



Personalized Medicine and Model Based Drug Development: Opportunities For Biomedical Informatics

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- Background
 - Personalized Medicine/Personalized Healthcare (PHC)
 - Modeling and Simulation (M&S) for PHC
- Current M&S types and gaps in drug development
- M&S by Biomedical Informatics filling the gaps
- Case studies
 - Case study 1: modeling for predicting treatment responders vs. non-responders for better efficacy
 - Case study 2: modeling for identifying patients with high safety risks
- M&S for PHC Integrated into a Clinical Program

Personalized Medicine or Personalized Healthcare



- Based on the recognition that unprecedented types of information will be obtainable from genetic, genomic, proteomic, imaging, etc, technologies, which will help us further refine known diseases into new categories
- Managing a patient's health based on the individual patient's specific characteristics vs. “standards of care”
- PHC in AZ to focus on therapies linked to diagnostics and tools to deliver superior outcomes to patients
- PHC in AZ to deliver:
 - Disease segmentation
 - Patient selection
 - Improved dosing





- Wide application of the new technologies to clinical trials has not come to reality in the pharmaceutical industry, for all kinds of reasons, such as
 - Limitations in trial designs
 - Extra cost and time
 - Uncertainty in regulatory and commercial consequences
- A cost-effective approach is M&S using available data and technologies
 - The industry and FDA have now a broader use and acceptance of M&S
 - Cheaper, faster, and easier to integrate into clinical programs (arguable)
 - Many M&S application types: biological (from cell to system to disease), pharmacological (PK/PD), clinical trial modeling and simulation, HEOR modeling, etc.

Major Types of M&S in Drug Development



Biological Modeling

(computational/systems biology)

To understand genetic, biochemical and physiological networks, as well as pathways and processes underlying disease and pharmacotherapy

Pharmacological Modeling

(pharmacometrics)

To guide clinical trial design, dose selection and development strategies

Statistical Modeling

(clinical trial design modeling)

To assess development strategies and trial designs in populations

Discovery

Preclinical Development

Early Clinical Development

Late Clinical Development

Product LCM

Discovery phase

- Target discovery and validation
- Efficacy and safety prediction using in vitro and in vivo models

Learning phase

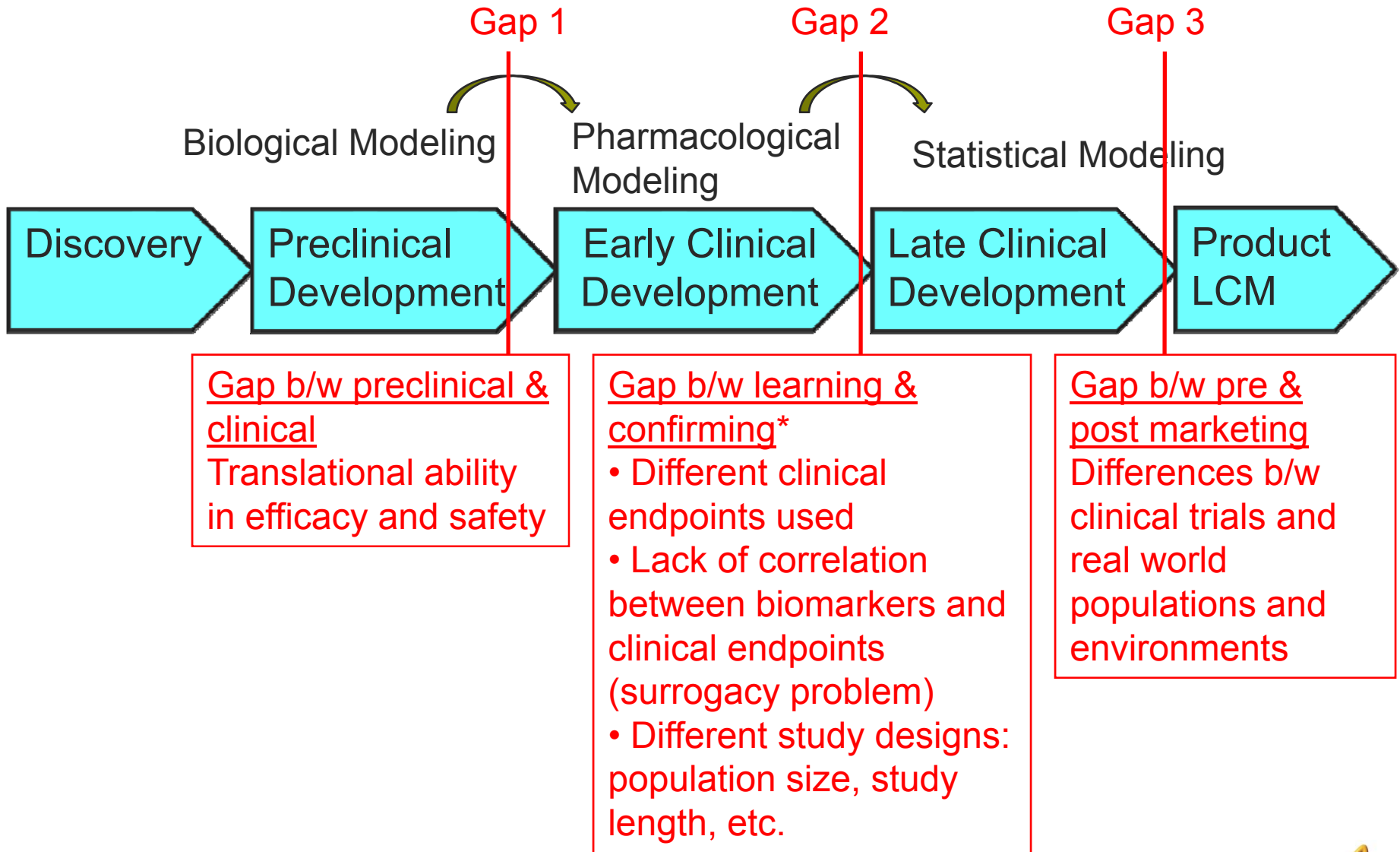
- Apply PK/PD modeling, biomarkers, and advanced statistical methodology
- Demonstrate PoC, determine safety, and establish dose selection

Confirmatory phase

- Verify effectiveness and monitor safety for long-term use
- Confirm optimal dose and dosing regimen
- Identify target patient population
- Establish the benefit/risk ratio

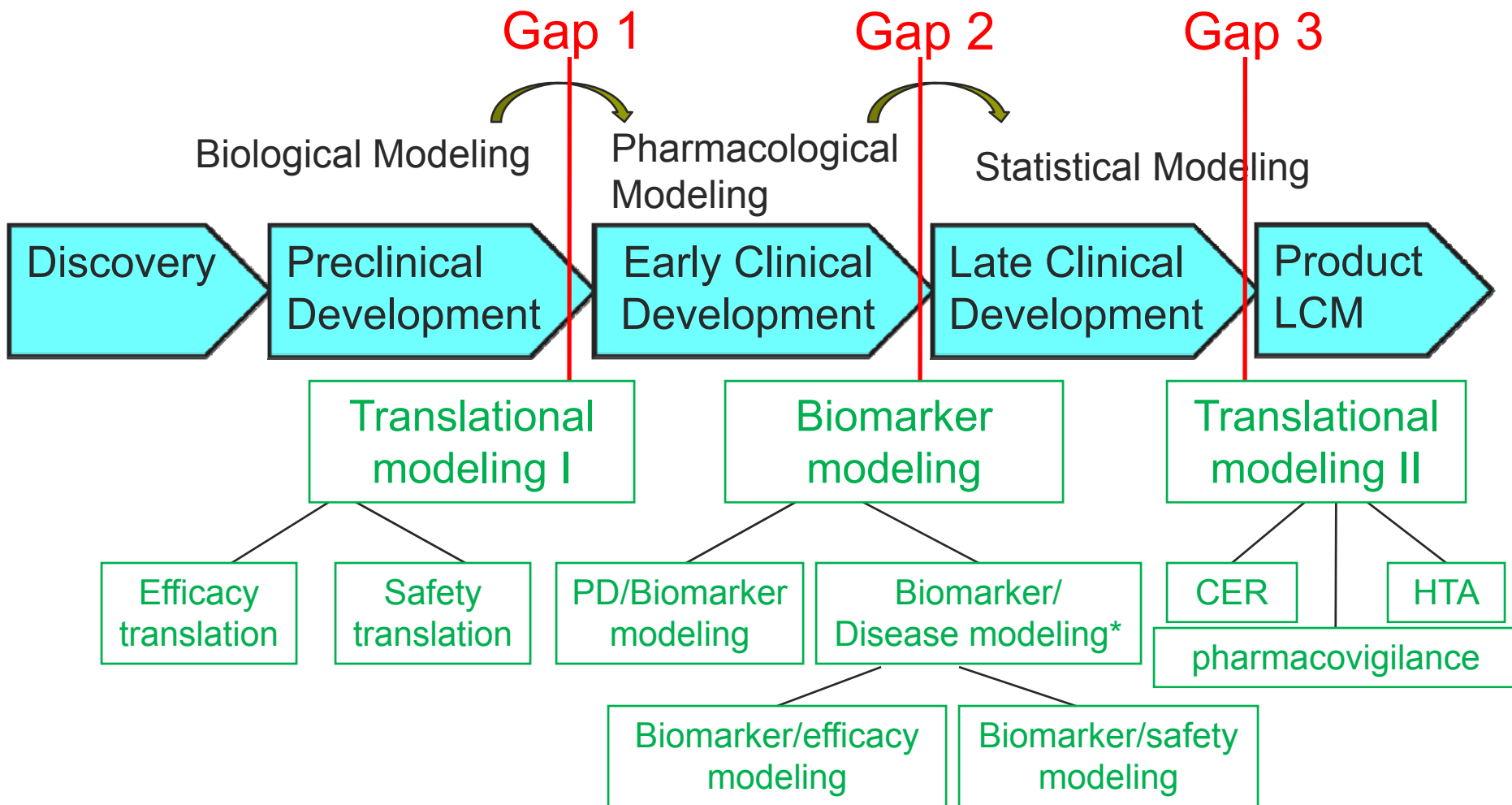
• Modified from Orloff et al, 2009

Current M&S Gaps in Drug Development



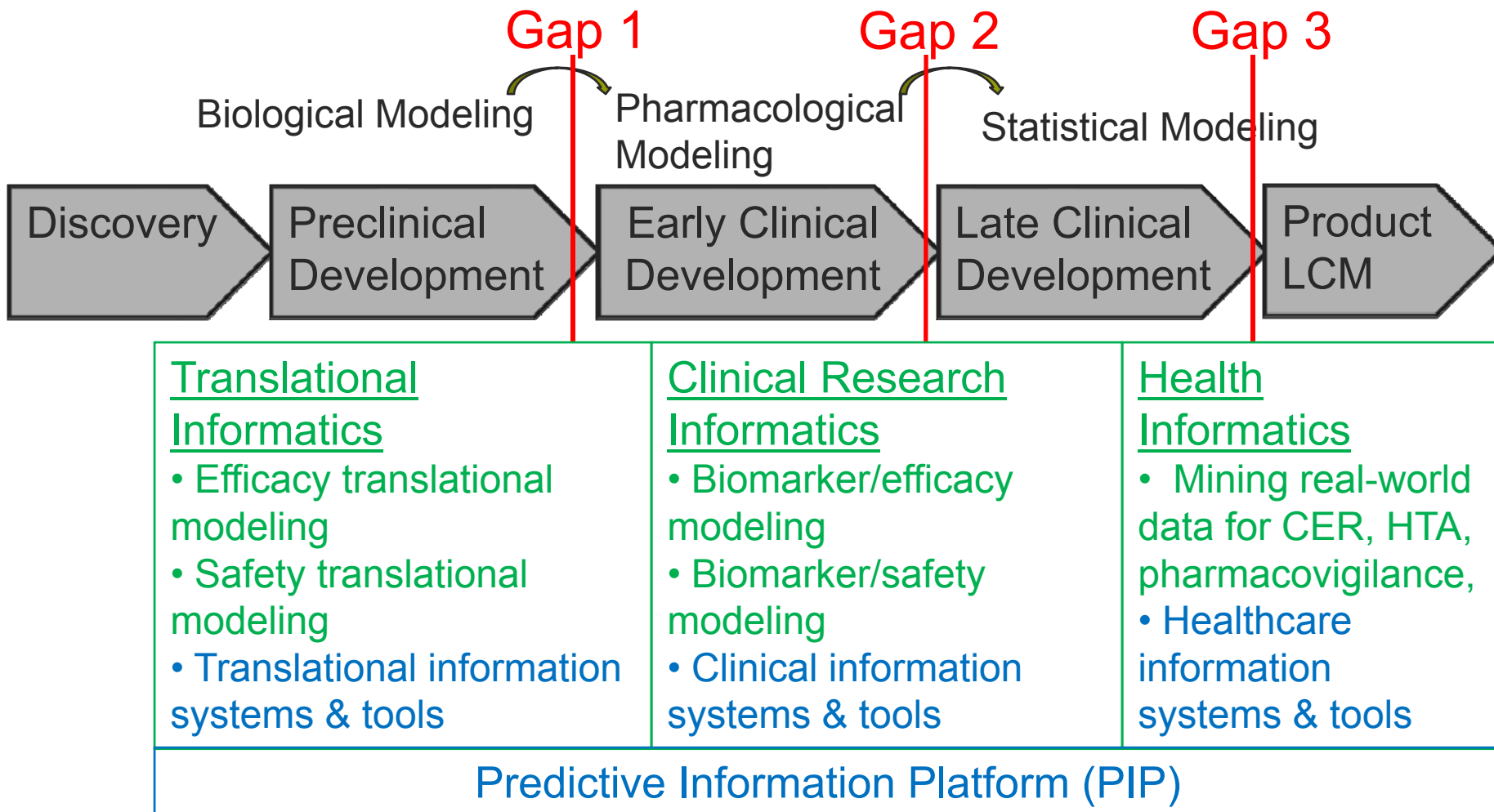
* See FDA examples from [FDA/PhRMA/DIA M&S workshop 2009](#)

What's Needed to Fill the Gaps?



* Modeling relationships between biomarkers and the clinical endpoints used for phase 3 trials, starting at phase 2 stage using available data.

Overview of Biomedical Informatics for MBDD



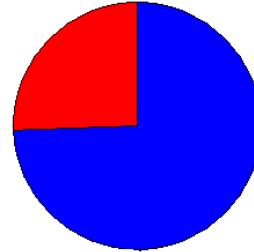
Case Study 1: Identify Treatment Responders



Treatment effect in overall patient population

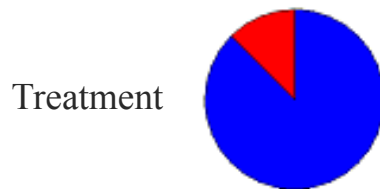
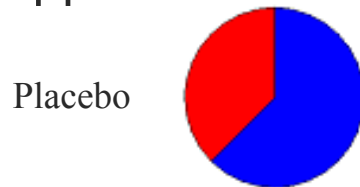


Placebo



Treatment

Treatment effect in patient subpopulations defined by baseline biomarker levels (enabling potential patient stratification in Phase 3, and a PHC approach for registration)

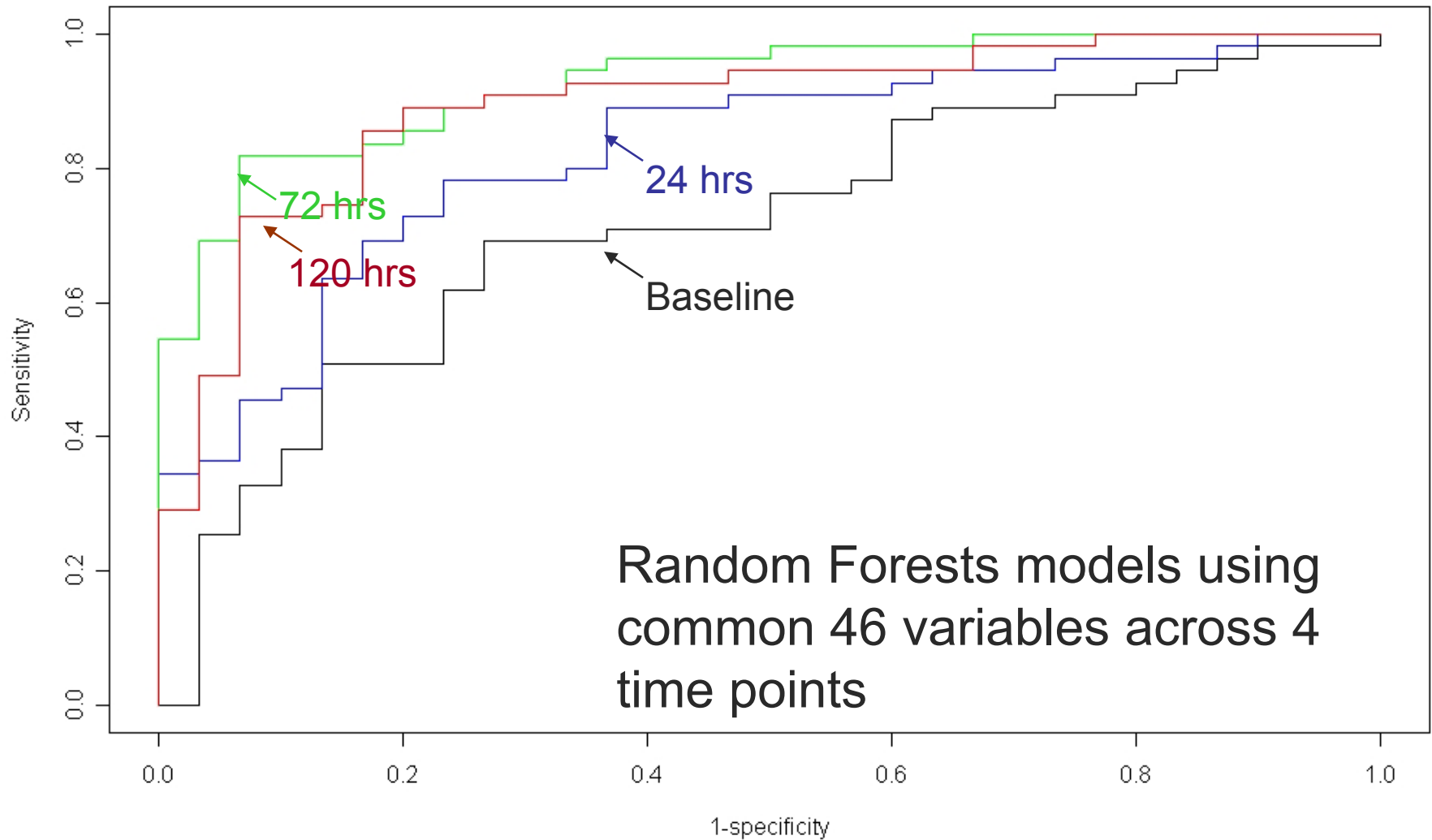


Marker A \leq xxx

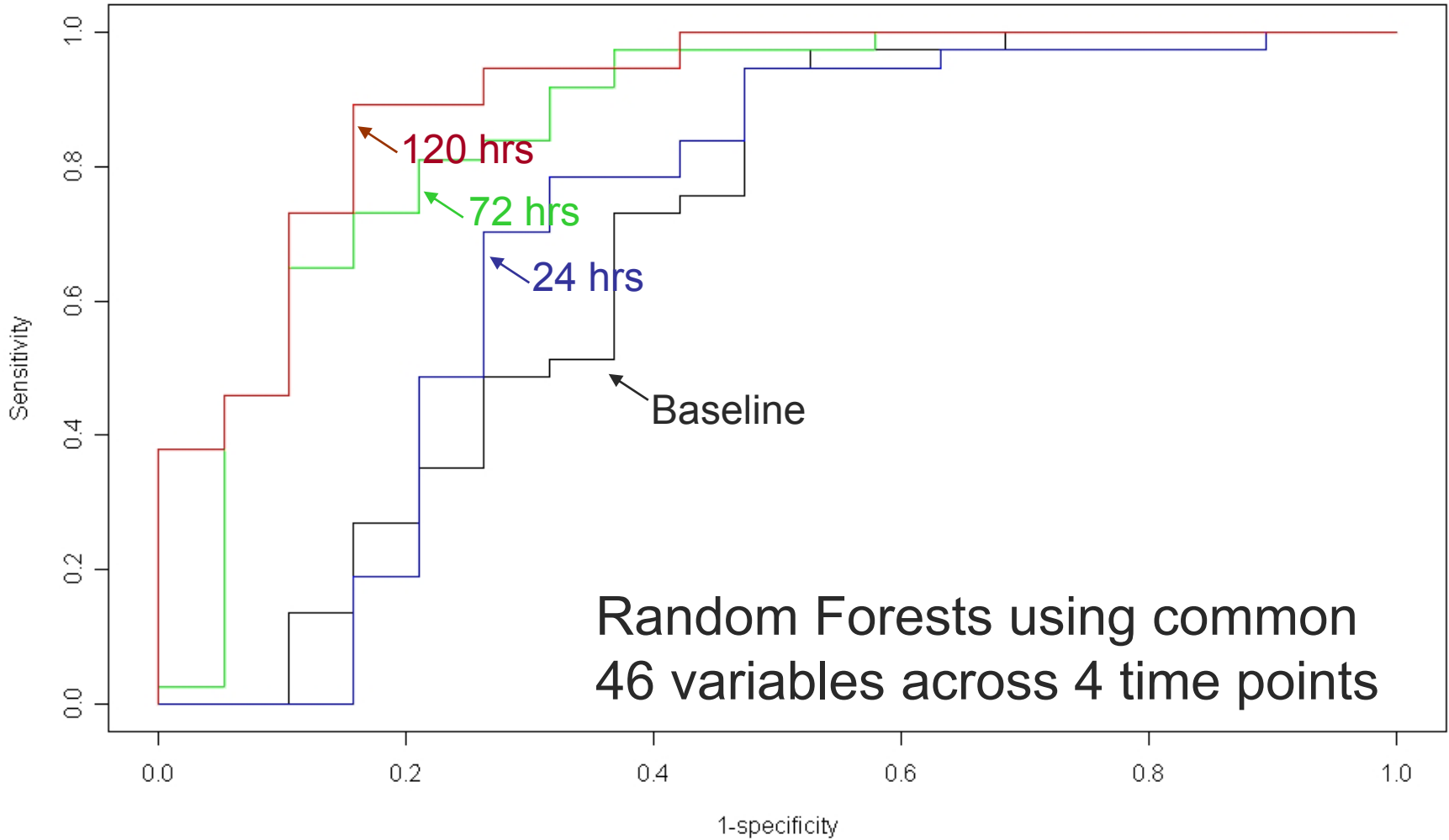
Marker A $>$ xxx

Blue: survivors
Red: non-survivors

Models to Predict Survival In Treatment Group



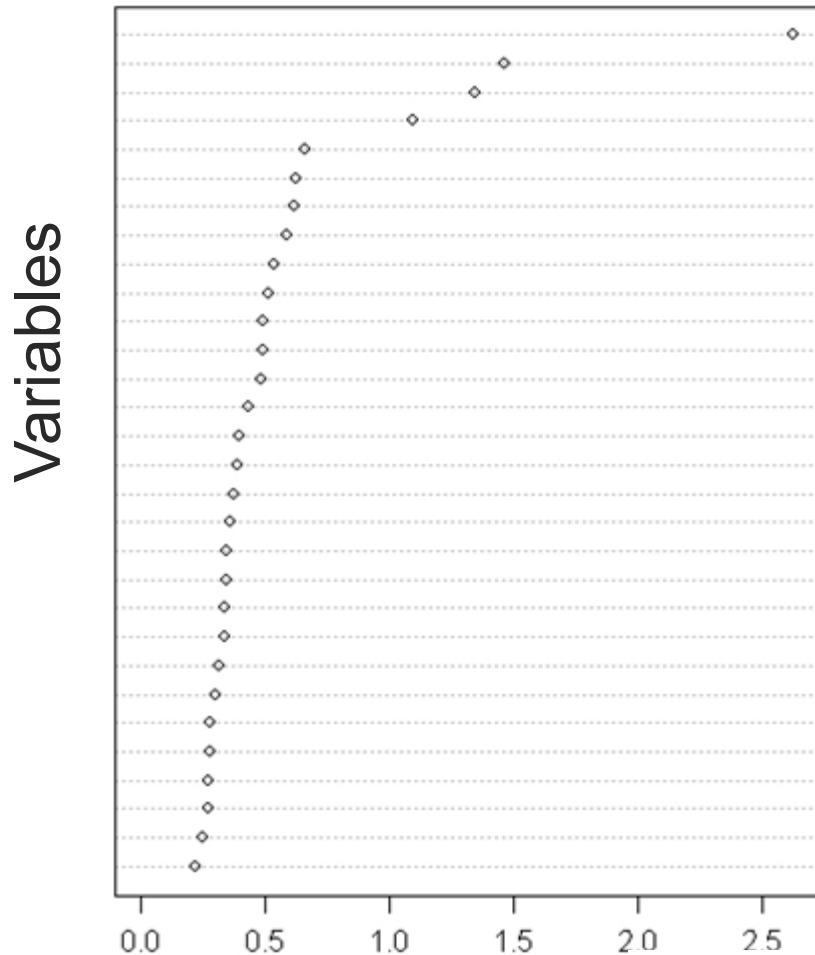
Models to Predict Survival In Placebo Group



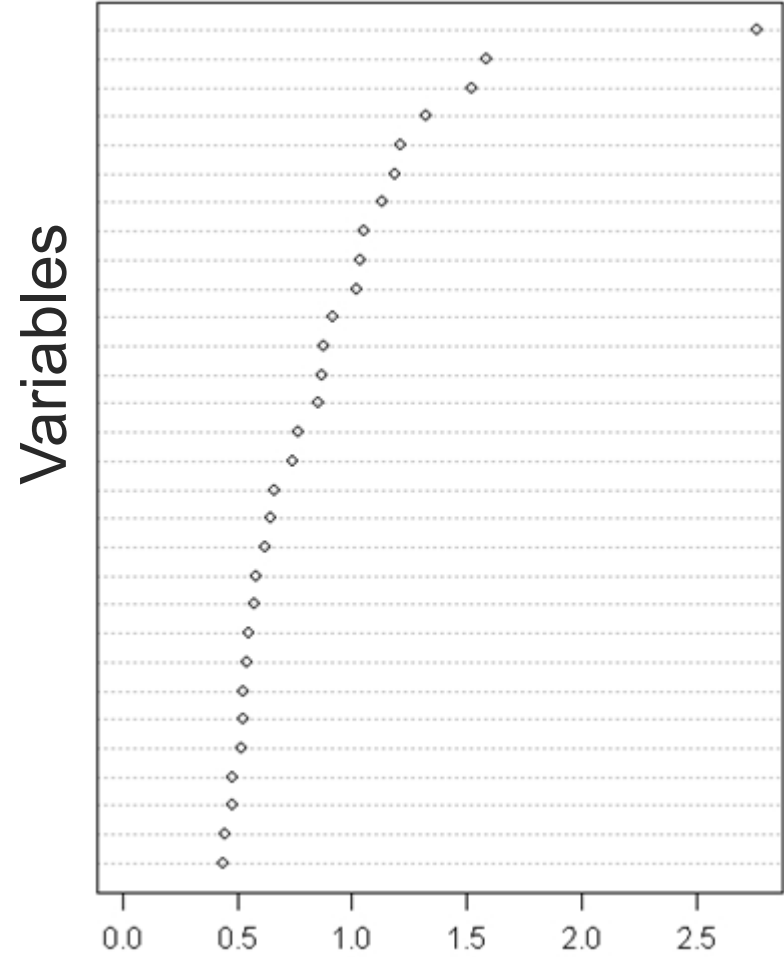
Variable Importance Plots



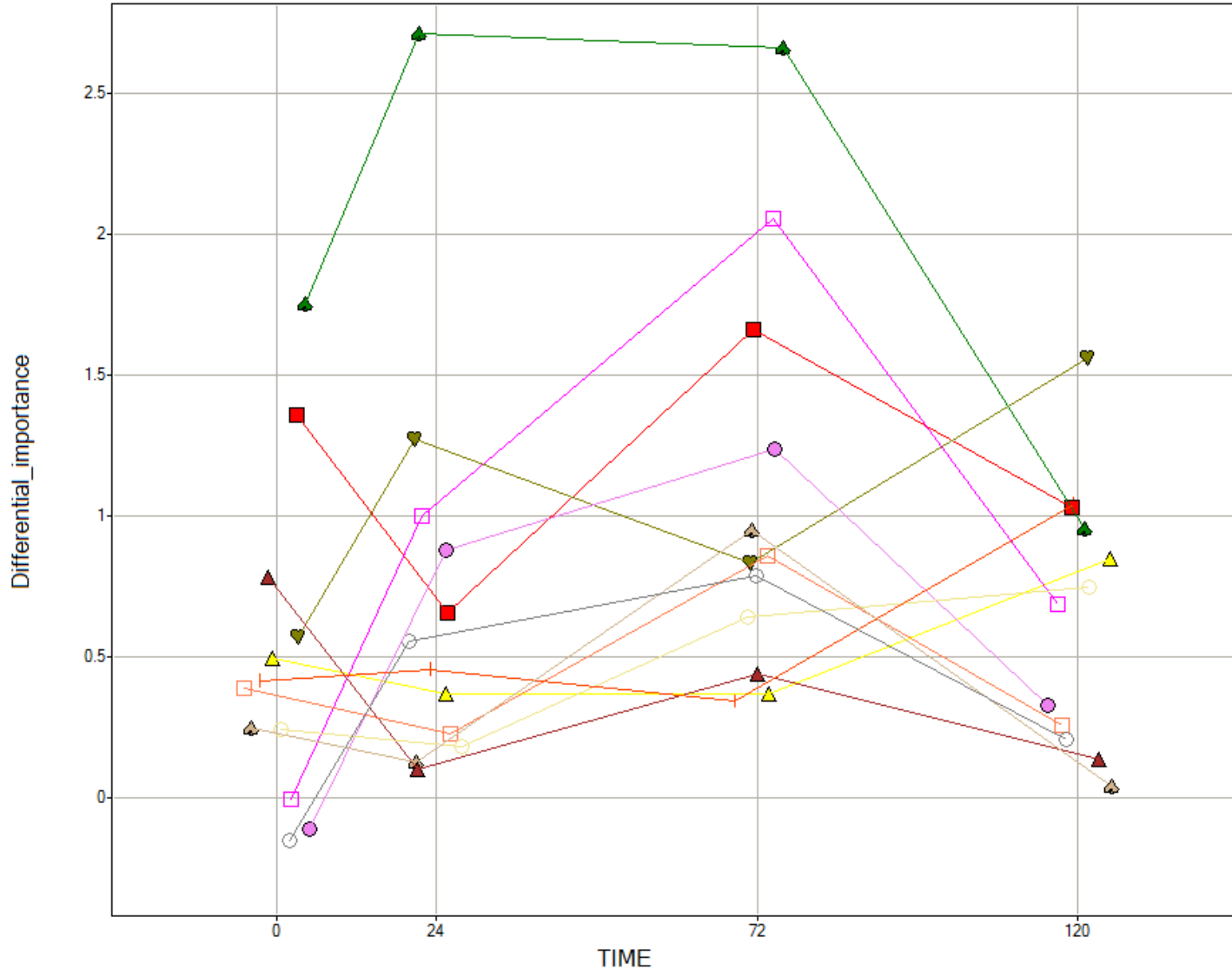
Top predictors in placebo group (prognosis markers)



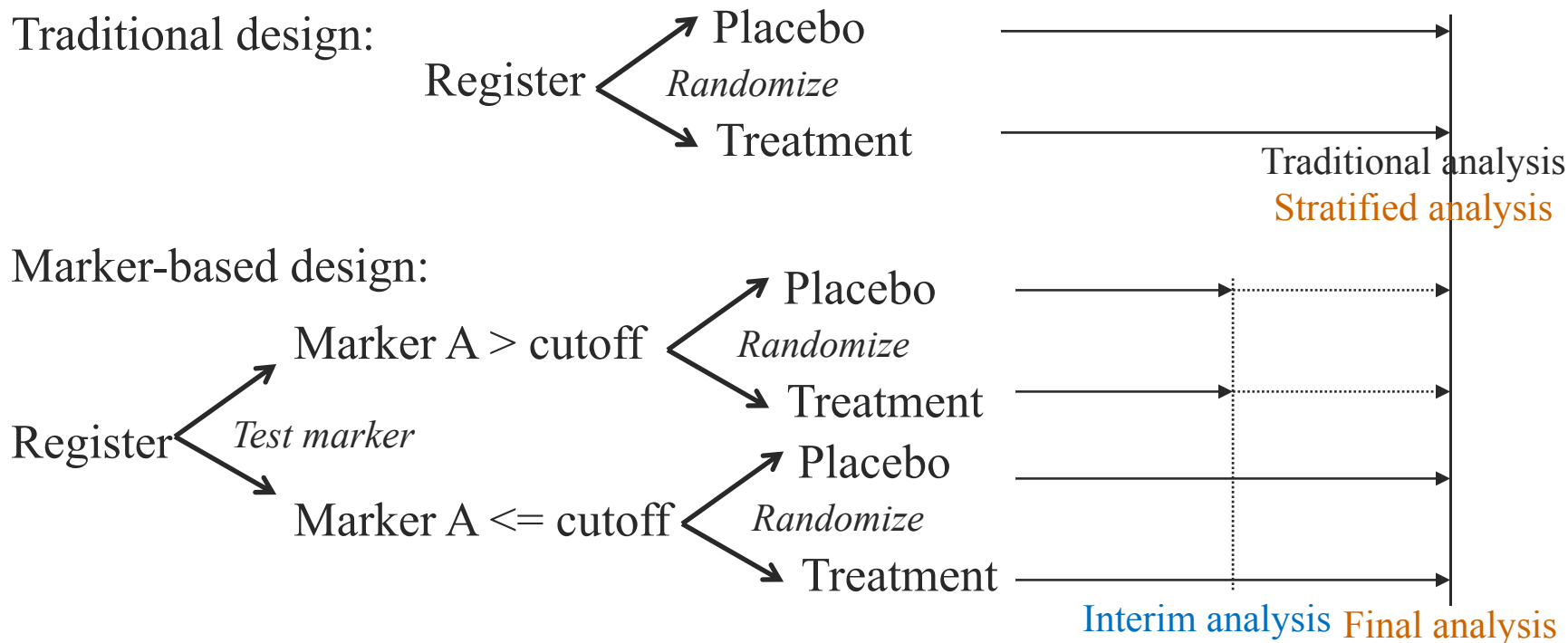
Top predictors in treatment group (efficacy markers)



Predictive Biomarkers: More Important For Survival On Treatment But Less Important On Placebo

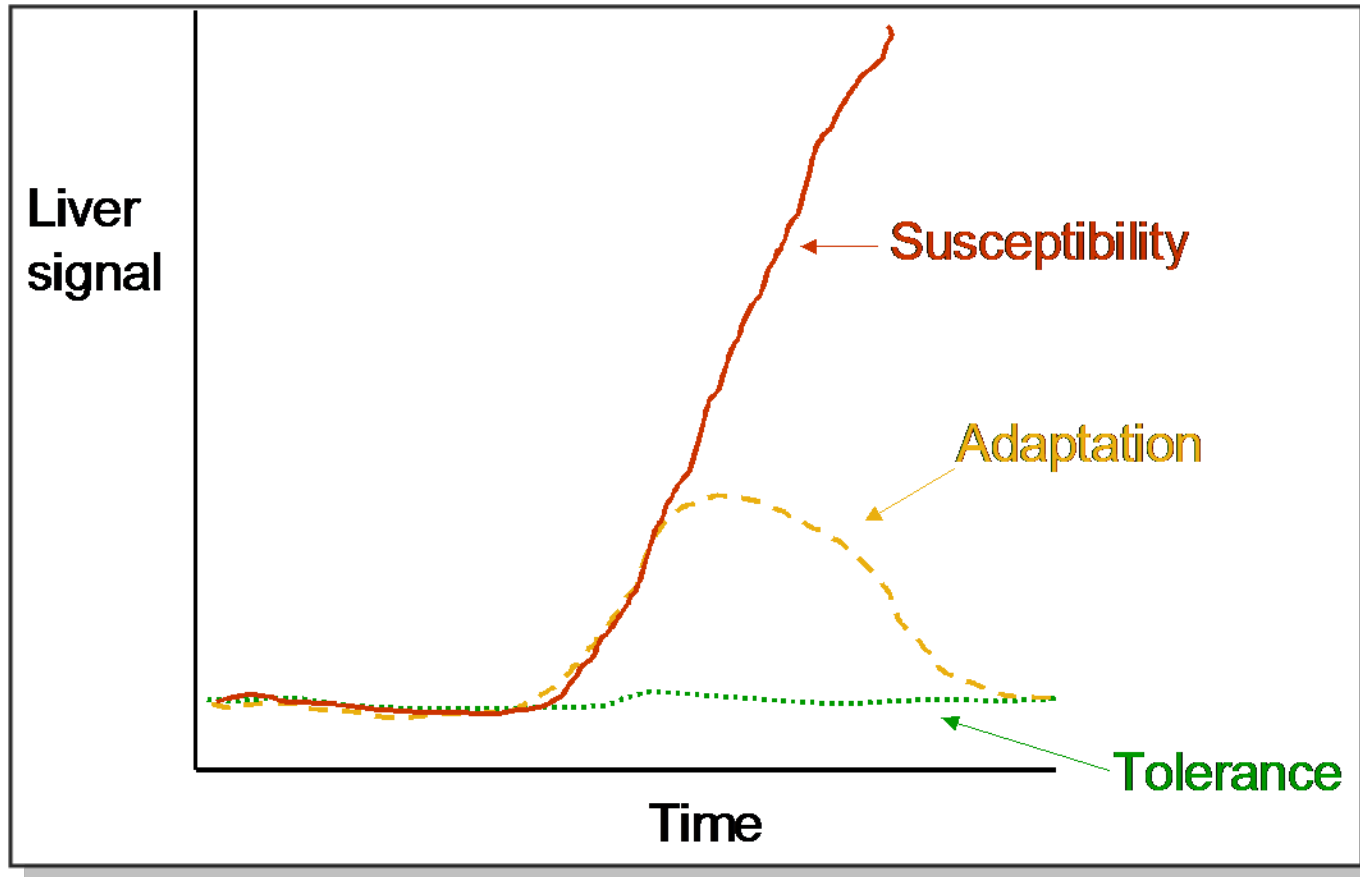


Potential Application to Phase 3: Marker-based Vs. Traditional Design (with and without stratified analysis)



- Additional risk: a test with a quick turn around time for Marker A
- Benefit:
 - ✓ Better chance to demonstrate mortality improvement and allow a personalized medicine approach with this product
 - ✓ Smaller sample size and shorter trial duration if interim analysis shows significance for Marker A \leq cutoff arms.
 - ✓ More ethical if the treatment is not beneficial to patients with Marker A $>$ cutoff

Case Study 2: Identify Patients at High Safety Risk

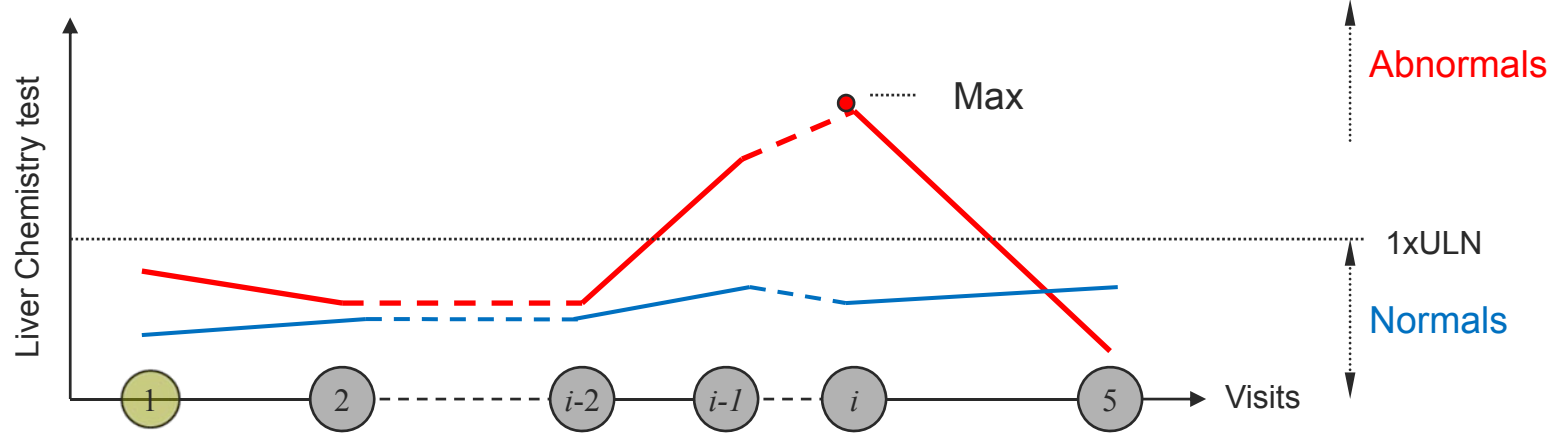


Using biomarkers to predict individual patient risk of developing liver signals in response to a drug

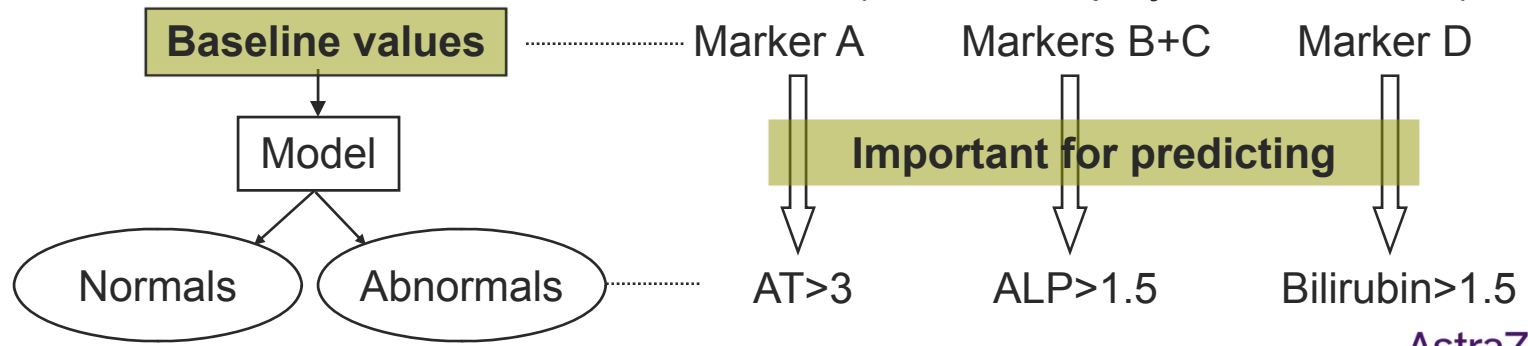


Question: Who will develop liver signals during the trial?

Purpose: risk stratification (with a PHC potential) and proactive surveillance
 Data: Baseline Labs+ Demographics + Concomitant Medications + Medical History
 What to predict: Patients on treatment w/ (Abnormals) or w/o liver signals (Normals)



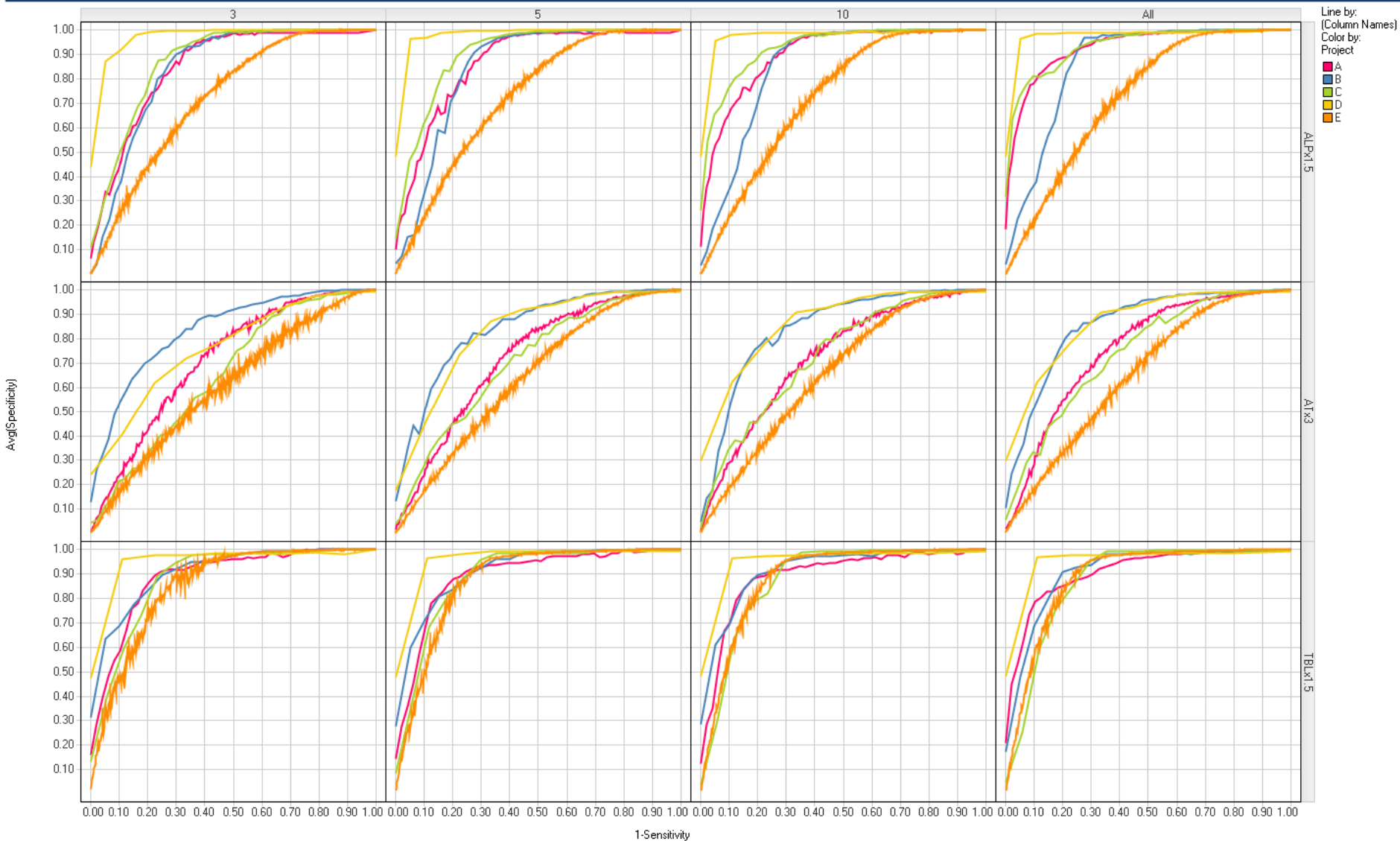
Result (based on 5 projects, 24 studies)



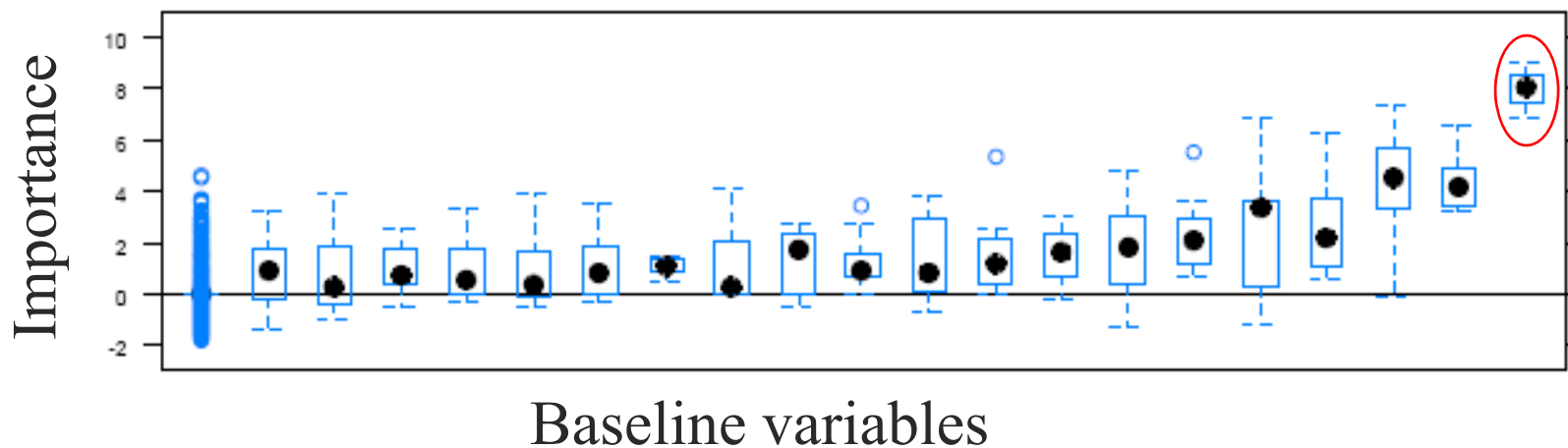
Predictive Models Using Baseline Information



Line Chart



Predictive Baseline Variables for Biochemical Hy's Law Cases During The Trials



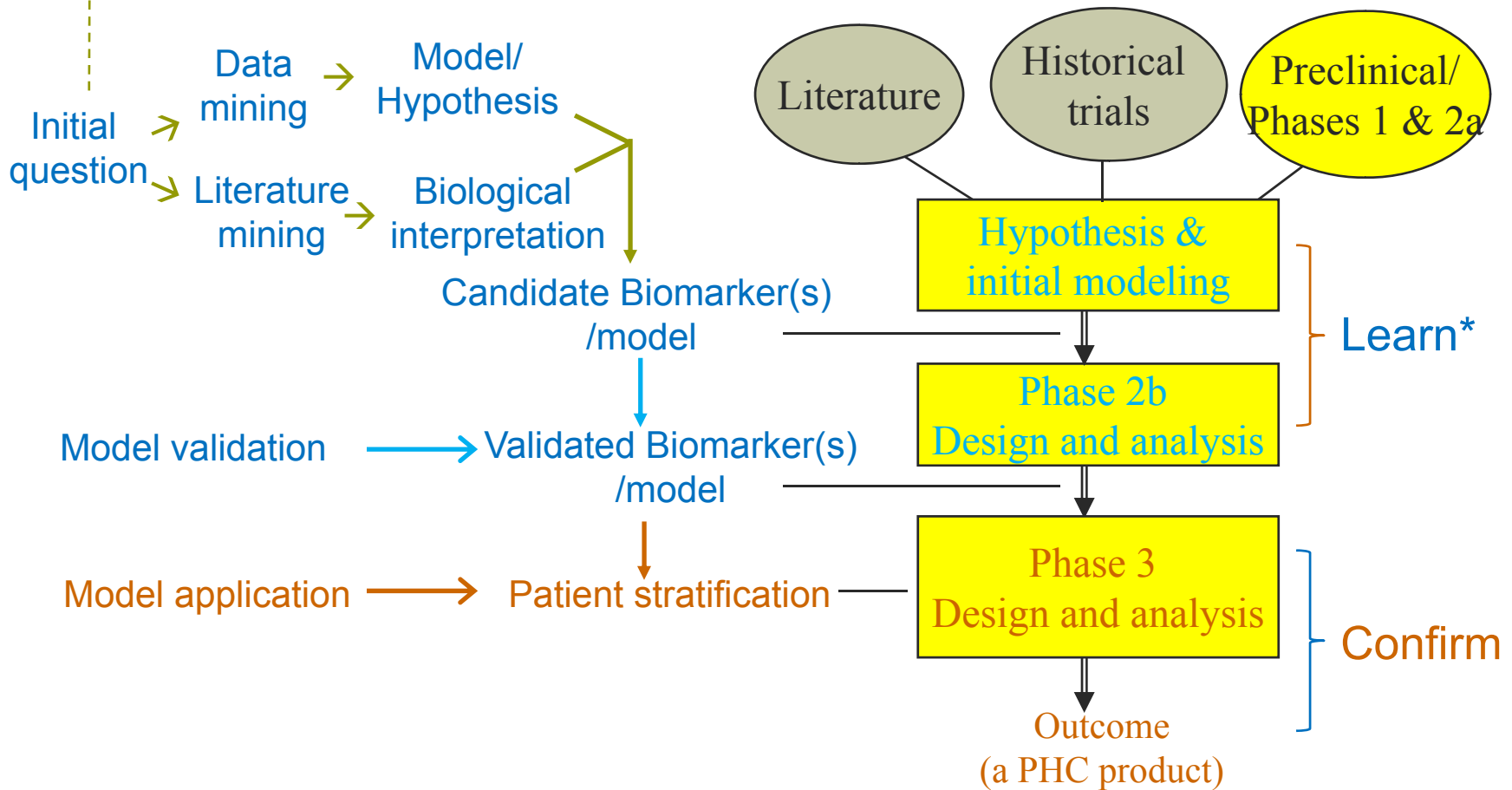


- Identify patients with high risk of developing liver signals
 - Better patient risk management
 - Cost-effective biomarker research
 - Being applied to a live project in transition to phase III
- Potential applications of the predictive biomarkers
 - Trial protocol for close monitoring of the high-risk subpopulation (e.g. those with marker $A > xxx$)
 - New exclusion criterion for trials as appropriate (e.g. excluding those with marker $A > xxx$)
 - Warnings in product label: marker A should be obtained before starting therapy. If marker $A > xxx$, do not start therapy or apply close monitoring

M&S for PHC Integrated into a Clinical Program



Which patients will benefit most from the therapy (i.e. w/ most effectiveness and least safety risk)?



* **Opportunities for BioMed Ix:** Modeling relationships between biomarkers and the clinical endpoints used for phase 3 trials, starting at phase 2 stage using available data.

Acknowledgements

- AZ Biomedical Informatics Network
 - AZ Hepatotoxicity Safety Knowledge Group
 - AZ Clinical Project Team for AZDxxxx
 - AZ Clinical Information Science Leadership
 - AZ Discovery Information
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- ASA Delaware Chapter

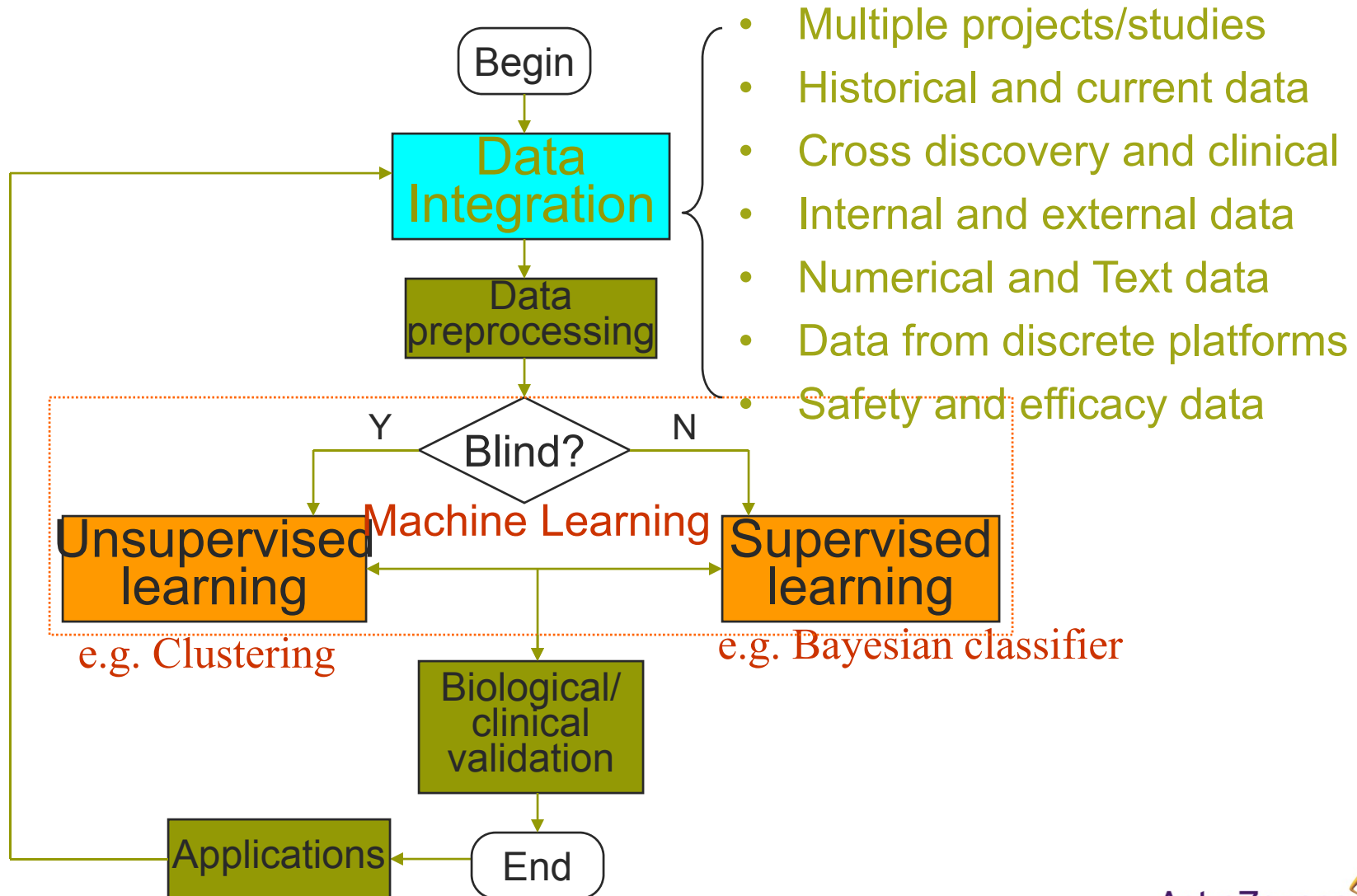
Thank you, and questions?



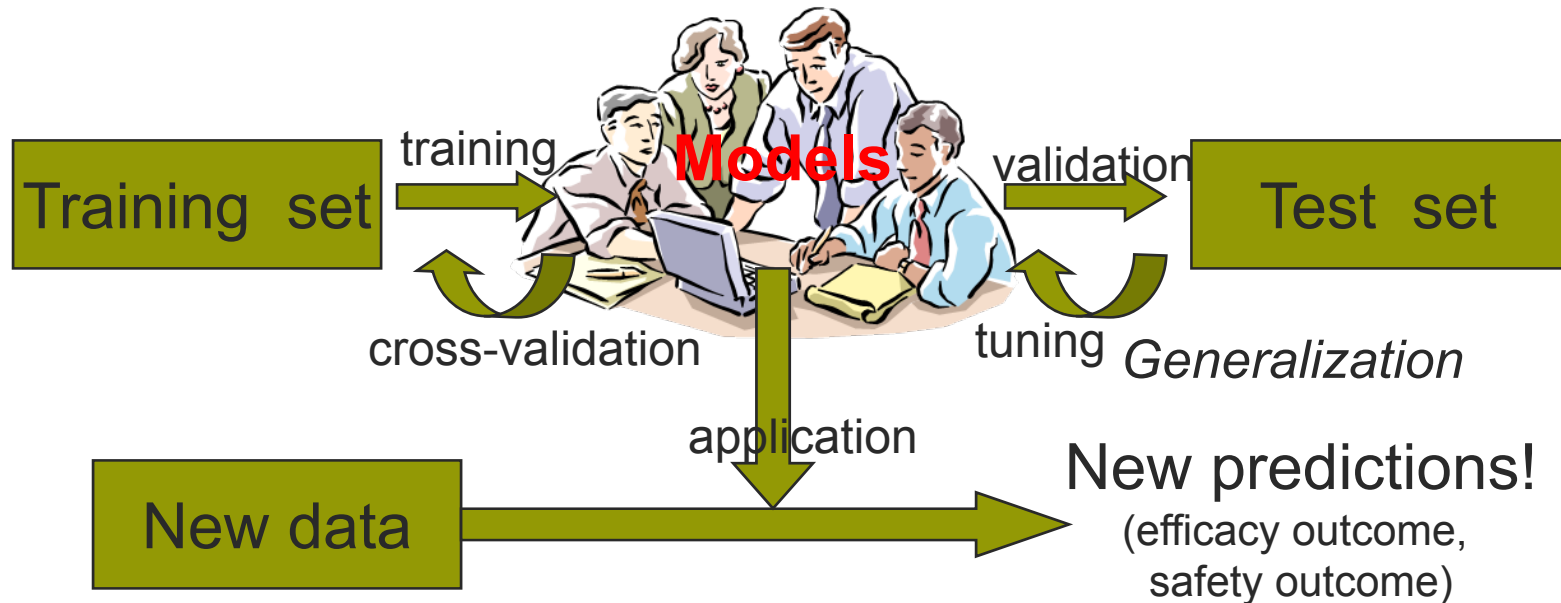
BACK UP SLIDES

(Informatics M&S Approaches & Methods)

Informatics Approach to M&S Using Machine Learning



Machine Learning Paradigm

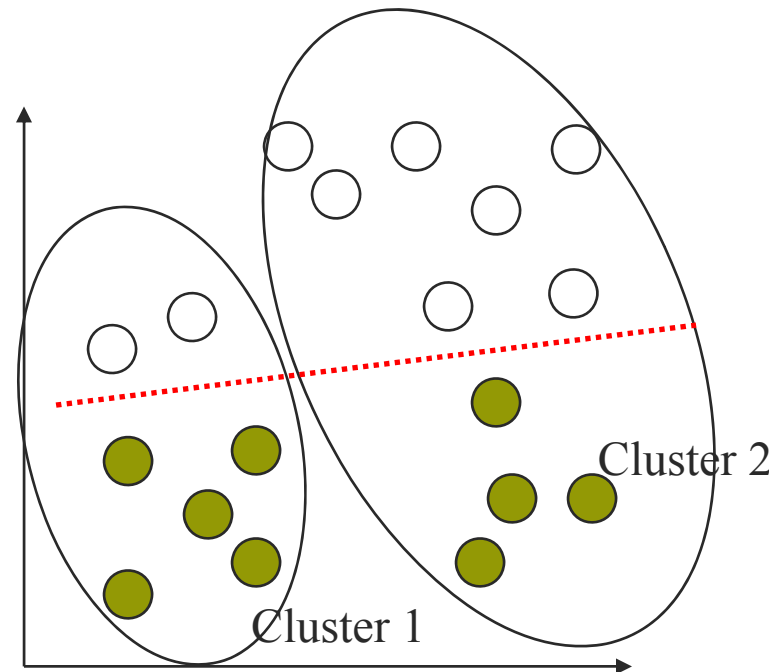
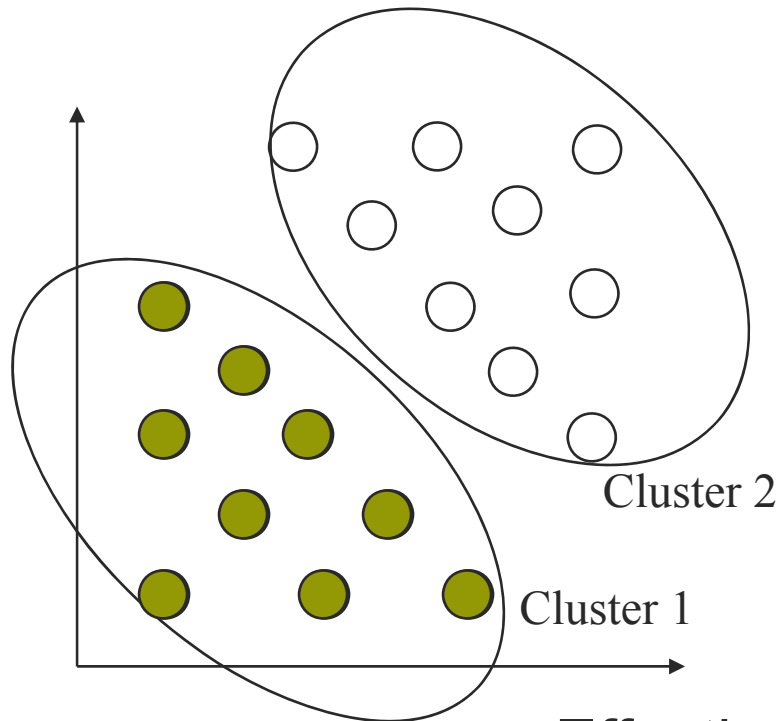


- do good job describing data (low error on training set)
- not too complex (feature selection)
- high cross-validation accuracy
- low validation error on test set (avoid overfitting)

Unsupervised and Supervised Machine Learning

- How do I recognize patterns without knowing the groups I want?
- It's a way to form **natural groupings**

- What separated the groups that I have known?
- Can I predict who will be in what group?



● Effective ○ No effect

Machine Learning Methods



- Supervised Methods
 - SDA, SRA
 - Bayesian Network, artificial neural networks (ANN),
 - Rules, decision trees, Random Forests
 - Support Vector Machines (SVM), Genetic Algorithms (GA)
 - ...
- Unsupervised Methods
 - Clustering,
 - PCA
 - Hidden Markov Model
 - Graphical models
 - ...