U.S. FOOD & DRUG ADMINISTRATION

Application of Quantitative Methods and Modeling to Generic Drug Development

Liang Zhao, PhD

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA

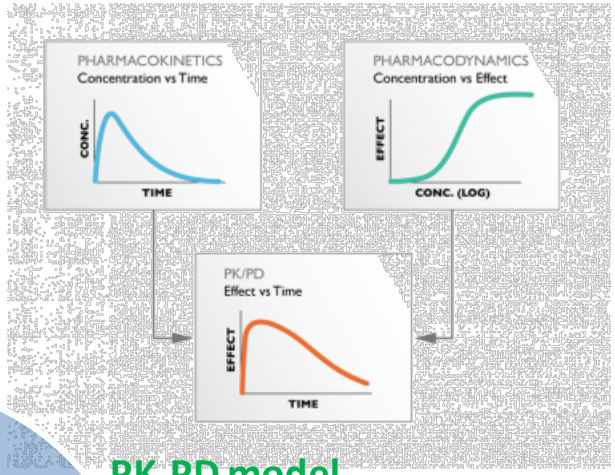
Modernize Drug Development Program to Make High Quality Generic Products Quickly Accessible

- Shorten drug development timeline
- Reduce costly but insensitive in vitro/in vivo studies
- Reduce chance of exposing human subjects to otherwise unnecessary studies
- Ensure timely availability of high quality and affordable generics for patients
- ***The above goals are especially important for locally acting, complex, and modified release products***

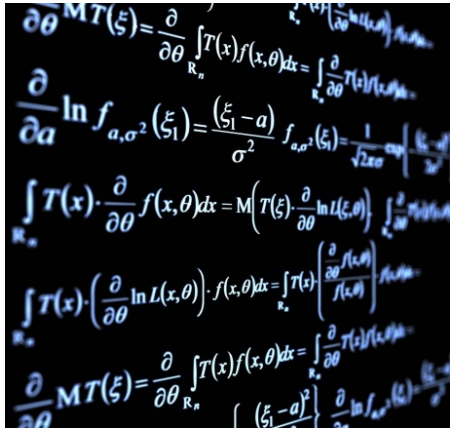
Pharmacometrics Tool Sets

Non-Oral Drug

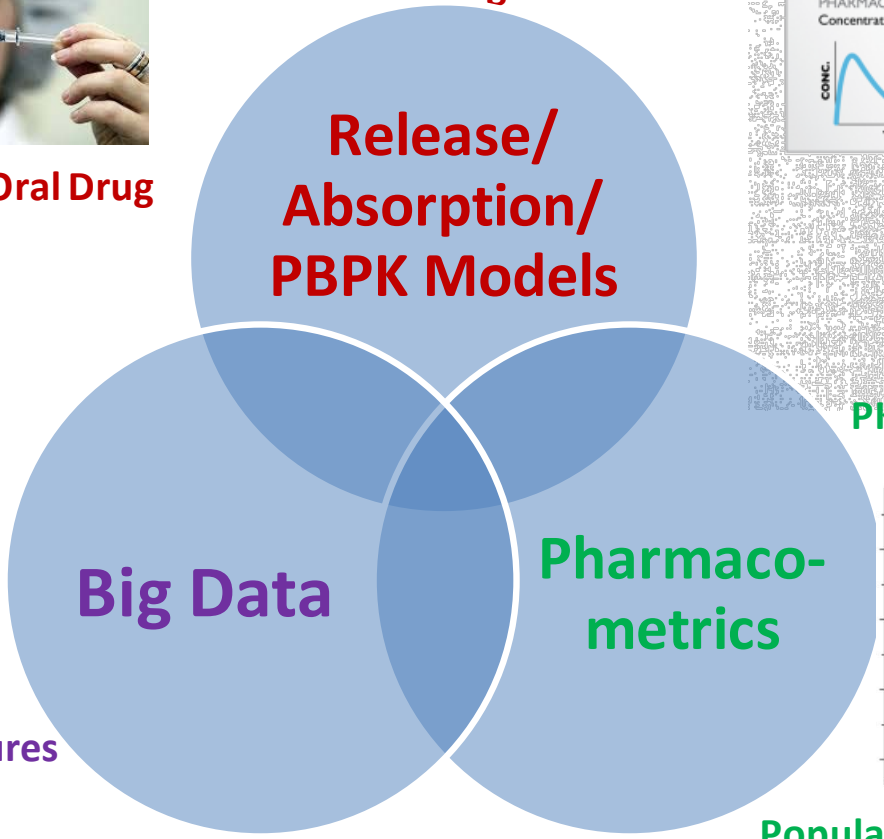
Oral Drug

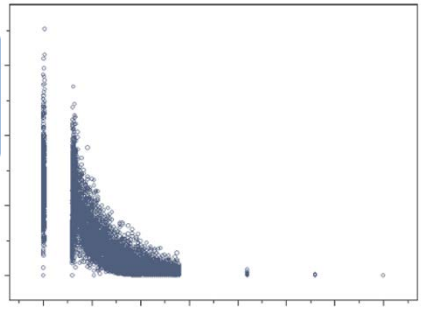


PK-PD model



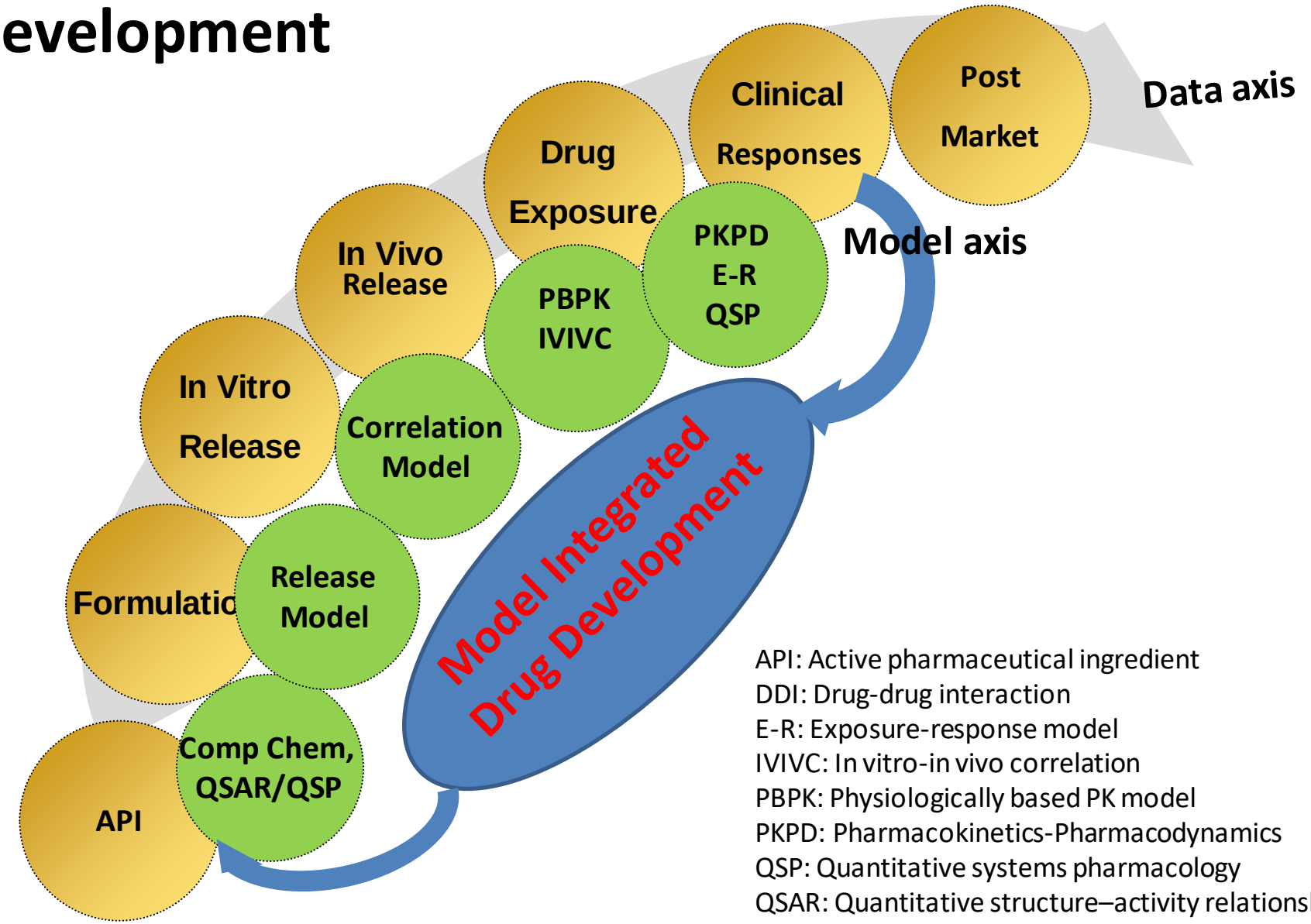
Machine learning toolsets
Analytics for complex mixtures
Systems pharmacology
Risk-based models
Business process models





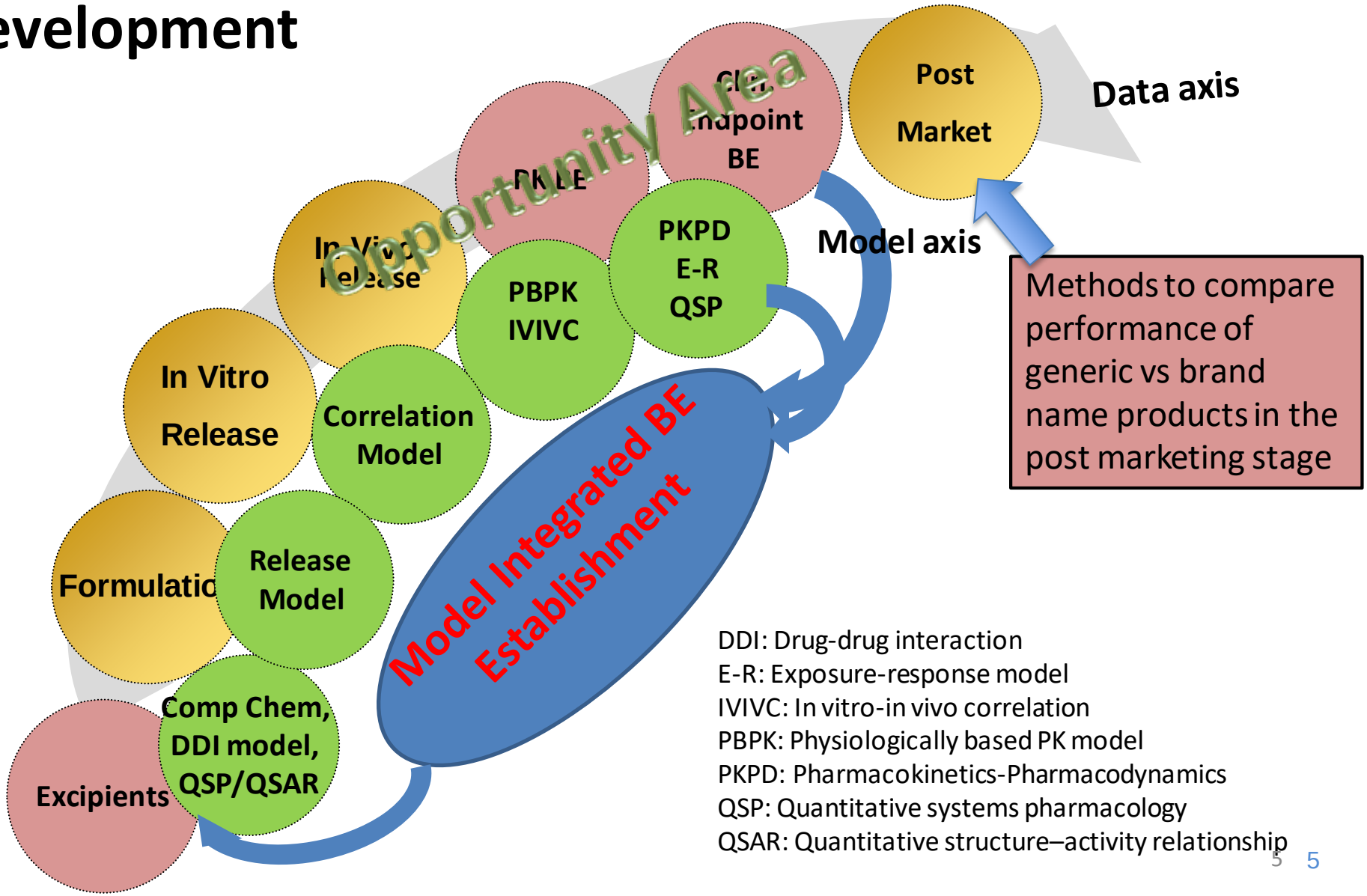
Population based model

An Integrated Modeling System for New Drug Development



API: Active pharmaceutical ingredient
DDI: Drug-drug interaction
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
PKPD: Pharmacokinetics-Pharmacodynamics
QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

An Integrated Modeling System for Generic Drug Development



DDI: Drug-drug interaction
E-R: Exposure-response model
IVIVC: In vitro-in vivo correlation
PBPK: Physiologically based PK model
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QSP: Quantitative systems pharmacology
QSAR: Quantitative structure–activity relationship

Relevant Research from Agencies

- GDUFA I supported the build out of the modeling and simulation tool chain for generic drugs

Public Research (1)

	Grants/Contracts	Institute	Start	End	Status
BE investigations	Wireless Sampling Pill to Measure in Vivo Drug Dissolution in GI Tract and Computational Model To Distinguish Meaningful Product Quality Differences and Ensure Bioequivalence (BE) in Patients	University of Michigan	9/2015	9/2018	Ongoing
	Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	University of Maryland	9/2015	9/2018	Ongoing
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2018	Ongoing
	Bioequivalence Study of Lamotrigine Extended Tablets in Healthy Subjects	Vince & Associates Clinical Research	9/2015	9/2017	Completed
	Bioequivalence and Clinical Implications of Generic Bupropion	Washington University	9/2013	8/2017	Completed
	Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus products in high risk Transplant Recipients	University of Cincinnati	9/2013	3/2017	Completed
	Evaluation of in vitro release methods for liposomal amphotericin B	ZoneOne Pharma	9/2014	9/2016	Completed
	Assessing Clinical Equivalence for Generic Drugs Approved By Innovative Methods	Brigham & Women's Hospital	9/2013	9/2015	Completed
	Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns	University of Michigan	9/2013	11/2015	Completed
	Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification	University of Michigan	9/2013	9/2015	Completed
New BE metrics	Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	University of Utah	9/2015	8/2018	Ongoing
	Pharmacokinetics study of opioid drug product following insufflation of milled drug products	Vince & Associates Clinical Research	9/2015	9/2017	Completed
	Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	Massachusetts General Hospital	9/2014	8/2017	Completed
	Pharmacometric modeling of immunosuppressant for evaluation of bioequivalence criteria	University of Utah	9/2014	2019	Ongoing
	BE and Characterization of Generic Drugs: Methylphenidate and Warfarin	Vince & Associates Clinical Research	9/2014	12/2016	Completed
Physiologically based models for systemic and locally acting products	Design, Development, Implementation and Validation of a Mechanistic Physiologically-based Pharmacokinetic (PBPK) Framework for the Prediction of the In Vivo Behavior of Supersaturating Drug Products	Simcyp, Ltd.	9/2016	8/2018	Ongoing
	Development and validation of dermal PBPK modeling platform toward virtual bioequivalence assessment considering population variability	Simcyp, Ltd	9/2014	8/2018	Ongoing
	Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	University of South Australia	9/2014	8/2018	Ongoing
	Enhancing the reliability, efficiency, and usability of Bayesian population PBPK modeling	Colorado State University	9/2016	8/2018	Ongoing
	A cluster-based assessment of drug delivery in asthmatic small airways	University of Iowa	9/2016	9/2018	Ongoing
	Novel Method to Evaluate Bioequivalence of Nanomedicines	Nanotechnology Characterization Lab	5/2016	4/2018	Ongoing
	Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action	University of Florida	9/2013	11/2017	Ongoing
	An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	CFD Corporation	9/2014	8/2017	Completed
	PBPK modeling and simulation for ocular dosage forms	Simulations Plus	9/2015	8/2017	Completed

Public Research (2)

	Grants/Contracts	Institute	Start	End	Status
Model based BE assessment	Evaluation and development of model-based bioequivalence analysis strategies	Uppsala University	6/2017	6/2019	Ongoing
	Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies	University of Paris	9/2016	9/2018	Ongoing
	Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products	University of Massachusetts	9/2015	8/2018	Ongoing
	Pharmacokinetic and pharmacodynamic (PK-PD) studies of cardiovascular drugs	University of Florida	9/2014	8/2018	Ongoing
	Computational drug delivery: leveraging predictive models to develop bioequivalent generic long-acting injections	Qrono, Inc.	9/2015	9/2018	Ongoing
	In Vivo Predictive Dissolution (IPD) to Advance Oral Product Bioequivalence (BE) Regulation	University of Michigan	9/2015	9/2018	Ongoing
	Prediction of In Vivo Performance for Oral Solid Dosage Forms	University of Michigan	9/2013	11/2017	Ongoing
	Correlation of Mesalamine Pharmacokinetics with Local Availability	University of Michigan	9/2013	9/2015	Completed
Post marketing evaluation	Generic drug substitution in special populations	Auburn University/ IMPAQ International	9/2016	8/2018	Ongoing
	Comparative Surveillance of Generic Drugs by Machine Learning	Marshfield Clinic, Inc.	9/2015	9/2018	Ongoing
	Novel approaches for confounding control in observational studies of generic drugs	Brigham & Women's Hospital	9/2015	8/2018	Ongoing
	Structural nested models for assessing the safety and effectiveness of generic drugs	Johns Hopkins University	9/2015	8/2018	Ongoing
	Base IDIQ for Postmarket Bioequivalence Study	Biopharma Services USA	5/2016	5/2018	Ongoing
	Pharmacometic modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment	University of Maryland	9/2014	2/2018	Ongoing
	A model and system based approach to efficacy and safety questions related to generic substitution	University of Florida	9/2014	8/2018	Ongoing
	Transplant outcomes using generic and brand name immunosuppressants: studying medications used by people who have received kidney and liver transplants	Arbor Research Collaborative for Health	9/2014	8/2017	Completed
	Post-market authorized generic evaluation (PAGE)	Auburn University	9/2014	8/2017	Completed
	Effect of Therapeutic Class on Generic Drug Substitutions	Johns Hopkins University	9/2014	4/2017	Completed
	Assessing the post-marketing safety of authorized generic drug products	Brigham & Women's Hospital	9/2014	6/2017	Completed
	Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns	University of Maryland	9/2013	10/2015	Completed
NTI classification	Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs	University of Maryland	9/2014	8/2018	Ongoing
	Clinical practice data to aid narrow therapeutic index drug classification	Duke University	9/2013	9/2016	Completed
	Therapeutic index evaluation for tacrolimus and levetiracetam	Johns Hopkins University	9/2013	3/2015	Completed

Modernize QMM Principles/Toolsets

- Time for model based BE assessment?
- Time for Bayesian approach and how?
- Machine learning as one of next generation toolset for strategic planning?
- Role of QMM in Pharmacoeconomics models and impact on understanding drug competition?
- What should be the role of QMM for post marketing evaluation? what can be the role of real world study?

Model Based BE

- A way to link to Bayesian inference in a systematic way
  - To leverage knowledge gained on RLD for an efficient generic review system
  - An efficient way to compare test and reference formulations
- Tool to conduct virtual BE studies
  - Have a formulation input that represents the difference between T and R (IVPD)
  - To extrapolate BE to specific populations or use scenarios
  - To assess alternative BE study designs
  - To determine sample size to control types I and II errors

Rob Lionberger: *You cannot accelerate access to complex generics without model-based BE*

Bayesian BE

- Use already existing data that persuaded the FDA for product approval
  - Distribution of bio drift?
- Employ other piece of prior information to link pharmacokinetics and clinical action
  - This give rise to the paradigm of the equivalence test where you do PK study with/without the reference?
- Bayesian adaptive approach for BE assessment
  - No penalty for multiple tests or protocol changes?
- Bayesian multivariate bioequivalence of Cmax and AUC
- Bayesian inference for regulatory review
  - Estimation vs hypothesis testing for approval and labeling

Carl Peck: *Bayesian approaches offer opportunities to streamline generic drug development and regulatory applications*

One of the Future Initiatives: Driving Decisions Based on Big Data

FDA

Big data

Social media

Commercial/Sales

NDA

Internet

Literature

Post Market

Data Mining/Selection

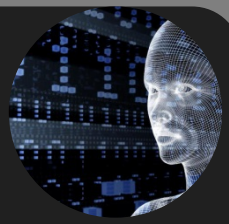
Proactively planned data collection

Secondary databases including Sentinel

Research/ Guidance Databases

Relational databases

Analytics including Artificial Intelligence



Research Optimization

(Case by Dr. Hu, Session III)

Generic Drug Competition

(Cases by Drs. Burnt and Conti, Session III)

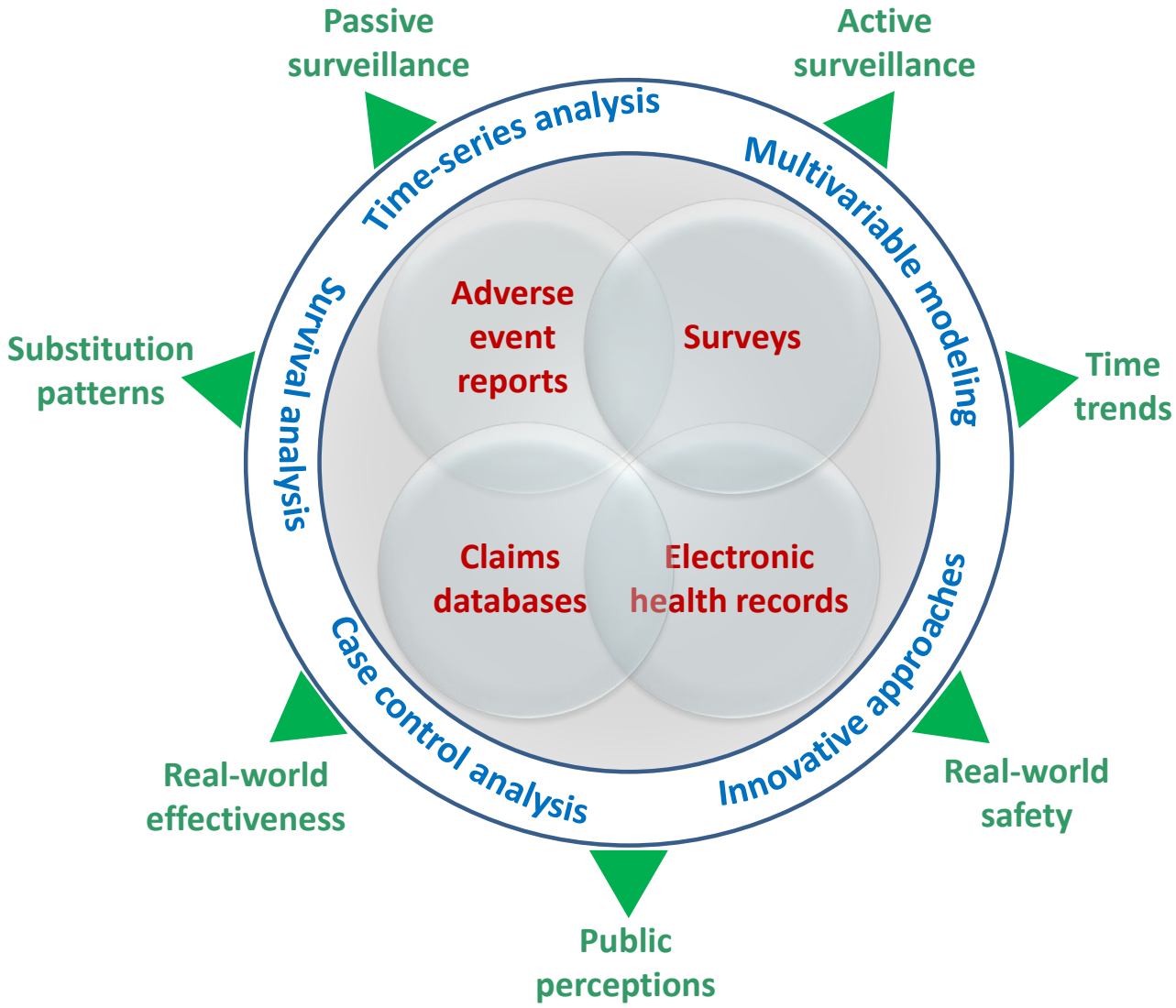
Generic Drug Substitution

(Cases by Speakers at Session IV)

Pharmacoeconomics in Understanding Drug Competition

- Pharmacoeconomics tools to analyze challenges and opportunities in maintaining competition in small generic drug markets
- Analyzing and learning from different use fee programs
- Root cause analysis and strategic solutions
  - Manufacturer concentration?
  - Dynamics between market entry and exit
- War game simulation to understand drug competition?

Quantitative Approaches in the Post-Marketing Evaluation of Generics



Take Home Messages

- QMM to modernize generic drug review especially for locally acting, complex, and/or modified release products
- Emerging tools like big data analysis can be used to aid product development, post-marketing evaluation, and workload management
- Global stakeholder engagement for QMM can greatly benefit the global generic enterprise as a whole

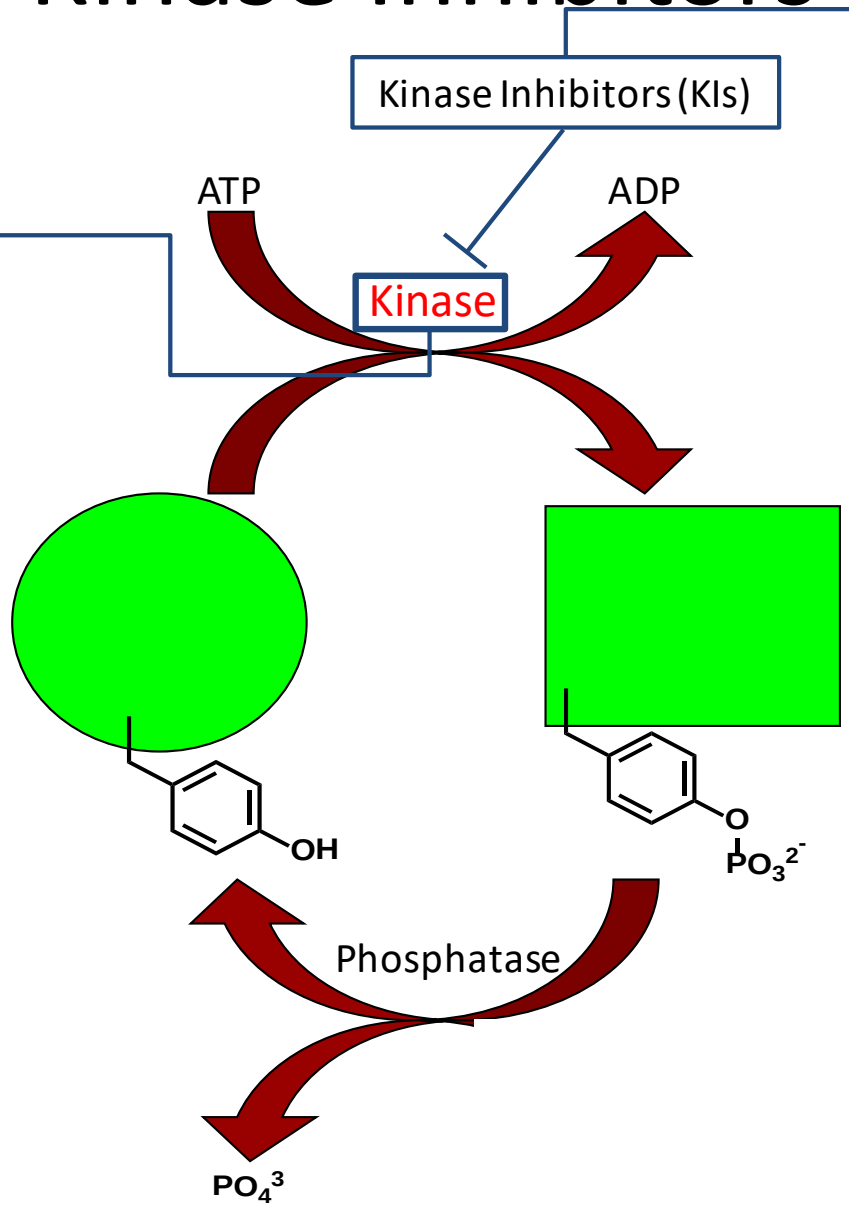
Case Example

Big Data to Understand Relationship Between the Biological Targets and Adverse Reactions for TKIs

- Tyrosine kinase inhibitors (TKIs): one of the most important classes of anti-cancer drugs
- Adverse reactions (ARs) by both on-target and off-target effects of TKIs
- Understanding the mechanisms of ARs are important for both drug development and post market evaluation of other agents
- Past research are mainly based on summarization of clinical practices or in vitro/in vivo experiments
- Meta-analysis intends to take advantage of both vast individual data from registrational Phase III studies and the advancement of cutting edge quantitative methodologies

Kinase Inhibitors

A kinase is a type of enzyme that transfers phosphate groups from high-energy donor molecules (such as ATP) to specific substrates, a process referred to as phosphorylation.



Kinase includes many oncogenes, so phosphorylation by kinases is a necessary step in some cancers.

Kinase inhibitors are used as drugs to treat these cancers by inhibiting kinases.

Adverse Reactions of KIs

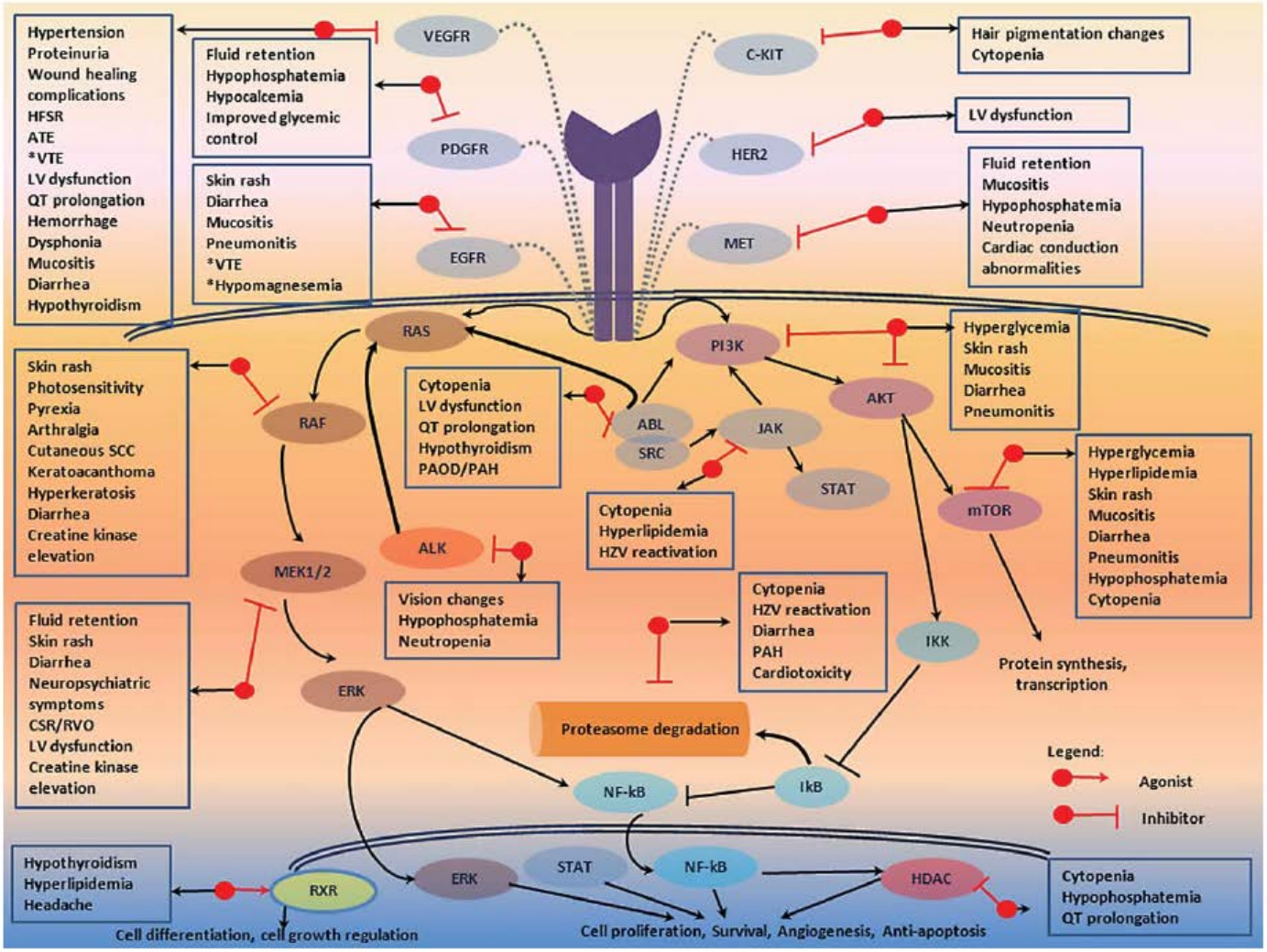


FIGURE 1. Toxicities Associated With Signal Transduction Inhibitors.*Associated predominantly with monoclonal antibodies. ATE indicates arterial thromboembolism; CSR, central serous retinopathy; HZV, herpes zoster virus; LV, left ventricular; PAH, pulmonary arterial hypertension; PAOD, progressive arterial occlusive disease; RVO, retinal vein occlusion; SCC, squamous cell cancer; VTE, venous thromboembolism.

Grace K. Dy and Alex A. Adjei, CA Cancer J Clin 2013; 63: 249–279

Results

Data from 17 Kinase Inhibitors

	Kinase Inhibitors (KIs)
1	Axitinib (Inlyta)
2	Pazopanib (Votrient)
3	Sorafenib (Nexavar)
4	Vandetanib (Caprelsa)
5	Crizotinib (Xalkori)
6	Erlotinib (Tarceva)
7	Gefitinib (Iressa)
8	Lapatinib (Tykerb)
9	Bosutinib (Bosulif)
10	Dasatinib (Sprycel)
11	Imatinib (Gleevec)
12	Nilotinib (Tasigna)
13	Sunitinib (Sutent)
14	Cabozantinib (Cometriq)
15	Ponatinib (Iclusig)
16	Regorafenib (Stivarga)
17	Afatinib (Gilotrif)

17 KIs

1. Incidence of adverse reactions (ARs)
2. Inhibitory percent (%) data against 283 kinases

Reference for inhibitory percent data:
Uitdehaag JC et al. PLoS One. 2014 Mar; 9(3): e92146

13 KIs

1. Pharmacokinetic (PK) data
2. Dissociation constant (K_d) data against 257 kinases

Reference for K_d data:
Davis MI et al. Nat Biotechnol. 2011 Oct; 29(11): 1046-51
Karaman MW et al. Nat Biotechnol. 2008 Jan; 26(1): 127-32

Aim and Methods Outline

Aim: to assess the association between kinase inhibition and adverse reactions

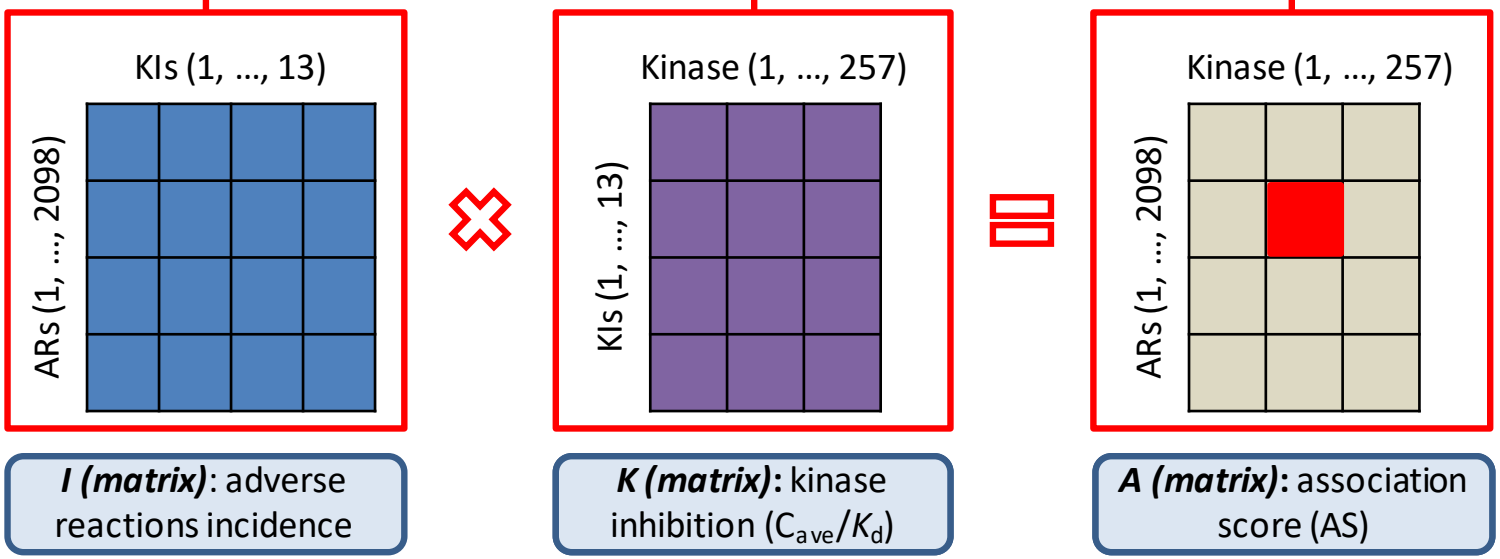
A (drug exposure, PK)	B (*in vitro* kinase inhibitory activity)	C (incidence of adverse reactions)
1. Collect pharmacokinetic (PK) data of current FDA-approved KIs 2. Conduct population PK modeling to calculate C_{ave} (average plasma concentration) at steady state	1. Literature search to collect constant dissociation (K_d) data 2. Literature search to collect inhibitory percent (%) data	1. Collect safety data of current FDA-approved KIs 2. Standardize ontology of adverse reactions (ARs) 3. Calculate incidence of ARs

D (association score)	An association score matrix of 2098 ARs (preferred terms) and 257 kinases

Methods

Association Score Matrix

$$\textbf{Association score: } I \times K = \sum(i_{zx}) \times \left(\frac{C_{ave}}{k_{xy}}\right) = A$$



I (matrix): adverse reactions incidence

K (matrix): kinase inhibition (C_{ave}/K_d)

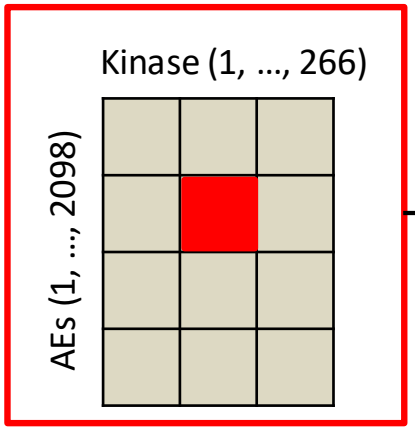
A (matrix): association score (AS)

Limitation	A false positive may be included when a high association score was obtained with high AR incidence but moderate kinase inhibition.

Solution	After identifying AR associated KIs, only keep the preliminary identified kinases (by association score) which can be inhibited with > 95% activity by any identified KIs.

To identify kinases associated with hypertension

An Example



Preliminary identified kinases leading to hypertension: VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR α, PDGFR β, TTK, … (27 kinases in total)

Identify hypertension associated KIs: pazopanib, axitinib, regorafenib, sorafenib, vandetanib, cabozantinib (6 KIs in total)

Only keep identified kinases which can be inhibited with > 95% activity by any identified 6 KIs.

Kinase	# Inhibition
VEGFR2	6
FLT1	6
FLT4	6
PDGFRA	6
PDGFRB	5
FGFR2	5
KIT	4
FGFR3	3
FGFR1	2
RAF1	2
AURKC	1

Results

4279 pairs of associations involving 534 ARs (preferred terms) and 140 kinases.

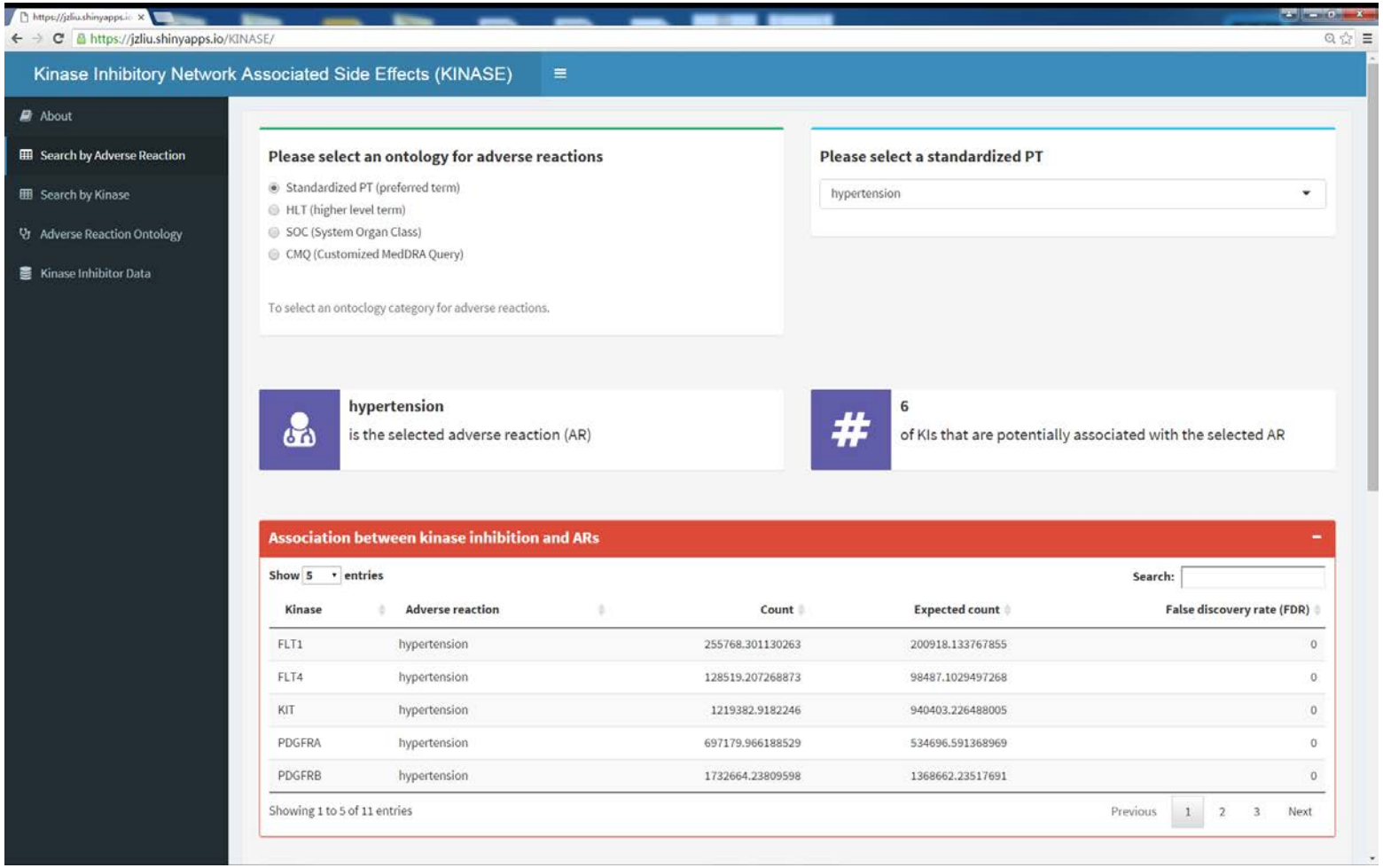
Well-established pairs of kinase inhibition and ARs were confirmed:

hypertension – VEGFR2;
acneiform rash – EGFR/HER4;
conjunctivitis – EGFR;
fluid retention – ABL;
hepatotoxicity – MET;
diarrhea – EGFR;
pulmonary hypertension – ABL;
QT prolongation – VEGFR;
proteinuria – VEGFR.

Visualize the results using a web app:
https://jzliu.shinyapps.io/KINASE

Results

KINASE: A Web App to Query the Results



YouTube by Dr. Liu: https://www.youtube.com/watch?v=O1kqbWFqhwc&t

What if We Apply Machine Learning Technique to the Same Dataset?

- A science evolves from the study of pattern recognition and computational theory in Artificial Intelligence
- Strong predictive performances through the use of computer
- It allows researchers, data scientists, and engineers to make reliable and repeatable decisions

Machine Learning for Correlation Identification

C_{AVG}/Kd

Subj#	Age	Gender	PT	AE_onset	K_1	K_2	…	K_p
1	53	M	A	12	$X1_1$	$X1_2$	…	$X1_p$
1	53	M	A	26	$X1_1$	$X1_2$	…	$X1_p$
1	53	M	B	6	$X1_1$	$X1_2$	…	$X1_p$
…	…	…	…	…	…	…	…	…
1	53	M	Z	130	$X1_1$	$X1_2$	…	$X1_p$
2	48	F	B	3	$X2_1$	$X2_2$	…	$X2_p$
2	48	F	B	78	$X2_1$	$X2_2$	…	$X2_p$
…	…	…	…	…	…	…	…	…
N	59	F	Y	58	XN_1	XN_2	…	XN_p

The time factor is taken into account!

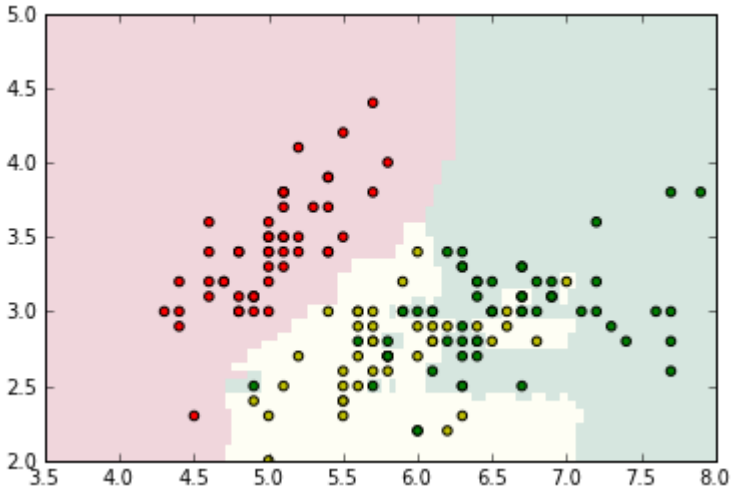
Traditional methods

- Regression-based
  - Proportional hazards model
  - Accelerated failure time model
  - *Cox model* (semi-parametric)

- Issues
  - Distribution assumption
  - Model is difficult to converge due to large number of predictive variables
  - Linear relationships

Machine learning

- Machine-learning-based
  - Artificial neural network
  - *Random forest*
  - Support vector machine

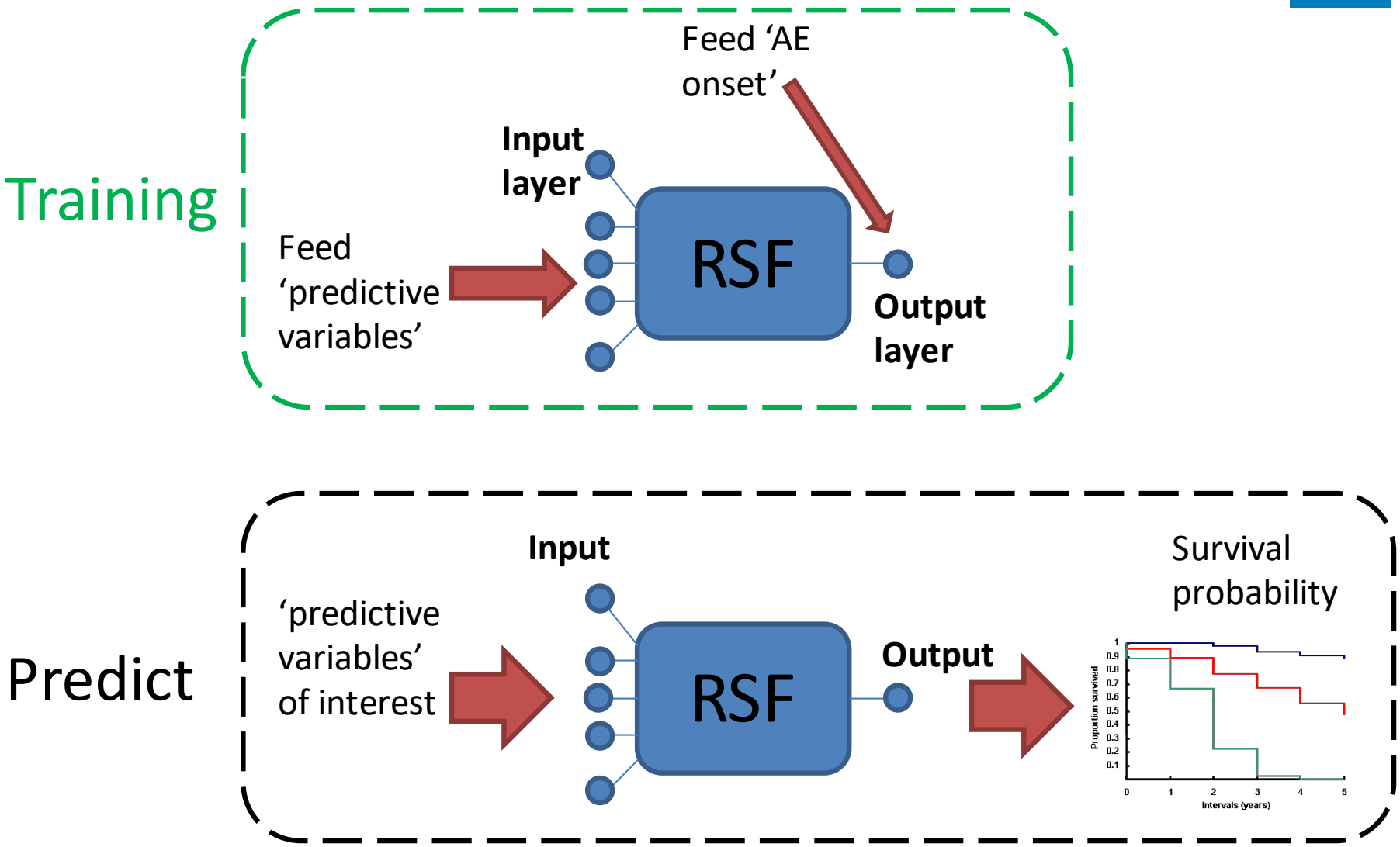


- Advantages
  - Less distribution assumption
  - Capable for large-feature problem
  - Nonlinear relationship
  - Able to describe the variable-variable interaction

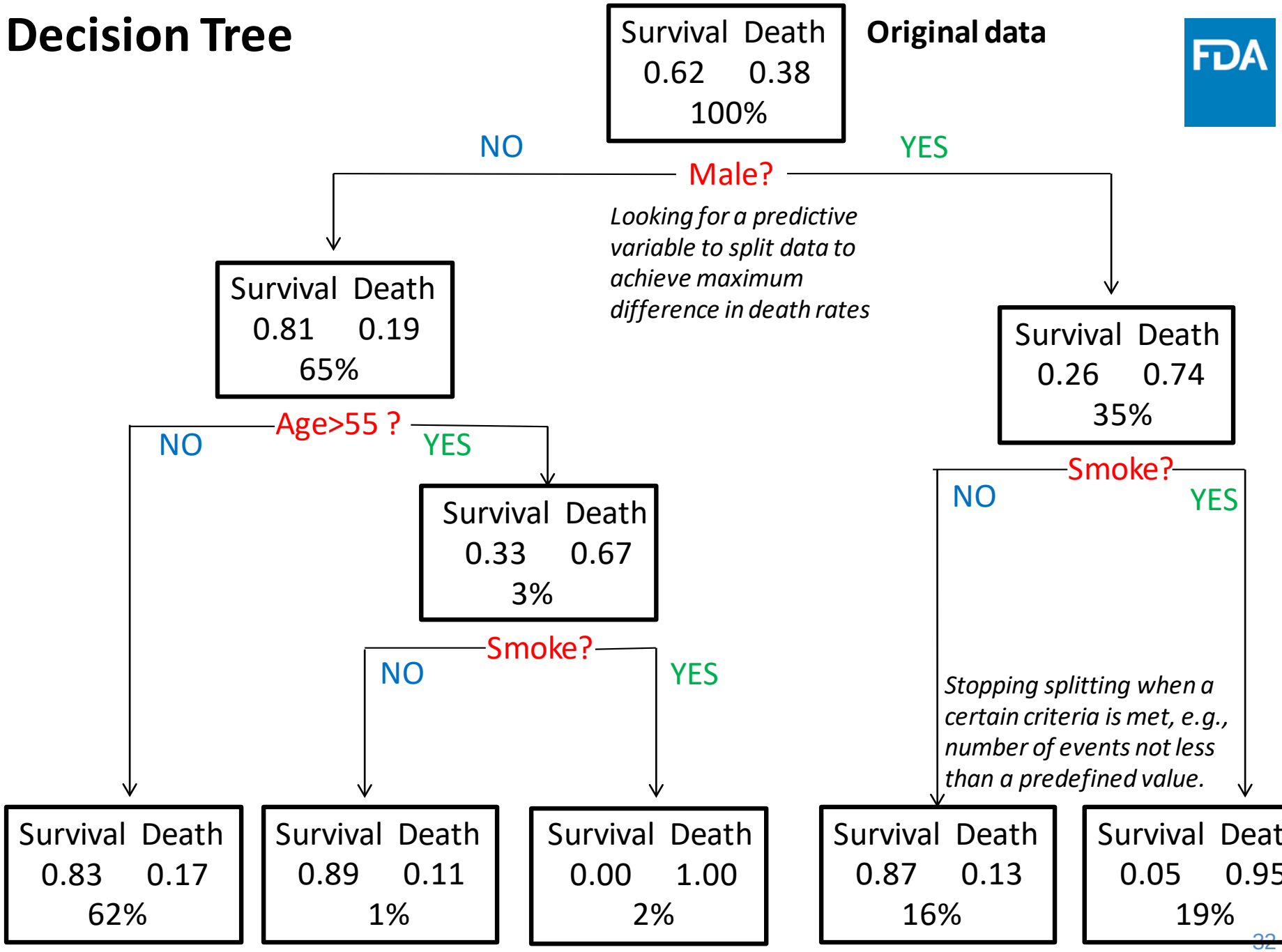
Random survival forest

- Artificial neural network
  - Over-learning
  - Inconvenient to identify importance of variable
- Support vector machine
  - Inconvenient to identify importance of variable
- ***Random survival forest***
  - Bagging (or boosting) technique to prevent from over learning
  - Established method to identify importance of variable
    - Variable importance
    - Minimal depth
    - Variable hunting

Random Survival Forest



Decision Tree



How to grow a decision tree

- How to split
  - Searching a predictive variable to maximize event (e.g., death rates) difference between daughter nodes
- How to stop
  - A certain criteria is met, e.g., number of events no less than a certain value

Why random forest?

- Decision tree is a '**greedy**' algorithm.
  - For example, given coins with values of 1, 15, 25 cents, how to get 30 cents using less coins.
  - Greedy: 30=25+1+1+1+1+1
  - Optimal: 30=15+15

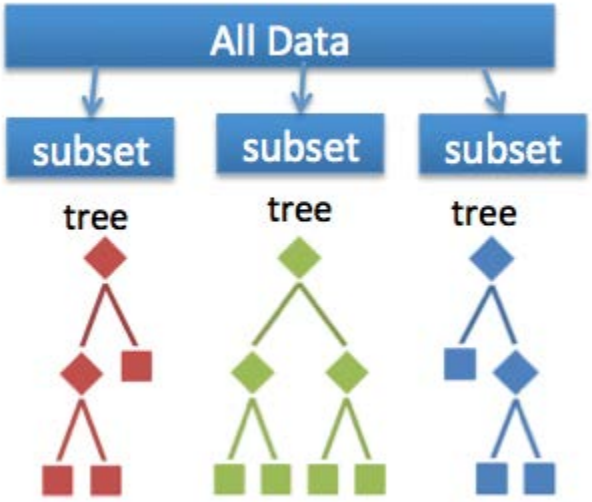
- Decision tree is prone to over-learning or over-fitting.

- Random forest consists of many decision trees, each of which grows by a part of data and predictive variables.

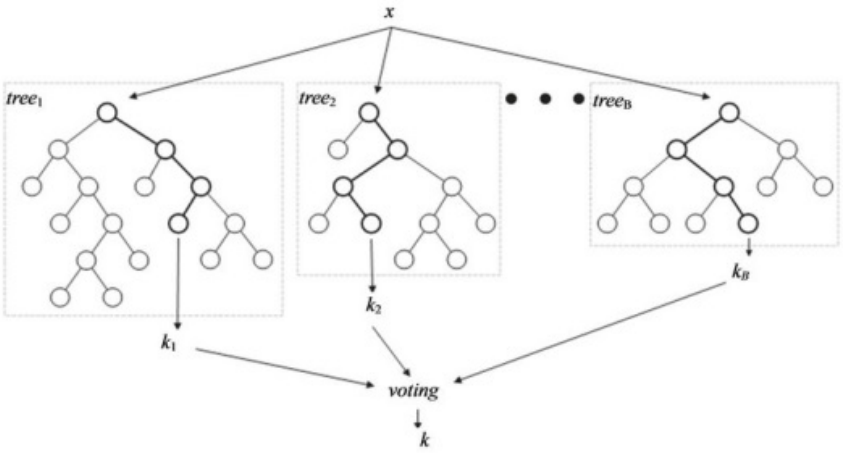
Random survival forest

- Decision survival tree shares the same pitfall with the decision tree, as a 'greedy' algorithm.
- Random survival forest was developed to improve the decision survival tree.

Training



Prediction

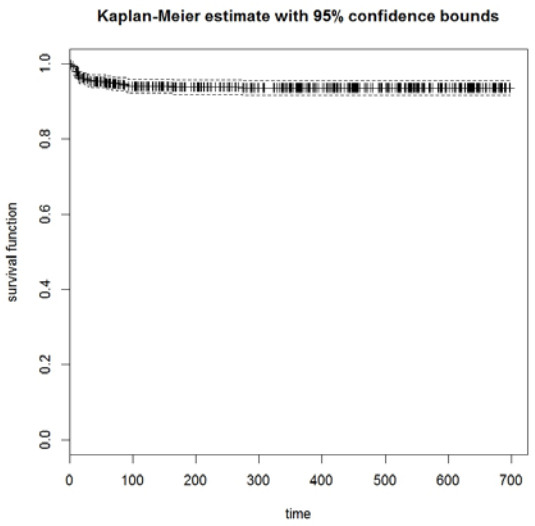


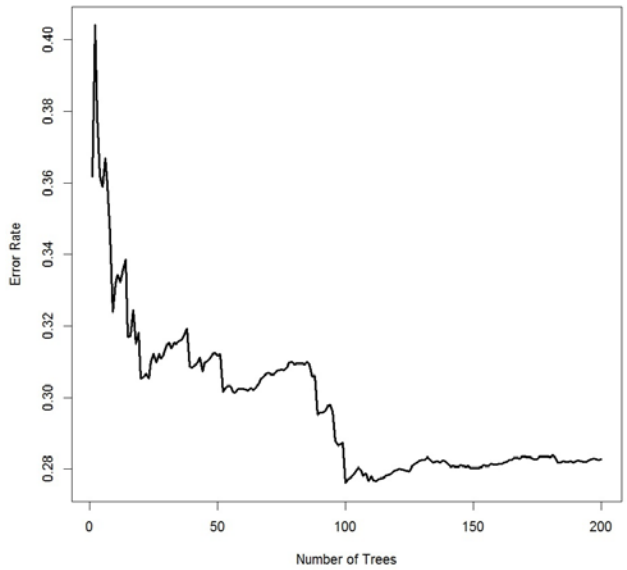
https://mapr.com/blog/predicting-loan-credit-risk-using-apache-spark-machine-learning-random-forests/
http://www.hallwaymathlete.com/2016/05/introduction-to-machine-learning-with.html

Machine Learning Results

Consistent with DPA and BCPNN finding in general

Dermatitis acneiform as an example





	Importance	Relative Imp
EGFR.G719S.	0.0086	1.0000
EGFR.L747.T751del.Sins.	0.0073	0.8550
EGFR.E746.A750del.	0.0072	0.8395
EGFR	0.0053	0.6214
EGFR.L747.E749del..A750P.	0.0051	0.6012
EGFR.L747.S752del..P753S.	0.0050	0.5866
JAK2.JH1domain.catalytic.	0.0050	0.5817
EGFR.T790M.	0.0048	0.5642
EGFR.G719C.	0.0039	0.4608
EGFR.L858R.T790M.	0.0036	0.4156
MKNK1	0.0033	0.3856
JAK3.JH1domain.catalytic.	0.0032	0.3746
ADCK4	0.0031	0.3653
ERBB2	0.0030	0.3526
DRAK1	0.0028	0.3302
TYK2.JH1domain.catalytic.	0.0025	0.2972
SYK	0.0025	0.2941
JNK2	0.0025	0.2903
EGFR.L858R.	0.0024	0.2856

Work in Progress and manuscript is in draft

Summary for the Case

- Meta-analyses are based on Phase III data from 17 TKIs
- Analysis results for associations between kinases inhibitions and adverse reactions are consistent with research finding
- Caveat should be given before experimentally verifying other associations or claiming a causal relationship
- Novel methods including machine learning techniques can be used for analysis

Thank you!

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DQMM: One of the Two Divisions (DTP+DQMM) under ORS/OGD

DQMM
Liang Zhao
Director
Myong Jin Kim
Deputy Director

OGD: Office of Generic Drugs
ORS: Office of Research and Standards
DQMM: Division of Quantitative Methods and Modeling;
DTP: Division of Therapeutic Performance
CE: clinical endpoint;
ADF: abuse deterrent formulations;
IVIVC(R): in vitro/in vivo correlation (relationship);

Team 1: Quantitative Clinical Pharmacology

Lanyan (Lucy) Fang
Team Leader

- Research/Grants-Pharmacometrics
- Review/Citizen Petition Consults
- Model based BE assessment
- Narrow Therapeutic Index drug classification
- Risk-benefit assessment for BE standard
- Product Specific Guidance development
- BE study design (PK + BE)
- Clinical endpoint qualification
- BE assessment based on CE
- PreANDA interactions
- Model based BE assessment
- Long acting injectables
- Metaanalysis (Eg, opioid ADFs)

Team 2: Locally Acting Products

Andrew Babiskin
Team Leader (Atg)

- Research/grants-PBPK toolsets
- PreANDA interactions
- Research/Guidance co-development
  - Ophthalmic
  - Inhalation/intranasal
  - GI locally acting/in vitro testing
  - Transdermal
  - Computational fluid dynamics for PBPK model
- Review/Citizen Petition Consults
- Product specific guidance co-development for locally acting/complex products
- IVIVC/IVIVR

Team 3: Modified Release Products

Sue Chih Lee
Team Leader

- Product specific guidance development and revision for MR products
- In vitro BE guidance and consults
- New BE method development
- Controlled correspondence and citizen petition review for MR products
- Research (formulation analysis) for MR products
- Quantitative analysis-based guidance development prioritization

Team 4: Health Outcomes and Data Analytics

Liang Zhao (atg)

- Research/grants: post market tool development; sentinel engagement
- Post market analysis to support MR team, OGD safety consults, guidance development needs, and NTI drug classification
- Big data analysis to support product specific guidance development and prioritization
- Data base construction and management