April 17, 2024

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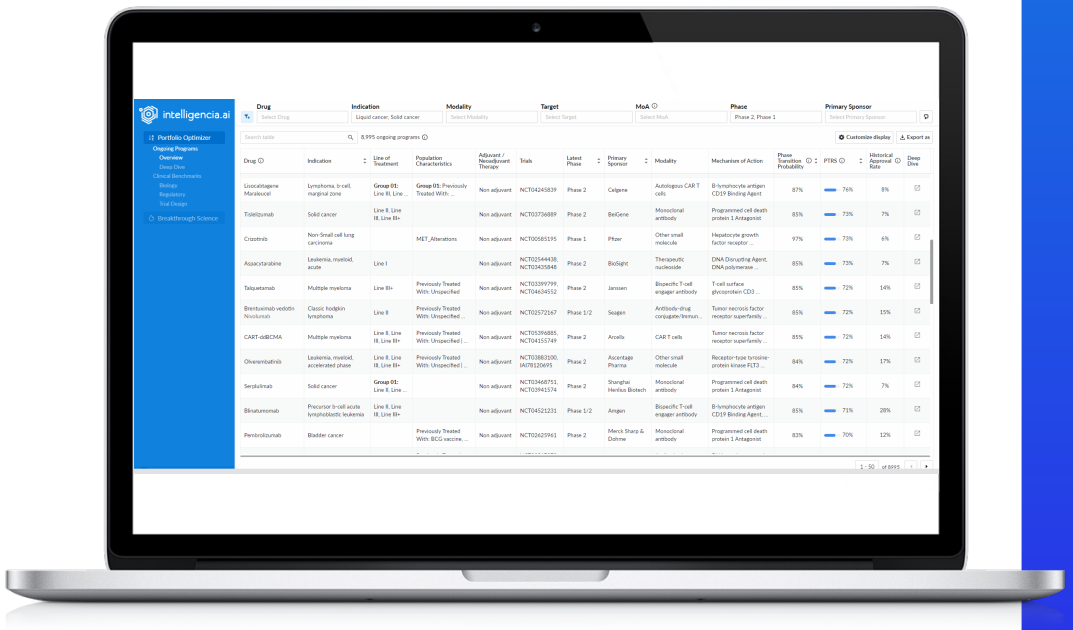
Moneyball in Drug Development

Learning about clinical trials from curated, publicly available clinical trial data

Intelligencia AI

Who They Are

- Founded in 2017 in New York
- 100+ people (>90% advanced degrees)
- Patented technology on Probability of Success
- Collaborations with leading pharmaceutical companies



What They Do

- **Expertly-curated & granular data on clinical trials**
- Proprietary and harmonized ontologies
- AI-driven PTRS & Explainability
- Modular and granular benchmarks & baselining
- Insights for Competitive Intelligence & Scenario Analysis

Intelligencia AI

For additional Information

Clinical Trial Data in These Studies

Expertly curated from ClinicalTrial.gov, announcements, conferences & publications

DRUGS

- Mechanisms of action
- Targets
- Modalities
- Genes
- Biological pathways
- Protein classes

PROGRAMS

Defined by the following dimensions:

- Primary drug
- Additional drugs
- Therapeutic area
- Lead indication
- Administration mode
- Intervention
- Primary drug dosage
- Indication
- Line of treatment
- Stage of disease
- Patient selection biomarker
- Other patient characteristics: Sex, Age, Smoking status
- Previously treated with …
- Adjuvant status
- Sponsor

TRIALS & COHORTS

Defined the program dimensions plus:

- Start date
- End date
- Termination date
- Basket
- Umbrella
- Allocation: random or not
- Masking: Open label, double blind…
- Intervention model: Single-Arm, parallel, crossover,…
- Safety result
- Trial size
- Endpoints

Moneyball Questions

1. **Impact of Trial Design on Phase PoS**
   1. **Patient selection biomarkers**
   2. Combo v. monotherapy
   3. Trial size
   4. Single arm vs. comparator
   5. Masked v. open label
   6. Randomize v. not randomized
   7. Dose & exploration
   8. Endpoints

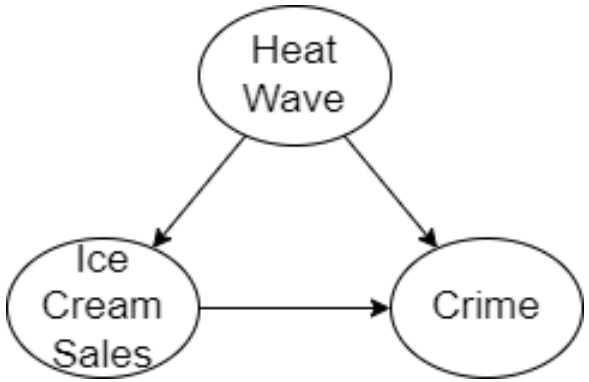
2. **Impact of prior clinical trials on Phase PoS**
   7. Same drug in different indication.
   8. Same target (different drug) in same indication.
   9. Same target, different drug, different indication

3. **Basket & platform trial (multiple shots on goal)**
   10. Impact on PoS
   11. Impact on false-positive rate
   12. Probability of false-negatives
   13. Optimal size of basket trial
   14. Correlation of the arms (common tumors, combos with common components)
   15. Any MAB boost?
   16. Exploration v. Exploitation
   17. Rate of accumulating information over time

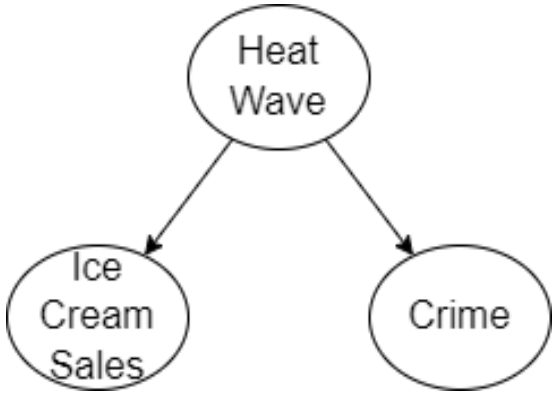
Introducing Causal Inference: The ladder of causation

Rung		Action	Question
3	Counterfactual	Imagining	If I had done X, what would Y be?
2	Intervention	Doing	What will happen to Y if I do X?
1	Association	Observing	How does observing X change my belief in Y?

Influence Diagram



Causal Diagram



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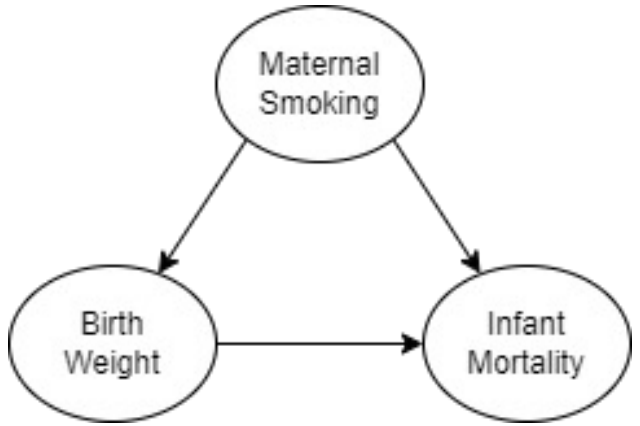
Causation v. Correlation: Observational vs. Experimental Data

1. Question: Does birthweight impact infant mortality?



2. Conditional probabilities are *different* *situations*:

   a) $p(\text{Motality}|\text{Birth Weight} = \text{High})$

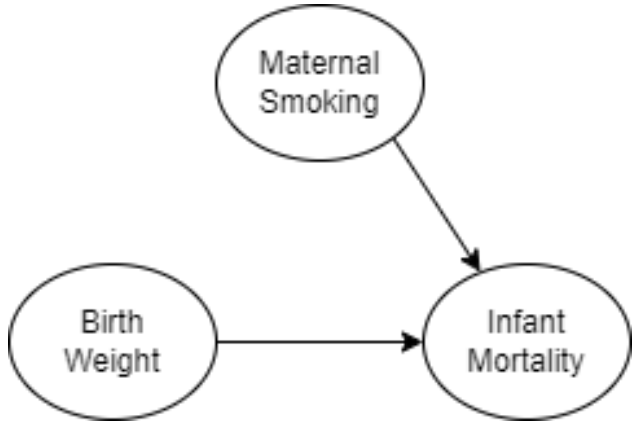
   b) $p(\text{Motality}|\text{Birth Weight} = \text{Low})$

3. We want the results of this *experiment*:

   c) Randomize birth weight

   d) $p(\text{Motality}|\text{Birth Weight} = \text{High})$

   e) $p(\text{Motality}|\text{Birth Weight} = \text{Low})$



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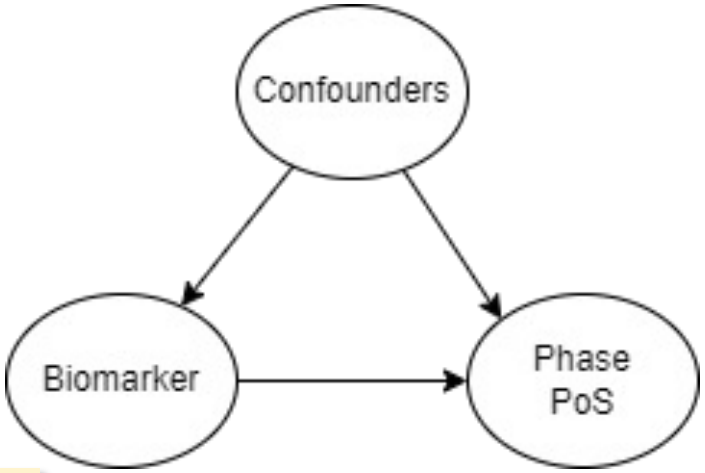
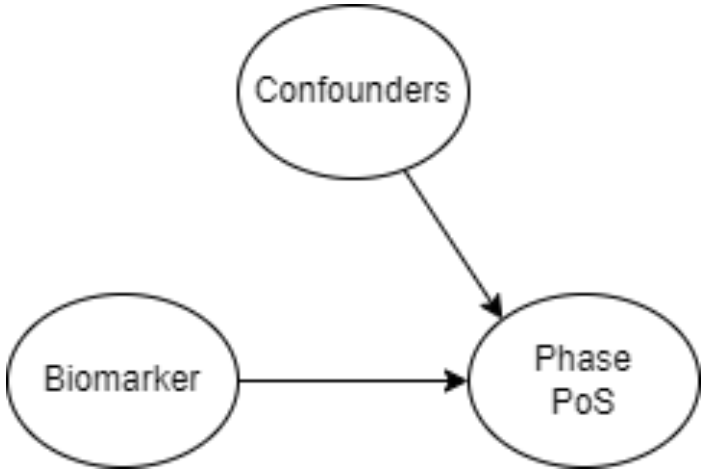
Getting experiments from observational data





Means intervention

(not observation)

$$p\big(\text{Success} \mid Do(BM = 1)\big) = \sum_C p(\text{Trial Success} \mid BM = 1, C = c)\ p(C = c)$$

$$p\big(\text{Success} \mid Do(BM = 0)\big) = \sum_C p(\text{Trial Success} \mid BM = 0, C = c)\ p(C = c)$$

Causal Effect: $p\big(\text{Success} \mid Do(BM = 1)\big) - p\big(\text{Success} \mid Do(BM = 0)\big)$

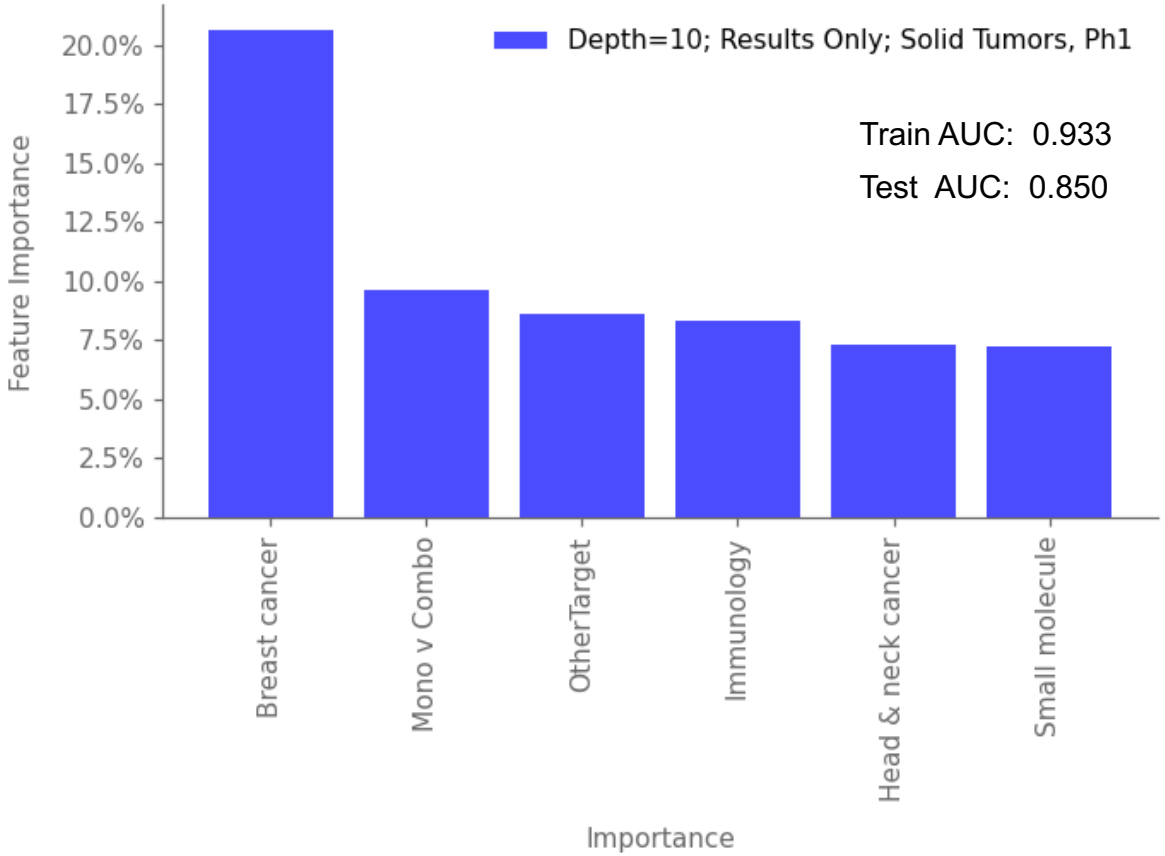
Previous Statistic's Advice on Selecting Controls

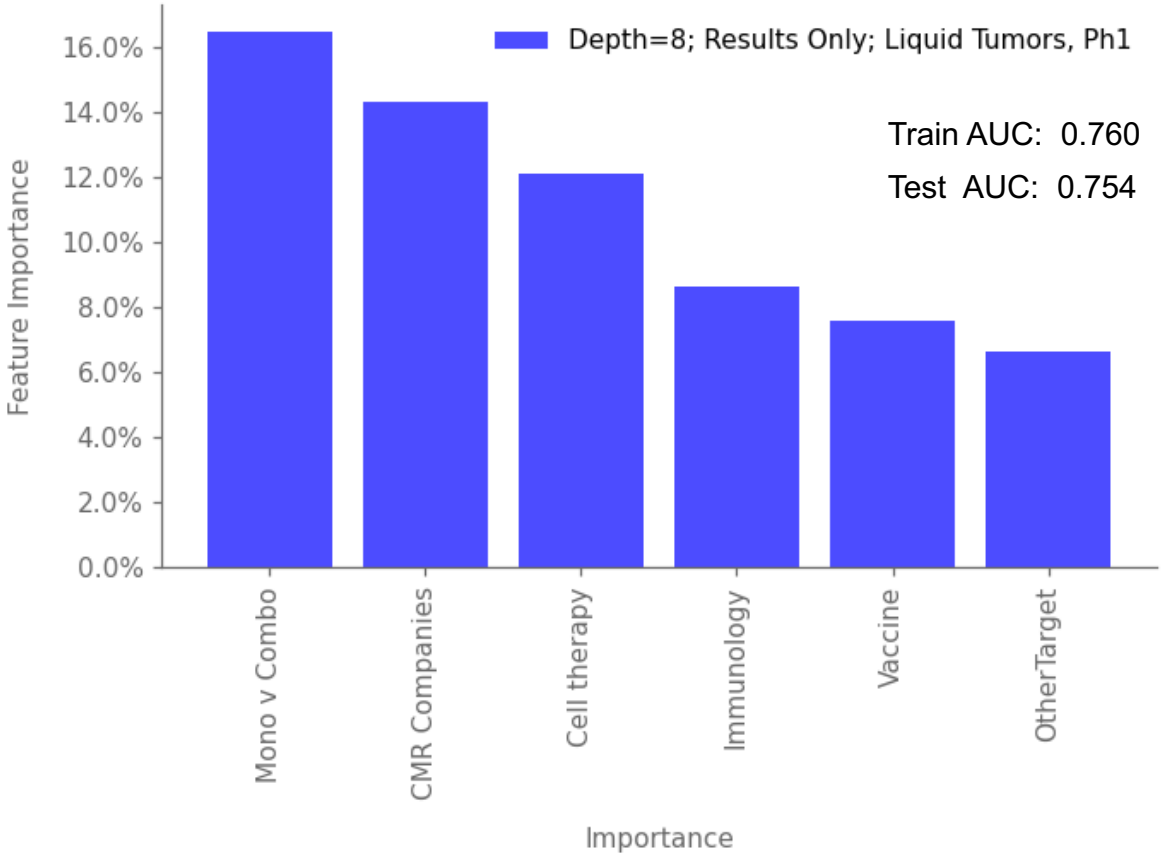
(Bad) Advice on controls

1. Include relevant variables.
2. Include independent variables unaffected by treatment.
3. If unsure whether to include a variable, omit it.
4. Do not include outcome variables.
5. Build models with and without the control variables and contrast the findings.

Causal salad: Tossing various "control" variables into analysis (ex: regression), observing changes in estimates, and telling a story about causation.

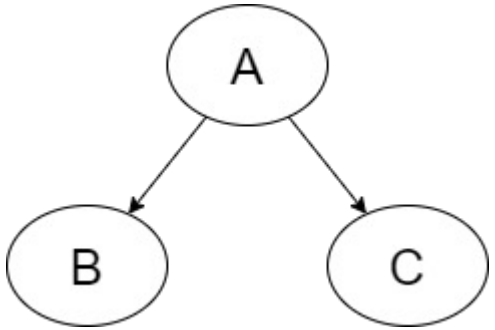
Do the situations differ? Yes, a lot.





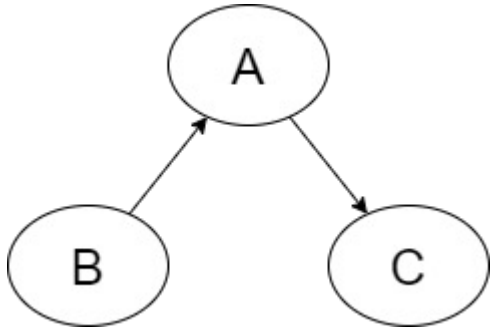
The Building Blocks for Causal Models

Fork



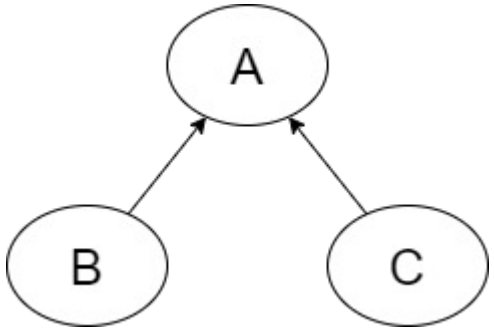
$B \perp C \mid A$

Pipe



$B \perp C \mid A$

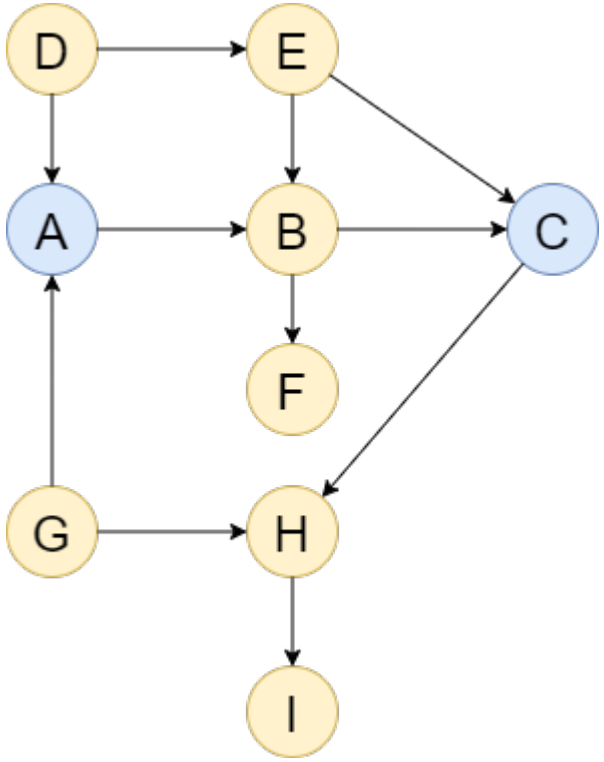
Collider

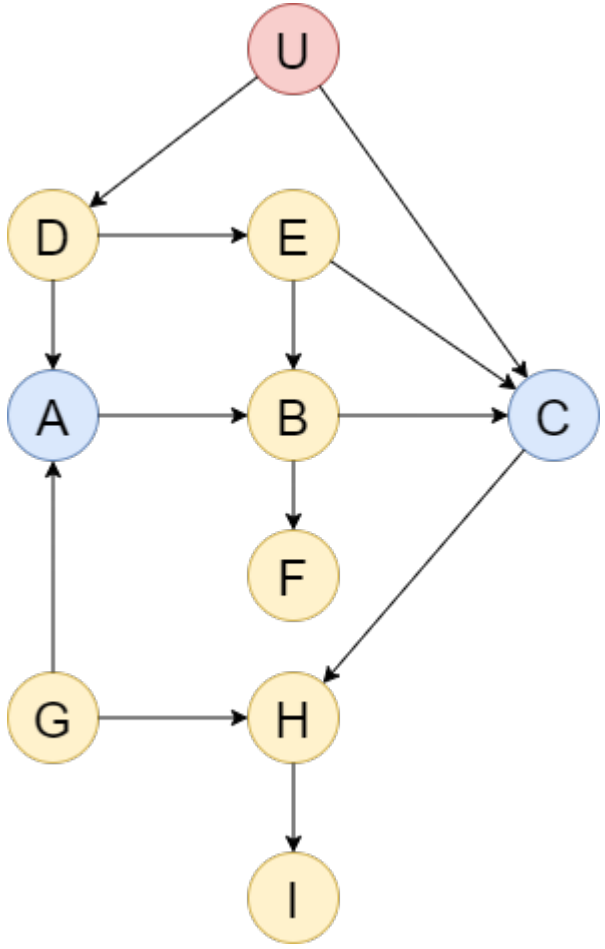


$B \perp C$

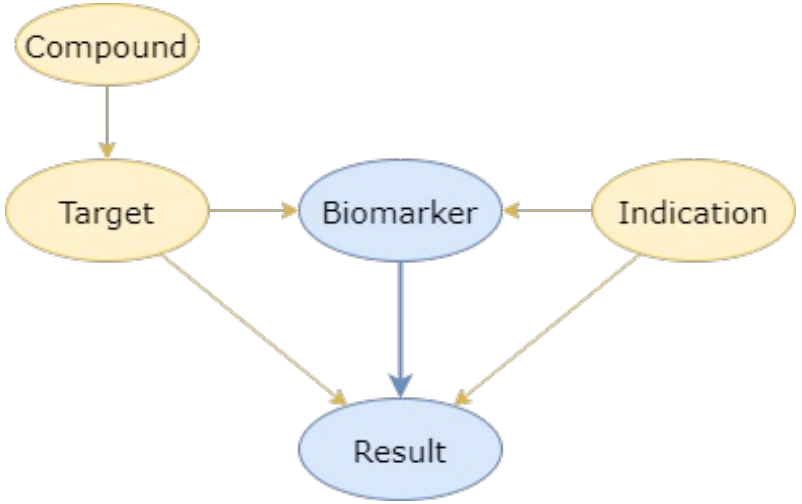
$B \text{ not} \perp C \mid A$

Close All the Back-Door Paths





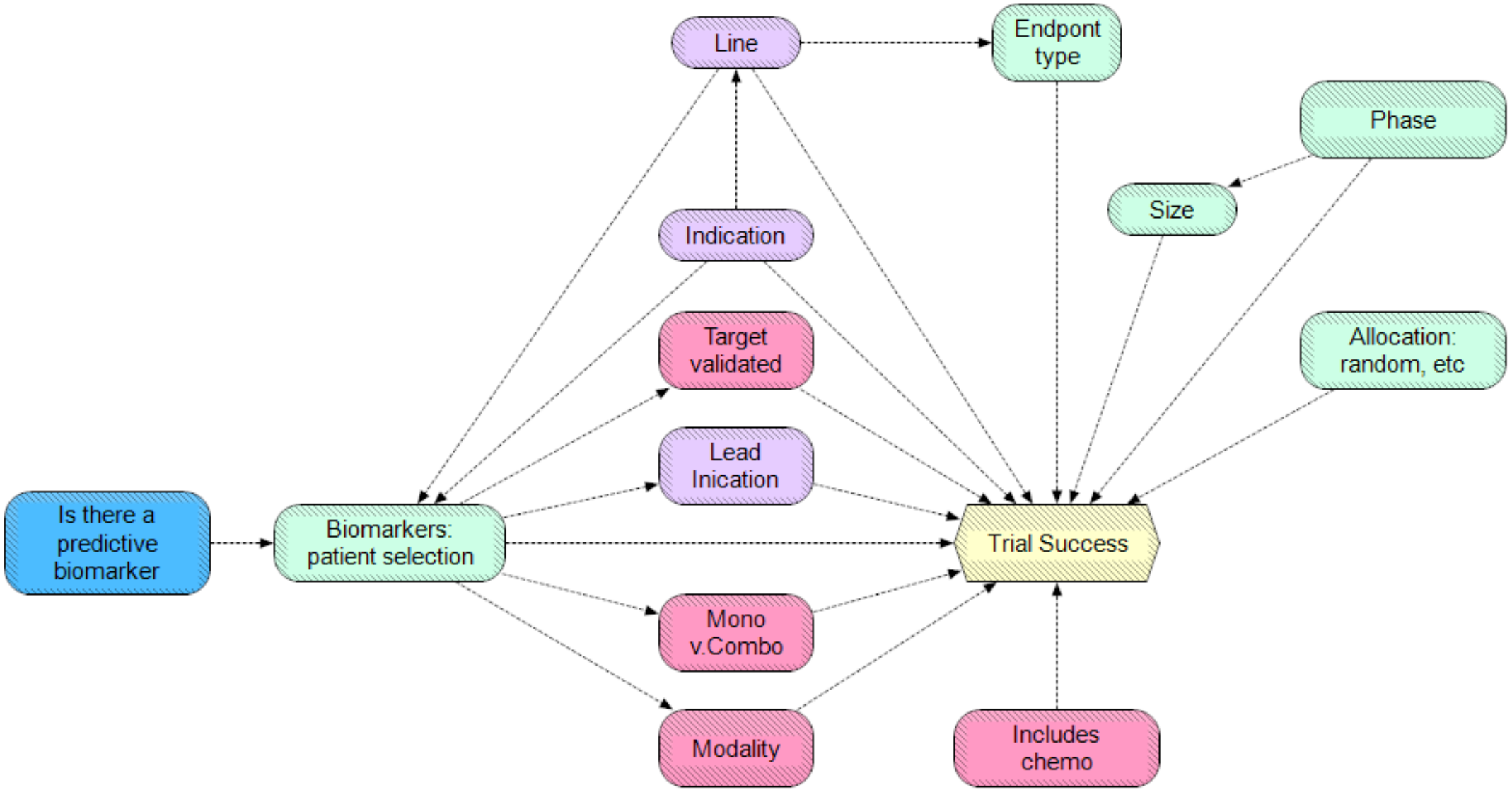
Data Can Help Create the Model – But it can't do everything



If 10 variables

- 45 pairs
- Max # of graphs: $3^{45} \approx 3\text{x}10^{21}$
- Min # of graphs: $2^{45} \approx 3.5\text{x}10^{13}$
- At 1,000,000/second: 1-93 million years

DAG created via a workshop with a few of GSK's oncology & Biostats experts

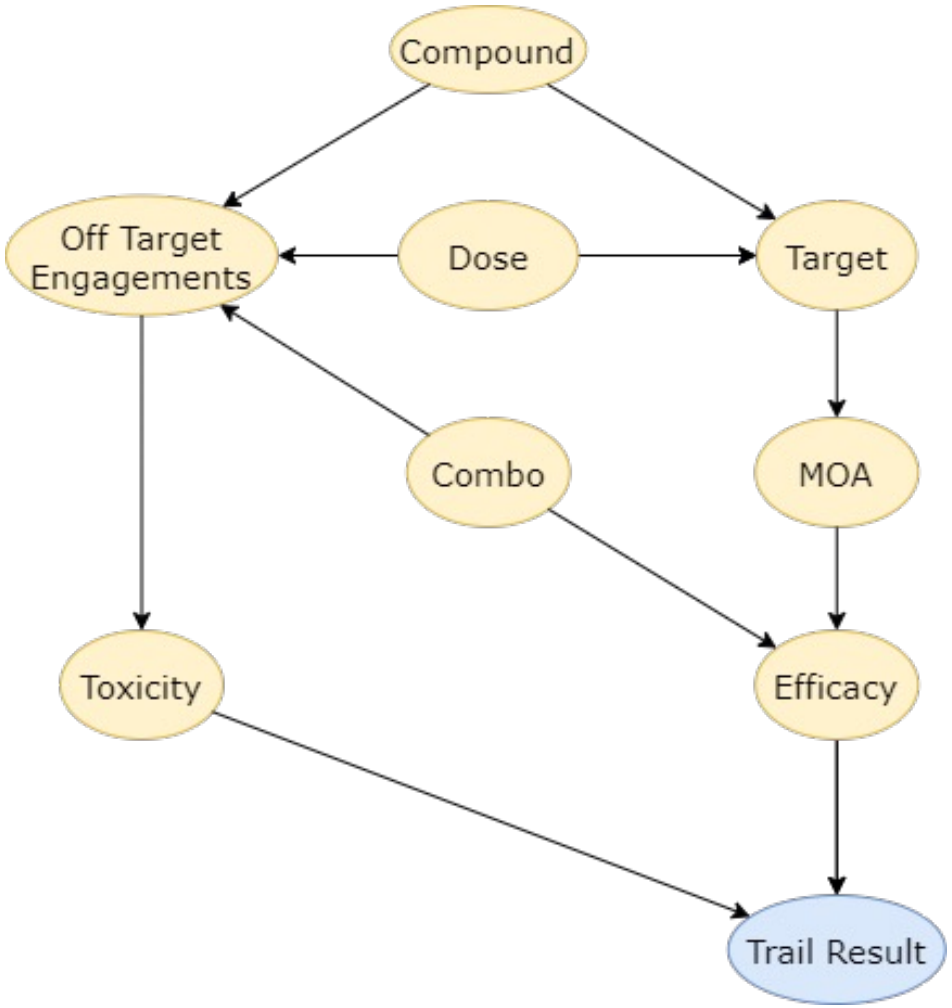


Workshop Problems

1. Focused on what is predictive, not causal.

2. Comments during workshop:
    - Set arrows with correlation matrix
    - Exclude variables for which we have no data
    - Make a small model and expand it later if needed

Finally! A good start



To focus on causality, ask these questions

A. Does X determine or affect the realization of Y?

B. Is it necessary to know X before determining Y?

C. Does knowing/determining X limit the available options for Y?

Apply Domain Knowledge

- 4 Pillars Framework: Compound->Target->MOA->Efficacy

How decisions affect correlations in data

Type of variables

A. Goal variables

B. Environmental variables

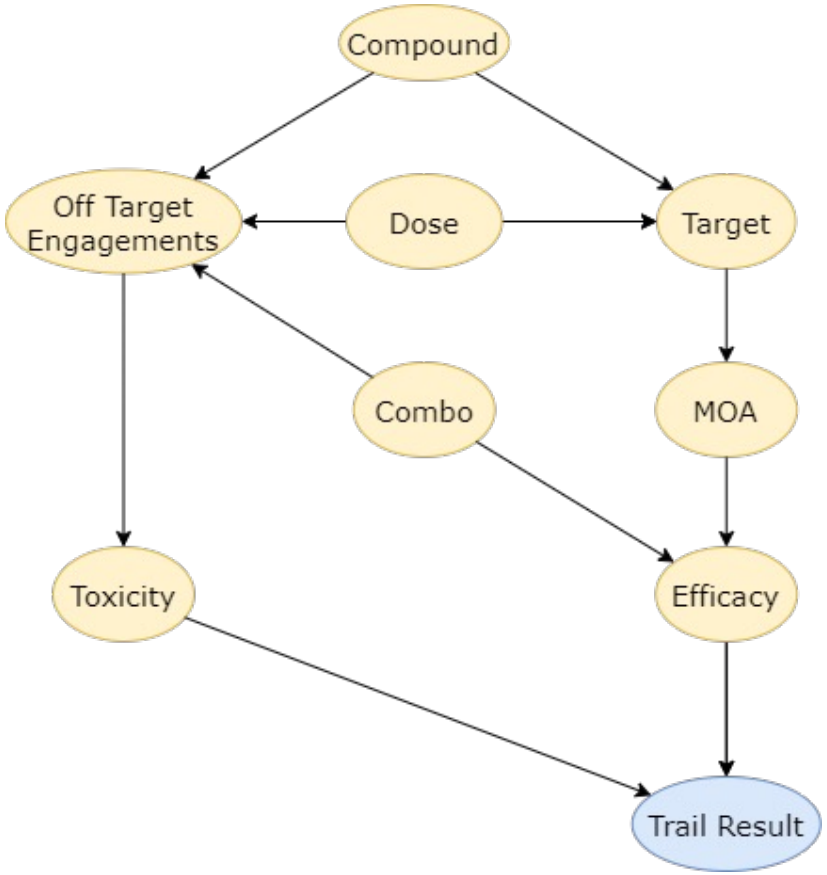
C. Decision variables

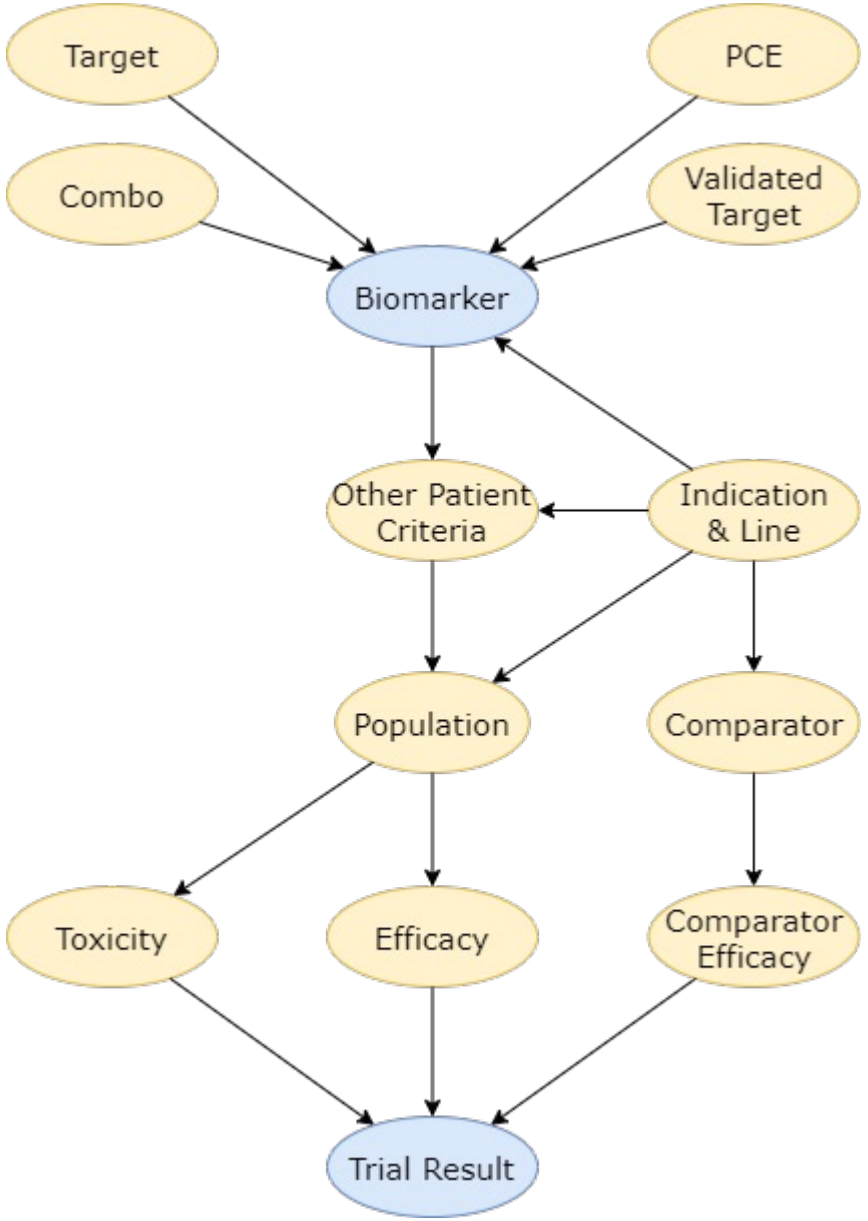
Must consider all types of variables: goal, environmental, and decision.

Hypotheses About the Use of Patient Selection Biomarkers

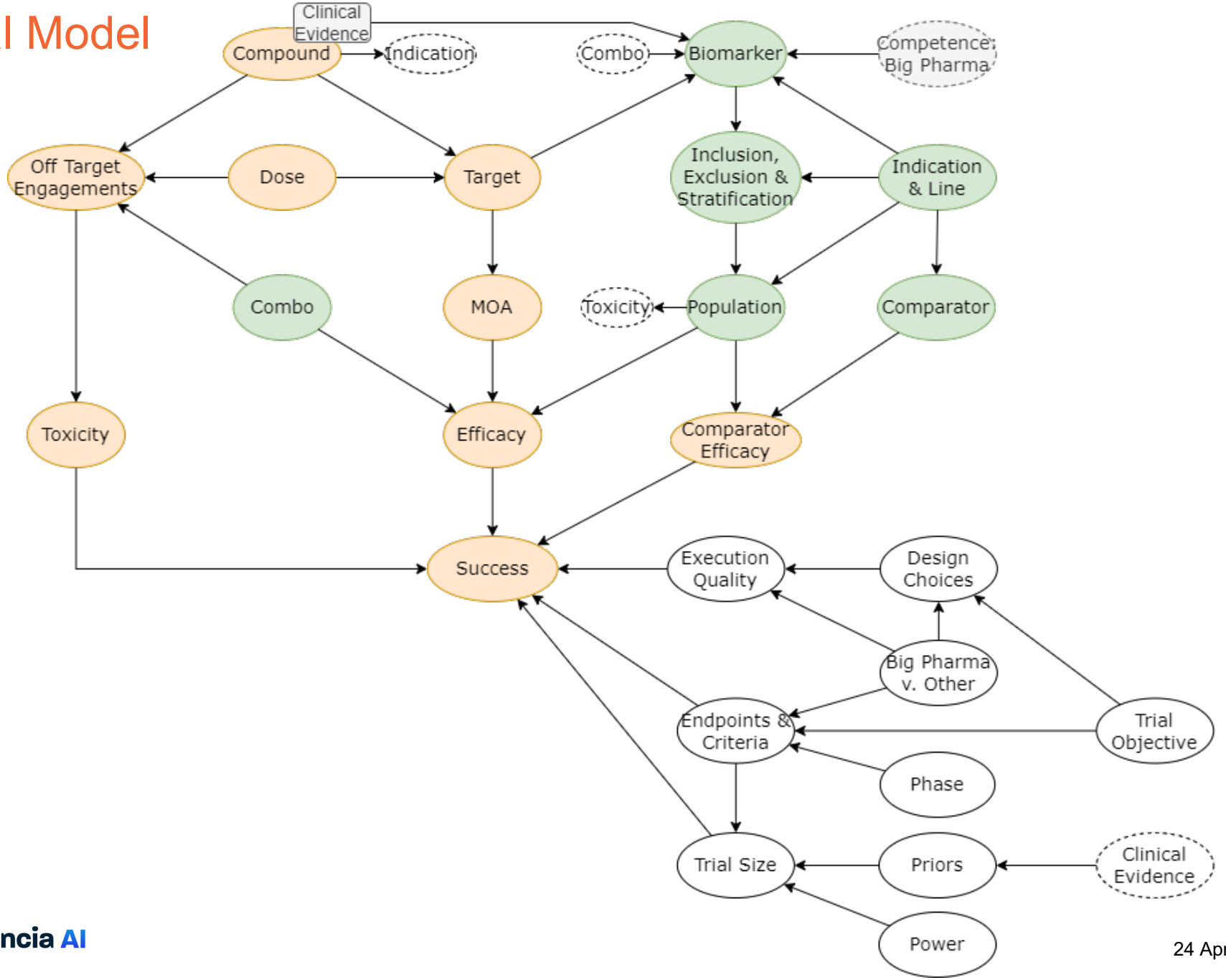
1. Biomarker use will vary by indication because of pharmacology & economics
2. Hard-to-treat cancers will use biomarkers to boost PoS
3. Biomarker use will vary by modality, but maybe conditionally independent of success.
4. Targeted therapies will use biomarkers more than non-targeted therapies
5. Biomarker use will vary by target class
6. Frequency of biomarker use will increase from 3L to 2L to 1L.
7. Targets with validated targets will use biomarkers more frequently than others.
8. Challenging cancers will use more combos
9. Use of combos will increase from 3L to 2L to 1L
10. Biomarker use will vary inversely to combo therapy
11. Combo therapies will use biomarkers more than mono therapies
12. As # of indication success increases, so will the percentage of trials with biomarkers.
13. Use of biomarkers will vary inversely with the support of PCE.

Add Population Decisions





The Full Causal Model



Hypothesized Confounders for Biomarker → Trial Result

Pharmacology & Pharmacology Info

1. Target Class
2. Targeted
3. Target Validated
4. Mono v. Combo
5. PCE

Trial Design Decisions

1. Indication
2. Line
3. Previous phase's design

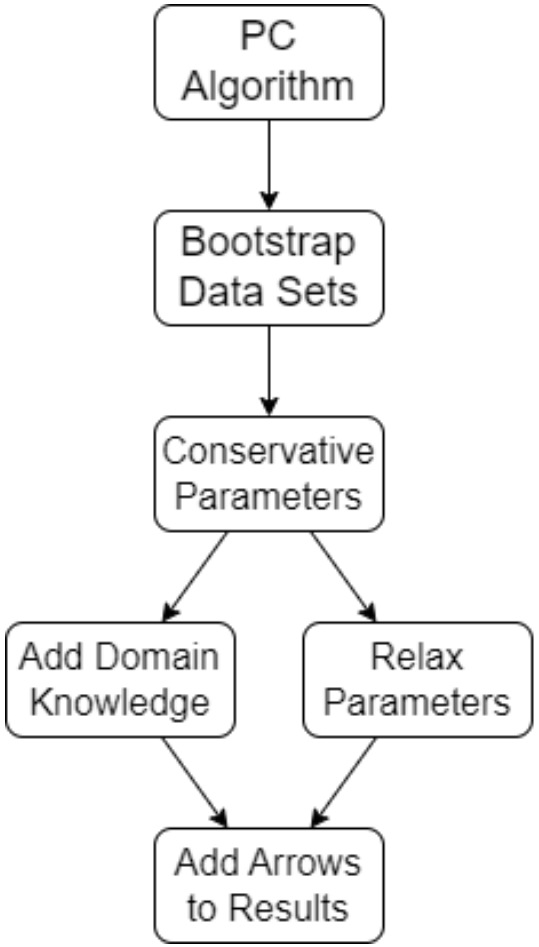
Other

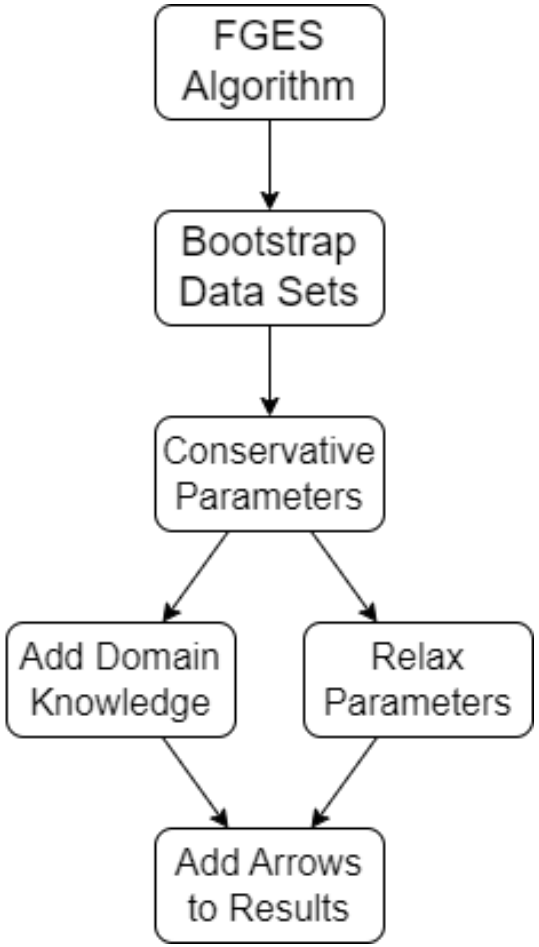
1. Big pharma v. not big pharma
2. Does biomarker assay exist

Population Decisions

1. Indication
2. Line

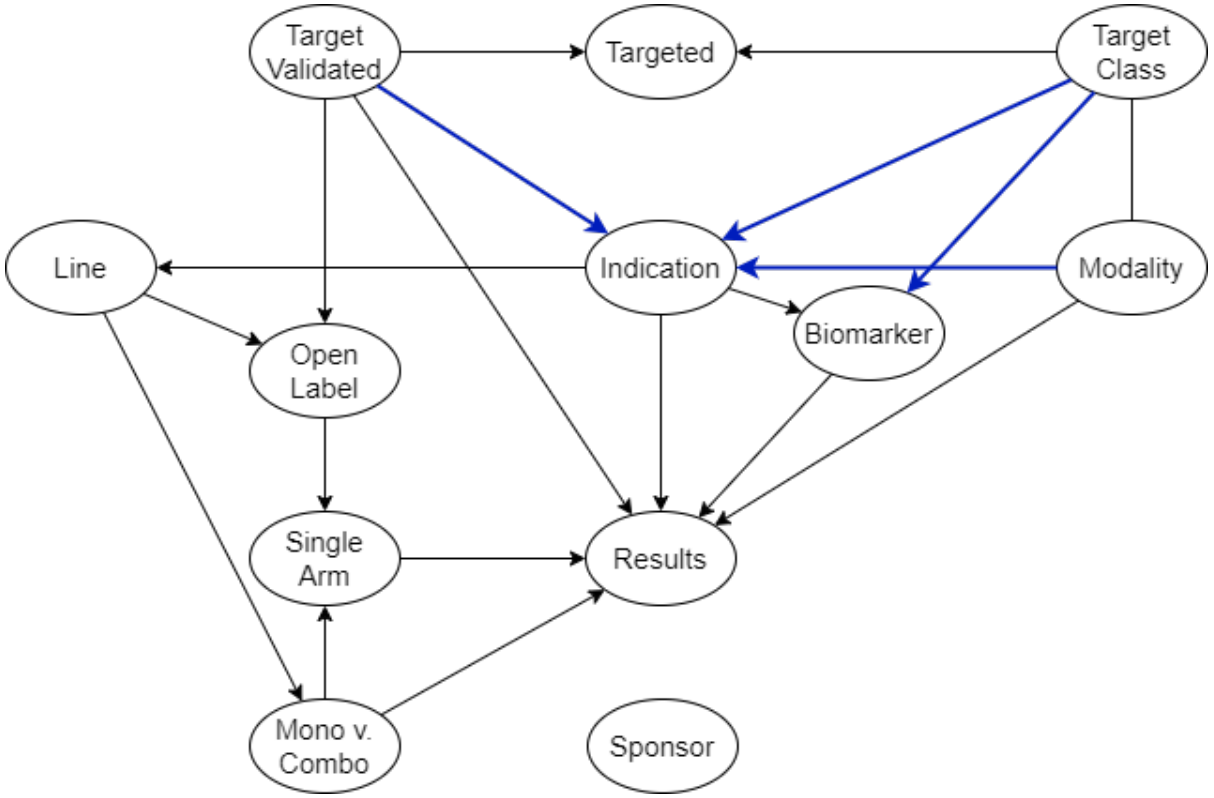
Causal Discovery: Causal Model Built from Data

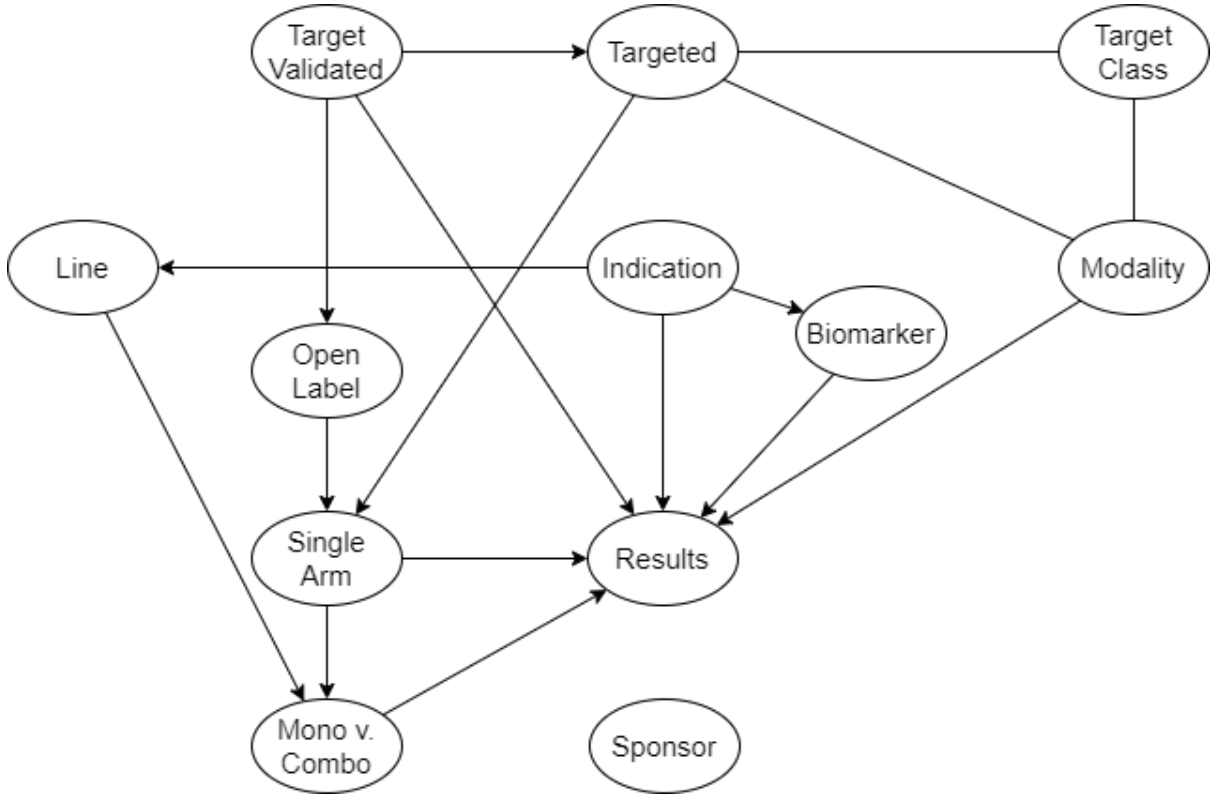




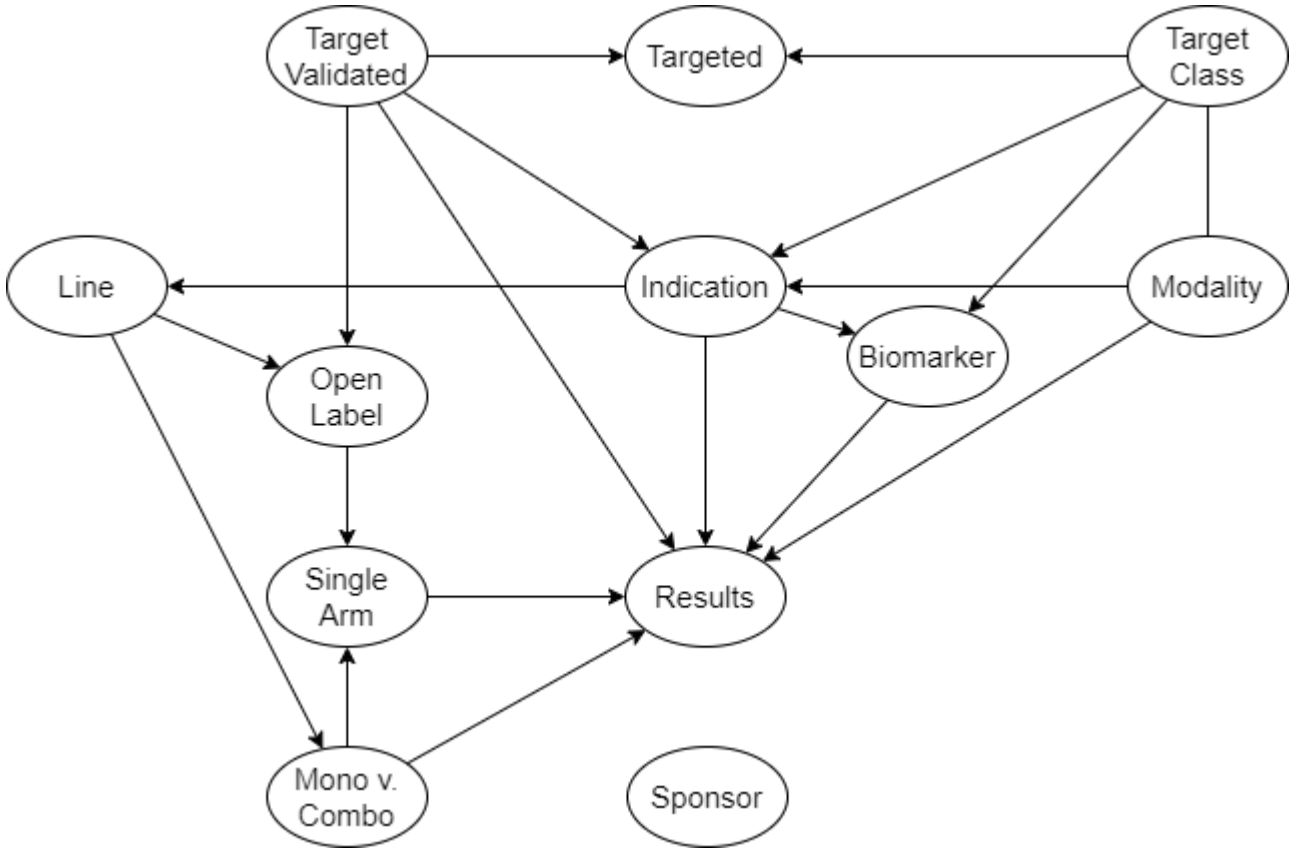
Tier	Variables
1	Sponsor, Modality, Target Class, Targeted, Target Validated
2	Indication, Line
3	Other Design Variables
4	Results

Ph2 Causal Models: PC (left) v. FGES (right)

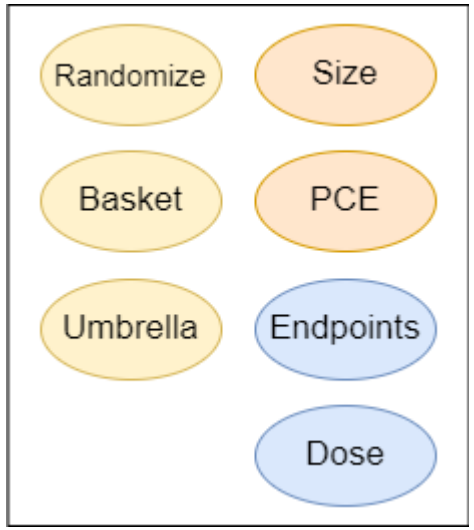




Ph2 Causal Model



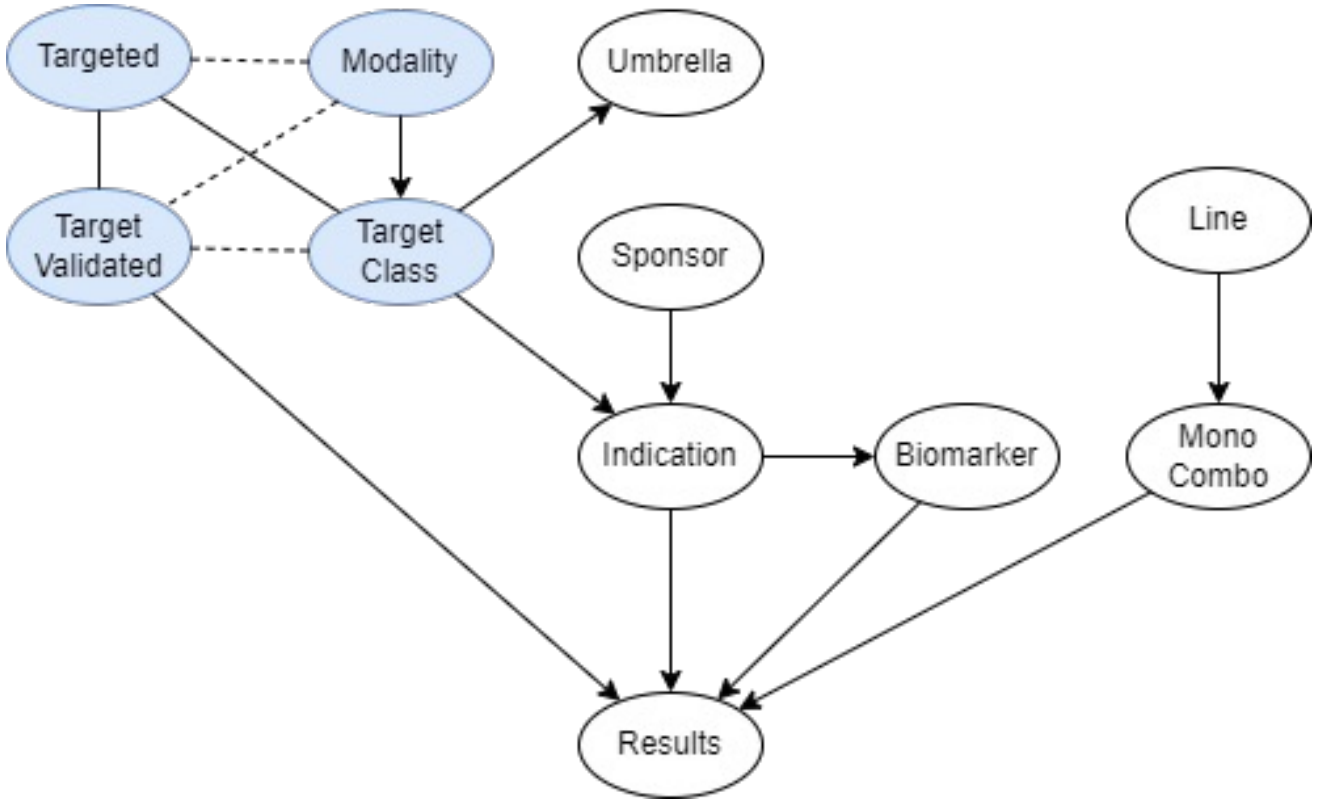
Variable	Variable	Chi-Square	p-value
Target Validated	Indication	33	6.6E-5
Modality	Indication	34	4.5xE-9
Target Class	Indication	159	9.1E-19
Target Class	Biomarker	19	8.0E-4

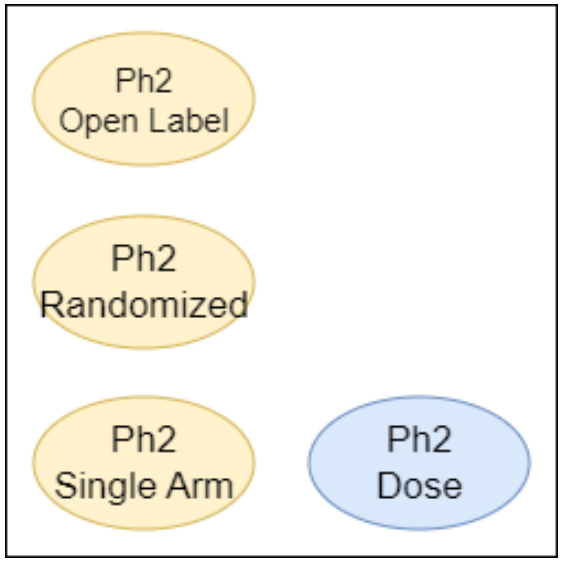


Phase 2: Variables for closing back door paths and studying front door components

Variable	Close Back Door Path	Front Door Components
Biomarker	Indication, Modality	None
Modality	Possibly target class	Indication
Indication	Validated Target, Modality	Biomarker, Line
Target Class	None	Modality, Targeted, Indication, Biomarker
Target Validated	None	Targeted, Indication, Open Label
Line	Indication	Mono v. Combo, Open Label
Open Label v. Blinded	Validated Target, Line/MonoCombo	None
Single Arm v. Multi	MonoCombo, Open Label/Validated Target	None
Mono v. Combo	Line	Single Arm
Randomized v. Not random		
Size		
PCE		

Ph3 Causal Model





Calculating Odds ratios

Breast

Biomarker	Trial Result: Success	Trial Result: Failure
True	15	19
False	0	1

Odds Ratio: #DIV/0

p-value: 30%

Myeloma

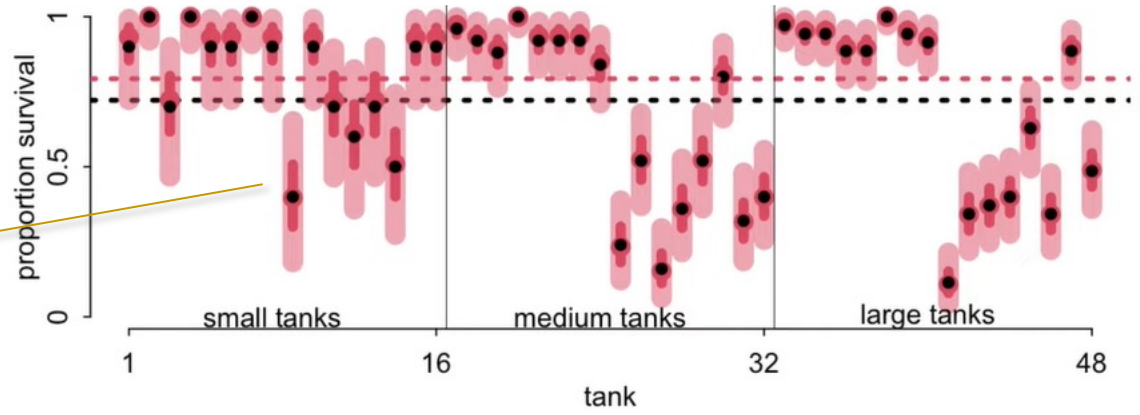
Biomarker	Trial Result: Success	Trial Result: Failure
True	7	2
False	8	6

Odds Ratio: 2.6

p-value: 40%

Hierarchical Bayesian Inference

Prior For Individual Tumor



Prior for Solid Tumor