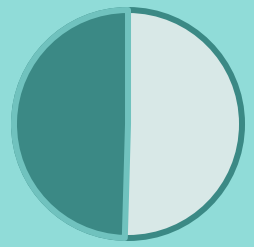
* Based on the National Ambulatory Medical Care Survey (NAMCS)



4th leading cause of ESKD

(after diabetes, hypertension, and glomerulonephritis)[3]; ~4.5% of ESKD cases[4]

ESKD = end-stage kidney disease



Nearly 50%

of all patients with ADPKD will reach ESKD by age 60[5]

1. Torres VE et al. *Lancet.* 2007;369(9569):1287-1301
2. Data on file. TOLV-004. Otsuka America Pharmaceutical, Inc.; Rockville, MD
3. United States Renal Data System. https://www.usrds.org/2016/download/v2_c01_IncPrev_16.pdf. Accessed January 12, 2020
4. National Institutes of Health. https://archives.nih.gov/asites/report/09-09-2019/report.nih.gov/nihfactsheets/ViewFactSheetc228.html?csid=29&key=A#A. Accessed January 15, 2020
5. Chebib FT, Torres VE. *Am J Kidney Dis.* 2016;67(5):792-810

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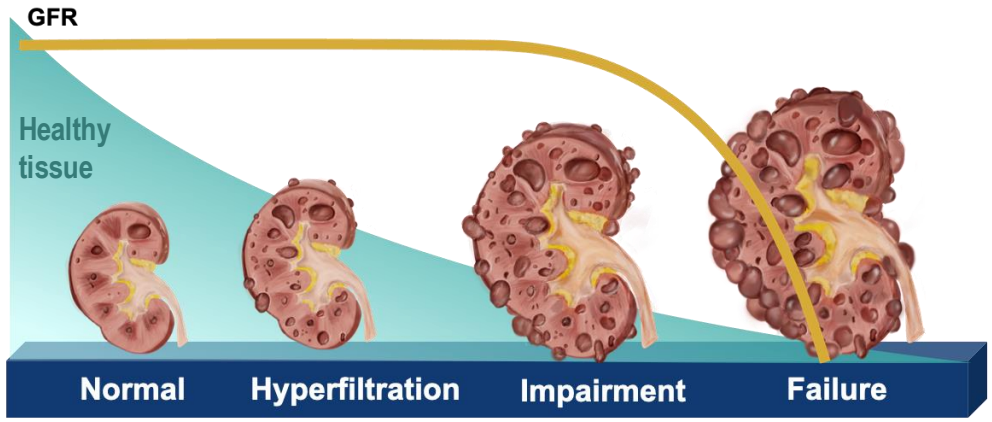
State of Therapeutics pre-PKD Consortium

Cyst Growth Precedes Kidney Function Decline by Many Years[1,2]



Cyst Development & Enlargement

- Patients with ADPKD may remain asymptomatic for years while the disease progresses,[3] likely due to compensatory hyperfiltration[4]
- Up to 50% of the renal parenchyma can be lost before declines in renal function are clinically evident[5,6]

1500

450 + YEARS

Basic Research

1588: First written description in man
1793: First formal identification
1957: First demographic study
1994: PKD1 gene identified
1996: PKD2 gene identified

Translational Research

1995-2011: Identification of disease pathways
- cAMP
- Vasopressin
- mTOR
- AKT

Clinical Trials

2000: CRISP Disease progression and TKV
2011: Tolvaptan Phase III trial
Additional Trials: Somatostatin, Sirolimus, Everolimus & Bosutinib

FDA Evaluation/ Approval

2010: PKD Outcomes Consortium
Analyze patient data for qualification of TKV as a target endpoint for clinical trials
No therapies have been approved to treat PKD

2017

Still waiting for treatments to slow or stop progression. Dialysis and transplantation remain the only options.

1. Grantham JJ et al. *Clin J Am Soc Nephrol*. 2006;1(1):148-157; 2. Grantham JJ et al. *Nat Rev Nephrol*. 2011;7(10):556-566; 3. Lanktree MB, Chapman AB. *Nat Rev Nephrol*. 2017;13(12):750-768; 4. Meijer E et al. *Clin J Am Soc Nephrol*. 2010;5(6):1091-1098; 5. Gaur P et al. *Br J Radiol*. 2019;92(1098):20190078; 6. Grantham JJ. *N Engl J Med*. 2008;359(14):1477-1485.

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Otsuka–people creating new products for better health worldwide

ADPKD JOURNEY

THE PEOPLE OF OTSUKA

have committed decades of their lives and careers to bringing a treatment for ADPKD to patients and families with the disease. Where other companies might have given up, **Otsuka has PERSEVERED for ADPKD patients.**

1982 PKRF Established

1993-1994 First human clinical trials of a vaptan

1999 First pre-clinical trials of vaptans for PKD

2000 NIH CRISP study begins

2003 Vaptans for ADPKD proposed at ASN

2004 Clinical dev. plan in ADPKD greenlighted

2005 IND for tolvaptan in ADPKD filed in the US

2006 TKV in ADPKD studies initiated

2007 First global pivotal trial in ADPKD

2009 tolvaptan Approved for HN

2010 Tolvaptan approved in Japan for fluid retention in CHF

2012 TEMPO 3:4 Published in NEJM

2013 NDA submitted for ADPKD, Complete Response Letter received

2014-2015 Tolvaptan approved in three non-US regions for ADPKD

2015-2016 TKV accepted as trial enrichment biomarker

2017 REPRISE Trial completed and Published in NEJM

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- Otsuka has conducted 14 clinical trials in ADPKD, more than any other pharmaceutical manufacturer to-date, and has conducted the largest clinical trials for ADPKD ever.
- In addition to the research funding that the PKD Foundation, NIH and others have devoted to finding a treatment for ADPKD, Otsuka has invested and committed significant resources and funding to clinical trials for tolvaptan in ADPKD.

Prognostic Biomarker Qualification: A Story of Perseverance

Data Standards → **Data Curation** → **Modeling** → **Model Refresh** → **Scientific Consensus** → **Regulatory Endorsement**

2011-2013

CDISC user guide

2010-2012

Data acquisition

three patient registry datasets and two observational NIH studies

2011-2015

Developed, refined, and validated a joint model

2015-2016

Received a Letter of Support from the FDA for the exploratory use of TKV in clinical trials for ADPKD

FDA draft guidance (August, 2015) and EMA qualification opinion (October, 2015)

Formal qualification of TKV as a prognostic biomarker (September, 2016)

FDA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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PKD Consortium: A Catalyst to ADPKD drug development

Patient Centric Mission

To facilitate and accelerate drug development, leading to novel treatments reaching patients more quickly

Scientific Rigor

To evaluate TKV as a biomarker to predict progression of ADPKD

- Construct a quantitative biomarker dynamics and disease progression model to ascertain linkage between TKV progression and decline of kidney function (joint model)

Regulatory Partnership

To achieve the appropriate level of regulatory endorsement of TKV as a biomarker for use in ADPKD trials (patient selection and endpoint)

PKD
POLYCYSTIC KIDNEY DISEASE
OUTCOMES CONSORTIUM

Streamlined ADPKD Drug Development

Impact and Importance of Public-Private Partnership to Galvanize ADPKD Drug Development

Regulatory acceptance

Better understanding of disease and application of biomarkers across all stakeholders including health authorities

Rapid implementation of biomarkers in clinical trials

Accepted under IND vs qualified

Patient stratification and disease monitoring biomarkers lead to efficient clinical trials, faster approvals

Change patient journey—precision therapeutic

Promoting diversity in clinical trials and supporting access for underserved populations

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THANK YOU!

Don't forget to answer survey questions.

For more information, email rdcadap@c-path.org

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