Role of Biomarker-Clinical Outcome Relationships in Clinical Drug Development: FDA Experience

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Indiana CTSI Symposium on Disease and Therapeutic Response Modeling

November 2-3, 2011

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No real or apparent conflicts of interest to disclose

ACKNOWLEDGEMENTS

Yaning Wang
Kevin Krudys
Pravin Jadhav
Raj Madabushi
Ying Chen
Joga Gobburu
PM Group members
Norman Stockbridge
Robert Temple
Abraham Karkowsky
Aliza Thompson
Jialu Zhang
John Lawrence

Overview

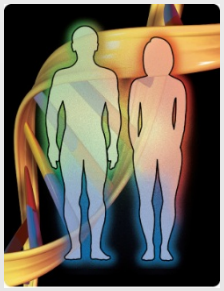
- Regulatory Uses of Biomarkers
- Quantitative Disease, Drug and Trial Models to Explore Biomarker-Clinical Outcome Relationships
- Current Efforts
- Case Studies

Regulatory Uses for Biomarkers

It's more than just surrogate endpoints

Surrogate Endpoints

Individualized Treatment



Pediatric Approval & Dosing

Predicting Safety

New Formulations, Indications, Populations

SURROGATE ENDPOINTS

Change in biomarker that can substitute for an observed clinically meaningful end point in evaluation of effectiveness

Examples

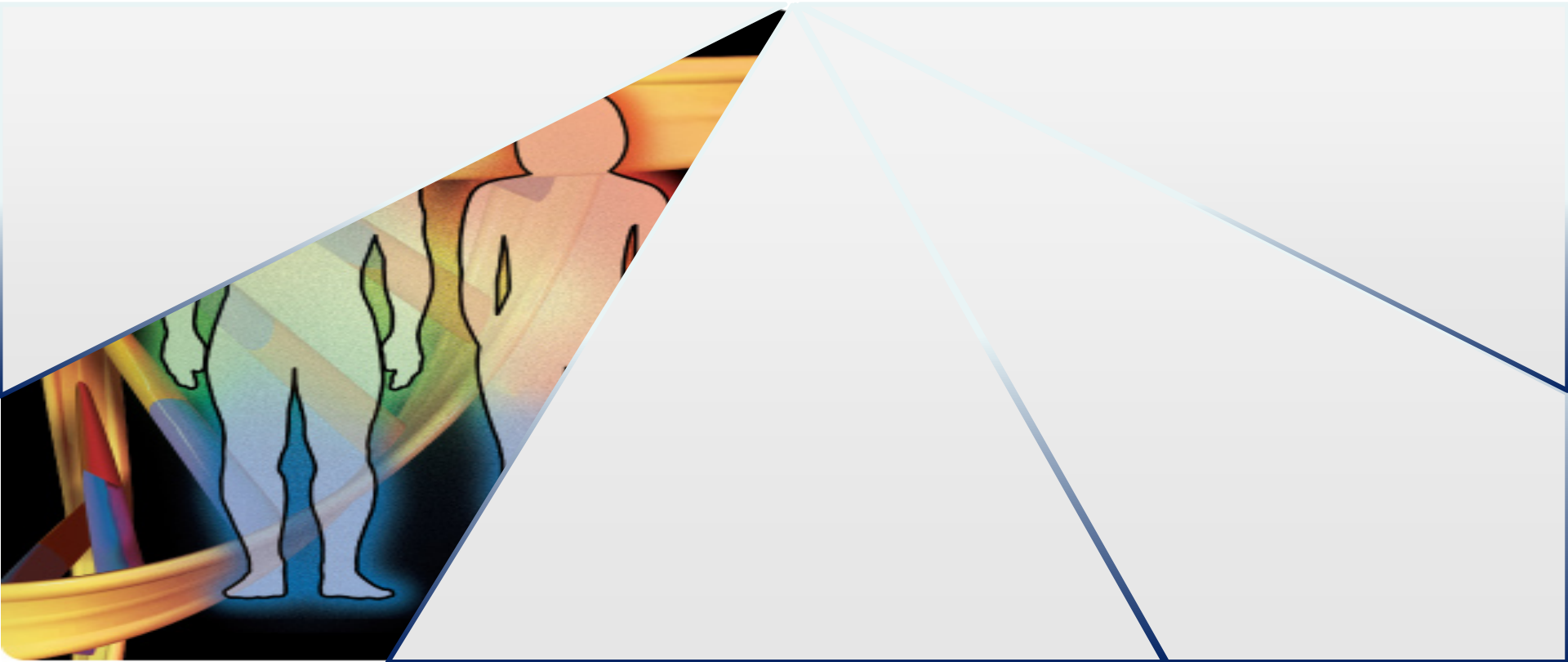
Blood pressure, serum creatinine, serum lipids, HIV-1 RNA, intraocular pressure, glycosylated hemoglobin

INDIVIDUALIZED TREATMENT

Biomarkers to help select responders or identify patients at increased risk of adverse event and aid in dose selection

Examples

- CCR5-tropic HIV (Maraviroc®)
- Her2 Overexpression (Herceptin®)
- CYP2C19 Variants (Plavix®)



PEDIATRIC APPROVAL & DOSING

If disease progress and treatment intervention is similar between adults and pediatrics, approvals may be based on biomarker data

Examples

- PK/PD relationship for QTc and heart rate (Sotalol)
- PK matching (piperacillin/ tazobactam injection)

PREDICTING SAFETY

Safety biomarkers can be used to predict clinical toxicity.

Examples

- Concentration-QTc Relationship
- HLA-B*5701 allele and hypersensitivity reaction to abacavir

NEW FORMULATIONS, INDICATIONS & POPULATIONS

Extensions to original approval may be based on biomarkers

Examples

- Approval of dosing regimen based on changes in bone mineral density (Risendronate)
- Approval of immediate release formulation based on β_1-blockade (Carvedilol)

Building Bridges between Biomarkers and Clinical Outcomes

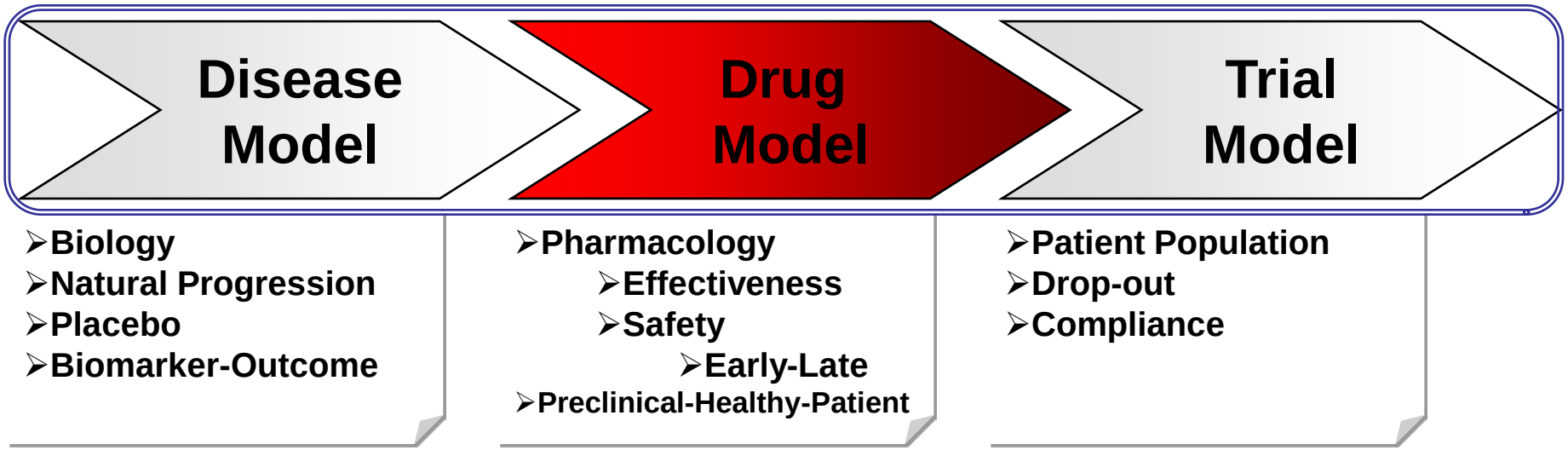
- Natural history/epidemiological data and numerous outcome trials of a variety of agents (surrogate endpoints, safety biomarkers)

- Leveraging information from original approvals (pediatrics, new formulations, new indications)

- Quantitative Disease Drug and Trial Models
  - Allows integration of knowledge across trials/drugs

Disease-Drug-Trial Models

learn from prior experience, summarize knowledge and apply



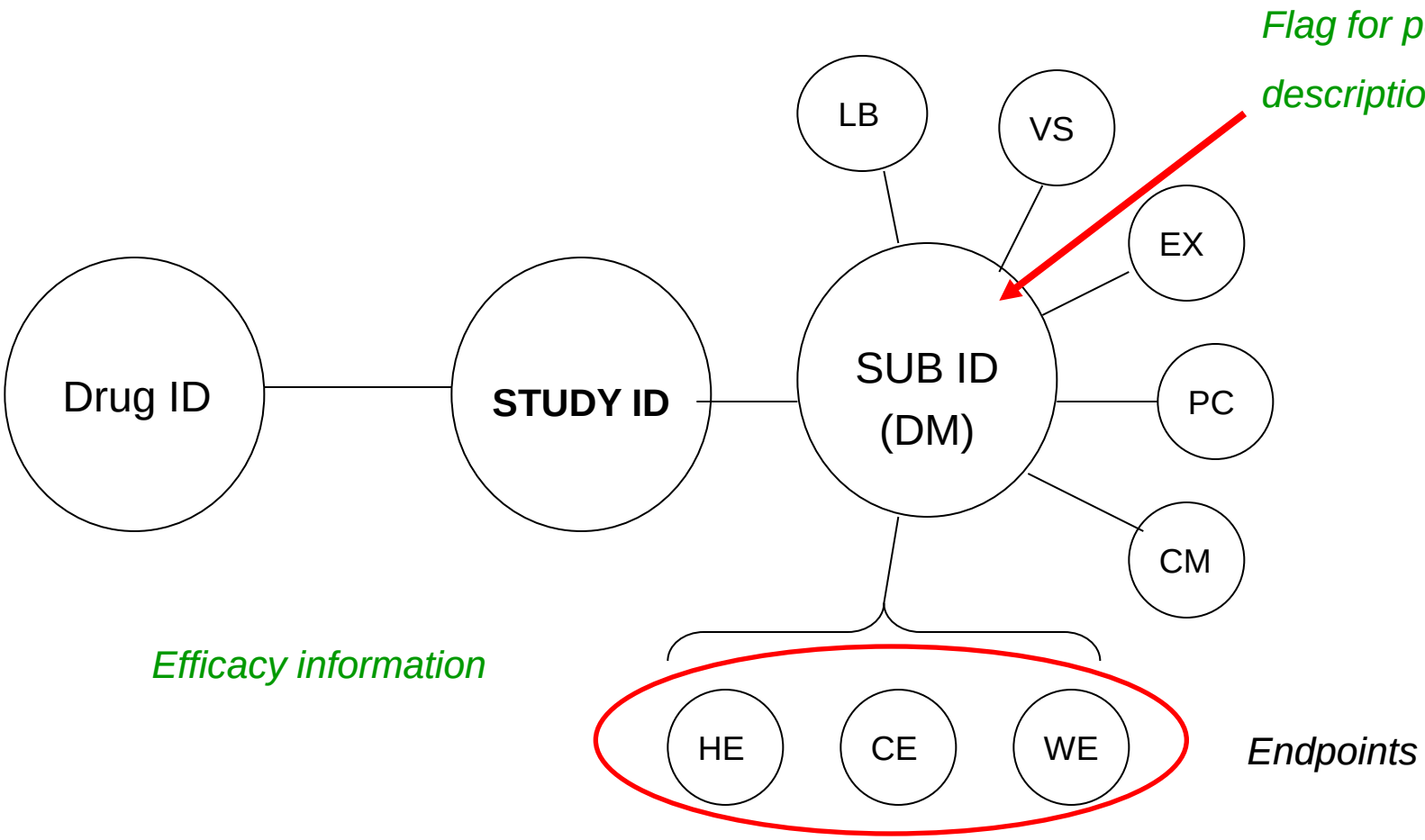
Gobburu JVS, Lesko LJ., Ann Rev Pharm Tox. 2009 Feb;49. 291-301. Epub 2008 Oct 13.

FDA – Pharmacometrics Efforts

- Disease databases
  - Pulmonary Hypertension
  - Multiple sclerosis
  - NSCLC
  - Alzheimer's disease
  - Hepatitis C
  - Huntington's disease

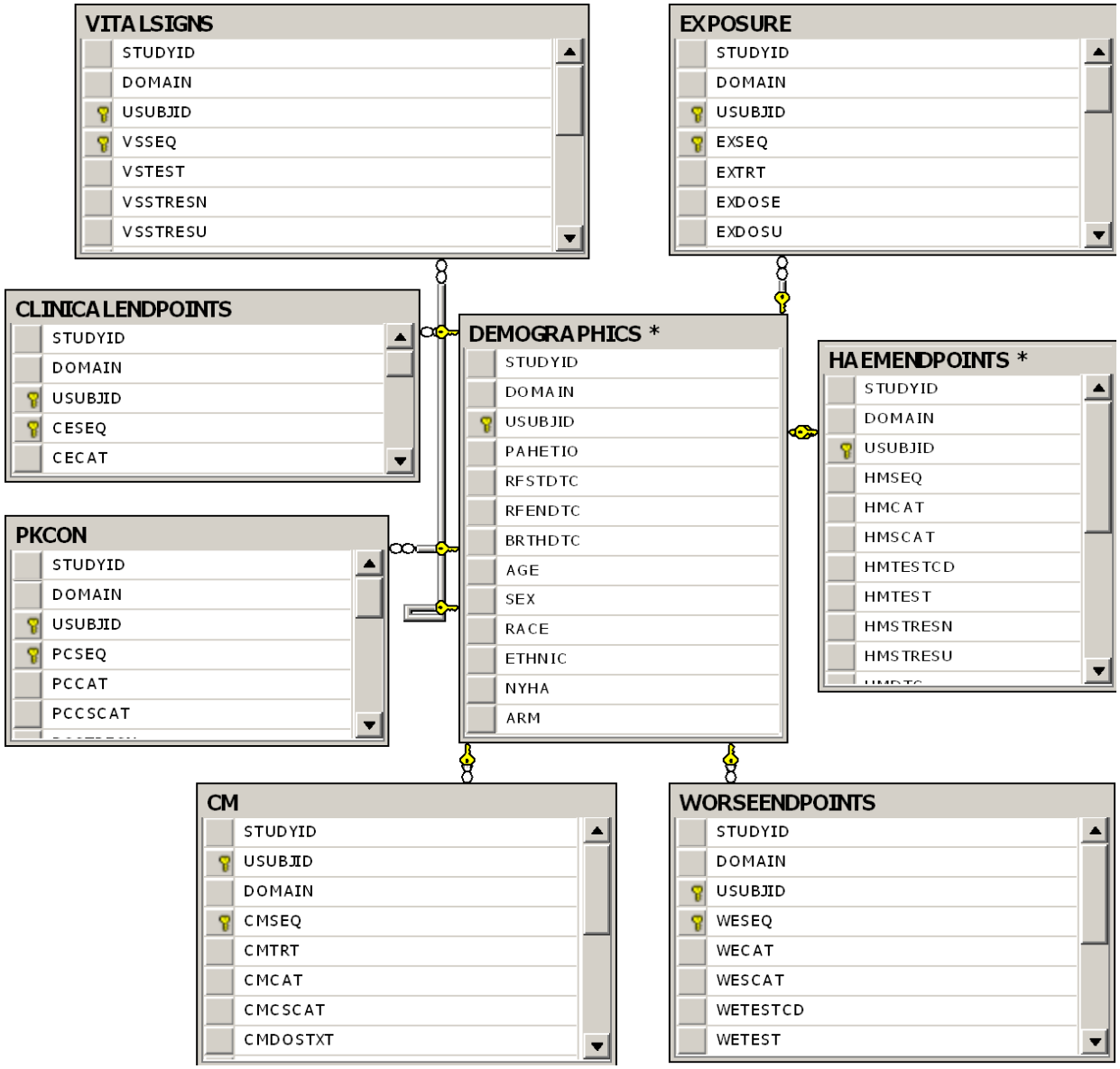
- Safety databases
  - QTc
  - Hepatotoxicity

Trial Database – General Structure



DM = demography, VS = Vital Signs, EX = Exposure, PC = PK Conc, CM = Co-meds

CE = Clinical Endpoint, WE= Worsening Endpoint, HE = Hemodynamic Endpoint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Case Study #1

What is the relationship between early tumor size reduction and patient survival in non-small-cell lung cancer (NSCLC)?

NSCLC Model: Objective

- Challenge
  - Oncology drugs have one of the lowest rates of successful drug development
- Objectives:
  - Integrate data from many clinical trials to describe quantitative relationship between tumor size related metrics and overall survival
  - Improve drug development process

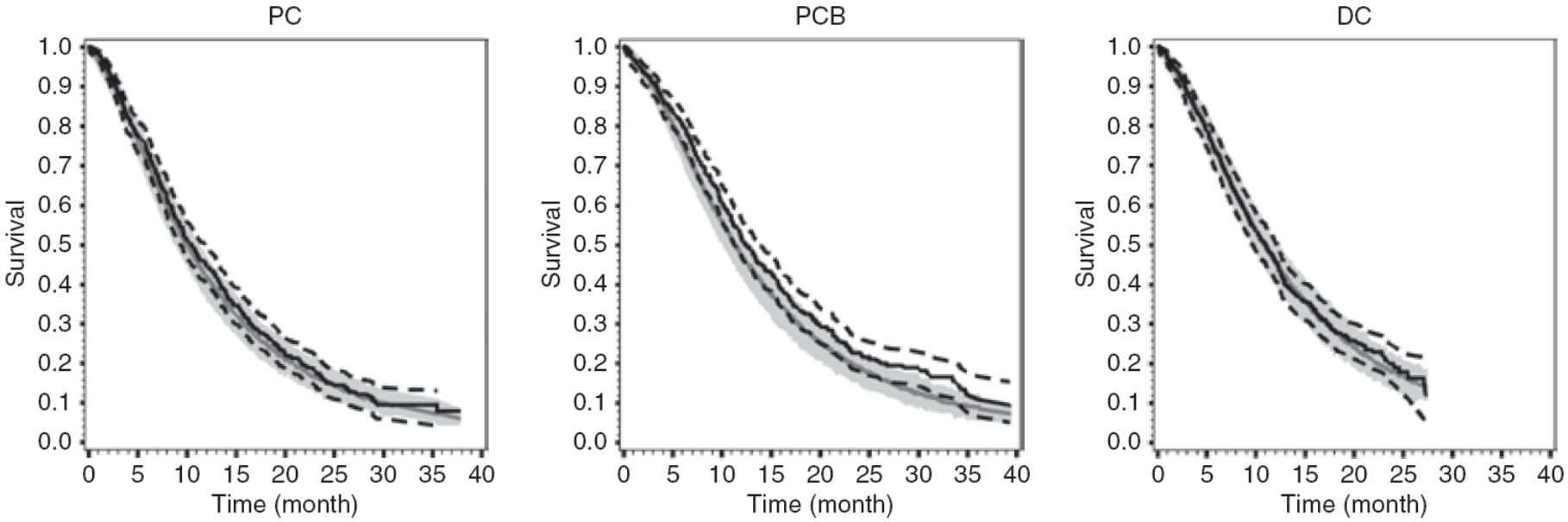
Tumor size (Biomarker) – Survival (Outcome) Model

- Data:
  - 4 Trials, 8 active treatments, 1 placebo ~3500 patients, first-line and second line treatment.

- Model:
  - ECOG status (0/1/2/3),
  - Baseline tumor size (centered at 8.5 cm) as covariates
  - Percentage tumor reduction from baseline at week 8 (PTR_{wk8})

$$\log(T) = \alpha_0 + \alpha_1 \cdot ECOG + \alpha_2 \cdot (Base - 8.5) + \alpha_3 \cdot PTR_{wk8} + \varepsilon$$

Model Provides Reasonable Prediction of Survival



Wang et al., Clin Pharmacol Ther. 2009 Aug;86(2):167-74. Epub 2009 May 13.

NSCLC Model: Value to Drug Development

- Allows early assessment of the activity of an experimental regimen
- Facilitates early screening of candidate drugs for NSCLC
- Optimize trial design through modeling & simulation

Case Study #2

Use of pulmonary vascular resistance index (PVRI) as the basis of approval for a Pulmonary Arterial Hypertension therapy in pediatrics.

Pediatric pulmonary arterial hypertension

- **<u>6-minute walk distance (6MWD)</u>**

- Primary endpoint for regulatory approval in adults.

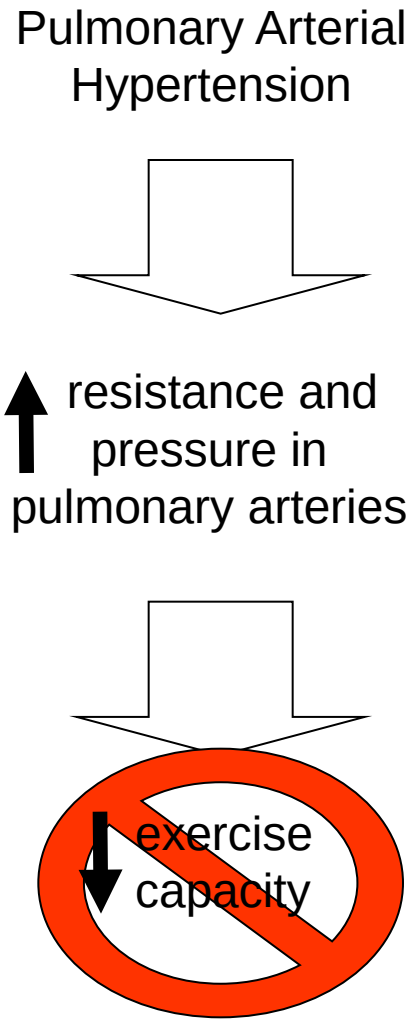
- Poor feasibility and interpretability in pediatrics.[1]

- **<u>Cardio-pulmonary hemodynamics</u>**

- Used for diagnosis and characterizes disease progression.

- Represents severity and predicts survival.[2]

- Closest measure to physiological target of PAH therapies.



[1]Garofano et al , Ped Card 1999, [2]Benza et al , PHA 2010

ΔPVRI (Biomarker) is a significant predictor of Δ6MWD (Outcome)

- *Database*

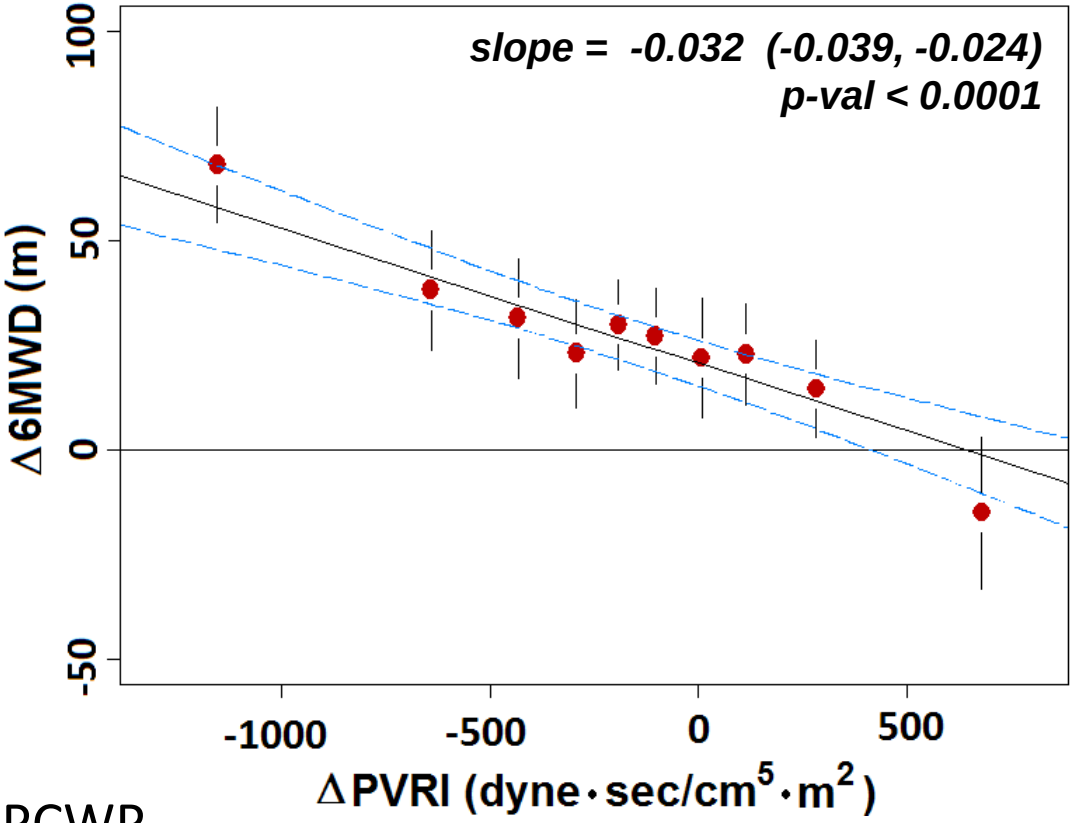
Data from **13** RCTs, **7** therapies

– PDE5 inhibitors, Prostacyclins, ERAs

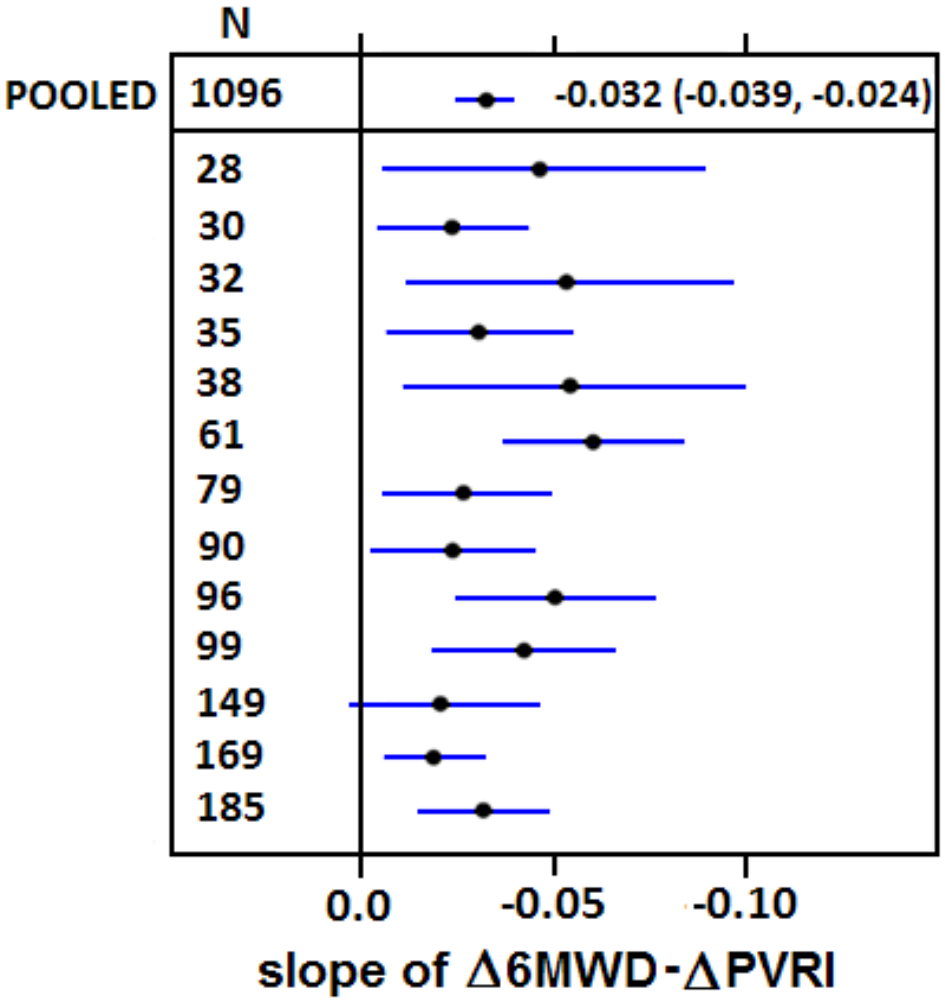
- Adult patients: only **WHO Group I, idiopathic/familial PAH** with complete efficacy data analyzed.

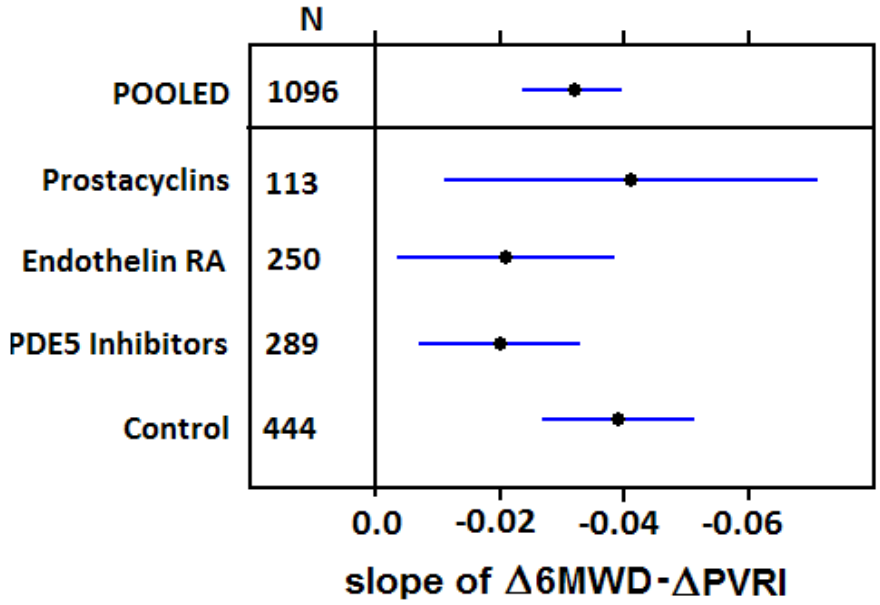
– n = **1096**

– hemodynamics (MAP, mPAP, PCWP, CI, RAP, and PVRI, SVRI) and 6MWD



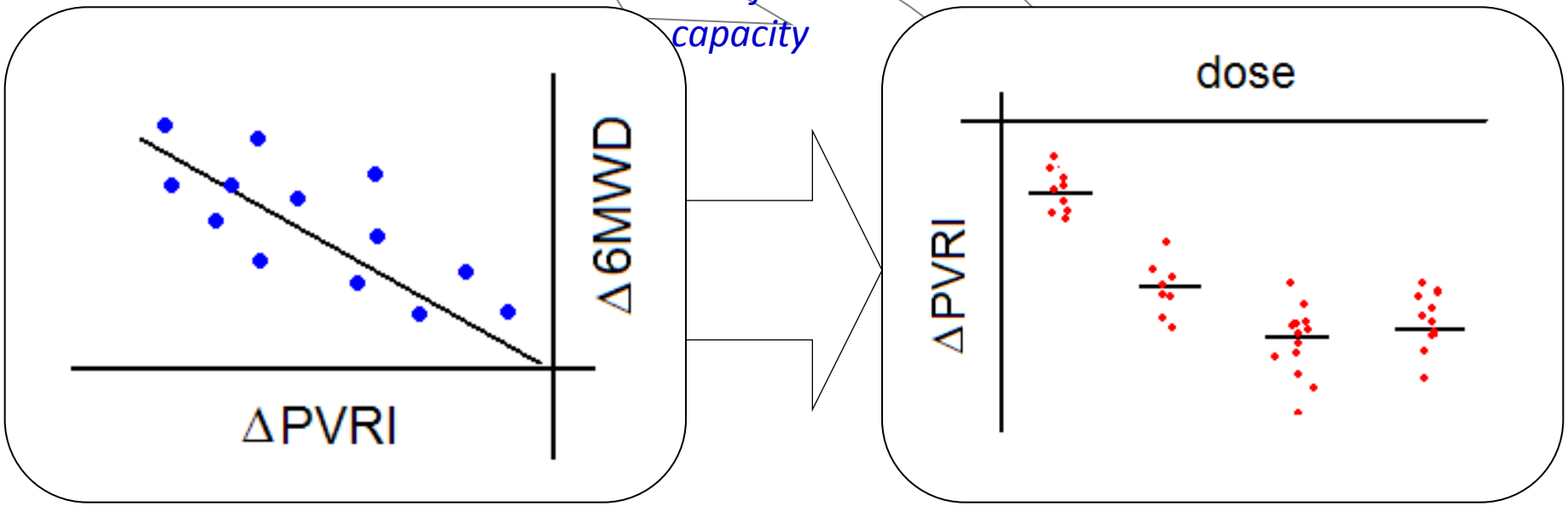
ΔPVRI is a significant and consistent predictor of Δ6MWD across trials and mechanism





ΔPVRI-Δ6MWD relationship can guide pediatric drug development

Derive dosing based on the desired benefit in exercise capacity



Adults: Establish a relationship between ΔPVRI and Δ6MWD to specify target for pediatrics.

Pediatrics: P*lacebo controlled,* dose ranging studies to be performed to achieve different degrees of hemodynamic benefit.

Status of PVRI for Pediatric PAH

- Now a “limited surrogate” in pediatric PAH therapy development – for therapies already approved in adults.

- PHIMS – Pulmonary Hypertension Information Management System

- Sponsors required to use modeling and simulation to support pediatric PAH trial design.

Biomarker-Outcome Relationships
Next Steps

- Tools need to be developed – Disease Database
  - Data Standards
  - Analysis
- Quantitative analysis should be routinely conducted
  - Plan collection of relevant biomarkers.
  - Specify as secondary analysis in all NDAs

- Inter-disciplinary and FDA-Academia-Industry scientists need to collaborate

QUESTIONS??