Model-Based Qualification of Biomarkers

Klaus Romero, MD MS FCP
Director of Clinical Pharmacology and Quantitative Medicine

CRITICAL PATH INSTITUTE

Critical Path Initiative (CPI)
Critical Path Institute (C-Path)

CRITICAL PATH INSTITUTE

Independent 501(c)3 founded in 2005 "… to foster development of new evaluation tools to inform medical product development"

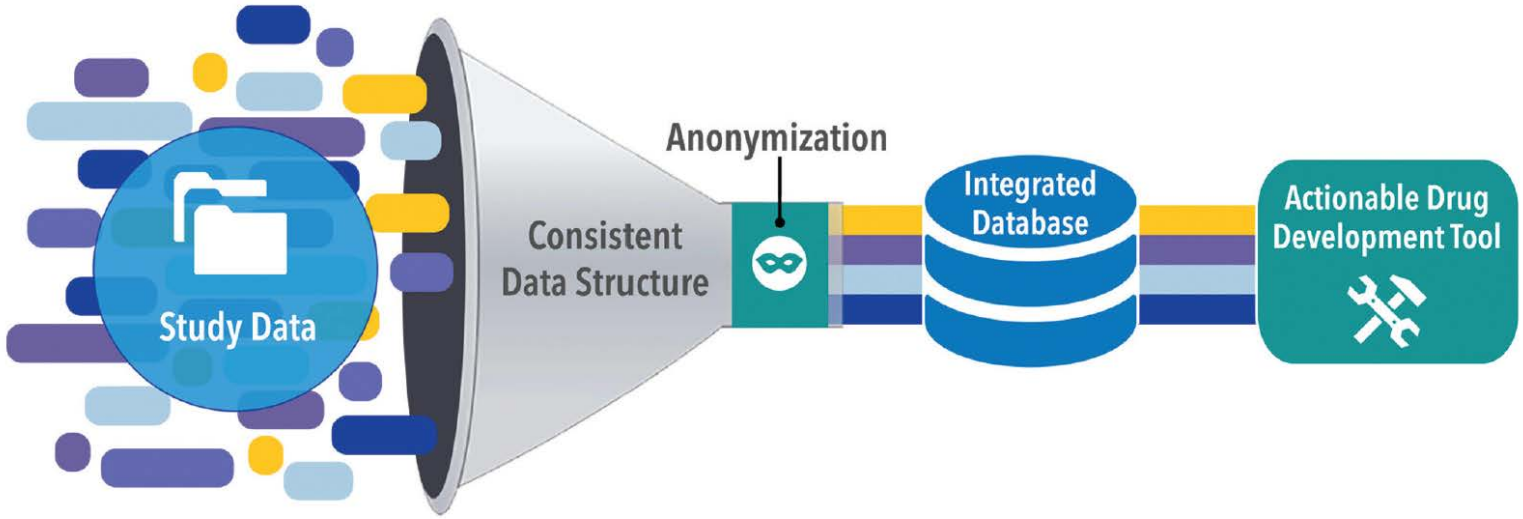
Memorandum of Understanding created between the FDA and C-Path in 2005

Coalition For Accelerating Standards & Therapies
C-Path Data Mapping and Integration Process

CRITICAL PATH INSTITUTE
collaborate · innovate · accelerate

+ CDISC® = CFAST
Coalition For Accelerating Standards and Therapies

Application of Clinical Data Interchange Standards Consortium (CDISC) data standards



This illustrates the process of taking non-standardized data from individual studies, applying CDISC standards so all the data can be aggregated, and utilizing that fully integrated database to support the delivery of drug development tools.

C-Path Consortia

Twelve global consortia collaborating with 1,450+ scientists and 84 organizations

Coalition Against Major Diseases
Focusing on diseases of the brain

Coalition For Accelerating Standards and Therapies
Data standards

Critical Path for Parkinson's Consortium
Enabling clinical trials in Parkinson's Disease

Critical Path to TB Drug Regimens
Accelerating the development of TB drug regimens and diagnostics

Duchenne Regulatory Science Consortium
Duchenne Muscular Dystrophy

International Neonatal Consortium
Neonatal clinical trials

Multiple Sclerosis Outcome Assessments Consortium
Drug Effectiveness in MS

Polycystic Kidney Disease Outcomes Consortium
New imaging biomarker for PKD

Patient-Reported Outcome Consortium
Assessing treatment benefit

Electronic Patient-Reported Outcome Consortium
Electronic capture of treatment benefit

Predictive Safety Testing Consortium
Drug safety

Pediatric Trials Consortium
Developing effective therapies for children

- ✓ Biomarkers
- ✓ Clinical outcome assessment instruments
- ✓ Clinical trial simulation tools
- ✓ Data standards
- ✓ In vitro tools

Regulatory Process for Qualification of Biomarkers

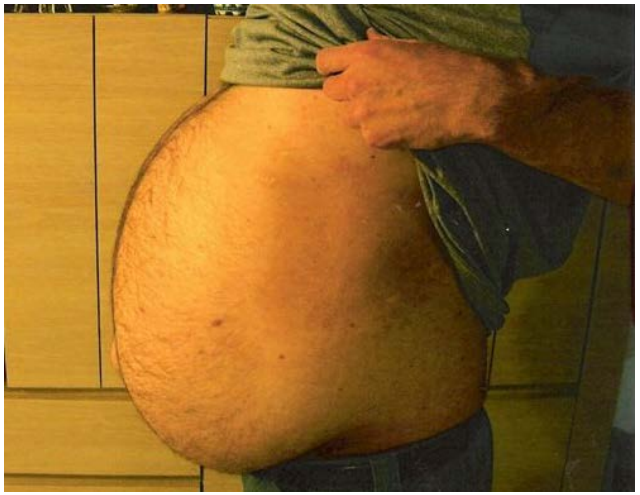
CRITICAL PATH INSTITUTE

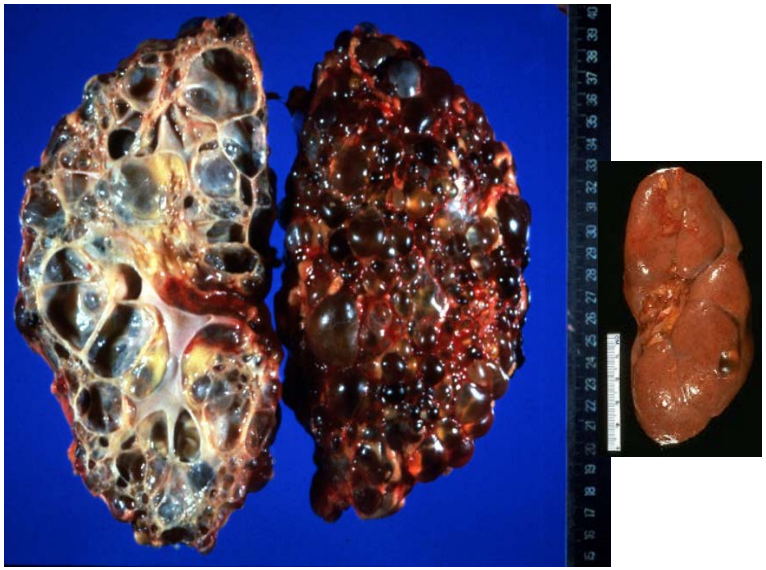
1. **Regulatory Process: Context-of-Use**
   - Context of use: manner and purpose of use of the drug development tool

2. **Drug Development Tool: Biomarker-Disease Model**
   - **Biomarker** (biochemical marker, imaging biomarker...)
     - susceptibility/risk biomarker
     - diagnostic biomarker
     - monitoring biomarker
     - prognostic biomarker
     - predictive biomarker
     - pharmacodynamic/response biomarker
     - safety biomarker
   - **Disease** (e.g., worsening, LFT, adverse events, transplant, mortality…)

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

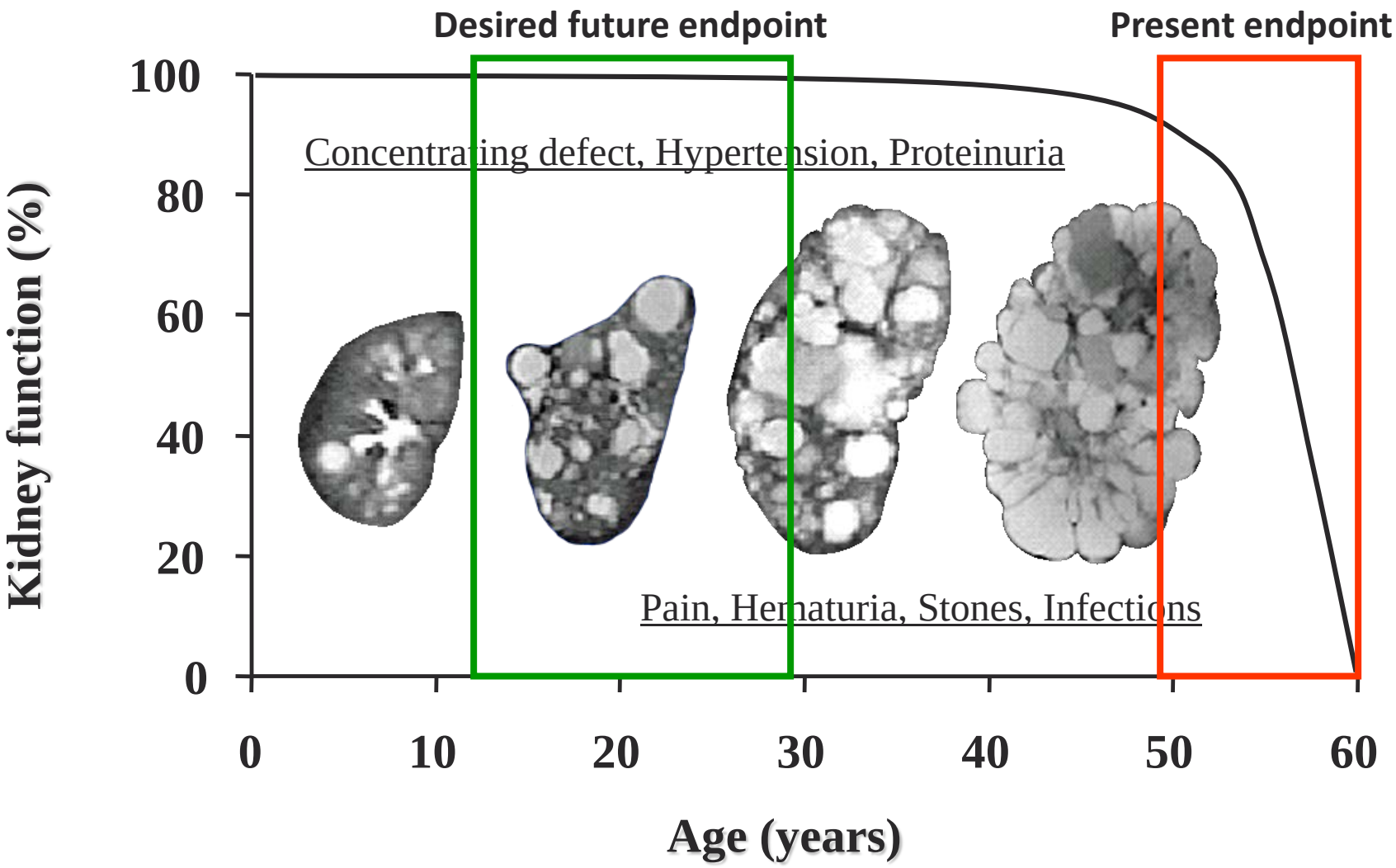
- Hereditary systemic disorder
- Bilateral kidney cysts leading to marked expansion of total kidney volume (TKV)
- Progressive reduction in kidney function
  - Accounts for 8-10% patients on dialysis
- Direct medical costs exceed $1.5 billion/year





Courtesy J. Grantham

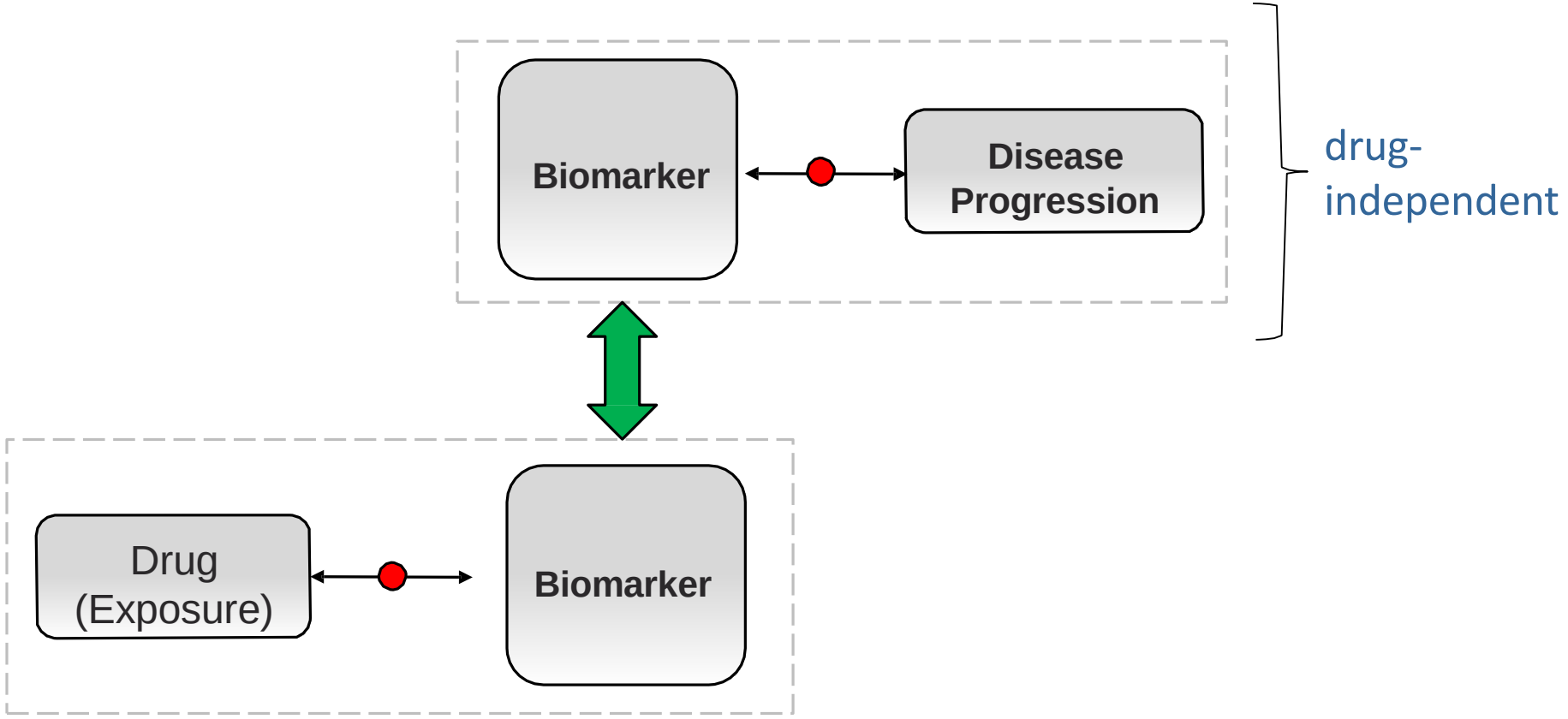
Changing The Paradigm For Predicting and Measuring Disease Progression



Courtesy V. Torres

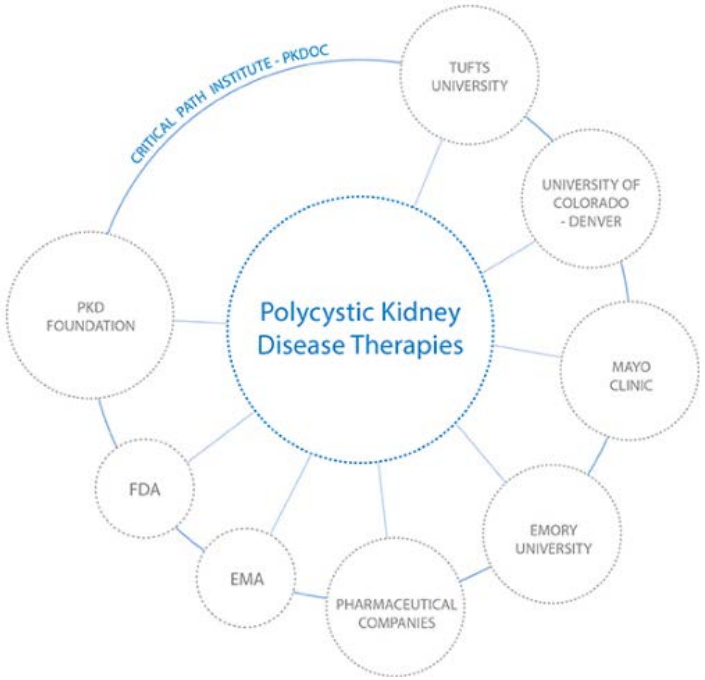
Development of Quantitative Tools to Support Biomarker Qualification

1. Fundamental component of biomarker-disease models
   - Biomarker-disease models are drug-independent
   - Can be customized by introducing a drug-biomarker



Polycystic Kidney Disease Outcomes Consortium: The Need

- **Autosomal Dominant Polycystic Kidney Disease** (ADPKD) is a debilitating genetic disease affecting more than 600,000 Americans and 12 million people worldwide and for which there is currently no known cure or effective treatment.
- **Critical need for a biomarker** that will predict disease progression at an earlier stage when patients may be more likely to respond to new therapies.



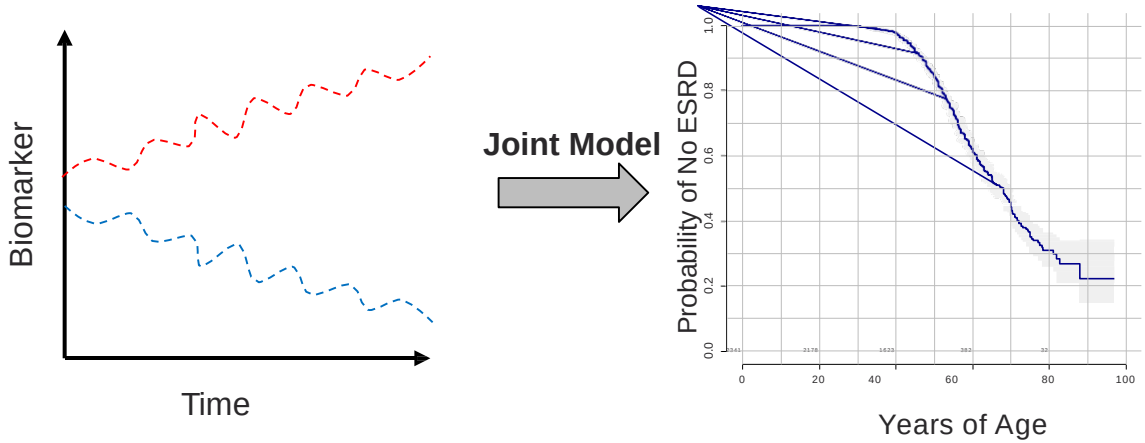
A total of 2355 patients with TKV measurement available in the database.

Observational data from the following five sources has been aggregated (CDISC SDTM):

- University of Colorado – Denver
- Mayo Clinic
- Emory University
- Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease 1 (CRISP1)
- Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease 2 (CRISP2)

Challenges

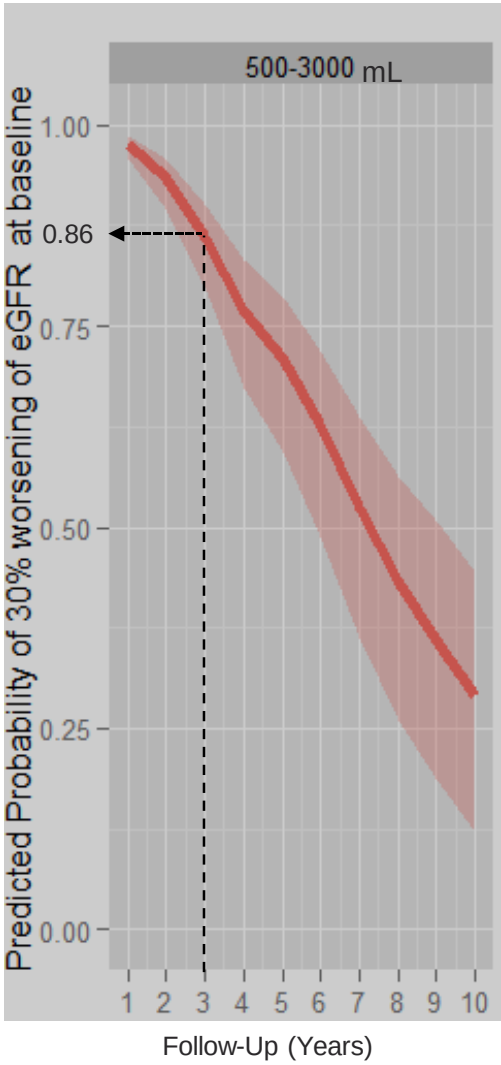
- This effort involved simultaneously modeling
  - Biomarker trajectory (longitudinal time-varying covariates)
  - Disease Endpoint, hazard function (time-to-event)



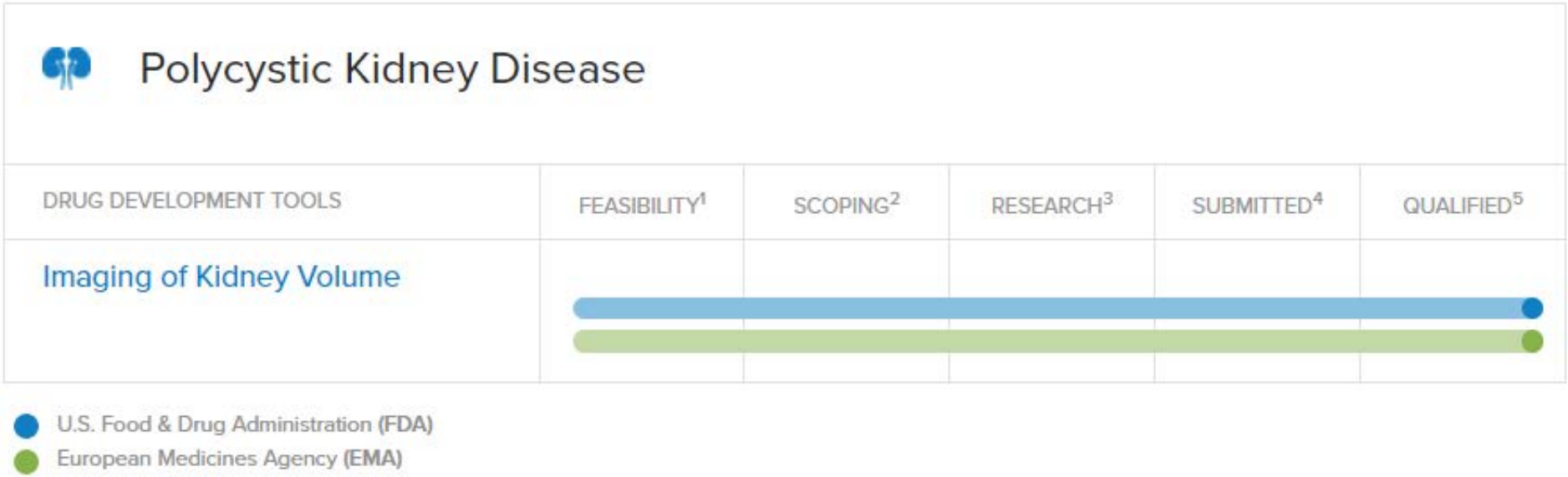
- Joint modeling is considered as the gold standard method for assessing the effect of longitudinal time-varying covariates in a time-to-event analysis of clinical endpoint (Sweeting et al., 2011; Tsiatis, & Davidian, 2004)

Clinical Trial Planning Example
30% Worsening of eGFR

Age	TKV	Follow-Up Period	1-Probability of 30% Worsening of eGFR		
			Median	Lower	Upper
Baseline age=30yrs	Baseline TKV 1.7L	1	0.98	0.96	0.99
		2	0.93	0.90	0.96
		3	**0.86**	0.80	0.90
		4	0.77	0.67	0.83
		5	0.71	0.59	0.79
		6	0.63	0.49	0.72
		7	0.52	0.36	0.64
		8	0.43	0.26	0.56
		9	0.36	0.19	0.51
		10	0.29	0.12	0.45

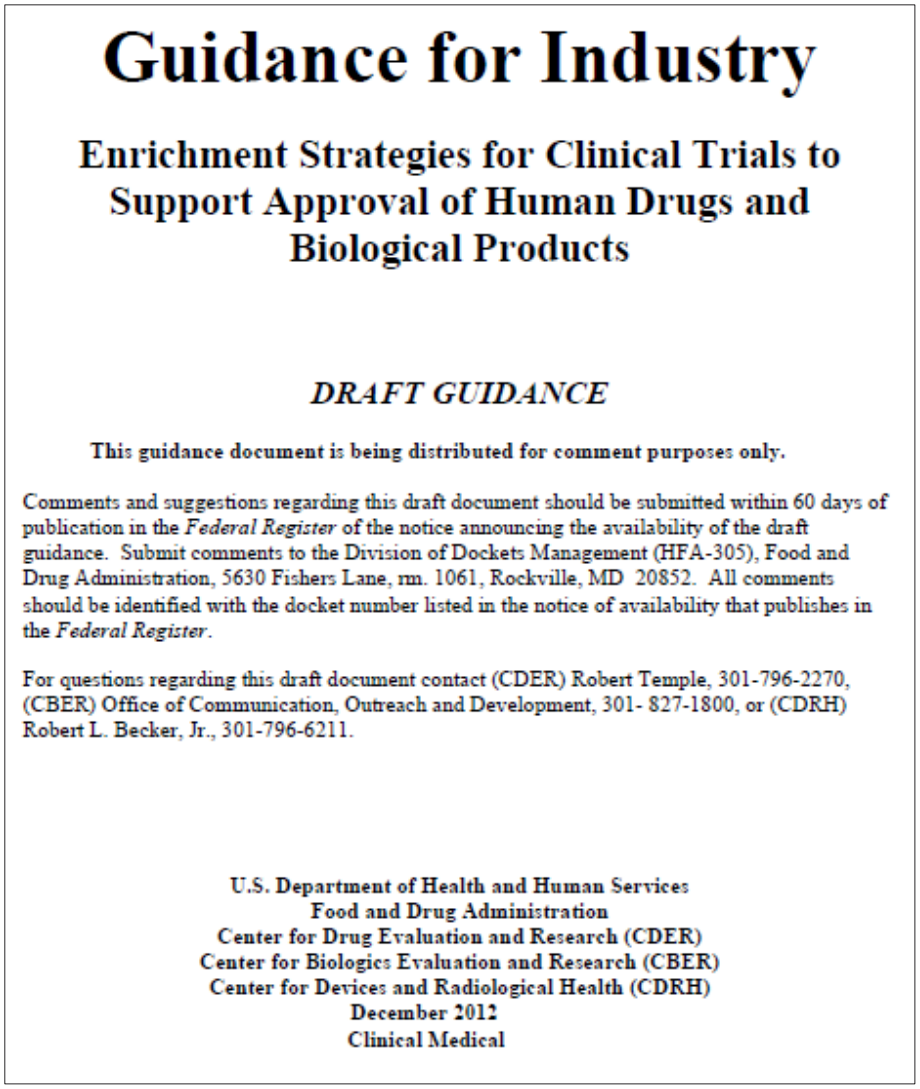


Polycystic Kidney Disease Outcomes Consortium: Regulatory Sciences Pipeline



Qualified prognostic enrichment biomarker

Application: Trial Enrichment



Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Robert Temple, 301-796-2270, (CBER) Office of Communication, Outreach and Development, 301- 827-1800, or (CDRH) Robert L. Becker, Jr., 301-796-6211.

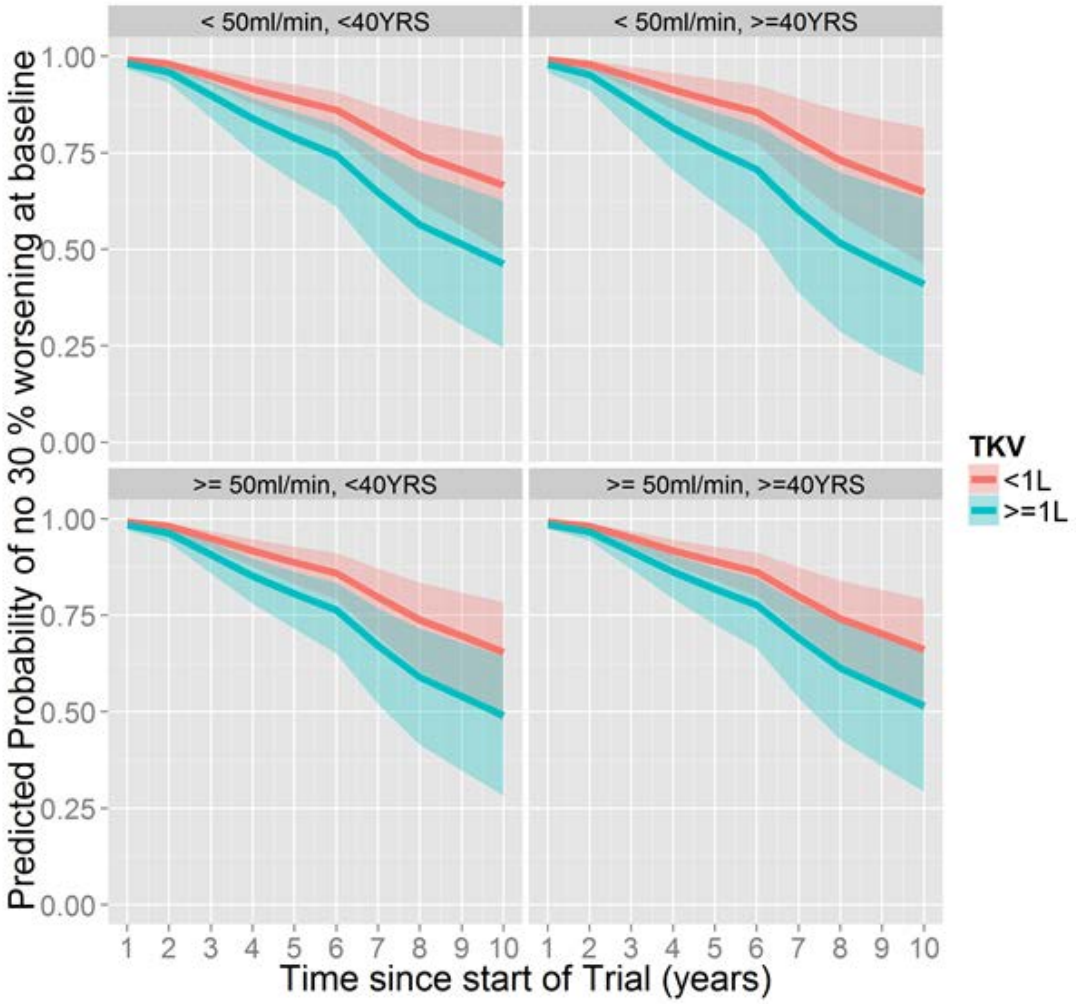
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
December 2012
Clinical Medical

Trial Enrichment

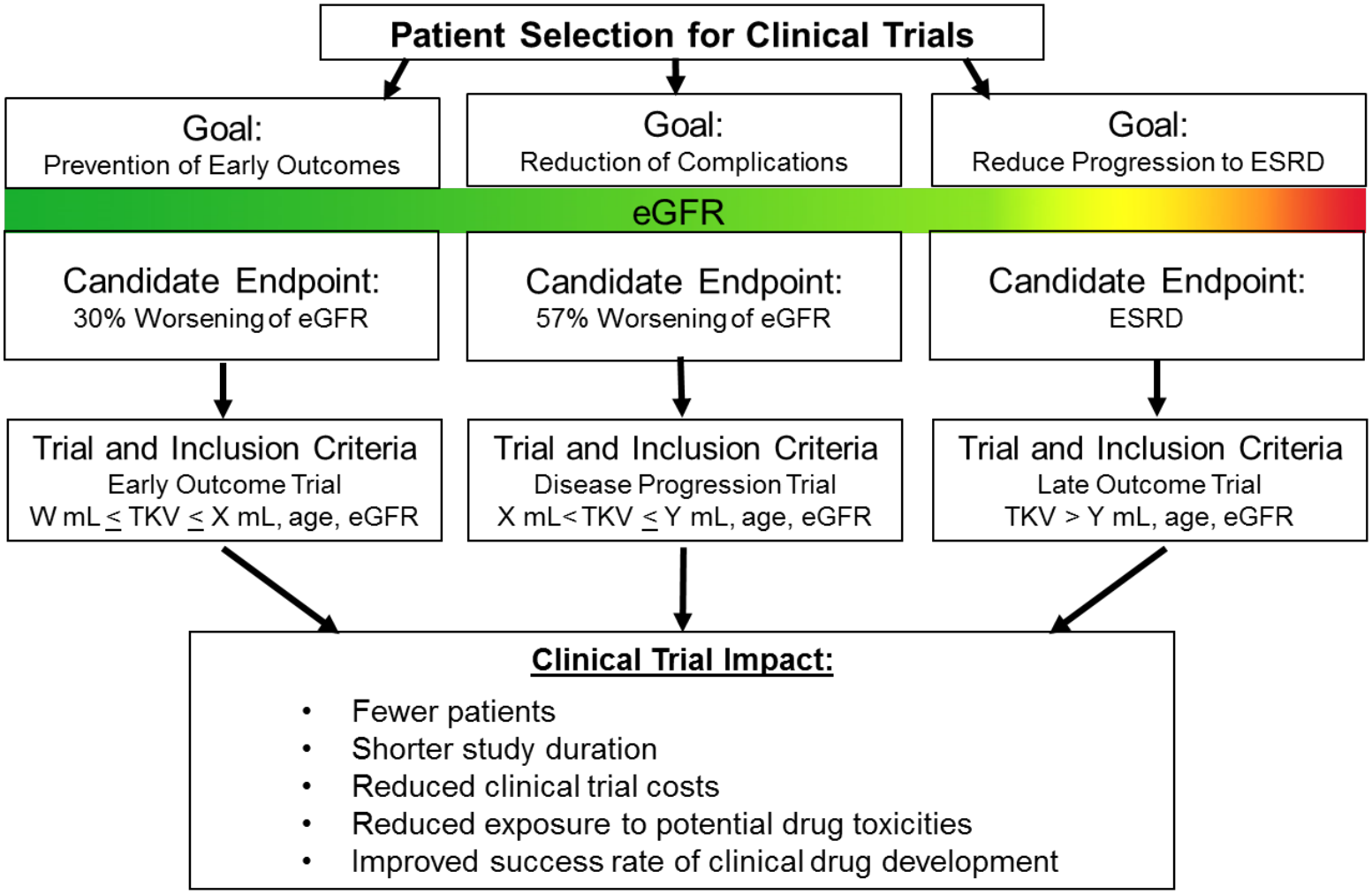
- Improve the likelihood of clinical trial success by identifying a patient population that can discriminate between active and inactive drug treatment.
- Calculations may be performed to determine the sample size for
  - specific clinical cut-offs
  - patient characteristics
  - study duration
- Provide sufficient power to detect statistically and clinically-relevant differences between a candidate drug vs. placebo

FDA and EMA Qualified Total Kidney Volume as a Prognostic Enrichment Biomarker for Use in PKD Trials

- **Baseline Total Kidney Volume (TKV)** is predictive of kidney function decline regardless of age or baseline kidney function

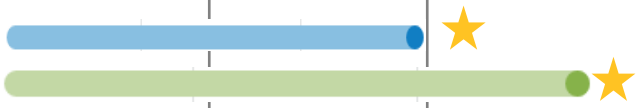
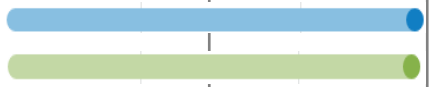


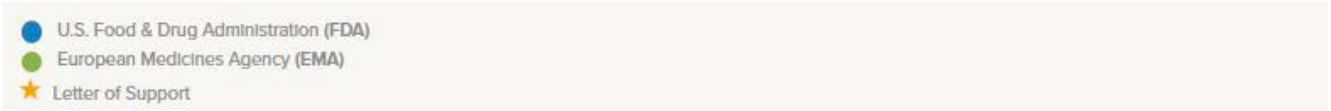
How TKV Can be Used for Patient Selection in Various Stages of Drug Development and the Anticipated Benefits



Critical Path for Parkinson's Consortium: Regulatory Sciences Pipeline

Parkinson's Disease (PD)

DRUG DEVELOPMENT TOOLS	FEASIBILITY	SCOPING	RESEARCH	SUBMITTED	QUALIFIED
PD Imaging Biomarker					
Disease Model of Early PD					



Prognostic enrichment biomarker

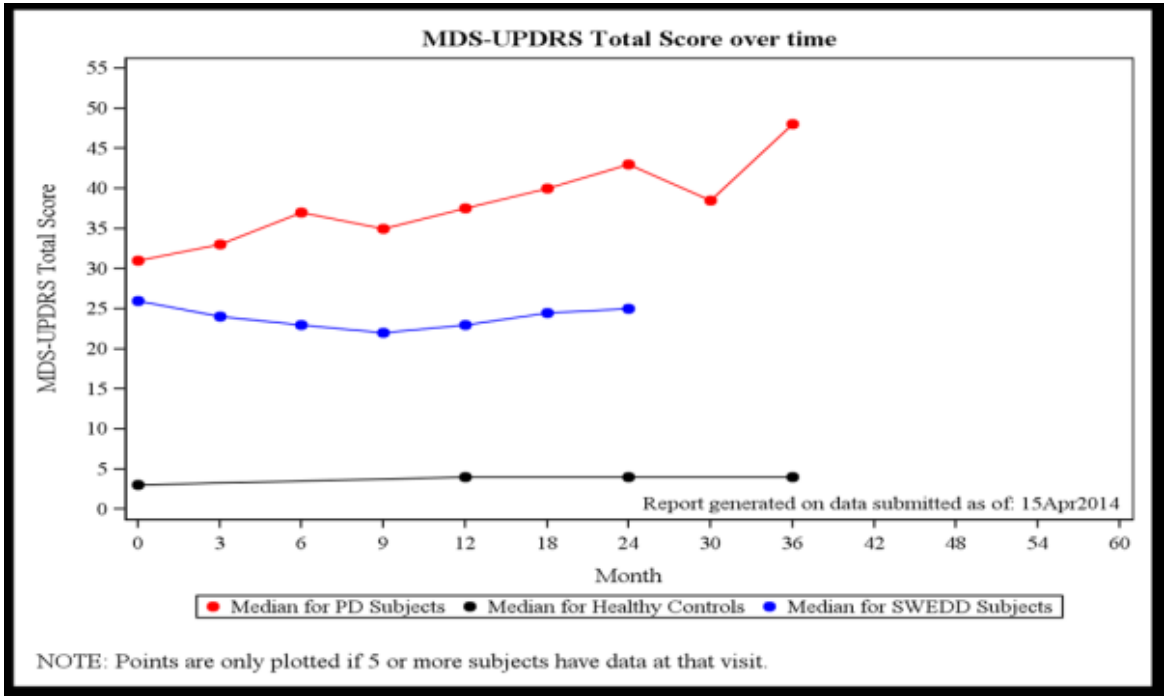
Disease progression model as fit for purpose

Molecular Neuroimaging of the Dopamine Transporter as a Prognostic Enrichment Biomarker in Early PD Trials

Stephenson D et al. https://c-path.org/wp-content/uploads/2016/05/ppmi_dat_poster_final_4-29-16_rev.pdf

DAT imaging illustrating reduced uptake in PD patients

PD patients (PPMI) with and without DAT deficit



FDA & EMA Issue Letter of Support for Use of DAT Imaging as Prognostic Enrichment Biomarker in Early PD Trials

DEPARTMENT OF HEALTH & HUMAN SERVICES — PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: March 16, 2015

ATTN: Diane Stephenson, Ph.D.
Executive Director, Coalition Against Major Diseases (CAMD)
Critical Path Institute
1730 E River Rd.
Tucson, Arizona 85718

Subject: Biomarker Letter of Support

Dear Dr. Stephenson:

We are issuing this Letter of Support to the Critical Path Institute's Coalition Against Major Diseases (CAMD) to encourage the further study and use of molecular neuroimaging of the dopamine transporter (DAT) as an exploratory prognostic biomarker for enrichment in trials for Parkinson's disease (PD).

"We encourage the use of this biomarker in clinical trials to evaluate it's utility for the identification of patients likely to show clinical progression of Parkinson's motor symptoms. We believe that sharing and Integrating data across trials can foster a more efficient path to biomarker qualification"

Sincerely,

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm434382.htm

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 September 2016
EMA/506726/2016
Executive Director

Letter of support for molecular imaging of the dopamine transporter biomarker as an enrichment biomarker for clinical trials for early Parkinson's disease

On 06 February 2016 the applicant Critical Path for Parkinson's (CPP) requested qualification of molecular neuroimaging of the dopamine transporter (DAT) as an enrichment biomarker for clinical trials for early Parkinson's disease pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

During its meeting held on 4 – 7 July 2016, the SAWP agreed on the advice to be given to the applicant. During its meeting held on 18 – 21 July 2016, the CHMP adopted the advice to be given to the applicant.

The biomarker letter of support is issued on the basis of the qualification advice.

"The EMA supports the primary objectives of the applicant and has decided to issue a letter of support to the Critical Path for Parkinson's (CPP) Consortium to encourage further development and validation of the proposed Biomarker."

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/10/WC500213914.pdf

Thank You

www.c-path.org

SCIENCE foundation ARIZONA
Innovation at Work

FLINN FOUNDATION

FDA

CRITICAL PATH INSTITUTE