



# Using Clinical Pharmacology and Biology to Anticipate and Account for Differences in Safety and Efficacy Across a Population

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Office of Translational Sciences | CDER | US FDA

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Clinical Trials: Assessing Safety and Efficacy for a Diverse Population

# In Memoriam



## Dr. David Flockhart, Scientist, Teacher, Friend

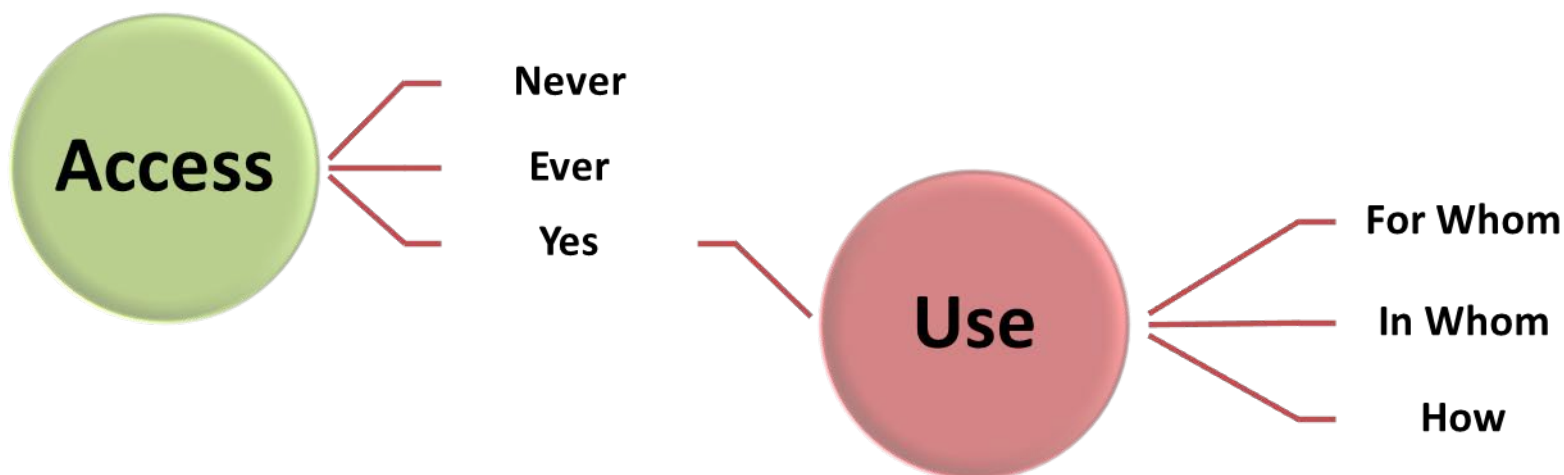
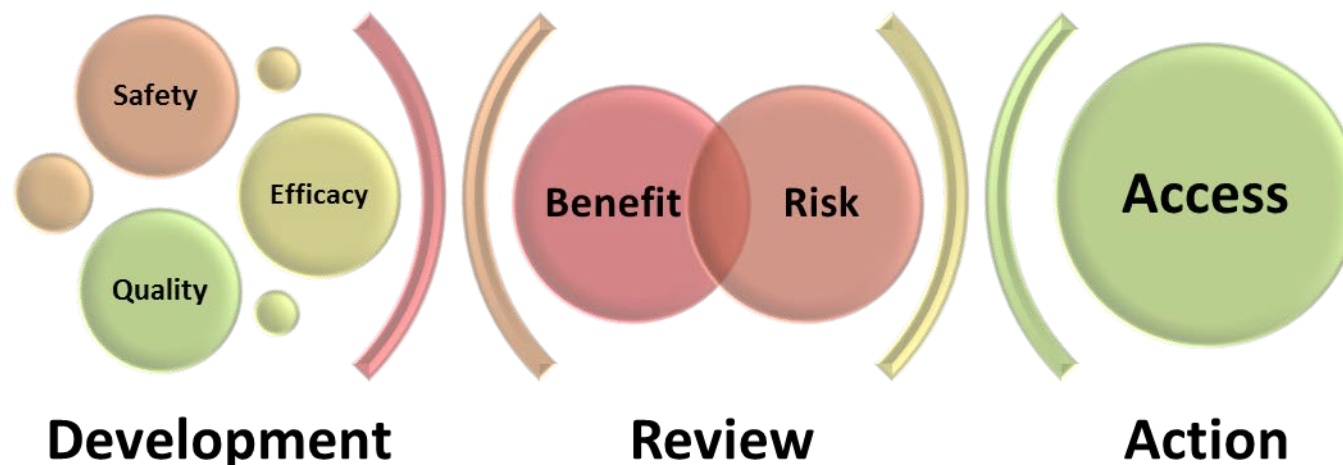
# Acknowledgments

- **Dr. Anuradha Ramamoorthy**
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- **Dr. Ping Zhao**
- **Dr. Robert Schuck**
- **Dr. Shiew Mei Huang**
- **Dr. Tom Colatsky**
- **Dr. Vikram Sinha**
- **FDA Office of Clinical Pharmacology and Partners**

# Themes

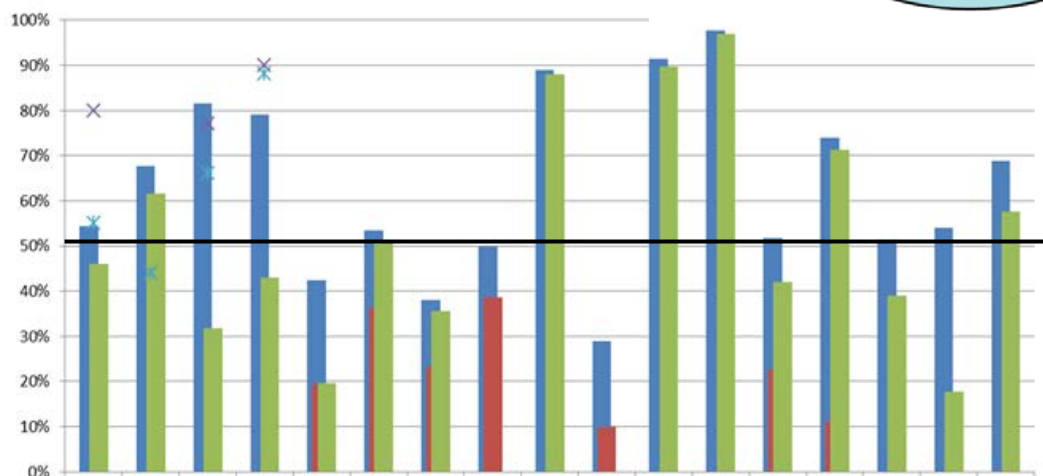
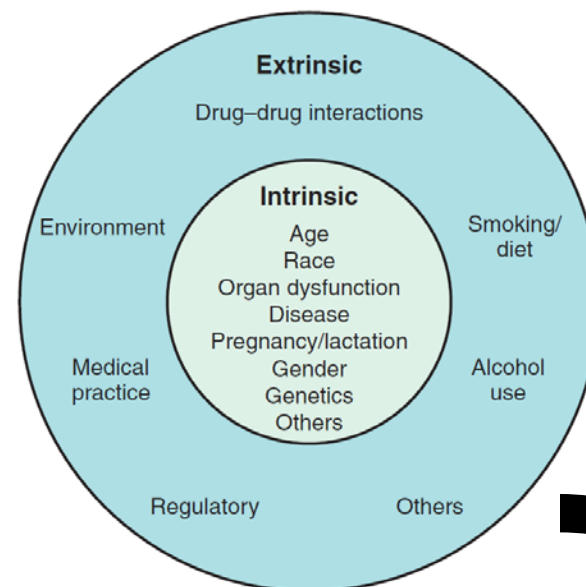
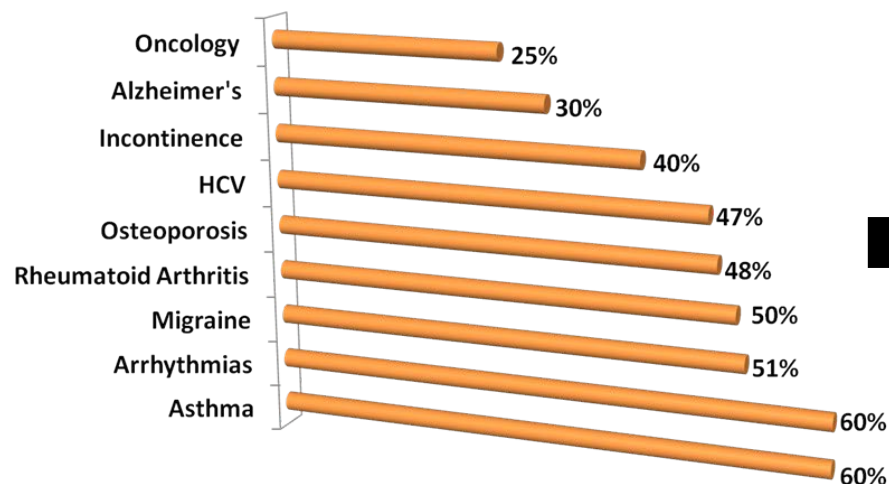
- **Planning for Drug Response Variability**
  - The Current Drug Development Paradigm
  - Reductionism and Integration
- **Accounting for and Forecasting Drug Response Variability**
  - Model-Informed Drug Development (MIDD)
    - Experience, Progress, and Challenges
- **Beating Biology: Next-Generation Medicine**
  - Precision Medicine Trends
  - Evolving Regulatory Policy
- **The Complexity of Communication\***
- **Summary**

# Critical Path of Informed Decision Making

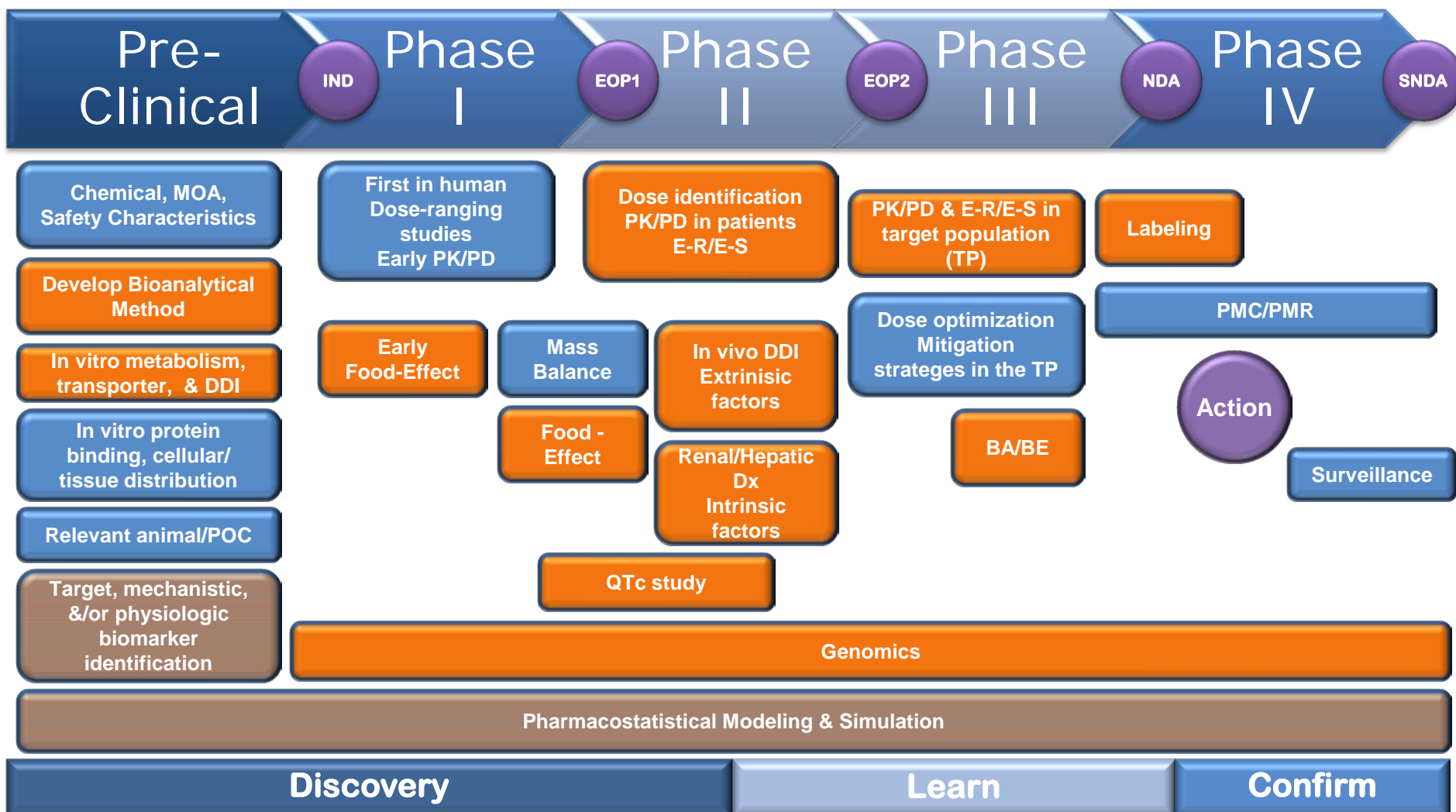




# Drug Response Prediction: From Game of Chance to Game of Skill



# Clinical Pharmacology in Drug Development and Evaluation



## “Dedicated” IEF Studies

### Advantages

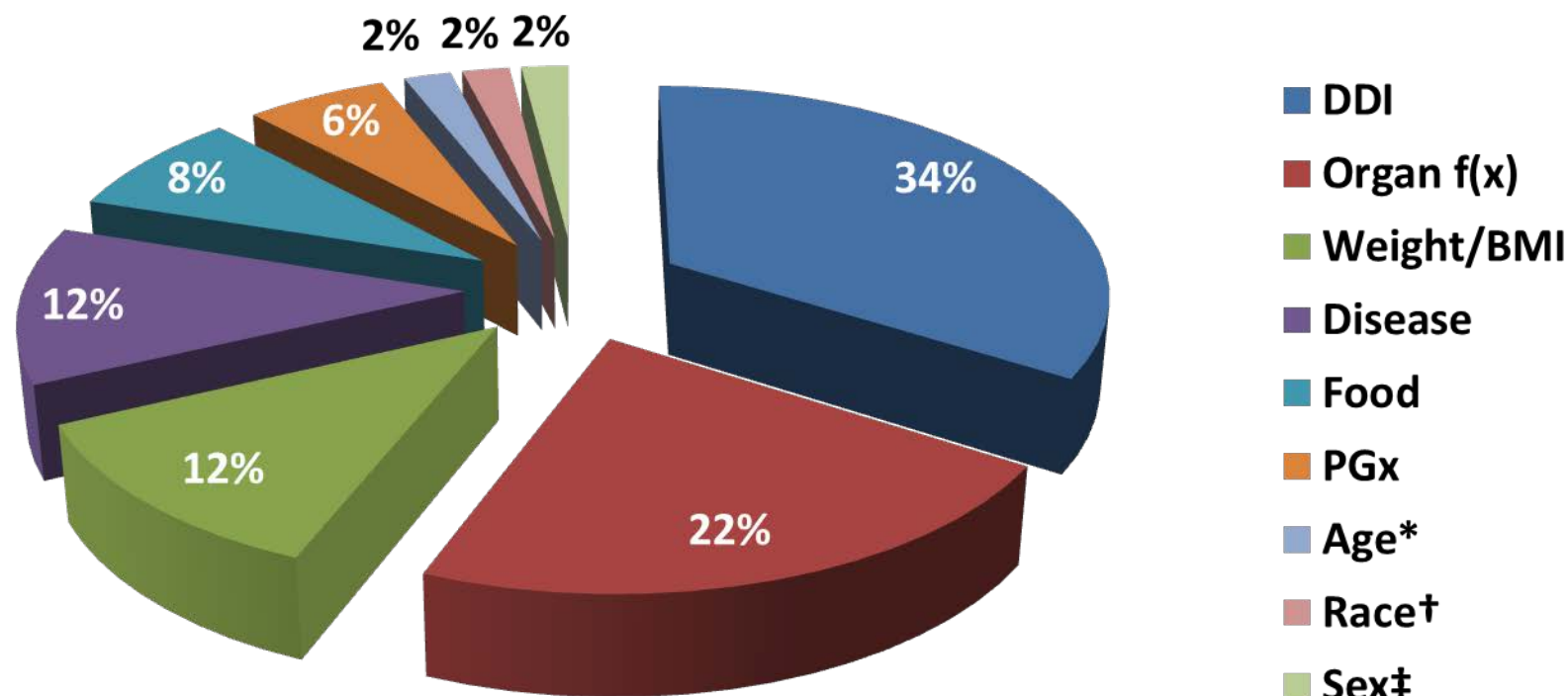
- Feasible
- Reduce noise
- Worst-case scenario
- Empirical
- Well-established
- Can be incorporated into real time development
- Decision support

### Limitations

- Small, limited phenotype information
- Highly contrived
- Not systems-oriented
- Often not incorporated into real time development
- Not a nimble “lifecycle” management strategy



# Labeling: PK/PD, Use, Dosing



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- Planning for Drug Response Variability
  - The Current Drug Development Paradigm
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- **Accounting for and Forecasting Drug Response Variability**
  - **Model-Informed Drug Development (MIDD)**
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# Model-Informed Drug Development

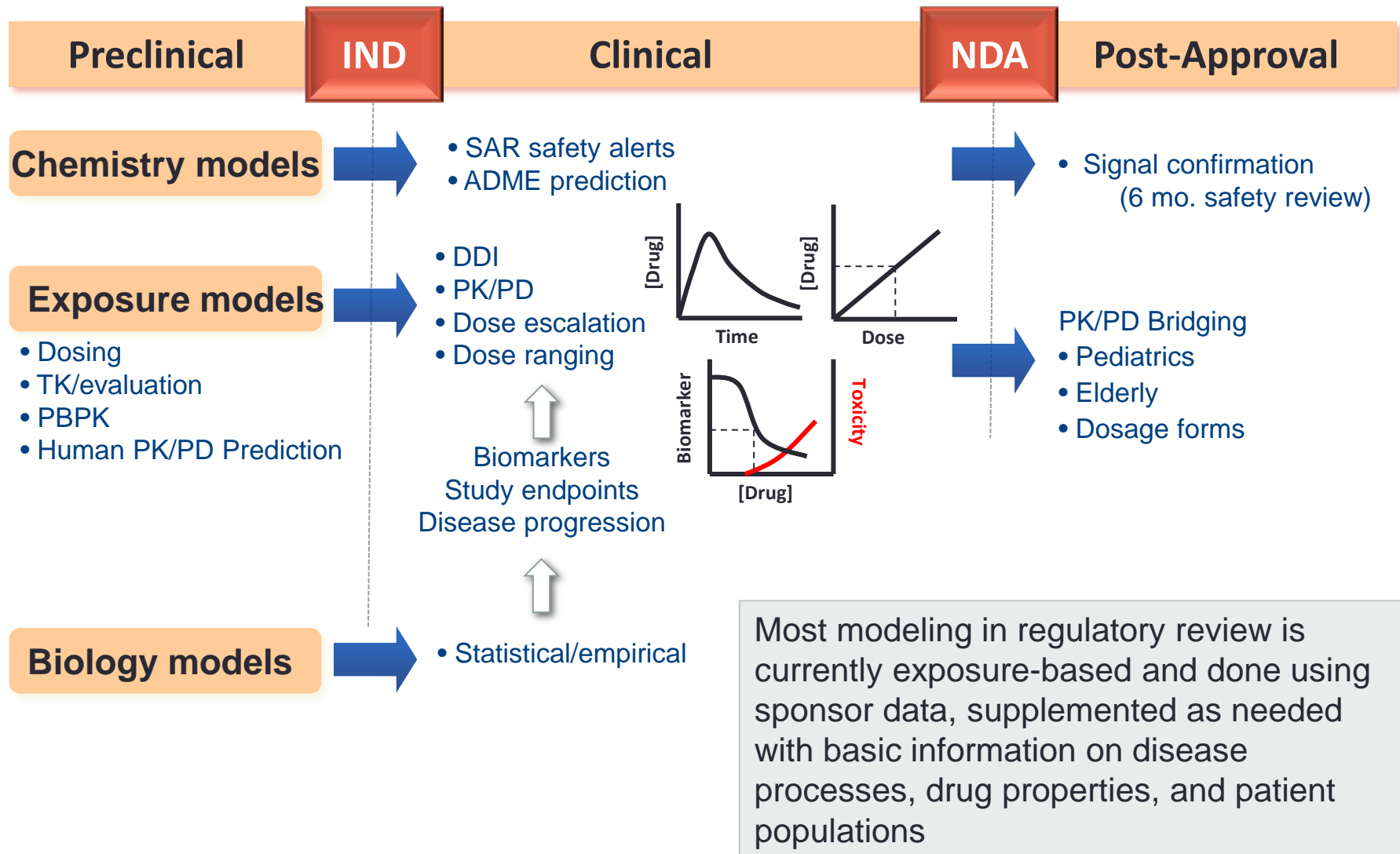
- “Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making” (Lalonde)

Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism <sup>a</sup>	Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose–response relationship	1,000 Fewer patients
Fibromyalgia	Prior data supplementation, model-based dose–response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Type 2 diabetes	Prior data supplementation, model-based dose–response relationship	120 Fewer patients, 1 year shorter study duration
Gastroesophageal reflux	Model-based dose–response relationship	1,025 Fewer patients
Rheumatoid arthritis	Model-based dose–response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success
Urinary incontinence	Meta-analysis	Increased probability of success

MBDD, model-based drug development.

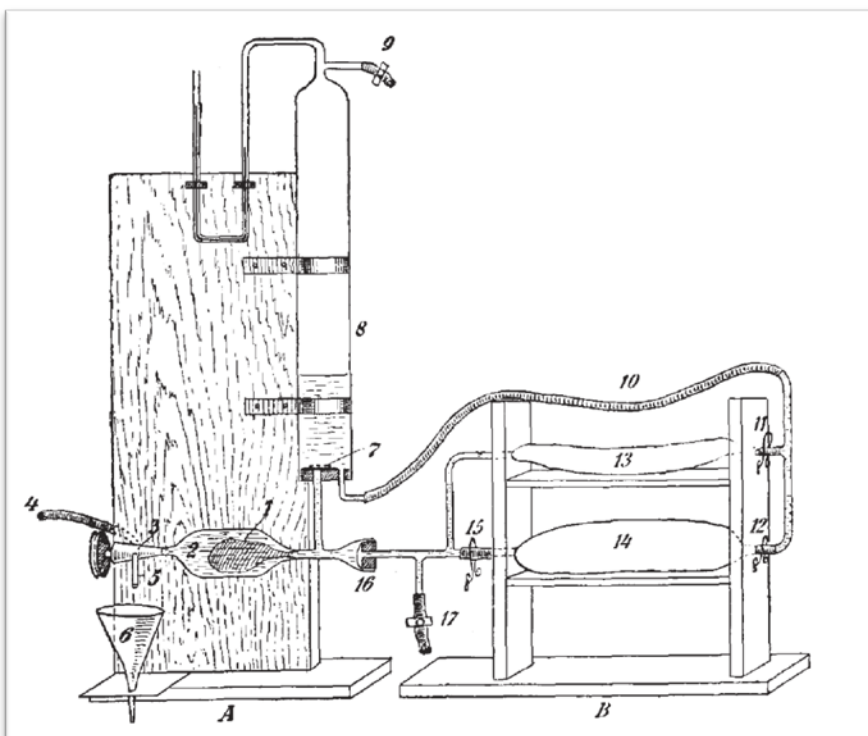
- FDA identified MIDD as an important pathway for lowering drug attrition and dealing with regulatory uncertainty

# Model-Informed Drug Development Today

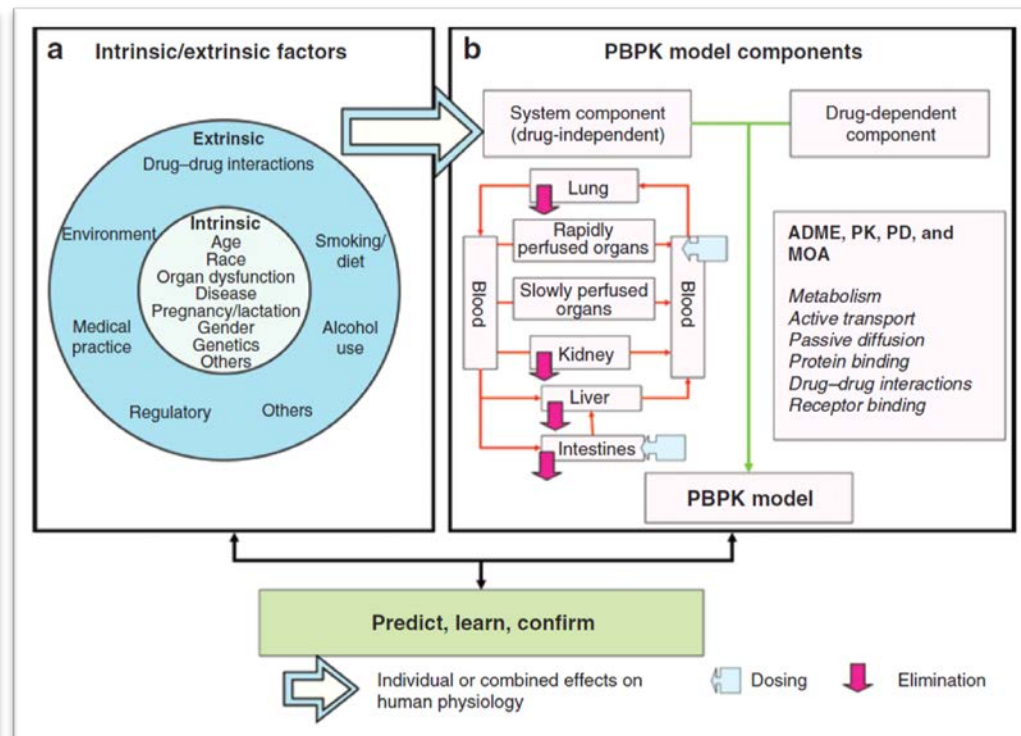




# Physiologically-based PK Modeling



**Circulation Model, Krogh 1912**



**PBPK Modeling, Present**

# PBPK: Current Status

Applications		Status
<b>Drug-drug Interactions</b>	<i>Drug as enzyme substrate</i>	<ul style="list-style-type: none"> <li>Substrate/inhibitor models verified with key clinical data can be used to simulate untested scenarios and support labeling</li> </ul>
	<i>Drug as enzyme perpetrator</i>	<ul style="list-style-type: none"> <li>Use to confirm the lack of enzyme inhibition</li> <li>Additional evidence needed to confirm predictive performance for positive interactions</li> </ul>
	<i>Transporter-based</i>	<ul style="list-style-type: none"> <li>IV/IVE extrapolation not mature</li> <li>Complicated by transporter-enzyme interplay</li> <li>Predictive performance yet to be demonstrated</li> </ul>
<b>Specific populations</b>	<i>Organ impairments (hepatic and renal)</i>	<ul style="list-style-type: none"> <li>Predictive performance yet to be improved</li> <li>System component needs update</li> </ul>
	<i>Pediatric</i>	<ul style="list-style-type: none"> <li>Allometry is reasonable for PK down to 2 years old</li> <li>Less than 2 years old ontogeny and maturation need to be considered</li> </ul>
<b>Additional specific populations and situations</b>	Pregnancy, race/ethnicity, geriatric, obesity, diseases Food effect, formulation change, pH effect Tissue concentration	<ul style="list-style-type: none"> <li>Limited experience to draw conclusions</li> </ul>

# Needs/Challenges with Model-Informed Strategies

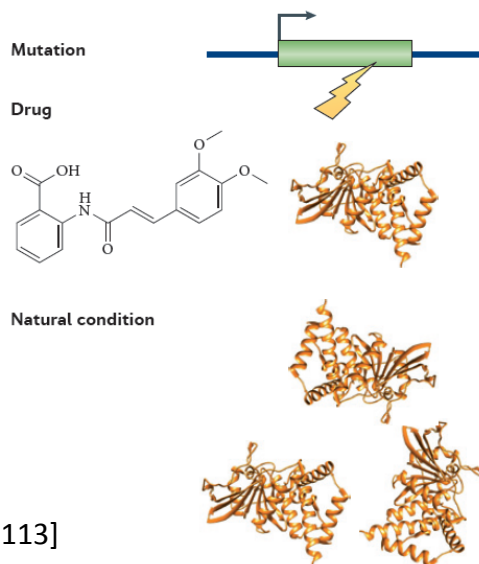
- **End-users are typically not modelers**
  - Don't have the bandwidth to explore the specifics of model construction and validation
  - If I make a decision based on this readout, am I making the right/best/best informed decision?
  - These end users (including regulators), in general, lean toward a lower level of risk tolerance
  - A reality that needs to be considered in framing all aspects of the scientific and drug development/regulatory dialogue
- **Transparency: identification and communication of assumptions and knowledge gaps**
  - PopPK, E/R – “Industry Standard” needed
  - Unlikely that PBPK is currently fit-for-purpose for all contexts of interest
  - Articulating, as a community, where our comfort lies is critical
- **Best practices for community endorsement of [mechanistic] models for a variety of uses (including regulatory)**
  - Qualification or validation
  - Development of performance/sensitivity analysis metrics
  - Need for ensuring platform-independence of findings
  - Risk-based regulatory evaluation should be risk-based: plan, waive, interpret, translate studies

# Themes

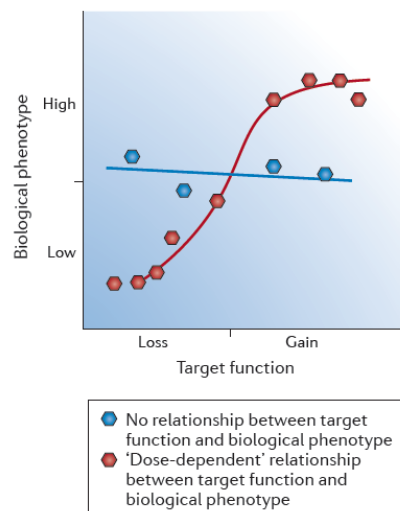
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# Precision Medicine Trends

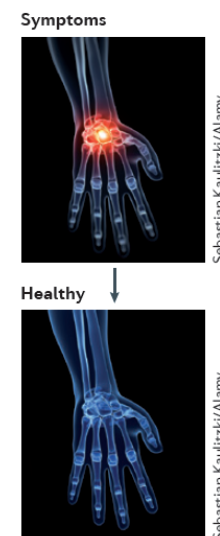
**a Target modulation**



**b Function-phenotype**

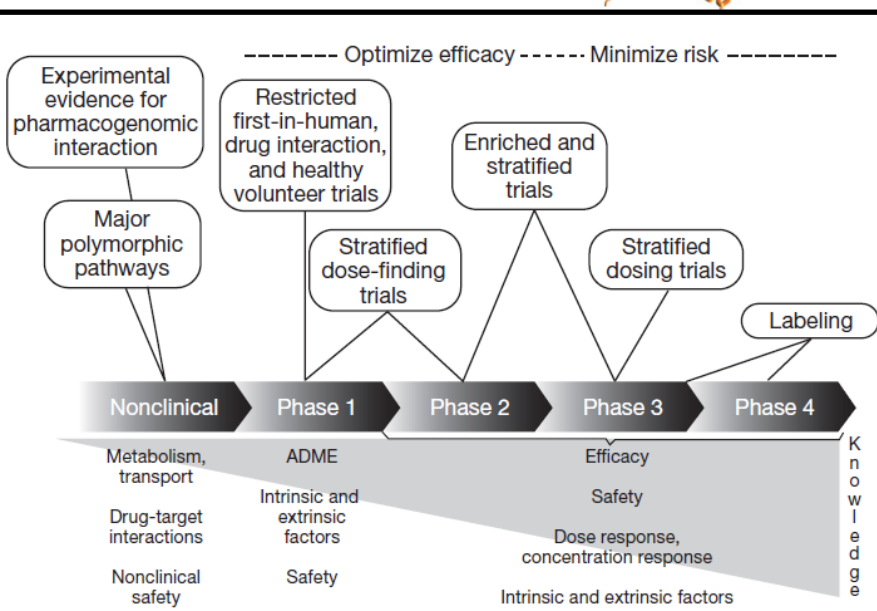


**c Clinical outcome**



Nelson [PMID 26121088]

Plenge [PMID 23868113]



Progression	$p(\text{progress} \text{genetic support})/(\text{progress} \text{no genetic support})$		
	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

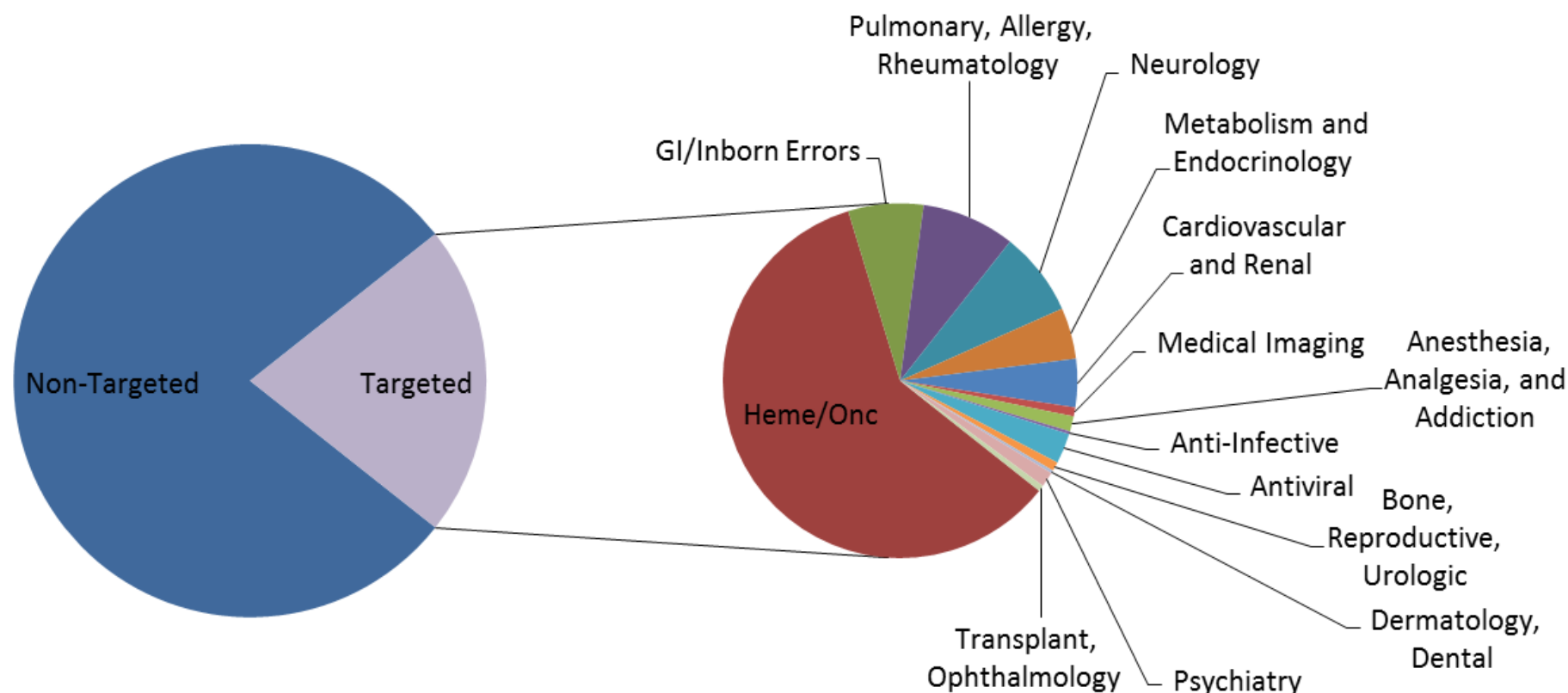
Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.

**Guidances/White Papers in the double digits**  
**PM strategies increasingly being used**  
**Approvals increasing**

Zineh [PMID 21923598]

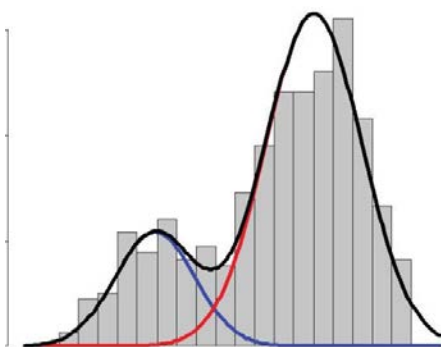


# Investigational Drug Landscape

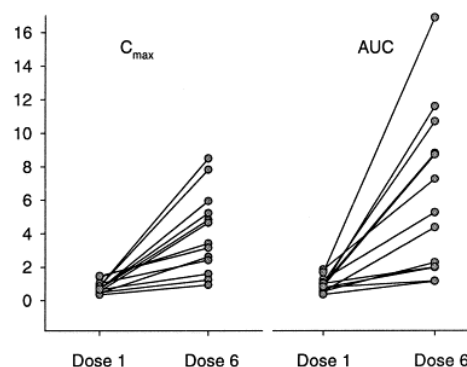


Estimated volume of meeting packages and protocols with biomarker-based objectives (e.g., enrichment, stratification, endpoints) based on ~1700 electronic submissions, May 2014-Mar 2015

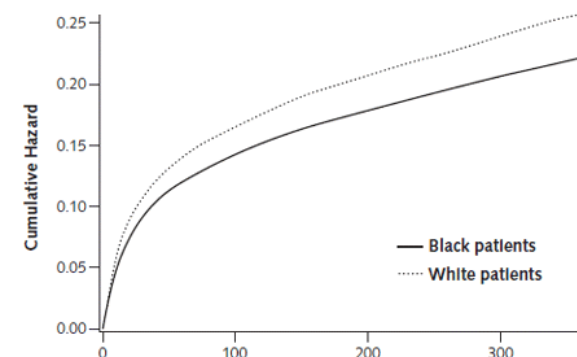
# Patient Subset Effects – Targeted Therapy Approaches



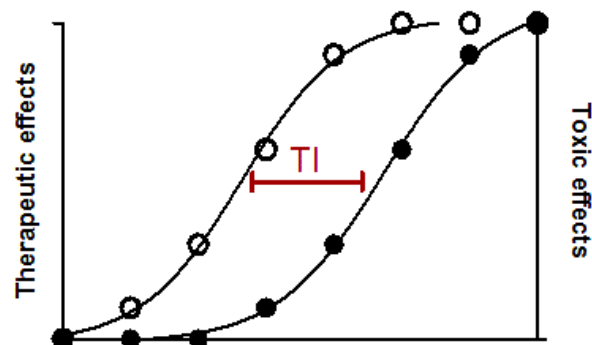
**Multimodal PK**



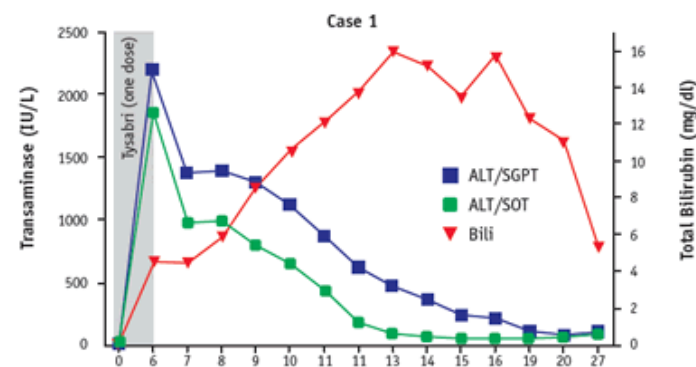
**High Variability**



**Race Effects**



**NTI**



**Safety**

# Characteristics in Support of Targeted Drug Development

**Biomarker is the major pathophysiological driver of the disease to be studied**

**Limited or adverse paradoxical activity of the drug is seen in a subgroup identified through in vitro or animal models (e.g., cell lines or animals without the biomarker)**

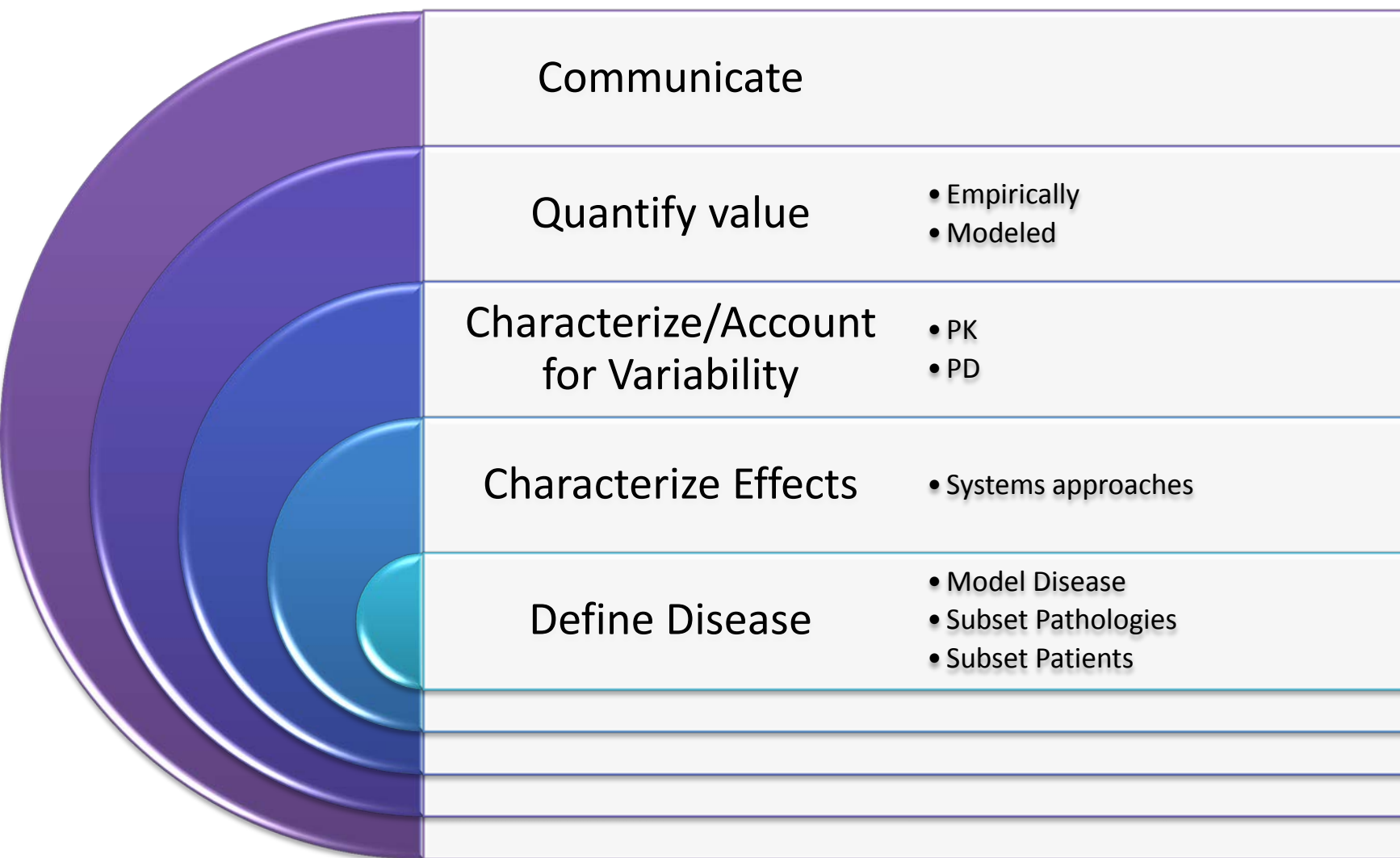
**The biomarker is the known molecular targeted of therapy**

**Preliminary evidence of harm from early phase clinical studies in patients without the biomarker**

**Preliminary evidence of lack of activity from early phase clinical studies in patients without the biomarker**

**Preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity**

# A Holistic (Pharmaco-biologic) View



# The Role of Clinical Pharmacology in Reducing Uncertainty

**“I took a test in Existentialism. I left all the answers blank and got 100.”**

**— Woody Allen**