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RESEARCH GROUP

New England Statistics Symposium
UCONN

Formalizing “Similarity” in Pediatric Extrapolation Plans using Causal Selection Diagrams

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The Consulting Challenge

How do we get from this world:

Pediatric Extrapolation Concept

Similarity of Disease and Response to Treatment Between Reference and Target Pediatric Population

ICH guideline E11A on pediatric extrapolation

To this world:

The structure of the problem permits us to satisfy condition 2 of Theorem 3, since Z is S-admissible and $P^*(z|\,\mathrm{do}(x))$ is trivially transportable. The former can be seen from $(S \perp\!\!\!\perp Y|X, Z)_{G_{\overline{X}}}$, hence $P^*(y|\,\mathrm{do}(x), z) = P(y|\,\mathrm{do}(x), z))$; the latter can be seen from the fact that X and Z and unconfounded, hence $P^*(z|\,\mathrm{do}(x)) = P^*(z|x)$. Putting the two together, we get

$$(5.8)\quad P^*(y|\,\mathrm{do}(x)) = \sum_z P(y|\,\mathrm{do}(x), z) P^*(z|x),$$

Pearl and Bareinboim, External Validity: From Do-Calculus to Transportability Across Populations, Stat. Sci. 2014.

And back again?

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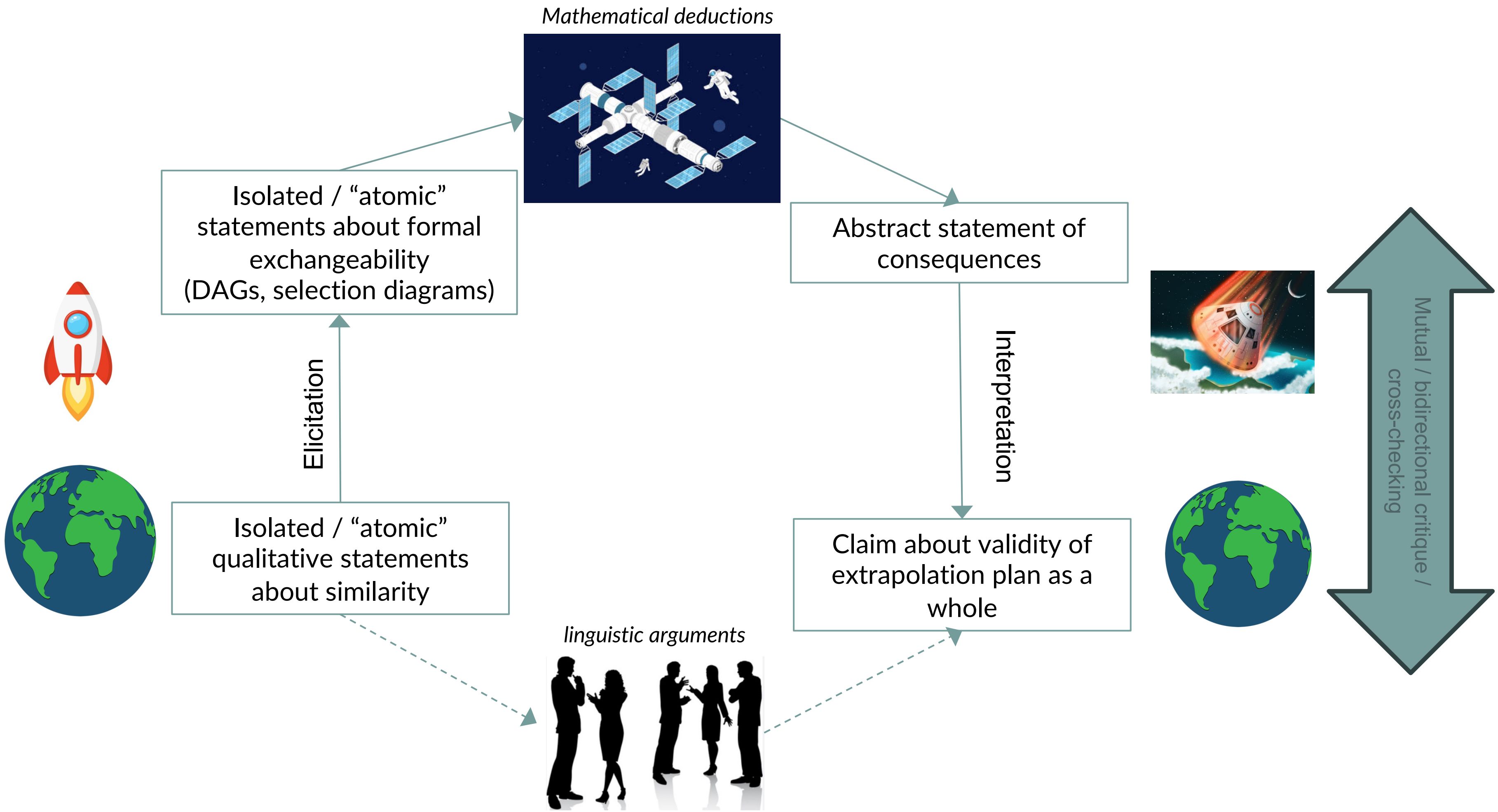
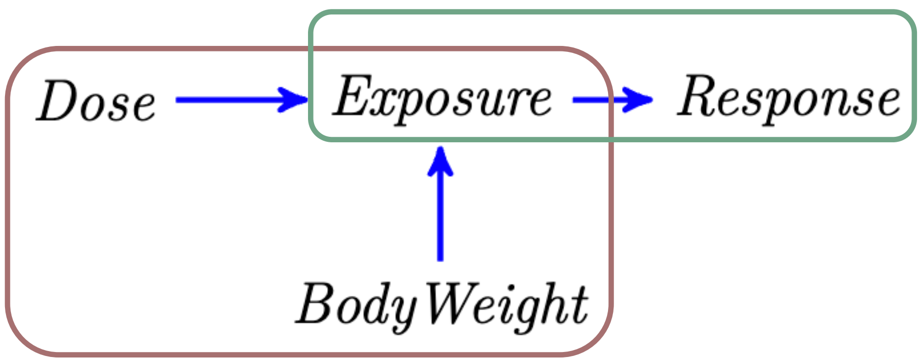

Mathematical deductions
Isolated / "atomic" statements about formal exchangeability (DAGs, selection diagrams)
Elicitation
Isolated / "atomic" qualitative statements about similarity
Abstract statement of consequences
Interpretation
Claim about validity of extrapolation plan as a whole
linguistic arguments
Mutual / bidirectional critique / cross-checking

Causal DAGs as Summaries of Within-Group Similarity Statements

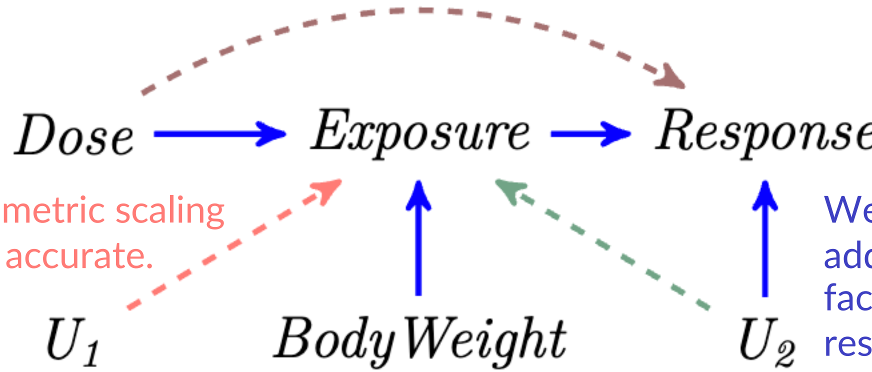
"We expect 2 different adults to have similar responses if they have similar exposure (even if they have different doses and/or bodyweights)"



"We expect 2 different adults to have similar exposure if they have the same dose and similar body weight"

Dialogue About Similarity Assumptions

Based on E-R analyses, substantial variation in the response is explained by variation in our measure of exposure, so we assume complete mediation / no pleiotropic effects



PK model with just allometric scaling by body weight is very accurate.

We do expect additional unknown factors to affect PD response …

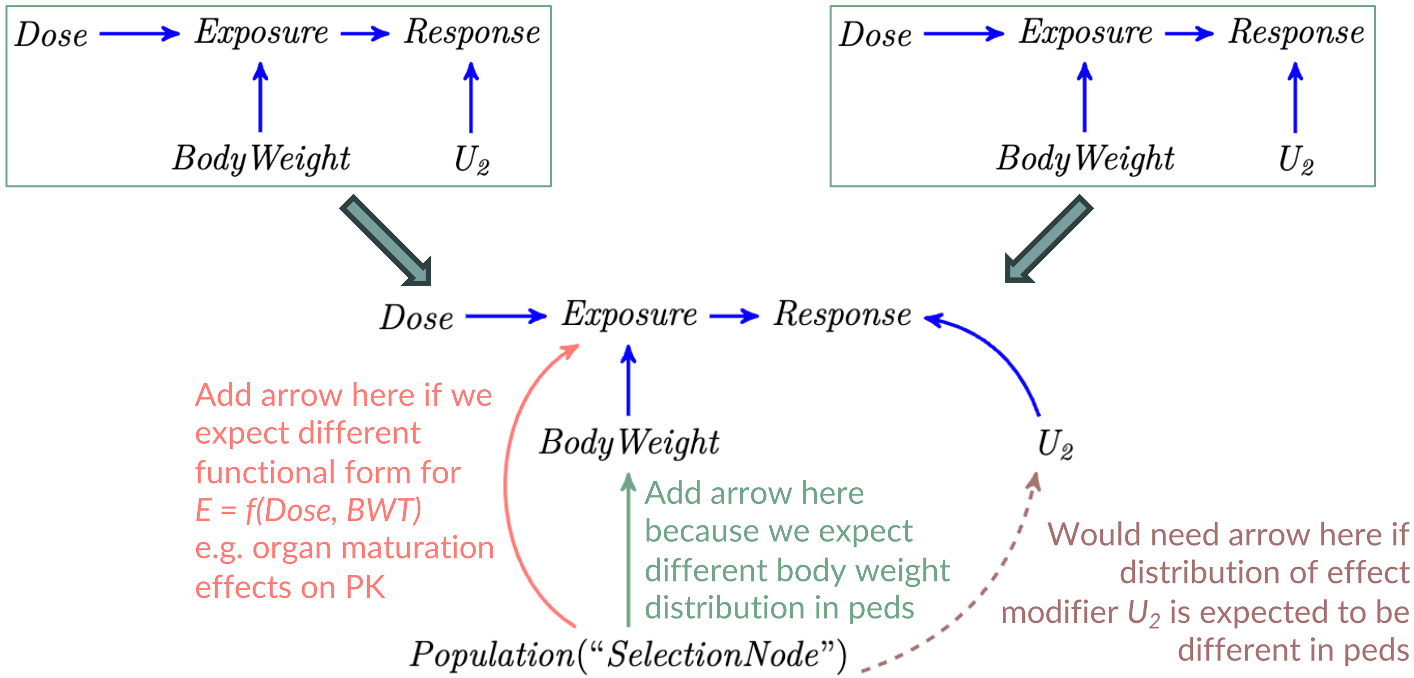
… but there is no easily-hypothesized pharmacology to suggest overlap in PK and PD factors, so we assume no confounding in E-R.

(all of these are just example justifications that could be given for excluding the dashed arrows, depending on context)

Between-Group (Dis)similarities

Working assumptions regarding similarities *within* adult population

Working assumptions regarding similarities *within* pediatric population



(this is what Pearl and Bareinboim call a "selection diagram")

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The Four Probability Spaces of Pediatric Extrapolation

Let $\boldsymbol{v}$ represent all variables in the within-group DAGs

We may not need this, if we have the right randomized studies in adults

We usually know some features of this distribution from a variety of sources, e.g. epi databases like NHANES, early phase ped data

	Adult	Pediatric
Observational	$P(\boldsymbol{v}\|D = d)$	$P^*(\boldsymbol{v}\|D = d)$
Interventional	$P(\boldsymbol{v}\|\text{do}(D = d))$	$P^*(\boldsymbol{v}\|\text{do}(D = d))$

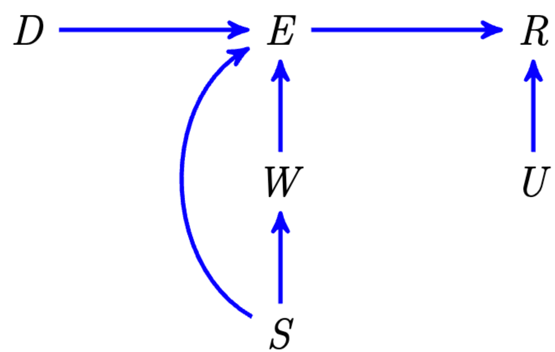
We know some features of this distribution, if we have randomized studies in adults

We likely need randomized studies in pediatrics to learn some features of this distribution, *but not necessarily studies of the clinical endpoint*

Goal: cobble these pieces together to determine $P^*(r|do(D = d))$

In Pearl and Bareinboim's terminology, a formula that accomplishes this is a "transport formula"

Selection Graph & Transport Formula for "Full Extrapolation" / "Exposure Matching"



D = dose or treatment status
E = exposure (summary metric)
R = Response
W = Body weight
U = Unmeasured effect modifier
S = Selection node (pediatric status)

Transport formula:

$$
\begin{aligned}
P^*(r \mid \mathrm{do}(D=d)) &= \textstyle\int_e P^*(r \mid e, \mathrm{do}(D=d)) P^*(e \mid \mathrm{do}(D=d))\mathrm{d}e && \text{(Law of total prb.)} \\
&= \textstyle\int_e P^*(r \mid e) P^*(e \mid \mathrm{do}(D=d))\mathrm{d}e && (D \perp R \mid E) \\
&= \textstyle\int_e P(r \mid e) P^*(e \mid \mathrm{do}(D=d))\mathrm{d}e && (S \perp R \mid E)
\end{aligned}
$$

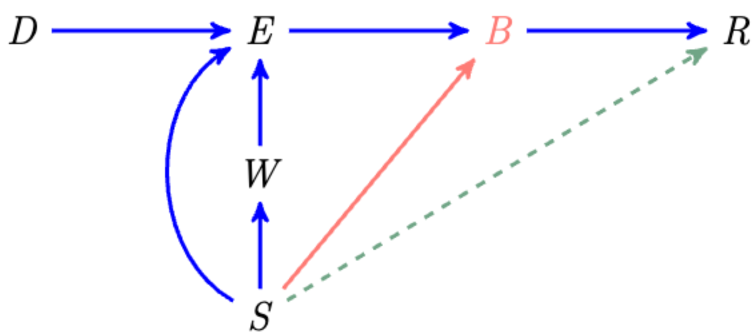
$P(r \mid e)$: Estimate with E-R model fit to adult data

$P^*(e \mid \mathrm{do}(D=d))$: Estimate with randomized study in peds with exposure endpoint

$(S \perp R \mid E)$: Conditional exchangeabilities derived from selection diagram

For example of justification to support full extrapolation, see Kalaria et al. CPT 2019.

Selection Graph & Transport Formula for "Bridging Biomarker" Approach



Introducing bridging biomarker *B* may make it easier to justify removal of *S* → *R*.

Especially true if *B* is known to be causally proximate to *R*

When this selection diagram does not include *S* → *R* :

$$
\begin{aligned}
P^*(r \mid \mathrm{do}(D=d)) &= \textstyle\int_b P^*(r \mid b, \mathrm{do}(D=d)) P^*(b \mid \mathrm{do}(D=d)) \mathrm{d}b && \text{(Law of total prb.)} \\
&= \textstyle\int_b P^*(r \mid b) P^*(b \mid do(D=d)) \mathrm{d}b && (D \perp R \mid B) \\
&= \textstyle\int_b \underbrace{P(r \mid b)}_{\text{Estimate with disease progression model fit to adult data}} \underbrace{P^*(b \mid do(D=d))}_{\text{Estimate with randomized study in peds with biomarker endpoint}} \mathrm{d}b && (S \perp R \mid B)
\end{aligned}
$$

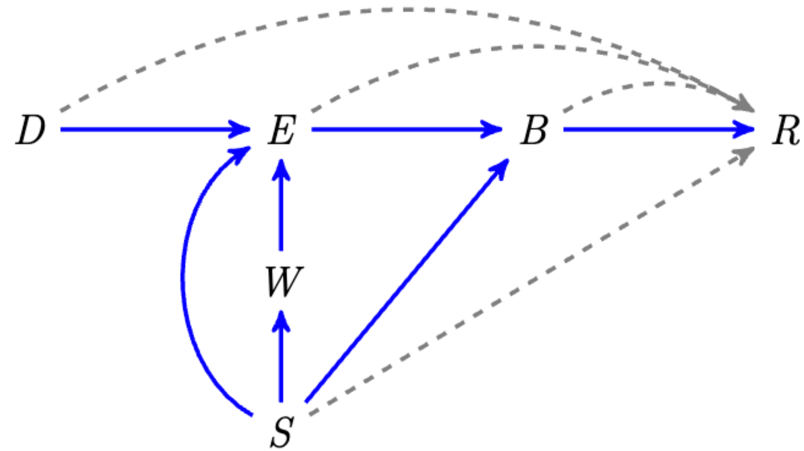
Estimate with disease progression model fit to adult data

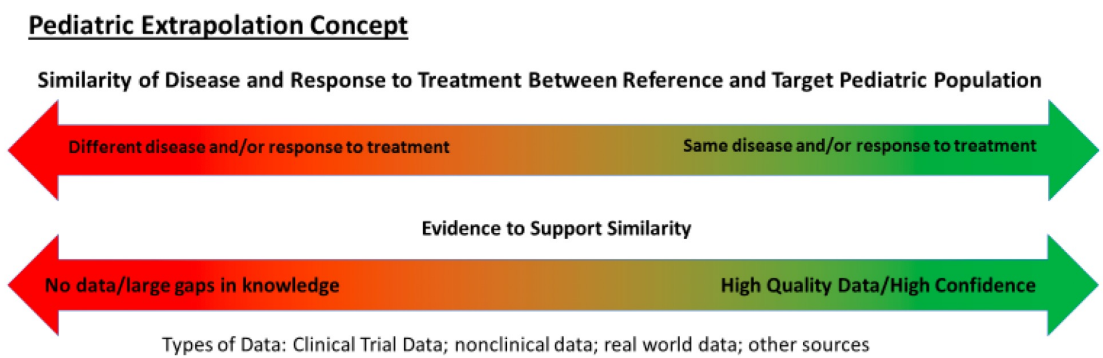
Estimate with randomized study in peds with biomarker endpoint

For discussion of bridging biomarkers, see Fleming et al. Ther. Innov. & Reg. Sci. 2022

What About All Those Arrows We Deleted?

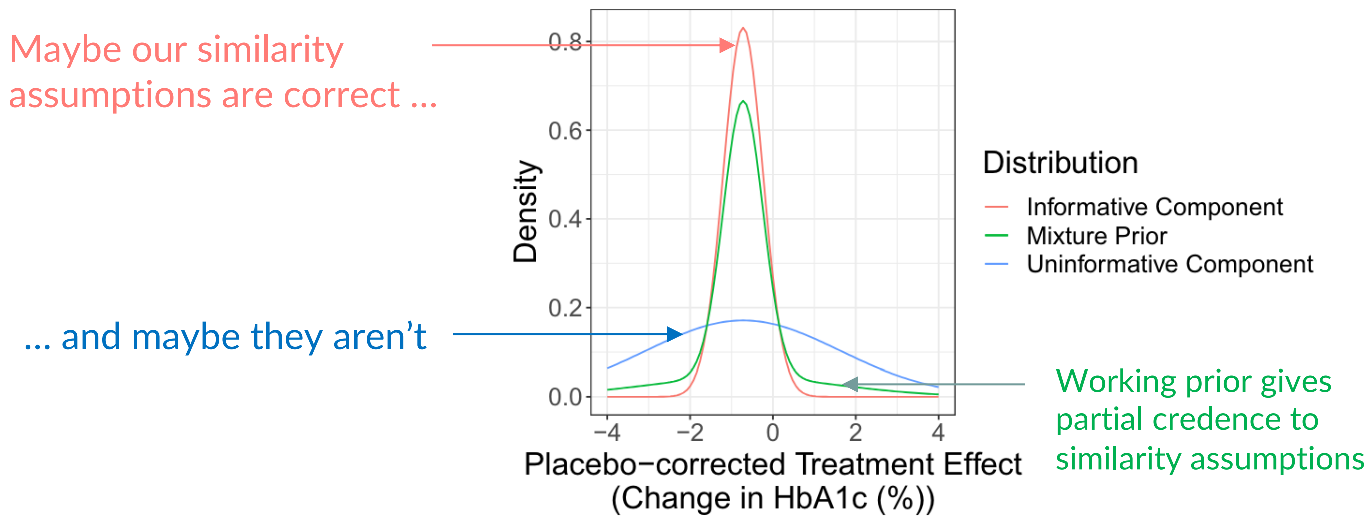
- Diagram creation fosters good conversations about assumptions (this is already a win)
- But: selection diagrams either include arrows or they don't
- If used in isolation, there is no room for the continuum of evidence described in ICH E11a





Bayesian Approach to Respect Continuum in Strength of Prior Evidence

- Bayesian prior based on working hypothesis that similarity assumptions are correct
- Robustify prior to acknowledge that assumptions / selection diagram could be wrong



Sailer, O., et al. Pharmacometrics-enhanced Bayesian borrowing for paediatric extrapolation - A case study of the DINAMO trial. PSI London (2023).
Johnston, C., et al. Bayesian Borrowing in the DINAMO Pediatric Study using Informative Priors Derived from Model-based Extrapolation. American Conference on Pharmacometrics (2023).

What Do We Gain With Diagrams?

01 If we take pains to develop a fancy selection diagram encoding conditional exchangeability assumptions,

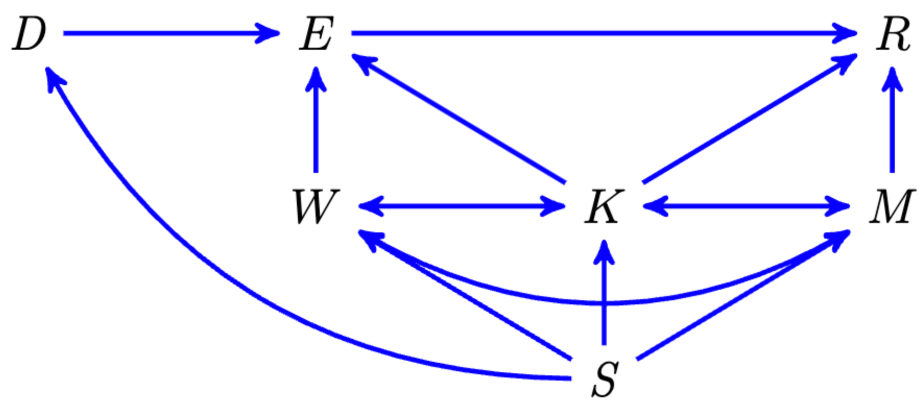
02 We still seem to give up:
"Maybe it's right, maybe it isn't; let's just be Bayesian"

03 However: along the way, **a richer conversation** about what we believe and why we believe it
(a consulting victory, not a Q.E.D.)

04 Result: more **transparent and collaborative justification of prior** + **better planning** to eliminate evidence gaps

"Among biostatisticians working in later phase drug trials, the working group observes that reluctance to use Bayesian methods appears to have three primary causes. First, the Bayesian approach does require an initial assessment of the commensurability of the various sources of information, which is often difficult for investigators to make." Gamalo-Siebers et al, Statistical modeling for Bayesian extrapolation of adult clinical trial information in pediatric drug evaluation. Pharm Stat. 2017

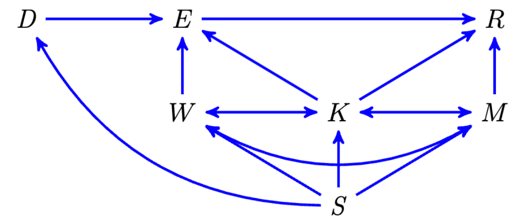
Transport With a More Complex Selection Diagram



D = dose or treatment status
E = exposure at PK steady-state
R = Change from baseline in hemoglobin A1c
W = Body weight
K = Kidney function (EGFR)
M = Concomitant medication usage

NB: the scientific rationale & evidence supporting this diagram will be presented at the *Graybill Conference*
Fort Collins, CO
June 9-12, 2024

More Complex Transport Formula



$$
\begin{aligned}
P^*(r \mid \mathrm{do}(d)) \\
&= \textstyle\int_w \int_k \int_m P^*(r \mid \mathrm{do}(d), w, k, m) P^*(w, k, m \mid \mathrm{do}(d)) \mathrm{d}m\mathrm{d}k\mathrm{d}w && \text{(Law of t.p.)} \\
&= \textstyle\int_w \int_k \int_m P^*(r \mid \mathrm{do}(d), w, k, m) P^*(w, k, m) \mathrm{d}m\mathrm{d}k\mathrm{d}w && ((W, K, M) \perp D)_{G_{\overline{D}}}
\end{aligned}
$$

$$
\begin{aligned}
&= \textstyle\int_e P^*(r \mid \mathrm{do}(d), e, w, k, m) P^*(e \mid w, k, m, \mathrm{do}(d)) \mathrm{d}e && \text{(Law of t.p.)} \\
&= \textstyle\int_e P(r \mid \mathrm{do}(d), e, w, k, m) P^*(e \mid w, k, m, \mathrm{do}(d)) \mathrm{d}e && (R \perp S \mid W, K, M)_{G_{\overline{D}}} \\
&= \textstyle\int_e P(r \mid \mathrm{do}(d), e, w, k, m) P^*(e \mid w, k, \mathrm{do}(d)) \mathrm{d}e && (E \perp M \mid W, K)_{G_{\overline{D}}} \\
&= \textstyle\int_e P(r \mid e, k, m) P^*(e \mid w, k, \mathrm{do}(d)) \mathrm{d}e && (R \perp (W, D) \mid W, K, M, E)_{G_{\overline{D}}}
\end{aligned}
$$

$$
P^*(r \mid \mathrm{do}(d)) \quad = \textstyle\int_w \int_k \int_m \int_e P(r \mid e, k, m) P^*(e \mid w, k) P^*(w, k, m) \mathrm{d}m\mathrm{d}k\mathrm{d}w\mathrm{d}e
$$

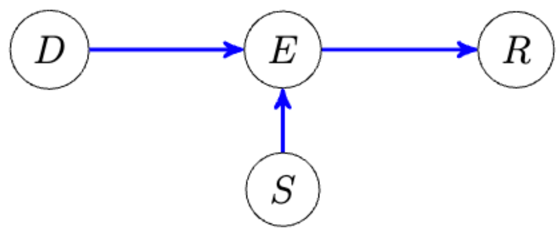
Estimate with E-R or PKPD model fit to adult data

Estimate with PK model fit to pediatric (or ped + adult) data

Estimate with empirical pediatric dist’n or epi database

In practice, the above integrals are estimated by averaging over Monte-Carlo simulations from the outcome models

Selection Diagrams Bridge Between Worlds

Non-statistician mood	Summary of assumptions	Statistician mood
	**Pediatric Extrapolation Concept** Similarity of Disease and Response to Treatment Between Reference and Target Pediatric Population 	
		
	The structure of the problem permits us to satisfy condition 2 of Theorem 3, since Z is S-admissible and $P^*(z \mid \mathrm{do}(x))$ is trivially transportable. The former can be seen from $(S \perp\!\!\!\perp Y \mid X, Z)_{G_{\overline{X}}}$, hence $P^*(y \mid \mathrm{do}(x), z) = P(y \mid \mathrm{do}(x), z)$; the latter can be seen from the fact that X and Z and unconfounded, hence $P^*(z \mid \mathrm{do}(x)) = P^*(z \mid x)$. Putting the two together, we get (5.8) $P^*(y \mid \mathrm{do}(x)) = \sum_z P(y \mid \mathrm{do}(x), z) P^*(z \mid x),$	

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Camille Vong (GSK)
Yuchen Wang (Pfizer)
Jixian Wang (BMS)
Theo Papathanasiou (GSK)

*special thanks to Tom for helping me apply *do*-calculus correctly on slide 14

Thank You

Get in touch with me:

jimr@metrumrg.com

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Sebastien, B. et al. Use of pharmacodynamic modeling for Bayesian information borrowing in pediatric clinical trials. J. Biopharm Stat. 2023, Vol. 33, No. 6, 726-736.

Science is about generalization, and generalization requires that conclusions obtained in the laboratory be transported and applied elsewhere, in an environment that differs in many aspects from that of the laboratory...
On the theoretical front, the standard literature on [extrapolation], falling under rubrics such as “external validity” …consists primarily of “threats,” namely, explanations of what may go wrong when we try to transport results from one study to another while ignoring their differences.
… this paper departs from the tradition of communicating “threats” and embarks instead on the task of formulating “licenses to transport,” namely, assumptions that, if they held true, would permit us to transport results across studies.

— Judea Pearl and Elias Bareinboim, Stat Sci 2014