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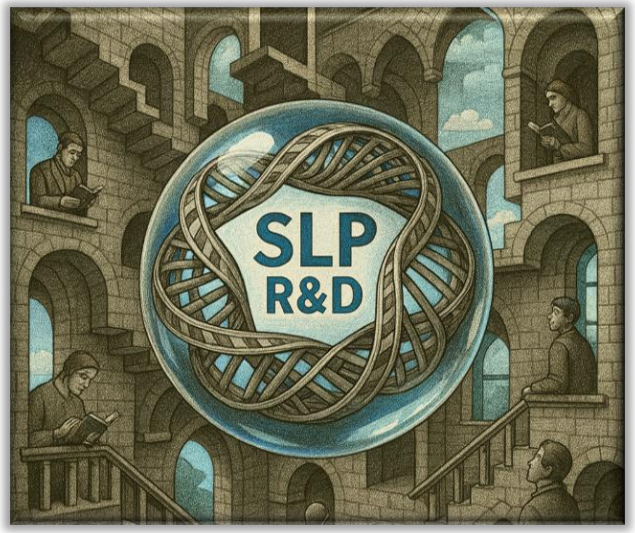
Beyond Disease Labels

Bridging Autoimmune Modeling and ML-enabled Precision Medicine

Noah Brostoff

Simulations Plus

10/28/26



Session Description and Objectives

Description

- Autoimmune treatment remains inefficient: in search of sustained response, patients may spend years if not decades cycling through the treatment options available for their disease-label
- While disease-label-based assessments are conventional, the underlying immune processes can be viewed as a shared mechanistic system, under which different perturbations can result in autoimmune-driven symptoms, with substantial symptom overlap across those disease-labels
- This presentation describes a disease-label-agnostic framework combining mechanistic quantitative systems pharmacology (QSP) modeling with interpretable machine learning to derive biomarker-based precision medicine treatment-assignment rules

Objectives

- Describe how a disease-label-agnostic autoimmune QSP framework can be combined with interpretable machine learning to guide precision medicine therapy-assignment
- Describe applications of the framework
- Describe benefits of the paradigm shift in thinking that the application suggests

Biography and Contact Information

- Noah Brostoff has 14 years of on-the-job experience in quantitative systems pharmacology (QSP) modeling
- He specializes in modeling underlying healthy and disease biology, therapeutic interventions, and clinical trial pipelines for virtual population fitting, validation, and prediction across autoimmune disease, oncology, clotting disorders, and physical trauma
- He bridges mechanistic modeling with machine learning to inform clinical trial design, translational strategy, and precision medicine, while leveraging AI to streamline scientific workflows and expand modeling capabilities
- He received a B.A. from Colorado College and an M.S. from The Ohio State University, before beginning his career at Immunetrics, and subsequently joining Simulations Plus and then Altaris through acquisitions

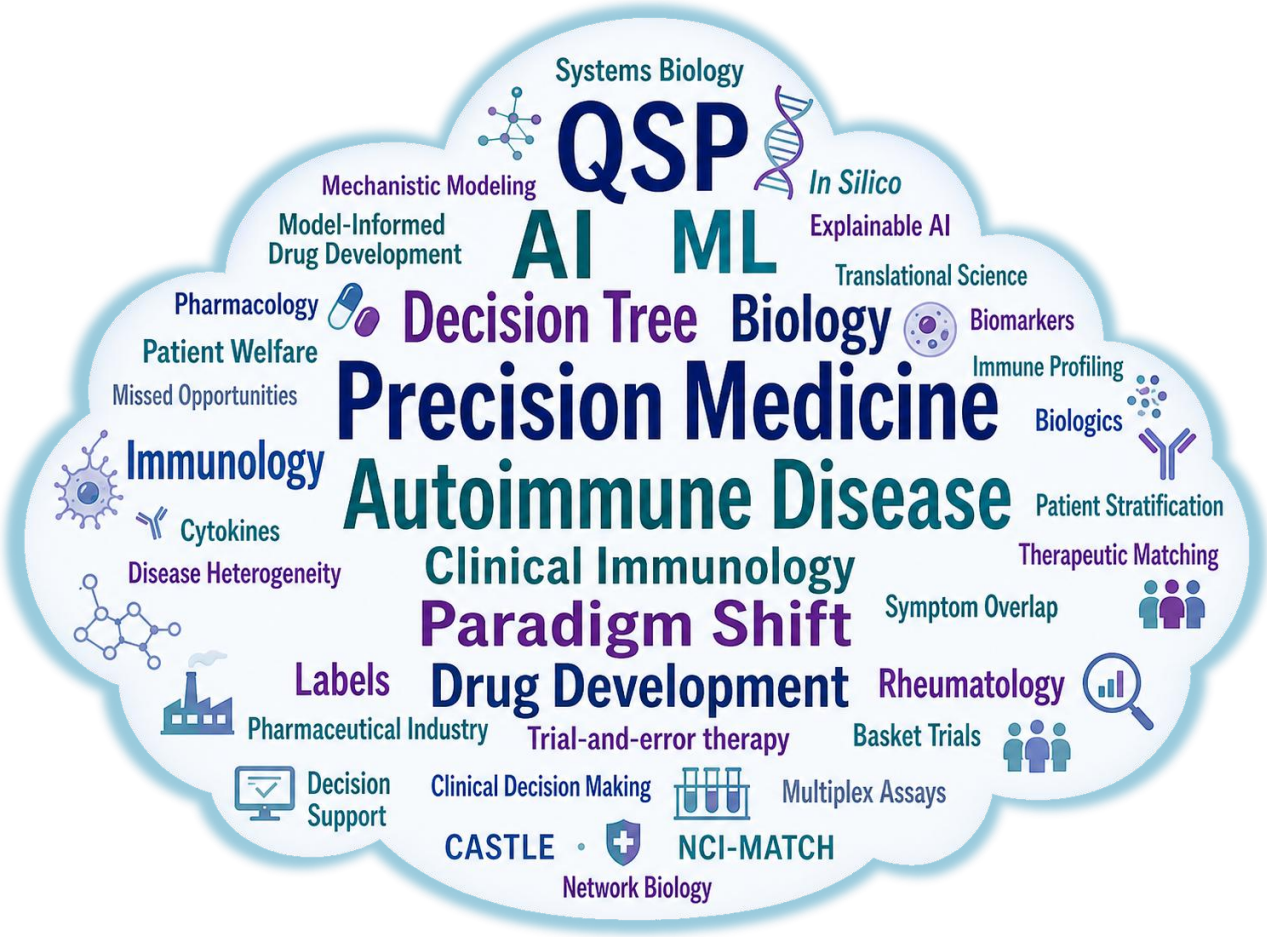
Noah.Brostoff@Simulations-Plus.com

Disease-Label-Agnostic (DLA)

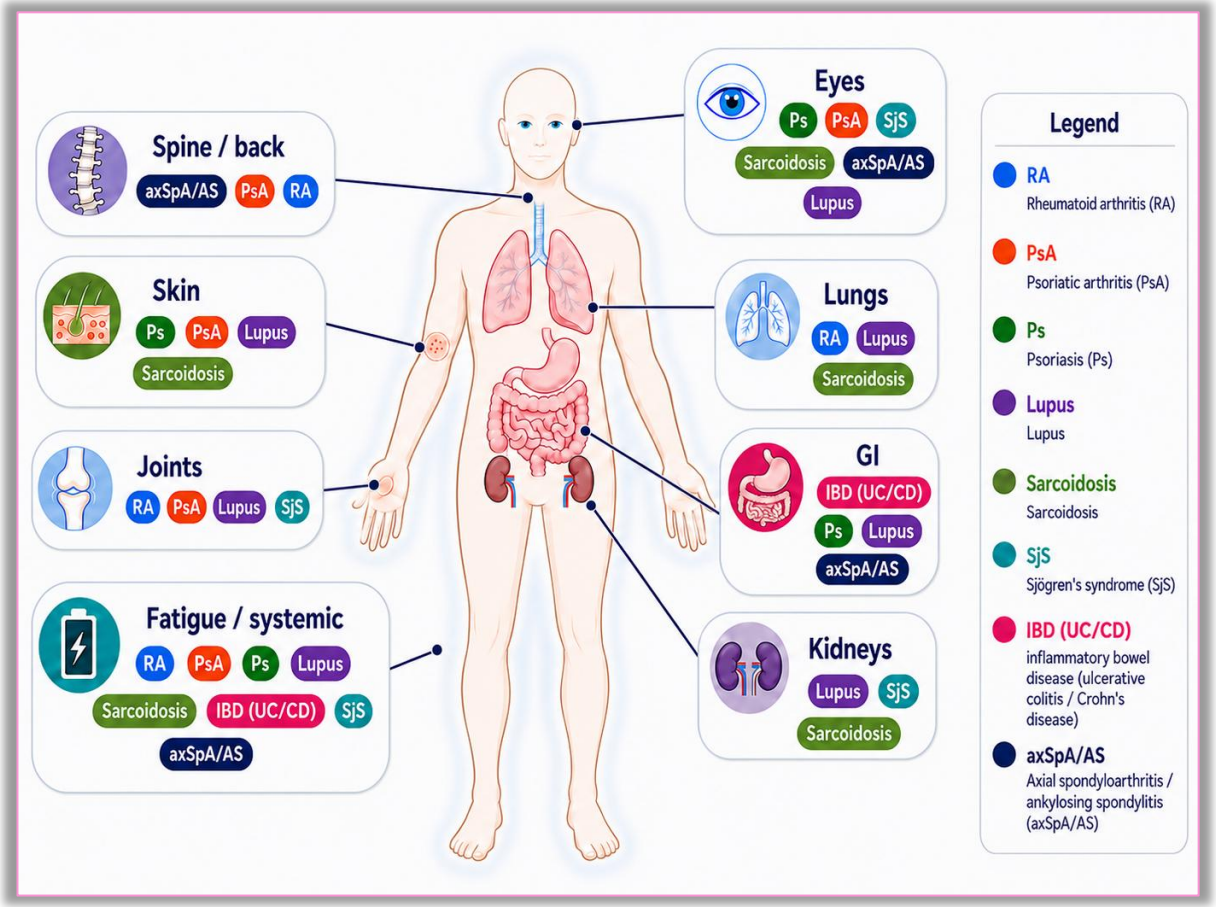
Quantitative Systems Pharmacology (QSP)
Autoimmune Precision Medicine Modeling Framework

In the prototype:

In a blind test set,
this DLA framework
improved the outcome versus
label-based treatment assignments
in 70% of patients



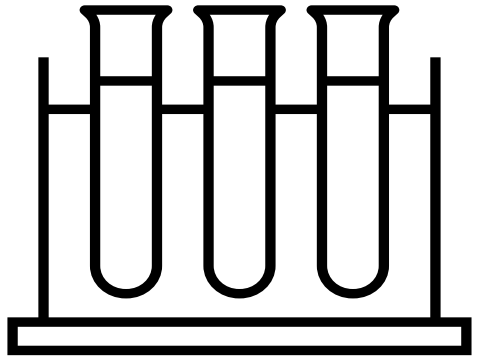
The Motivation



- Autoimmune illness stems from both unique and shared triggers and pathways
- This results in overlapping symptom domains across traditional disease-labels
- Treatment coverage is based on disease-label assignment and high percentages of inadequate responders exist
  - Easily incurred misdiagnoses due to symptom overlap exacerbate this
  - There is a lack of biomarker-based precision mappings from therapies to responders
- By going beyond the disease-labeling paradigm and establishing a *disease-label-agnostic* biomarker-based precision medicine treatment-assignment scheme, we seek to remedy this situation

Disease-Labeling for Autoimmune Patients



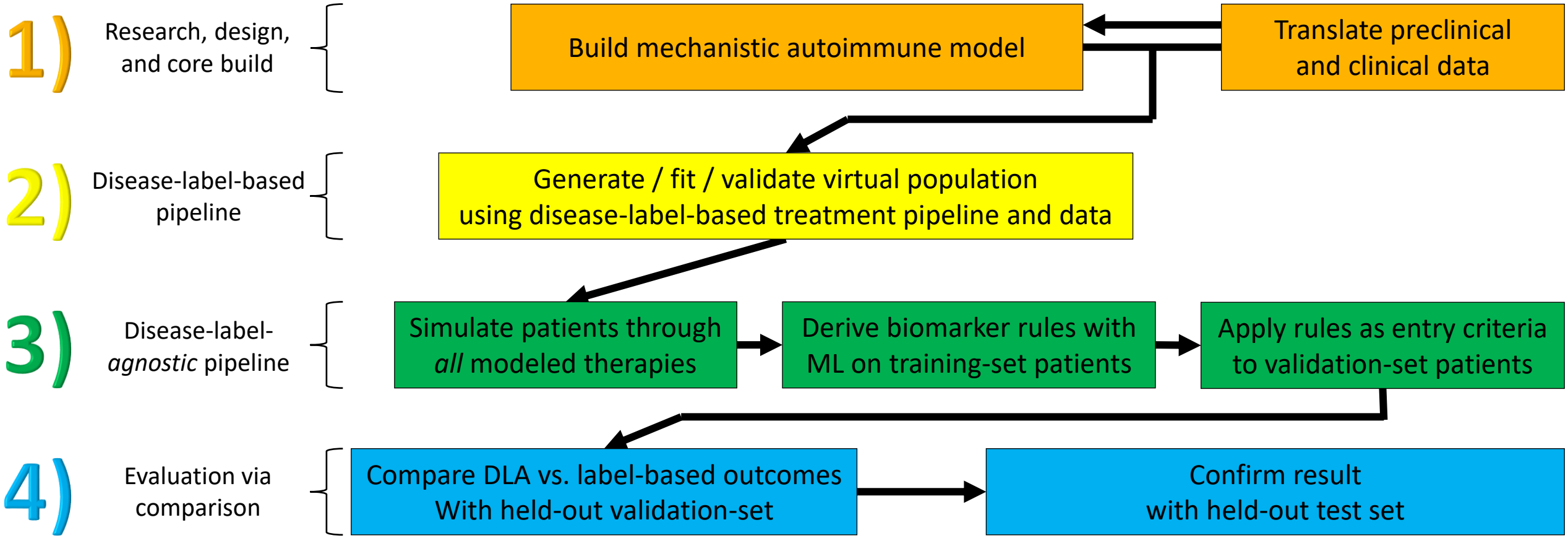


Measure	RA	SLE	PsA	Healthy
RF	+	-	-	-
Anti-dsDNA	-	+	-	-
ESR (& standard inflammation labs)	Elevated	Elevated	Elevated	Normal
Joint Symptoms	Yes	Yes	Yes	No

Rheumatoid Arthritis (**RA**),
Systemic Lupus Erythematosus (**SLE**),
and Psoriatic Arthritis (**PsA**)
form the basis for the prototype model

Patients with any of these disease-labels may present with **joint symptoms**, demonstrating a symptom overlap

The DLA Process

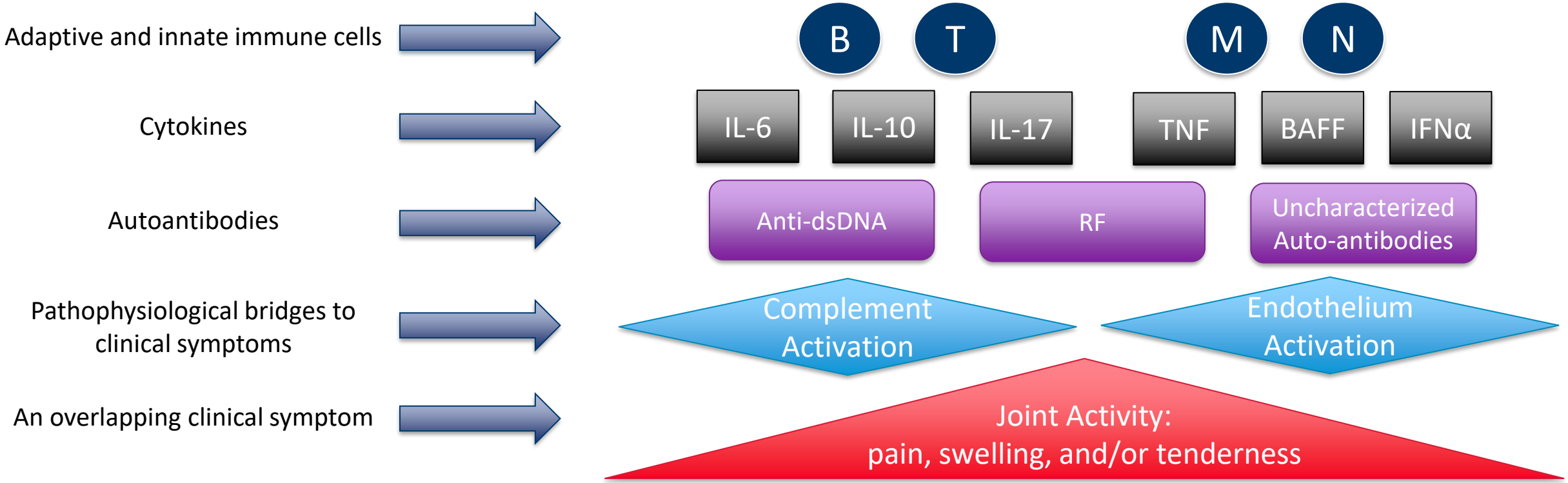


Prototype Model Species

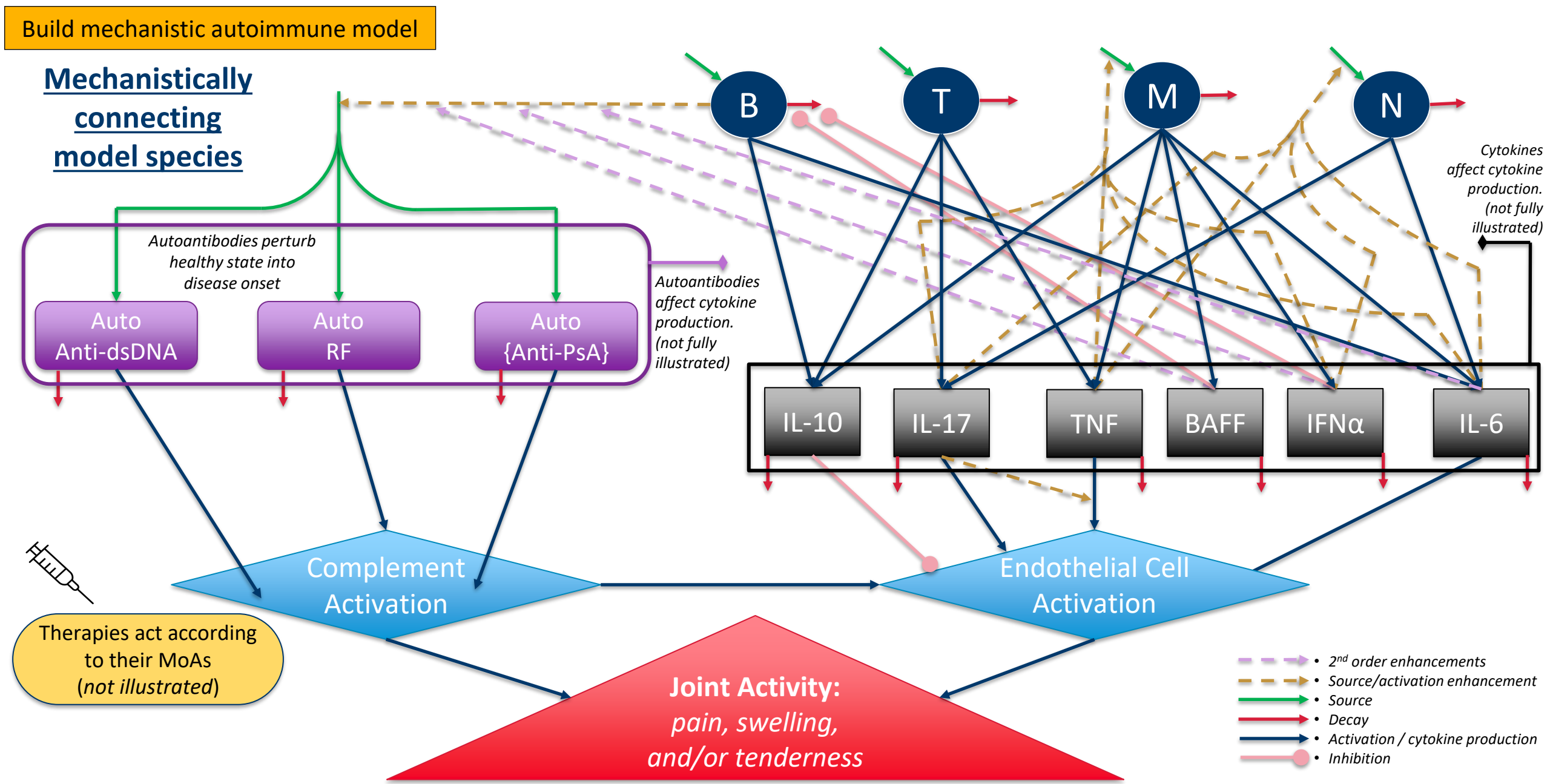
Build mechanistic autoimmune model

The Simulations Plus library of (label-specific) autoimmune disease models provides a basis for modeling healthy and disease biology

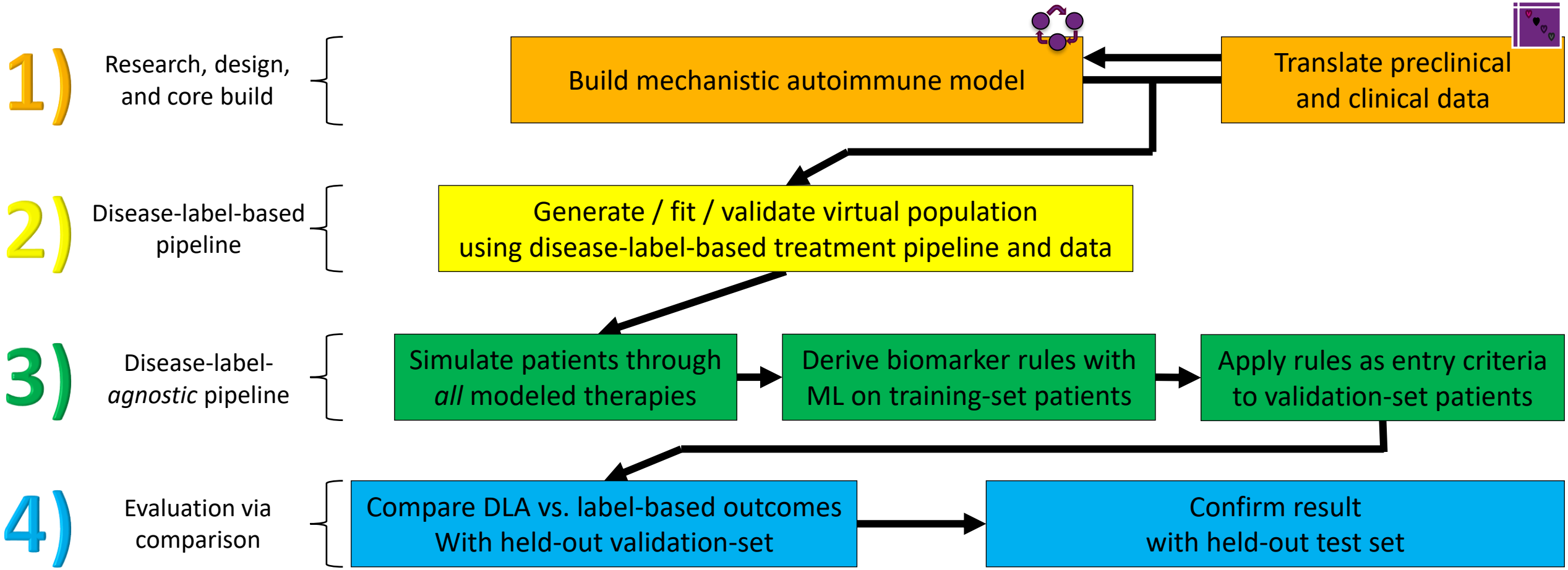
This DLA prototype provides sufficient structure/realism to support disease dynamics with different pathways leading to joint symptoms, and relevant therapeutic targets



Build mechanistic autoimmune model



The DLA Process



Generate / fit / validate virtual population using disease-label-based treatment pipeline and data

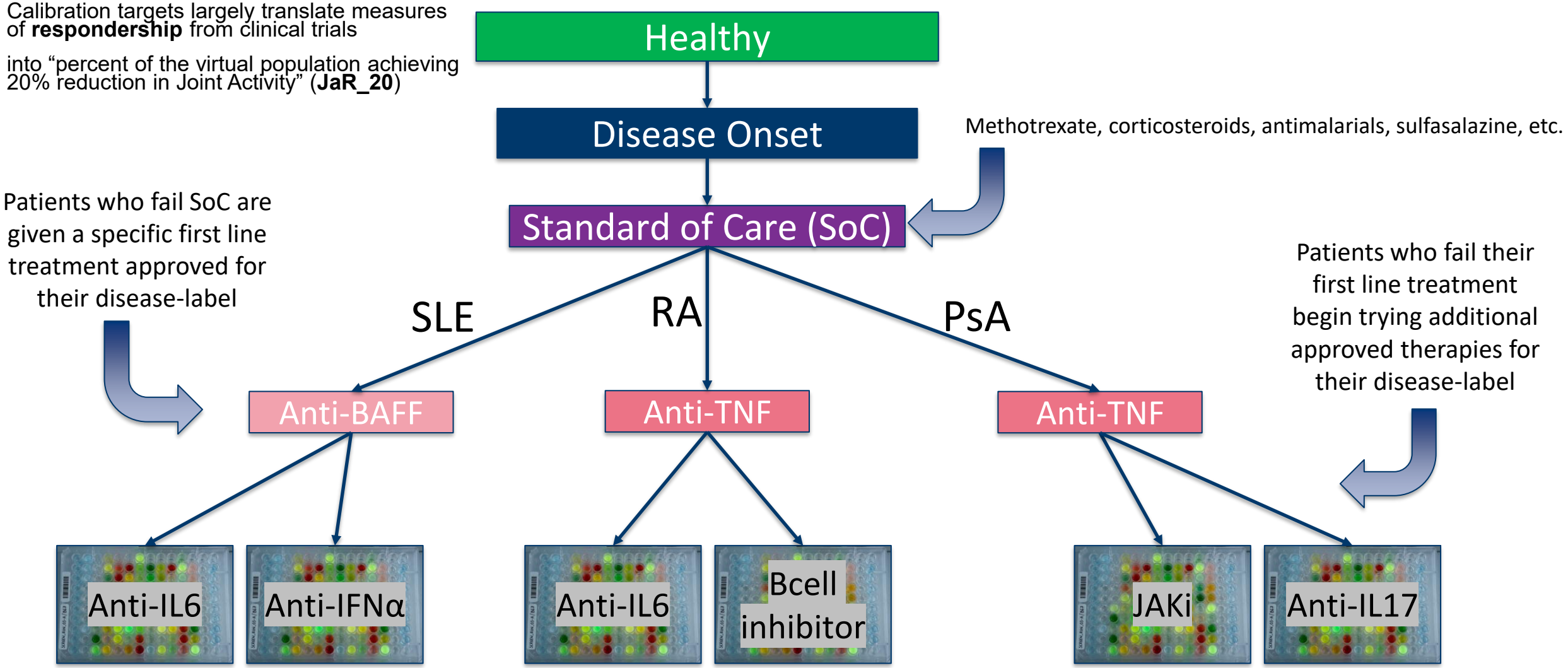
Current Paradigm: Disease-Label-Based Pipeline

Each Disease-Label has Approved Treatments to be Tried in Partially Prespecified Orders

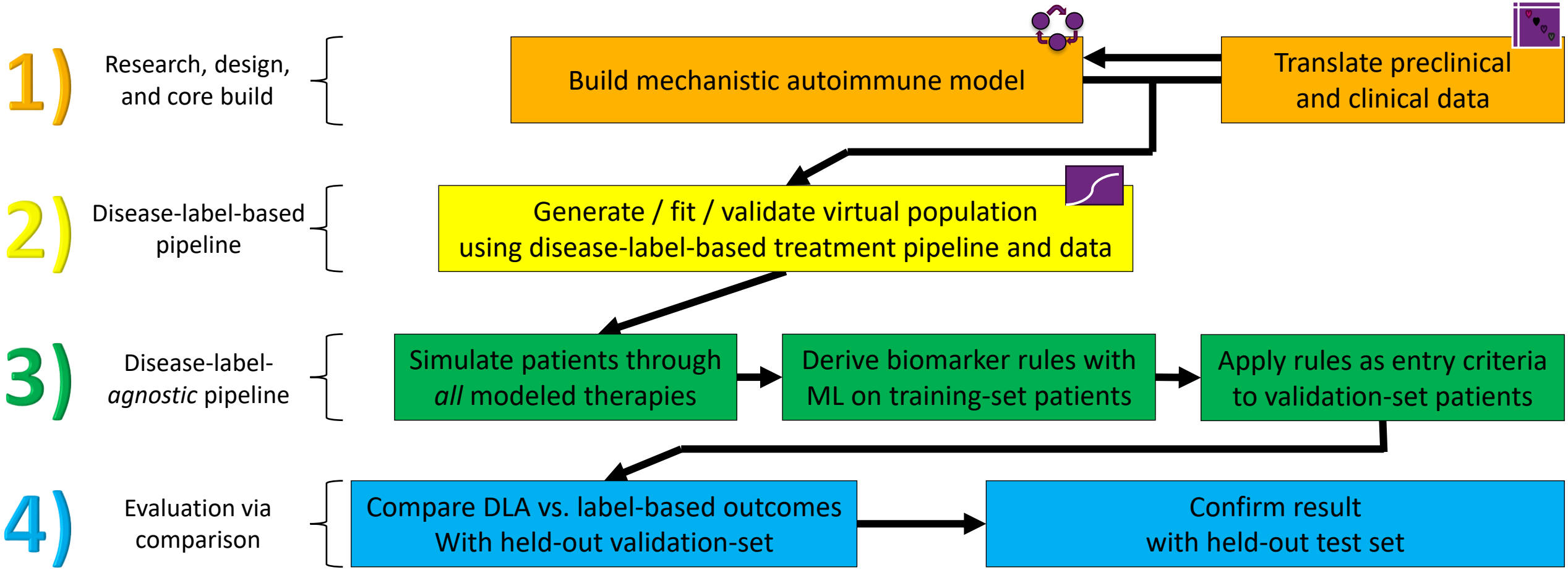
In the prototype:

Calibration targets largely translate measures of **respondership** from clinical trials

into "percent of the virtual population achieving 20% reduction in Joint Activity" (**JaR_20**)



The DLA Process



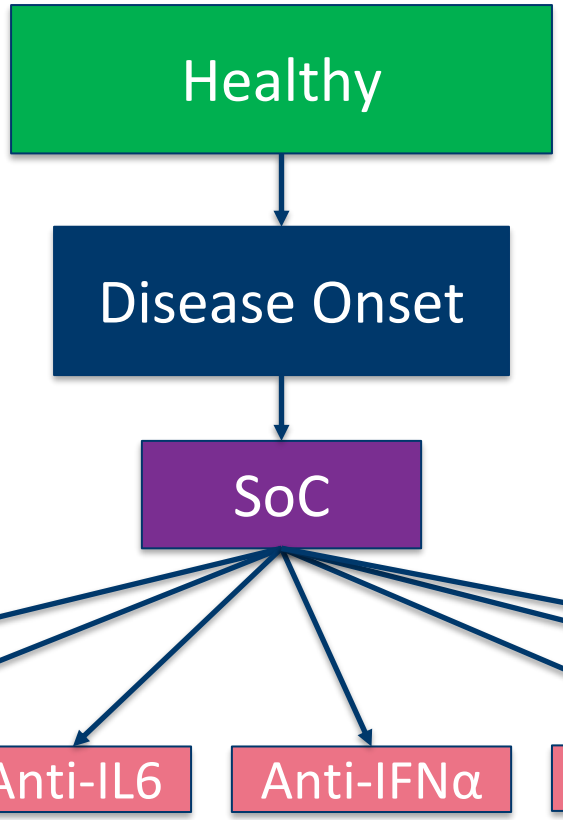
Simulate patients through *all* modeled therapies → Derive biomarker rules with ML on training-set patients → Apply rules as entry criteria to validation-set patients

Shifting the Paradigm:
Precision Medicine Therapy Assignment



Pass 1: *The Decision Tree*

- **Derive therapy-assignment rules** from measurable/modeled species
  - Uses training-set split; replicated into all therapies
  - Optimizes for most efficacious therapy
  - Assignment is disease-label-agnostic





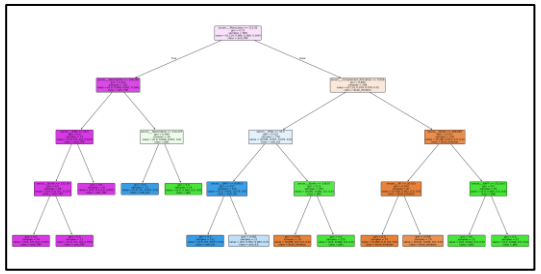


Pass 2: *The Precision Medicine Therapy Assignment*

- Applied decision tree rules as entry criteria
  - Assigns a specific therapy to each patient
  - Validation-set and Test-set patients are utilized as a blind assessment

Simulate patients through *all* modeled therapies → Derive biomarker rules with ML on training-set patients → Apply rules as entry criteria to validation-set patients

Decision Tree Results



Visual depiction of true/false decision tree branching

- The decision tree derives interpretable threshold functions of measurable biomarkers
  - This supports usability in trial design and clinical practice
  - Example: if Biomarker_A > X and Biomarker_B < Y, then give drug (class) Z

Give **anti_TNF** if:
Thresholds_Function(Monocytes, Neutrophils)

- Give **JAKi** if any of the following are true:
  - *Thresholds_Function(Monocytes, Neutrophils), or*
  - *Thresholds_Function(Monocytes, Complement_Activation, IFNα, Bcells), or*
  - *Thresholds_Function(Monocytes, Complement_Activation, Bcells)*

Give **anti_IL6** if any of the following are true:
Thresholds_Function(Monocytes, Neutrophils), or
Thresholds_Function(Monocytes, Complement_Activation, IFNα)

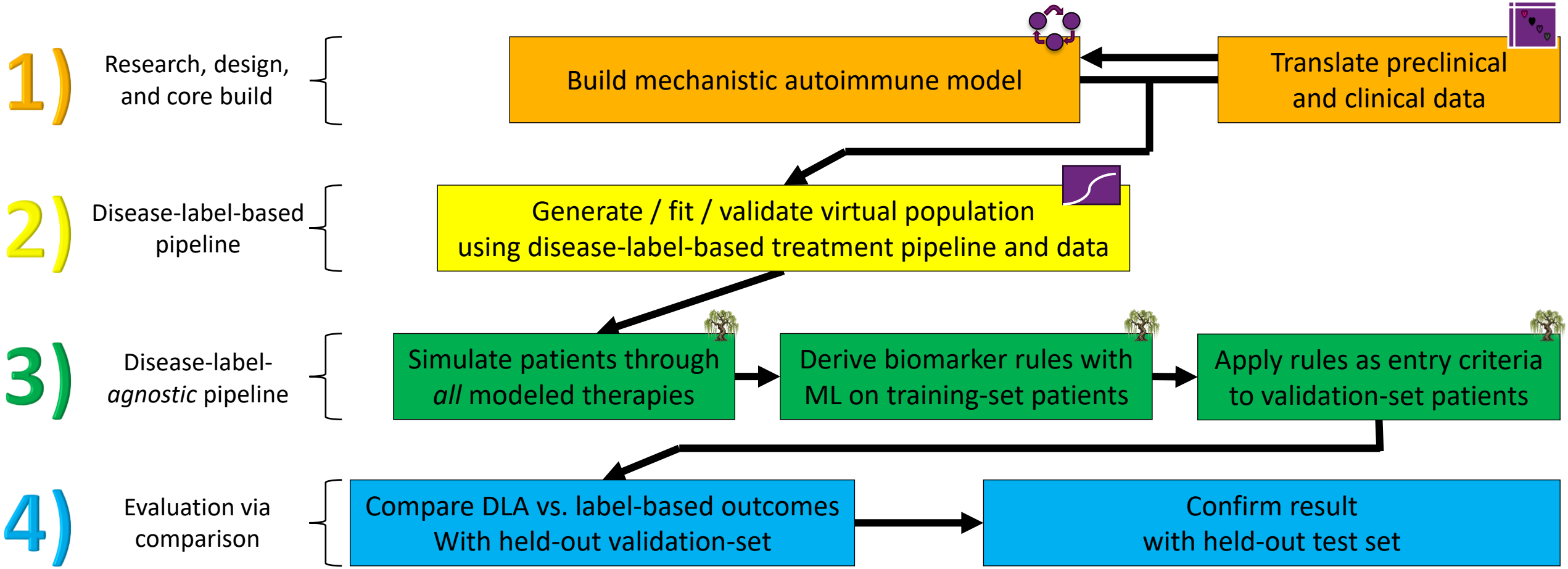
- Give **Bcell_Inhibitor** if any of the following are true:
  - *Thresholds_Function(Monocytes, Complement_Activation, IFNα, Bcells), or*
  - *Thresholds_Function(Monocytes, Complement_Activation, Bcells)*

- *Interestingly, the auto-antibodies that define the conventional disease labels were (available but) not selected as part of the emergent entry criteria*
  - *This supports the label-agnostic premise*

- **Therapies never assigned in this result**
  - anti_BAFF
  - anti_IFNα
  - anti_IL17

- *Interesting, but not to be taken this as a real-world conclusion*
  - *Prototype; decision tree goal metric & included biology matter*

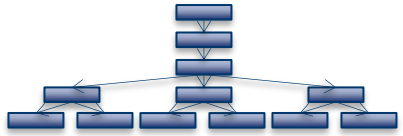
The DLA Process



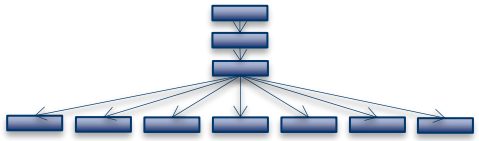
Compare DLA vs. label-based outcomes
With held-out validation-set → Confirm result
with held-out test set

Which is Better?

Label-based



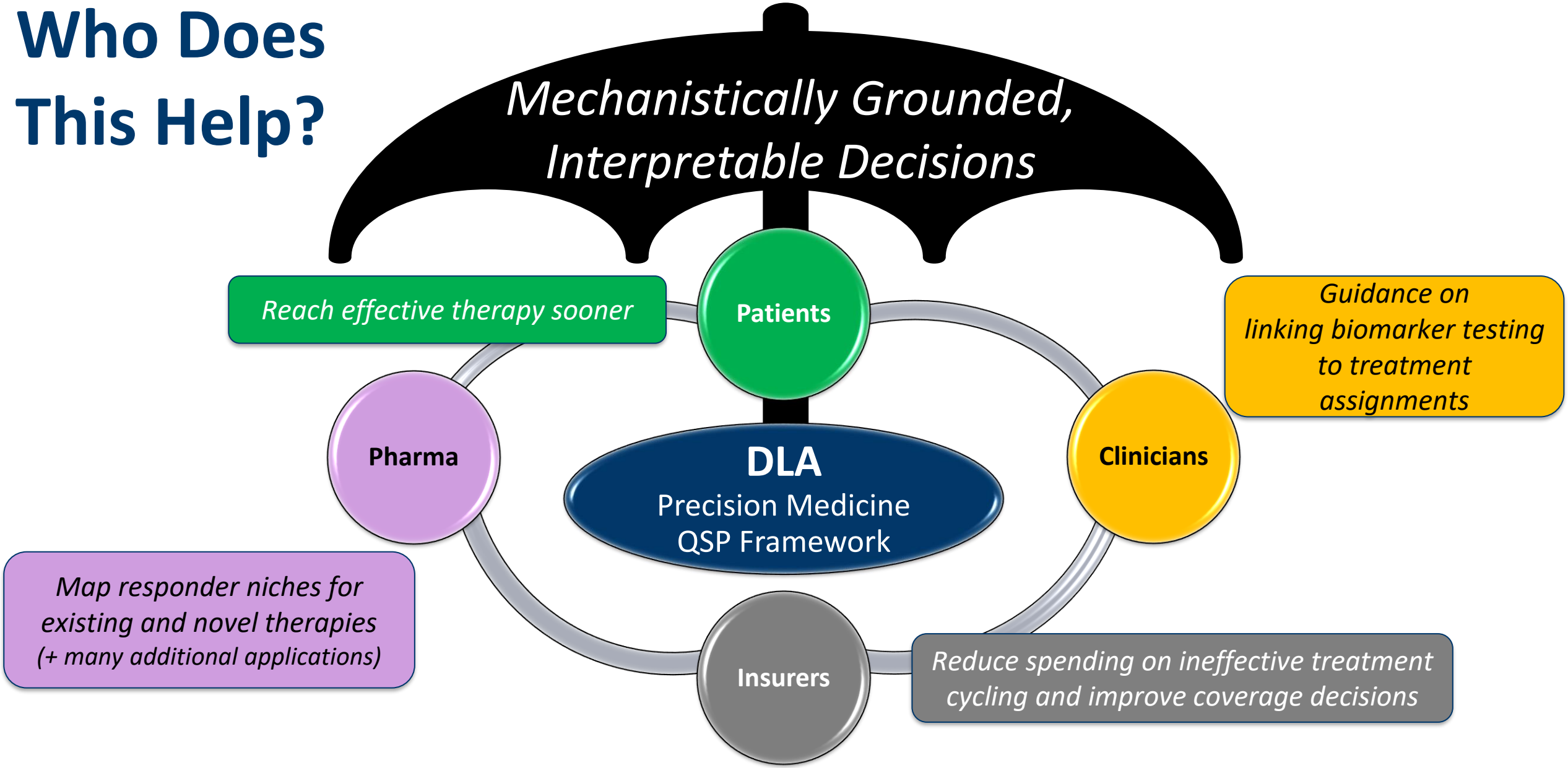
DLA



Assessment: Each patient's JaR is compared between the two pipelines

- **The DLA scheme shows a clear net benefit in therapy assignment in the held-out test set**
  - **70% of the patient weight has a better outcome using the DLA precision medicine scheme**
  - 17% of patient weight has an equivalent outcome
  - 12% has a worse outcome
- Additional metric: "Time to Response"
  - Among responders, **the DLA reduced weighted mean time to sustained response from 25 weeks to 11 weeks**
  - Reducing time to response is a core motivation for this work

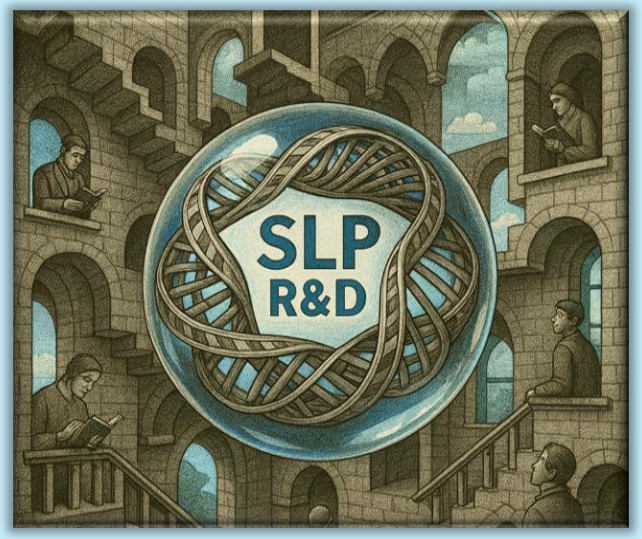
Who Does This Help?



Questions?

The DLA

Ask me anything about this application



Noah Brostoff

Noah.Brostoff@Simulations-Plus.com

A provisional patent for this application has been submitted

There's much more to this — ask me about…

1. Characterizing "**off-label responders**", and **ubiquitously out-competed therapies**
2. **Drug discovery**: finding MoAs to help non-responders to all available therapies
3. Tradeoffs between faster response and deeper response; **multi-objective weighting**
4. **Novel therapy** evaluation and **basket trials**
5. Applicability to **cancer** and other disease areas
6. Benefits of **Individual patient data** and client partnership
7. Therapy MoA's / model designs
8. Training/Validation/Test splitting, decision tree parameters, and alternate ML types
9. QSP explainability: model analysis and visualization
10. Data fitting, additional constraints, and clinical data translations/assumptions
11. The future of the product: expanding, refining, and maturing
12. The 20-year call to action for precision medicine in autoimmune disease literature, and the staggering trial failure and non-response statistics