Session II: Challenges and Solutions for Advancing DPM Uptake

Moderator: **Raj Madabushi**, Associate Director, Guidance and Scientific Policy, Office of Clinical Pharmacology, FDA

CTTI

Welcome Back!

- **Session II Objectives:**
  - Explore barriers for advancing the use of disease progression modeling to aid in decision making
  - Discuss essential needs to advance the use of disease progression modeling

- **Approach: Panel → Break Out Groups**
  - Panel focus: DPM Applications & Decision Making
  - Break Out Group focus: Essentials to Advance DPM & Accountability

Panel: DPM Applications & Decision Making

Hao Zhu

FDA

CJ Musante

Pfizer

Dave Miller

Unlearn.Ai

Klaus Romero

Critical Path Institute

Moderator: **Raj Madabushi**, FDA, CTTI Project Team Lead

CTTI

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Use of Disease Progression Models to Support New Drug Development

Hao Zhu, Ph.D., M.stat.
Division Director
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/FDA

CTTI
March 6, 2023

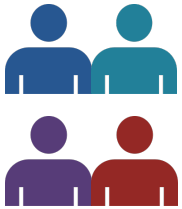
* Disclaimer: The views in this presentation are my personal and should not be construed as the official position of the US Food and Drug Administration.

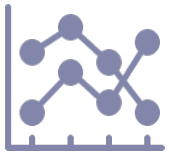
Outline

- Introduction
  - Disease Progression Models
- Disease Models at FDA and Case Examples
  - Disease Models at FDA

    (OCP's Efforts and Examples of Disease Models)
  - Case Examples
    - Pediatric Extrapolation: Schizophrenia Disease-Drug-Trial Model
- General Considerations for Disease Progression Models
- Take Home Message

Quantitative Disease-Drug-Trial Models





Disease Model

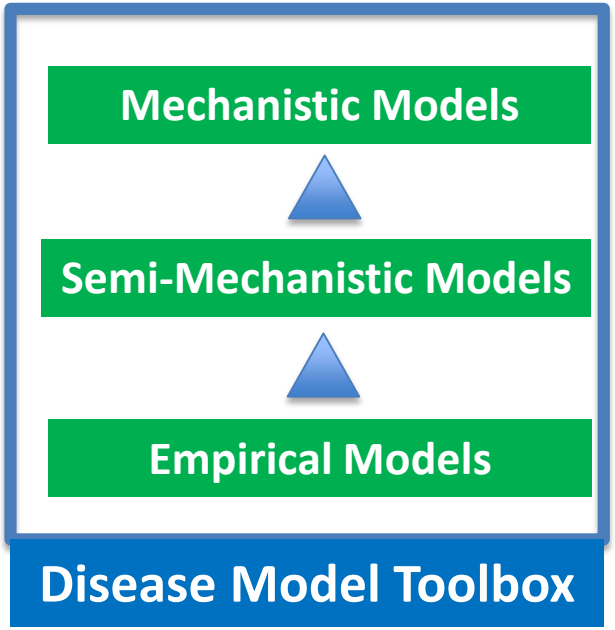
Drug Model

Trial Model

Natural Progression Biomarker vs. Outcome

Exposure-Response for Efficacy & Safety

Drop Out

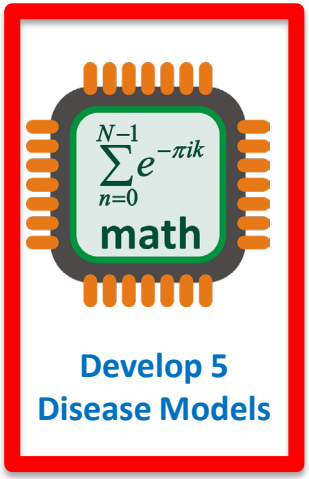


*: Jogarao V S Gobburu, Lawrence J Lesko. **Quantitative disease, drug, and trial models.** *Annu. Rev. Pharmacol. Toxicol. 2009. 49:291–301.* doi: 10.1146/annurev.pharmtox.011008.145613.

History: 2020 Strategic Goals

Train 20 Pharmacometricians

Implement 15 Standard Templates



Develop 5 Disease Models

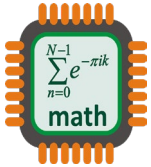
International Harmonization

Integrated Quantitative Clinical Pharmacology Summary

Design By Simulation

2010 2020

Disease Model Examples from FDA

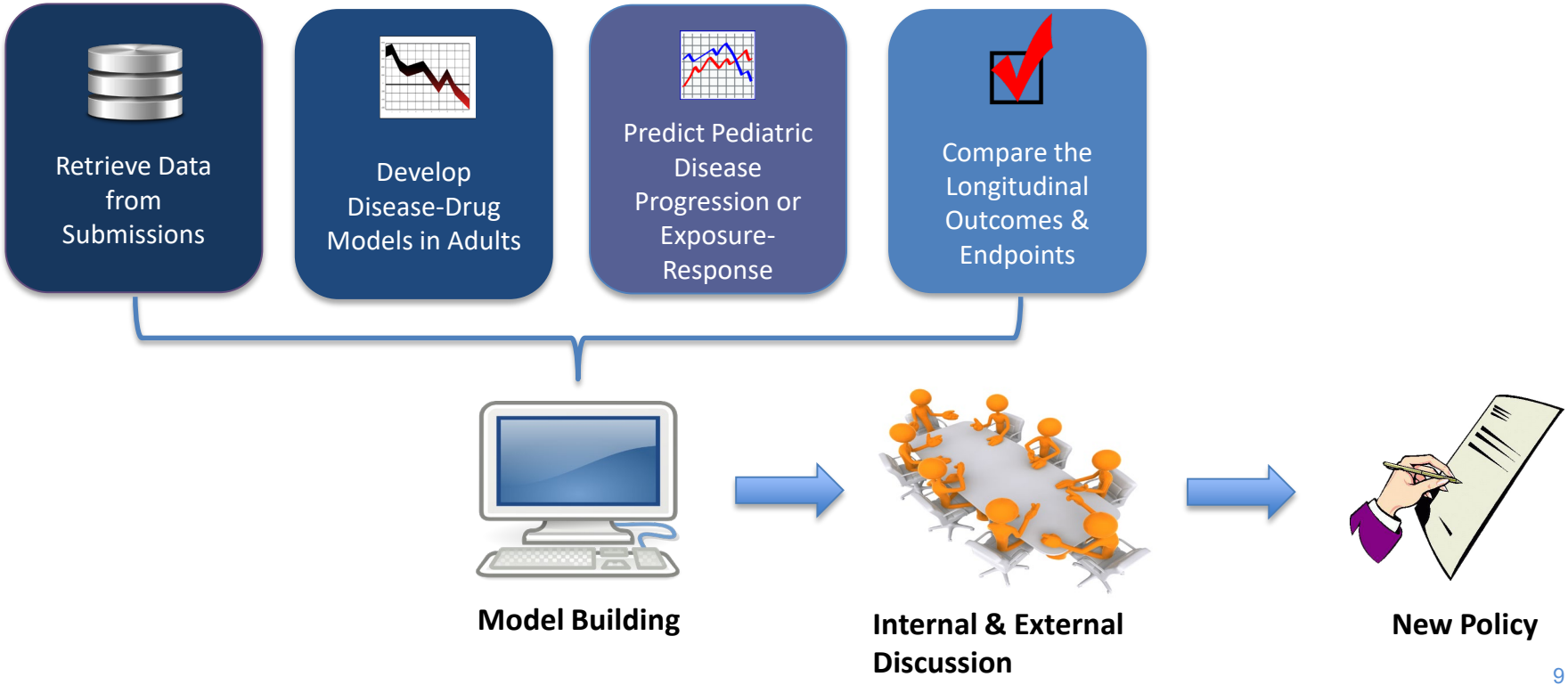


No	Disease Model	Use
1	NSCLC Model [1]	Late Phase Trial Design.
2	Parkinson's Disease Model [2]	Endpoint Selection and Clinical Trial Design
3	Alzheimer's Disease Model [3]	Endpoint Selection and Clinical Trial Design
4	Diabetes Disease Model [4]	Clinical Trial Design
5	Huntington's Disease Model [5]	Patient Enrichment, Clinical Trial Design
6	DMD Disease Model [6]	Patient Enrichment, Clinical Trial Design
7	HIV Model [4]	Clinical Trial Design
8	Schizophrenia Model [7]	Pediatrics Extrapolation
9	Bipolar I disorder Model [8]	Pediatrics Extrapolation
10	Weight Loss Model [9]	Clinical Trial Design
11	Bone Density Model [10]	Clinical Trial Design
12	Idiopathic Pulmonary Fibrosis Model [11]	Patient Enrichment, Clinical Trial Design
13	Rheumatoid Arthritis Model [12]	Patient Enrichment, Clinical Trial Design
14	Pulmonary Arterial Hypertension Model [13]	Endpoint Selection and Clinical Trial Design

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-pharmacometrics.

Case Example: Disease Model for Schizophrenia

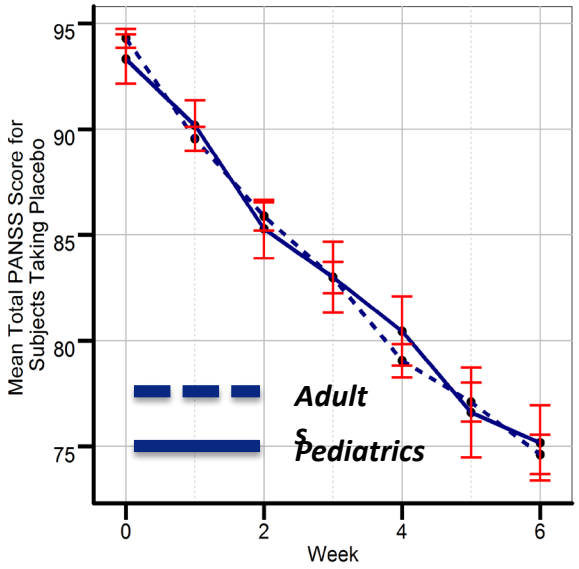
Characterize the Profile of the Disease Progression and ER

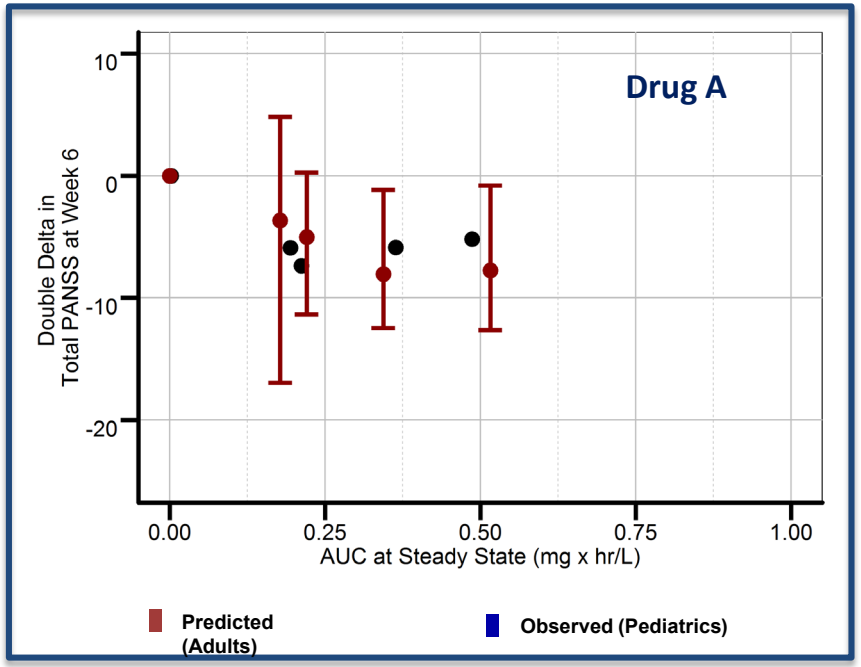


Evidence to Demonstrate Disease Similarity and Response

Disease Model

Disease Progression over a Typical 6-Week Trial is Similar Between Adults and Adolescents Completers (Observed)

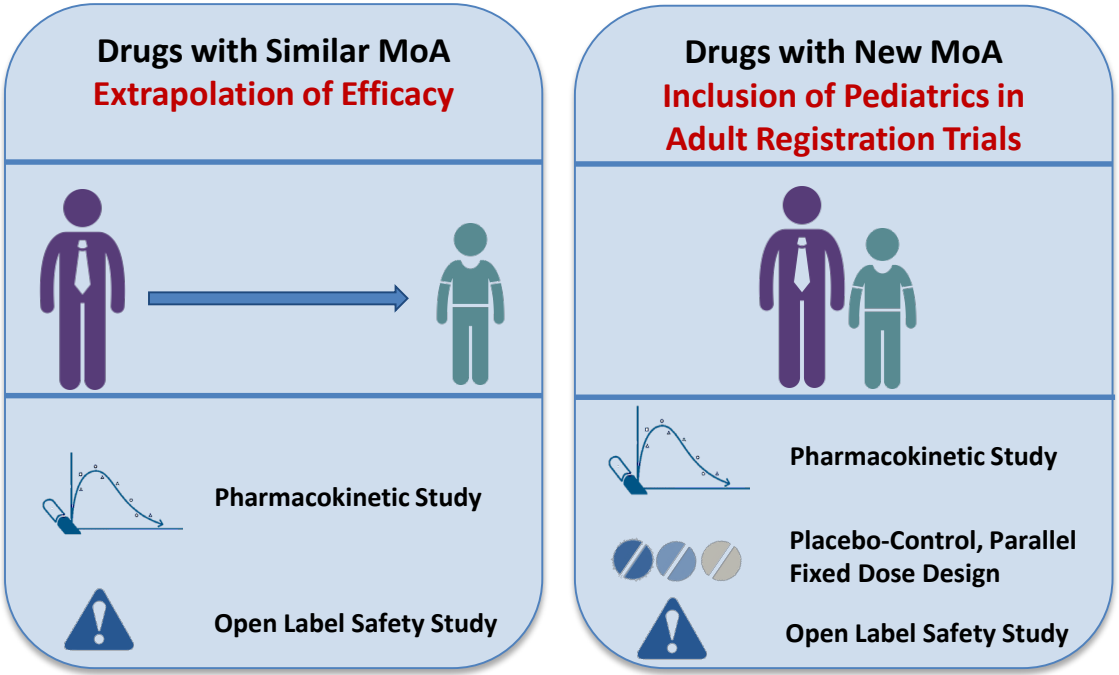




Shamir N Kalaria, Hao Zhu, Tiffany R Farchione, Mitchell V Mathis, Mathangi Gopalakrishnan, Ramana Uppoor, Mehul Mehta, Islam Younis. **A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials. Clin Pharmcol. Ther.** 2019 Nov;106(5):1046-1055. doi: 10.1002/cpt.1501. Epub 2019 Jul 3

Extrapolation of Efficacy from Adults to Pediatrics

Schizophrenia Program



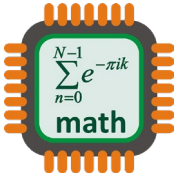
*Juvenile animal studies needed for bipolar I indications less than 12 years of age

**Open label safety studies could concurrently enroll patients with bipolar I and schizophrenia adult and pediatric patients

Shamir N Kalaria, Tiffany R Farchione Ramana Uppoor, Mehul Mehta , Yaning Wang , Hao Zhu · **Extrapolation of Efficacy and Dose Selection in Pediatrics: A Case Example of Atypical Antipsychotics in Adolescents With Schizophrenia and Bipolar I Disorder. J Clin. Pharmcol.** 2021 Jun;61 Suppl 1:S117-S124. doi: 10.1002/jcph.1836

General Considerations for Disease Modeling

- Modeling Objectives: (critical to determine subsequent actions)
- Data: (General principles for meta-analysis: source, information collected, endpoints, assay, study design, enrollment criteria, observational study vs. clinical trial, patient subgroups, handling of missing values, outliers, etc)
- Assumptions: (mathematical / statistical assumptions, biological assumptions, assumptions for information borrowing, etc)
  - Model Structure (e.g., linear vs. non-linear, current understanding of mechanism)
  - Covariate selection (e.g., missing covariates, imbalanced information from trials)
  - Parameters (e.g., borrowing information from different sources)
- Validation and verification (inline with the context of use, needed level of validation needs to be adjusted)
- Decision making (risk-based, factor in uncertainty)
- Reporting

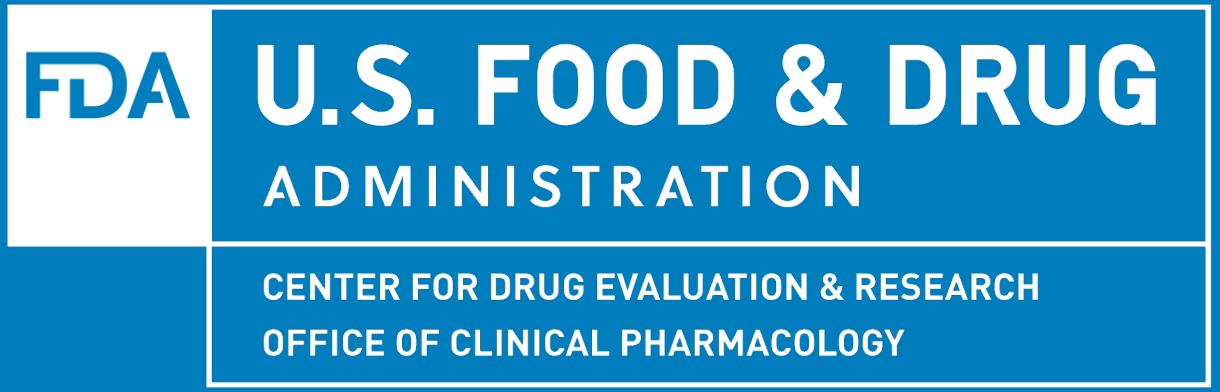


Take Home Messages

- Disease-Drug-Trial Models are important tools for MIDD.
- FFP, MIDD, and CID programs allow direct interactions between industry and FDA on various modeling approaches.
- Several steps should be considered to ensure that the established disease model can be applied to support the targeted usage.

Acknowledgement

- Dr. Rajnikanth Madabushi
- Dr. Qi Liu
- Dr. Yaning Wang
- Dr. Shiew-Mei Huang
- Dr. Issam Zineh
- DPM Members
- OCP Members
- Other Collaborators at FDA or Outside FDA


FDA
U.S. FOOD & DRUG
ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

March 6, 2023

Applications of DPM: Attributes and Limitations – Sponsor perspective

C.J. Musante, VP & Global Head of QSP, Pfizer

Disclaimer

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative or the presenter's employer.
- The presenter is an Employee of Pfizer Inc.

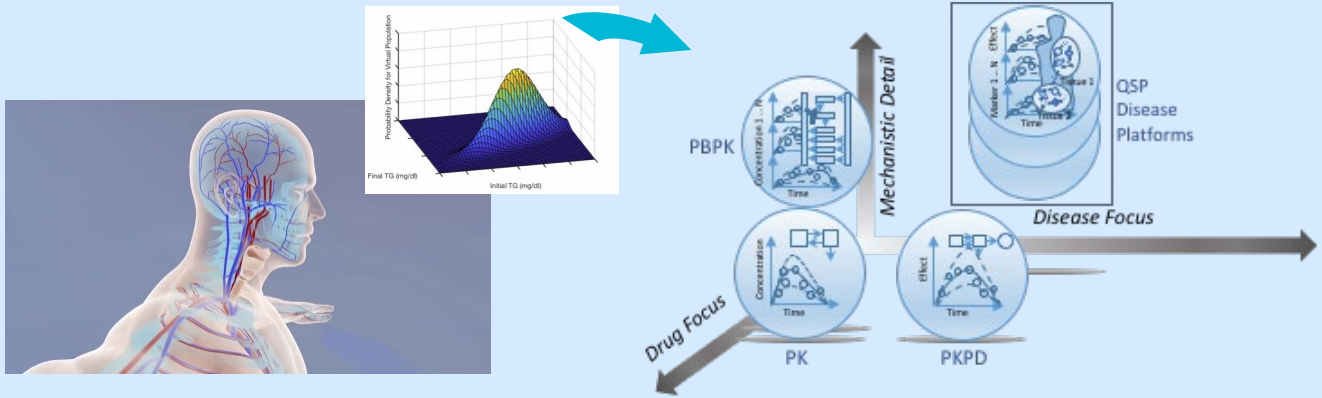
Quantitative Systems Pharmacology (QSP) Examples

DPM to Advance Decision Making Throughout the Medical Product Development Lifecycle

CTTI

What is a QSP DPM?

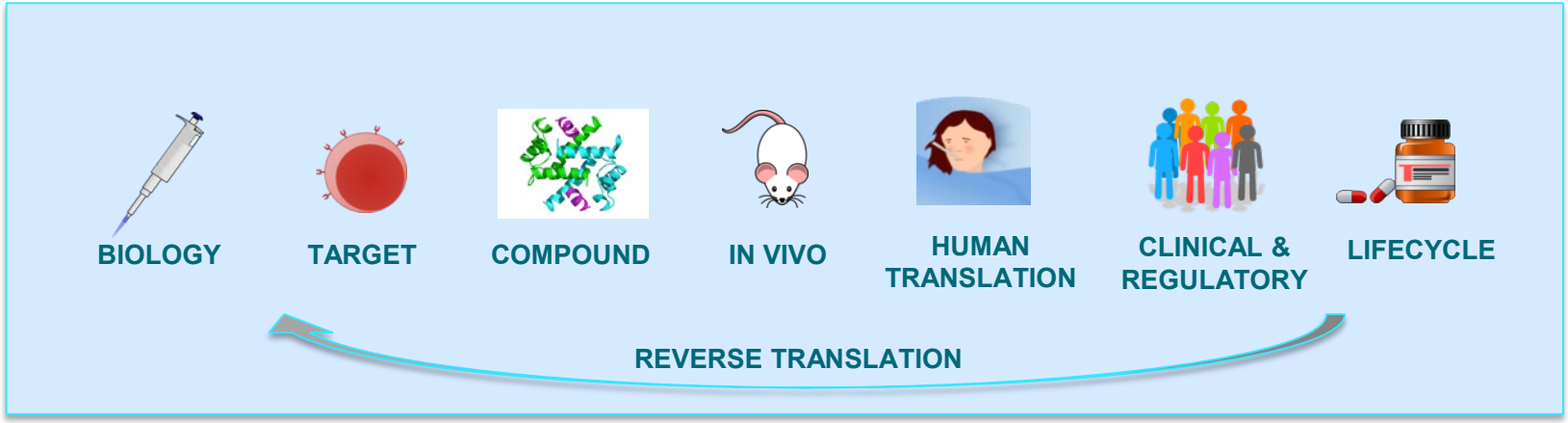
… a modeling & simulation approach that mathematically describes the mechanistic relationships between target modulation and disease biomarkers & outcomes over time…



Musante, CJ, Ramanujan S, et al (2017), Quantitative Systems Pharmacology: A Case for Disease Models. Clin. Pharmacol. Ther., 101: 24-27.

…to predict and interpret clinical responses to pharmacological intervention as part of a model informed drug development (MIDD) paradigm.

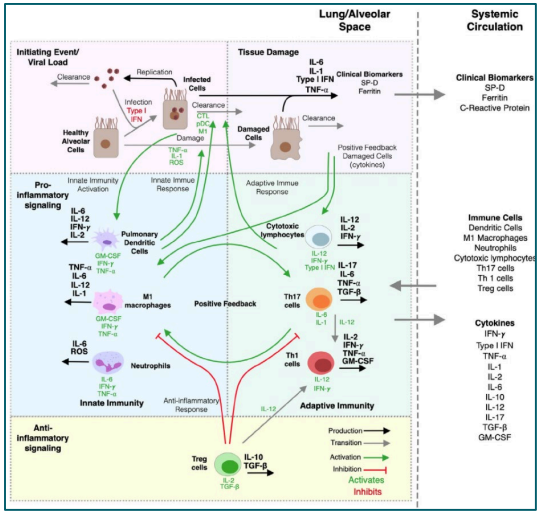
QSP DPM Applications in MIDD



SOURCE: Adapted from Ramanujan et al., Systems Pharmacology & Pharmacodynamics, ed. D Mager & H. Kimko, 2016.

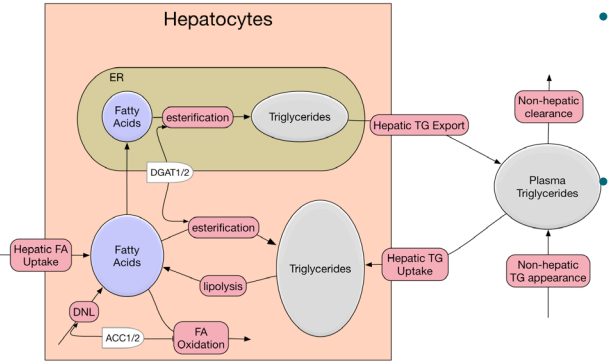
Different Examples - Common Themes

QSP Model of the Immune Response to SARS-CoV-2



- Preclinical to clinical translation
- Dose-response predictions
- Dose timing and treatment duration vs time of infection
- Comparative efficacy
- Efficacy predictions in different populations

QSP Model of Non-Alcoholic Fatty Liver Disease (NAFLD)



- Predicting combo efficacy in NAFLD based on healthy data for single agents
- Clinical trial simulations for single & combo arms in Ph 2 trial
  - Study duration
  - Doses
- Comparative efficacy

Left: Dai, W., Rao, R., et al. (2021), "A Prototype QSP Model of the Immune Response to SARS-CoV-2 for Community Development." CPT Pharmacometrics Syst. Pharmacol., 10: 18-29. https://doi.org/10.1002/psp4.12574

Right: Rieger, T. "Development of virtual populations for prediction of the response to treatments for non-alcoholic fatty liver disease." Presented at the 9th American Conference on Pharmacometrics, October 2019.

Key Common Themes

- Each model
  - was based on mechanistic understanding (*at the time of development)* of the target and disease
  - was used to extrapolate to new conditions
  - informed clinical trial design and accelerated the programs
  - predictions were subsequently confirmed by trial results

Key Common Themes & One Difference

- Each model was based on mechanistic understanding (*at the time of development)* of the target and disease
- Each model was used to extrapolate to new conditions
- Each model informed clinical trial design and accelerated the programs
- Predictions from each model were subsequently confirmed by trial results
  - However, the QSP NAFLD model initially mis-predicted a change in a key biomarker, resulting in a missed opportunity to address earlier in development

What can we learn from these examples?

Two Examples: Compare & Contrast

QSP Model of the Immune Response to SARS-CoV-2

- Novel infectious disease of global concern
- Many biotech/pharma advancing vaccines & anti-virals, at unprecedented speed, several with EUA
- Clinical trial and real-world data rapidly emerging and submitted for peer-review publication and/or included in EUA submissions

- At the time of our clinical trial simulations, mAb and preliminary competitor anti-viral summary data were publicly available
- Relative confidence in mechanism of action, based on preclinical and clinical data

QSP Model of Non-Alcoholic Fatty Liver Disease (NAFLD)

- Under-studied/diagnosed disease with unmet need
- Highly competitive field with many agents in development; several fast-tracked
- Limited data available on disease progression in published literature; RWE lacking

- At the time of initial simulations, clinical data were not publicly available for this mechanism of action (MoA)
- Preclinical data did not translate to understanding the regulation of hepatic lipid metabolism in humans
- Once competitor data with same MoA were published, model was updated & successfully used to inform Phase 2

Summary: QSP DPMs

- Represent complex interactions *in time* between multiple drug targets, pathways, tissues, and organs/systems
- Mechanistically link target modulation to biomarker response &/or clinical outcomes
- Include untreated and treated patients and a range of disease phenotypes via virtual patients, populations, and trial simulations
- Allows for hypothesis testing & extrapolation beyond available data

- "Success" largely dependent on confidence in the target and the mechanism(s) in the context of human disease

Acknowledgments

- Rohit Rao
- Richard Allen
- Theodore Rieger

- Gianluca Nucci
- Brian Corrigan

- Project team members and clinical trial participants

CTTI

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

@CTTI_Trials

C.J. Musante

cynthia.j.musante@pfizer.com

THANK YOU

www.ctti-clinicaltrials.org

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

March 6, 2023

AI/ML: Value for DPM and Adoption Challenges

David P. Miller

Chief Science Officer, Unlearn.ai

Disclaimer

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.
- The presenter is an Employee of Unlearn.ai and owns equity in Unlearn.ai.

AI/ML → Deep Learning

- What is it?
- What is it good for?
- Why aren’t we already using it broadly today?

Deep Learning
What Is It?

← Thread

Yann LeCun
@ylecun

Some folks still seem confused about what deep learning is. Here is a definition:

DL is constructing networks of parameterized functional modules & training them from examples using gradient-based optimization....
facebook.com/722677142/post...

7:32 AM · Dec 24, 2019

Clear enough?

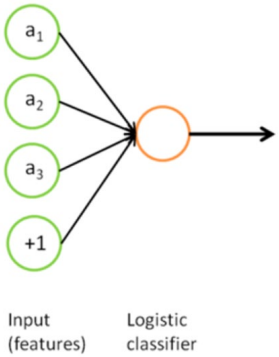
CTTI

Can you tell the difference between a cat and a dog?

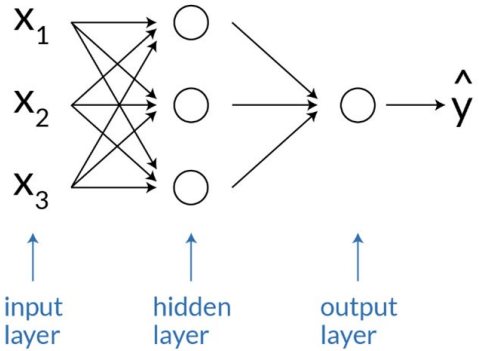
How do you know the cat is a cat?
Size? Color? Posture? Ears? Fluffiness?

Features and Parameters

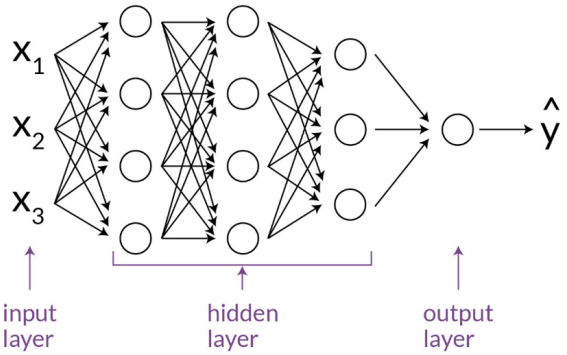
Logistic Regression



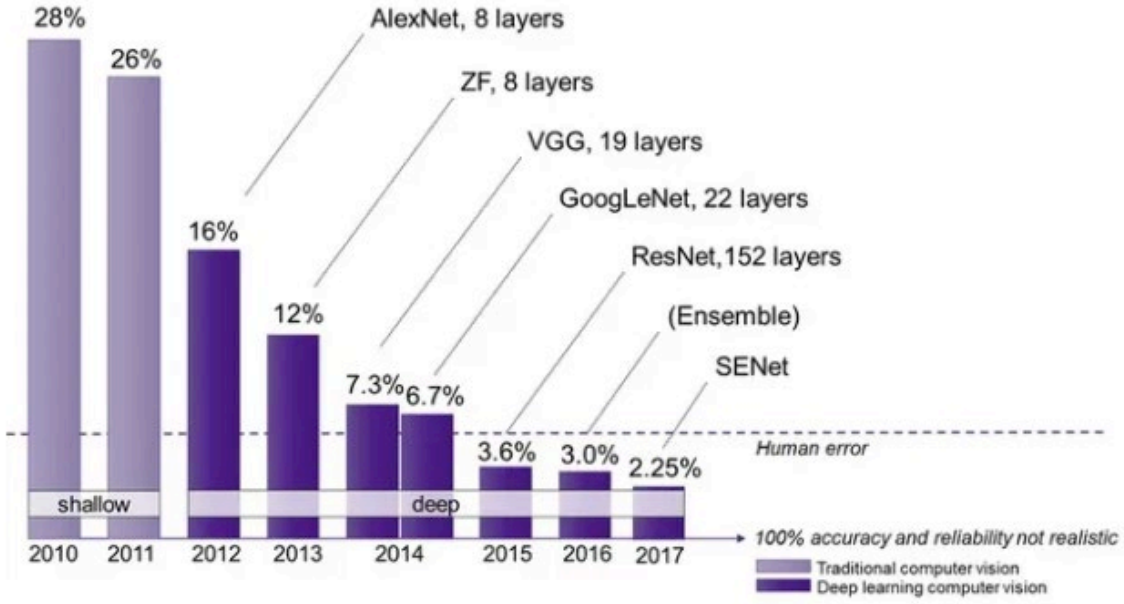
Shallow Neural Network



Deep Neural Network



What if pictures had more than cats and dogs?



AlexNet Ushered in a New Era of ML in 2012

CTTI

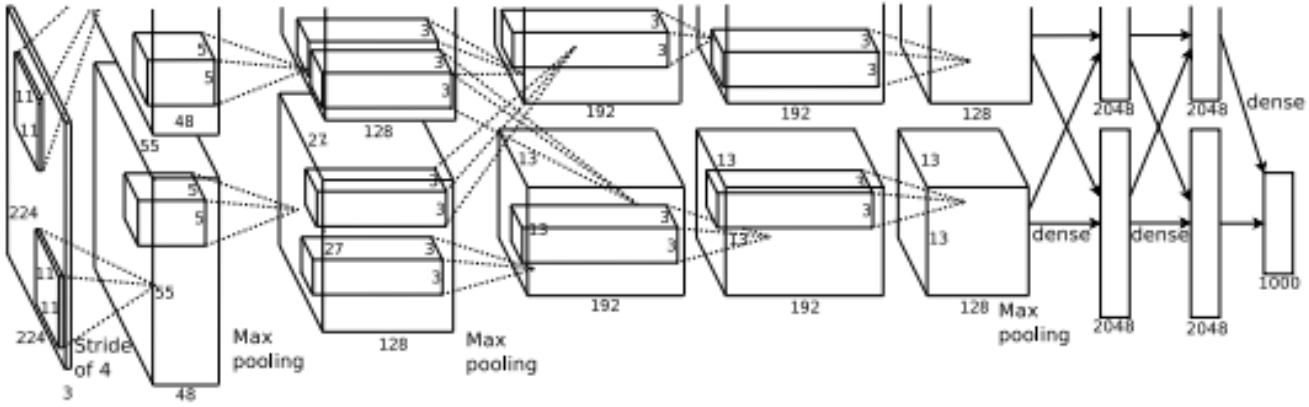


Figure 2 from Krizhevsky, Sutskever, and Hinton

Deep Learning
What Is It Good For?

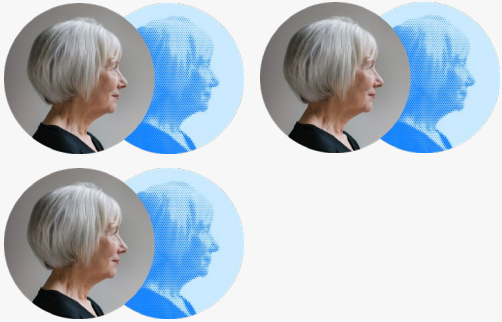
AI-generated Digital Twins provide a rich set of explanatory data for every participant in an RCT

Control Arm

Treatment Arm

AI-Generated Digital Twins + Real Participants = Faster, Smaller Trials

Control Arm



Treatment Arm

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP qualifies PROCOVA

What are the key points in the qualification?

- Suitable for primary analysis of phase 3 pivotal studies
- Unbiased estimation of treatment effect
- Increased power
- Reduced sample size

The PROCOVA™ Procedure has 3 Steps

Step 1

"Training and evaluating a prognostic model to predict control outcomes"

Step 2

"Accounting for the prognostic model while estimating the sample size required for a prospective study"

Step 3

"Estimating the treatment effect from the completed study using a linear model while adjusting for the control outcomes predicted by the prognostic model"

Deep Learning
Why Aren't We Already Using It Broadly Today?

Charles Fisher

Founder and CEO

Unlearn.AI

Unlearn is accelerating clinical trials with AI.

"The biggest challenge in commercializing AI-based tech in healthcare is "the discernment problem" – most prospective customers can't easily distinguish between companies using sophisticated AI and other companies selling nonsense as AI.

As a result, they assume you're guilty until proven innocent. To overcome this, you need to do something big to stand out from the crowd.

In Unlearn's case, we've focused on paving the regulatory path and became the first company to receive a regulatory qualification for an AI-based approach to accelerating clinical trials. What can you do to show you're a cut above the rest?

CTTI

EMA vs FDA

- Submission April, 2021
- First meeting May, 2021
- Comments from EMA May, 2021
- Updated submission June, 2021
- EMA formal questions Sep, 2021
- Additional questions Dec, 2021
- Draft qualification Feb, 2022
- Public consult March, 2022
- Qualification Sep, 2022

- CPIM meeting March, 2020
- ISTAND submission June, 2021
- Eleven separate updates that there was no update (July, 2021 through June, 2022)
- Communication that there would be no more applications accepted in 2022 (July, 2022)
- Confirmation that ISTAND was the right path and there are no available resources to review (Dec 2022)

CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

@CTTI_Trials

THANK YOU

www.ctti-clinicaltrials.org

Disease Progression Modeling Without Tears

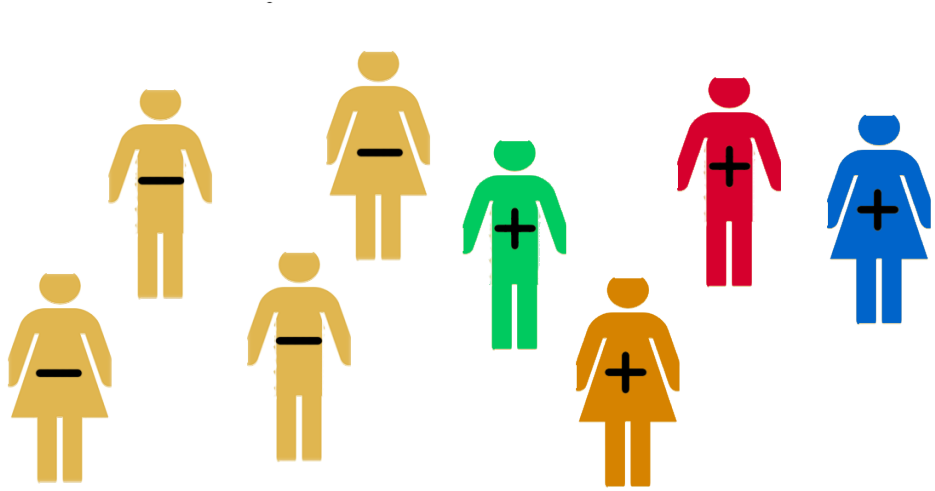
Transforming data into actionable knowledge for drug development

Klaus Romero MD MS FCP
Chief Science Officer

CRITICAL PATH INSTITUTE

Critical questions for trial design

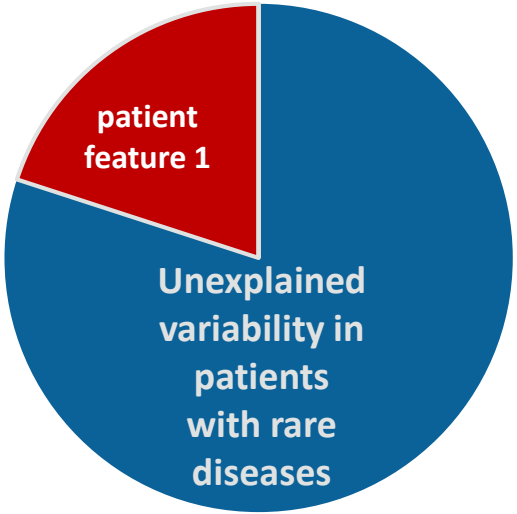
- How many patients should be recruited to properly power the trial?
- What should be the inclusion criteria?
- Can the control arm be optimized?
- What types of progression rates are expected for different subpopulations?
- What measures of progression are most adequate, at which stages of the disease continuum?
- How long should the trial duration be?
- How often should I assess?
- What is the time-varying probability of dropouts, and what are their predictors?

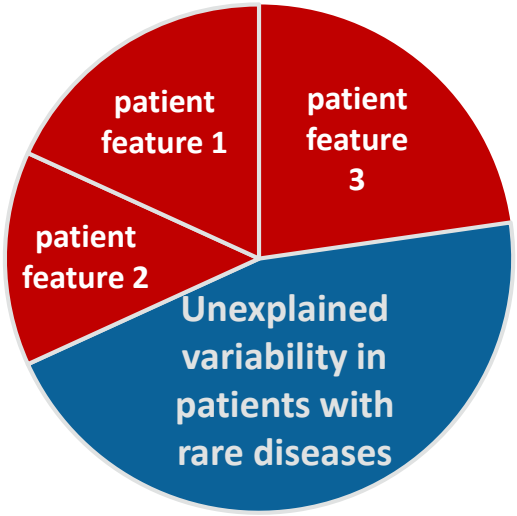


How should one go about providing sound quantitative answers to these questions?

Answer 1: Quantifying variability

Quantifying multiple sources of variability simultaneously within the patient population reduces overall unexplained variability



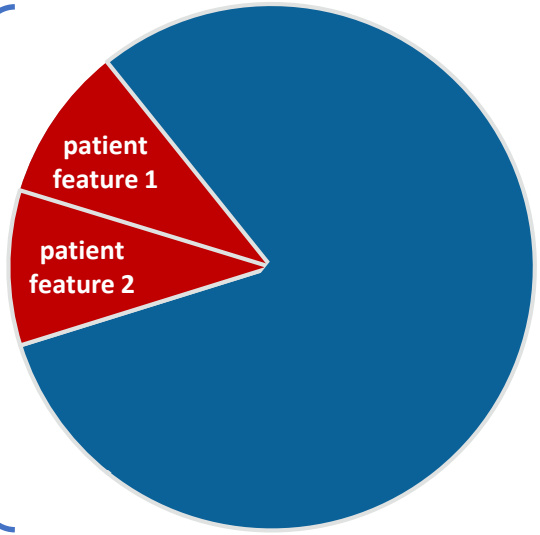


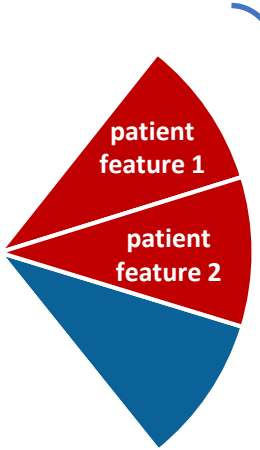
Result: The ability to predict more accurate progression rates for heterogeneous subpopulations of patients in clinical trials

Answer 2: Multiple data sources

Understanding the 'universe' of a given disease's heterogeneity

Unexplained variability in <u>ALL</u> patients with rare diseases

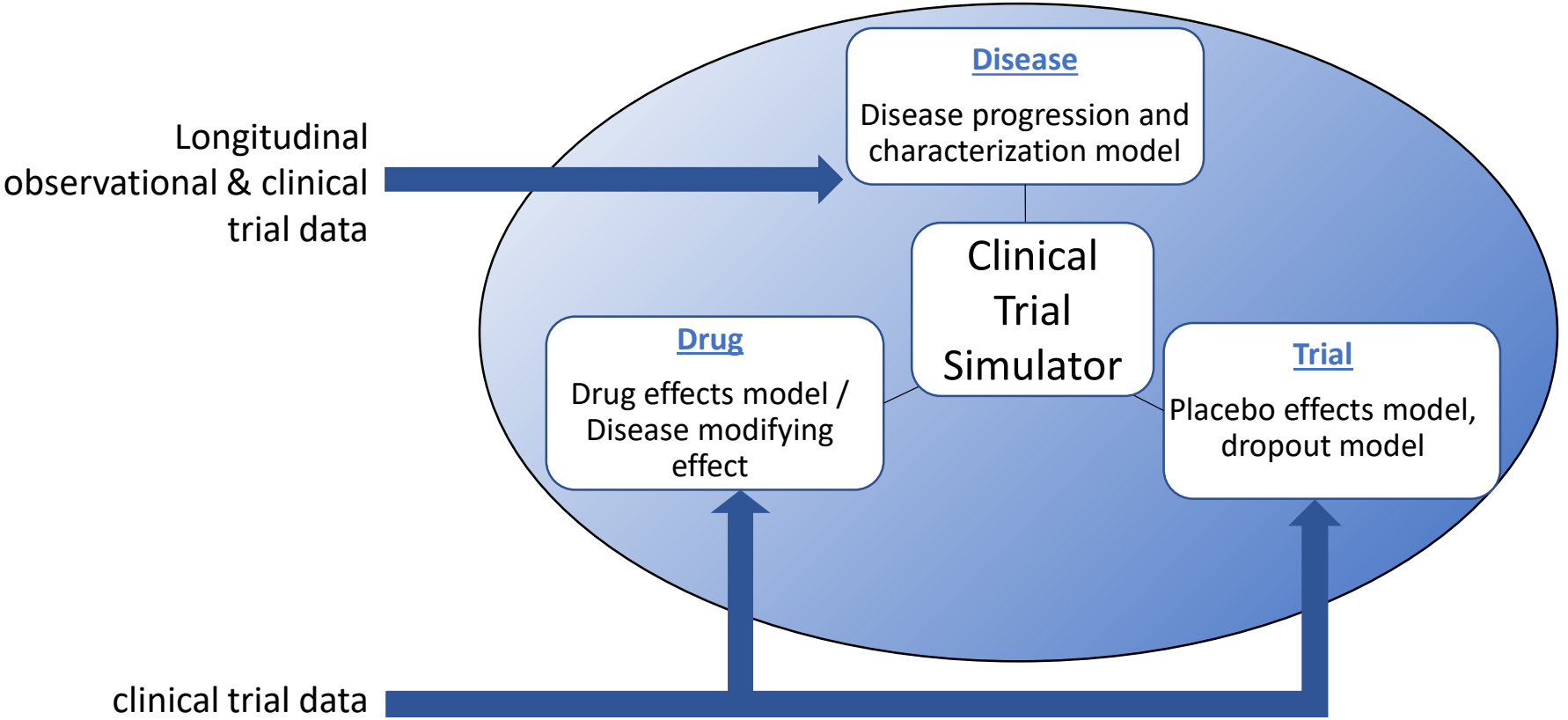




Unexplained variability in patients with rare diseases from <u>a single study</u>

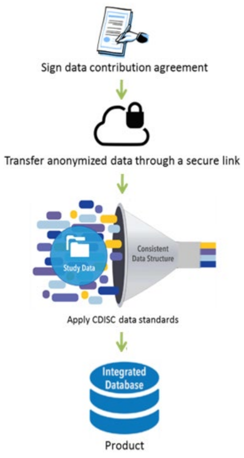
Result: The ability to more accurately account for the heterogeneity in rare diseases and avoid biased conclusions on few data sources

Answer 3: Drug-disease-trial modeling



Putting it altogether

- Start with an understanding of what sponsors can practically use to design clinical trials, and reverse engineer

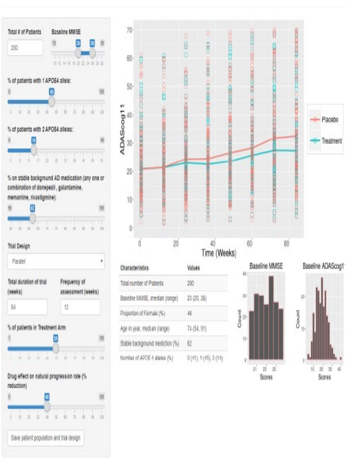


STUDYID	USUBJID	AGE	SEX	ARM	ACTARM	SITEID	SWEDD
PD-1000	PD-1000/C	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/C	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/C	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/C	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/C	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/C	67	1	Parkinson	Parkinson	NA	NA

$$S(t) = \frac{S_0}{\left[S_0^{\beta} + \left(1 - S_0^{\beta}\right) e^{-\beta r t}\right]^{1/\beta}}$$

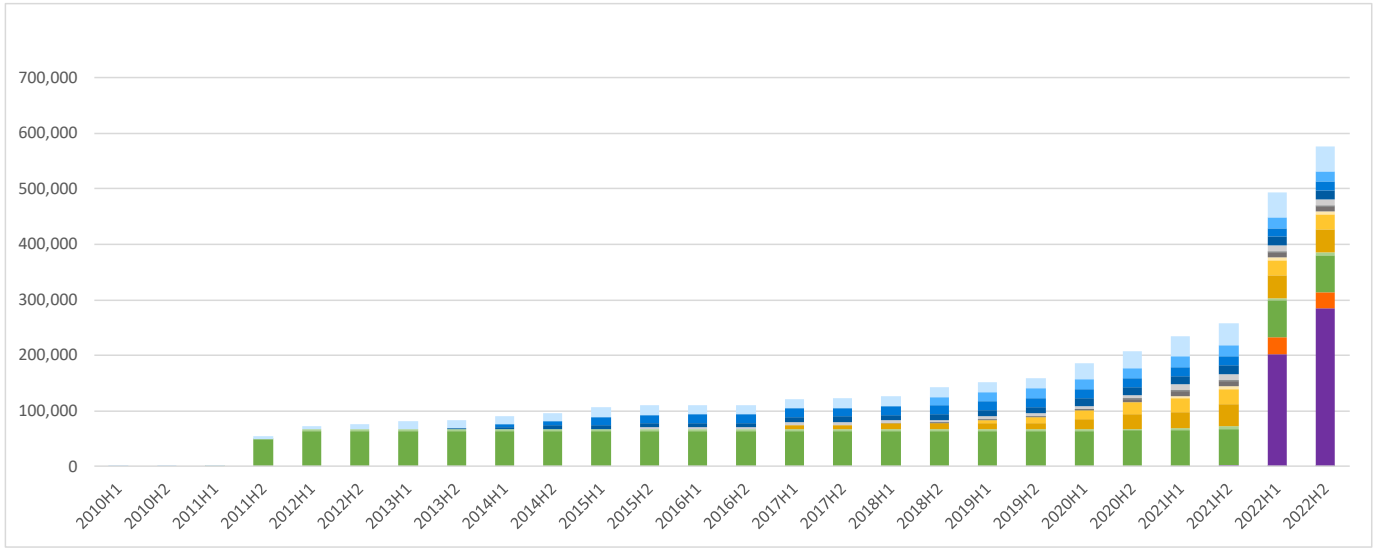
$$TVP_i = \theta_i \left(\frac{cont_i}{ref}\right)^{\theta_{power}} \theta_{coeff}^{cat_i}$$

$$f(S;\, \alpha, \beta) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)+\Gamma(\beta)} \cdot S^{(\alpha-1)} \cdot (1-S)^{(\beta-1)}$$



Execution

Total Data Contributed



Clinical Data	
Studies	390
Participants	605,708

Non-Clinical Data	
Studies	148
Participants	11,084

Neuro	
Alzheimer's Disease	44,131
Huntington's Disease	19,665
Multiple Sclerosis	15,626
Parkinson's Disease	15,926

Rare	
Duchenne's Muscular Dystrophy	11,442
Friedreich's Ataxia	1,572
Rare Diseases	8,196

IHP	
Sickle Cell Disease	6,240
Transplant Therapeutics	26,264
Type 1 Diabetes	42,287

TSSP	
Polycystic Kidney Disease	4,422
Safety Testing	66,295

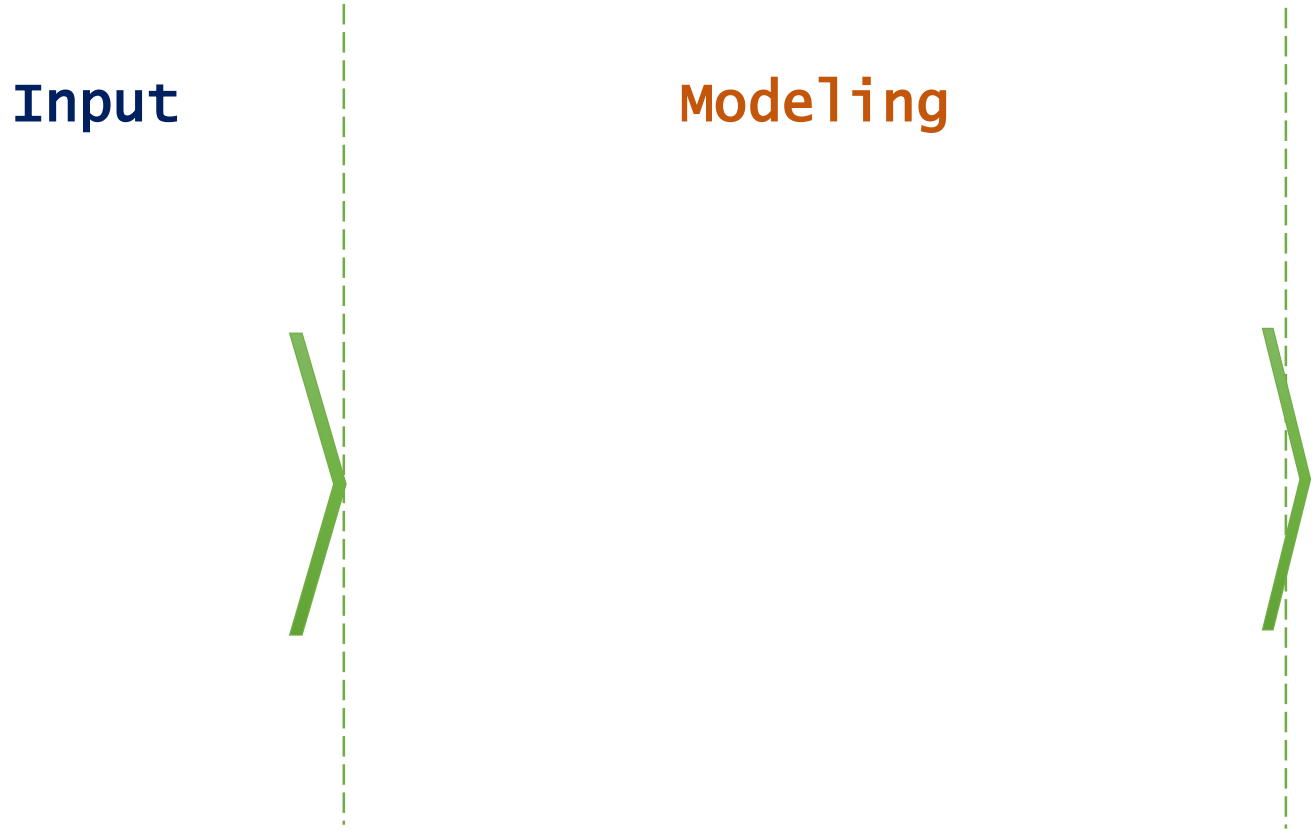
CURE Drug Repurposing	29,618

Neonatal	283,565

Tuberculosis	829

Note: Studies currently undergoing curation are only counted in Total Studies until evaluated.

Disease Progression Model



Disease Progression Model

CRITICAL PATH INSTITUTE

Input

Patient-level data

Modeling

Output

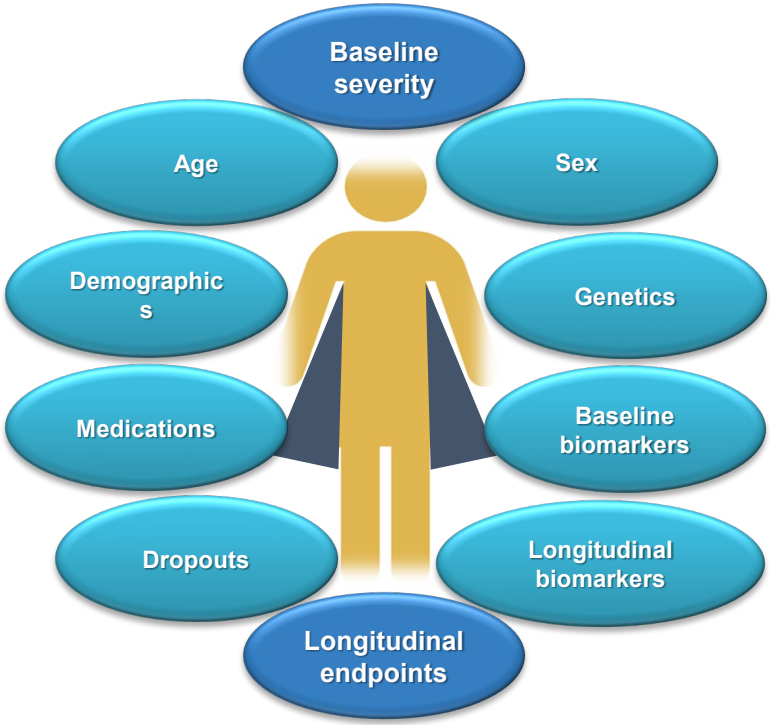
Disease Progression Model

CRITICAL PATH INSTITUTE

Input

Patient-level data

Modeling



Output

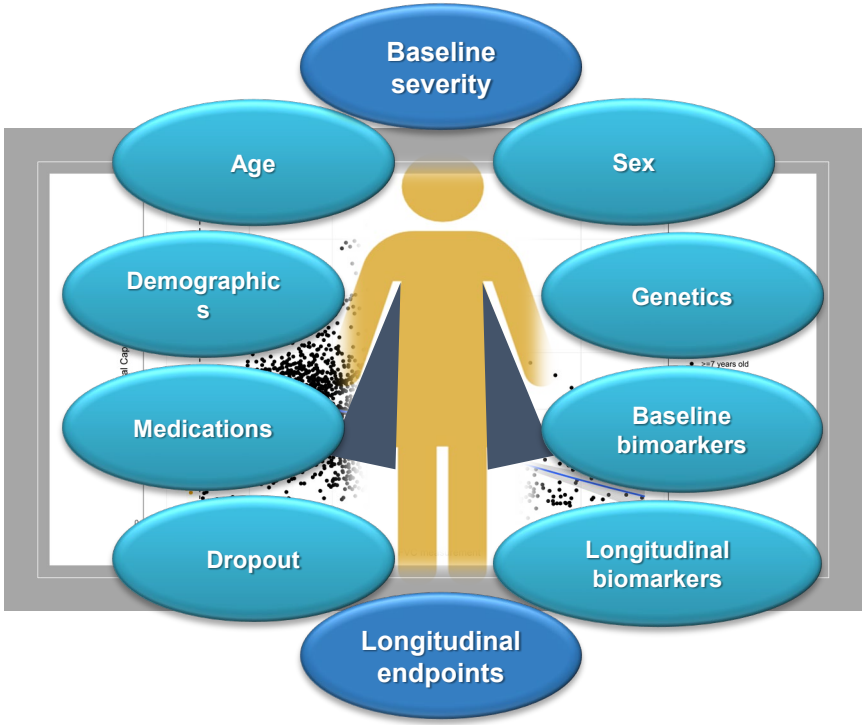
Disease Progression Model

CRITICAL PATH INSTITUTE

Input

Clinical studies

Modeling



Output

Understanding of disease worsening

Trajectory

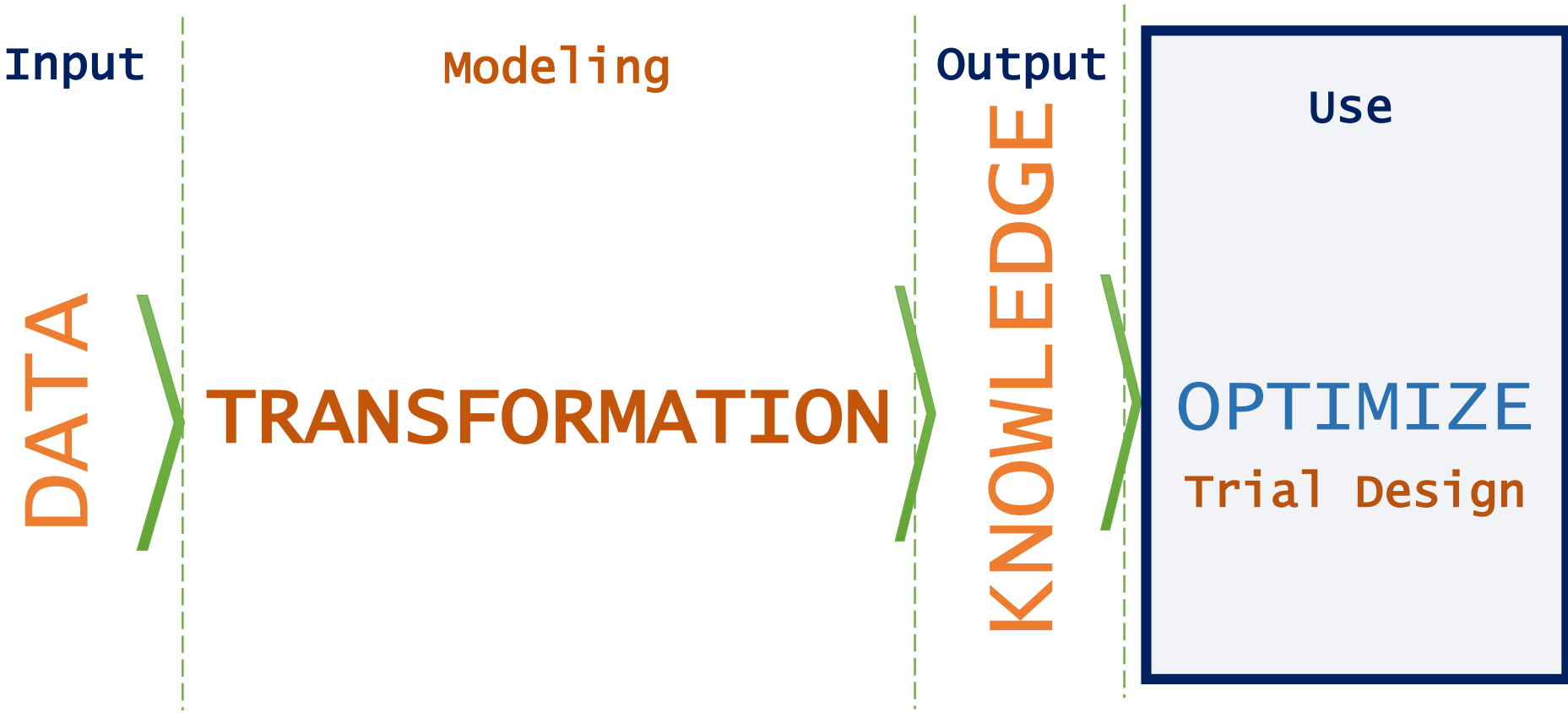
Rate

Predictors

Web Clinical Trial Simulator

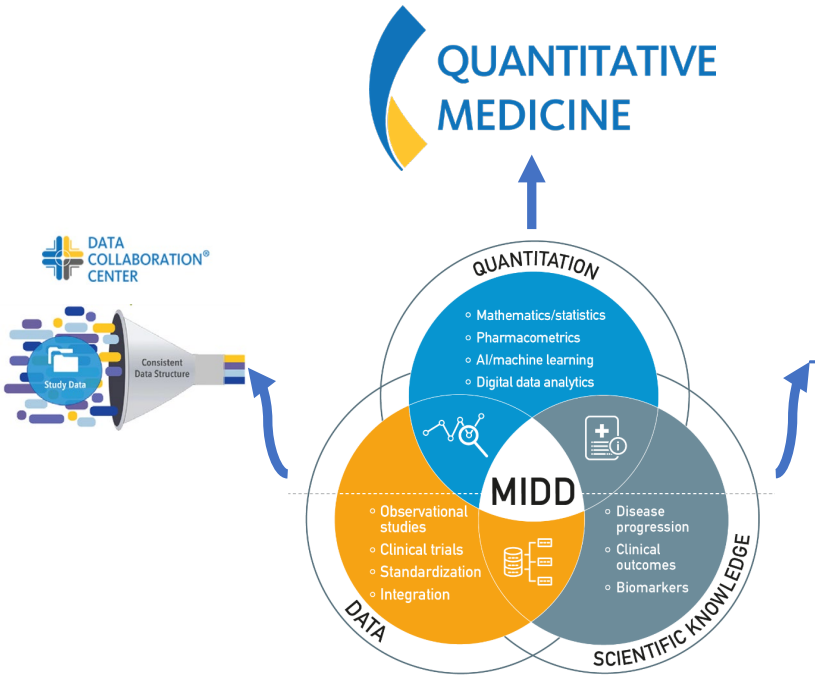
Disease Progression Model

Disease Progression Model



From data, to solutions, to impact

QUANTITATIVE MEDICINE
CRITICAL PATH INSTITUTE



Indication	Solutions	Impact
Alzheimer's disease	2CTS tools, 2 biomarkers	First 2 disease-modifying drugs
Tuberculosis	Multiple quantitative tools	First new drug and drug regimen
PKD	PKD	First disease-modifying drug
Type 1 Diabetes	Model-based biomarkers	First prevention drug
Duchenne Muscular Dystrophy	5 disease progression models	Transformed trial design paradigm
Kidney Transplantation	Composite biomarker endpoint	Transformed trial design paradigm
Parkinson's disease	3 CTS tools, 1 biomarker, multiple DHT solutions	Transformed trial design paradigm
Huntington's disease	Staging system, 3 disease progression models	Transformed trial design paradigm

Thank you!

CRITICAL PATH INSTITUTE

collaborate · innovate · accelerate

Q & A