



# Treatment Effects ARE Heterogeneous What Should We Do About It?

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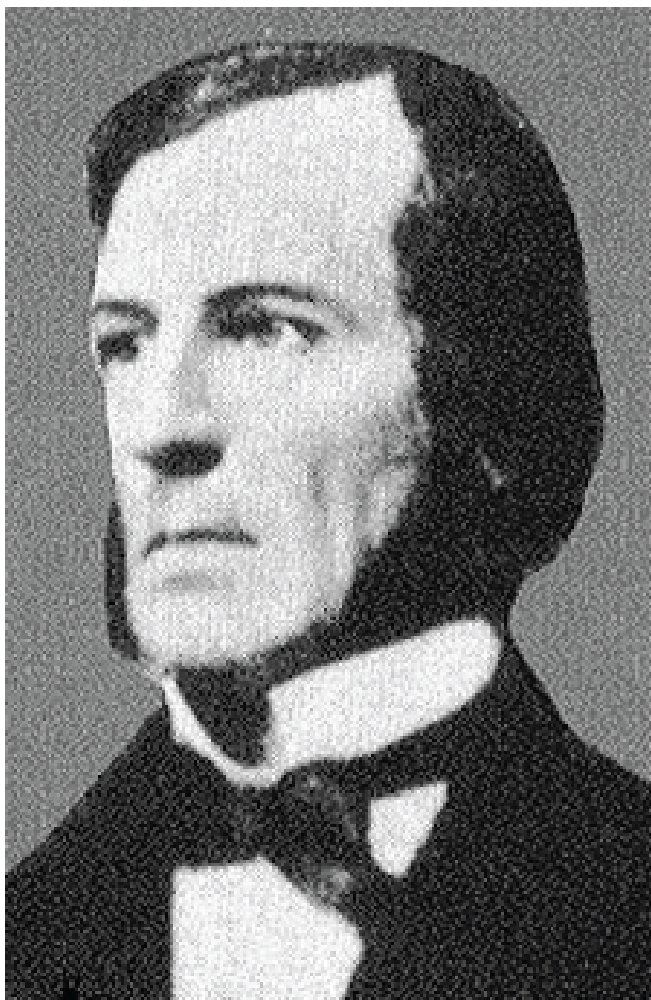
# Talk Outline

- **The Stew**
  - All treatments have heterogeneous effects
- **Patient's View**
  - What is my health state?
  - What is my health trajectory;? W
  - What is the expected effect of my trajectory for each of the available interventions?
- **What To Do?**
  - Statistical science
  - Clinical science
  - Health Systems
  - FDA/Government
- **Review**

# The Stew

# Axiom: All treatments have heterogeneous effects

# Boole -a- Bayes



George Boole 1815-1864



Thomas Bayes 1701-1761

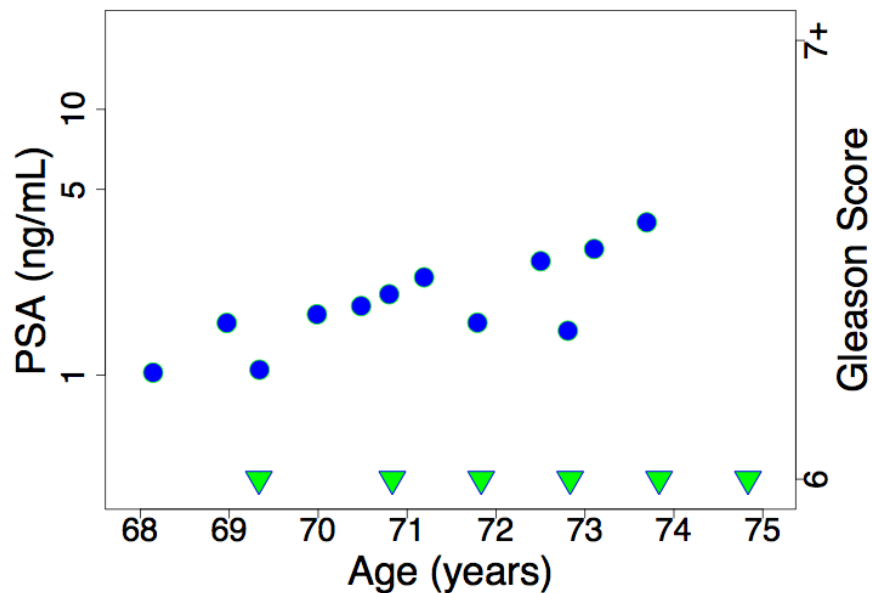


# Bouillabaisse

## Boole – a – Bayes



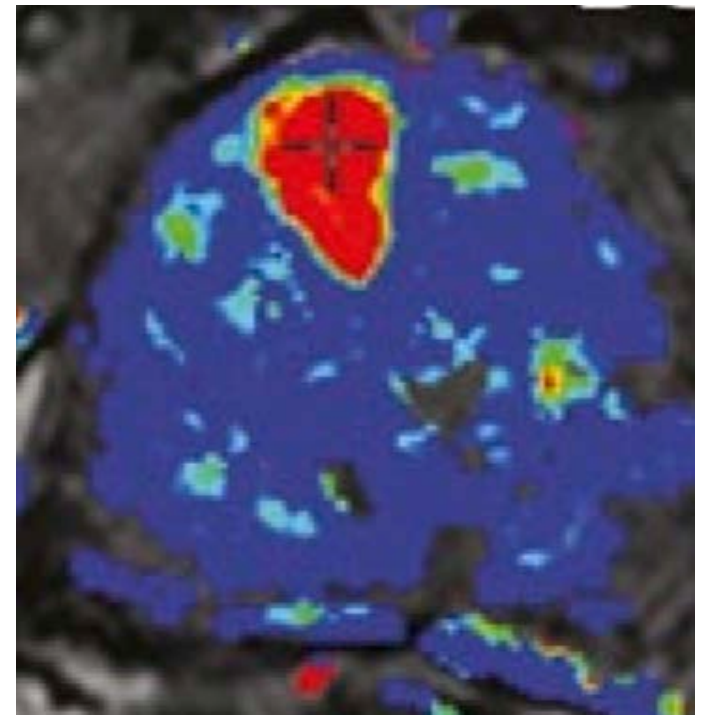
# Patient's View



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Is my tumor indolent or life-threatening?

Should I get a biopsy today or wait a year?

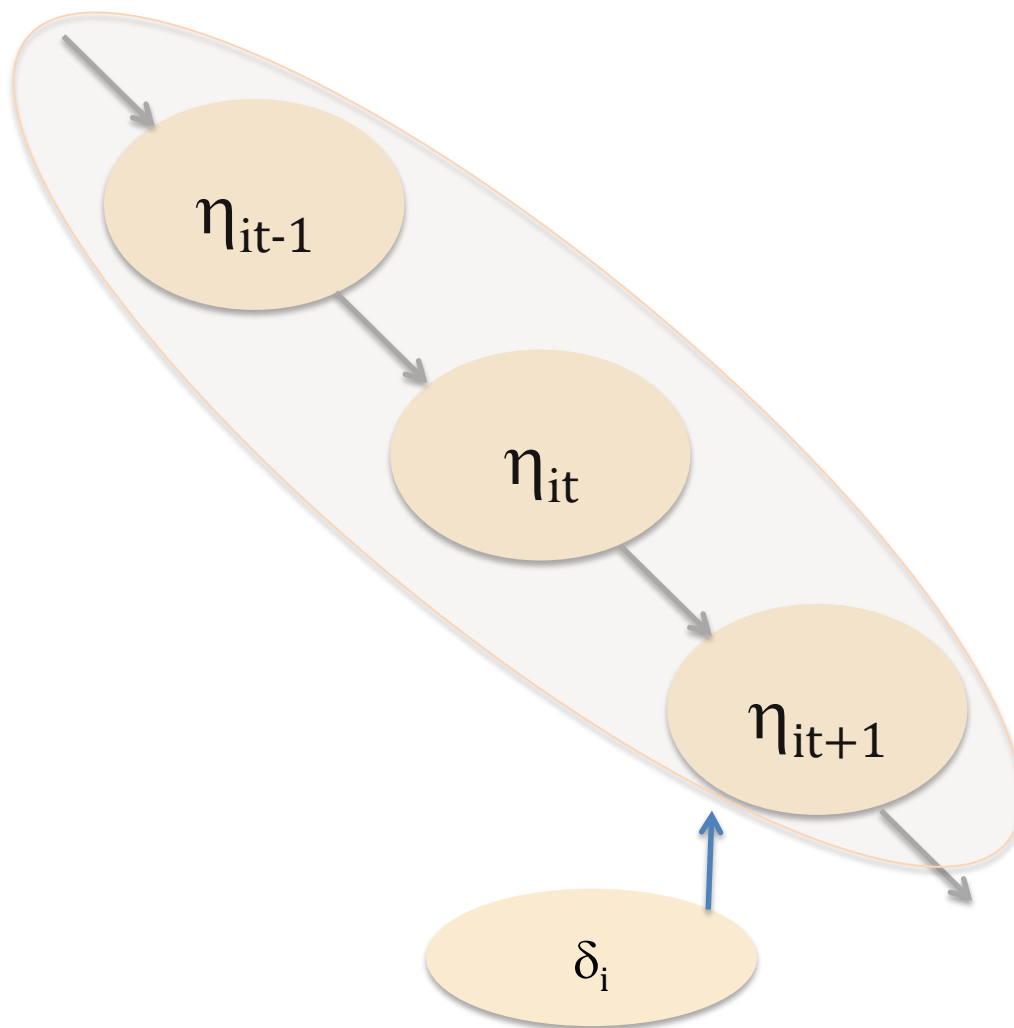
Should I continue annual check-ups or have my prostate removed or irradiated?



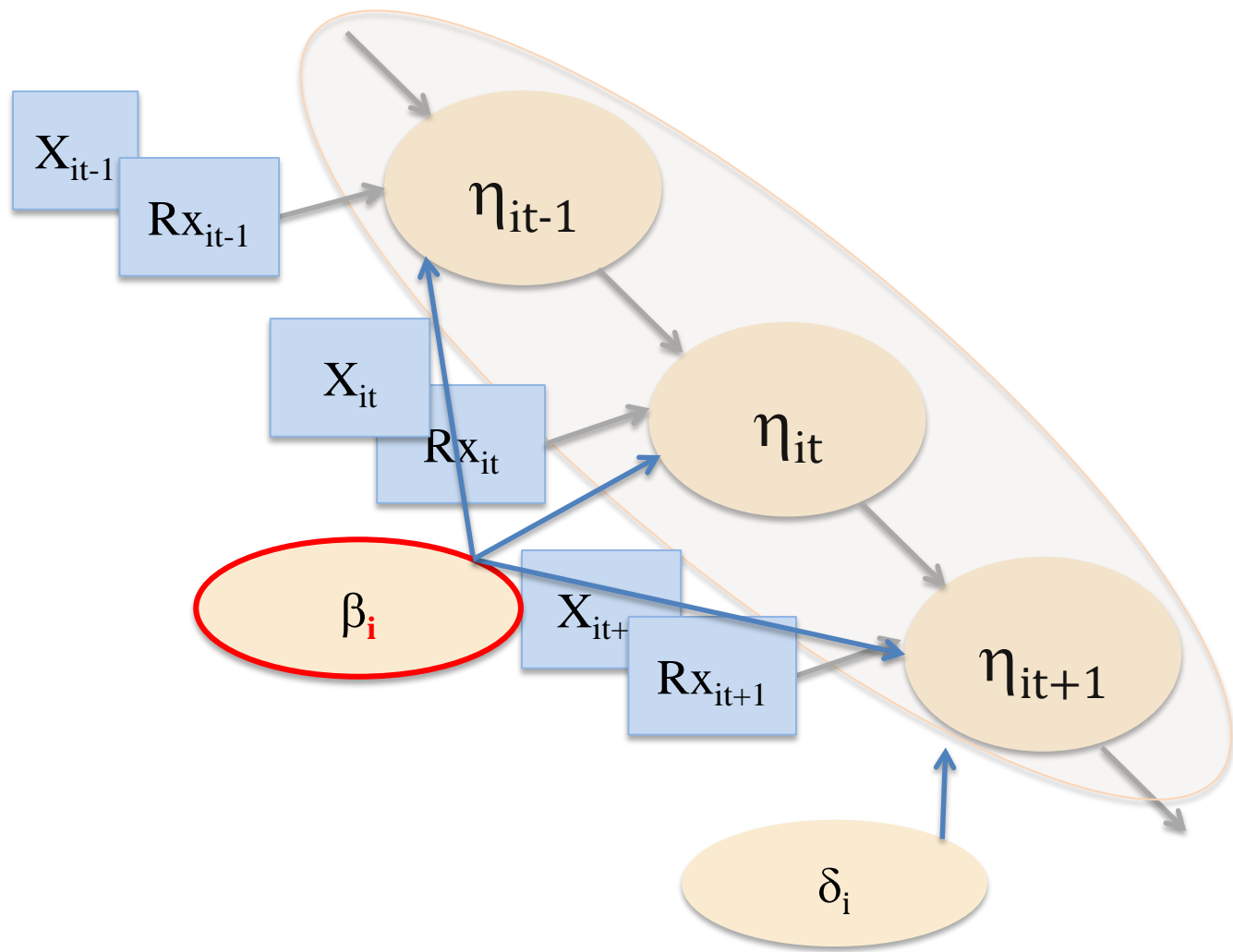
# Common Generic Questions

1. What is my health state?
2. What is my trajectory?
3. What other measurements might help clarify my state?
4. Which intervention is best for me today?

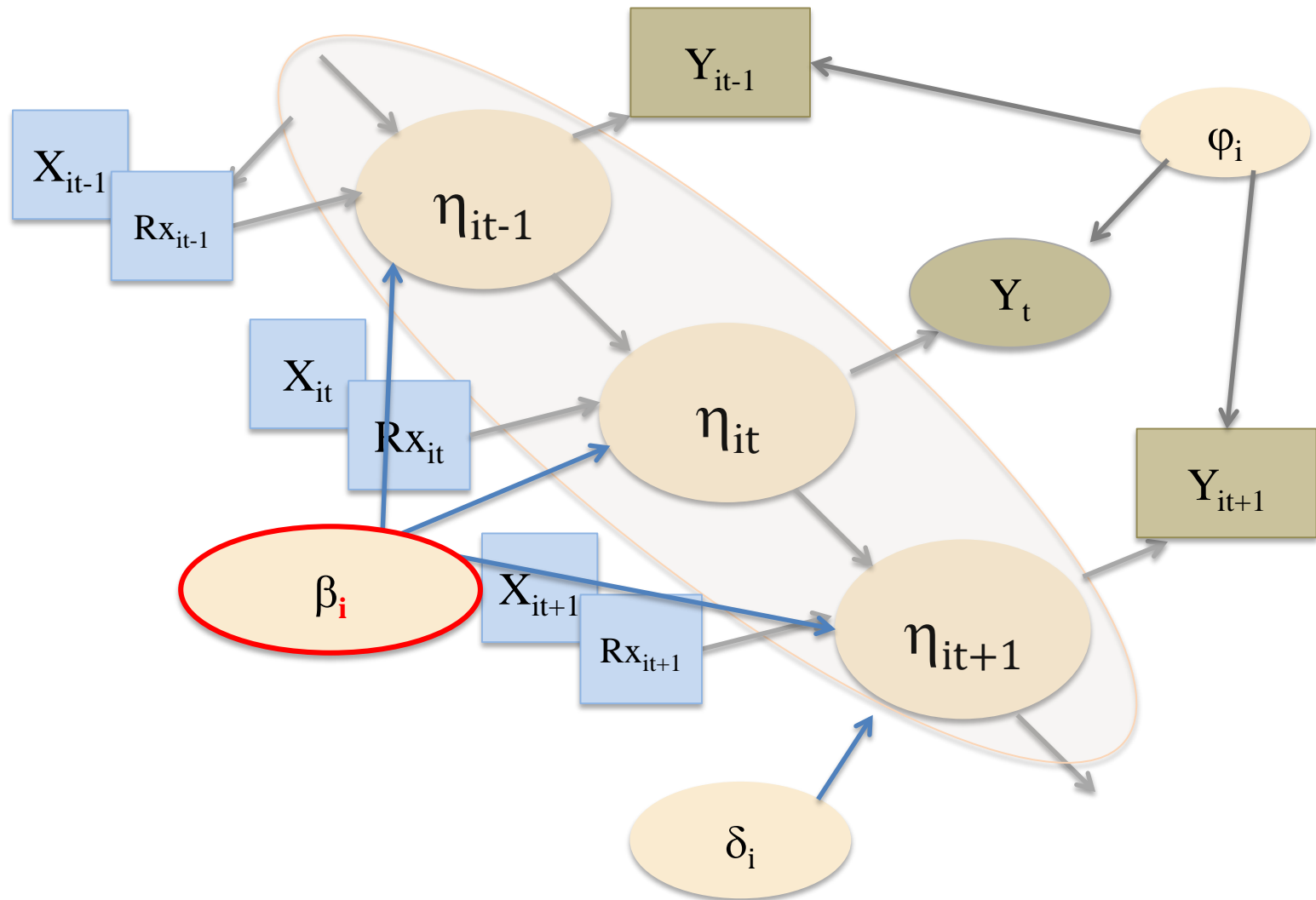
# Hierarchical Model for Health State/Trajectory ( $\eta_{it}$ ) with Person-specific Indicator ( $\delta_i$ )



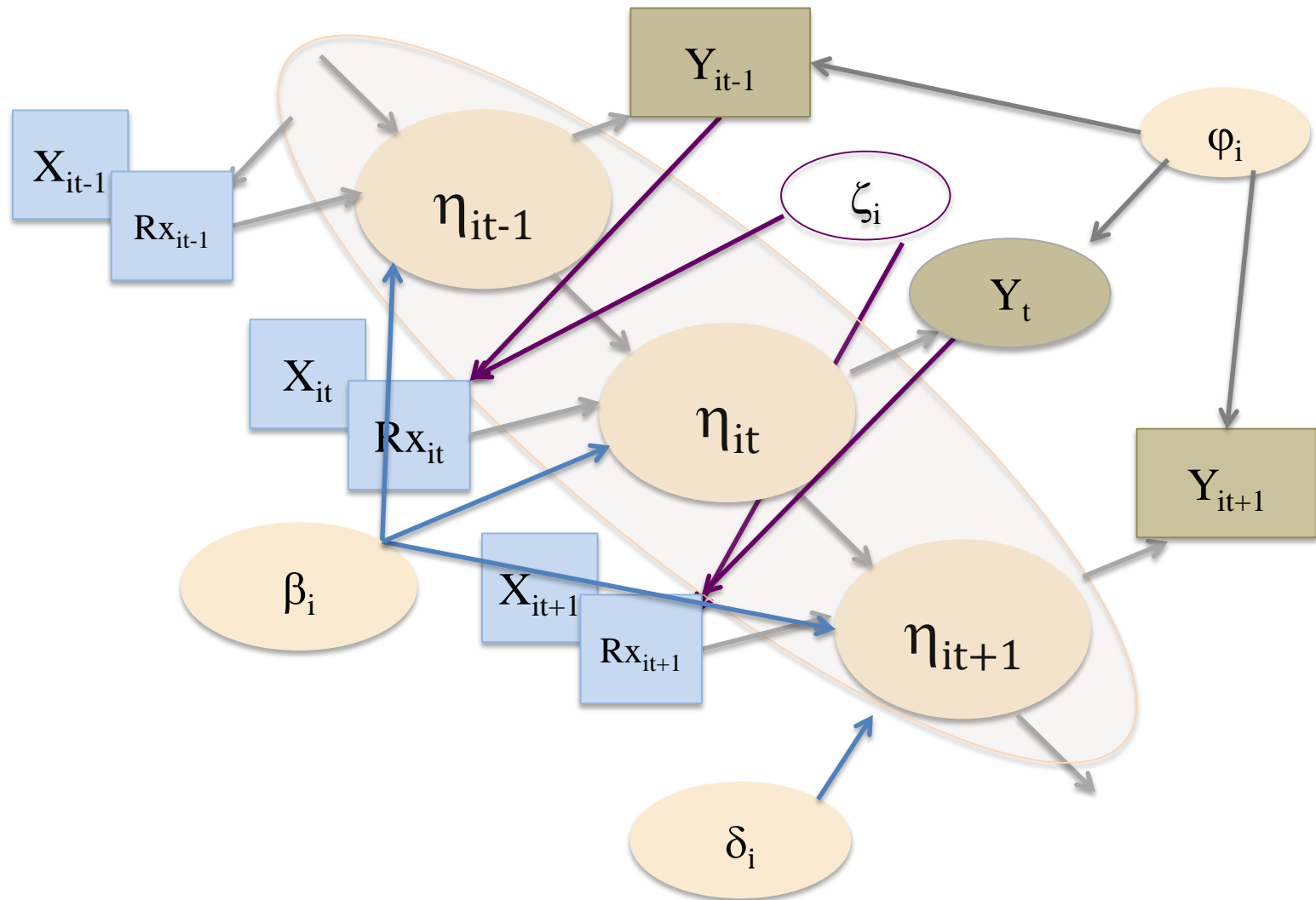
# Effects of Exogenous (X) and Endogenous (Rx) Covariates on Health State/Trajectory with Person-specific Regression Coefficients ( $\beta_i$ )

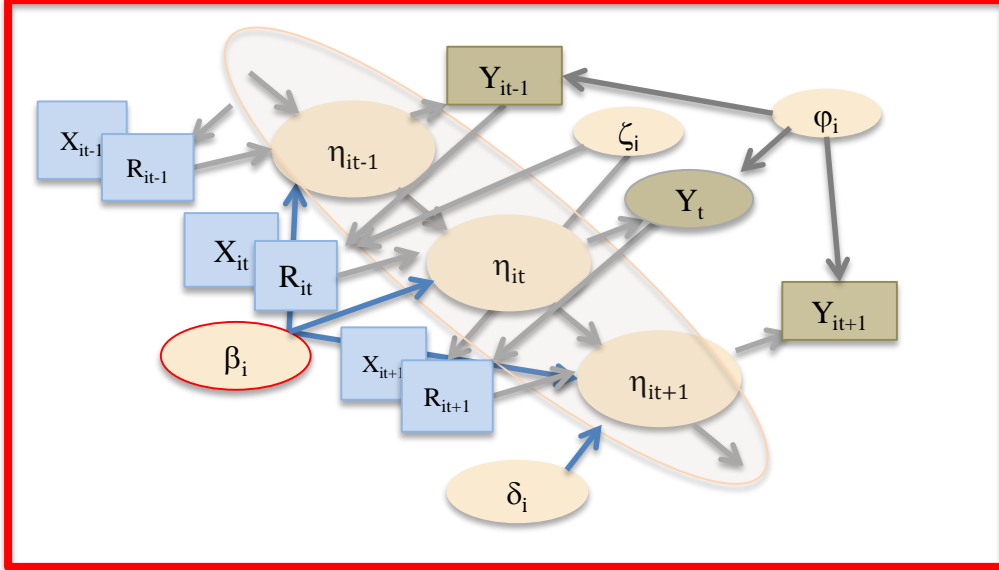


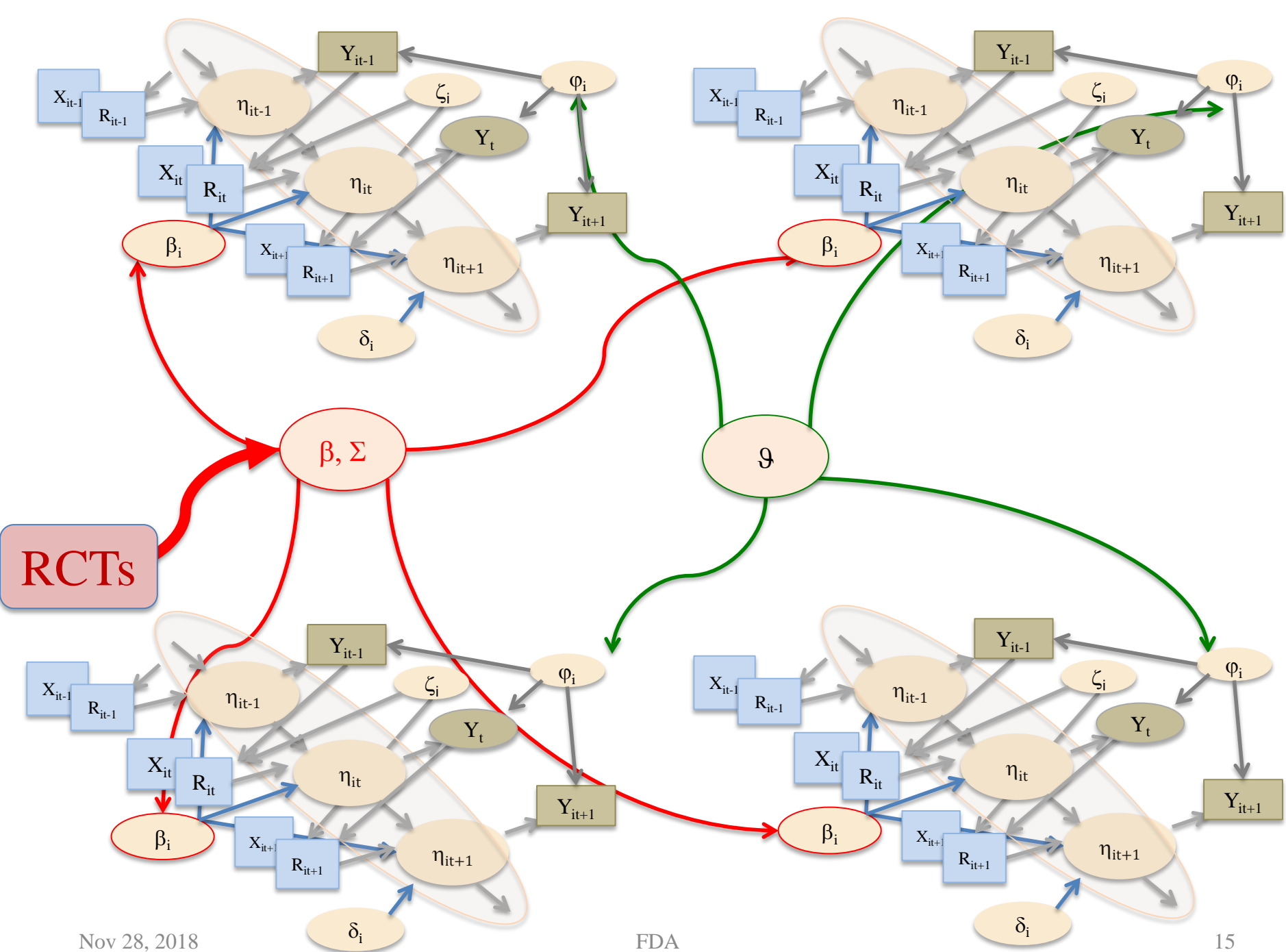
# Observations (Y) that Inform about Health State through Coefficients ( $\phi_i$ )

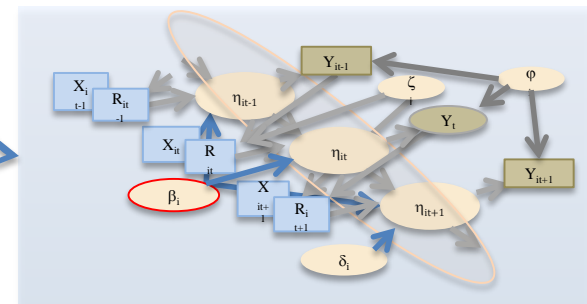
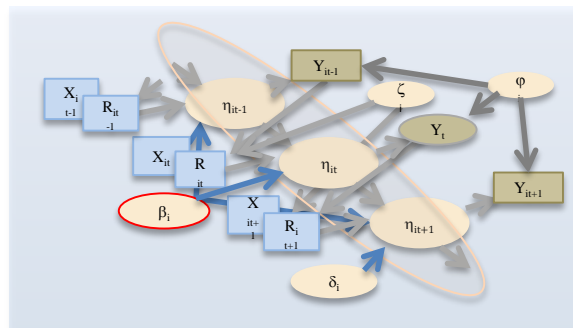
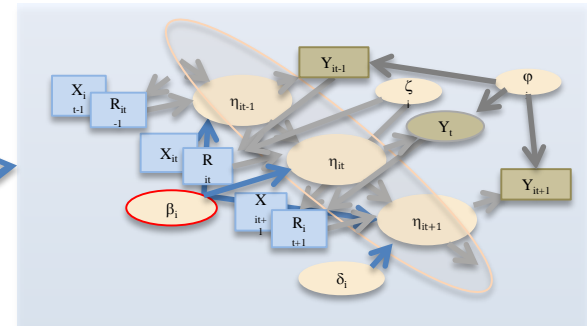
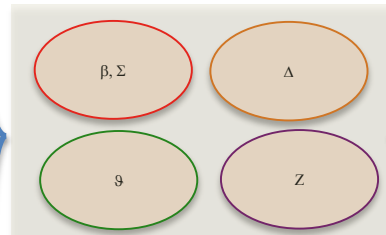
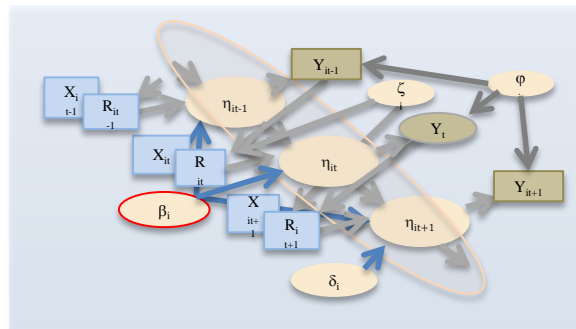


# Treatment Decisions Depend on Past Measured Outcomes through Parameters ( $\zeta_i$ )

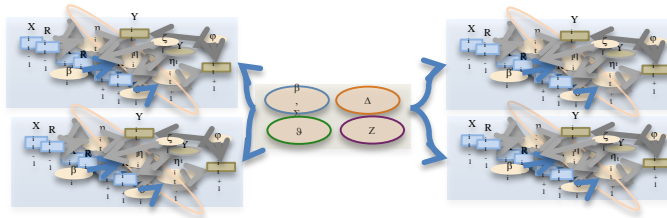
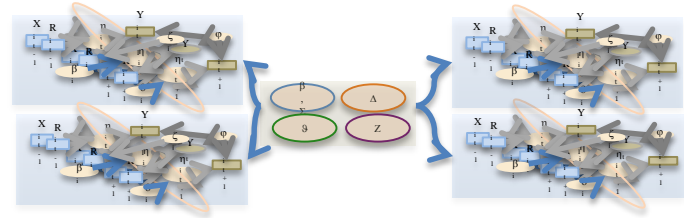
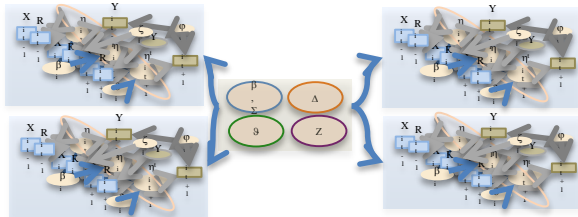
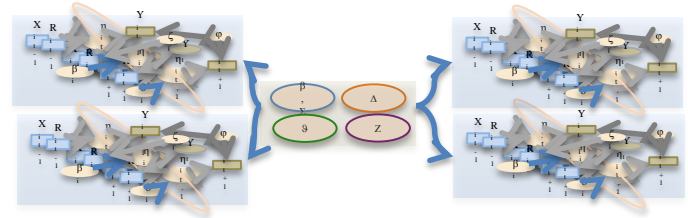
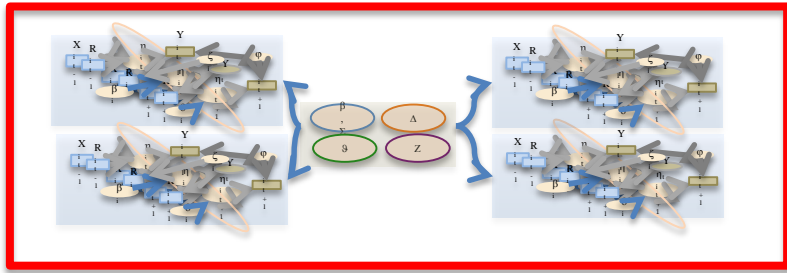


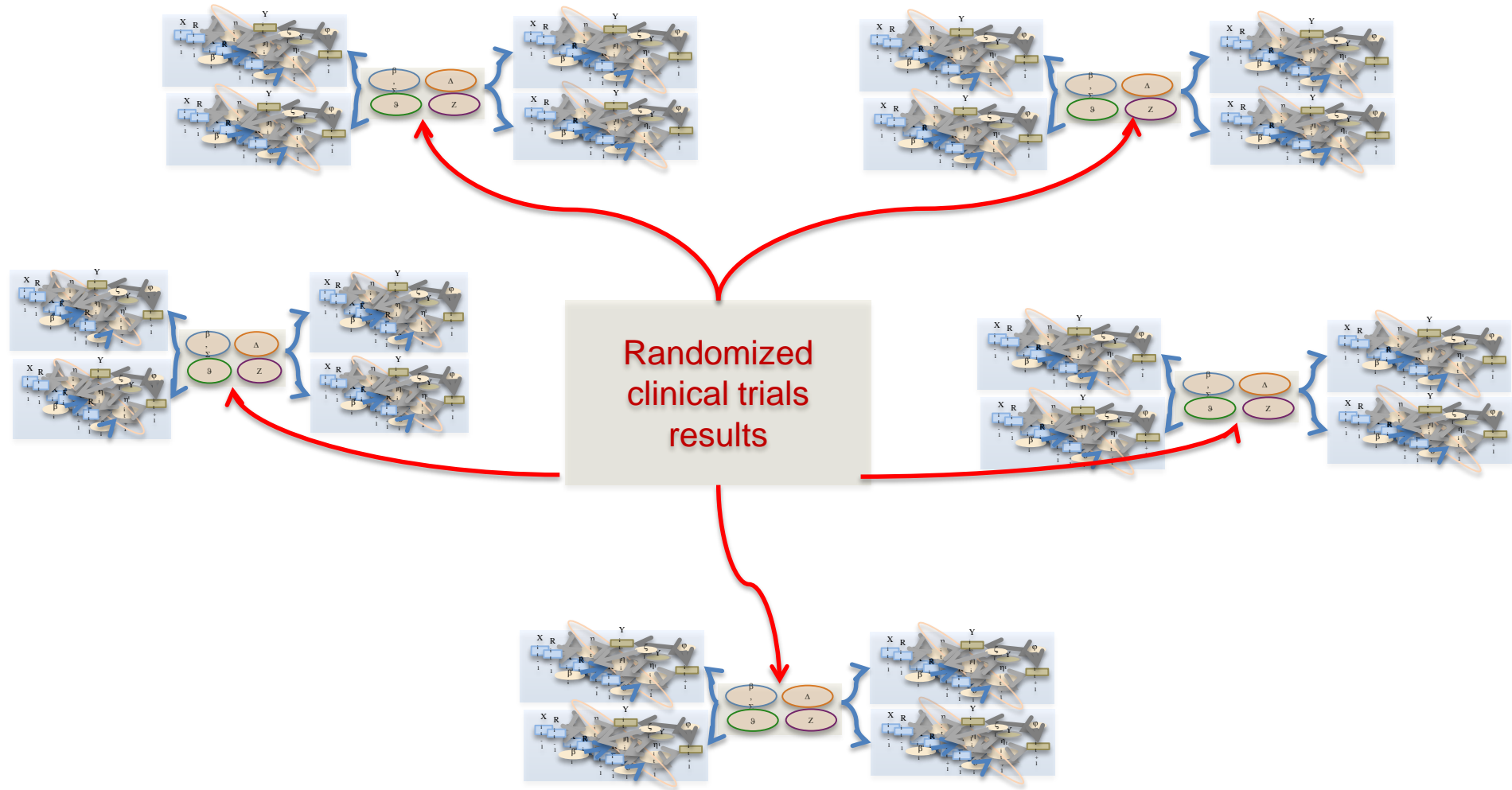












# Statistical Comments

- When *unverifiable* assumptions are added, many call these “causal models” or “structural equation” models; we prefer “predicting intervention effects (pie or  $\pi$ ) models
- Models can be partially identifiable
- Well-controlled, embedded clinical trials data are core data for these predictions
- Communication to patients and clinicians is hard, but critical

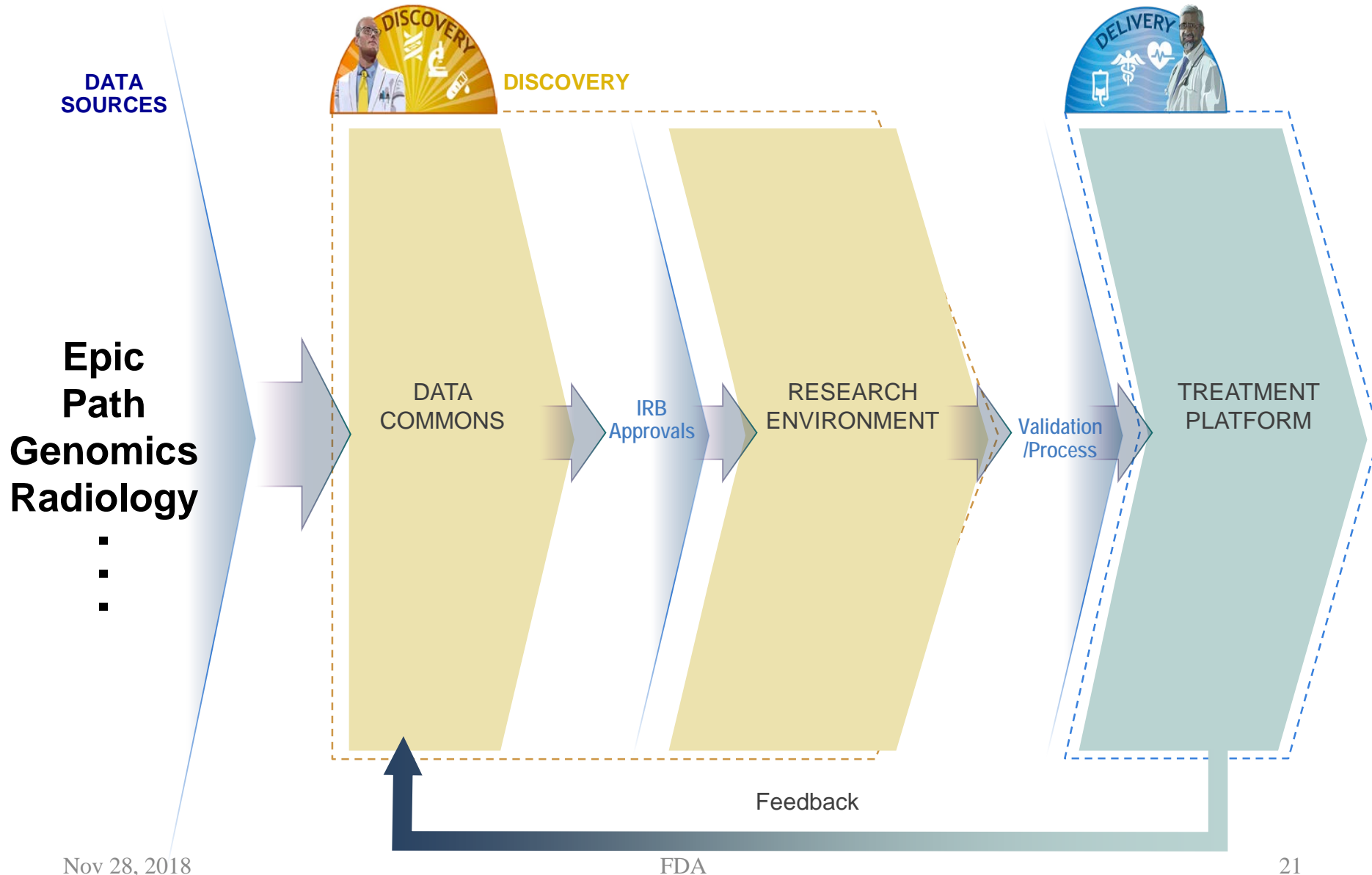
# What to Do?

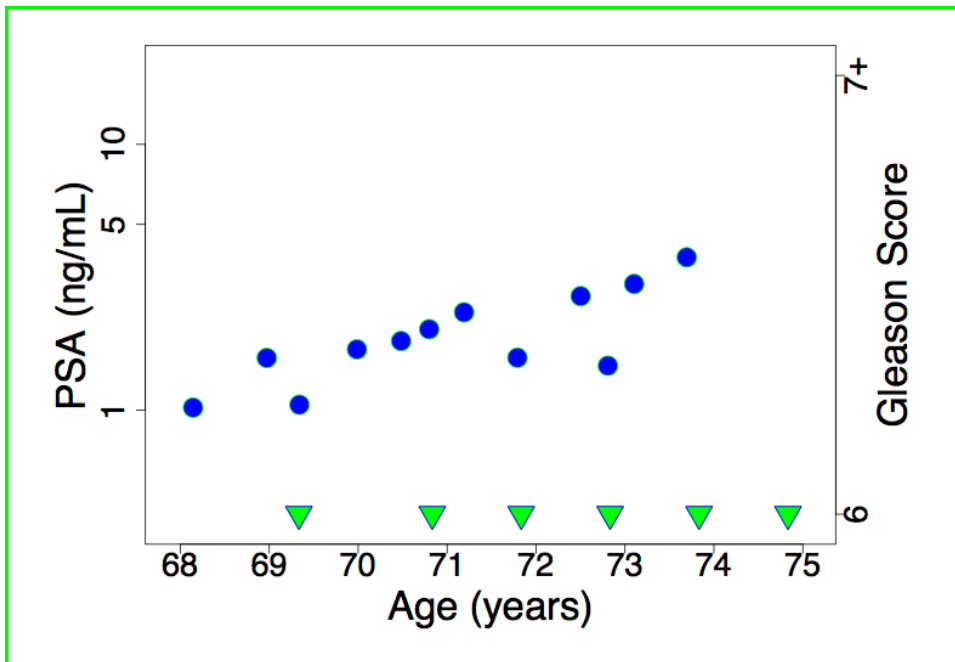
Statisticians: Predicting intervention effects ( $\pi$ ) models for populations and people

Clinical Research Groups: Clinical cohort databases

Health Systems: Deliver essential evidence relevant to each decision to the point of care

# PMAF – Precision Medicine Analytics Platform









Patient

MRN JH25386645

DOB 06/22/1956

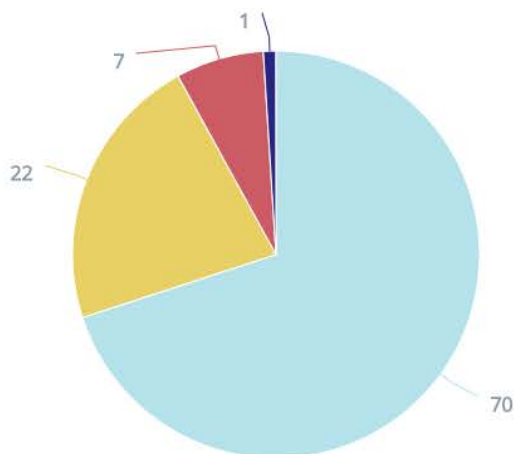


Patient lookup

## Predicted Prostate Cancer Outcomes

If 100 men with a similar age, diagnosis, and PSA and biopsy history had their prostate surgically removed today, **what cancer grade would be found?**

Click on a section of the pie chart to learn about longterm outcomes for men in each grade group or see outcomes for all 100 men like you.



Grade group 1

Grade group 2

Grade group 3

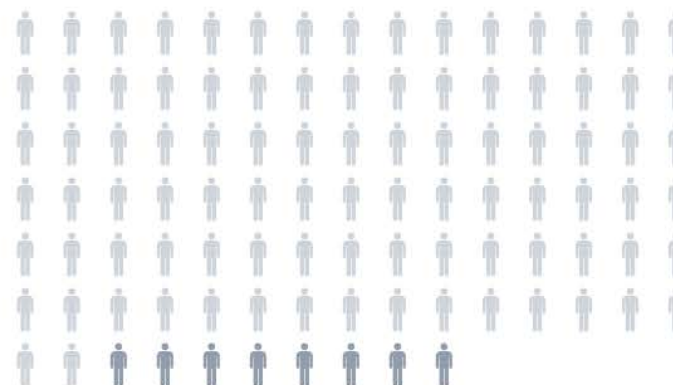
Grade group 4-5

5 YEARS

10 YEARS

ALL 100 MEN LIKE YOU

If 100 men like you had their prostates surgically removed today, after 5 years...



92

8

&lt; 1

WOULD BE CURED

WOULD HAVE PSA RECURRENCE

WOULD HAVE METASTATIC DISEASE



# Steps for More Coherent Health Decisions

1. Frame unmet health need
2. Specify biomedical model of current knowledge
3. Wrangle relevant data into a clinical cohort database (CCDB) (RCTs, Clinical observations)
4. Predicting intervention effects models
5. Design and test users' interface for population health manager, clinician and/or patient
6. Design and test on-going tool evaluation/curation
7. Devise business model to sustain/improve tool
8. Scale through consortia

# 3 Opportunities for FDA/ Other Regulatory Agencies

1. Randomized Consumer Trials to improve safety rating and estimate treatment heterogeneity
2. Incent public availability of patient-level clinical trials data
3. Promulgate methods for approving, then curating clinical decision **support** tools

# Main Points Once Again

- The Stew
  - All treatments have heterogeneous effects
- Patient's View
  - What is my health state?
  - What is my health trajectory?
  - What is the expected effect of my trajectory for each of the available interventions?
- What To Do?
  1. **Statistical science:** partner with clinical investigators to build models that use scientific evidence to address *the patients' questions as accurately and precisely as the data will allow*
  2. **Clinical science:** create and use research quality *clinical cohort databases*
  3. **Health Systems:** inform decisions with *relevant evidence at the point of care*
  4. **Government:** high standards for evidence about the ATE for initial licensing; incent post-licensing, Randomized Customer Trials (RCoTs) and public access data sets to drive 1-3 above.

Thank you

## Two Ideas to Generate More Knowledge about Heterogeneous Efficacy and Safety Faster

- Drop “safe” in favor of “safe-level k”
- Drop the complete separation of product research from product use
  - Already being done in observational research
  - Why not in experimental research

“Randomized Consumer Trials”