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

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Presentation Outline

• 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
M&S for PHC: Opportunities for Biomedical Informatics

• 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

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**Discovery**

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

**Preclinical Development**

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

**Early Clinical Development**

- **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

**Late Clinical Development**

- **Product LCM**

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- Modified from Orloff et al, 2009
Current M&S Gaps in Drug Development

Gap 1
- Biological Modeling
- Preclinical Development
- Gap b/w preclinical & clinical
- Translational ability in efficacy and safety

Gap 2
- Pharmacological Modeling
- Early Clinical Development
- Gap b/w learning & confirming*
  - Different clinical endpoints used
  - Lack of correlation between biomarkers and clinical endpoints (surrogacy problem)
  - Different study designs: population size, study length, etc.

Gap 3
- Statistical Modeling
- Late Clinical Development
- Product LCM
- Gap b/w pre & post marketing
  - Differences b/w clinical trials and real world populations and environments

* See FDA examples from FDA/PhRMA/DIA M&S workshop 2009
What’s Needed to Fill the Gaps?

Gap 1: Biological Modeling
- Discovery
- Preclinical Development
- Early Clinical Development
- Translational modeling I
  - Efficacy translation
  - Safety translation
  - PD/Biomarker modeling
  - Biomarker/efficacy modeling

Gap 2: Pharmacological Modeling
- Preclinical Development
- Early Clinical Development
- Late Clinical Development
- Biomarker modeling
  - Biomarker/safety modeling
  - Biomarker/efficacy modeling
  - Biomarker/Disease modeling
  - Pharmacovigilance

Gap 3: Statistical Modeling
- Late Clinical Development
- Product LCM
- Translational modeling II
  - CER
  - HTA
  - Pharmacovigilance

* 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

Discovery → Preclinical Development → Early Clinical Development → Late Clinical Development → Product LCM

Gap 1: Biological Modeling
Gap 2: Pharmacological Modeling
Gap 3: Statistical Modeling

Translational Informatics
- Efficacy translational modeling
- Safety translational modeling
- Translational information systems & tools

Clinical Research Informatics
- Biomarker/efficacy modeling
- Biomarker/safety modeling
- Clinical information systems & tools

Health Informatics
- Mining real-world data for CER, HTA, pharmacovigilance,
- Healthcare information systems & tools

Predictive Information Platform (PIP)
Case Study 1: Identify Treatment Responders

Treatment effect in overall patient population

Placebo  Treatment

Marker A ≤ xxx  Marker A > xxx

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

Placebo  Treatment

Blue: survivors  Red: non-survivors
Models to Predict Survival In Treatment Group

Random Forests models using common 46 variables across 4 time points
Models to Predict Survival In Placebo Group

Random Forests using common 46 variables across 4 time points
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)

- **Traditional design:**
  - Register
  - Randomize
  - Placebo → Treatment
  - Placebo → Treatment

- **Marker-based design:**
  - Register
  - Randomize
  - Placebo → Treatment
  - Placebo → Treatment
  - Test marker

- **Interim analysis**
  - Traditional analysis
  - Stratified analysis

- **Final 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 <= 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)
- Marker A
- Markers B+C
- Marker D

Important for predicting
- AT>3
- ALP>1.5
- Bilirubin>1.5
Predictive Models Using Baseline Information
Predictive Baseline Variables for Biochemical Hy’s Law Cases During The Trials
Biomarker-based Risk Stratification to Improve Patient Safety

• 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. with most effectiveness and least safety risk)?

Initial question

- Data mining
- Literature mining
- Model/Hypothesis
- Biological interpretation

Hypothesis & initial modeling

Candidate Biomarker(s)/model

Validated Biomarker(s)/model

Phase 2b Design and analysis

Phase 3 Design and analysis

Historical trials

Preclinical/Phases 1 & 2a

Outcome (a PHC product)

Learn*

Model application

Patient stratification

Model validation

*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
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- AZ Clinical Information Science Leadership
- AZ Discovery Information

- ASA Delaware Chapter

Thank you, and questions?
BACK UP SLIDES
(Informatics M&S Approaches & Methods)
Informatics Approach to M&S Using Machine Learning

Begin

Data Integration

Data preprocessing

Blind? (Y N)

Unsupervised learning
  e.g. Clustering

Supervised learning
  e.g. Bayesian classifier

Applications

End

- Multiple projects/studies
- Historical and current data
- Cross discovery and clinical
- Internal and external data
- Numerical and Text data
- Data from discrete platforms
- Safety and efficacy data
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?
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
  - ...