




SimulationsPlus

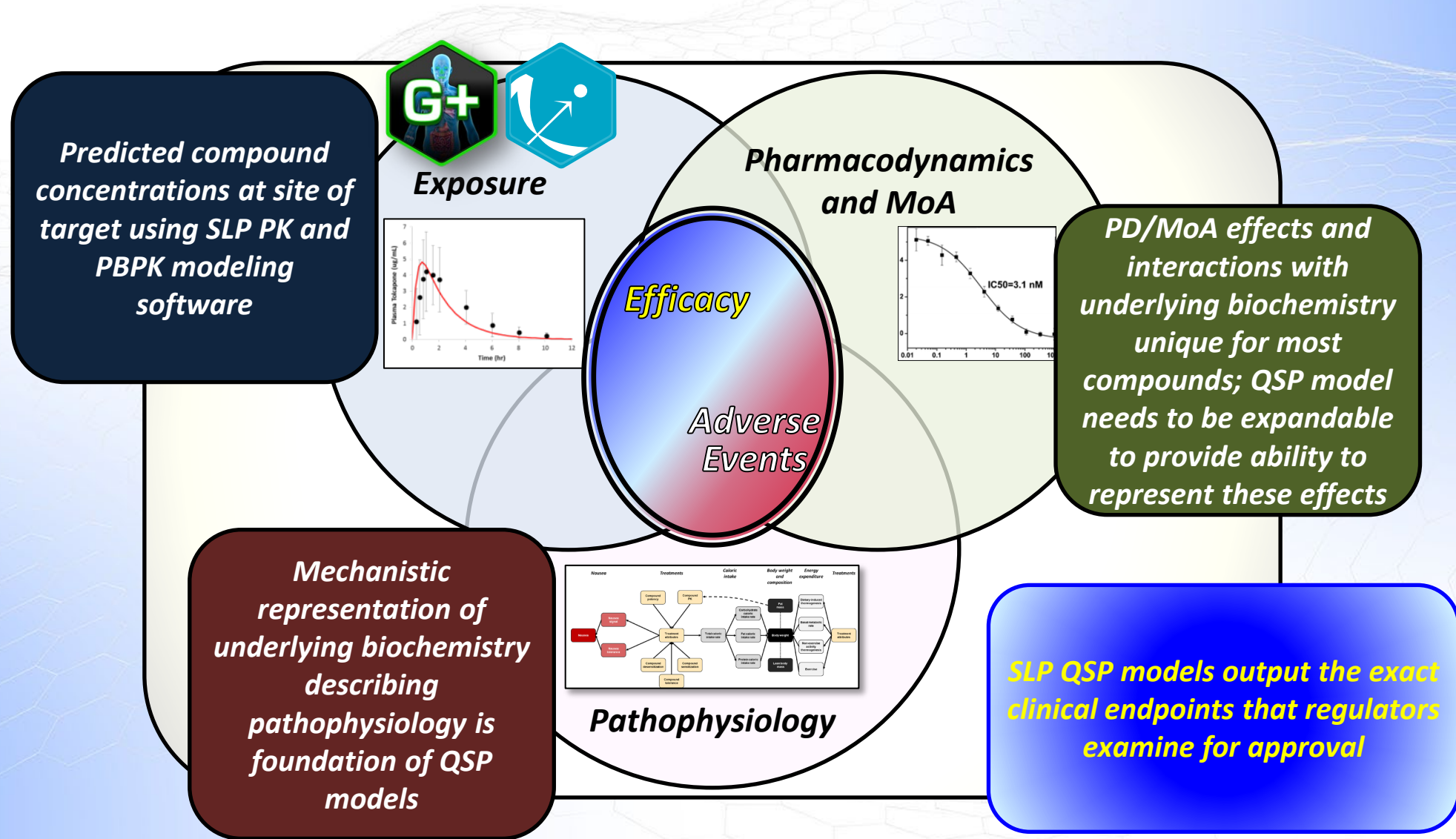
**Thales: A unified framework for
clinical-scale QSP modeling**



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Predicting Clinical Efficacy in QSP



Unifying our approach

- Historically, we have used multiple tools chained together
 - This introduces a degree of fragility in the computational pipeline
- From a consulting perspective, QSP modeling should balance both scientific and economic needs
 - Better would be a “1-stop shop” for QSP modeling for this application
 - **Visualization of model components** is one aspect with high potential to accelerate QSP workflows



An integrated system for all stages of model development: *model design, implementation, fitting, debugging, analysis, prediction*





VISUALIZATION TO SUPPORT KNOWLEDGE TRANSFER

Standardized model development in Thales

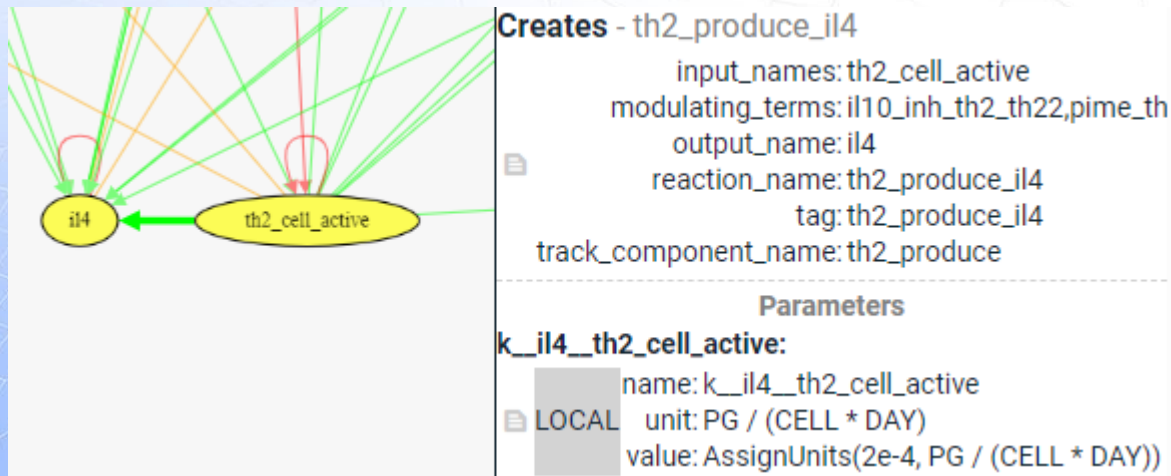
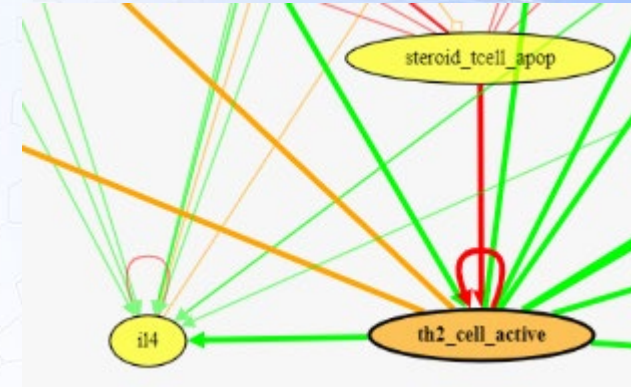
- Thales standard objects for model building are called “primitives”
 - They lower the barrier to entry and facilitate knowledge transfer
 - They enable automation for modeling workflows
- Biological processes
 - The pre-built primitives define a set of objects designed for accessibility
- Dosing regimens
 - The “Scenario” primitive defines a specific simulation segment and hooks for automatic integration of data

```
# IL17 cytokine dynamics
- !Creates
  input_names: conc_th17_cell_active
  output_name: il17
  modulating_terms: il10_inh_th1_th17
  track_component_name: th17_cell_produces
```

```
- !Scenario
  key_tuple: [adalimumab, adalimumab, 40mg]
  times: !FloatRange
    start: 0
    end: 112
    step: 7
  event_specs:
    - !ScheduledEventSpec
      description: AddAda40mg
      map_time_to_set_expressions:
        0:
          CentralSerum__adalimumab_sc: 40 * CentralSerum__ada_sc_bioavailability
```

Network visualization

- Standard objects enable automated network visualization
 - Nodes are species and edges are processes defined by Thales primitives
 - The diagram is automatically generated from the objects' metadata



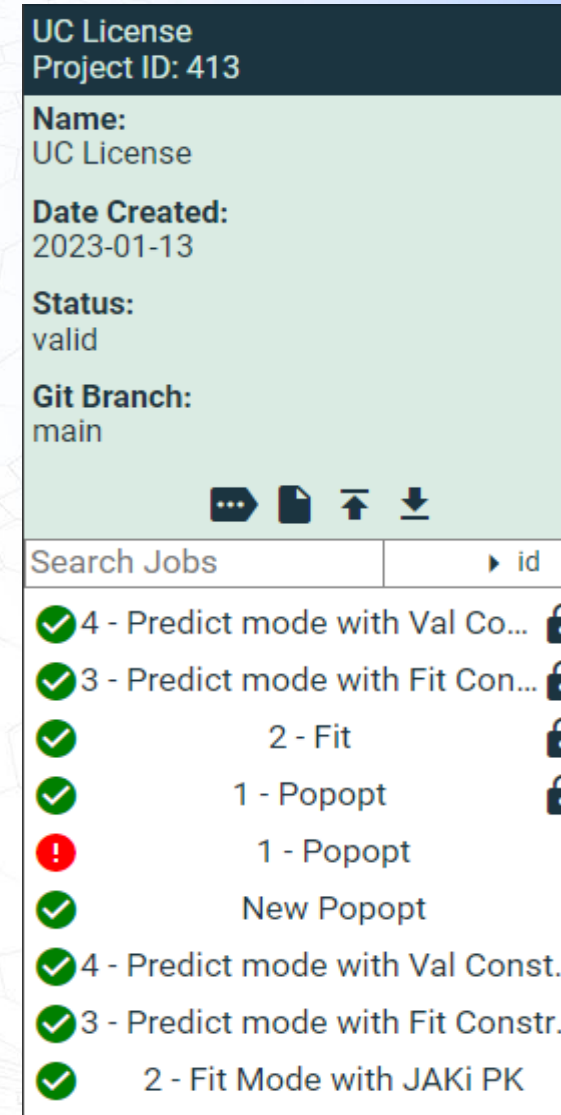
- Interactivity is supported and provides links to model code (left)
 - The resulting graph is useful for targeted learning or reference for users unfamiliar with Thales code



VISUALIZATION TO SUPPORT MODEL REVIEW

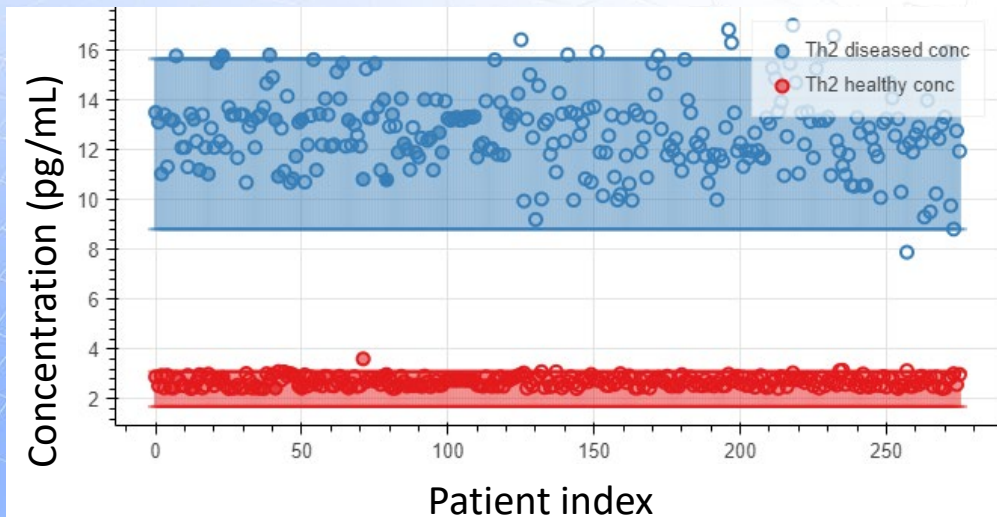
Accessibility and reproducibility

- Thales provides a project-level interface designed to be sufficiently accessible for both novice and expert QSP modelers
- Reproducibility and transference/sharing of results between projects and users is a core feature
 - Model state is retained by default
 - Projects can be shared in a read-only mode
 - These include code, results and graphs

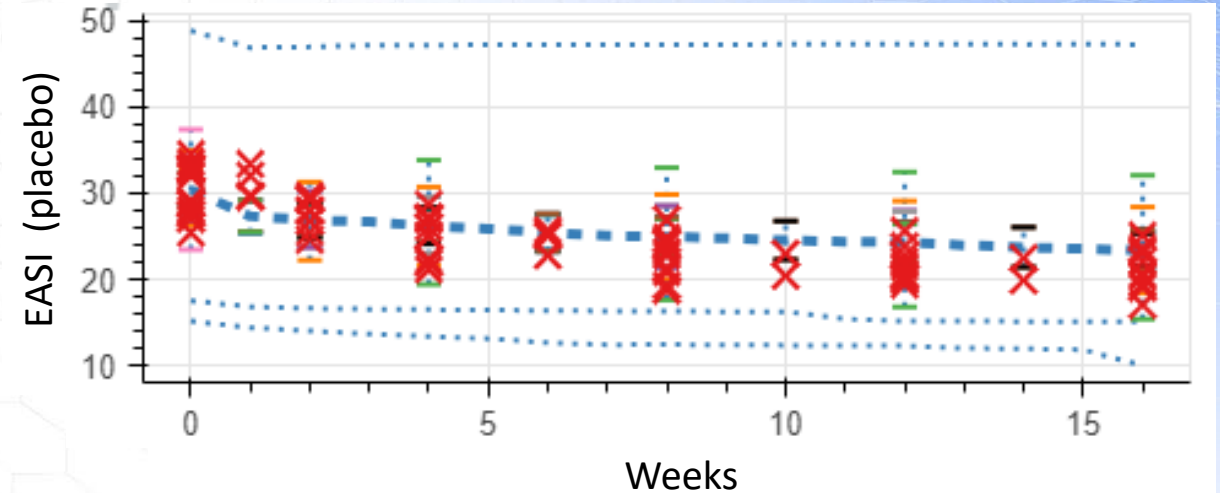


Visualization (plotting results)

- Visualization for simulation analysis
 - Standard graphs and calculations are provided
 - A plotting API is provided for more advanced, custom analyses
- Customizable plot types include
 - Timecourses
 - Individual patient distributions
 - Qualitative pass/fail checks
- Thales workflows enable rapid feedback for optimization jobs



Left:
The graph shows expected ranges for Th2 levels in healthy patients (red) and AD patients (blue)
- Circles: values at baseline per patient
- Shaded regions: Valid range for specific model value informed by data

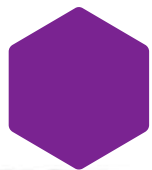


Above:
The shown timecourse contains both simulated and actual data:
- Red X: population means from clinical data
- Bold blue dashed line: SimPop weighted mean
- Blue dotted lines: 1st, 2nd, and 3rd quartiles
- Error bars: 90% confidence interval for model mean



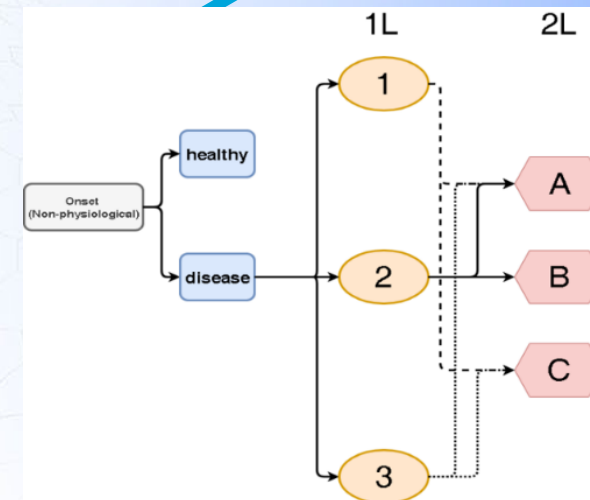
VISUALIZATION TO SUPPORT MODEL EXPANSION

Simulating Disease Progression and Treatments



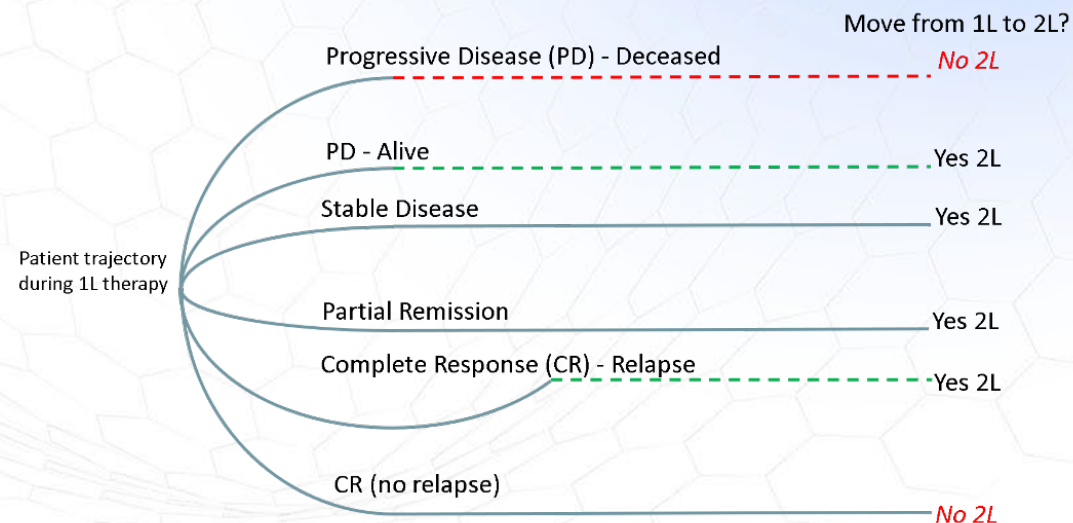
Thales enables straightforward specification of increasingly complex disease progression pipelines

- The diagram shows a typical IO model pipeline with scenarios representing disease onset, first line therapies, and second line therapies
- Note that patients in distinct first line therapies can enter the same second line therapy
- Thales “stage” objects enable users to easily control the flow of virtual patients between different stages



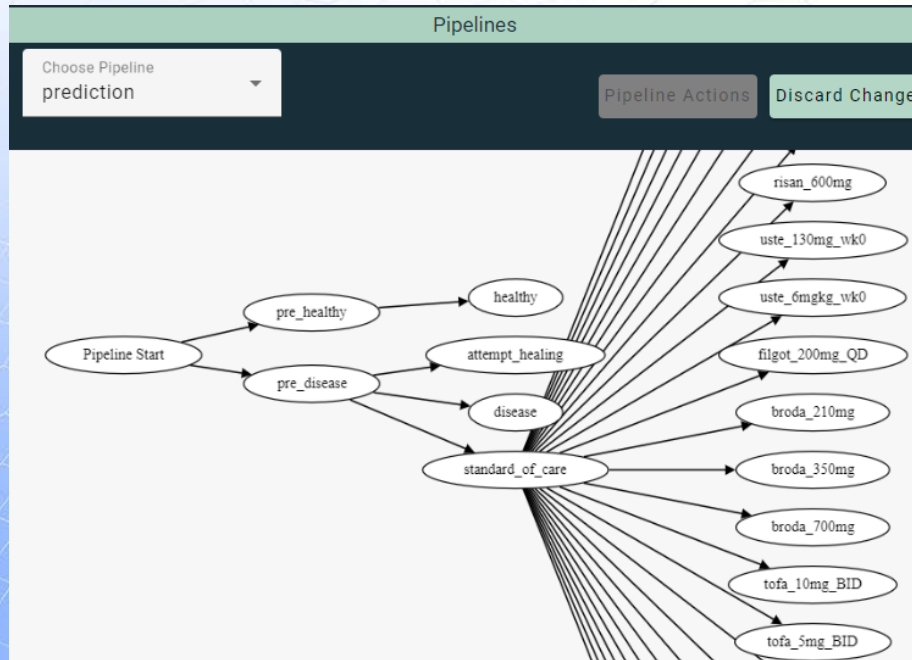
Example: Cancer therapies

- Patient treatments often depend on response to prior therapies or patient features (e.g. specific cancer genotypes)
- Thales automatically manages which patients are allowed into which scenarios
- Visualizing the pipeline facilitates insertion of new scenarios into the correct locations



Visualization (new predictions)

- Thales provides a graphical interface to easily add new simulation scenarios for an existing SimPop (right)
 - Scenarios or stages can be added or edited, to represent new dosing regimens or trial protocols



- Visualization of the simulation pipeline facilitates placement of new stages
 - Placement of a late-line regimen may have early-line dependencies
 - Patients move through all paths in the tree unless filtered out by trial protocols

saved: No Stage name: certo_400mg_0_2_4_then_q4w

itted: 9:5

Edit Stage Definition - certo_400mg_0_2_4_then_q4w

Name: certo_400mg_0_2_4_the

Description: Description

Scenario: [Certolizumab 400mg wk 0, 2, 4, then Q4W, Certolizumab, 400

Use stage criteria: Use stage criteria

Sequence criteria: Sequence criteria

Abort criteria: Abort criteria

es: 05

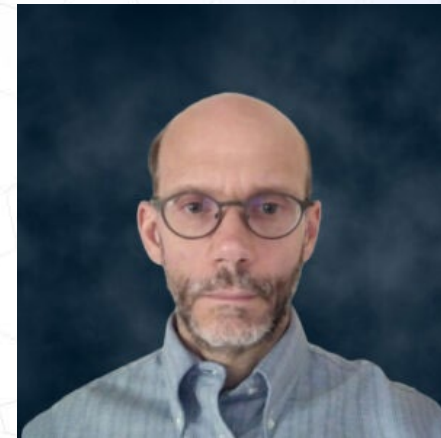
Post sim transforms:

Transform	
X	PredictorOutputs
X	CalculateCustomClinicalOutputs

0b

Conclusions & Acknowledgments

- Our experience with Thales at Simulations Plus highlights the utility of visual features and graphical interfaces in modeling workflows
 - Visual representation of models facilitate knowledge transfer/retention
 - Graphical interfaces assist with model accessibility
 - Graphical tools enable the practical use of QSP models without the need for mathematical or computational expertise
- Thales provides many other integrated features for QSP modeling outside of visualization that we are happy to discuss in person



Both Steven Chang and John Bartels conceived of Thales as a tool for QSP modeling.