Causal Inference for Medical Decision Making

Sharon-Lise Normand

Harvard Medical School
Harvard T.H. Chan School of Public Health

April 2018

OUTLINE

- Regulatory Science
- What is Evidence?
- Assumptions
- Concluding Remarks

HEALTH CARE & PUBLIC HEALTH

1. Medical product entry
   - **Food & Drug Administration**: evaluate medical product safety, efficacy, and quality.
     - **Safety** assessment relies heavily on observations **after** market release
2. Medical products/services insurance coverage
   - **Medicare Evidence Development and Coverage Advisory Committee**: evaluates medical literature, technology assessments, etc. on benefits, harms, and appropriateness of medical items and services to make health care coverage recommendations.
     - Clinical trial enrollment of heart attack patients $\geqslant$ 75 year about 9% but they comprise 37% of target population (Lee et al., 2001)
     - Must **extrapolate** the treatment benefit to their population ($\geqslant$ 65 yrs)

Therefore, must rely on **observational** data

REFORMULATIONS (Huskamp et al., 2009)

- Manufacturer reformulate existing products to extend product life cycle (1984 Hatch-Waxman Act)
- Shift demand for original formulation (soon lose patent protection) to the reformulation
- Reformulations involve less frequent dosing, gradual release of active ingredient, or easier to administer
- Antidepressant reformulations common (**original** vs reformulation):
  - **Celexa** vs Lexapro (single isomer); **Paxil** vs Paxil CR (controlled release); **Remeron** vs Remeron Soltab (disolvable tablet)
- Clinical trial evidence is sparse; mixed at best

Do **anti-depressant reformulations** decrease medication discontinuation rates compared to **original formulations**?

SCIENTIFIC EVIDENCE FOR MEDICAL DECISIONS

- **Accumulation** of information to support or refute a theory or hypothesis*
- Replication important
- Underlying mechanism important

*Normand, McNeil, 2010

What is Best Evidence? Hierarchy of Levels of Evidence

Source: quoteimg.com Research Evidence Hierarchy Pyramid

Therefore, **many** designs contribute to evidence base

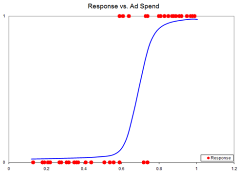
STATISTICAL & CAUSAL INFERENCE

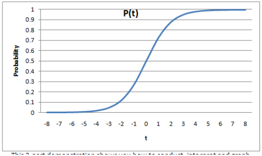
1. **ALL** methods make assumptions
   - Either implicit or explicit
   - Statistical and causal assumptions
2. Fewer assumptions better than many assumptions
   - Typically more robust
3. Must assess all assumptions
   - Quantify robustness of results if assumptions are violated
   - **Infrequently** undertaken

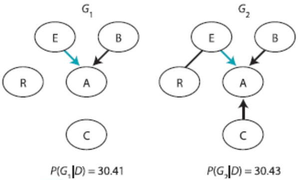
CAUSAL ASSUMPTIONS

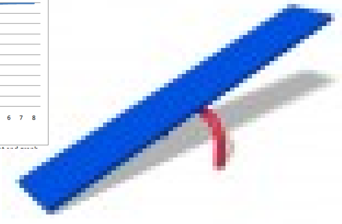
1. Sample is representative of **target** population
2. Outcomes for one subject independent of treatment assignment of other subjects **and** treatments are well-defined & the **same** for all subjects (SUTVA)
3. Within subpopulations defined by the confounders, treatments are randomly assigned
   - Untestable assumption (sensitivity analysis, multiple comparison groups, control outcomes)
4. There are subjects at every combination of observed confounders so probability of treatment bounded away from zero
   - **Structural** violations when subjects characterized by specific covariate values cannot possibly get the treatment
   - Practical violations due to **finite** sample size***
   - Statistically **testable**
5. Constant Treatment Effect

EXAMPLE: ASSUMPTIONS









Bayesian Network

Logistic Regression

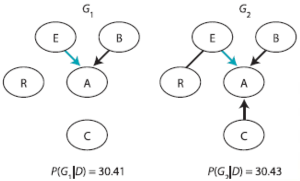
EXAMPLE: ASSUMPTIONS

Logistic Regression	Bayesian Network
	Statistical
Generalized Linear Model	Structured Directed Graph for Joint Probability Distn
$\text{logit}(p(X_1 = 1)) = \sum_{j=2}^{M} \beta_j X_j$	$P(X_1, \cdots, X_M) = \prod_j^M P(X_j \mid (PX)_j)$
Parametric linear relationship	Markov assumptions
Bernouilli variance	Hypothesis space of potential network models
Prior for β_j	Prior for probability tables

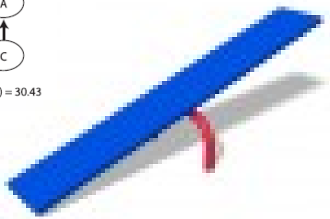
EXAMPLE: ASSUMPTIONS

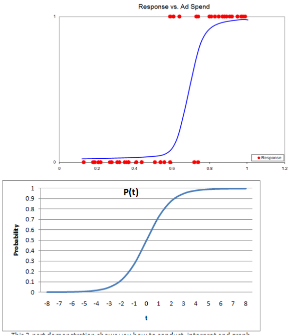
Logistic Regression	Bayesian Network
Statistical	
Generalized Linear Model	Structured Directed Graph for Joint Probability Distn
$\text{logit}(p(X_1 = 1)) = \sum_{j=2}^{M} \beta_j X_j$	$P(X_1, \cdots, X_M) = \prod_j^M P(X_j \mid (PX)_j)$
Parametric linear relationship	Markov assumptions
Bernouilli variance	Hypothesis space of potential network models
Prior for β_j	Prior for probability tables
Causal	
No unmeasured confounders	No latent/hidden variables
$0 < P(\text{Treatment} \mid \mathbf{X}) < 1$	$0 < P(\text{Treatment} \mid \mathbf{X}) < 1$
Representative sample	Representative sample
SUTVA	SUTVA

EXAMPLE: ASSUMPTIONS



Bayesian Network





Logistic Regression

KEY PRINCIPLES

- Avoid **strong** parametric specifications
  - Likely in settings with many confounders to get model wrong
- Adhere to causal inference **assumptions**
  - Validate assumptions
- Adopt a **design-based** approach
  - Separate treatment from outcome during modeling process
- Reflect all **uncertainty** in estimates

Thank You

- Kunz L, Rose S, Spiegelman D., Normand S-L. An overview of statistical approaches for comparative effectiveness research. Chapter in Methods in Comparative Effectiveness Research. Eds: Gatsonis C. and Morton S. CRC Press, 2017.
- Normand S-LT. Some old and some new statistical tools for outcomes research. Circulation 2008; 118:872-884. PMC2535854

References

- Huskamp H, Busch A, Domino M, Normand S-L. Antidepressant reformulations: Who uses them and what are the benefits? Health Affairs 2009; 28(3):734-745. PMC2752284
- Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. Journal of the American Medical Association, 2001;286(6):708-713.
- Normand S-L, McNeil BJ. What is evidence? Statistics in Medicine, 2010;29:1985-1988.