Good twins and evil twins

What “digital twins” actually do in clinical trials

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tl;dr

- “Digital twins” (DT) is a marketing term with **no specific meaning**
  - Adds nothing; useful as a red flag
- Some methods that have been or could be called DT are **fine in some contexts**
  - … some are not

What gives me the right?

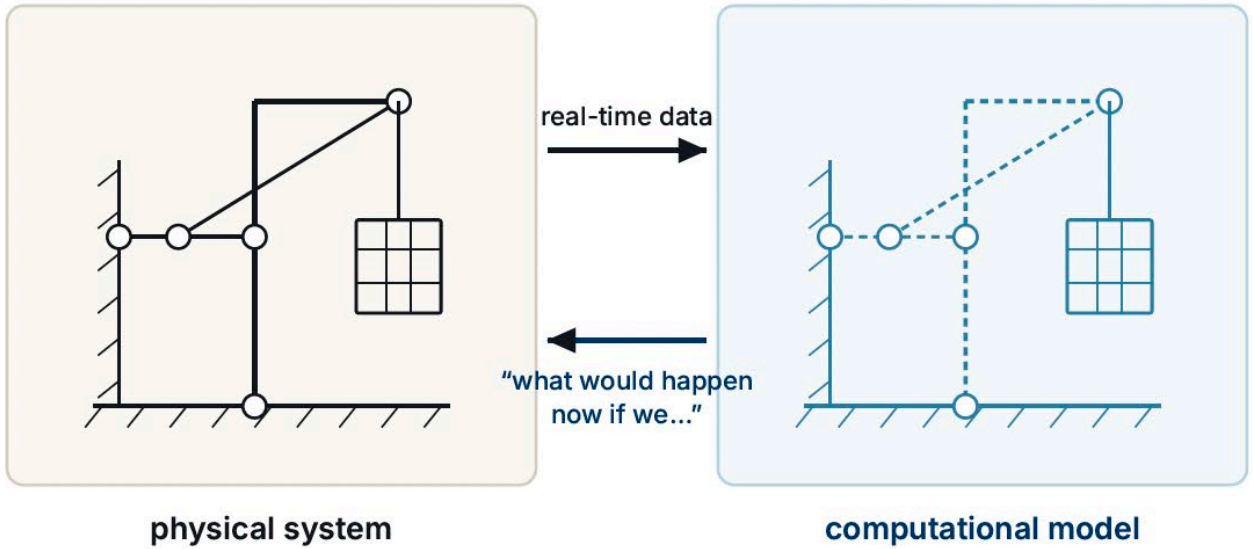
- Assistant Professor of Biostatistics at Berkeley
  - expertise in advanced methods for trials
- Previously: employee 14 at Unlearn.ai, a “digital twins” company
  - inventor of their most important IP (PROCOVA)

Where the term comes from

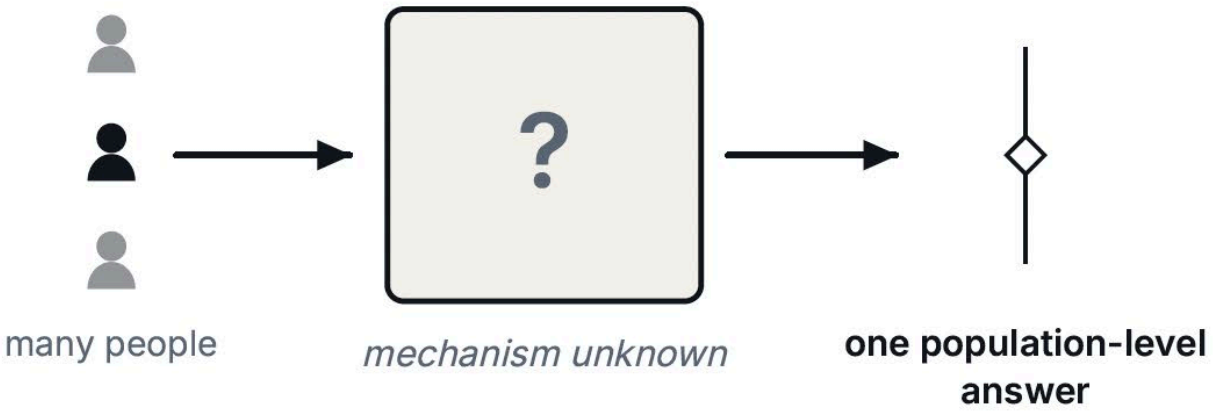
DT comes from engineering, where it means a **computational simulation of a physical system that is updated with real-time data**.

- Used to answer *“what would happen now if we…”*
- Assumes **individual-level knowledge** of the system

The model is built from physics. You can ask it anything because you already know how the system works.



Contrasting: clinical trials

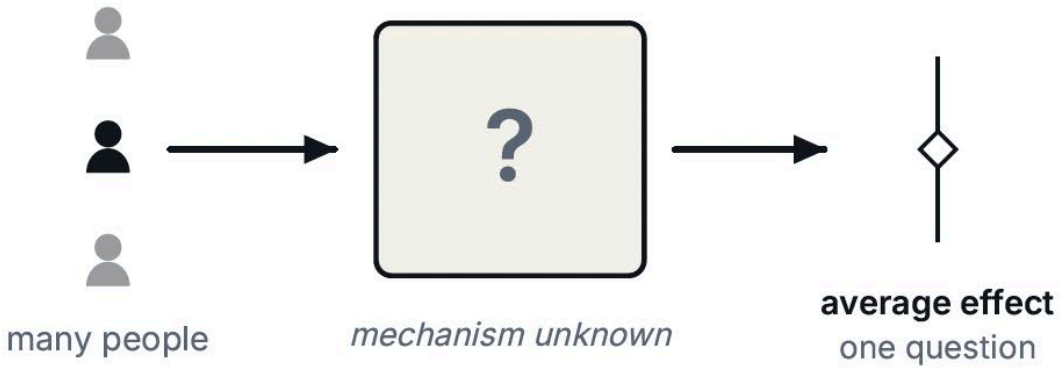


- **Builds or verifies** functional knowledge of disease
- **Population-level** answers
- **One** question at a time

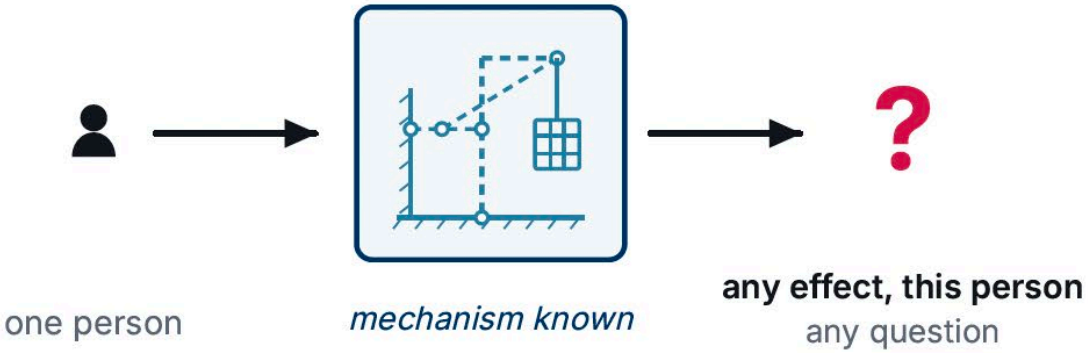
If we could already build "digital twins" for people, there would be no need for trials.

Trial vs. digital twin

Trial

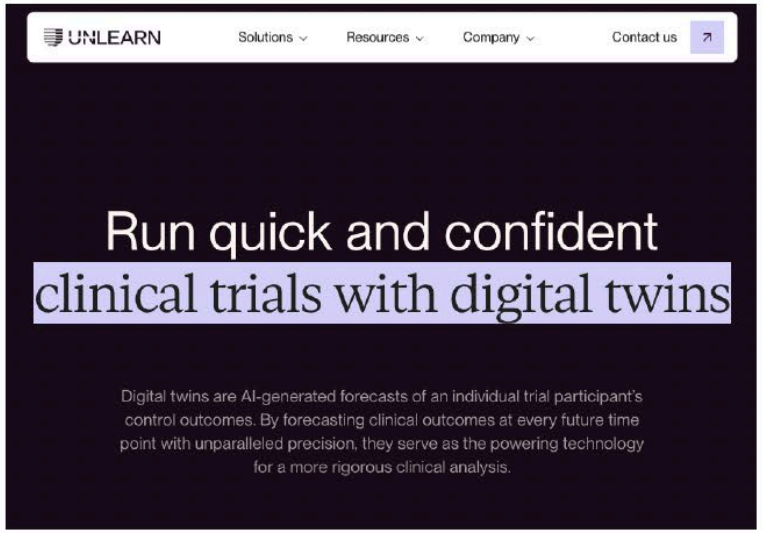


Digital twin



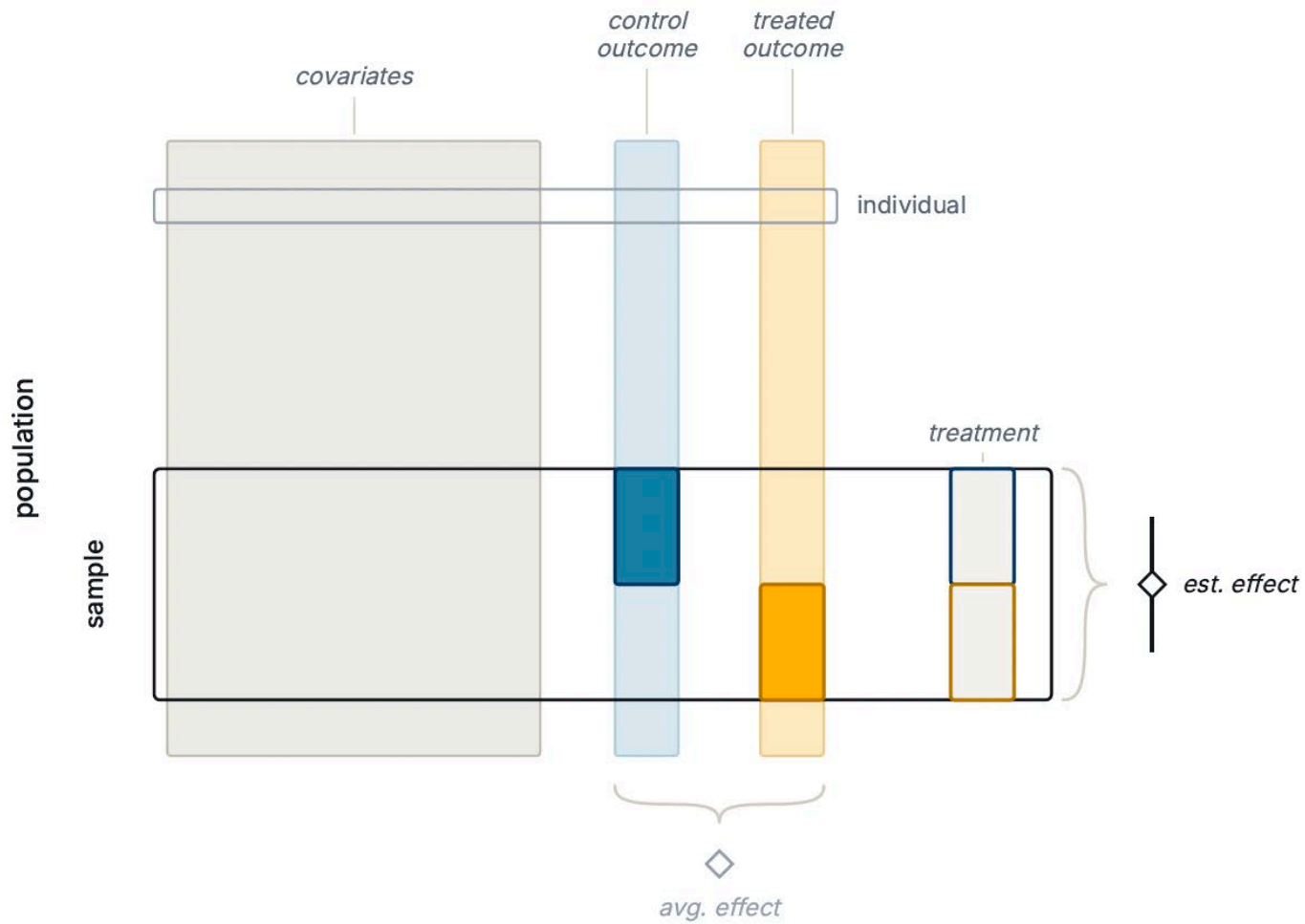
Trials **verify** functional causal relationships. Digital twins **assume** them.

Nonetheless…



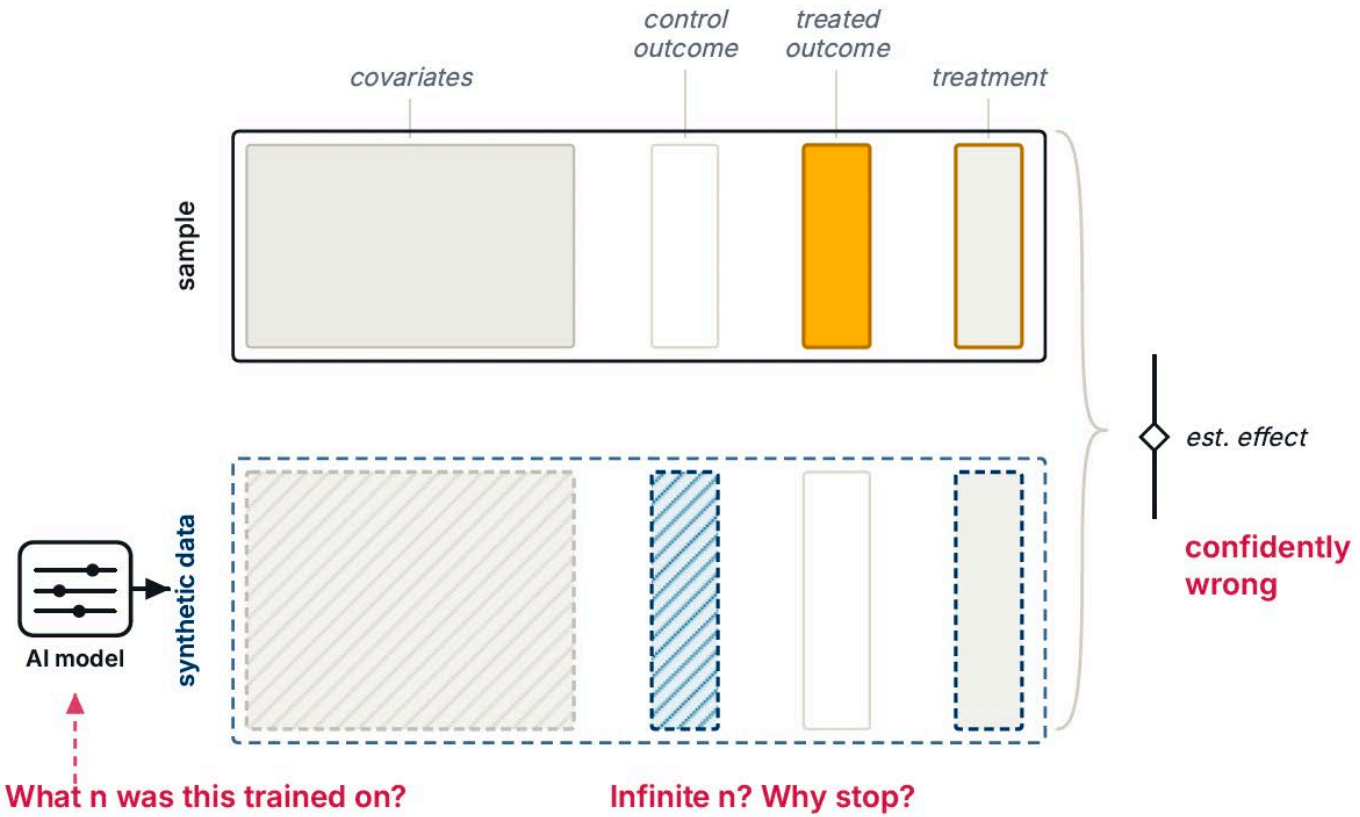
What are they actually doing?

To understand DT methods, let's level-set on trials



- Confounding eliminated by *randomization*
- Uncertainty remains from *sampling*

DT method 1: synthetic data

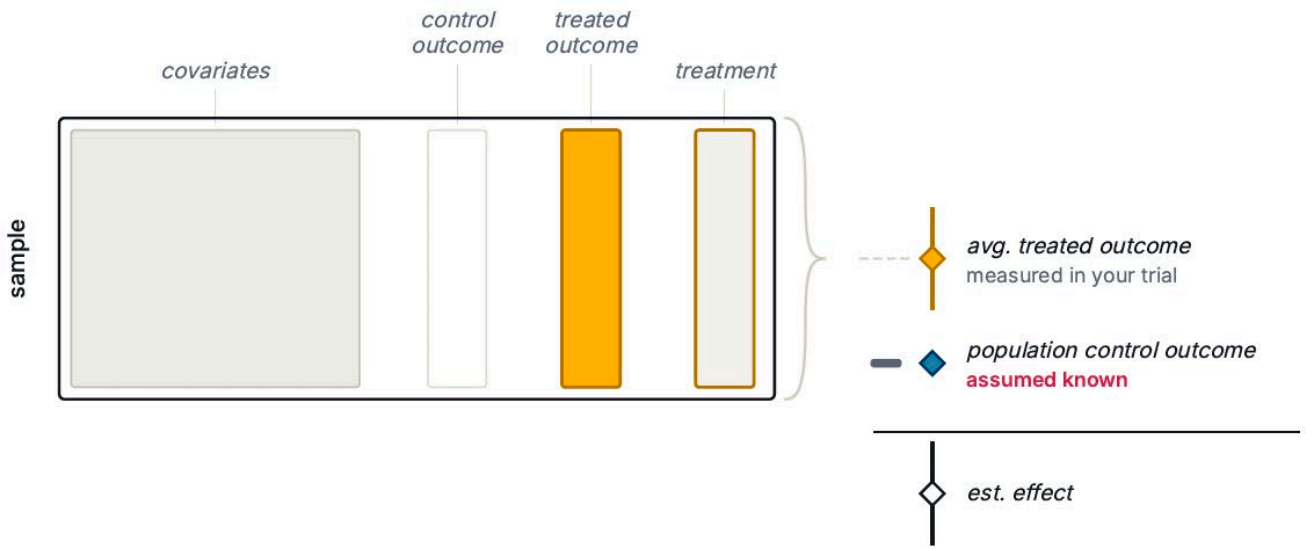


Run a single-arm trial, then have a generative model manufacture the control arm.

The AI model is built from data! Statistical similarity, not mechanistic understanding.

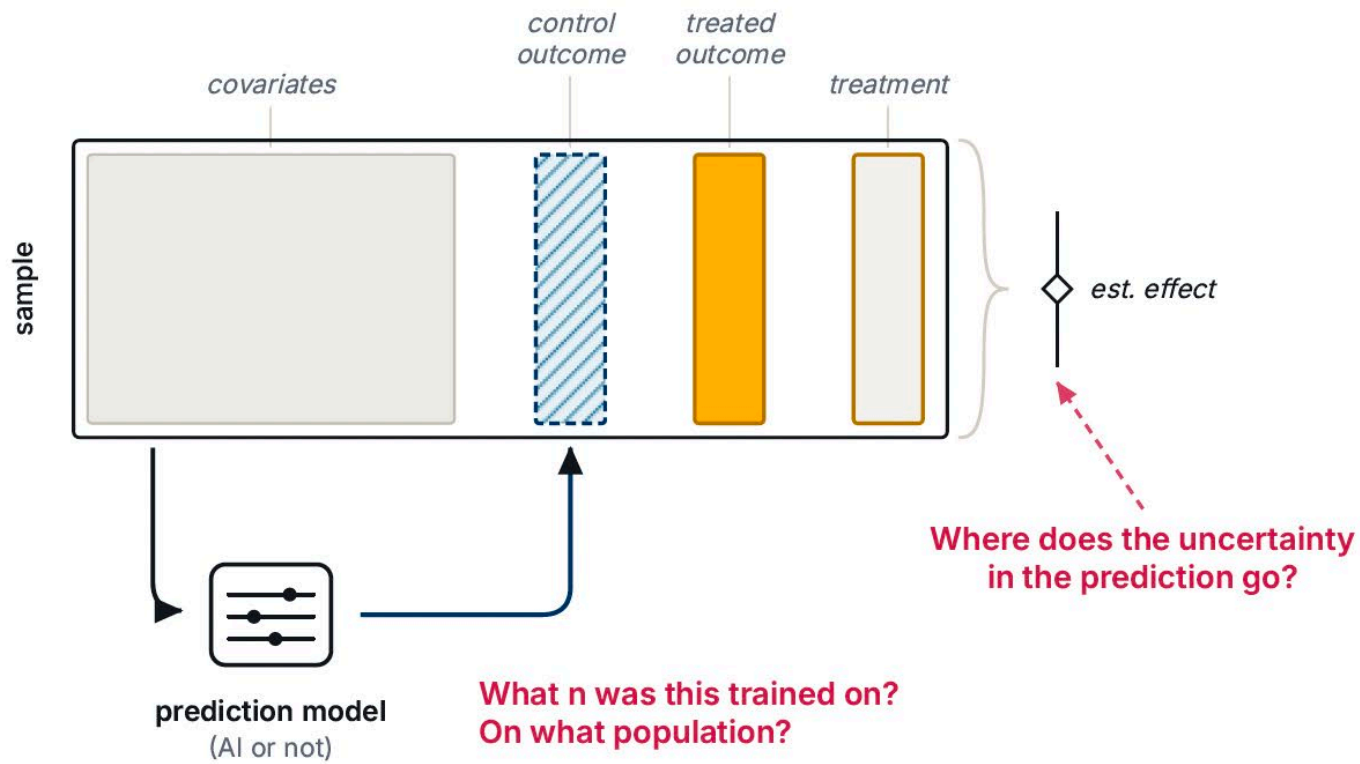
Savelli G, et al. In silico clinical trial for osteoporosis treatments to prevent hip fractures: simulation of the placebo arm. Ann Biomed Eng 2025;53(3):578–587.

All a Rube Goldberg machine to assume the control outcome is known



- More transparent
- Big power gain trades for big **type I error risk**
- Sensible in rare situations
  - e.g. deterministic death with no treatment

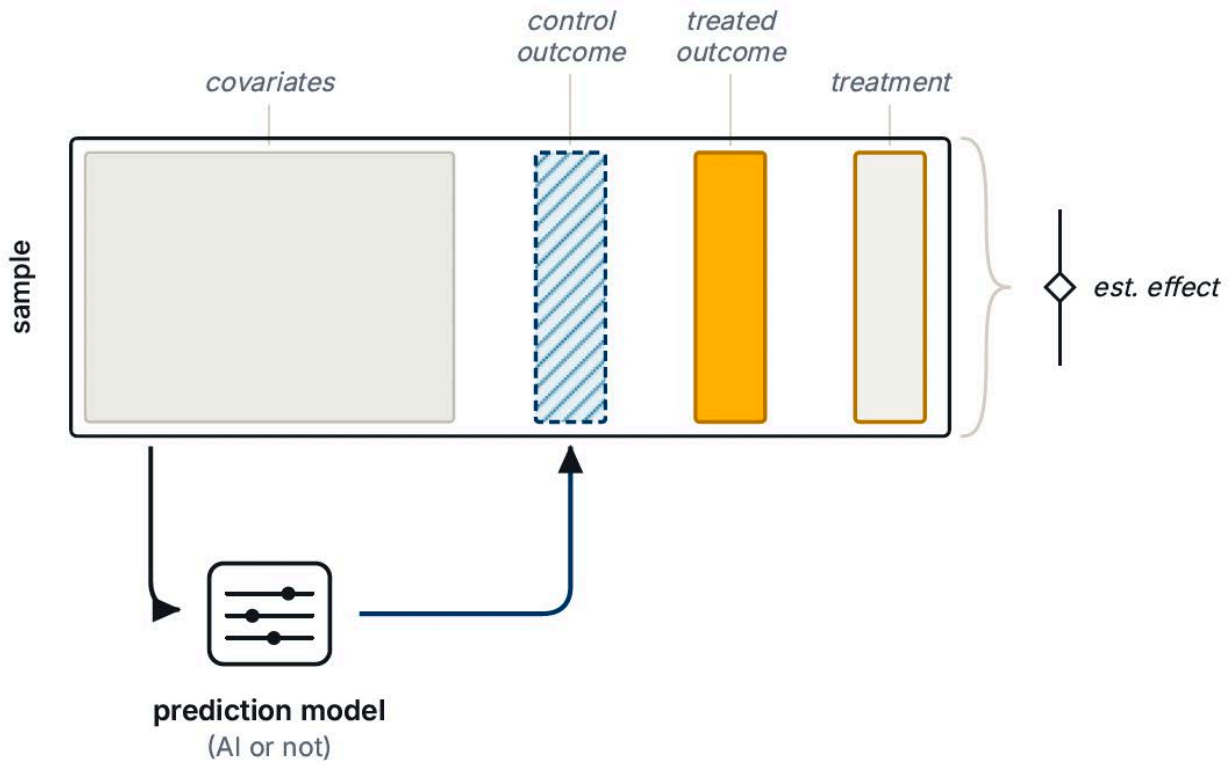
DT method 2: synthetic outcomes



Keep the real people. Have a model predict what *would* have happened to them under control, then treat that prediction as the control outcome.

Bertolini D, Fuller F, Smith AM, Walsh JR, Zhuang R. Digital twins as synthetic controls in single-arm trials. arXiv:2605.12832, 2026. (Unlearn.AI)

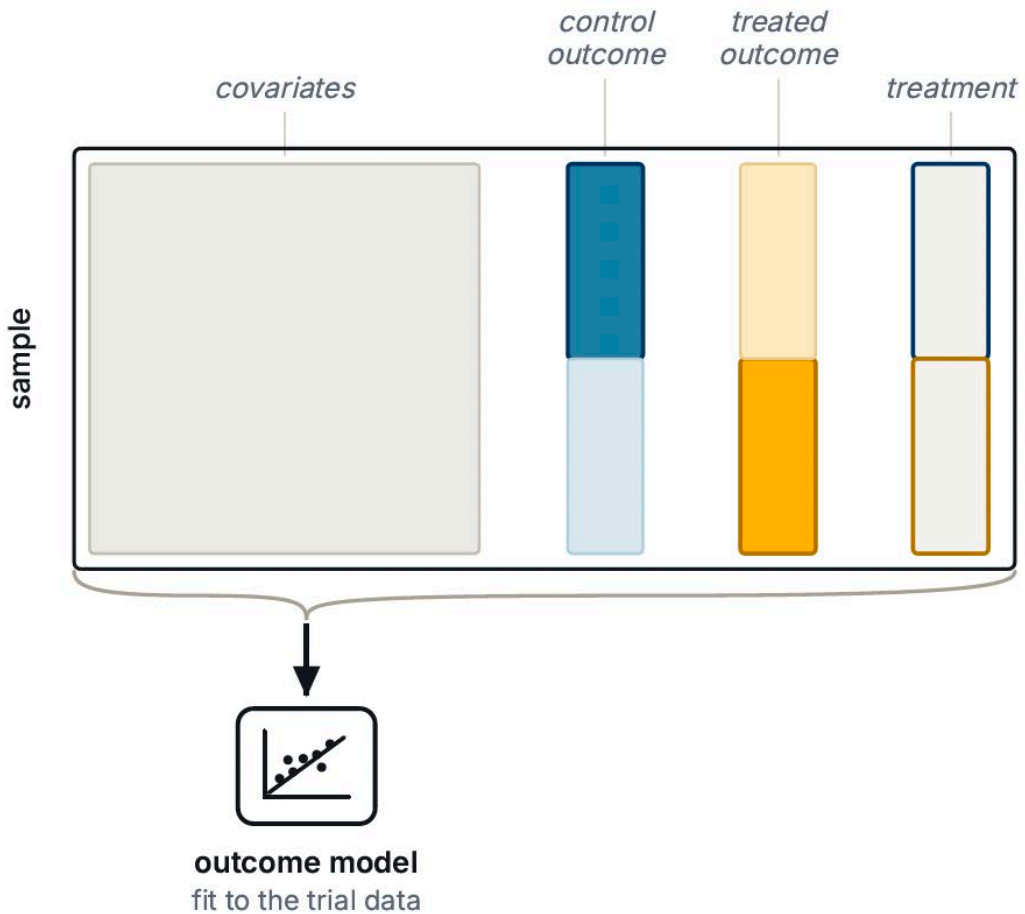
DT method 2: the verdict



- Essentially the same assumptions as synthetic data
  - though it only assumes knowledge of the outcome mechanism
- Big power gain trades for big **type I error risk**
- Sensible in rare situations
  - e.g. deterministic death with no treatment

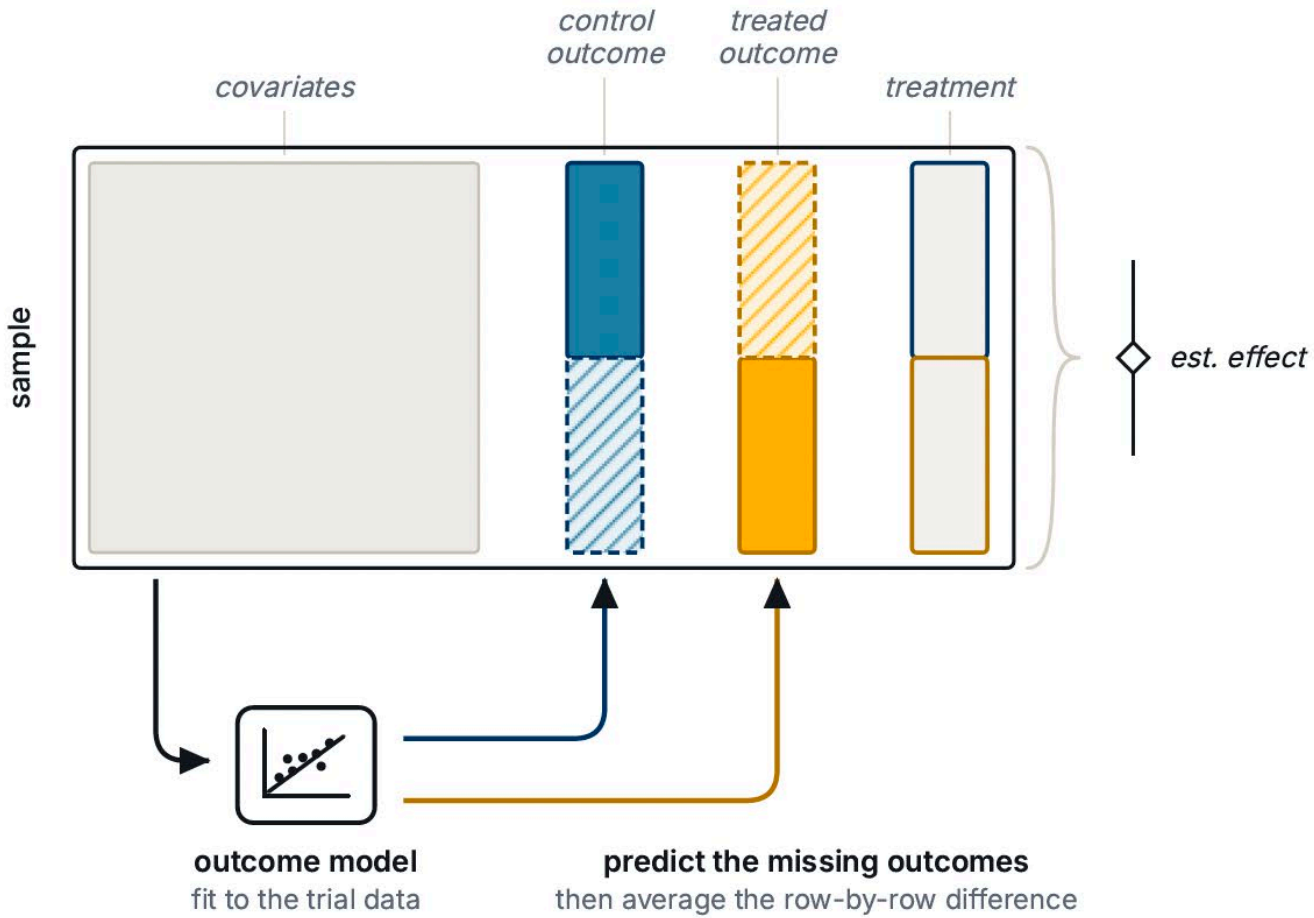
Bertolini D, Fuller F, Smith AM, Walsh JR, Zhuang R. Digital twins as synthetic controls in single-arm trials. arXiv:2605.12832, 2026. (Unlearn.AI)

Interlude: regression analysis (ANCOVA)



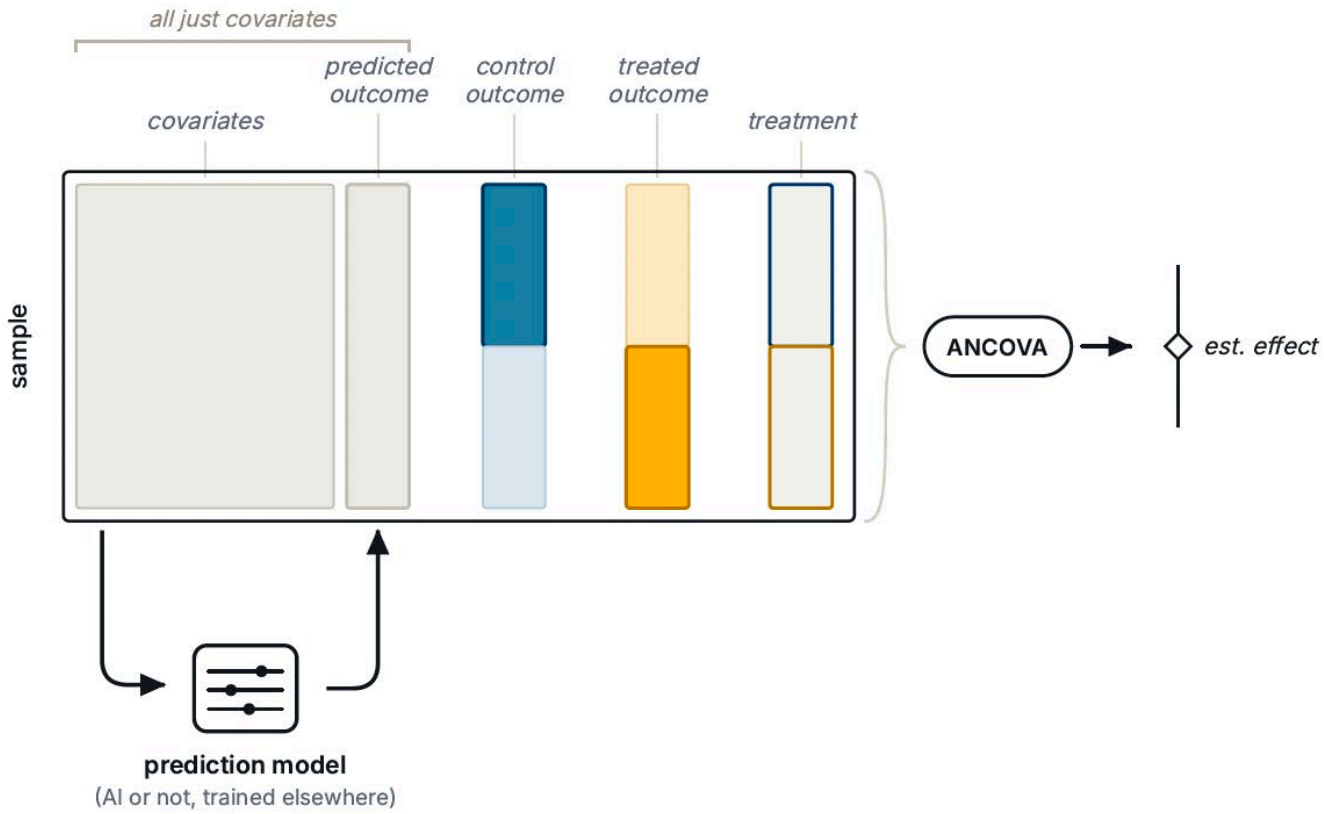
- **Step 1:** fit a regression model that describes how observed outcomes depend on treatment and covariates

Interlude: regression analysis (ANCOVA)



- **Step 2:** use it to predict the *unobserved* counterfactual outcomes, then average the row-by-row differences
  - the regression coefficient *is* that average
  - abstracts away coefficients
- Same idea as synthetic outcomes, except **the model comes from the trial**
  - no assumptions about external data or model quality

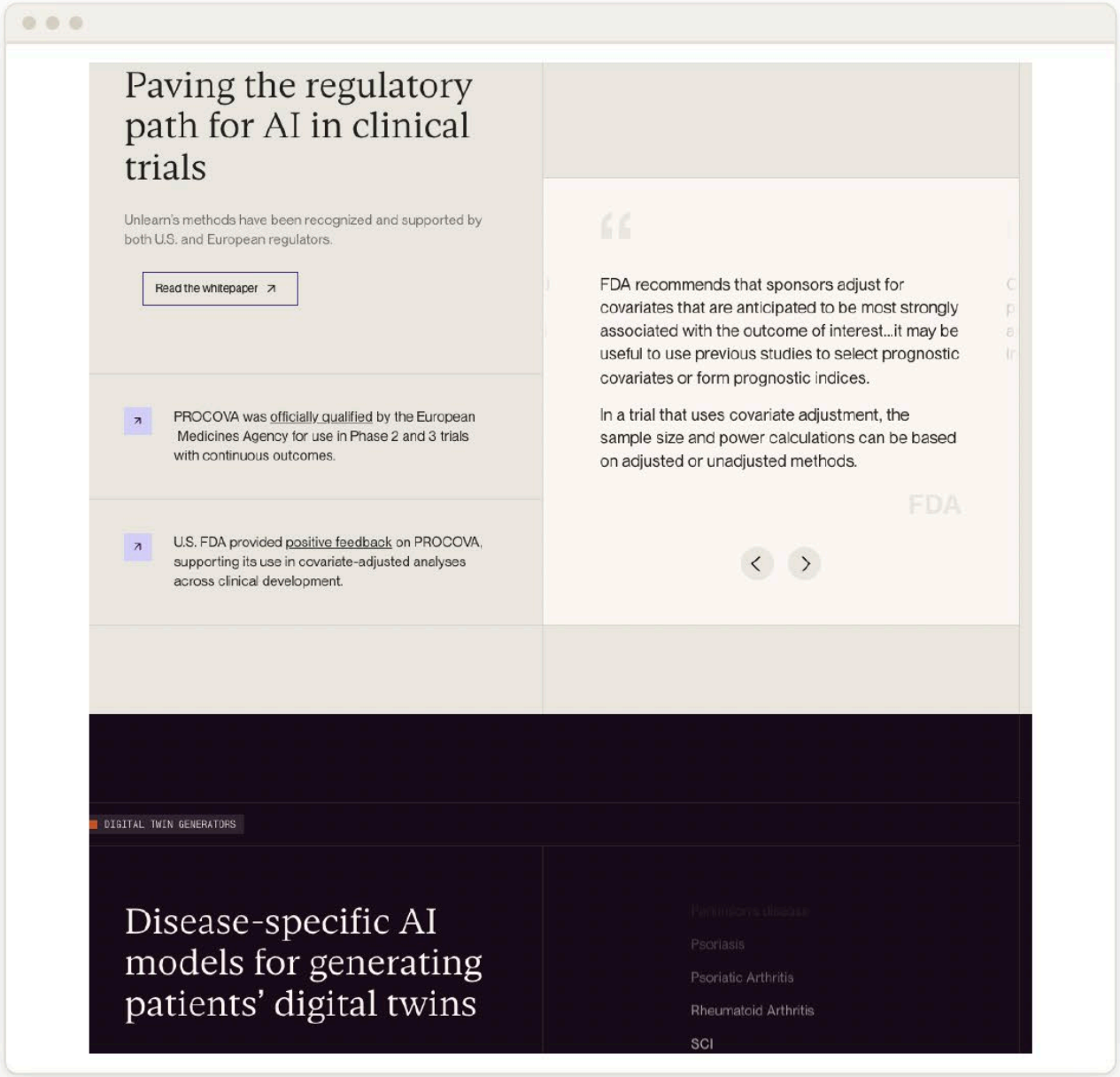
DT method 3: prognostic adjustment



- No fake outcomes, no fake rows
  - prediction is used as a “super-covariate”: fixed transform of other covariates
- Small or moderate power increase if the model is good
- **Guaranteed type I error control** regardless

Schuler A, Walsh D, Hall D, Walsh J, Fisher C. Increasing the efficiency of randomized trial estimates via linear adjustment for a prognostic score. Int J Biostat 2021;18(2):329–356.

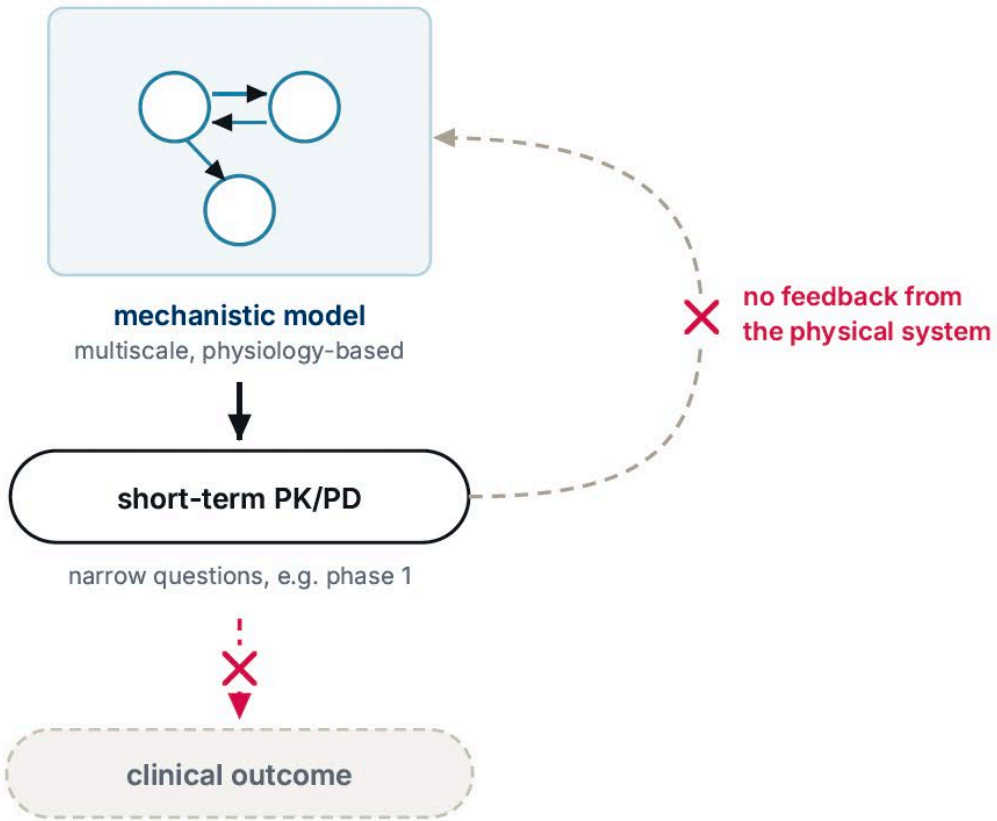
So what is being sold?



Can this really be called "digital twins"?

Covariate adjustment for a prognostic score is sensible regardless of what you call it.

Actual mechanistic models



- Some companies do sell mechanistic or multiscale models
- Could be useful for very specific short-term pharmacodynamics
  - in specific contexts, e.g. phase 1
- Extending this to clinical outcomes is not sensible
- And even here, where is the **feedback** from the physical system?
  - not DTs in the engineering sense

e.g. doc.jinko.ai/docs/human-expertise/digital-twins

Did we learn anything?

What we learned

- Most DT methods in trials don’t qualify as “digital twins”
  - no mechanistic model, no continuous feedback
  - all these methods pre-date the term
- Some methods are ok in some circumstances
  - more power generally means more type I error
- Be wary of snake oil, reason from first principles

The Future of Clinical Trials Artificial Intelligence

The future of clinical trials: What can AI do for us?

- Different stakeholders: patients, pharma, academia

  Reduce : Cost & Time

- Reduce N (still include sites, diverse geography; maintain rigor)

- Agree: Reduce regulatory, monitoring, reporting, site initiation, activation, budgeting, enrollment, screening & matching, consent process. Administrative tasks.

- Operations and data management

- Can AI help us leverage data and models to address the scientific question?

What is the hype about AI?

- Electronic medical record (registries, standardization, EPIC)
- High dimensional data (genomic, imaging, pathology)
- LLM (systematic data extraction from unstructured data /text notes)

Data Augmentation

Data augmentation or data enrichment

- Augmenting clinical trial evidence
- Leveraging real-world data to complement clinical trial data

- AI based data augmentation

Definitions of data augmentation

- Priors in Bayesian analysis
- Synthetic data – RWE, RWD
- Resampling – imputation
- Big data expand n (rows - units) and/or x (columns - variables)

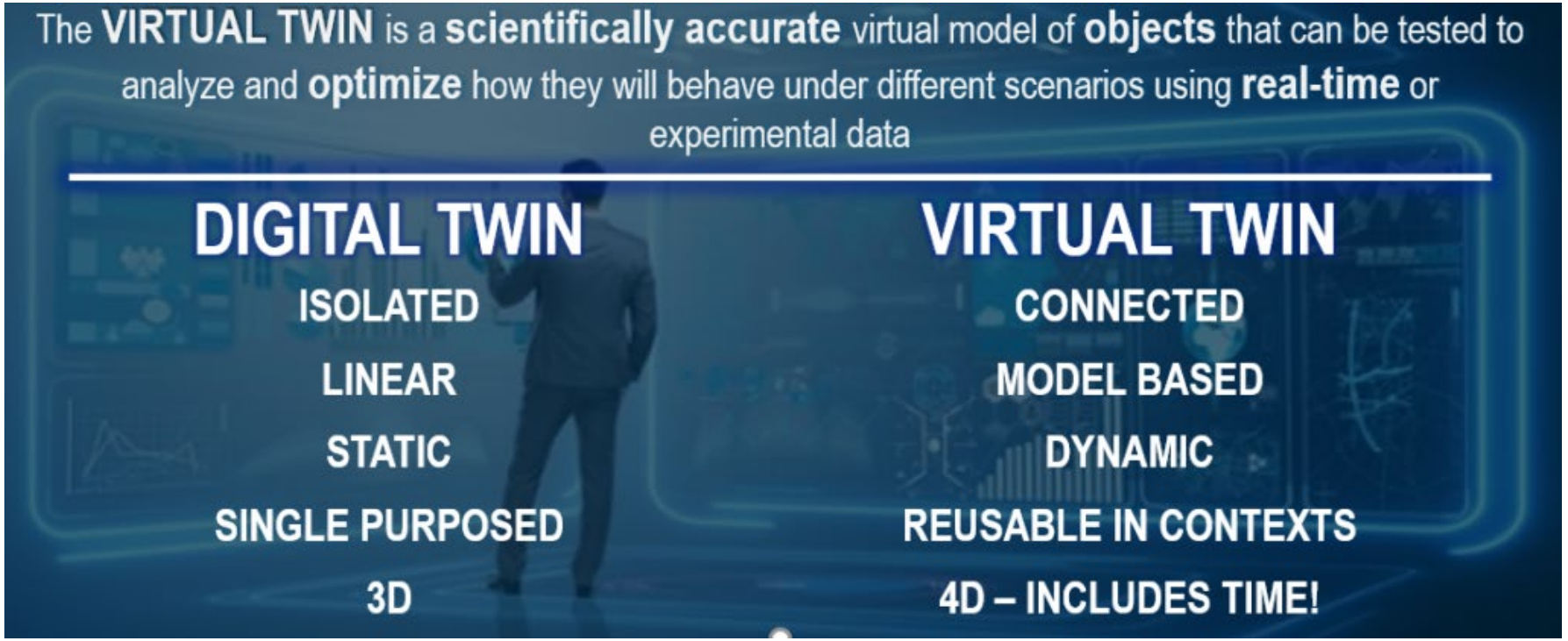
Challenges

- Challenges remain in data quality, interpretability, regulatory acceptance, and ethical governance.
- Continued collaboration between AI experts, pharmaceutical industry partners, and regulatory bodies will be essential to fully harness AI’s potential in identifying novel treatments.
- Terminology

Digital Twins

Virtual patient versus Digital Twin

- A **Digital Twin** is an in-silico framework that replicates a biological cell, sub-system, organ, or a whole organism, with a transparent predictive model of their relevant causal mechanisms and response to interventions. Simulation based.
- **Virtual Twin:** Not only how they present (known) but also how they will react (outcome)



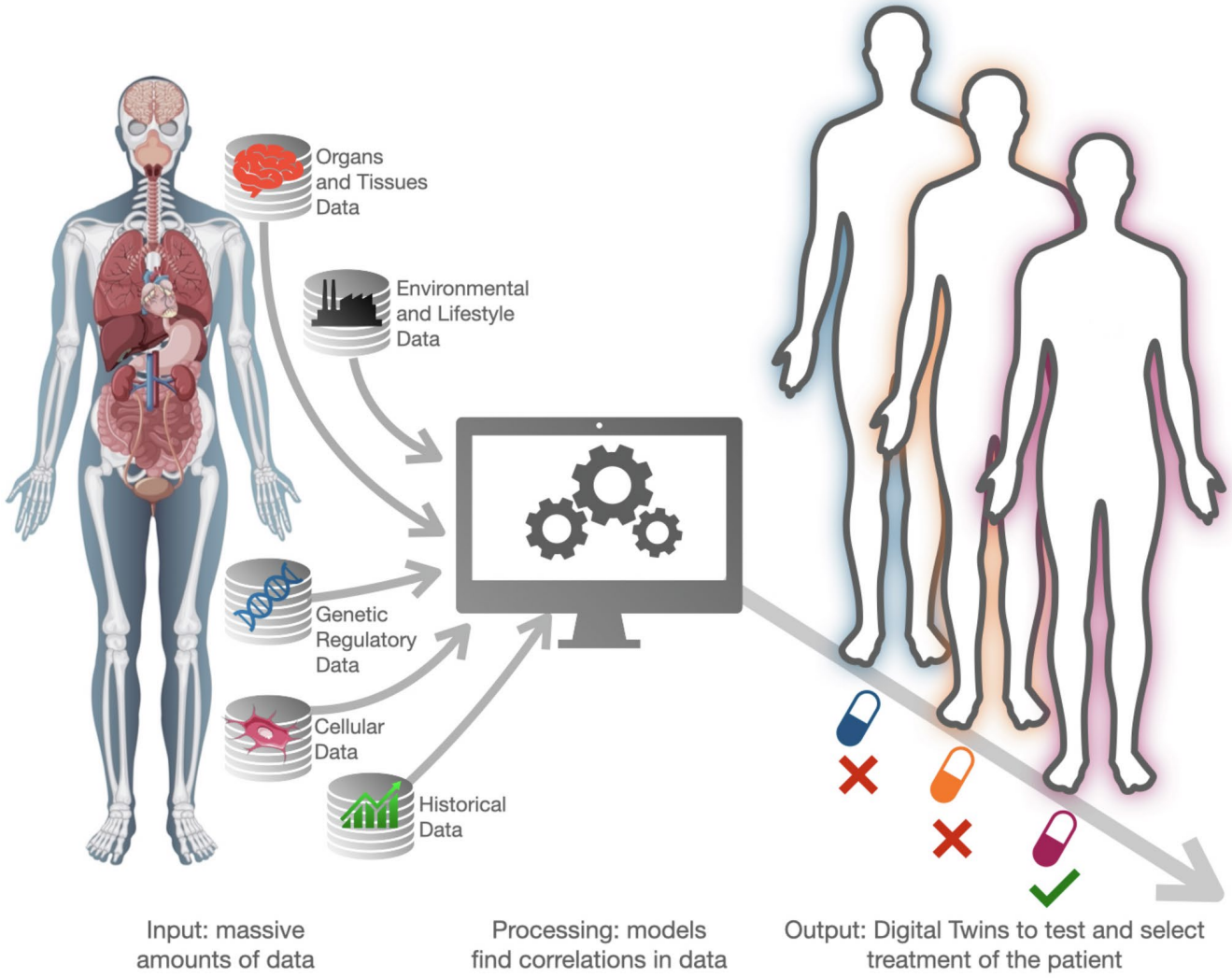
Digital Twins

X variables

Things we know at baseline

Baseline/ Time 0

Patients' characteristics



Y outcome

Answer

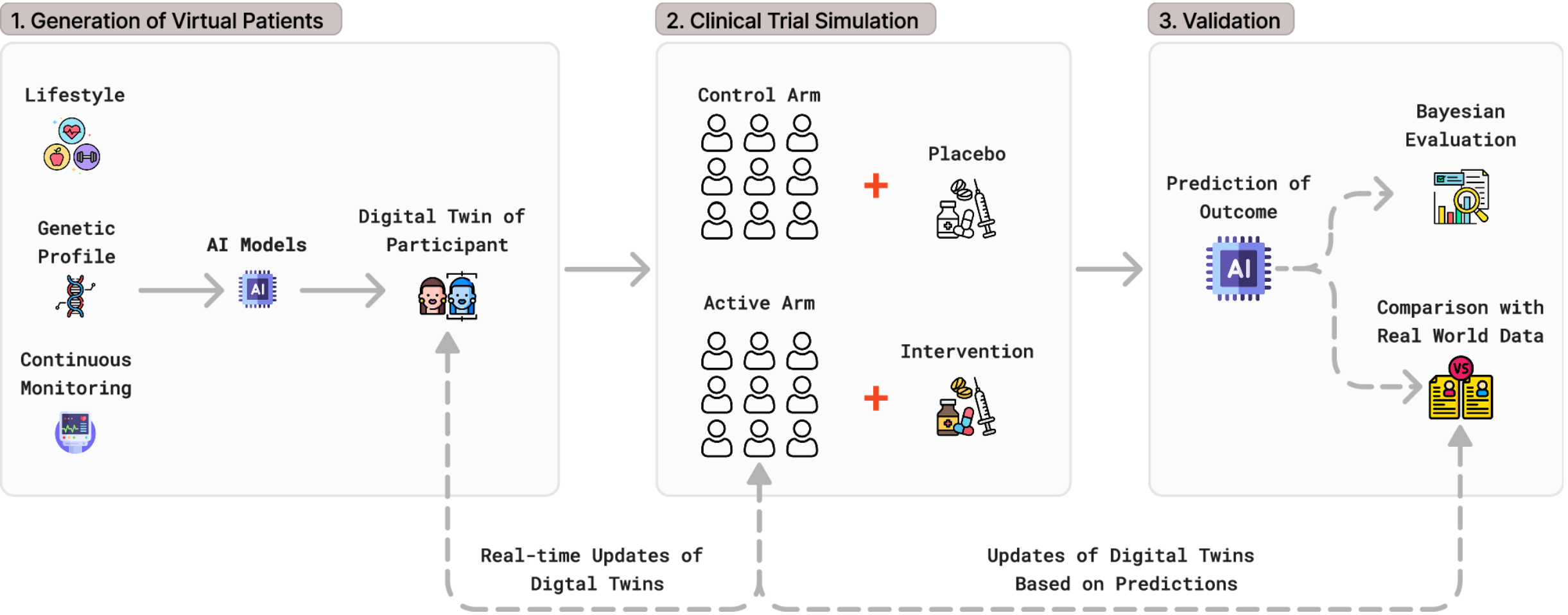
Use predictions as Data

https://doi.org/10.1038/s41746-024-01402-3

Real observations vs Predictions

Labeled Data	Unlabeled Data
You have the Y (outcome)	You only have $\hat{Y}$
Real observations	Predictions

Simulated patient digital twins and monitoring patient digital twins



Use predictions as Data

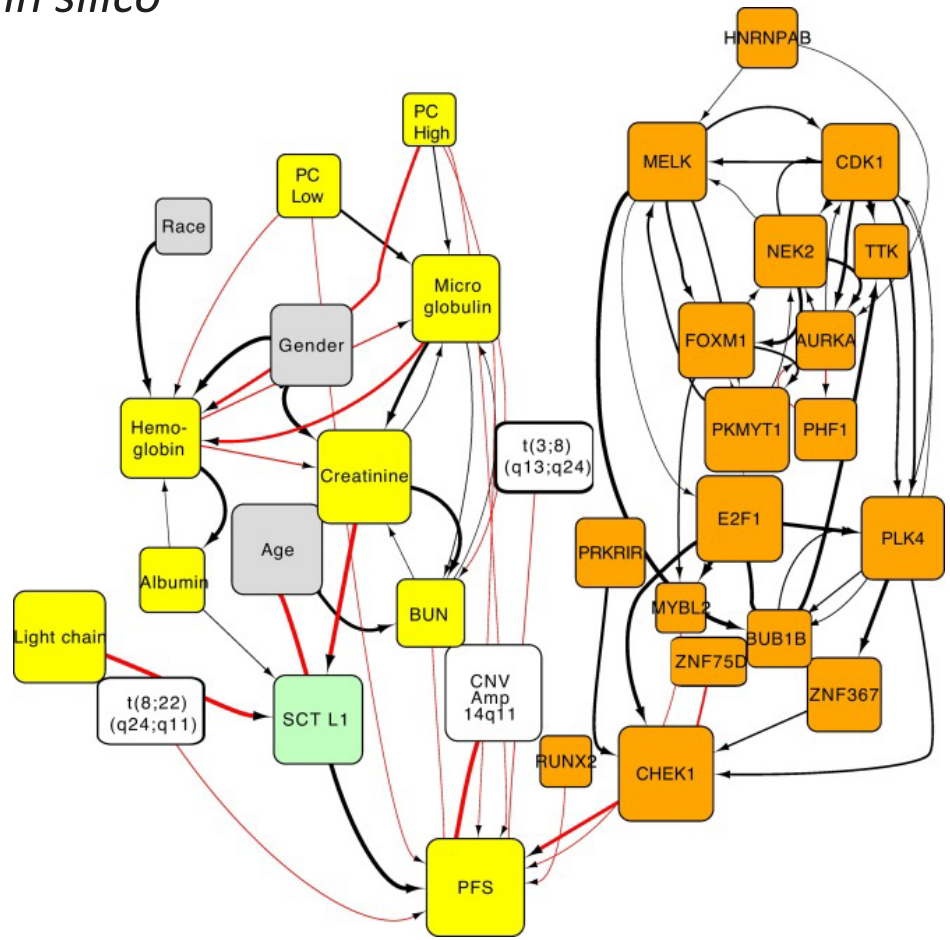
https://doi.org/10.1038/s41540-025-00592-0

Causal network: *in silico* Trials

The case for AI-driven cancer clinical trials – The efficacy arm *in silico*

In silico clinical trials develop virtual cohorts or case studies from patient-specific and disease-specific computational models to test the safety and efficacy of medical interventions. The foundation of ISTs depends on the ability to recreate human physiology and path.

Estimates the effect of interventions by simulating how changes in values of variables affects other variables downstream in the networks. Orange are genes, yellow are laboratories, gray are demographics, white are somatic variants, and green are treatment variables. The size of the nodes is relative to the estimated size of the effect from simulations, the width of the edges represents the confidence in the connection and the color represent whether the relationship between variables is direct or inverse.



R Parikh et a 2021; https://doi.org/10.1016/j.bbcan.2021.188572