FDA-C-Path-ISoP Workshop.

Session II

Industry Perspective on Applying Modeling & Simulation in Regulatory Decision-Making and in Translational Pharmacology: Successes and Lessons Learned.

Quantitative Tools to Support Biomarker Qualification

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Overview

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1. Qualification Process for Drug Development Tools (DDT)
   - Regulatory Components (e.g., nature of biomarker, context of use…)

2. Quantitative Tools to Support Biomarker Qualification
   - Linkage between Biomarker and Disease Progression => DDT
   - How do we construct these models/tools?
   - How do we implement these models/tools?

3. Case Study: Qualification of an Imaging Biomarker (DDT)
   - Total Kidney Volume as a Prognostic Biomarker in Patients with ADPKD
   - Implementation of the DDT (Trial Enrichment)
   - Other Applications

Regulatory Qualification of Biomarker
FDA Guidance

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Guidance for Industry

Qualification Process for Drug Development Tools

Additional copies are available from:
Office of Communication
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/cder/guidance/index.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2010
Clinical/Medical

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

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Regulatory Process for Qualification of Biomarkers

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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...)
  - Prognostic biomarker
  - Predictive biomarker
  - Pharmacodynamic (or activity) biomarker
  - Surrogate biomarker
- **Disease** (e.g., worsening, LFT, adverse events, transplant, mortality…)

3. Methodology: Quantitative Tools

- Exploratory Analyses (Univariate Cox, Multivariate Cox & Kaplan Meier)
- Joint Modeling: Linkage between a longitudinal measurement (biomarker) and an event (disease outcome)
- Model Validation (Cross-validation & Predictive Performance of the model)

Development of Quantitative Tools to Support Biomarker Qualification

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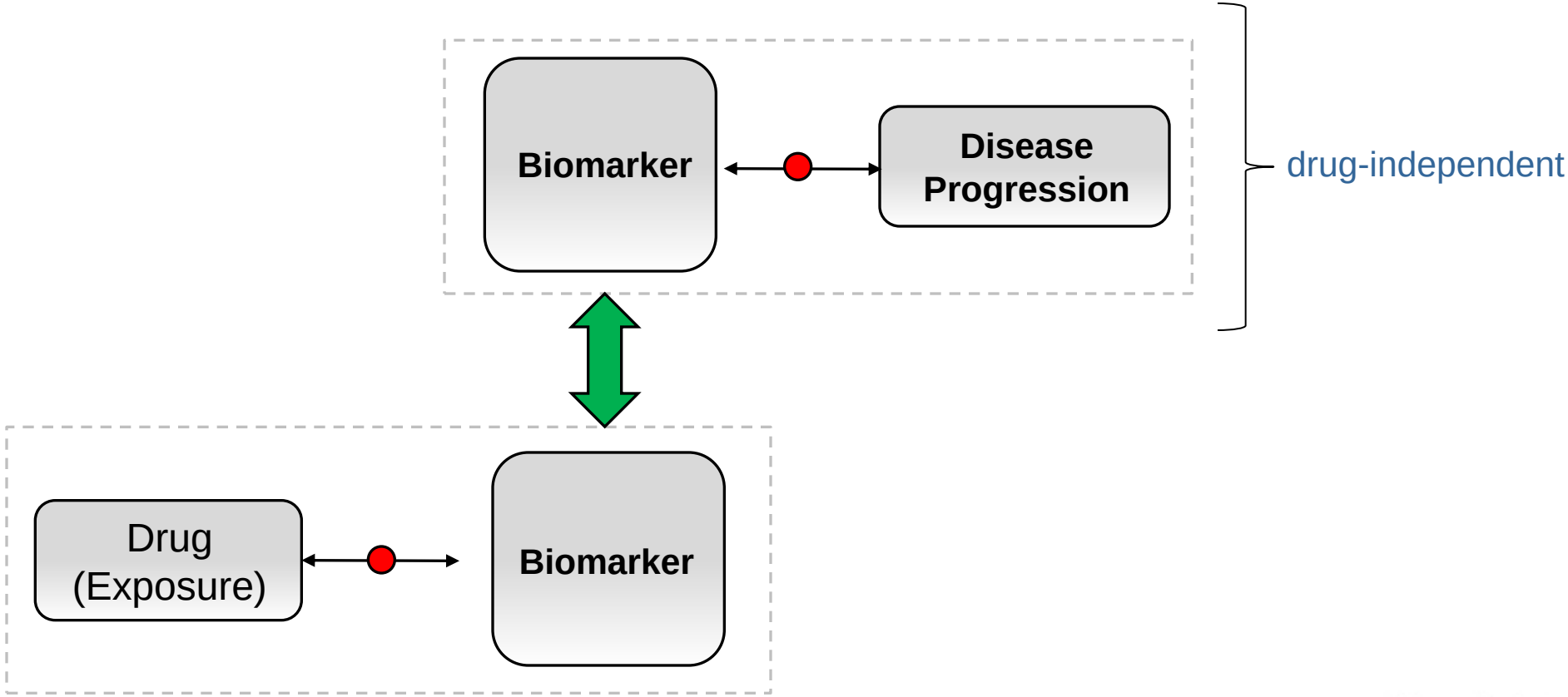
1. Fundamental component of biomarker-disease models
   - Biomarker-disease models are drug-independent
   - Can be customized by introducing a drug-biomarker



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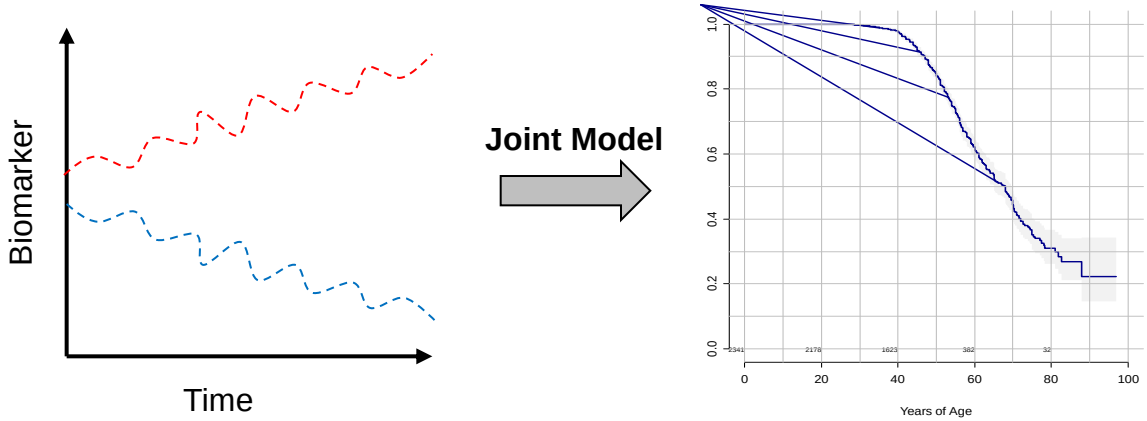
Challenges
Biomarker-Disease Models

- Need to simultaneously model
  - Biomarker trajectory (longitudinal time-varying covariates)
  - Disease Endpoint, hazard function (time-to-event)



- Not widespread in the field of Pharmacometrics (mainly used in biostatistics).
- 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).

Tool: Joint Modeling

Joint Modeling approach using the R package JM (http://jmr.r-forge.r-project.org/index.html).

Briefly, joint modeling is performed using a 3-step approach.

1- A linear mixed-effects model for the longitudinal variable is constructed

```
fitLME <- lme(I(log(MPVOL)) ~ MPYRS, random= ~ MPYRS | UDERID, data = alltkvdataj,
control = list(msVerbose = 1, maxIter=100, msMaxIter=1000, niterEM=1000))
```

2- A time-to-event model using important covariates is constructed (Cox, Weibull…). The JM package will allow specifying various parametric survival functions

```
fitSURV <- coxph(Surv(MPYRS, EVFL) ~ 1+I(AGERFST-40) ,data=e57endpointj, x = TRUE)
```

3- The final step is to "join" model #1 and #2. Various hazard functions and ways to link the longitudinal outcome to the hazard can be developed

```
fit.tkv_e57_all<- jointModel(fitLME, fitSURV,timeVar="MPYRS",verbose=T,method="piecewise-
PH-aGH")
```

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CASE STUDY

Qualification of Total Kidney Volume as a Prognostic Biomarker for use in Clinical Trials Evaluating Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Critical Path Institute's Polycystic Kidney Disease (PKD) Consortium

1. ADPKD is a debilitating genetic disease affecting more than 12 million people worldwide for which there is currently no known cure or effective treatment.

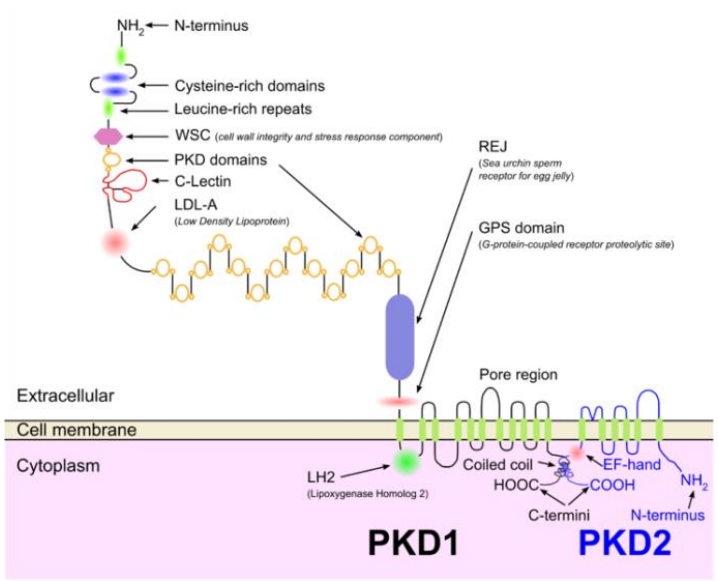
2. Goals of Collaboration
   - Qualify Total Kidney Volume (TKV) as a biomarker that can be used as a measure of the progression of ADPKD
   - Develop a tool that can improve the efficiency and predictive accuracy of clinical trials that investigate ADPKD.

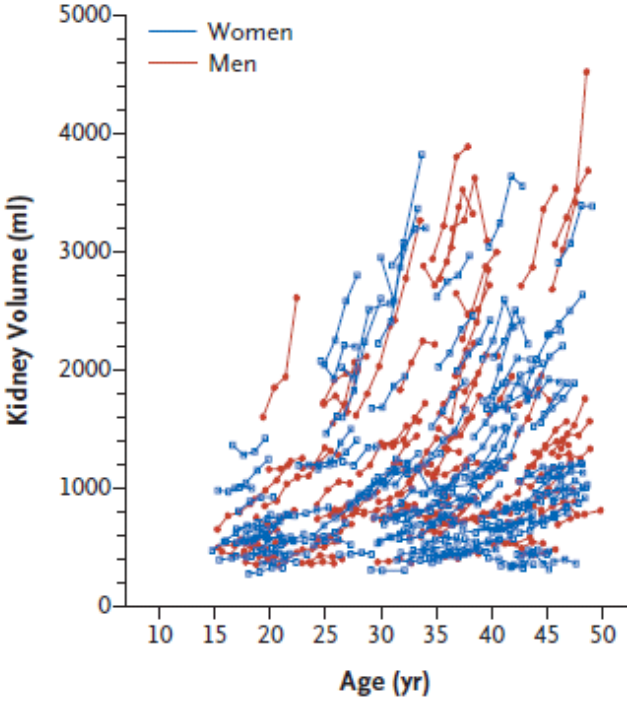
3. The PKD Consortium is a successful collaboration of the following:
   - Critical Path Institute
   - The PKD Foundation
   - Clinical Data Interchange Standards Consortium (CDISC)
   - Various Academic Centers
     - Tufts University
     - University of Colorado
     - Emory University
     - Mayo Clinic
   - Pharmacometrics Consulting Organization (Pharsight, A Certara Company)

Introducing ADPKD

Autosomal dominant polycystic kidney disease (ADPKD)

- Caused by mutations in the gene PKD1 or PKD2



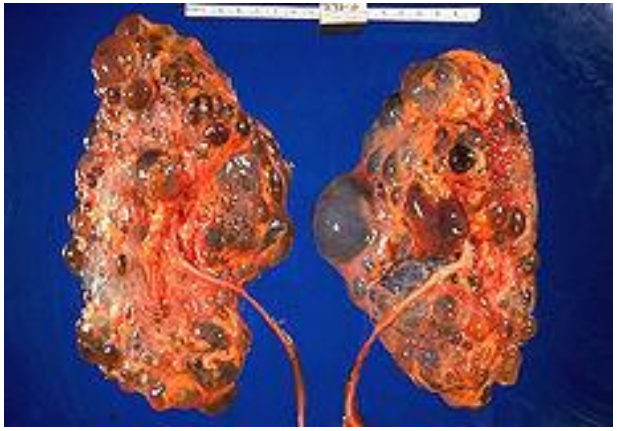


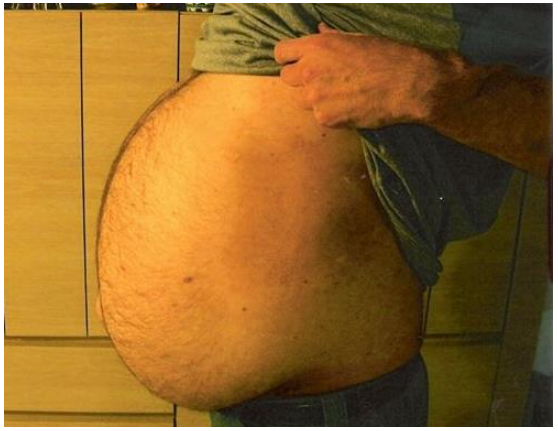
- Hundreds to thousands of renal cysts develop and grow over time, some as large as 10-20 cm in diameter.
- Cysts grow exponentially.

Introducing ADPKD

Autosomal dominant polycystic kidney disease (ADPKD)

- Nephrons get crushed



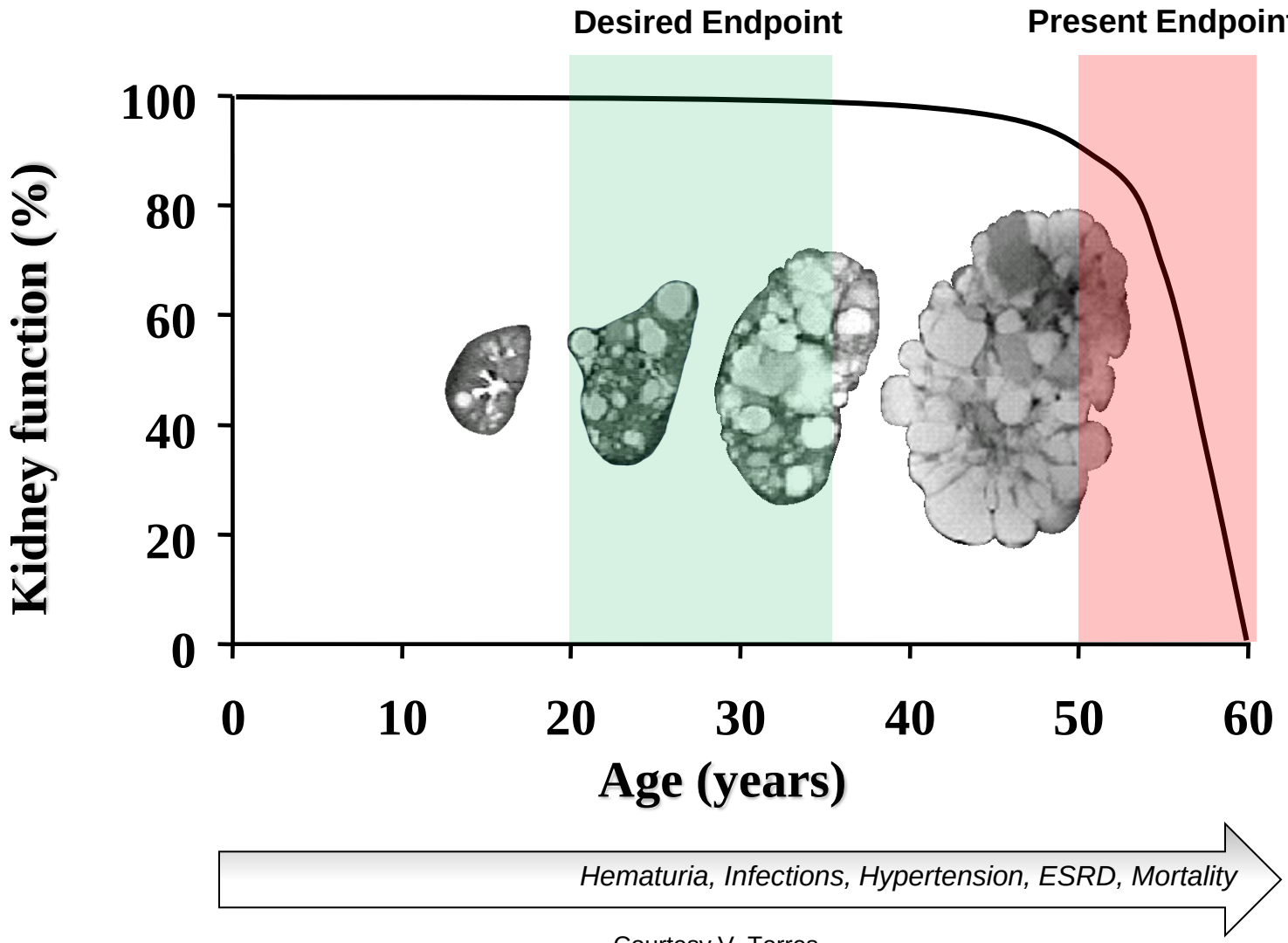


- ~50% will develop ESRD, require dialysis or kidney transplantation.
- Progression to ESRD happens in the 4th to 6th decades of life.
- Other: infections, hypertension, pain
- Current treatment for ADPKD

  Symptomatic drug (pain killers antibiotics, antihypertensive)

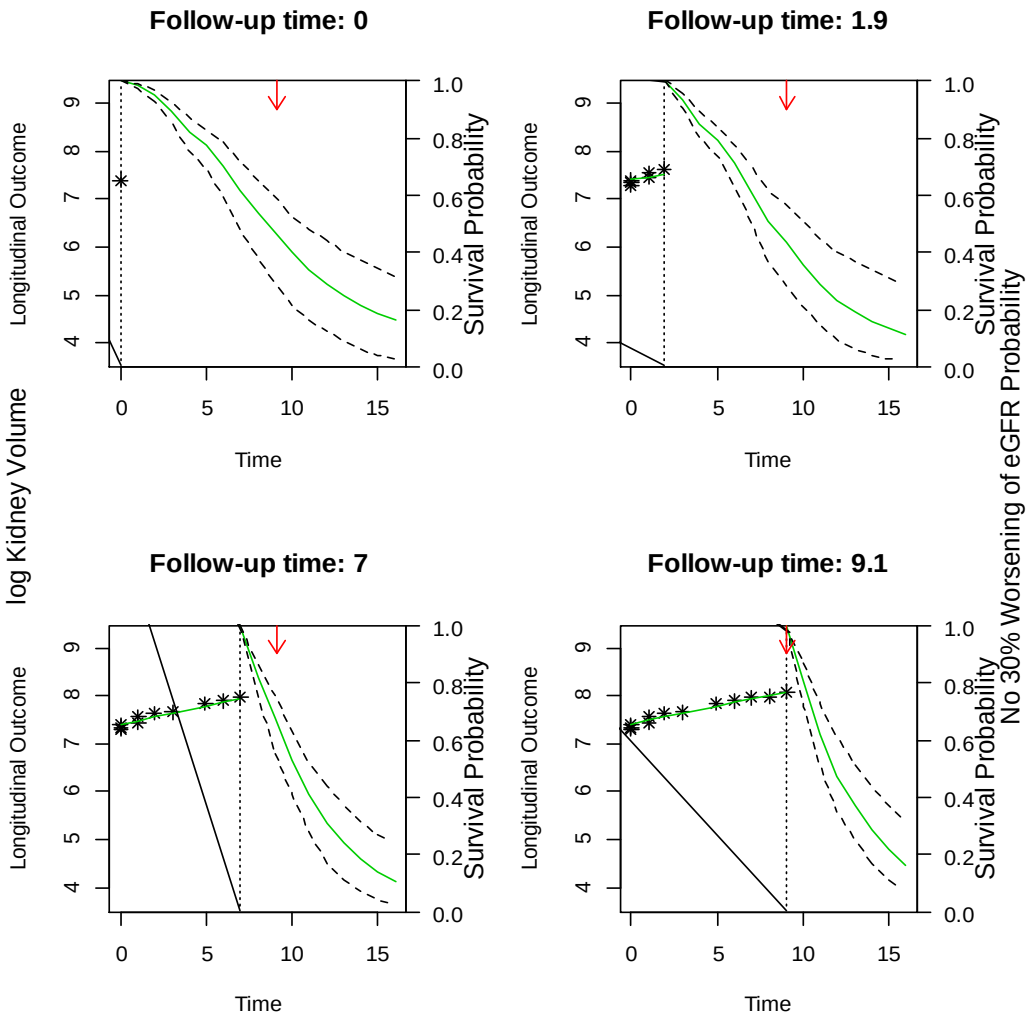
  No disease-modifying drugs…

Changing The Paradigm for Measuring Disease Progression of PKD



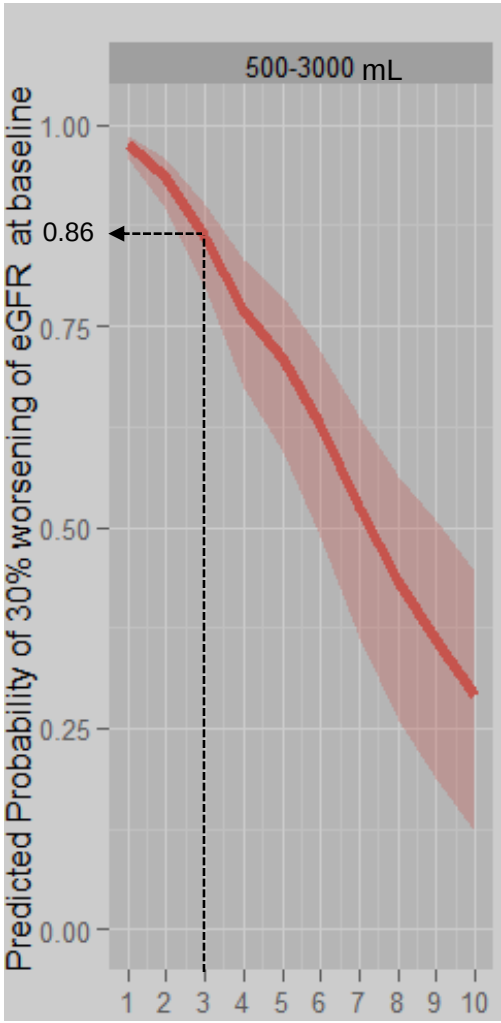
Courtesy V. Torres

Joint Model: Longitudinal TKV and Probability of Disease Outcome



Clinical Trial Planning Example
30% Worsening of eGFR

Age	TKV	Follow-Up Period	Probability of No 30% Worsening of eGFR		
			Median	Lower	Upper
Random uniform distribution between 18 and 40 years	Random uniform distribution between 500 and 3000 mL	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



Application: Trial Enrichment

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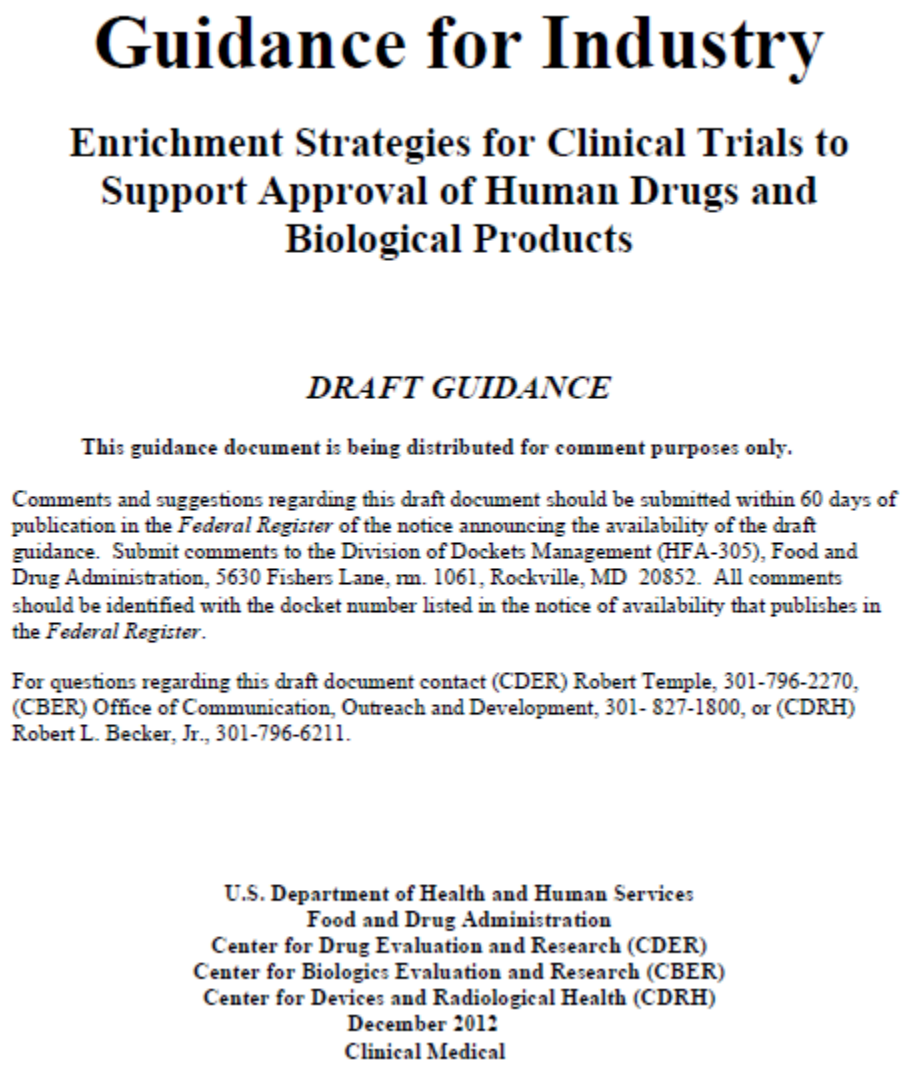

Guidance for Industry

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)
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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

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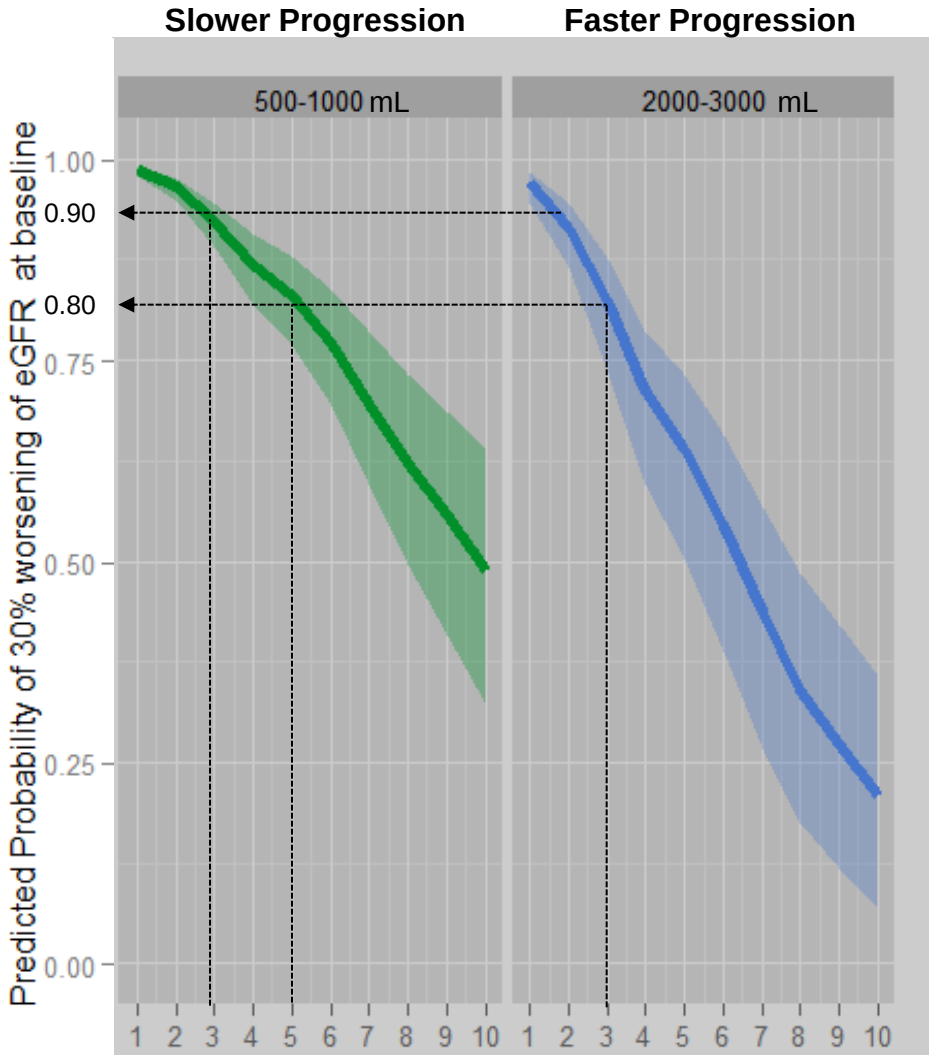
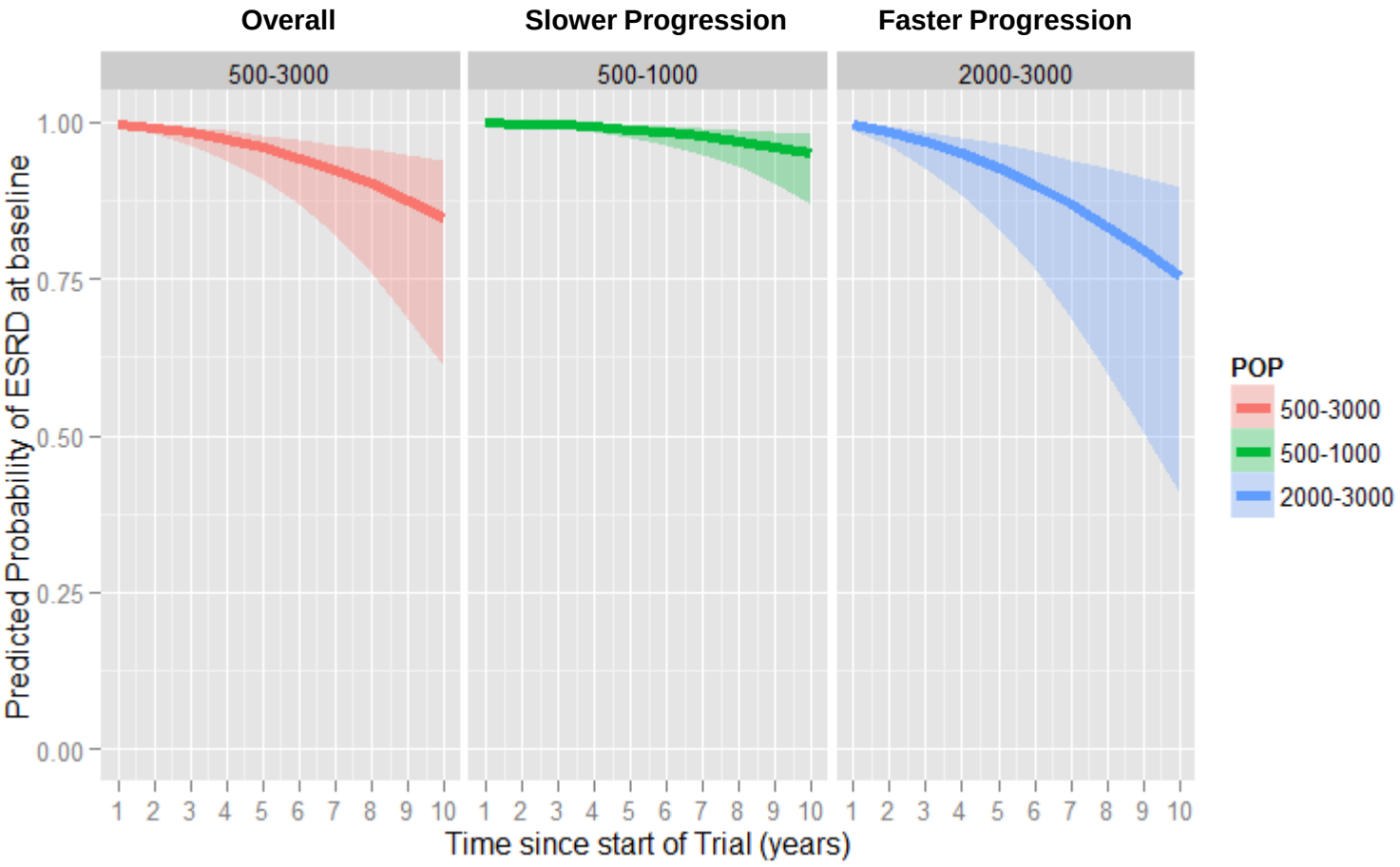
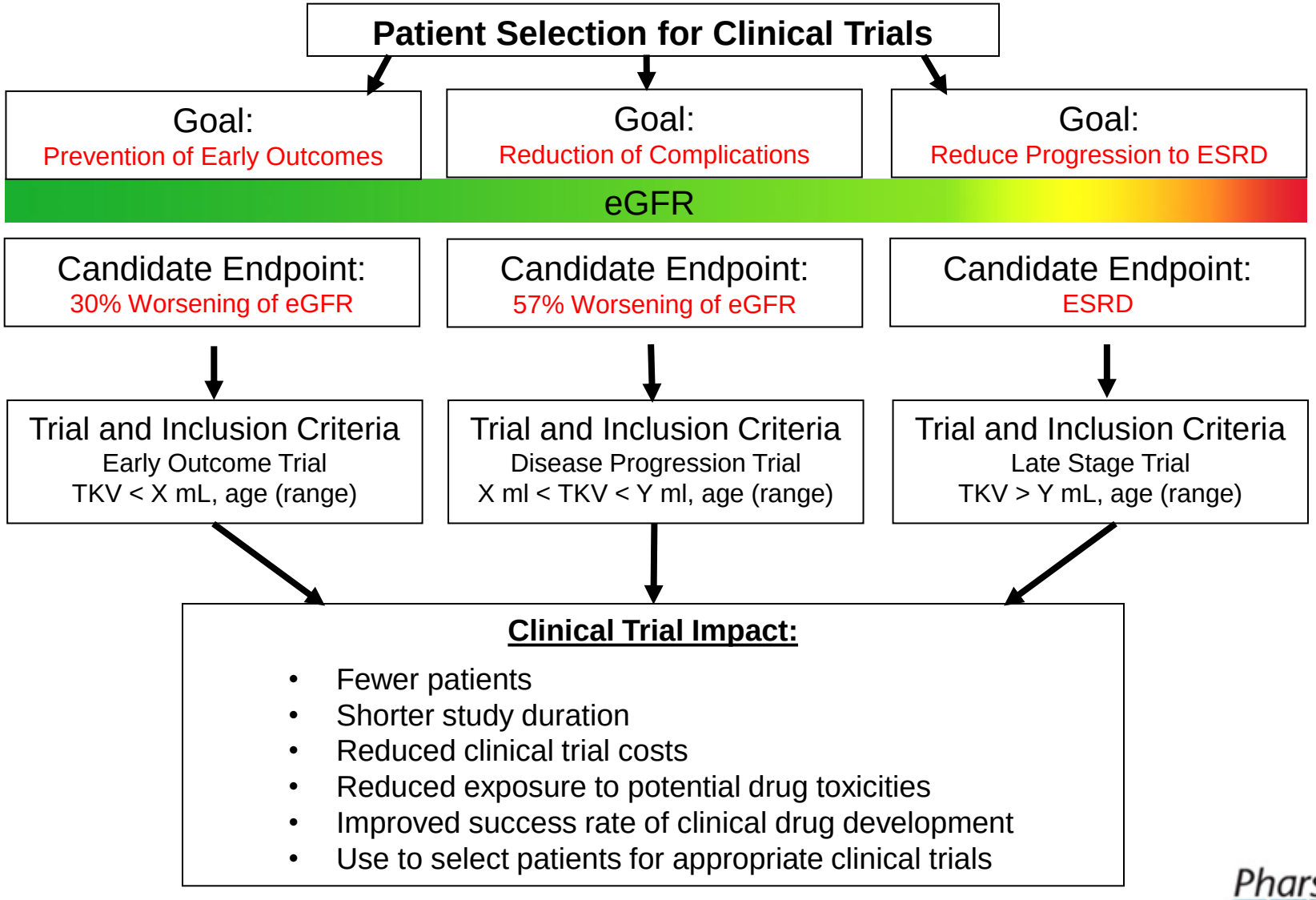
Trial Enrichment
30% Worsening of eGFR



End-Stage-Renal-Disease



Example of a Decision Tree for Clinical Trial Enrichment



Other Applications
Imaging Biomarkers

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1. Alzheimer's Disease
   - Linkage between Biomarker and Disease Progression
   - **Biomarker:** Hippocampal volume (HV), as measured by imaging
   - **Endpoint:** Conversion from mild cognitive impairment (MCI) to dementia (using clinical dementia rating sum of boxes scores)
   - **Application:** Trial Enrichment (patient characteristics)

2. Oncology
   - **Biomarker:** Quantitative measurement of lesion such as volume and density, or tumor vascularization
   - **Endpoint:** OS, PFS…
   - **Application:** Pick the right drug (e.g., anti-angiogenic vs. cytotoxic drugs)


THANK
YOU