



The Lion Man of Stadel Cave, 40'000 BC

Estimands – A PMX Perspective

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Method vs Use Effectiveness

Sheiner LB, Rubin DB. *Clin Pharmacol Ther.*1995;Jan;57(1):6-15. Intention-to-treat analysis and the goals of clinical trials

- **Use effectiveness:** the causal effect of prescribing a drug
 - Minimum requirement for drug approval
 - Generally determined in confirmatory trials
 - Traditionally assessed by intention to treat analyses
 - Informs treatment policy, but of limited relevance to label
- **Method effectiveness:** the causal effect of taking a drug
 - Necessary for robust dose-regimen-finding
 - Requires model-based methods
 - Sometimes difficult to implement in confirmatory setting
 - Important for label recommendations
 - Essential for individualizing dose

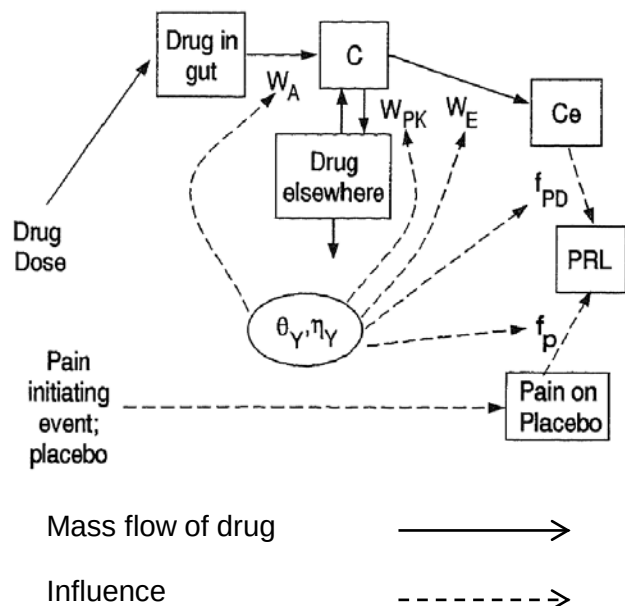
When to learn and when to confirm

Sheiner LB. *Clin Pharmacol Ther.* 1997 Mar;61(3):275-91 Learning versus confirming in clinical drug development.

1. Identify whether the question is 'learning' or 'confirming' and design appropriately within programme or trial, e.g. dose-finding
 - “Traditional statistical **pairwise comparisons** in phase 2 trials to support dose selection by testing for statistically significant differences between the groups **are not a regulatory requirement and are suboptimal in terms of dose selection**”.
 - “Mathematical, statistical and pharmacological methodologies to characterise **D-E-R** and optimal dose selection are scientifically well developed, available for application and welcomed by regulators. These should be **tailored to the specific development needs**” **EMA workshop on dose finding 2014**
2. If the question is primarily 'confirming', focus prospectively on defining the 'what' and methods that support the primary analysis and facilitate learning within the trial or potentially across trials.

PMX models and causality: demonstrate efficacy and estimate dose response

“Schematic of causal model for pain relief”



“Analyses based on few assumptions allow certain inferences relevant to the data at hand, but analyses based on more extensive assumptions may be required to reach conclusions relevant to future data” (Counterfactual)

Sheiner LB, Beal SL, Dunne A. JASA 1997;92:1235-1244. Analysis of nonrandomly censored categorical longitudinal data from analgesic trials

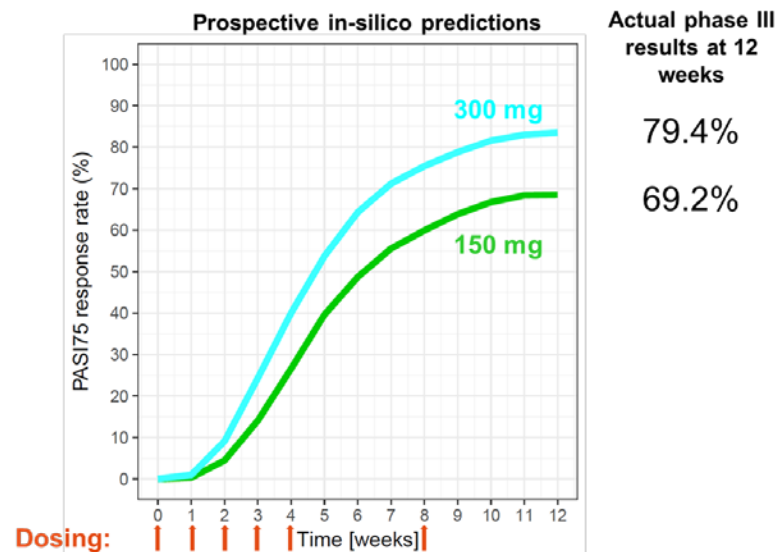
Cosentyx: Analytical Challenge

Dose-finding in psoriasis

- How do you find the best route and dosing regimen for
 - a delayed
 - non-steady-state response
 - with a variety of doses
 - regimens
 - and 2 administration routes to choose from?
- Constraints – Opportunities
 - Endpoint can be measure longitudinally and is ‘well-behaved’
 - Parenteral administration by physician
 - PK ‘well-behaved’
 - 2 Phase I and 3 Phase II trails covering wide dynamic range of inputs and reading out sequentially

Cosentyx: Solution *Learn & Confirm*

1. **Learn** about DER relationship with model and good trial data
2. Generate confidence in causal model through repeated external qualification
 - Integrate data sequentially into a PK/PD model from the Phase I and II trials as they emerge and predict outcome of 'next' trial prospectively
3. Use 'final' causal model to predict regimens that deliver good benefit-risk relative to competitors (***counterfactual***)
4. **Confirm** performance of novel regimen in Phase III



Zortress: Analytical challenge

Demonstrate contribution of drug to combination in liver transplant

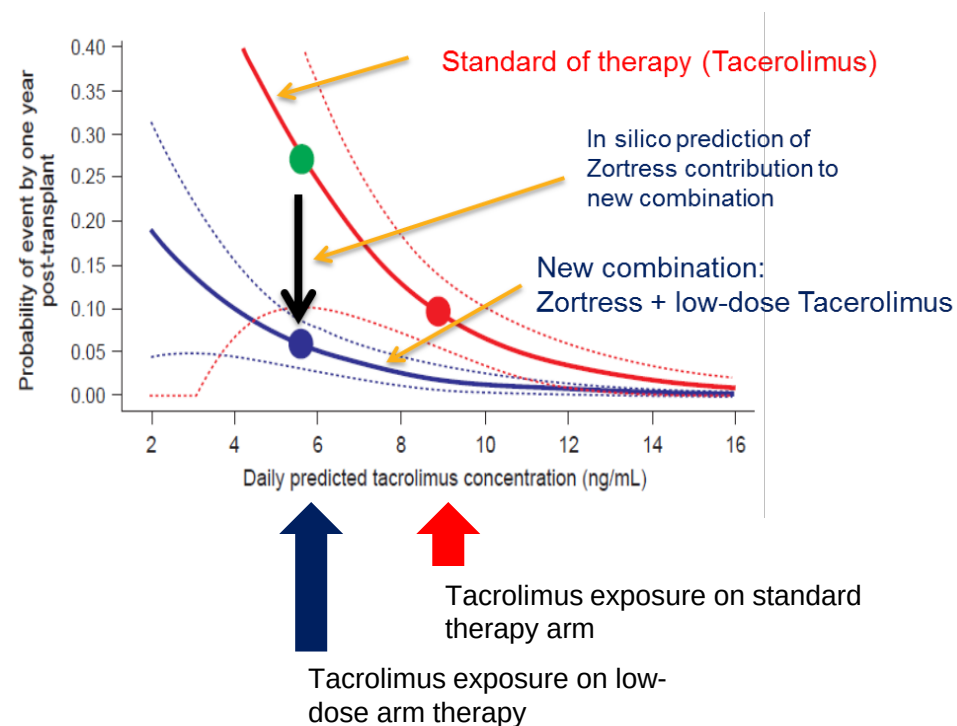
- Trial has 2 arms:
 - Tacrolimus (standard therapy)
 - Low-dose tacrolimus + Zortress
- Outcome shows that novel combination has non-inferior efficacy to standard, but much better safety profile
- How do you demonstrate the contribution of a new drug in combination with **‘low-dose’ standard drug** when it is unethical to administer the ‘low-dose’ alone?
 - What is the contribution of Zortress to the overall efficacy signal?

Zortress: Solution

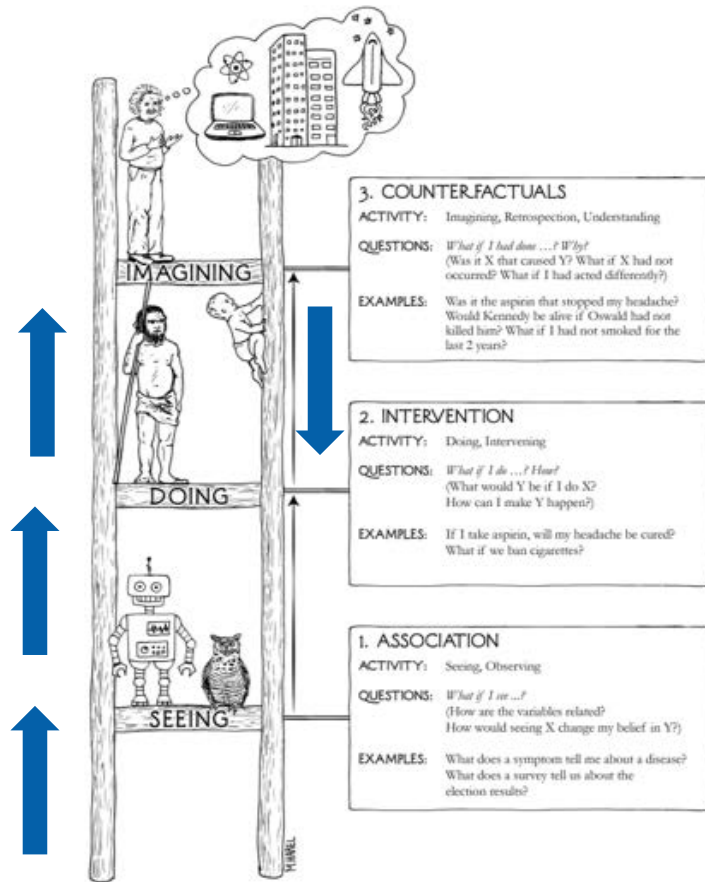
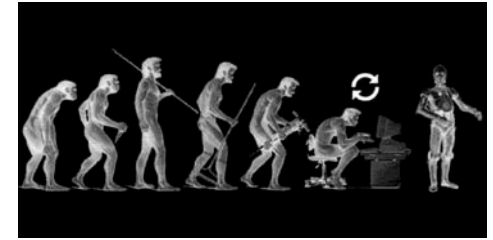
Use tacrolimus exposure-response to bridge to low-dose arm

- Estimate the ER relationship for tacrolimus in a retrospective analysis of both arms
- Difference at any given concentration is the contribution of Zortress

- Dumortier T. CPT 2015;97:411-418. Estimating the Contribution of Everolimus to Immunosuppressive Efficacy When Combined With Tacrolimus in Liver Transplantation: A Model-Based Approach
- Wang Y. CPT 2015;97:404-410. Justification of noninferiority margin: Methodology considerations in an exposure–response analysis



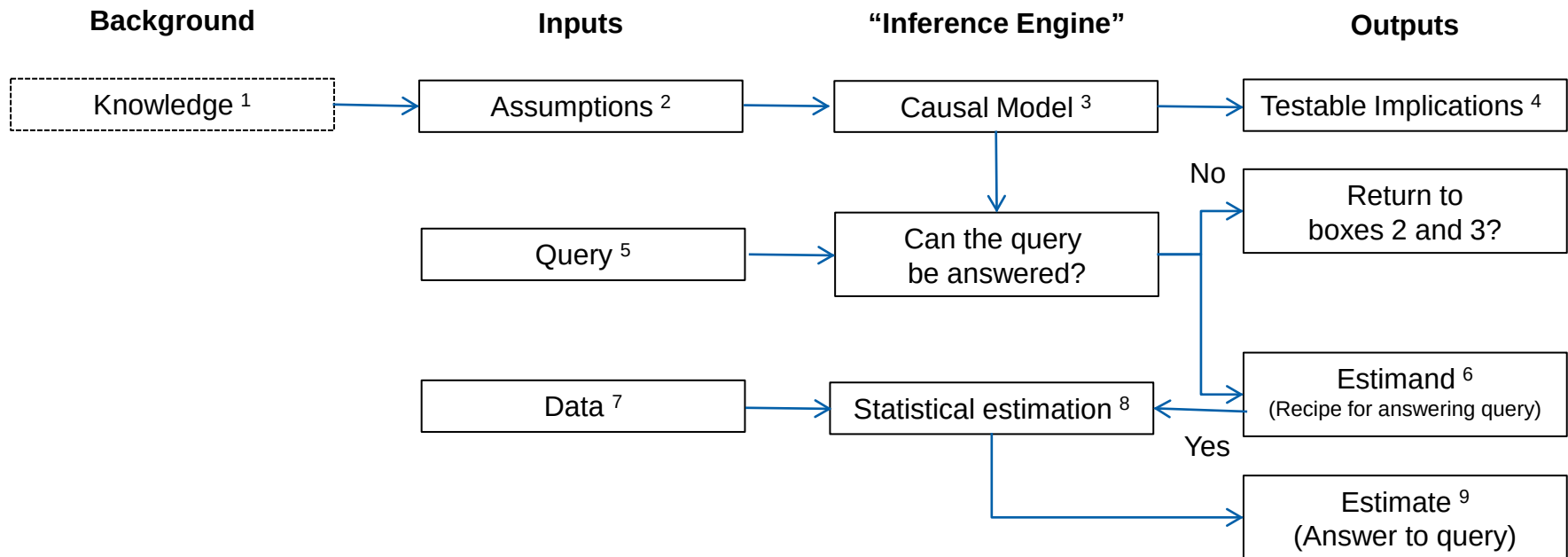
The Causal Hierarchy



- Learning from past, learning from other fields, applying laws of physics, predicting new scenarios
 - e.g. extrapolation, predict untested regimens, design new interventions
- Controlled experiments, RCTs, prior causal models + observational data
 - establish causal relationships, use or method effectiveness, mechanistic predictive models
- Observational data, RWE, statistical summaries, correlations, curve fitting, black-box predictors, machine learning, neural networks, deep learning
 - Gambling, Strategy, procedural optimization, operating characteristics, many types of problem solving (good predictions don't need good explanations)

The Book of Why – The new science of cause and effect. Allen Lane, 2018. Judea Pearl, Dana Mackenzie

“Causal Inference Engine” requires causal knowledge and statistical inference to support decision making under uncertainty

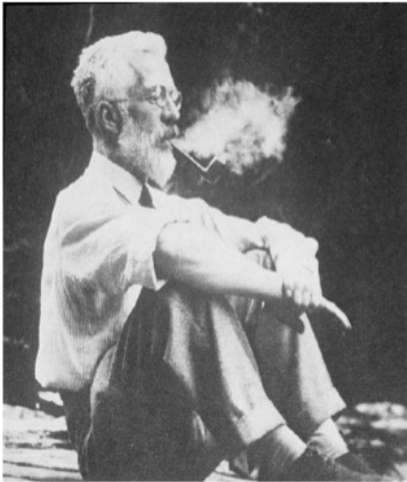


The Book of Why – The new science of cause and effect. Allen Lane, 2018. Judea Pearl, Dana Mackenzie

Development of Causal Estimands needs PMX and Biostatistics

1. The intellectual illness of clinical drug evaluation can be cured, and it will be cured when we re-store intellectual primacy to the questions we ask, not the methods by which we answer them. (Sheiner 1991)
2. This is the goal of the Estimand Framework
3. Sheiner (1997) proposed PMX model based methods as causal estimands to provide valid estimates of method effectiveness even in the presence of inter-current events
4. Regulators now encourage the use of tailored DER models for key questions such as dose finding and extrapolation
5. The inherent complexity of biological systems will always require causal models to be embedded in an appropriately rigorous statistical framework to develop the most useful causal estimands
 - This means even deeper integration of PMX and Biostatistics

Causality up in smoke



Ronald Fischer

- Father of modern statistics
- Founder of population genetics
- Inventor of randomization as the statistical tool for exploring causality
- Believed smoking did not cause cancer



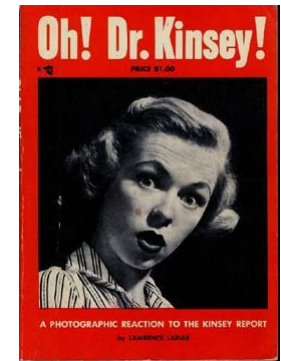
Stanton A Glantz

- Engineer
- Author: Primer in Biostatistics, Primer of Applied Regression and Analysis of Variance
- Leading researcher and activist in the nonsmokers' rights movement since 1978



John Wilder Tukey

- Mathematician
- Author: Statistical Problems of the Kinsey Report: *A random selection of three people would have been better than a group of 300 chosen by Mr. Kinsey*
- *Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.*
- *The combination of some data and an aching desire for an answer does not ensure that a reasonable answer can be extracted from a given body of data.*



Some useful literature referenced in presentation

1. Nedelman JR, Rubin BR, Sheiner LD. *Stat Med* 2007; 26:209-308. Diagnostics for confounding in PK/PD models for oxcarbazepine.
2. Sheiner LB. *Clinical Pharmacology and Therapeutics*. 1991. The intellectual health of clinical drug evaluation.
3. Sheiner LB, Rubin DB. *Clin Pharmacol Ther*.1995;Jan;57(1):6-15. Intention-to-treat analysis and the goals of clinical trials.
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8. Pearl J, Mackenzie, D. 2018. *The Book of Why – The new science of cause and effect*. Basic Books, New York.
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11. Wang Y. *CPT* 2015;97:404-10. Justification of noninferiority margin: Methodology considerations in an exposure–response analysis.