FROM MOLECULE TO PATIENT

SATURDAY, MARCH 16, 2019

12:30 PM – 2:30 PM

NOVEL FORMAT

MID3: Mission Impossible or Model-Informed, Drug Discovery and Development? Point / Counterpoint Discussions on Key Challenges

D D R U

Pharmacometrics & Pharmacokinetics, Regulatory Science

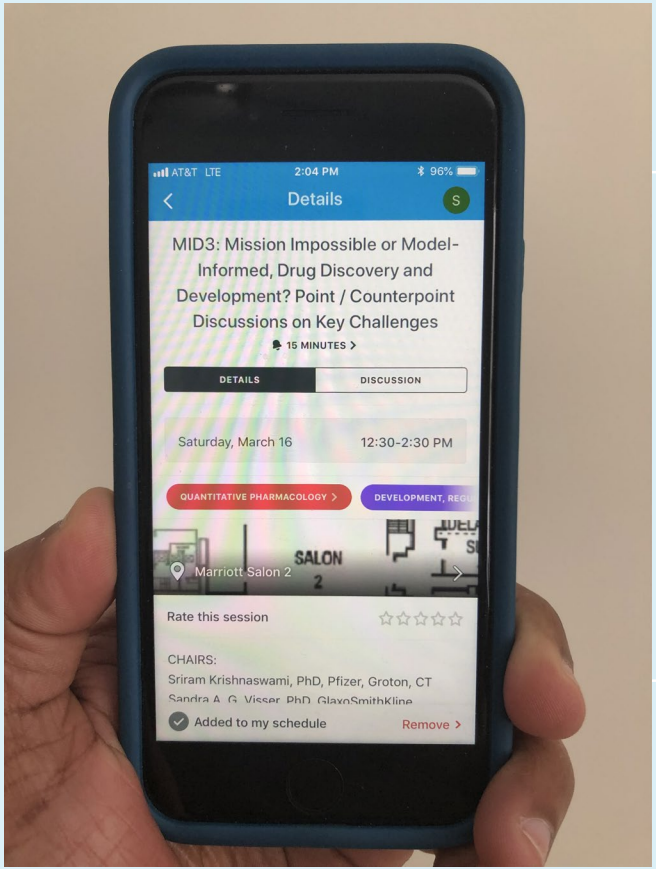
Chair: *Sriram Krishnaswami, PhD*
Pfizer, Groton, CT
Chair: *Sandra A.G. Visser, PhD*
GlaxoSmithKline, Collegeville, PA

Thank you for the Feedback !

(Pre-meeting survey)

FROM MOLECULE TO PATIENT

FROM MOLECULE TO PATIENT



How energized are you feeling this afternoon?

(1 = no energy, 5 = super energized)

Point: Counterpoint Topics

Theme	Point	Counter-point
1. State of the art	MIDD/MID3 has been a smashing success	No. MIDD/MID3 has fallen short of expectations
2. Primary Limitations to success	Model less, communicate more	Talk less, model more
3. All models are wrong but some are useful	Wrong models are dangerous	Wrong models are useful
4. Transforming Clinical Trial Design Decision making	All clinical trials should be informed by simulations	Simulations are unnecessary and time consuming in most cases
5. Disruptive Innovations necessary for the future	Industrialize current models & methodologies	Future lies in machine learning and systems models
6. The ideal MID3 scientist for the future	Best pharmacometricians have training in mathematics and statistics	Best pharmacometricians have training in medicine and pharmacology
7. Organizational Opportunities in R&D	Pharmacometricians have a strategic role and hence need to be part of the core development team	Pharmacometricians provide technical solutions but are not part of drug development teams

1. State of the Art

MIDD/MID3 has been a smashing success
(Joga Gobburu)
Vs.
No. MIDD/MID3 has fallen short of expectations
(Oscar Della Pasqua)

Point!

LEARN & APPLY

MIDD is a smashing success

Joga Gobburu PhD FCP MBA

Professor

School of Pharmacy

University of Maryland

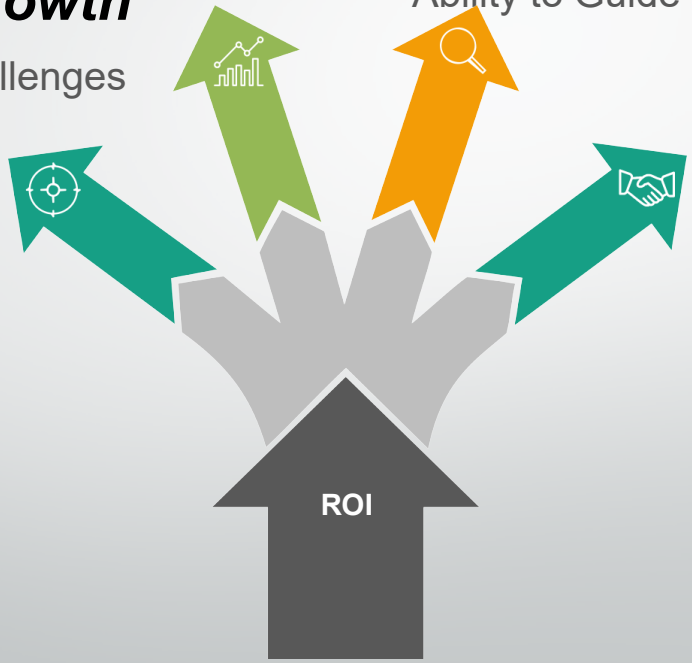
MIDD has been a Smashing Success !!!

Professional Growth

Progress & Take-up More Challenges

Public Health

Ability to Guide Decisions Not Possible Before



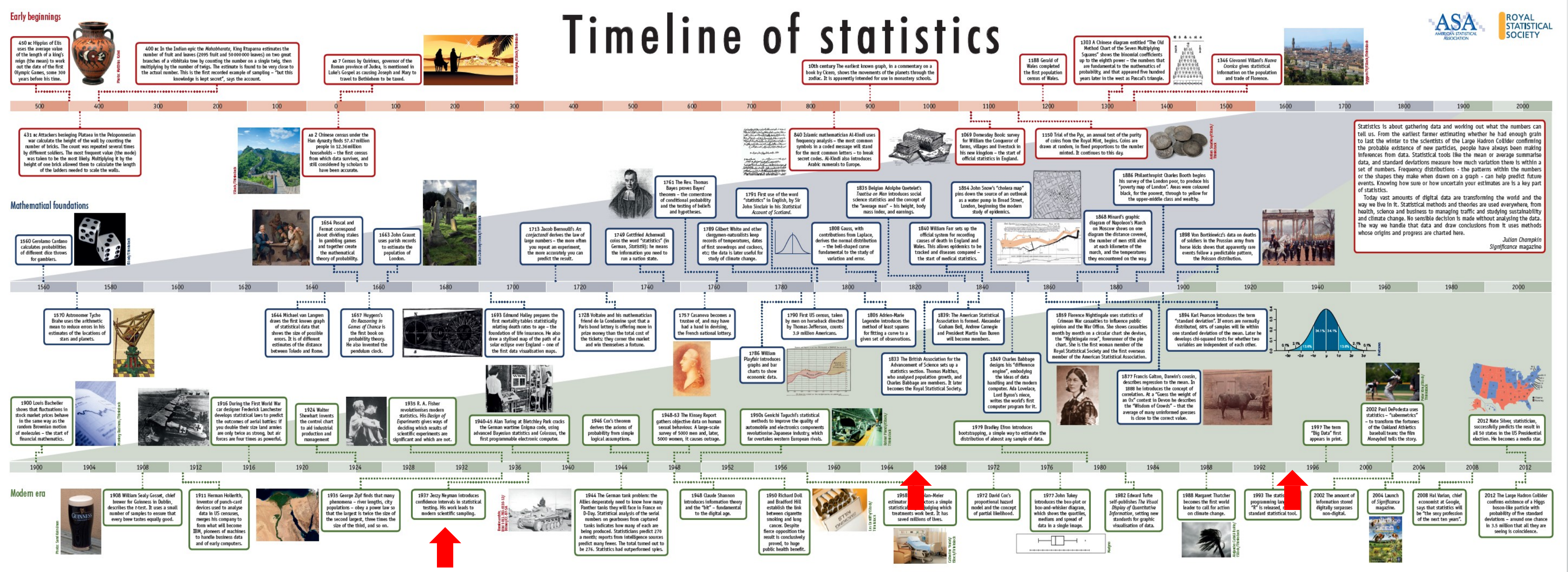
Power

Influence Key Decisions

Economics

Sustained Investment
At-Par Remuneration

LEARN & APPLY


Timeline of statistics
ASA
AMERICAN STATISTICAL ASSOCIATION
ROYAL STATISTICAL SOCIETY
Early beginnings
450 BC Hippias of Elis uses the average value of the length of a king's reign (the mean) to work out the date of the first Olympic Games, some 300 years before his time.
400 BC In the Indian epic the Mahabharata, King Rtuparna estimates the number of fruit and leaves (2095 fruit and 50 000 000 leaves) on two great branches of a vibhitaka tree by counting the number on a single twig, then multiplying by the number of twigs. The estimate is found to be very close to the actual number. This is the first recorded example of sampling – "but this knowledge is kept secret", says the account.
AD 7 Census by Quirinus, governor of the Roman province of Judea, is mentioned in Luke's Gospel as causing Joseph and Mary to travel to Bethlehem to be taxed.
10th century The earliest known graph, in a commentary on a book by Cicero, shows the movements of the planets through the zodiac. It is apparently intended for use in monastery schools.
1188 Gerald of Wales completed the first population census of Wales.
1303 A Chinese diagram entitled "The Old Method Chart of the Seven Multiplying Squares" shows the binomial coefficients up to the eighth power – the numbers that are fundamental to the mathematics of probability, and that appeared five hundred years later in the west as Pascal's triangle.
1346 Giovanni Villani's Nuova Cronica gives statistical information on the population and trade of Florence.
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431 BC Attackers besieging Plataea in the Peloponnesian war calculate the height of the wall by counting the number of bricks. The count was repeated several times by different soldiers. The most frequent value (the mode) was taken to be the most likely. Multiplying it by the height of one brick allowed them to calculate the length of the ladders needed to scale the walls.
AD 2 Chinese census under the Han dynasty finds 57.67 million people in 12.36 million households – the first census from which data survives, and still considered by scholars to have been accurate.
840 Islamic mathematician Al-Kindi uses frequency analysis – the most common symbols in a coded message will stand for the most common letters – to break secret codes. Al-Kindi also introduces Arabic numerals to Europe.
1069 Domesday Book: survey for William the Conqueror of farms, villages and livestock in his new kingdom – the start of official statistics in England.
1150 Trial of the Pyx, an annual test of the purity of coins from the Royal Mint, begins. Coins are drawn at random, in fixed proportions to the number minted. It continues to this day.
Statistics is about gathering data and working out what the numbers can tell us. From the earliest farmer estimating whether he had enough grain to last the winter to the scientists of the Large Hadron Collider confirming the probable existence of new particles, people have always been making inferences from data. Statistical tools like the mean or average summarise data, and standard deviations measure how much variation there is within a set of numbers. Frequency distributions - the patterns within the numbers or the shapes they make when drawn on a graph - can help predict future events. Knowing how sure or how uncertain your estimates are is a key part of statistics.
Today vast amounts of digital data are transforming the world and the way we live in it. Statistical methods and theories are used everywhere, from health, science and business to managing traffic and studying sustainability and climate change. No sensible decision is made without analysing the data. The way we handle that data and draw conclusions from it uses methods whose origins and progress are charted here.
Julian Champkin
Significance magazine
Mathematical foundations
1560 Gerolamo Cardano calculates probabilities of different dice throws for gamblers.
1654 Pascal and Fermat correspond about dividing stakes in gambling games and together create the mathematical theory of probability.
1663 John Graunt uses parish records to estimate the population of London.
1713 Jacob Bernoulli's Ars conjectandi derives the law of large numbers – the more often you repeat an experiment, the more accurately you can predict the result.
1749 Gottfried Achenwall coins the word "statistics" (in German, Statistik); he means the information you need to run a nation state.
1761 The Rev. Thomas Bayes proves Bayes' theorem – the cornerstone of conditional probability and the testing of beliefs and hypotheses.
1789 Gilbert White and other clergymen-naturalists keep records of temperatures, dates of first snowdrops and cuckoos, etc; the data is later useful for study of climate change.
1791 First use of the word "statistics" in English, by Sir John Sinclair in his Statistical Account of Scotland.
1808 Gauss, with contributions from Laplace, derives the normal distribution – the bell-shaped curve fundamental to the study of variation and error.
1835 Belgian Adolphe Quetelet's Treatise on Man introduces social science statistics and the concept of the "average man" – his height, body mass index, and earnings.
1840 William Farr sets up the official system for recording causes of death in England and Wales. This allows epidemics to be tracked and diseases compared – the start of medical statistics.
1854 John Snow's "cholera map" pins down the source of an outbreak as a water pump in Broad Street, London, beginning the modern study of epidemics.
1868 Minard's graphic diagram of Napoleon's March on Moscow shows on one diagram the distance covered, the number of men still alive at each kilometre of the march, and the temperatures they encountered on the way.
1886 Philanthropist Charles Booth begins his survey of the London poor, to produce his "poverty map of London". Areas were coloured black, for the poorest, through to yellow for the upper-middle class and wealthy.
1898 Von Bortkiewicz's data on deaths of soldiers in the Prussian army from horse kicks shows that apparently rare events follow a predictable pattern, the Poisson distribution.
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1570 Astronomer Tycho Brahe uses the arithmetic mean to reduce errors in his estimates of the locations of stars and planets.
1644 Michael van Langren draws the first known graph of statistical data that shows the size of possible errors. It is of different estimates of the distance between Toledo and Rome.
1657 Huygens's On Reasoning in Games of Chance is the first book on probability theory. He also invented the pendulum clock.
1693 Edmund Halley prepares the first mortality tables statistically relating death rates to age – the foundation of life insurance. He also drew a stylised map of the path of a solar eclipse over England – one of the first data visualisation maps.
1728 Voltaire and his mathematician friend de la Condamine spot that a Paris bond lottery is offering more in prize money than the total cost of the tickets; they corner the market and win themselves a fortune.
1757 Casanova becomes a trustee of, and may have had a hand in devising, the French national lottery.
1786 William Playfair introduces graphs and bar charts to show economic data.
1790 First US census, taken by men on horseback directed by Thomas Jefferson, counts 3.9 million Americans.
1805 Adrien-Marie Legendre introduces the method of least squares for fitting a curve to a given set of observations.
1833 The British Association for the Advancement of Science sets up a statistics section. Thomas Malthus, who analysed population growth, and Charles Babbage are members. It later becomes the Royal Statistical Society.
1839: The American Statistical Association is formed. Alexander Graham Bell, Andrew Carnegie and President Martin Van Buren will become members.
1849 Charles Babbage designs his "difference engine", embodying the ideas of data handling and the modern computer. Ada Lovelace, Lord Byron's niece, writes the world's first computer program for it.
1859 Florence Nightingale uses statistics of Crimean War casualties to influence public opinion and the War Office. She shows casualties month by month on a circular chart she devises, the "Nightingale rose", forerunner of the pie chart. She is the first woman member of the Royal Statistical Society and the first overseas member of the American Statistical Association.
1877 Francis Galton, Darwin's cousin, describes regression to the mean. In 1888 he introduces the concept of correlation. At a "Guess the weight of an Ox" contest in Devon he describes the "Wisdom of Crowds" – that the average of many uninformed guesses is close to the correct value.
1894 Karl Pearson introduces the term "standard deviation". If errors are normally distributed, 68% of samples will lie within one standard deviation of the mean. Later he develops chi-squared tests for whether two variables are independent of each other.
0.1%
2.1%
13.6%
34.1%
34.1%
13.6%
2.1%
0.1%
-3σ
-2σ
-1σ
μ
1σ
2σ
3σ
1900 Louis Bachelier shows that fluctuations in stock market prices behave in the same way as the random Brownian motion of molecules – the start of financial mathematics.
1916 During the First World War car designer Frederick Lanchester develops statistical laws to predict the outcomes of aerial battles: if you double their size land armies are only twice as strong, but air forces are four times as powerful.
1924 Walter Shewhart invents the control chart to aid industrial production and management
1935 R. A. Fisher revolutionises modern statistics. His Design of Experiments gives ways of deciding which results of scientific experiments are significant and which are not.
1940-45 Alan Turing at Bletchley Park cracks the German wartime Enigma code, using advanced Bayesian statistics and Colossus, the first programmable electronic computer.
1946 Cox's theorem derives the axioms of probability from simple logical assumptions.
1948-53 The Kinsey Report gathers objective data on human sexual behaviour. A large-scale survey of 5000 men and, later, 5000 women, it causes outrage.
1950s Genichi Taguchi's statistical methods to improve the quality of automobile and electronics components revolutionise Japanese industry, which far overtakes western European rivals.
1979 Bradley Efron introduces bootstrapping, a simple way to estimate the distribution of almost any sample of data.
1997 The term "Big Data" first appears in print.
2002 Paul DePodesta uses statistics – "sabermetrics" – to transform the fortunes of the Oakland Athletics baseball team; the film Moneyball tells the story.
2012 Nate Silver, statistician, successfully predicts the result in all 50 states in the US Presidential election. He becomes a media star.
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Modern era
1908 William Sealy Gosset, chief brewer for Guinness in Dublin, describes the t-test. It uses a small number of samples to ensure that every brew tastes equally good.
1911 Herman Hollerith, inventor of punch-card devices used to analyse data in US censuses, merges his company to form what will become IBM, pioneers of machines to handle business data and of early computers.
1935 George Zipf finds that many phenomena – river lengths, city populations – obey a power law so that the largest is twice the size of the second largest, three times the size of the third, and so on.
1937 Jerzy Neyman introduces confidence intervals in statistical testing. His work leads to modern scientific sampling.
1944 The German tank problem: the Allies desperately need to know how many Panther tanks they will face in France on D-Day. Statistical analysis of the serial numbers on gearboxes from captured tanks indicates how many of each are being produced. Statisticians predict 270 a month; reports from intelligence sources predict many fewer. The total turned out to be 276. Statistics had outperformed spies.
1948 Claude Shannon introduces information theory and the "bit" – fundamental to the digital age.
1950 Richard Doll and Bradford Hill establish the link between cigarette smoking and lung cancer. Despite fierce opposition the result is conclusively proved, to huge public health benefit.
1958 ...lan-Meier estimator ...ctors a simple statistical ... judging which treatments work best. It has saved millions of lives.
1972 David Cox's proportional hazard model and the concept of partial likelihood.
1977 John Tukey introduces the box-plot or box-and-whisker diagram, which shows the quartiles, medians and spread of data in a single image.
1982 Edward Tufte self-publishes The Visual Display of Quantitative Information, setting new standards for graphic visualisation of data.
1988 Margaret Thatcher becomes the first world leader to call for action on climate change.
1993 The statis... programming lan... "R" is released, ... standard statistical tool.
2002 The amount of information stored digitally surpasses non-digital.
2004 Launch of Significance magazine.
2008 Hal Varian, chief economist at Google, says that statistics will be "the sexy profession of the next ten years".
2012 The Large Hadron Collider confirms existence of a Higgs boson-like particle with probability of five standard deviations – around one chance in 3.5 million that all they are seeing is coincidence.

Future Holds Tremendous Promise

Future State

The next BIG thing in our field

Current State

Galvanizing Networks

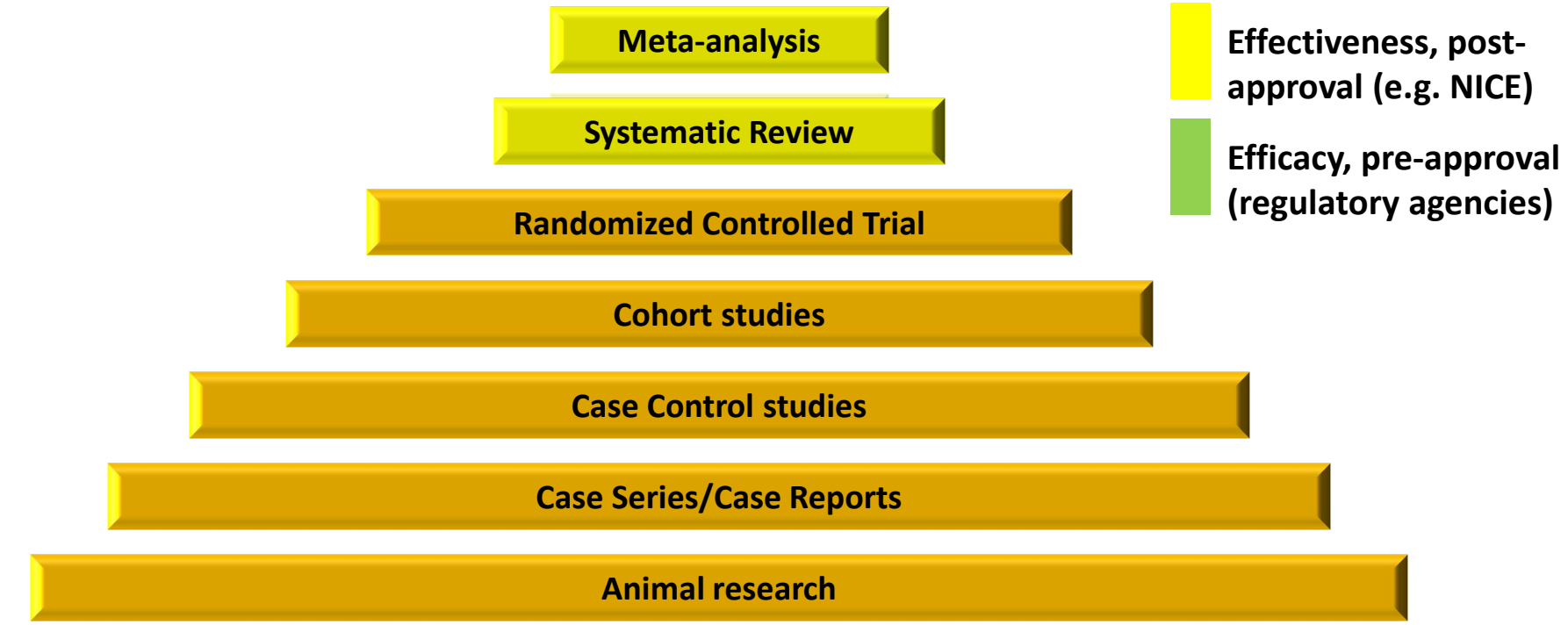
FROM MOLECULE TO PATIENT

Counterpoint!

No. MIDD/MID3 has fallen short of expectations

Oscar Della Pasqua
University College London,
London, United Kingdom

Decision-making is mostly driven by p-values
The learning-confirming paradigm still succumbs to hypothesis testing



Clark N, 2003 - Oxford Centre for Evidence-based Medicine

Drug-disease modelling is not part of the evidence pyramid

FROM MOLECULE TO PATIENT

Personalised Medicine pp 179-197 | Cite as

The Power of Zebrafish in Personalised Medicine

Authors | Authors and affiliations

Sarah Baxendale, Freek van Eeden, Robert Wilkinson

Chapter
First Online: 25 August 2017

Part of the Advances in Experimental Medicine and Biology book series (AEMB, volume 1007)

Abstract

The goal of personalised medicine is to develop tailor-made therapies for patients in whom currently available therapeutics fail. This approach requires correlating individual patient genotype data to specific disease phenotype data and using these stratified data sets to identify bespoke therapeutics. Applications for personalised medicine include common complex diseases which may have multiple targets, as well as rare monogenic disorders, for which the target may be unknown. In both cases, whole genome sequence analysis (WGS) is discovering

M&S approaches seem disconnected from Big Data and Personalised Medicine

Word search→ No. of hits

Pharmacometrics		0
Modeling	0	
Simulation	0	
Clinical trial simulation		0
PKPD		
MIDD	0	
MID3	0	

M&S is <u>not</u> mentioned or formally recognised as a toolkit for innovation

FROM MOLECULE TO PATIENT

Tpoxx

CDER approved the first new drug to treat smallpox, helping to protect the U.S. from bioterrorism.

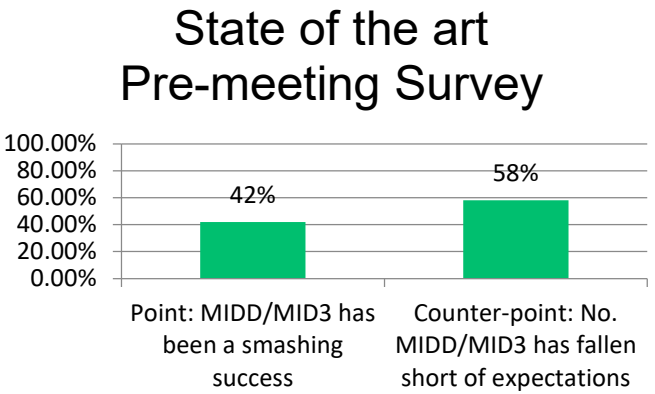
Tpoxx (tecovirimat), the first drug with an indication for treatment of patients with **smallpox**, a contagious and sometimes fatal disease. Although the World Health Organization declared smallpox to be eradicated in 1980, there have been longstanding concerns that smallpox could be used as a bioweapon. Because smallpox no longer occurs, the drug could not be tested on humans with the disease. Instead, this drug was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support an FDA approval when it is not feasible or ethical to conduct efficacy trials in humans.

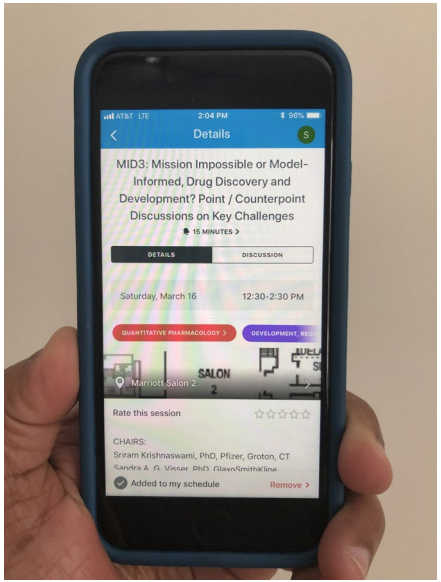
M&S is <u>not</u> mentioned or formally recognised as a toolkit for innovation

FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll
1. State of the art





MIDD/MID3 has been a smashing success

Vs.

No. MIDD/MID3 has fallen short of expectations

2. Primary Limitations to Success

Model less, communicate more
(Stacey Tannenbaum)
Vs.
Talk less, model more
(Oscar Della Pasqua)

Point!

Model less, communicate more !

Stacey Tannenbaum
Astellas Pharma
Northbrook, IL

FROM MOLECULE TO PATIENT

Goal: build something to sit on.

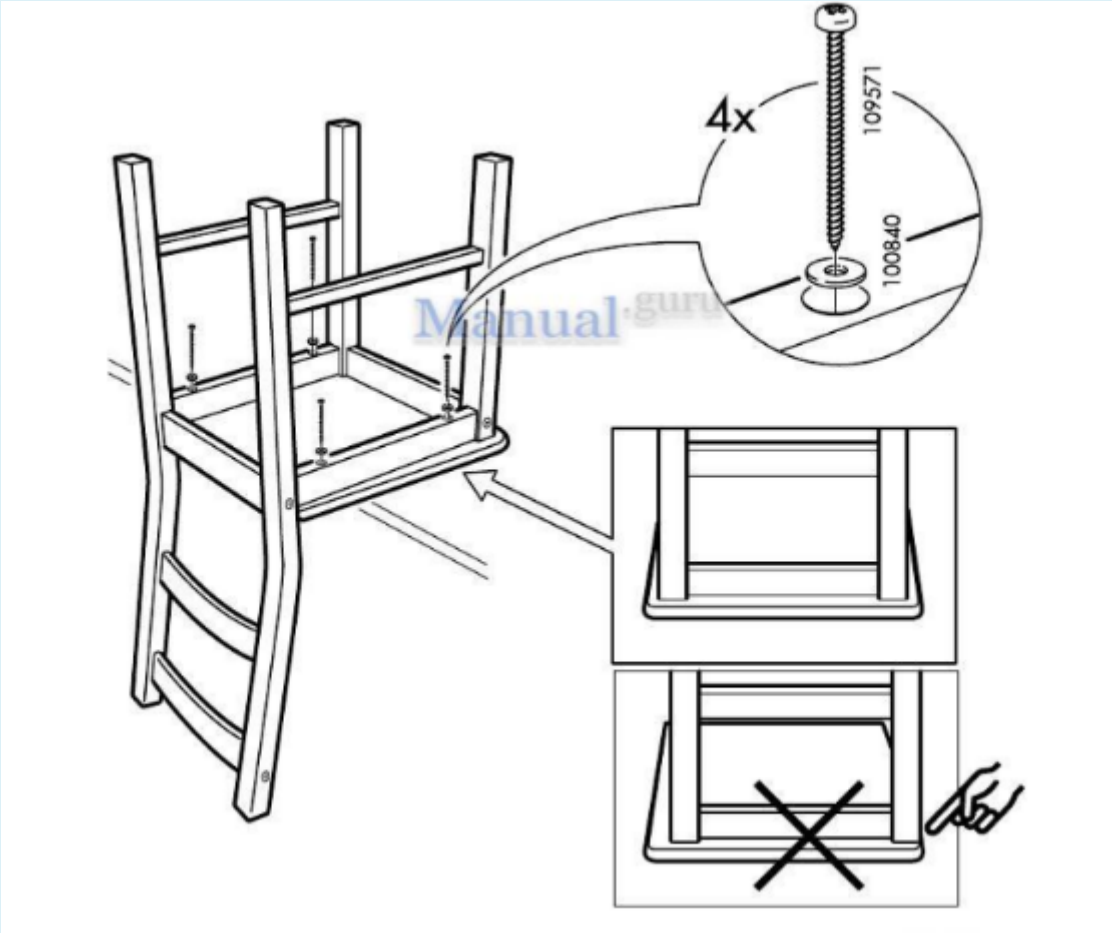
FROM MOLECULE TO PATIENT

What you started with

Image

What you built

What the team needed


4x
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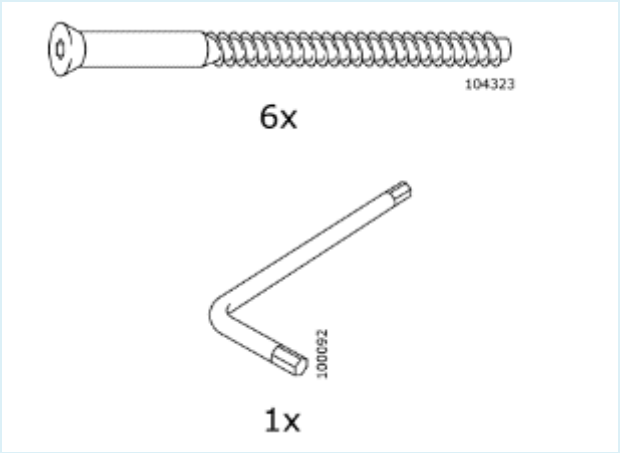
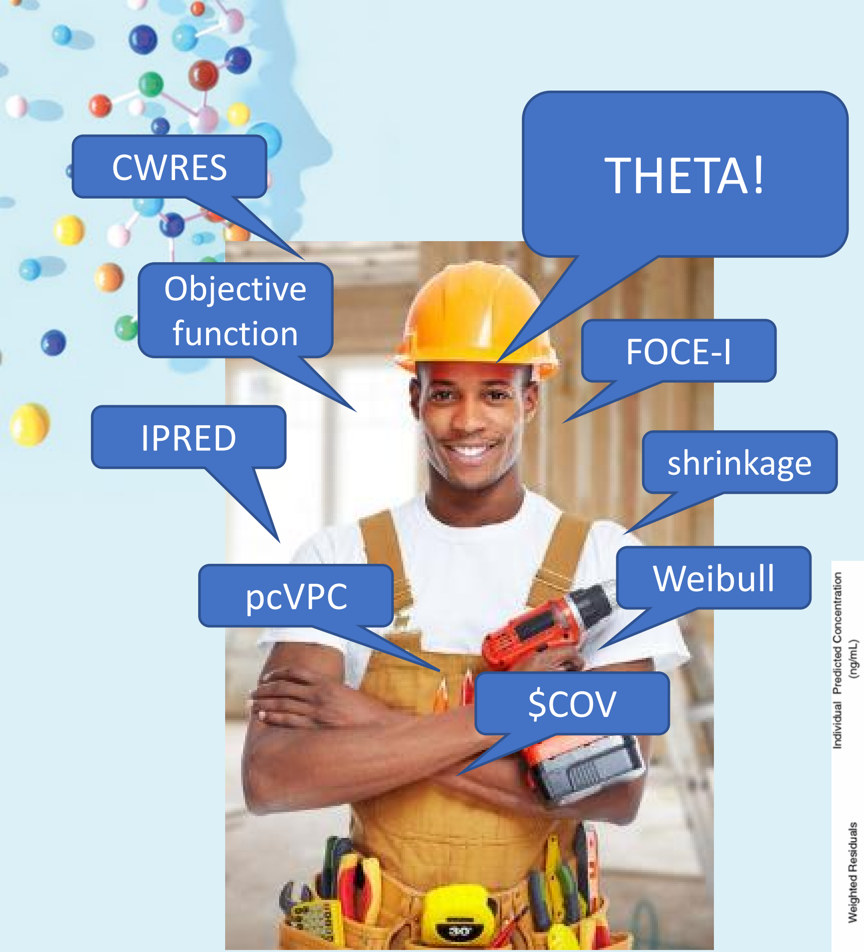
Manual·guru

What you communicated to the team

Tested for: 243 lb
Width: 16 1/8 "
Depth: 19 5/8 "
Height: 37 3/8 "
Seat width: 15 3/8 "
Seat depth: 15 3/4 "
Seat height: 17 3/4 "



https://www.ikea.com/us/en/assembly_instructions/ivar-chair__AA-908032-2_pub.pdf


CWRES
Objective function
IPRED
pcVPC
THETA!
FOCE-I
shrinkage
Weibull
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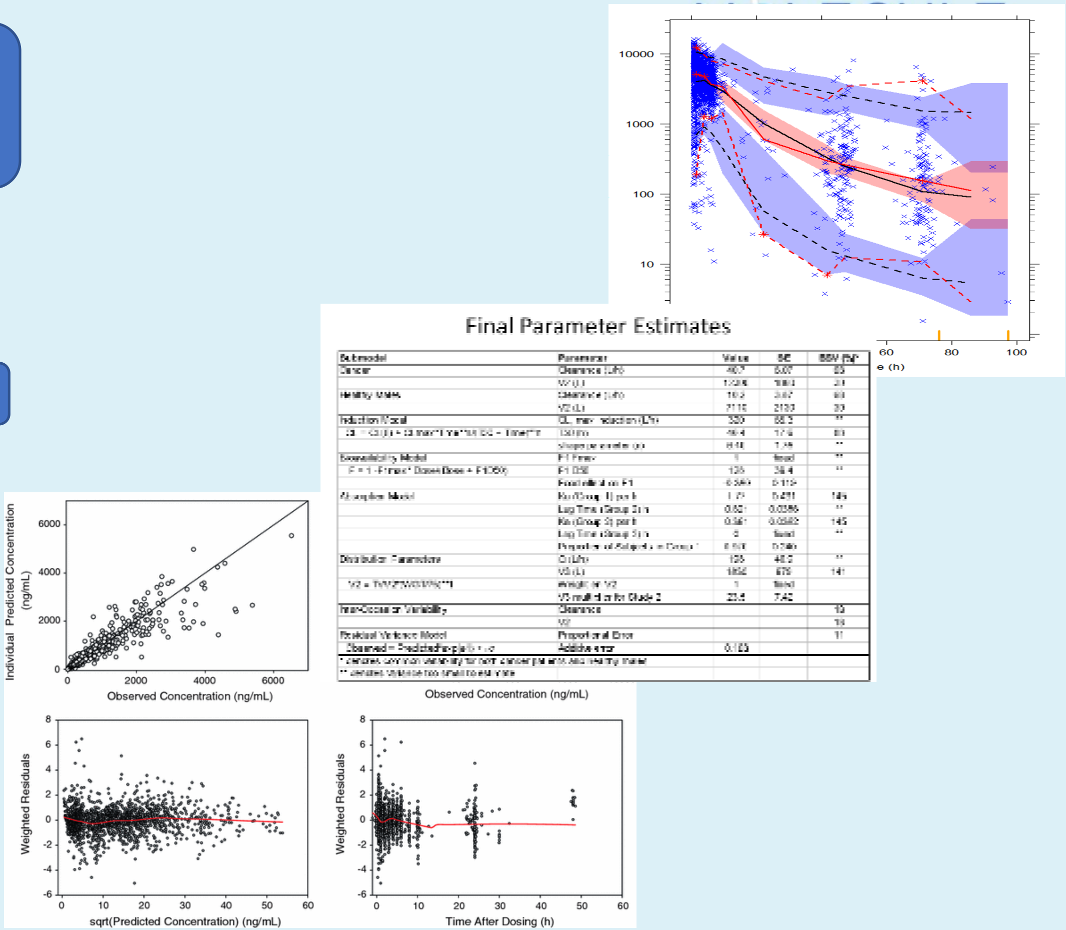

Final Parameter Estimates
Individual Predicted Concentration (ng/mL)
Observed Concentration (ng/mL)
Weighted Residuals
sqrt(Predicted Concentration) (ng/mL)
Time After Dosing (h)

FROM MOLECULE TO PATIENT

What the team wanted to know

Can I sit on it?

FROM MOLECULE TO PATIENT

TUTORIAL

Communicating to Influence Drug Development and Regulatory Decisions: A Tutorial

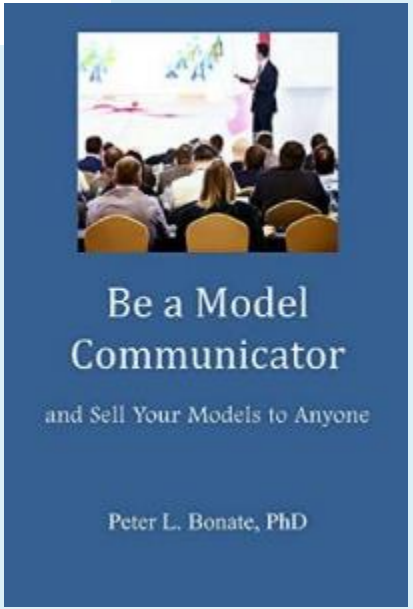
S Mehrotra and J Gobburu*

Pharmacometricians require three skills to be influential: technical, business (e.g., drug development), and soft skills (e.g., communication). Effective communication is required to translate technical and often complicated quantitative findings to interdisciplinary team members in order to influence drug development or regulatory decisions. In this tutorial, we highlight important aspects related to communicating pharmacometric analysis to influence decisions.

CPT Pharmacometrics Syst. Pharmacol. (2016) 5, 163–172; doi:10.1002/psp4.12073; published online 14 April 2016.

https://www.certara.com/2016/06/21/effective-communication-for-pharmacometricians-with-joga-gobburu/?

https://www.certara.com/2015/06/05/how-to-explain-the-value-of-modeling-and-simulation-to-your-grandma/?

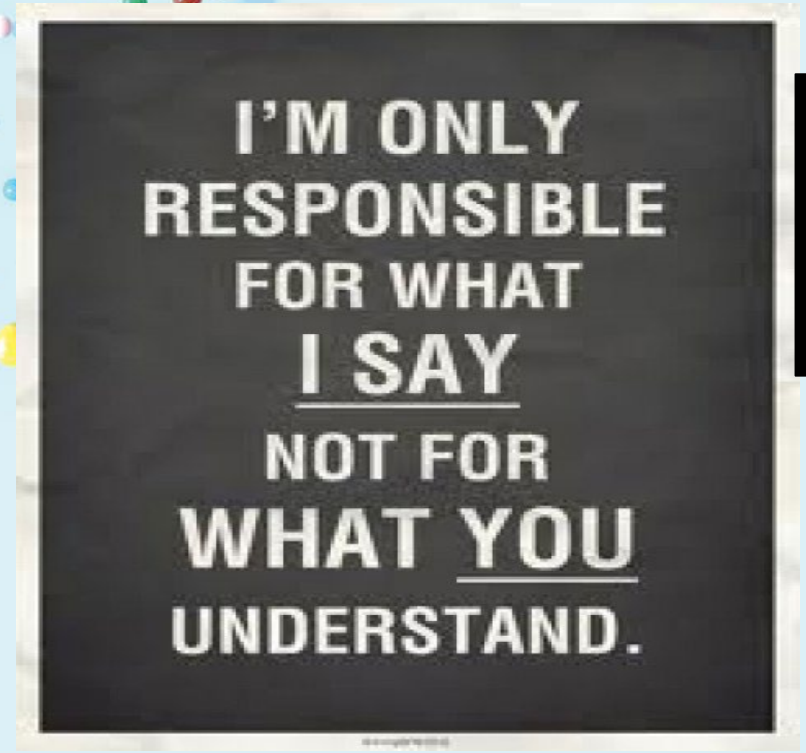


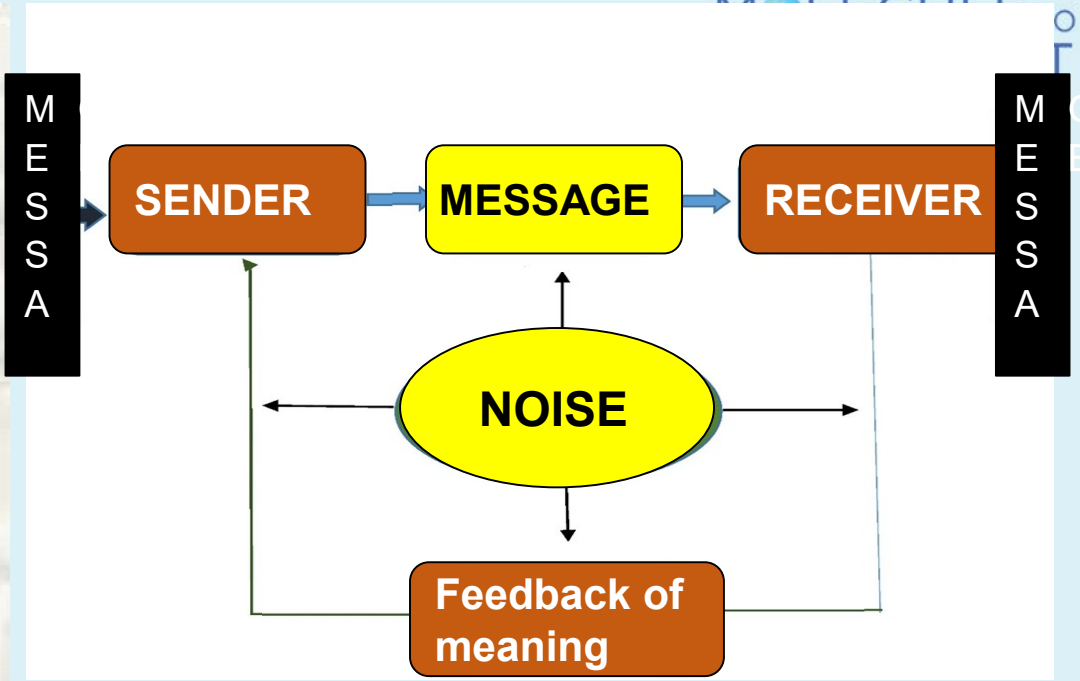
FROM MOLECULE TO PATIENT

Counterpoint!

Talk less, model more !

Oscar Della Pasqua
University College London
London, United Kingdom





A little Learning is a dang'rous Thing
(*Essay on Criticism, Alexander Pope, 1711*)

A little Learning is a dang'rous Thing
(*Essay on Criticism, Alexander Pope, 1711*)

Deceptive: Models can be “unidimensional”

Clin Pharmacokinet. Author manuscript; available in PMC 2010 Jul 21.
Published in final edited form as:
Clin Pharmacokinet. 2007; 46(3): 221–234.
doi: 10.2165/00003088-200746030-00003
INSERM Subrepository

PMCID: PMC290741
HALMS: HALMS159124
PMID: 17328581

Are population pharmacokinetic and/or pharmacodynamic models

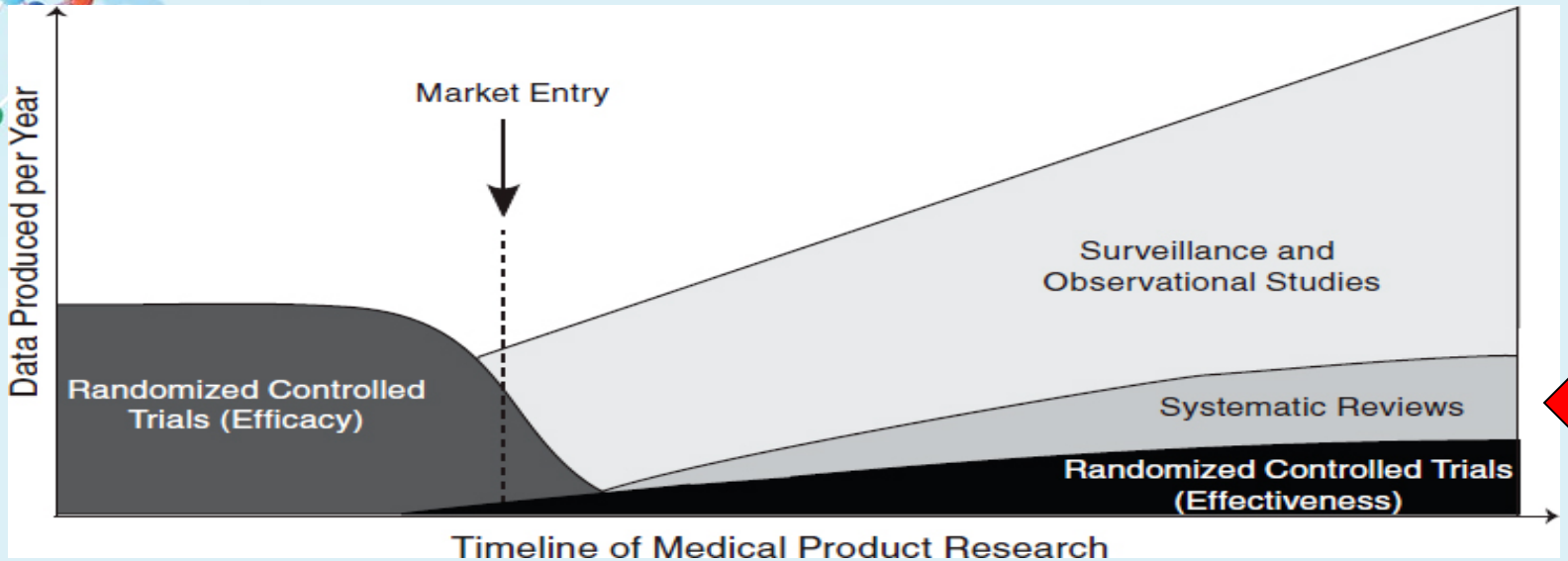
Citation: CPT Pharmacometrics Syst. Pharmacol. (2018) 7, 331–341; doi:10.1002/psp4.12290

ARTICLE

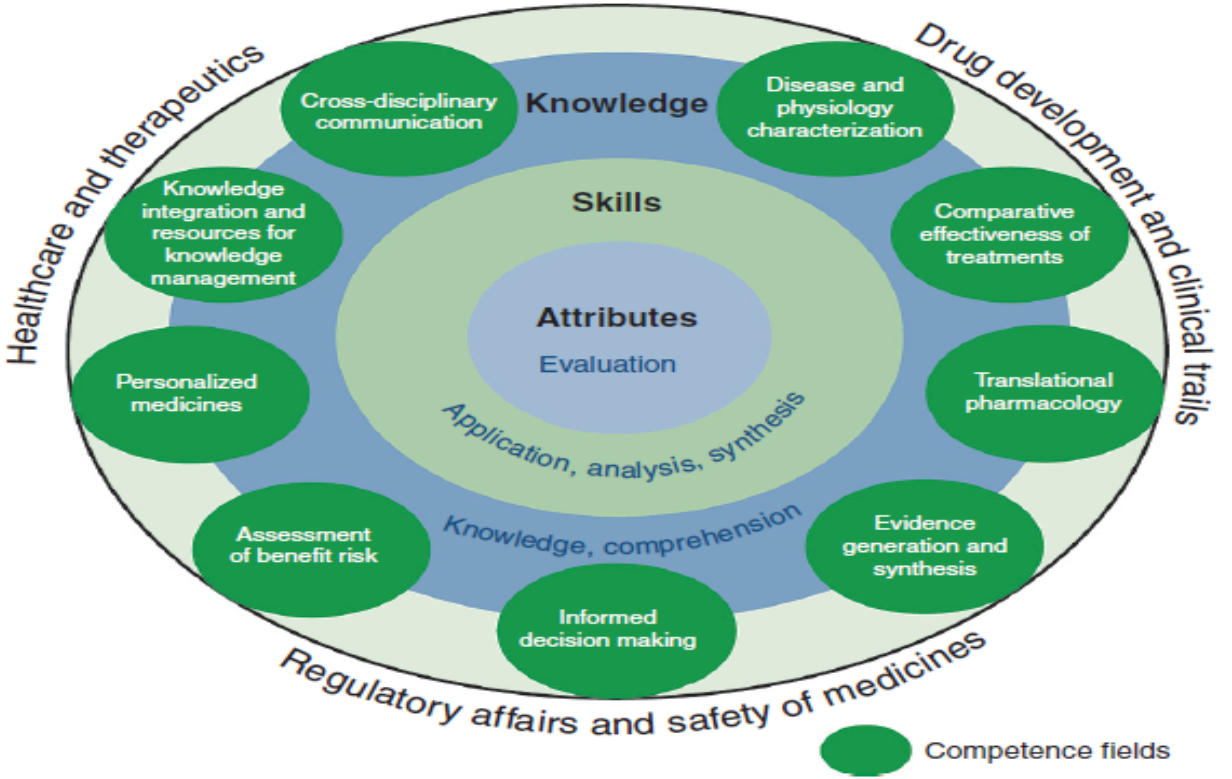
Comparison of Power, Prognosis, and Extrapolation Properties of Four Population Pharmacodynamic Models of HbA1c for Type 2 Diabetes

Gustaf J. Wellhagen, Mats O. Karlsson and Maria C. Kjellsson*

Why bother about predictive performance?



Models should become an integral part of the evidence synthesis framework



Vlasakakis et al., CPT:PSP 2013; 2:e40

Pluralitas non est ponenda sine necessitate
("Plurality should not be posited without necessity“ (William of Ockham)

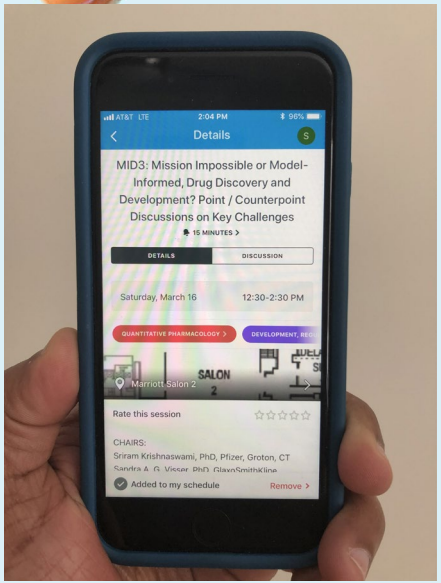
When you earnestly believe you can compensate for a lack of skill by doubling your efforts, there's no end to what you can't do.

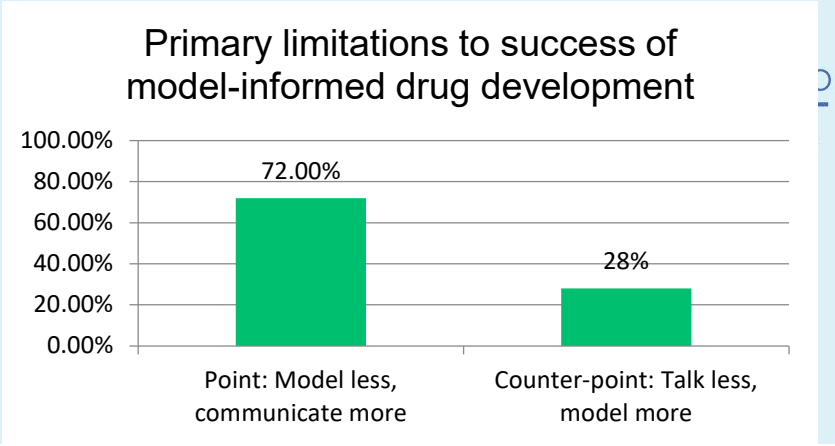
FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll

2. Primary Limitations to Success





Model less, communicate more

Vs.

Talk less, model more

3. All models are wrong but some are useful

Wrong models are dangeours
(Stacey Tannenbaum)
Vs.
Wrong models are useful
(Piet van der Graaf)

Point!

FROM MOLECULE TO PATIENT

Wrong Models can be DANGEROUS

Stacey Tannenbaum

MID3: Mission Impossible or Model-Informed, Drug Discovery and Development?

FELIX SALMON BUSINESS 02.23.09 12:00 PM

RECIPE FOR DISASTER: THE FORMULA THAT KILLED WALL STREET

ECULE TO PATIENT

$$\Pr[T_A<1, T_B<1] = \Phi_2(\Phi^{-1}(F_A(1)), \Phi^{-1}(F_B(1)), \gamma)$$

Here's what killed your 401(k) *

Franken-algorithms: the deadly consequences of unpredictable code

Uber's self-driving car saw the pedestrian but didn't swerve – report

Tuning of car's software to avoid false positives blamed, as US National Transportation Safety Board investigation continues

Discriminating algorithms: AI showed prejudice

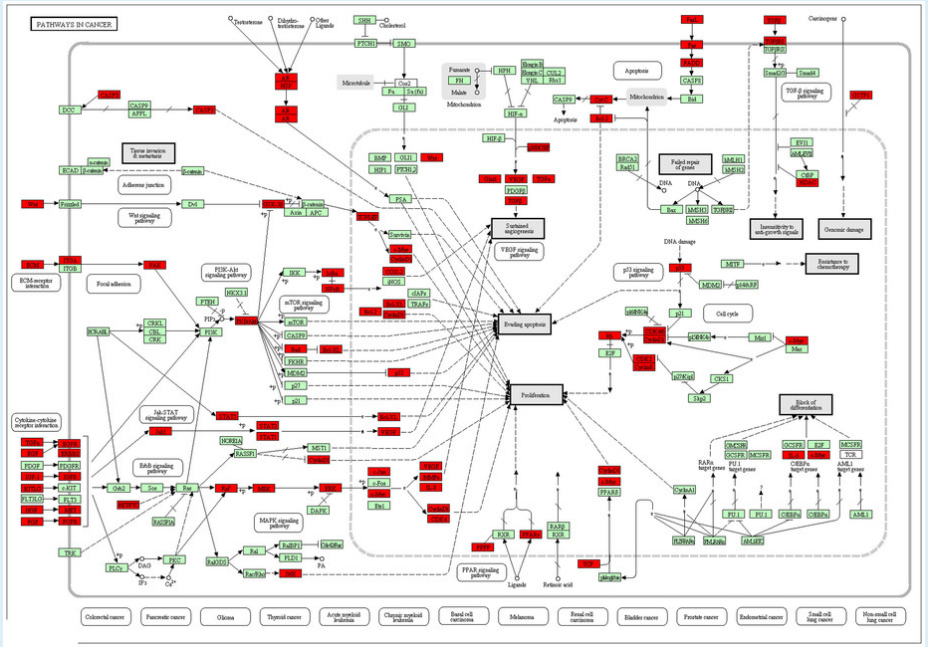
Artificial intelligence is supposed to make life easier for us all – but it is also amplify sexist and racist biases from the real world

The Most Dangerous Equation

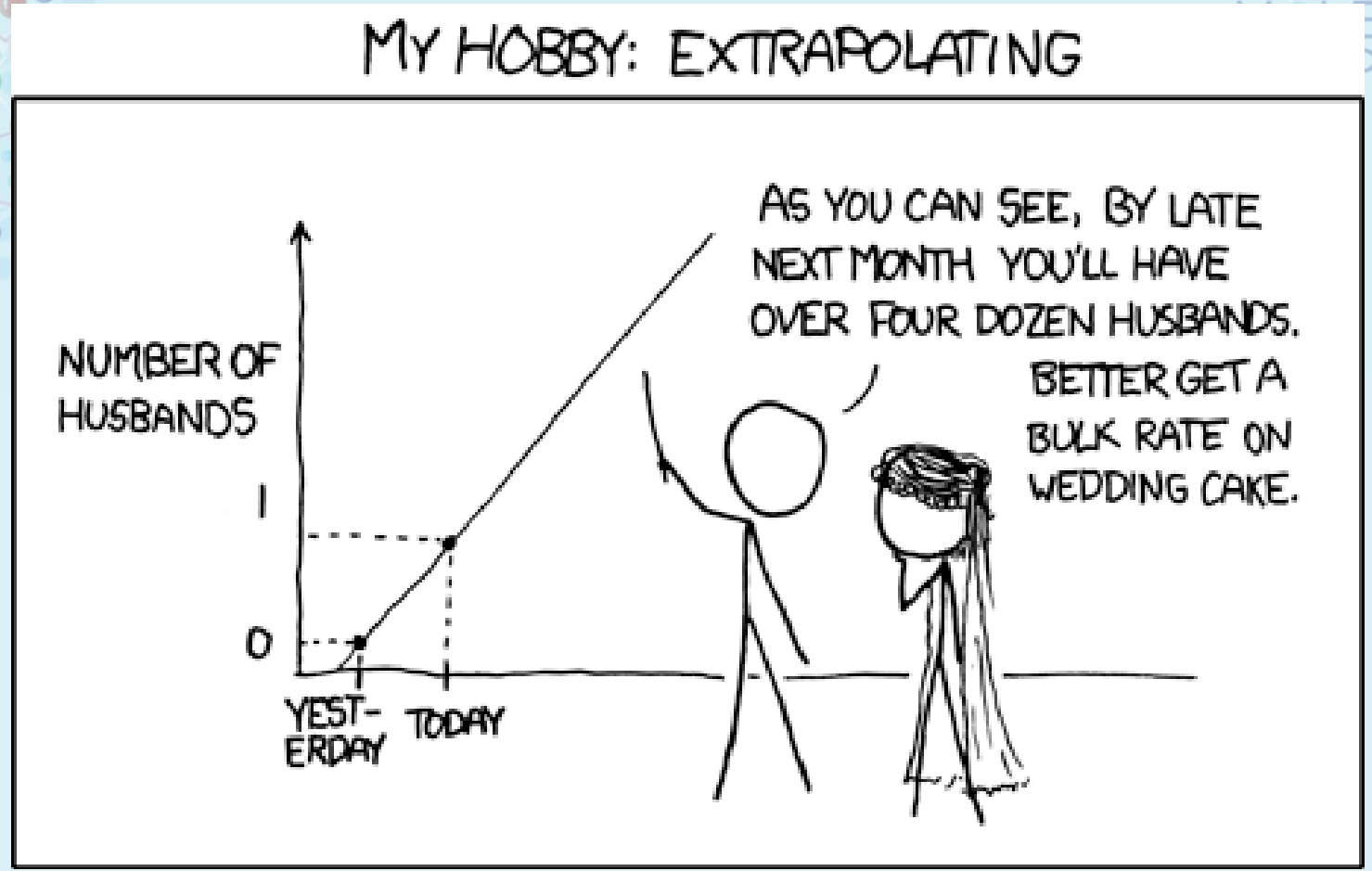
Ignorance of how sample size affects statistical variation has created havoc for nearly a millennium

Cathy O'Neill: Weapons of Math Destruction, mathbabe

FROM MOLECULE TO PATIENT



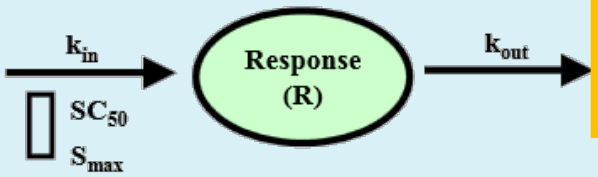
Yu et al. Scientific Reports 5 (2015)

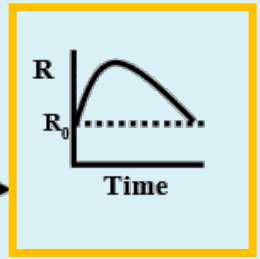


https://imgs.xkcd.com/comics/extrapolating.png

FROM MOLECULE TO PATIENT

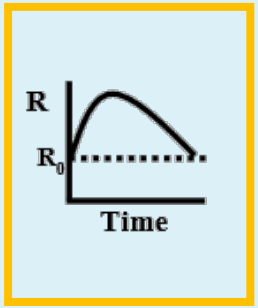
III. *STIMULATION - k_{in}*





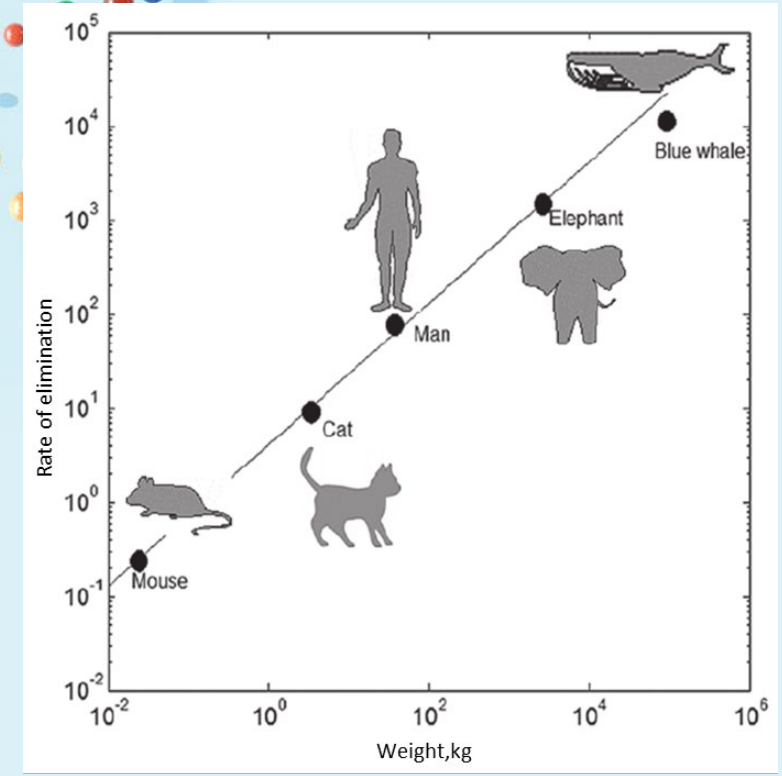
$$\frac{dR}{dt} = k_{in}\left(1 + \frac{S_{max} \cdot C_p}{SC_{50} + C_p}\right) - k_{out} \cdot R$$

II. *INHIBITION - k_{out}*



$$\frac{dR}{dt} = k_{in} - k_{out}\left(1 - \frac{I_{max} \cdot C_P}{IC_{50} + C_P}\right) \cdot R$$

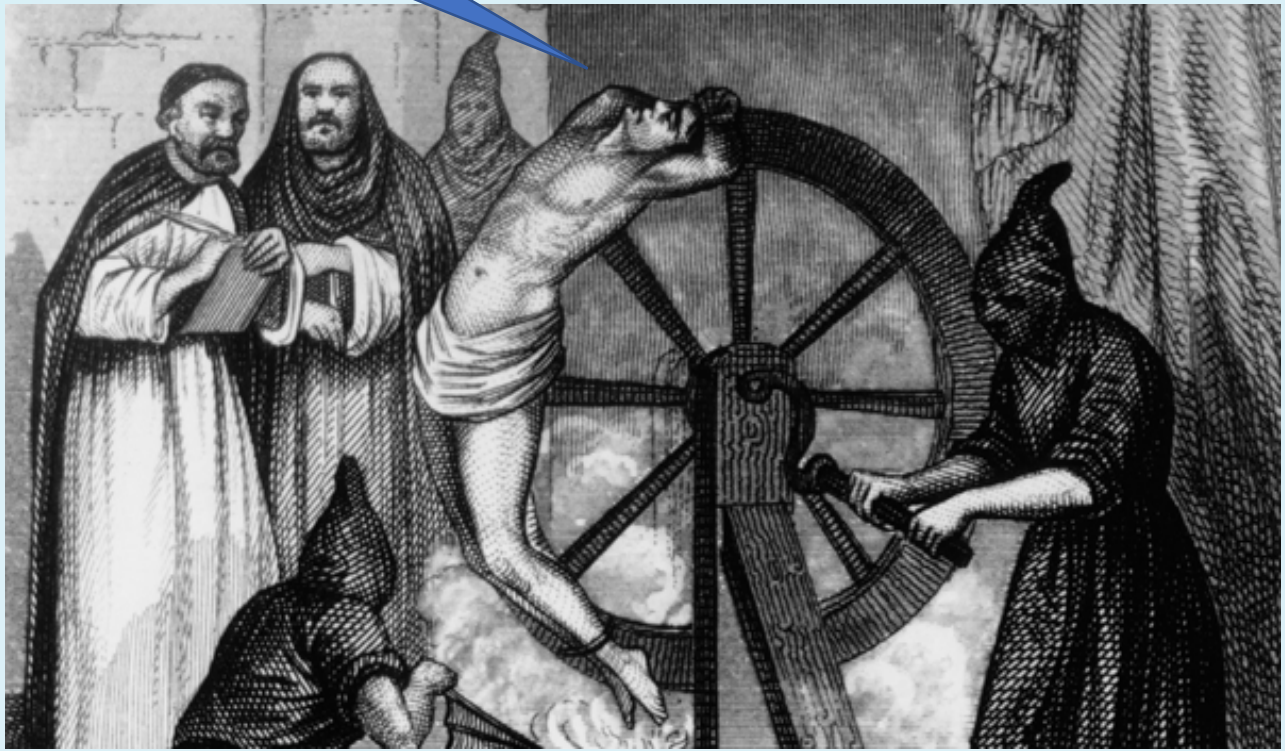
Sharma and Jusko, BJCP 1998
http://accp1.org/pharmacometrics/pkpdcourse2006/lecs/lec2/IDR.pdf


Rate of elimination
Weight,kg
Mouse
Cat
Man
Elephant
Blue whale

CL ~ BW???

Shoe size is a significant covariate!

"If you torture the data long enough, it will confess."
Ronald H. Coase



https://bleacherreport.com/articles/430196-your-tax-dollars-at-work-garbage-in-garbage-out


CRASH!


HONDA
CR-V

FROM MOLECULE TO PATIENT

Wrong Models can be

FROM MOLECULE TO PATIENT

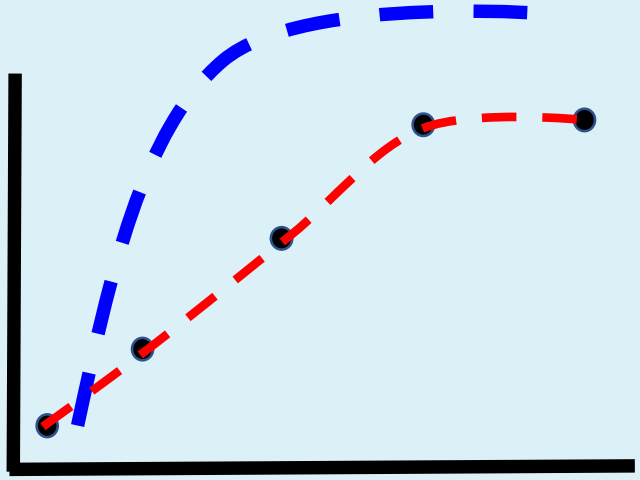
Counterpoint!

Wrong models are useful

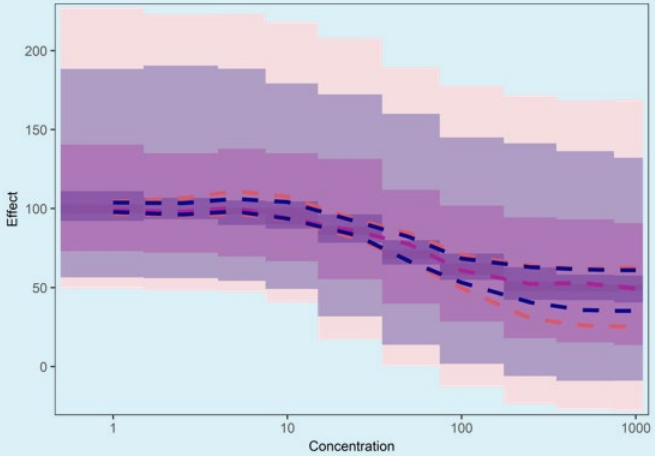
Piet van der Graaf
Certara
Canterburry, United Kingdom

Wrong? / Useful?

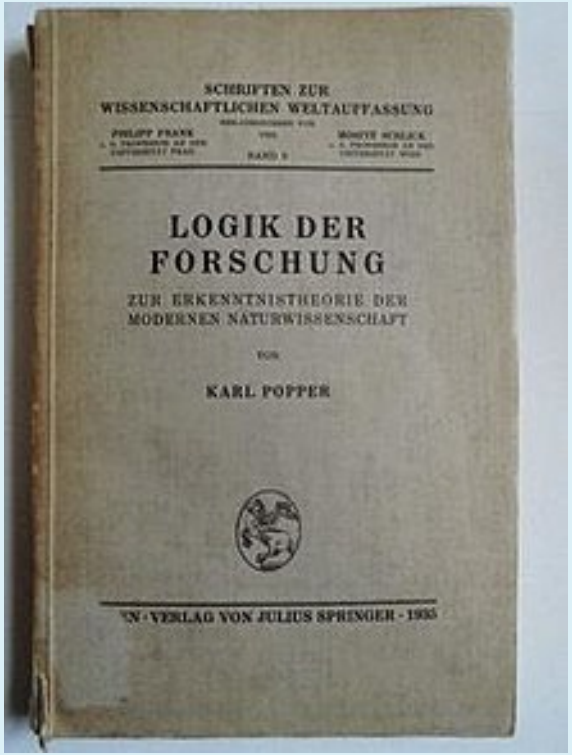
Heart Rate = -10 x Concentration



“All models are wrong but some are useful”



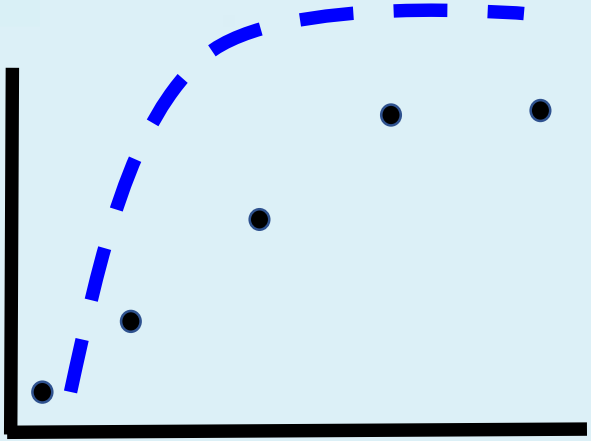
All models are hypotheses



"The criterion of the scientific status of a theory is its falsifiability, or refutability, or testability"

FROM MOLECULE TO PATIENT

Wrong models are useful



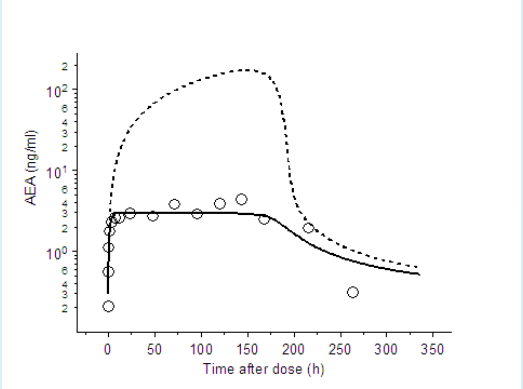
Citation: CPT: Pharmacometrics Systems Pharmacology (2014) 3, e91; doi:10.1038/psp.2013.72

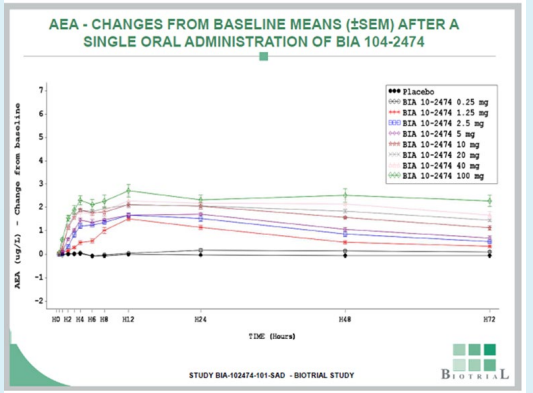
www.nature.com/psp

ORIGINAL ARTICLE

A Systems Pharmacology Perspective on the Clinical Development of Fatty Acid Amide Hydrolase Inhibitors for Pain

N Benson[1], E Metelkin[2], O Demin[2], GL Li[3], D Nichols[4] and PH van der Graaf[5]





Summary

1. **Pharmacometricians should stop quoting Box:**
   - It undermines the credibility and scientific status of the discipline

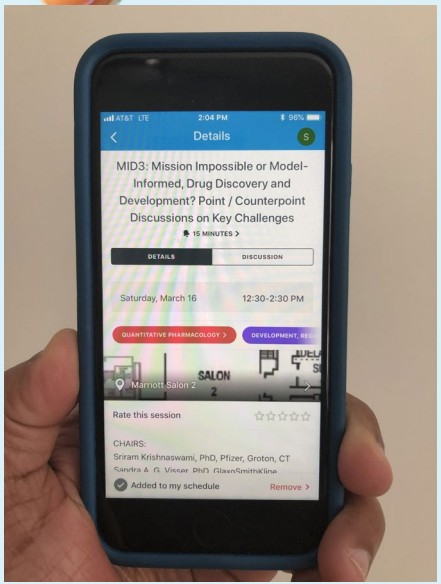
2. **A mechanistic model is always useful when it is "wrong" (and not always when it is "right"):**
   - It falsifies a hypothesis/assumption and as a consequence we learn and can design the next experiment intelligently

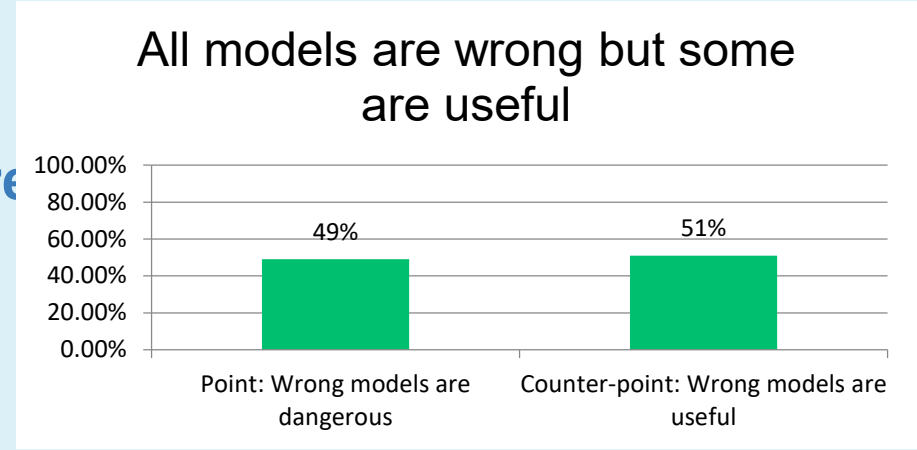
FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll

3. All models are wrong but some are useful





Wrong models are dangerous

Vs.

Wrong models are useful

4. Transforming Clinical Trial Design Decision Making

All clinical trials should be informed by simulations

(Marc Gastonguay)

Vs.

Simulations are unnecessary and time consuming in most cases

(Daniele Ouellet)

Point!

FROM MOLECULE TO PATIENT

All clinical trials should be informed by simulations

Marc Gastonguay
Metrum Research Group
Boston, MA

All clinical trials should be informed by simulations

FROM MOLECULE TO PATIENT

- Pharma decision making process is broken
  - Too dependent on individual intuition and power structures
  - Lacking objective, quantitative, assessment

- All DECISIONS should be informed by simulations

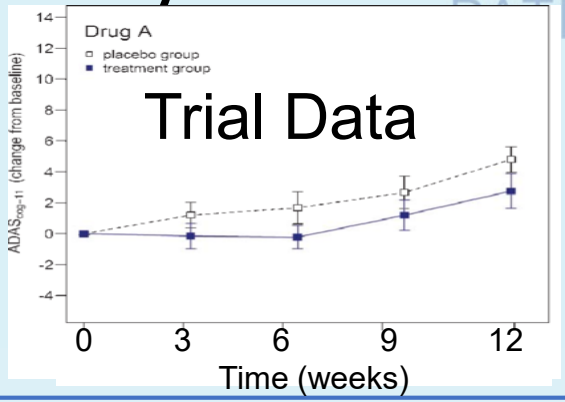
- Start with simulating each trial at time of protocol writing
  - Prepare all analysis in advance on simulated data
  - Deliver input rapidly after database lock
  - Feed into model-based decision-making

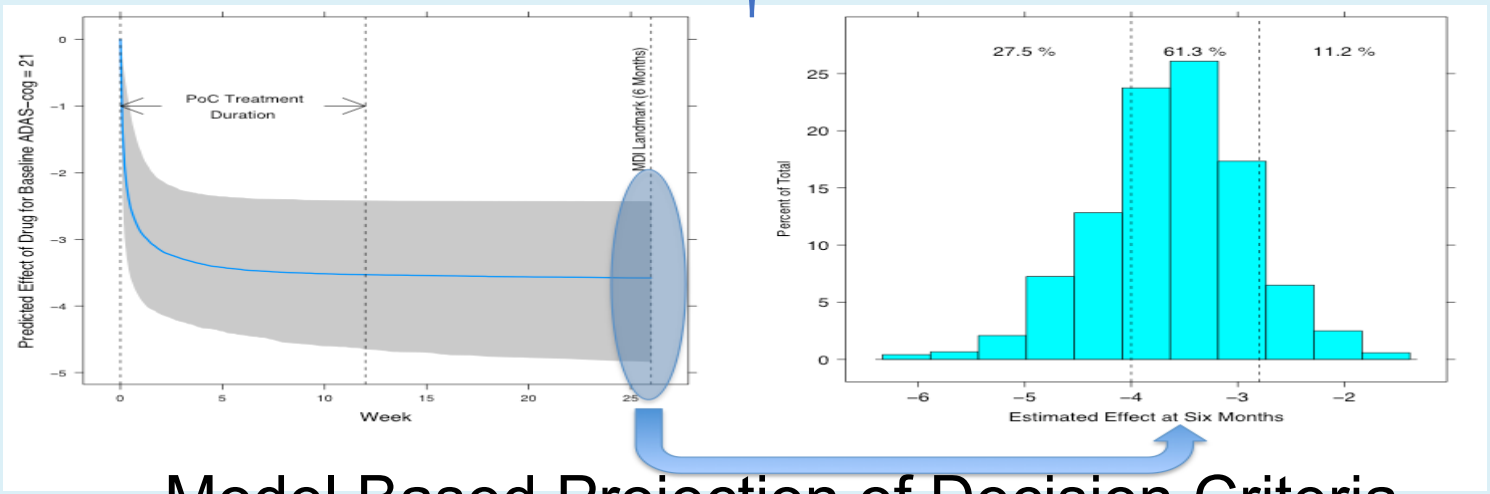
All DECISIONS should be informed by simulations

$$g(\theta_{ipk}) = \eta_{pk} + \alpha_{pk} t_{ipk} + E_{\mathrm{PBO}}(t_{ipk}) + E_{\mathrm{DRG}}(t_{ipk}, D_{ipk})$$

+

Prior Model





Model Based Projection of Decision Criteria

All clinical trials should be informed by simulations

FROM MOLECULE TO PATIENT

- Pharma decision making process is broken
- Change needed
  - focus quantitative resources earlier
  - invest in restructuring decision process
- All DECISIONS should be informed by simulations
- Even more important when uncertainty is large
- Start with simulating each trial at time of protocol writing
- Arrive at model-based projection of decision criteria

FROM MOLECULE TO PATIENT

Counterpoint!

FROM MOLECULE TO PATIENT

Simulations are unnecessary and time consuming in most cases

Daniele Ouellet
Pfizer
Collegeville, PA

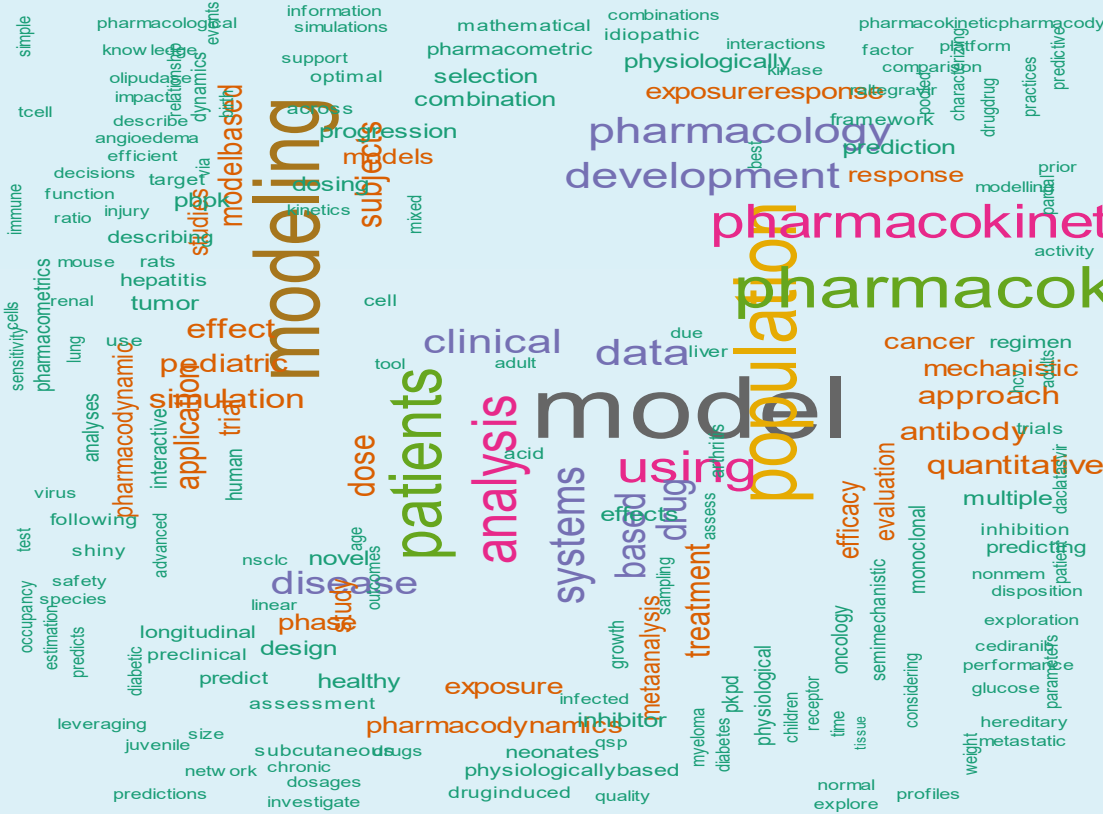
Informing Clinical Trial Design

All clinical trials should be informed by pharmacometric simulations

Simulations are unnecessary and time consuming in most cases

Simulations are unnecessary and time consuming in most cases

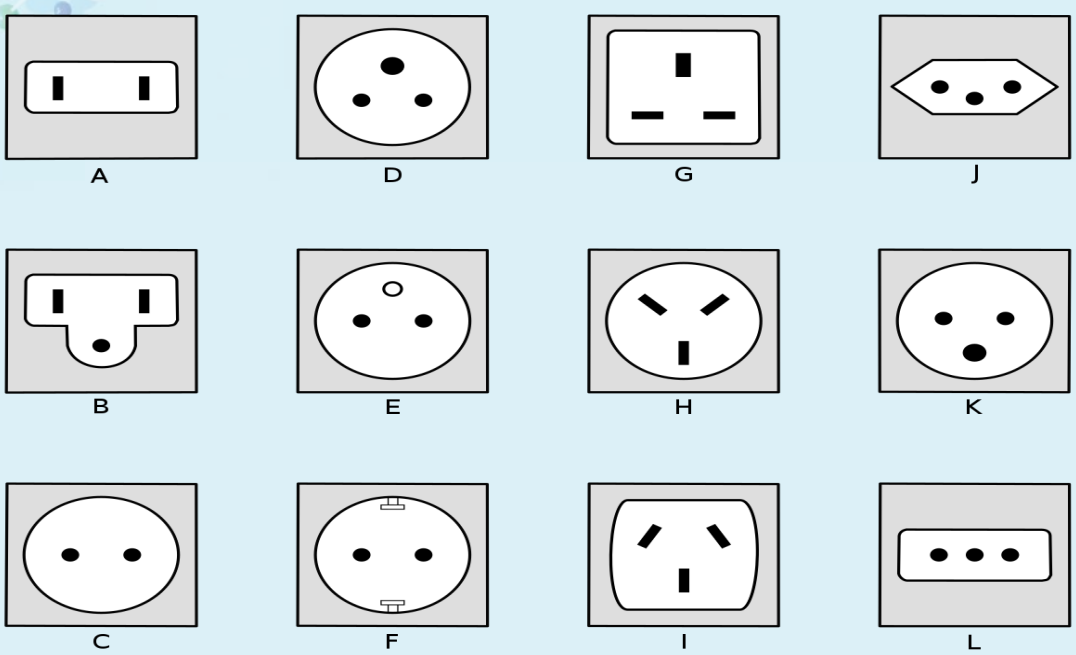
- Great examples where M&S had great impact on trial design
- Understanding dose/exposure response
- Assessment of benefit risk in target patients
  and in special populations
- Select dose(s), inform effect size, select time points, ets
- USE M&S wisely when it can have a large impact



ACoP Meeting, 2016

Fit for Purpose: There are other options to ensure efficient study design

Power = Study Design



Fit for Purpose: Outcome of M&S can be trumped by other considerations

Efficient, Innovative, More risk

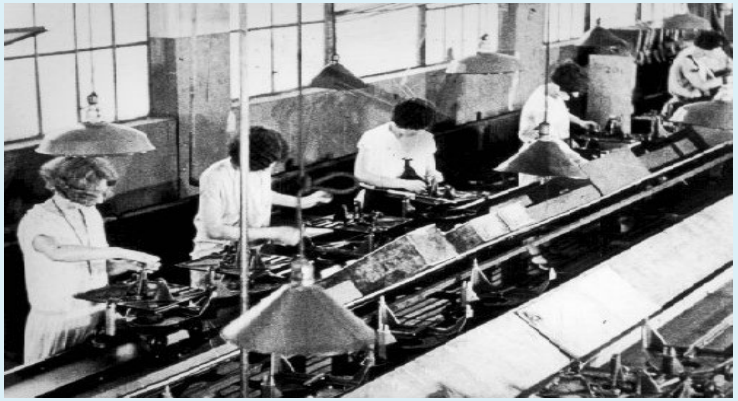
Treatment duration has to be 12 weeks;
Need 700 patients*exposure

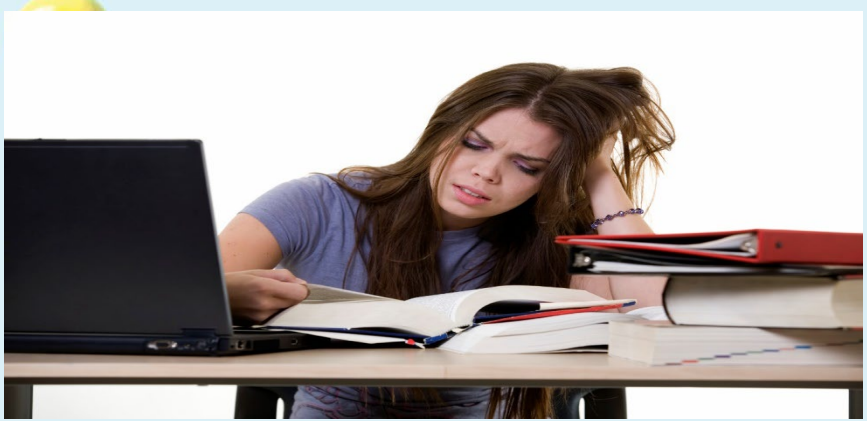
Emphasis on Speed & Being Transformational Breakthrough Drugs to Patients

FROM MOLECULE TO PATIENT

We still lack standards, automation and efficiency: not industrialized enough

FROM MOLECULE TO PATIENT





Let’s be smart

THE HEAVYWEIGHT CHAMPIONSHIP OF THE WORLD

MAIN EVENT - 15 ROUNDS

"THE RUMBLE IN THE JUNGLE"

GEORGE FOREMAN

HEAVYWEIGHT CHAMPION OF THE WORLD

VS

MUHAMMAD ALI

FORMER HEAVYWEIGHT CHAMPION OF THE WORLD

TUES. SEPT. 24

DIRECT FROM RINGSIDE - KINSHASA, ZAIRE

NO HOME TV

See it "LIVE" ON BIG CIRCUIT TV

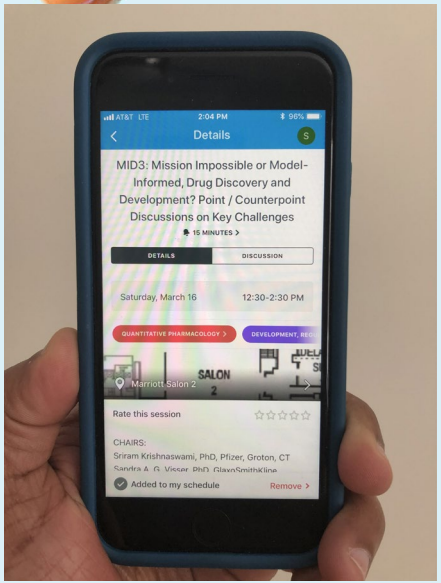
PRESENTED BY HEMDALE LEISURE CORPORATION • DON KING PRODUCTIONS

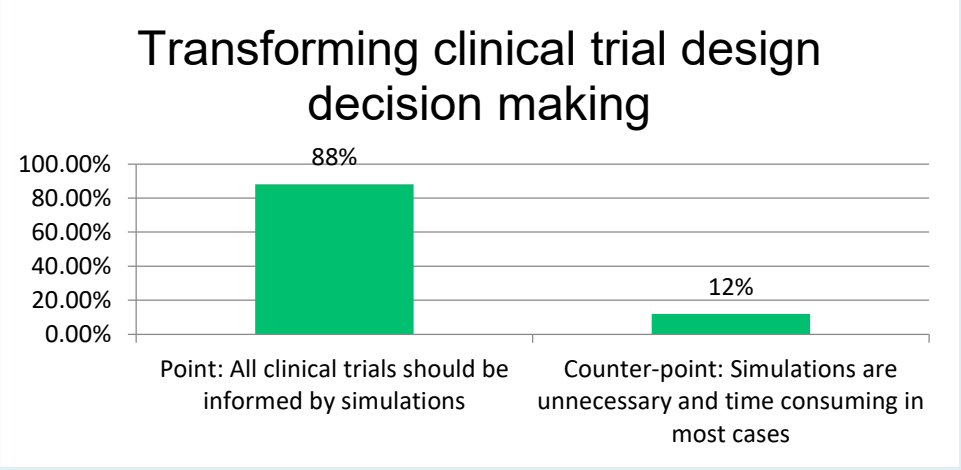
FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll

4. Transforming Clinical Trial Design Decision making





All clinical trials should be informed by simulations

Vs.

Simulations are unnecessary and time consuming in most cases

5. Disruptive Innovations Necessary for Future

Industrialize current models and methodologies

(Joga Gobburu)

Vs.

Future is in machine learning and systems models

(Marc Gastonguay)

Point!

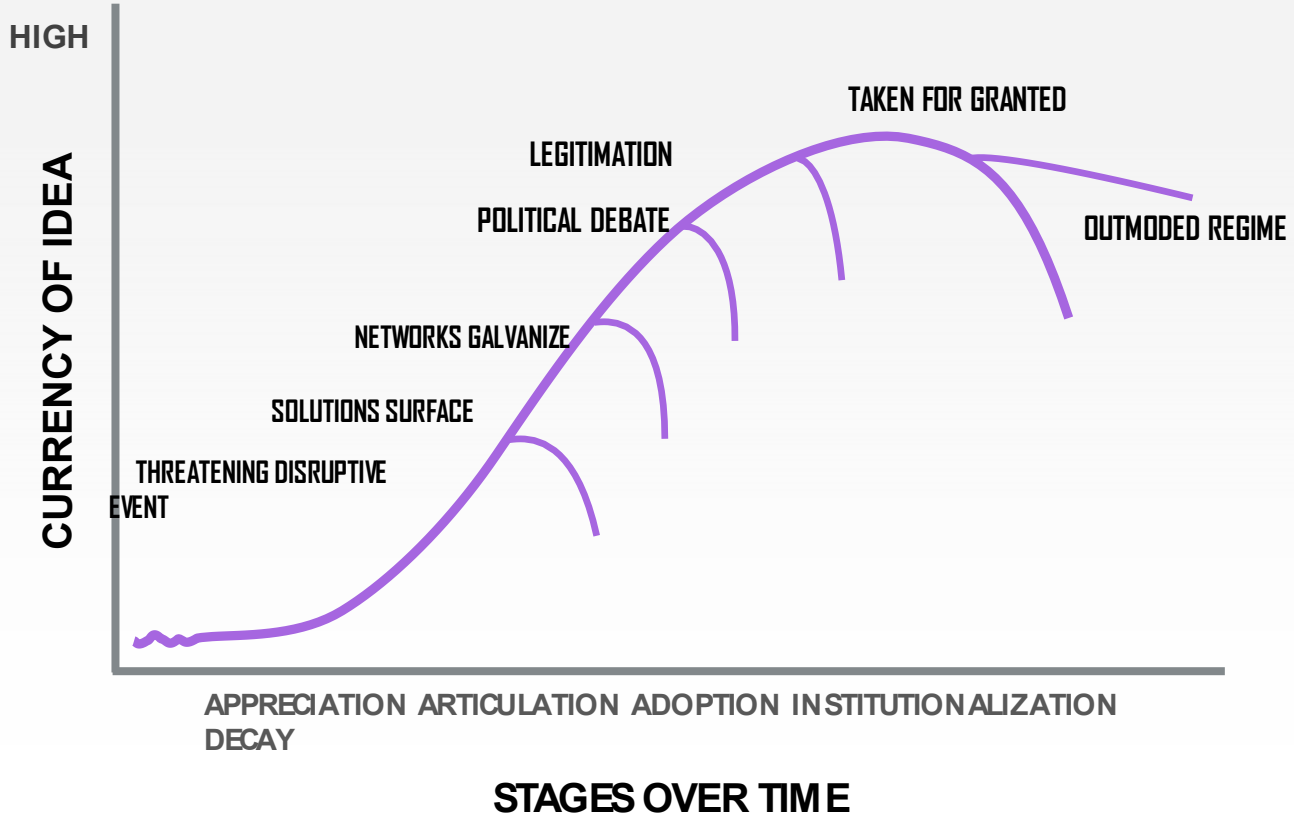
LEARN & APPLY

Industrialize Current Models and Methodologies

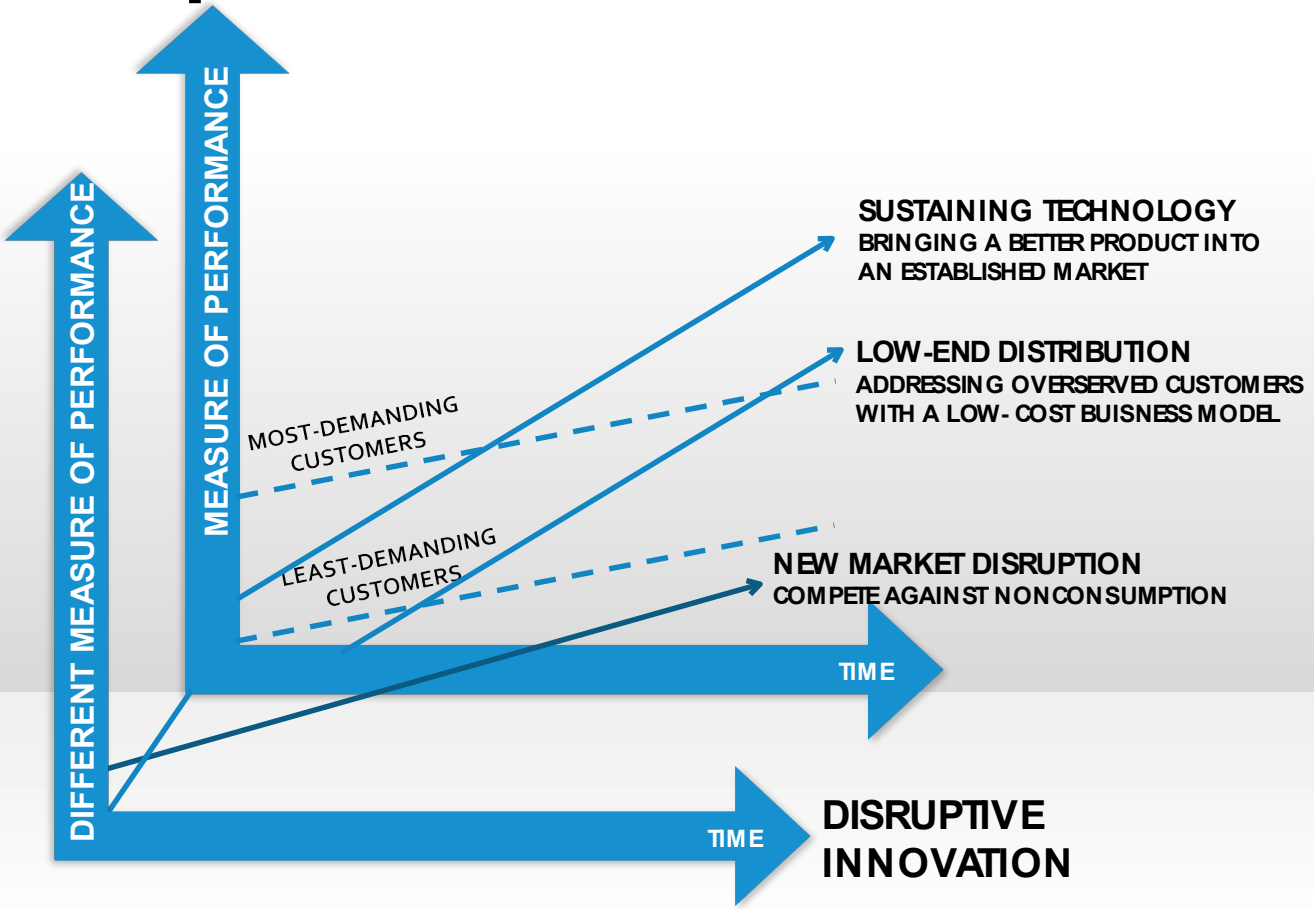
Joga Gobburu PhD FCP

MBA Professor, School of Pharmacy University of Maryland

Where is the automobile in 1915?



Disruptive Innovation Chart



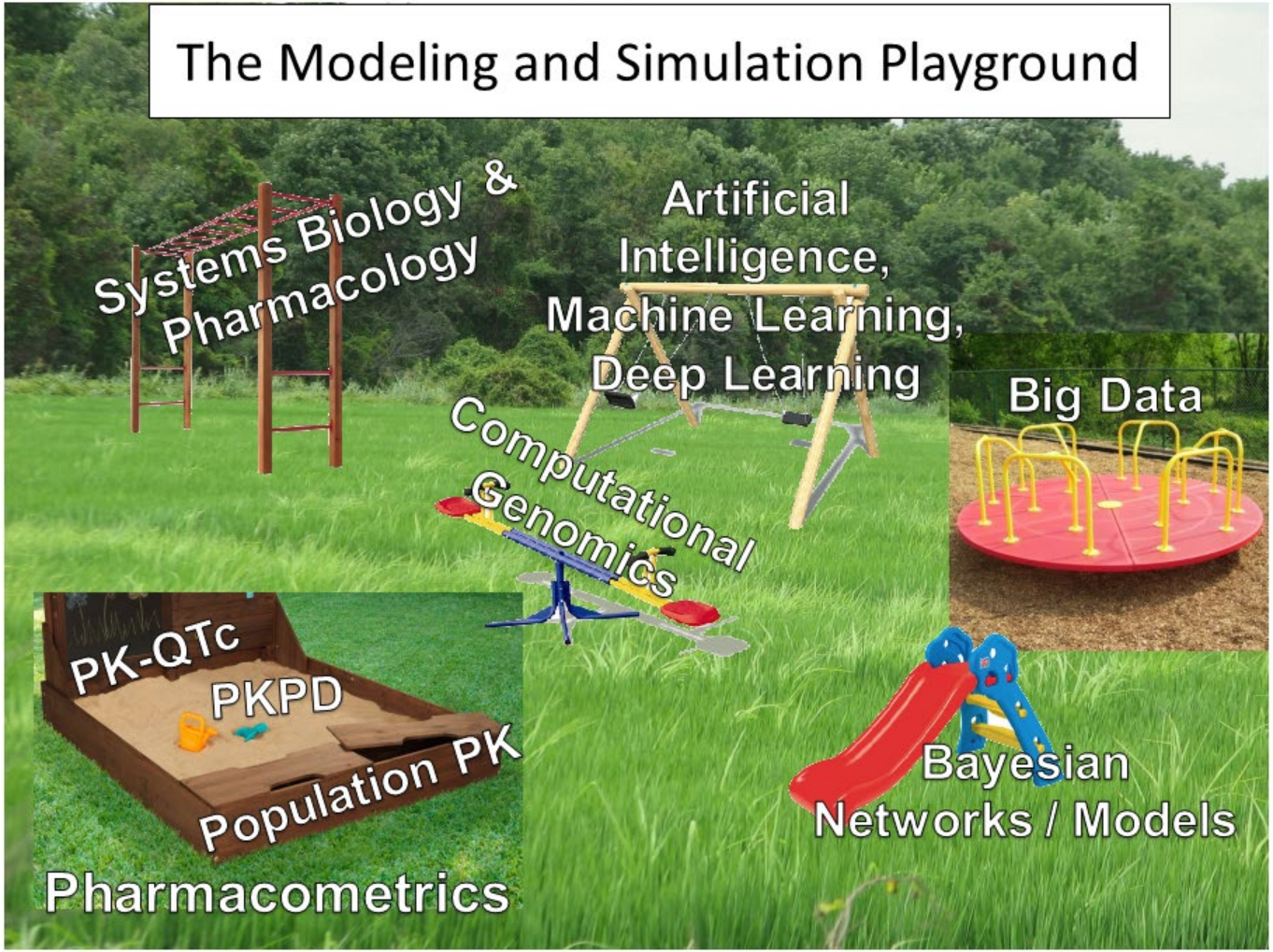
FROM MOLECULE TO PATIENT

Counterpoint!

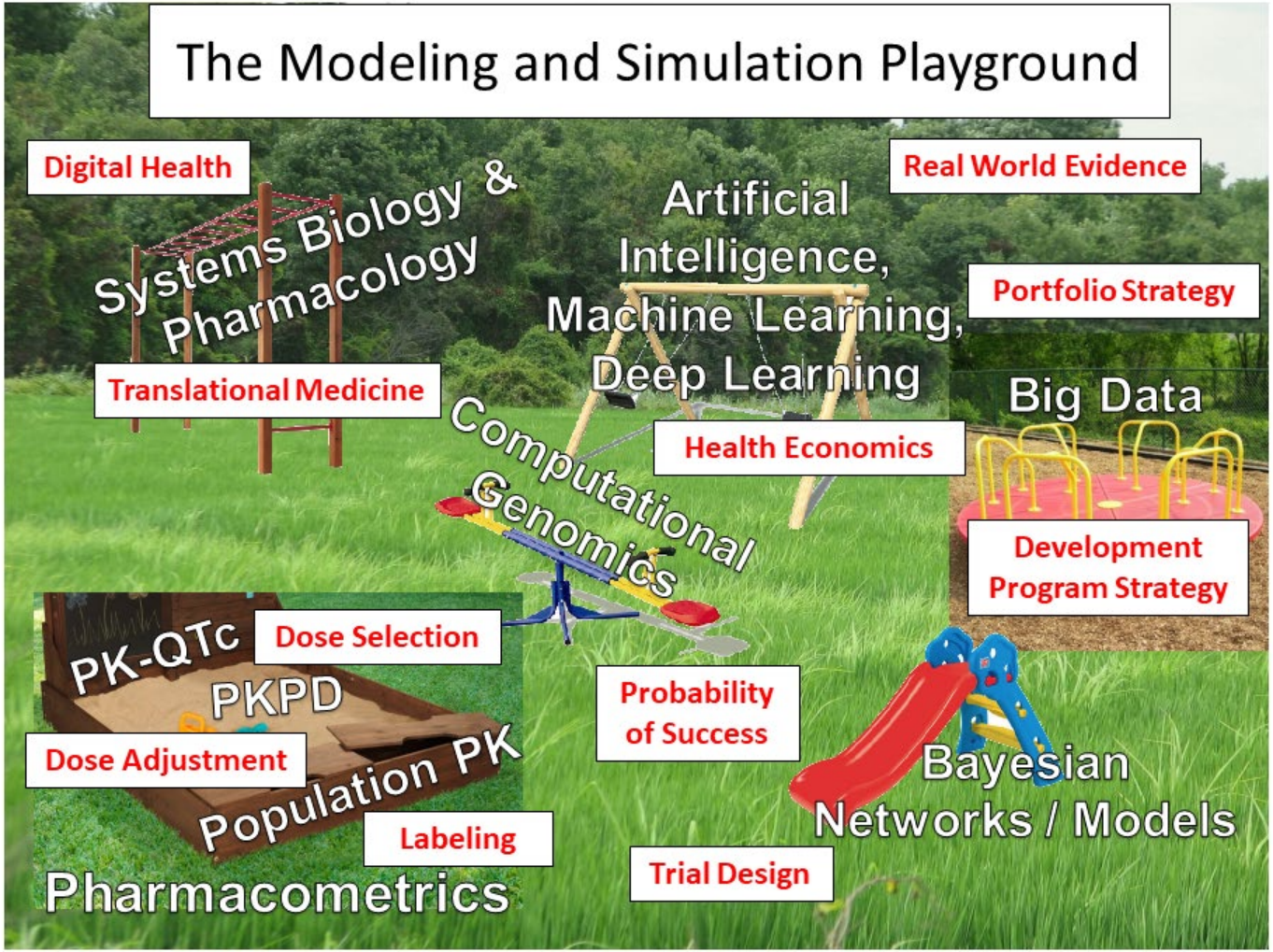
FROM MOLECULE TO PATIENT

Future is in machine learning and systems models

Marc Gastonguay
Metrum Research Group
Boston, MA



CULE TO ATIENT



CULE TO ATIENT

Future Lies in New Methodologies

FROM MOLECULE TO PATIENT

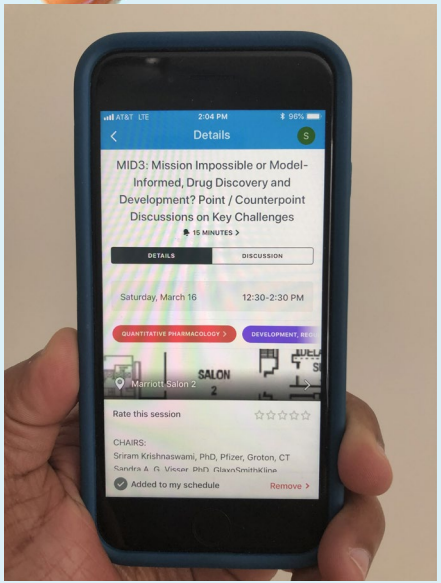
- **Automation without innovation leads to stagnation**
  - Pharmacometrics impact is limited to same old questions
  - Automation allows us not to think about the problem
- **Embrace new methods**
  - Beware of hype; thoughtful application is warranted
  - Methods are a bridge to other disciplines & questions
  - Innovate at the intersection & improve decisions
  - Opportunity to learn

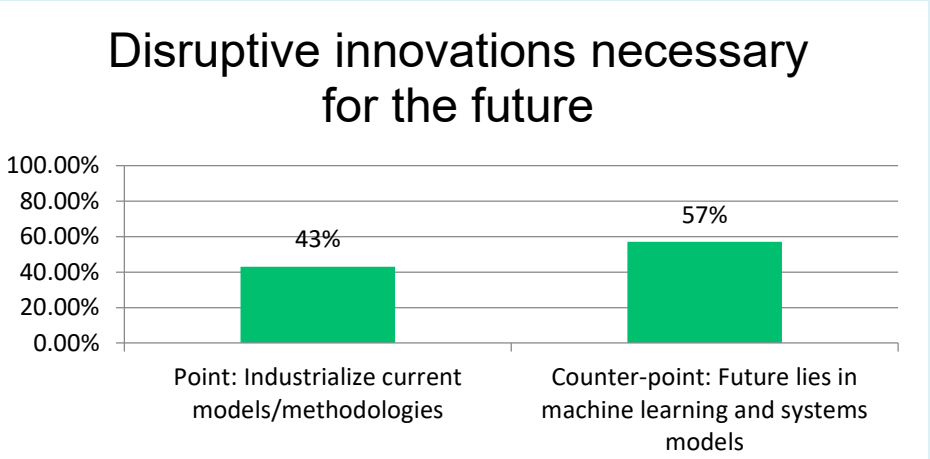
FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll

5. Disruptive Innovations





Industrialize current models and methodologies

Vs.

Future is in machine learning and systems models

6. Ideal MID3 scientist for the future

Best pharmacometricians have training in mathematics and statistics
(Daren Austin)
Vs.
Best pharmacometricians have training in medicine and pharmacology
(Piet van der Graaf)

Point!

FROM MOLECULE TO PATIENT

The best pharmacometricians have a training in mathematics and statistics

Daren Austin
GlaxoSmithKline
London, United Kingdom

MID3: Mission Impossible or Model-Informed, Drug Discovery and Development?

Statistics is the **lingua franca** of drug discovery and development

How non-mathematicians see modelling: Point and click – driverless?


The reality!
ETPHOTOS.NET
Image Copyright © Joshua Ru

Modelling is too important to be left to hobbyists and amateurs

FROM MOLECULE TO PATIENT

Counterpoint!

FROM MOLECULE TO PATIENT

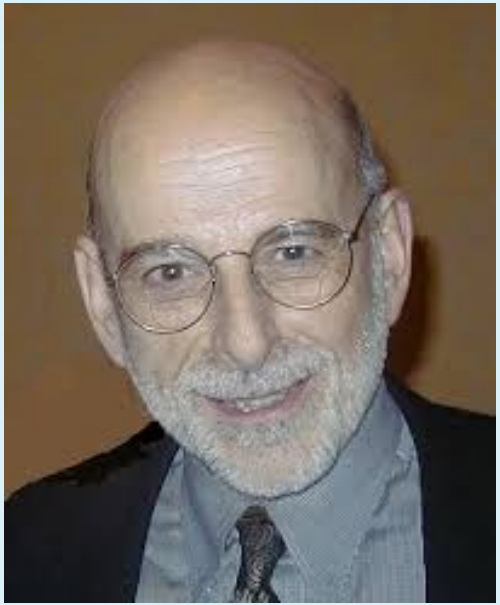
Best pharmacometricians have trained in medicine and pharmacology

Piet van der Graaf

Certara

Canterbury, UK

Let the data speak



ISoP Fellowship

Richard Brundage
David D'Argenio
Marc Gastonguay
Raymond Miller
Marc Pfister
Stacey Tannenbaum
Jill Fielder-Kelly
Nick Holford
William Jusko
Matts Karlsson
Jogarao Gobburu
Donald Mager
Stephen Duffull
Jeffrey Barrett
France Mentre
Daniele Ouellet
Yaning Wang

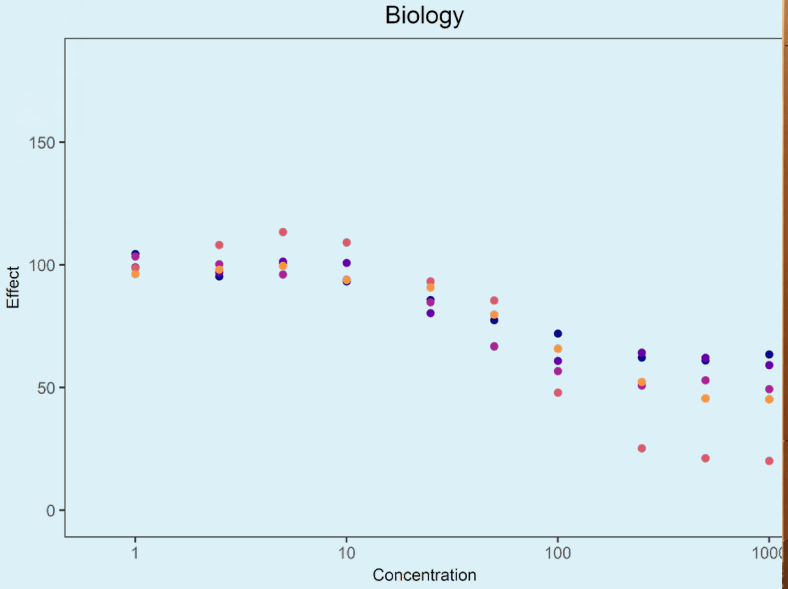
FROM MOLECULE TO PATIENT

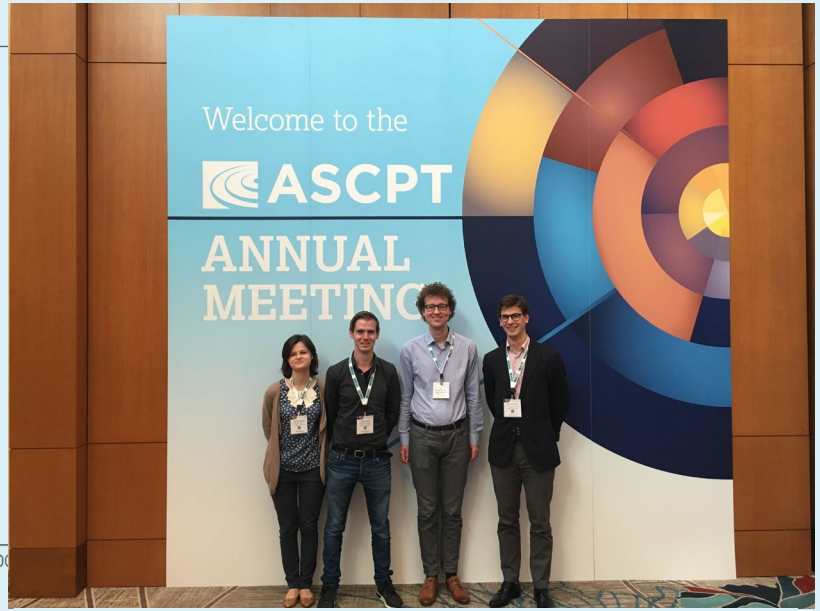
Who needs statistics?

Although the study didn't meet any of the clinical endpoints, Company X presented the Phase 2B results as "promising," based on non-significant trend observed in a subgroup analysis.

If I need a statistician to tell me if my compound has worked or not it will not be a drug

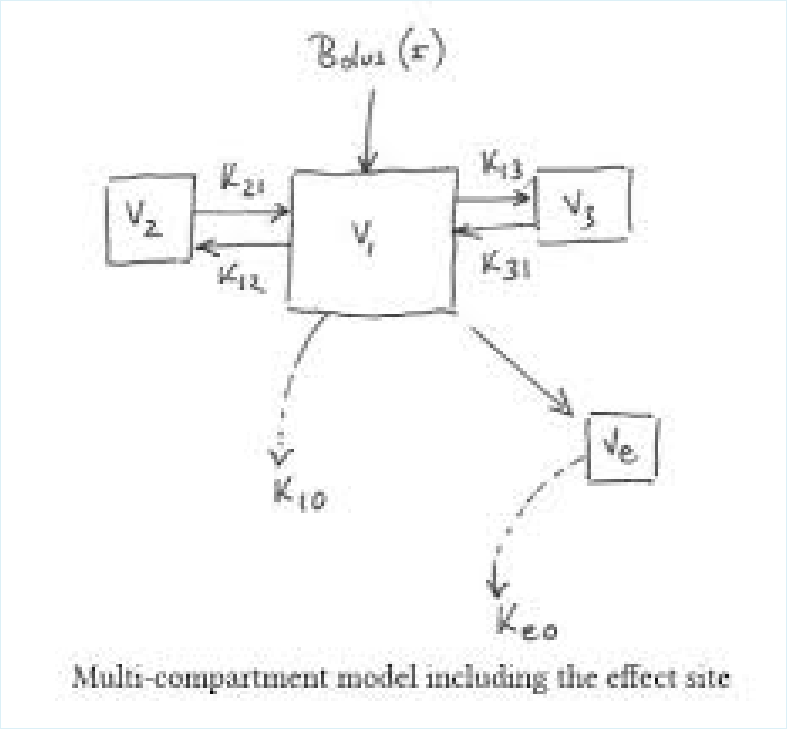
Harmful Statistics





FROM MOLECULE TO PATIENT

Harmful Mathematics



Multi-compartment model including the effect site

Dividing by V_D yields the steady state plasma drug concentration C_1

$$C_1 = \frac{k_{e0} D_e}{k_{1e} V_D} \quad \ldots(14)$$

$$D_e = \frac{D_0 k_{1e}}{(k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t})$$ from eq.…(10)

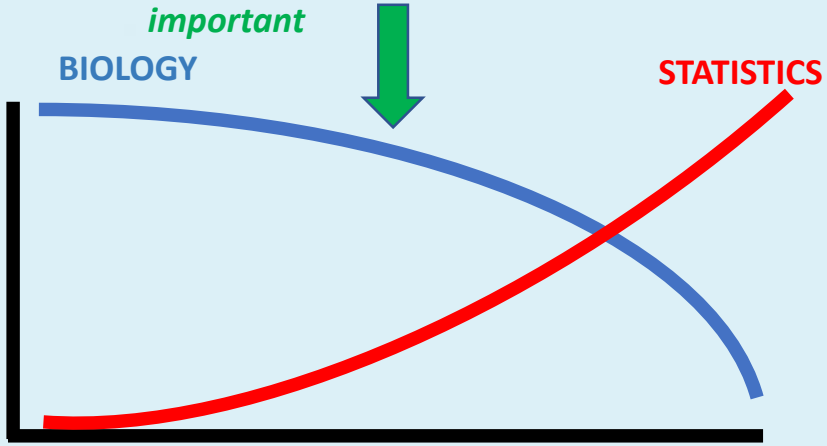
substituting D_e in equation (14)

$$C_1 = \frac{k_{e0} D_0 k_{1e}}{k_{1e} V_D (k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t}) \quad \ldots(16)$$

$$C_1 = \frac{k_{e0} D_0 k}{V_D (k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t}) \quad \ldots(17)$$

MID3: Biology *versus* Statistics

- ***Most compounds/projects fail before statistics becomes critically important***



- ***Late-stage statistical support already very-well covered by expert statisticians***
- ***Pharmaco-statistics typically a bounded problem: machines will take over***

Summary

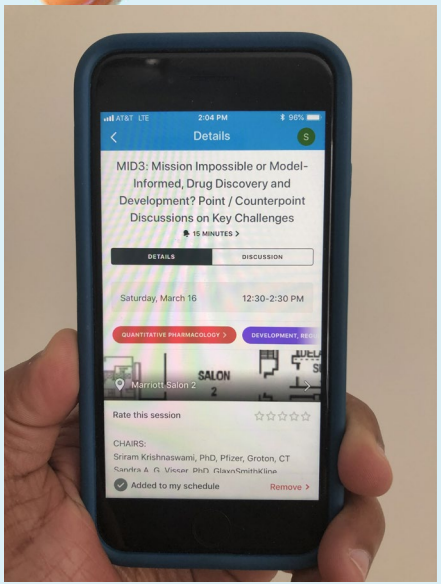
1. **“Best” pharmacometricians** trained in (bio)medical sciences
2. Statistics has **never discovered a drug**
3. **Compounds fail** before statistics becomes critically important
4. Pharmacometrics without biology is **harmful** in early R&D
5. Statistics of vital importance in **late-stage development**:
   - Too important to leave to non experts
   - Machines (not pharmacometricians) will take over

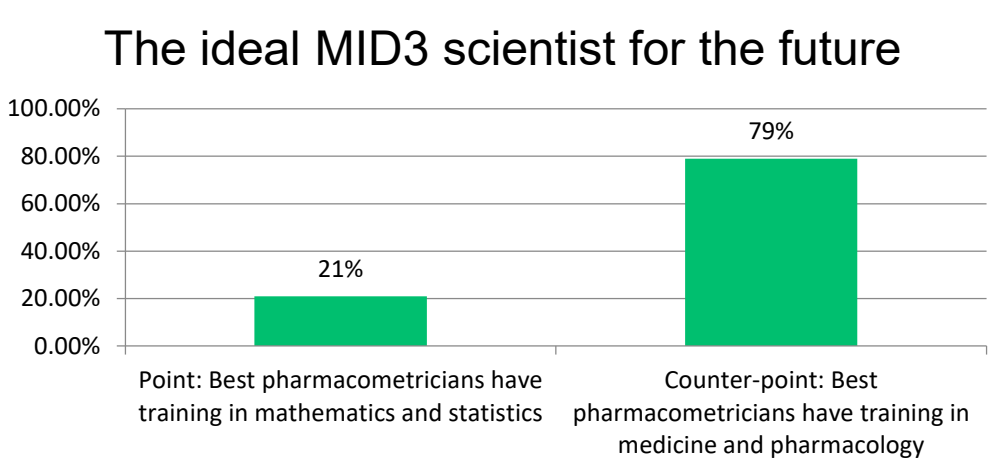
FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll

6. The Ideal MID3 Scientist





Best pharmacometricians have training in mathematics and statistics

Vs.

Best pharmacometricians have training in medicine and pharmacology

7. Organizational Opportunities in R&D

Pharmacometricians have a strategic role and hence need to be part of the core development team
(Daniele Ouellet)

Vs.

Pharmacometricians provide technical solutions but are not part of drug development teams
(Daren Austin)

Point!

Pharmacometricians have a strategic role and hence need to be part of the core development team

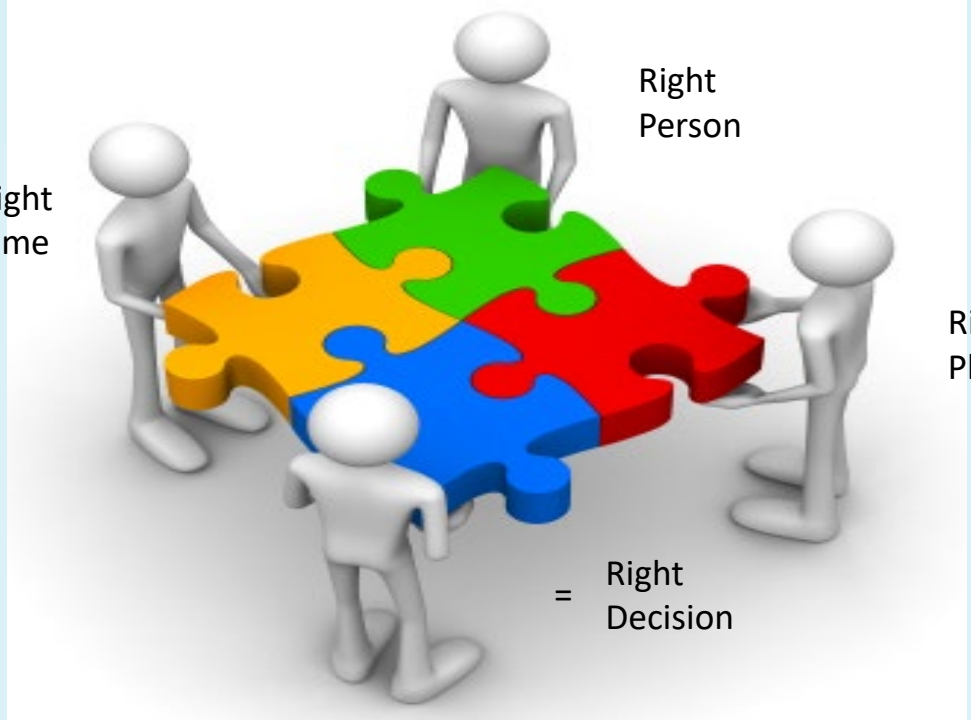
Daniele Ouellet

Pfizer

Collegeville, PA

Pharmacometricians have a strategic role and hence need to be part of the core development team

WHY?



Pharmacometricians have a strategic role and hence need to be part of the core development team

WHY?

Right Time

Right Person

Right Place

Pharmacometricians have a strategic role and hence need to be part of the core development team

WHY?

=

FROM MOLECULE TO PATIENT

Counterpoint!

Pharmacometricians provide technical solutions but are not part of drug development teams

Daren Austin
GlaxoSmithKline
London, United Kingdom

FROM MOLECULE TO PATIENT

Modelling is a perishable skill

FROM MOLECULE TO PATIENT

FROM MOLECULE TO PATIENT

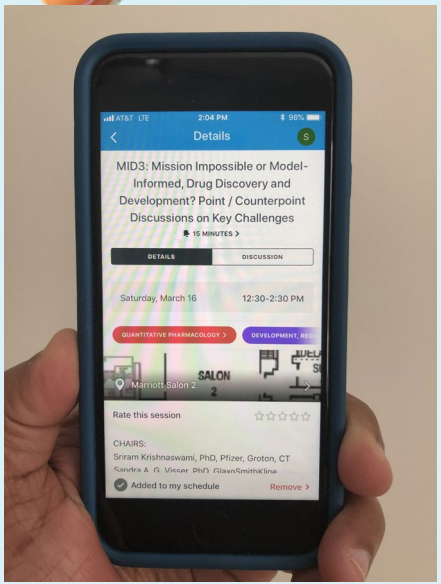
FROM MOLECULE TO PATIENT

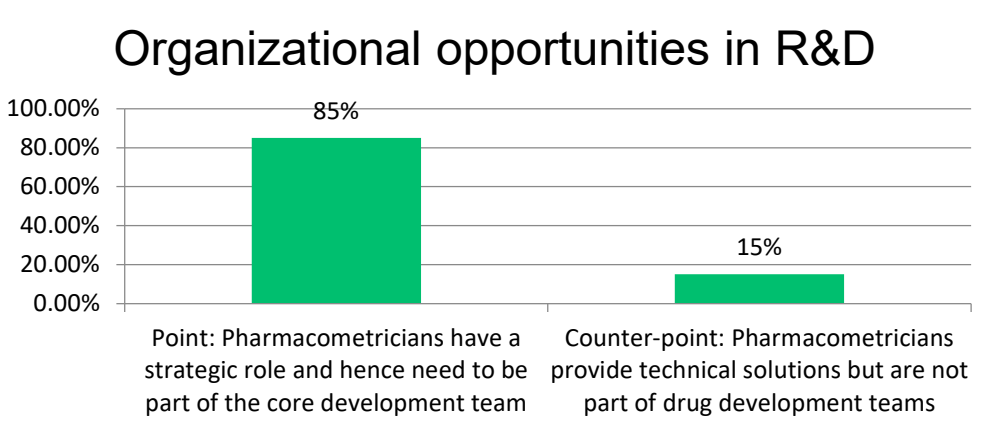
FROM MOLECULE TO PATIENT

Refutations and Rebuttals !

Time for a Live Poll

7. Organizational Opportunities in R&D





Pharmacometricians have a strategic role and hence need to be part of the core development team

Vs.

Pharmacometricians provide technical solutions but are not part of drug development teams

FROM MOLECULE TO PATIENT

THANK YOU !