



Keynote 1: Model-Informed Drug Development (MIDD) in Alzheimer's disease: From Data Sharing to Actionable Solutions

October 27, 2020



Jackson Burton, Executive Director, Quantitative Medicine

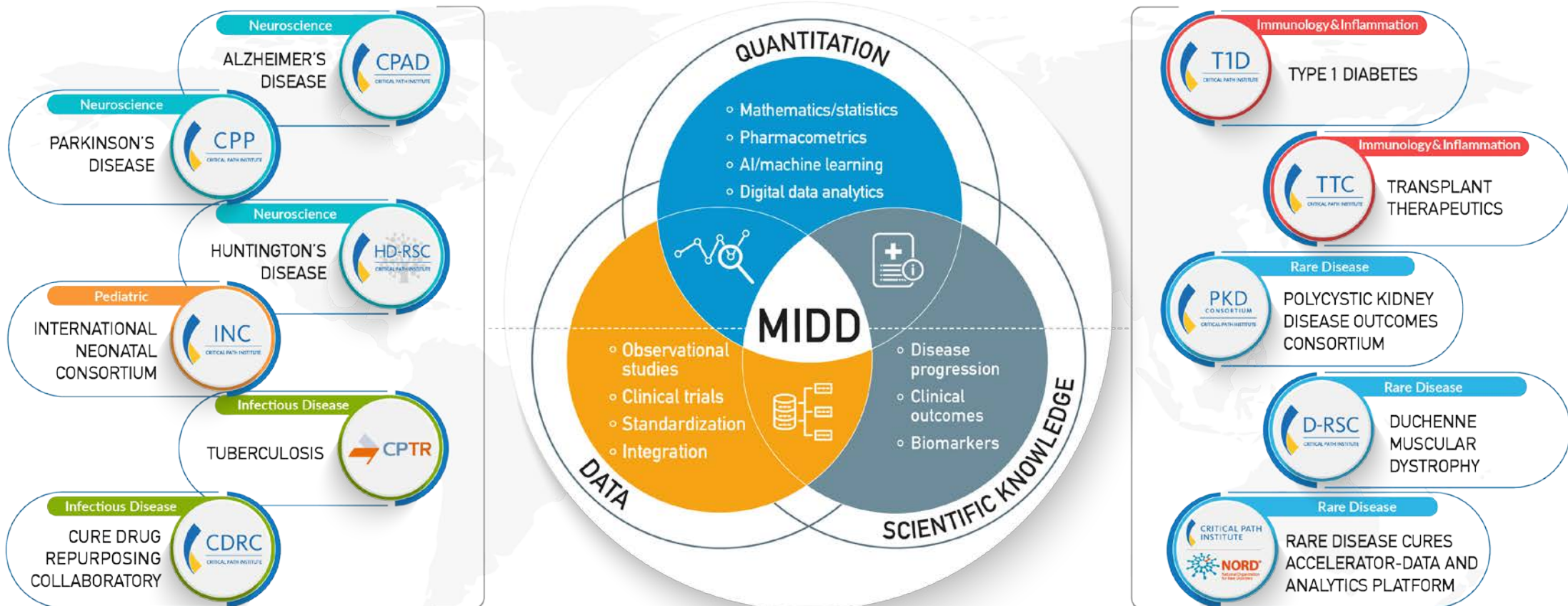
CONFIDENTIAL



Public-Private Partnerships Enable Data Sharing

C-PATH'S QUANTITATIVE MEDICINE PROGRAM

Creating solutions for drug development through Model-Informed Drug Development (MIDD)



Please email questions to ykarten@c-path.org

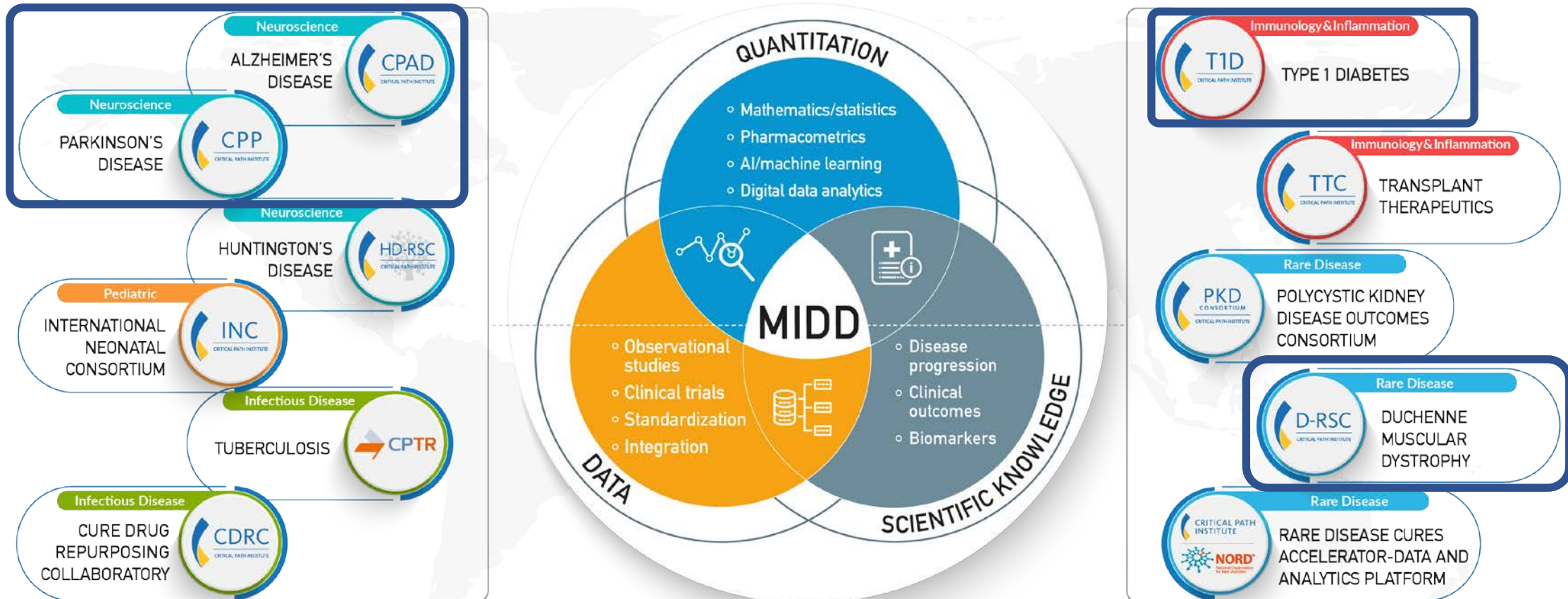
CONFIDENTIAL

www.c-path.org/cpad

Public-Private Partnerships Enable Data Sharing

C-PATH'S QUANTITATIVE MEDICINE PROGRAM

Creating solutions for drug development through Model-Informed Drug Development (MIDD)



Please email questions to ykarten@c-path.org

CONFIDENTIAL

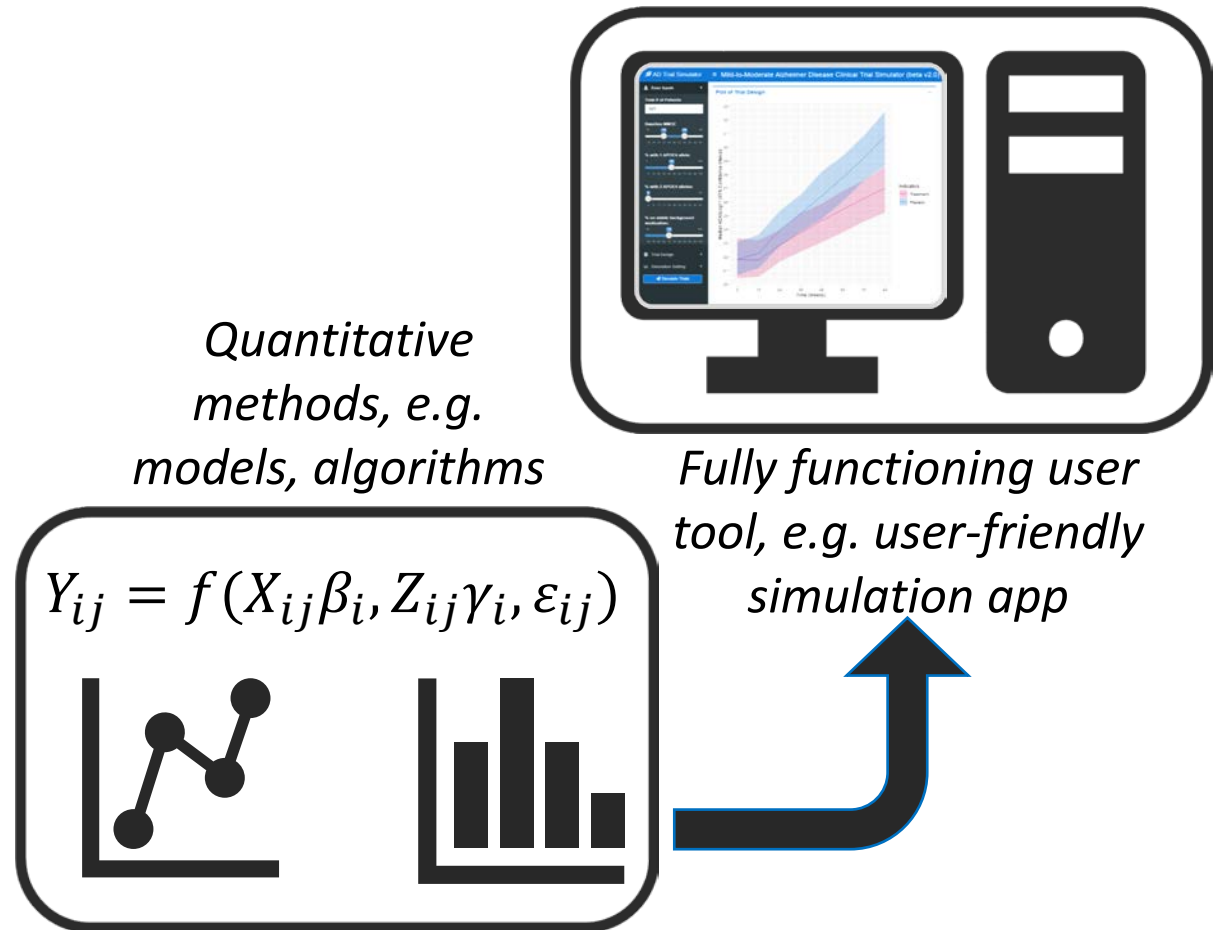
www.c-path.org/cpad

Building quantitative tools for drug development

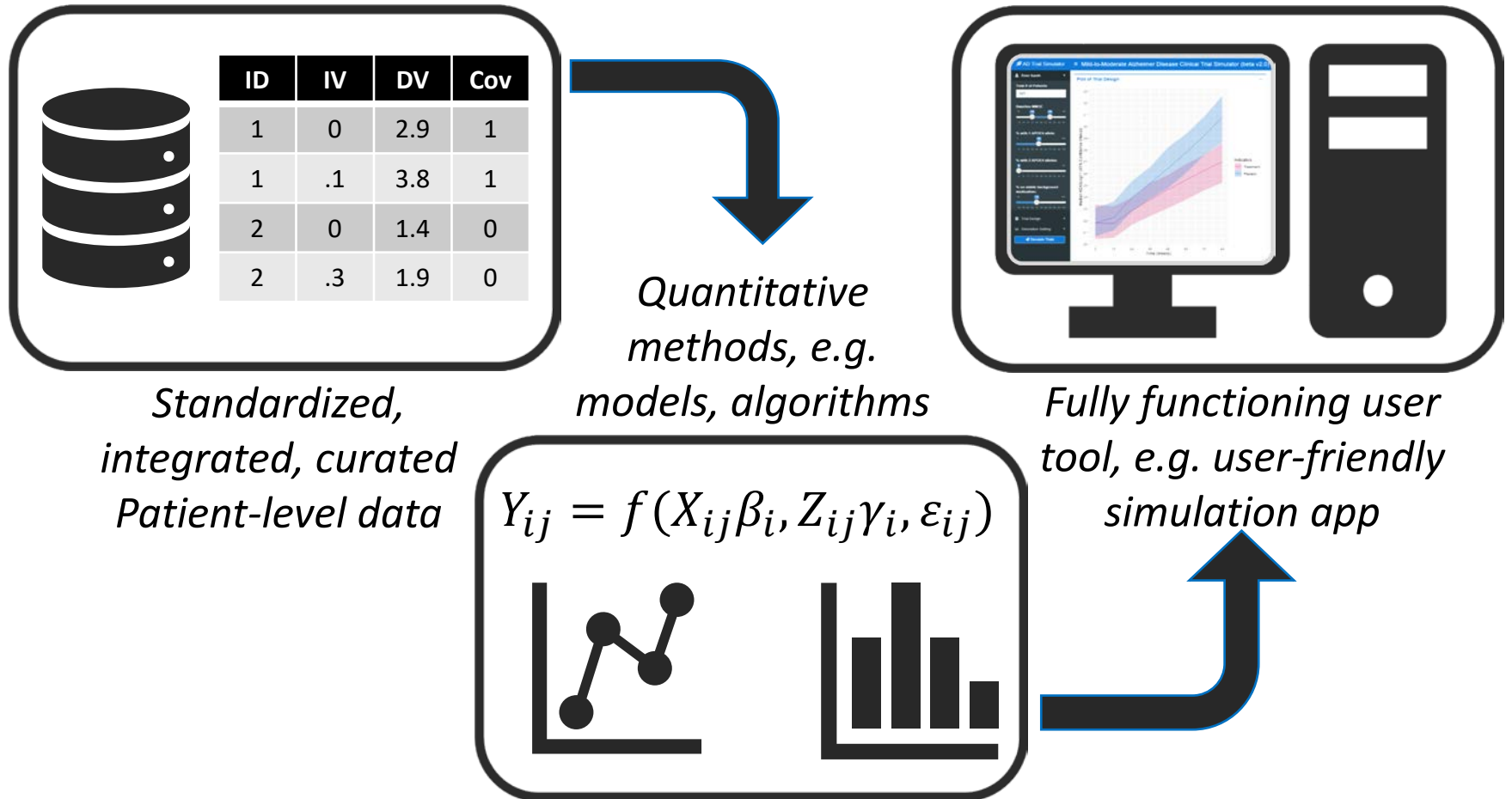


Fully functioning user tool, e.g. user-friendly simulation app

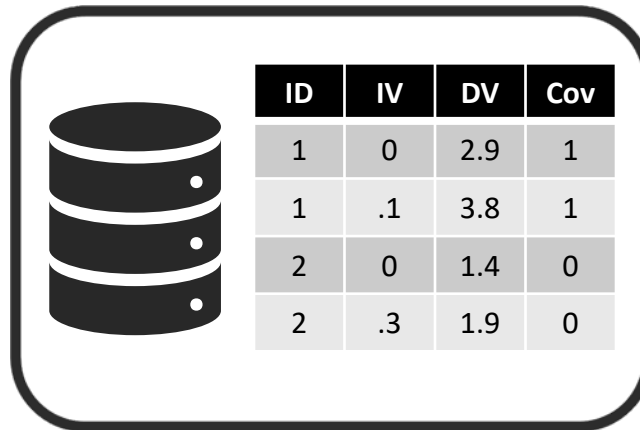
Building quantitative tools for drug development



Building quantitative tools for drug development



Building quantitative tools for drug development

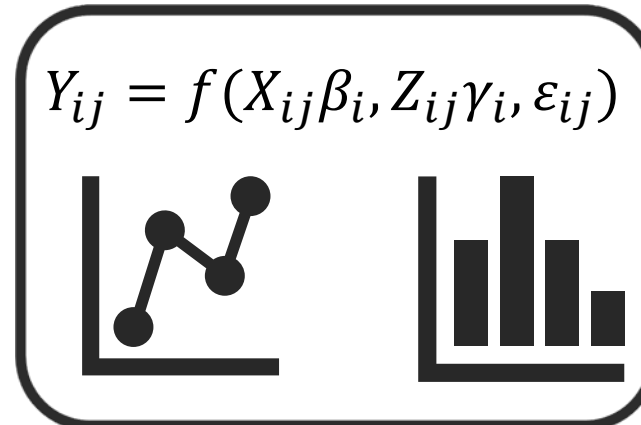
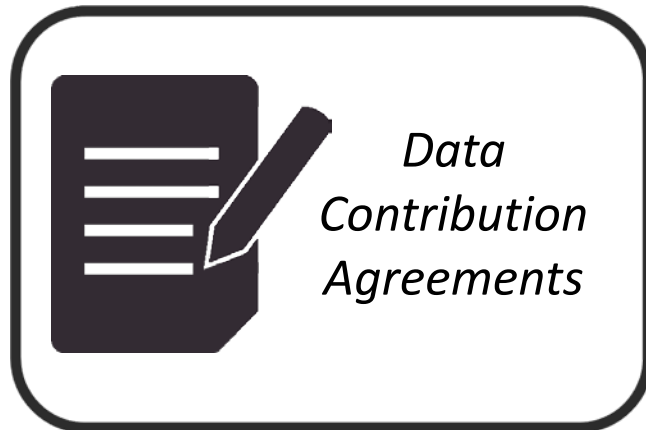


*Standardized,
integrated, curated
Patient-level data*

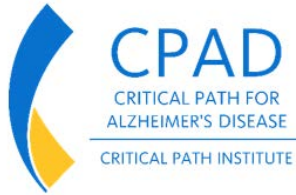
*Quantitative
methods, e.g.
models, algorithms*



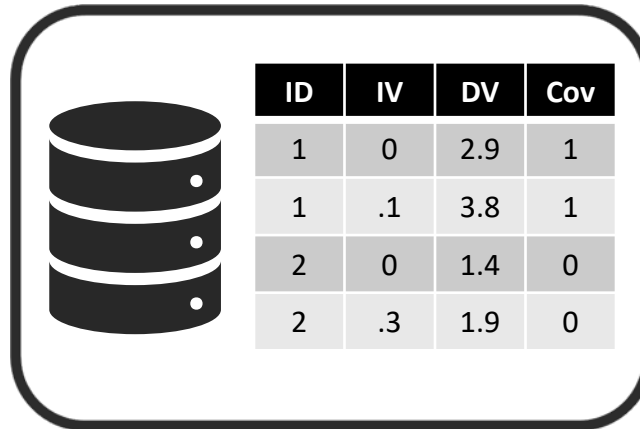
*Fully functioning user
tool, e.g. user-friendly
simulation app*



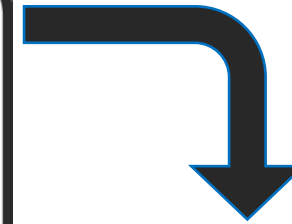
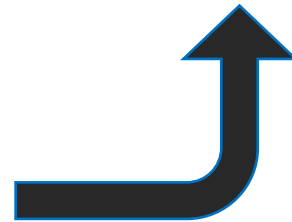
Building quantitative tools for drug development



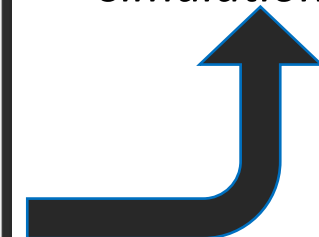
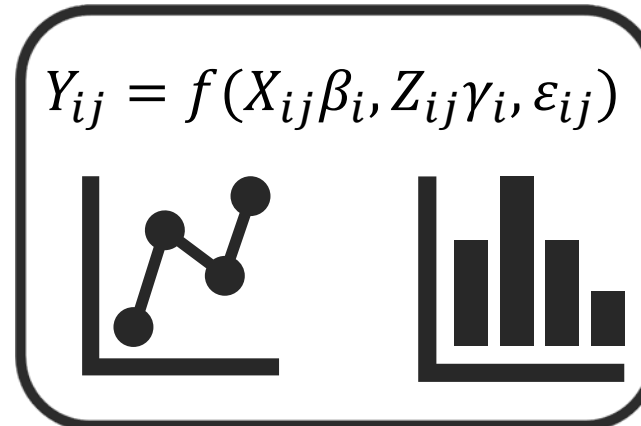
*Foster pre-competitive
collaboration*



*Standardized,
integrated, curated
Patient-level data*

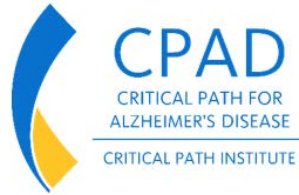


*Quantitative
methods, e.g.
models, algorithms*

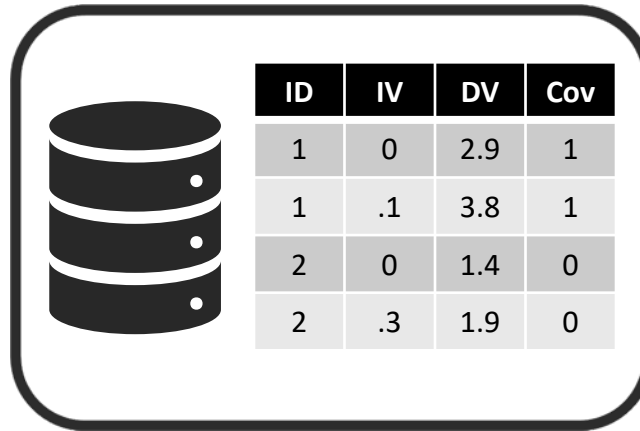
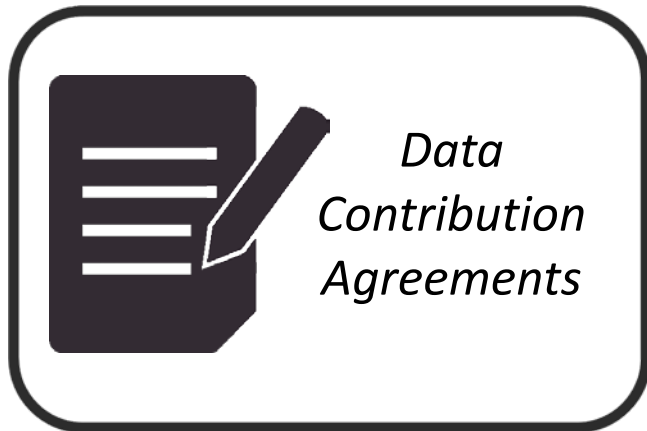


*Fully functioning user
tool, e.g. user-friendly
simulation app*

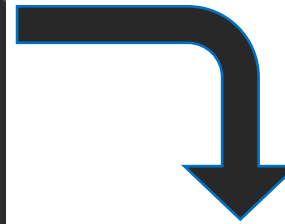
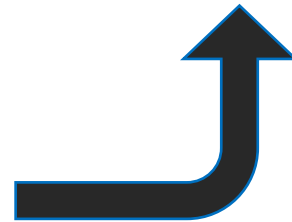
Building quantitative tools for drug development



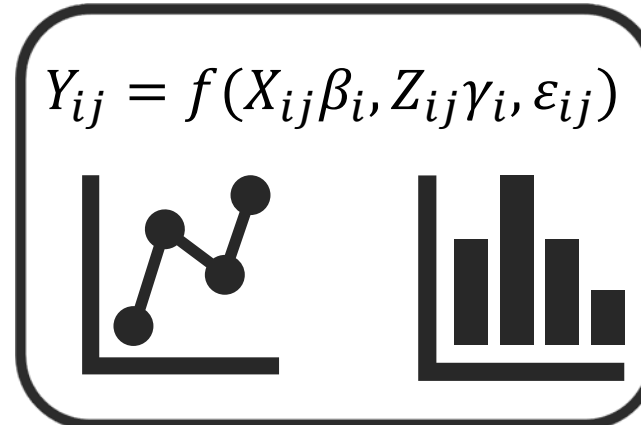
Foster pre-competitive
collaboration



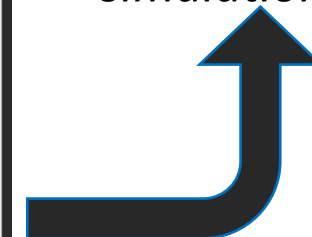
Standardized,
integrated, curated
Patient-level data



Quantitative
methods, e.g.
models, algorithms



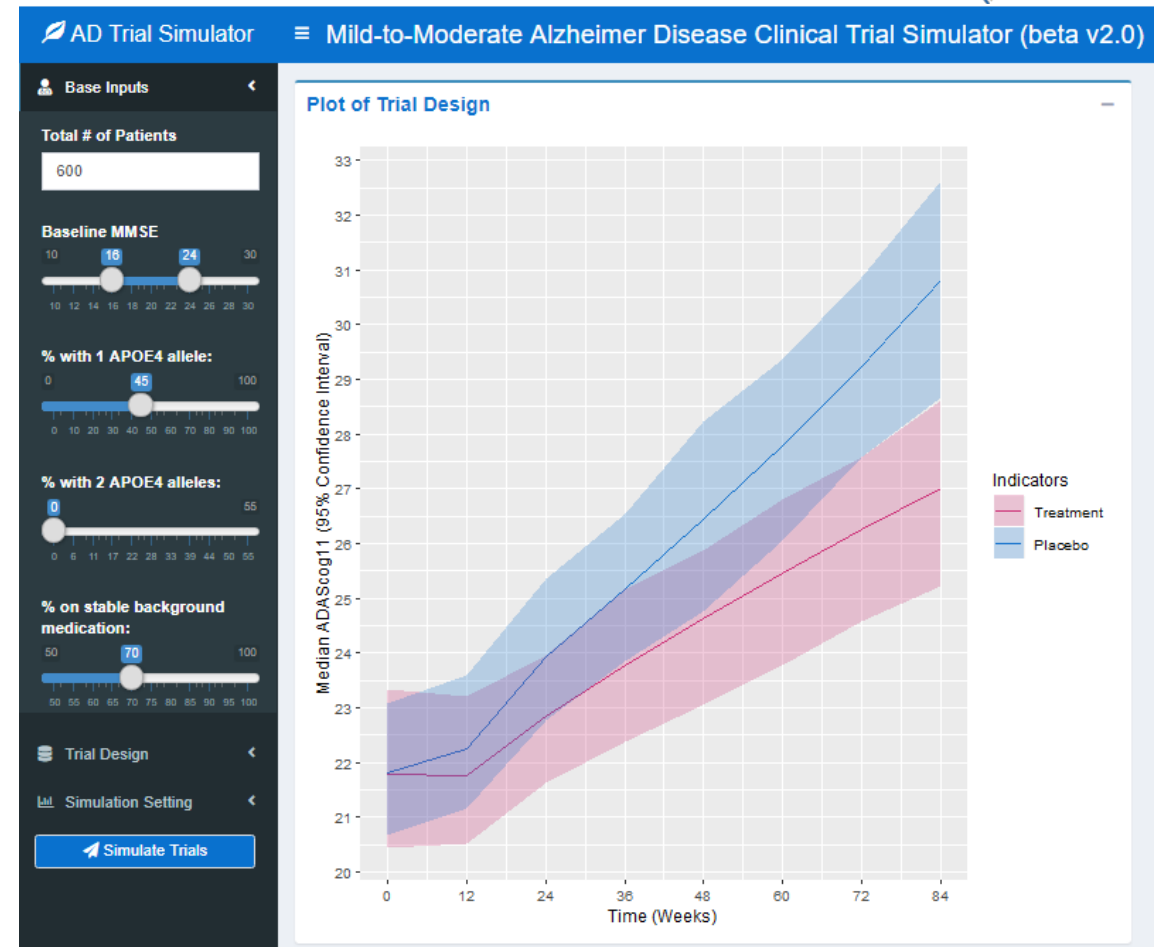
Fully functioning user
tool, e.g. user-friendly
simulation app



Alzheimer's Disease (AD)

- A mild-to-moderate AD clinical trial simulation tool (built on 3000+ patients, 10 studies) was endorsed by FDA and EMA for optimizing clinical efficacy studies in AD
- Development of a publicly available user-friendly graphical user interface allows all members of a clinical development team to utilize the tool:

<https://cpath.shinyapps.io/adctsgui/>



Alzheimer's Disease (AD)

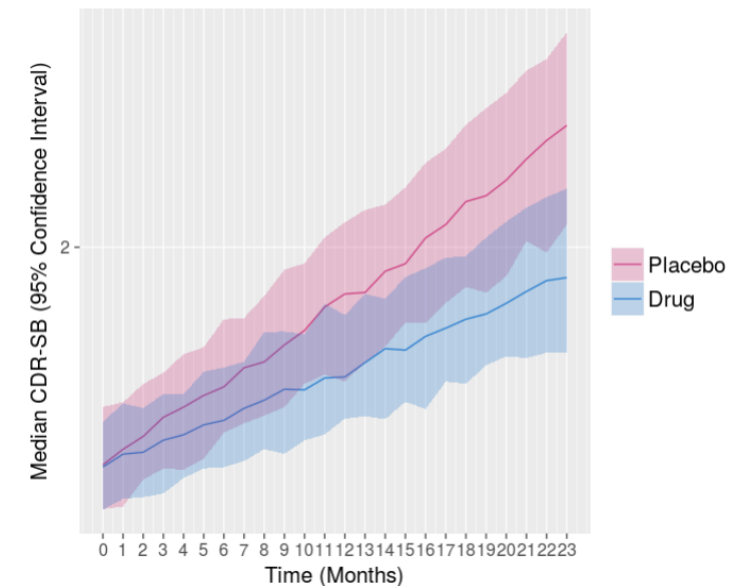
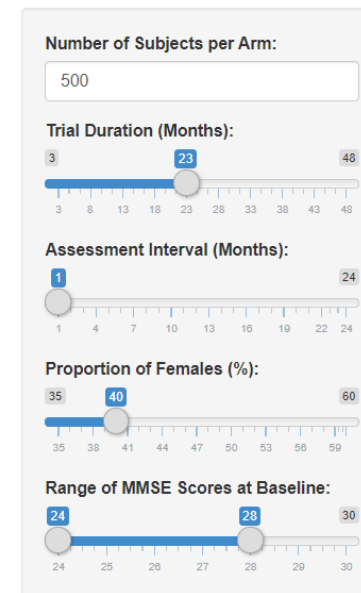
- A predementia CTS tool was developed (built on 682 patients, 10 studies) and received a letter of support from EMA for optimizing clinical efficacy studies in AD

- The tool utilizes baseline hippocampal volume as a prognostic factor for informing disease progression measured by CDR-SB in addition to other patient features

<https://cpath.shinyapps.io/predemctegui/>

Hippocampal Neuroimaging-Informed Amnesic MCI Clinical Trial Simulator

Simulate clinical trials on patients with amnesic mild cognitive impairment



Complete

MIDD Beyond AD...

- Beyond AD, several quantitative solutions are being developed to address key drug development needs:
 - Trial simulation tools
 - Biomarker-based time-to-event analyses
 - Outcome measure analyses using Item Response Theory

Parkinson's Disease (PD)



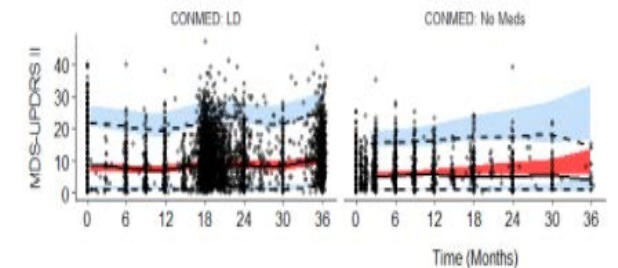
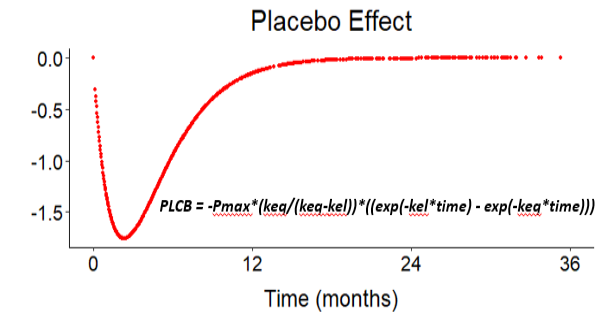
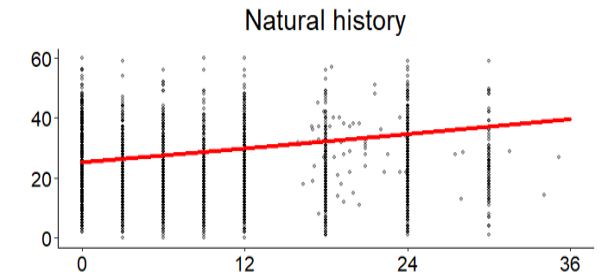
- PD disease progression modeling for submission to FDA and EMA as a clinical trial simulation tool to optimize trial design



- Based on a large aggregated database (built 5000+ subjects, 17 studies) it was possible to quantify disease progress, placebo effects, and medication effects on outcome measures



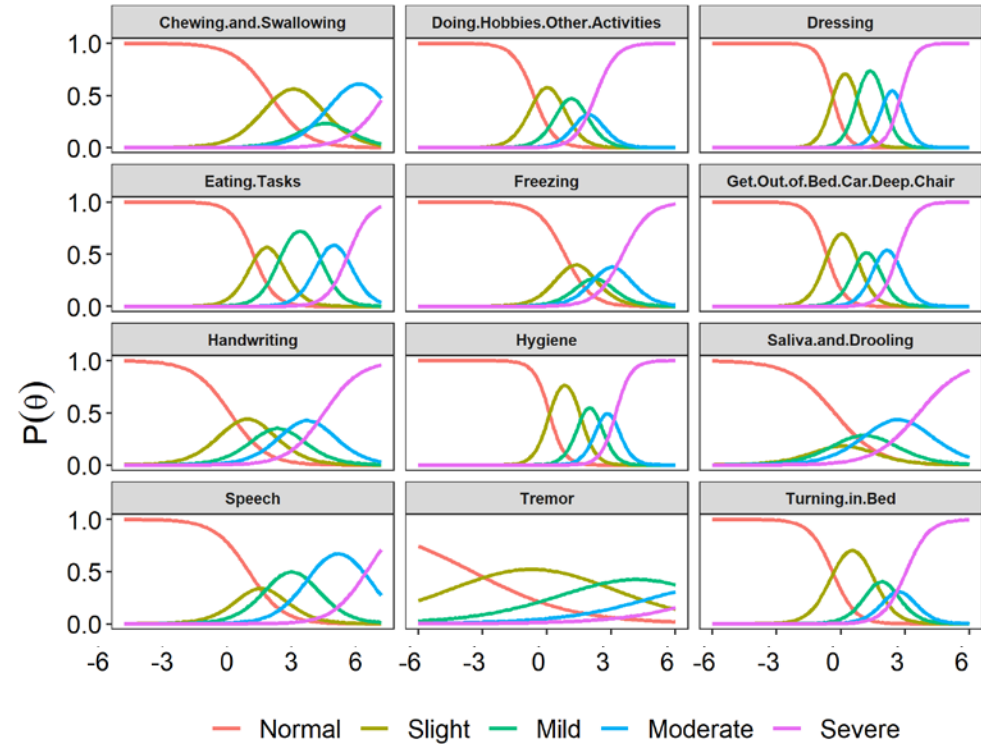
Structure
$\frac{dScore_i}{dt} = r_i$
$\frac{dScore_i}{dt} = r_i$ $Score_i = \text{logit}^{-1}(Score_{0i} + r_i \times t)$
$\frac{dScore_i}{dt} = r_i$ $Score_i = \text{logit}^{-1}(Score_{0i} + r_i \times t)$ $r_i = \theta_r \times \left(\frac{Score_{0i}}{\text{ref}(Score_0)}\right)^{\theta_{power}}$
$\frac{dScore_i}{dt} = r_i \times Score_i \times \left[1 - \frac{Score_i}{\max(Score_i)}\right]$
$\frac{dScore_i}{dt} = r_i \times Score_i \times \left[1 - \left(\frac{Score_i}{\max(Score_i)}\right)^\beta\right]$
$\frac{dScore_i}{dt} = r_i \times Score_i \left[\ln\left(\frac{\max(Score_i)}{Score_i}\right)\right]^Y$



Parkinson's Disease (PD)



- Longitudinal Item Response Theory is being applied to MDS-UPDRS part II to quantify the longitudinal dynamics item (5000+ patients with 15000+ item level observations)
- The analysis helps quantify the discriminatory power of the individual items as they compare with each other
- This aims to provide granular understanding of composite measures in PD



$$P(x > j | \theta, a, b_j) = \frac{1}{1 + e^{-a(\theta - b_j)}}$$

$$P_j(\theta) = P(x > j) - P(x > j + 1)$$

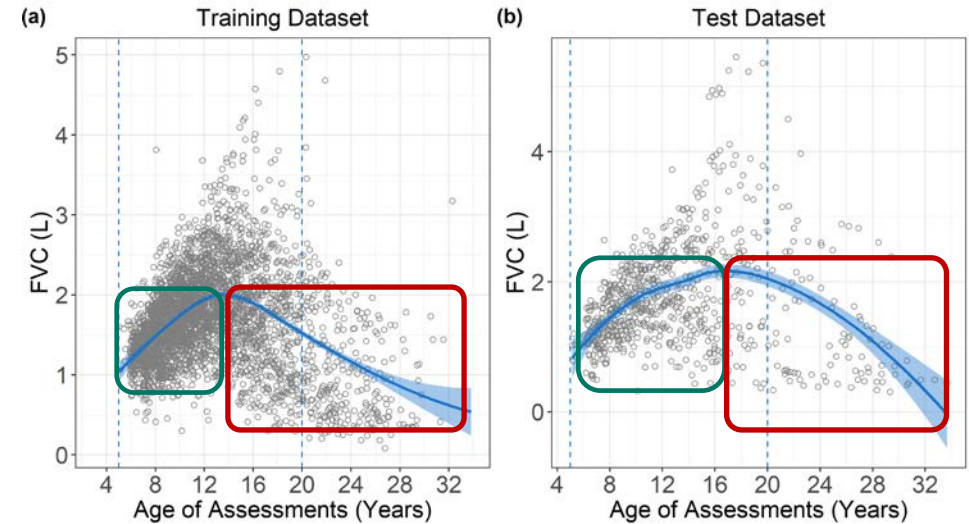


Duchenne Muscular Dystrophy (DMD)



- DMD is a rare genetic based muscular disease occurring in boys, lead to an average life span of 25 years
- Five disease progression models were developed based on stage specific endpoints on the largest analysis dataset in DMD (1100+ subjects, 15 studies)
- Currently submitting to FDA and EMA for regulatory endorsement

Forced Vital Capacity (FVC) vs. Age of Assessments



$$\text{Score}_i = G_{\max,i} (1 - e^{-g_i \times \text{Age}}) \times \left(1 - \frac{DP_{\max,i} \times \text{Age}^{\gamma,i}}{DP_{50,i}^{\gamma,i} + \text{Age}^{\gamma,i}} \right)$$

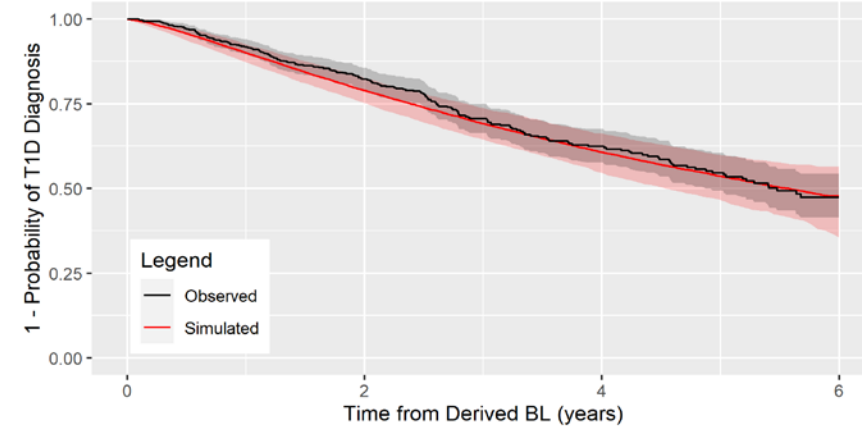


Type-1 Diabetes (T1D)

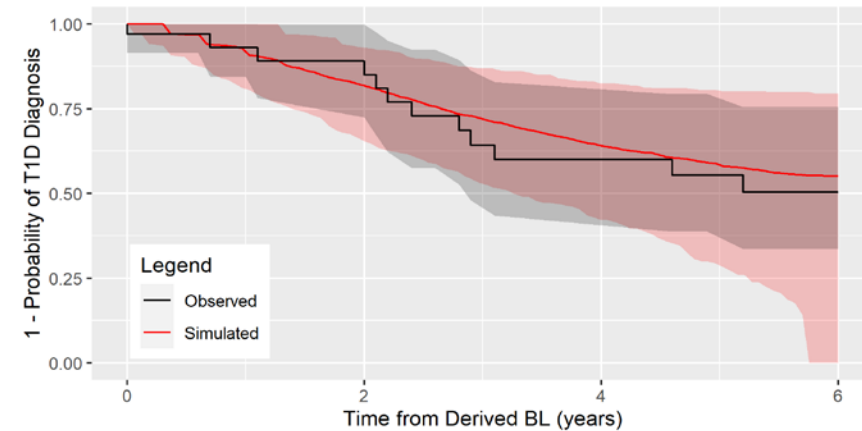


- Presence of Islet Auto Antibodies have been long known to lead to onset of T1D, but no analysis to predict timing to T1D has been done on aggregated patient-level data
- The T1D consortium and Quantmed have worked to develop a robust time-to-event model that predicts T1D diagnosis timing based on IAAs, patient demographics, and glycemic measures
- Currently finalizing qualification opinion with EMA

CV on pediatric population (age < 12) - alt_mod3



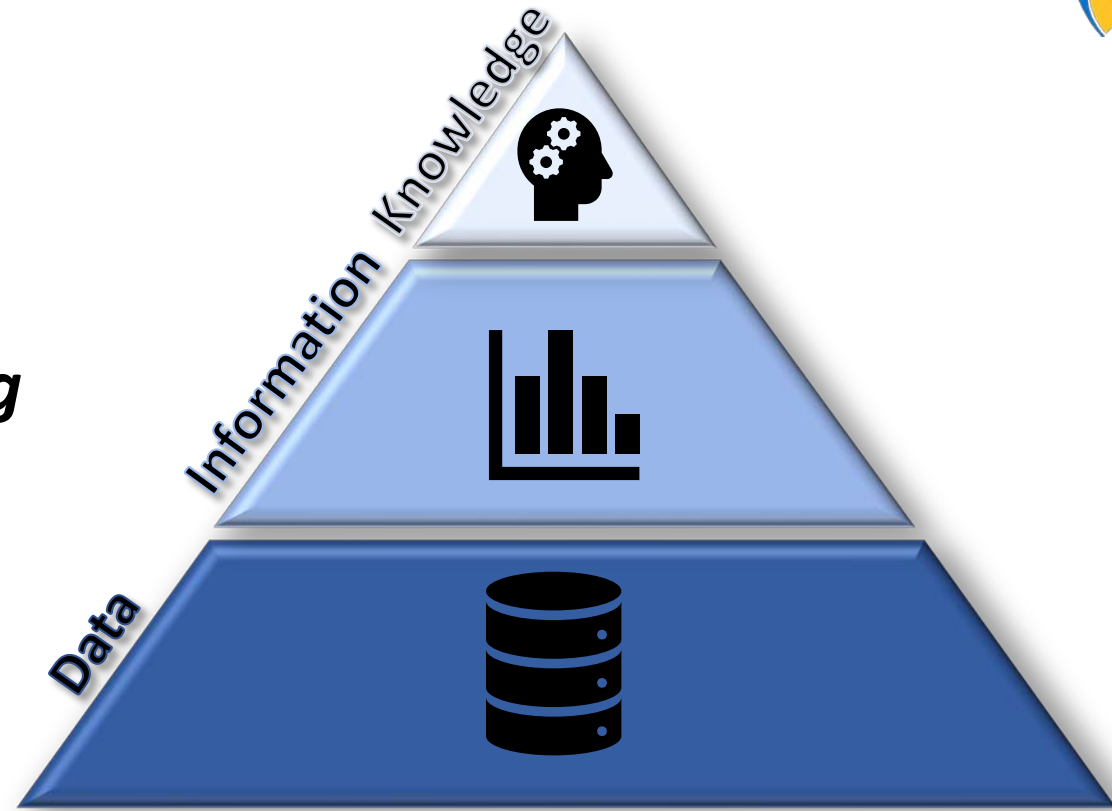
External Validation using DAISY dataset - alt_mod3



Complete

In Summary

- Where we have been... **MIDD**
- Where do we want to go...
“Quantitatively-Informed Drug Development (QIDD)”
- How...



...by transforming data into actionable knowledge through collaboration