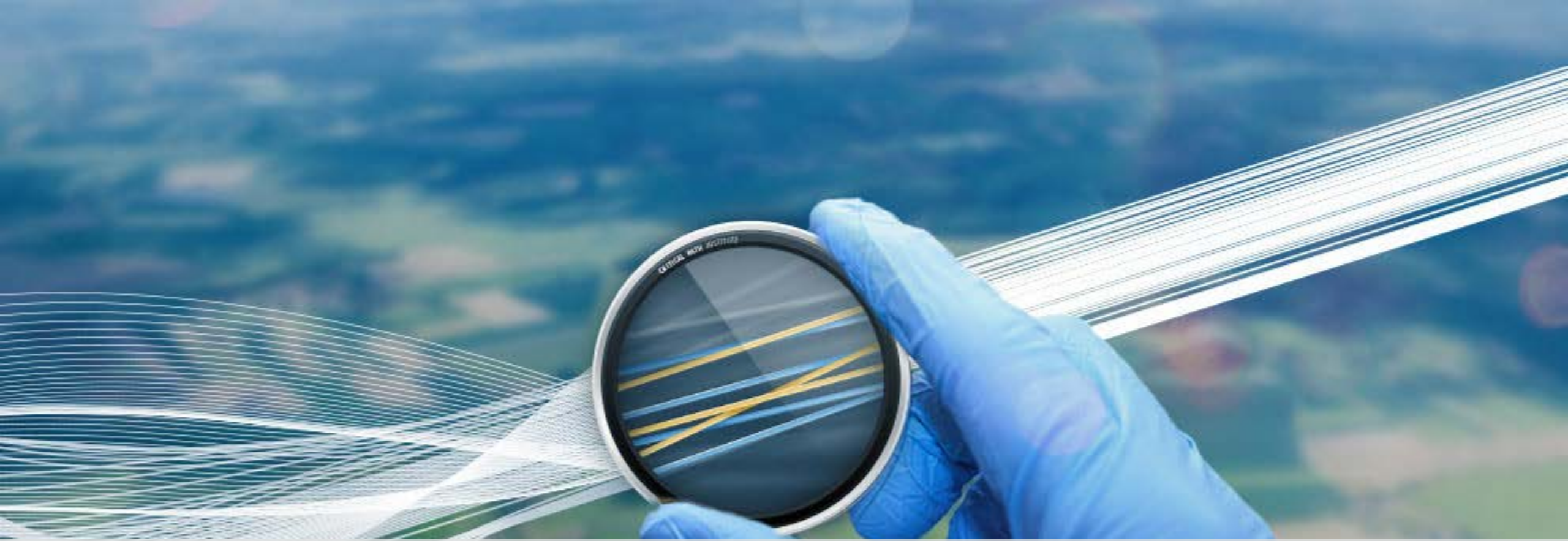

Data-driven models for drug development

Jackson Burton PhD, Scientific Director of Mathematical and Statistical Medicine

Addressing Drug Development Gaps through Data Sharing: Converting Data into Knowledge

C-Path Biomarker Program Workshop

CRITICAL PATH INSTITUTE

Biomarkers and Models – Bridging the Gap

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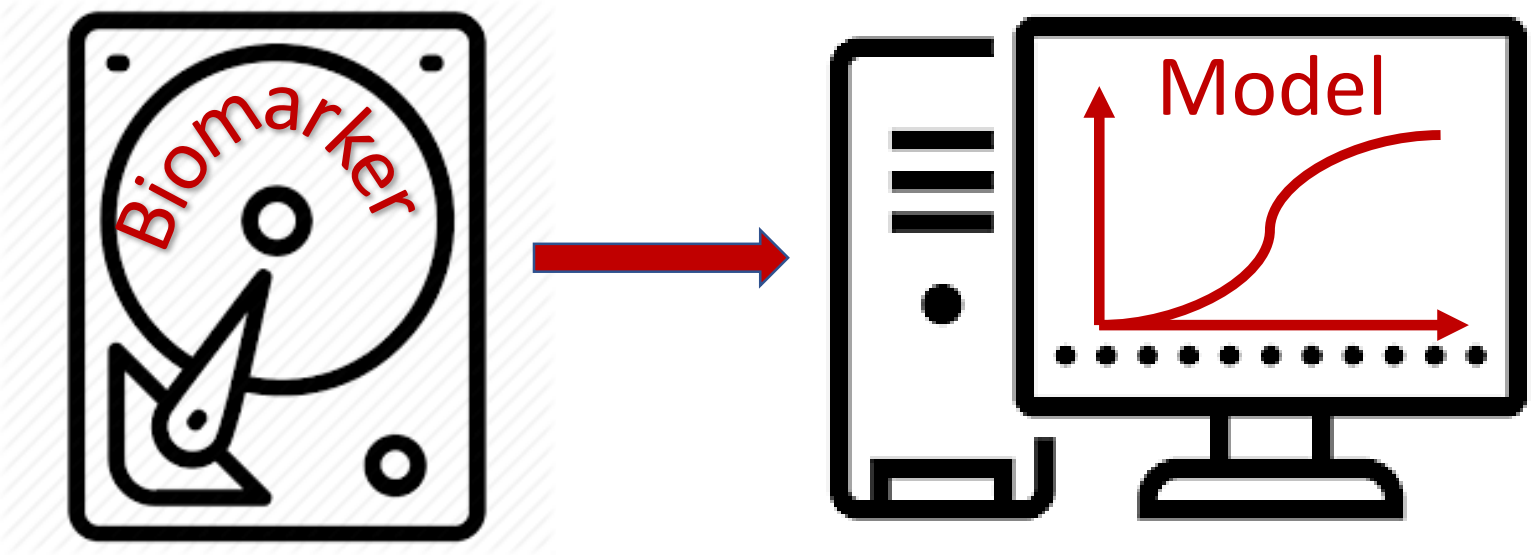
What is the connection between biomarkers and models?

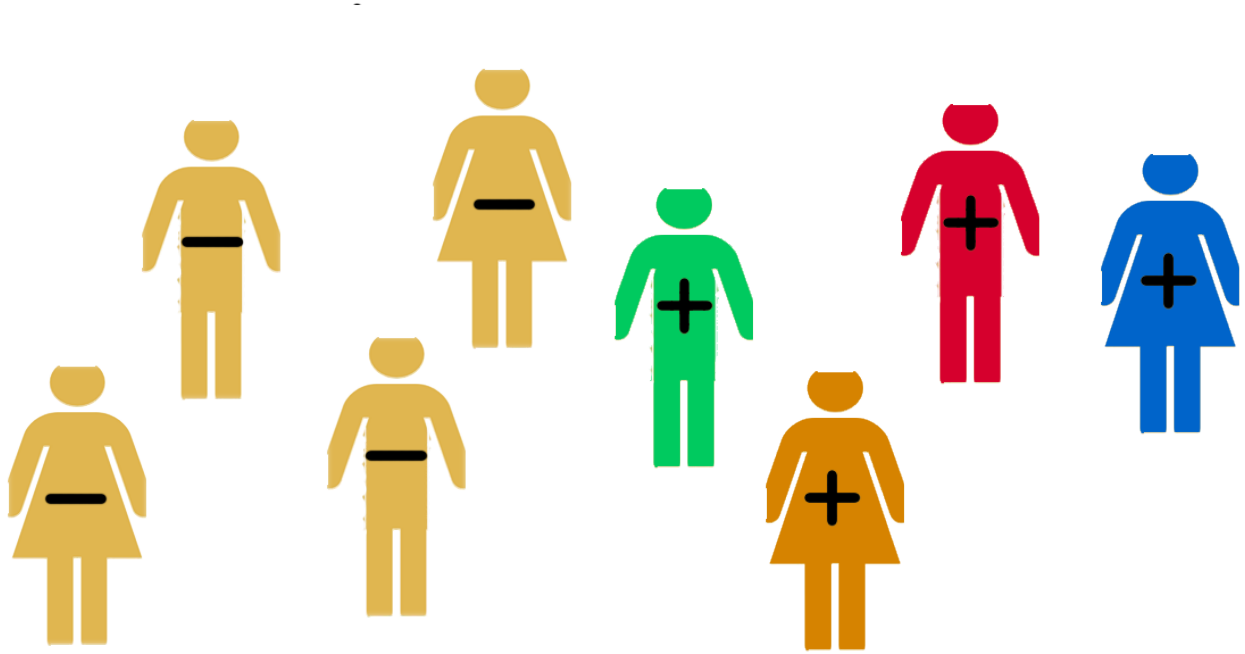


Models are a special class of quantitative methods used to answer specific questions in drug development, including how biomarkers can be used.

What are important questions are important for trial design?

Ex) For a prognostic biomarker:

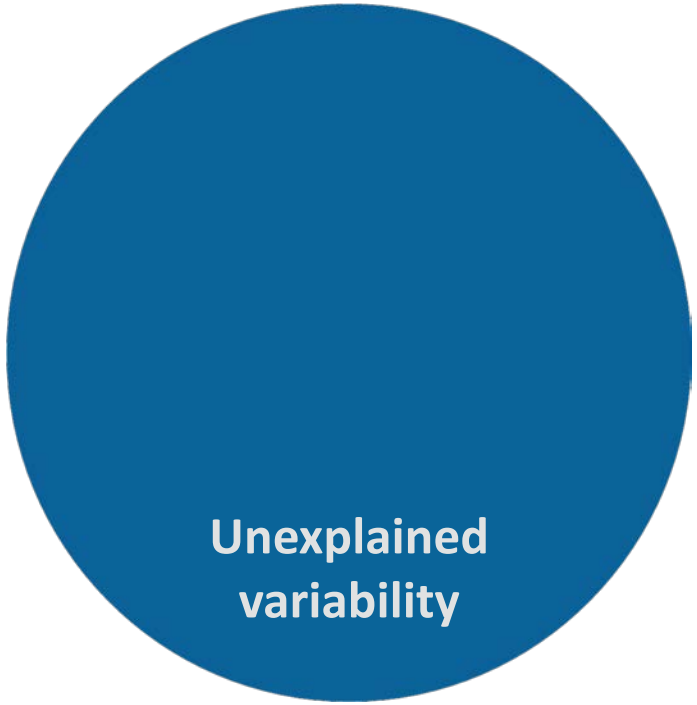
- If the biomarker is binary, what impact will recruiting less than 100% biomarker positive individuals have on disease progression?
- If the biomarker is continuous, how will the distribution of the values of the biomarker impact disease progression?
- How many patients are needed to power the trial based on the biomarker values ?

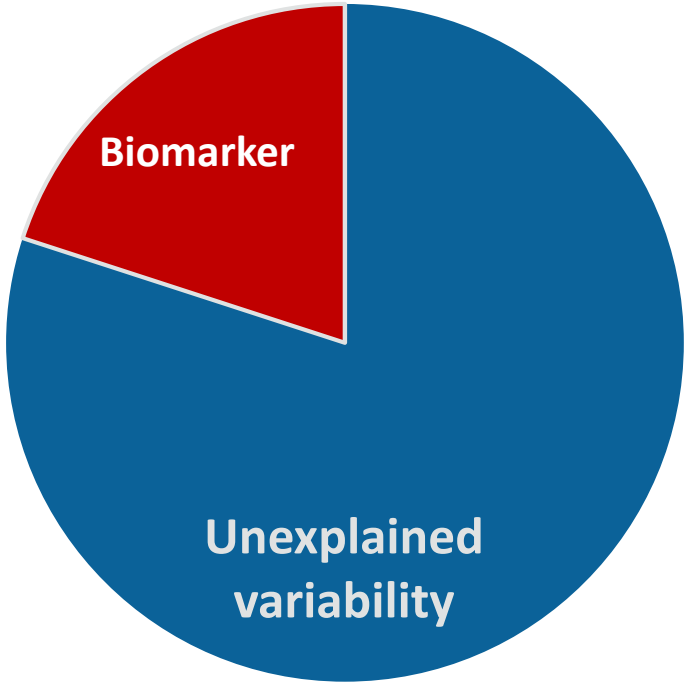


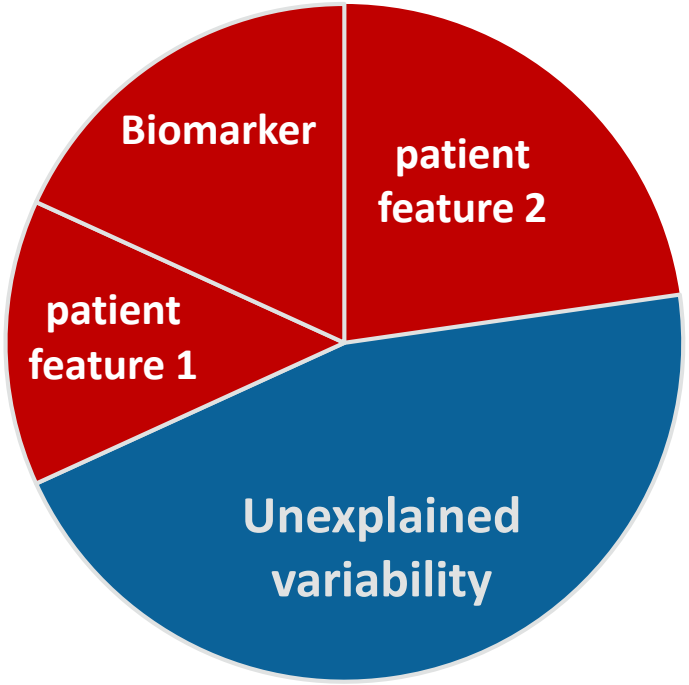
Such questions are fundamentally addressed by considering biomarkers as a source of variability among other sources.

How do biomarkers get used in models?

A biomarker is a key source of variability out of many sources of variability in patient populations



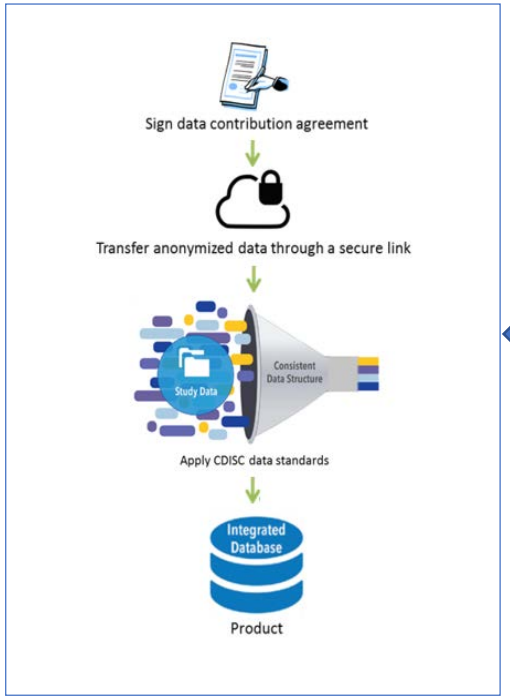


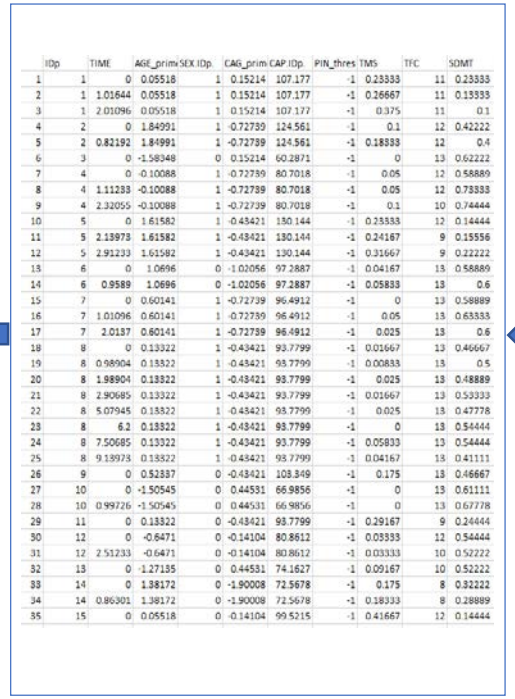


Accounting for more variability, whether it's a biomarker or not, provides more predictive power

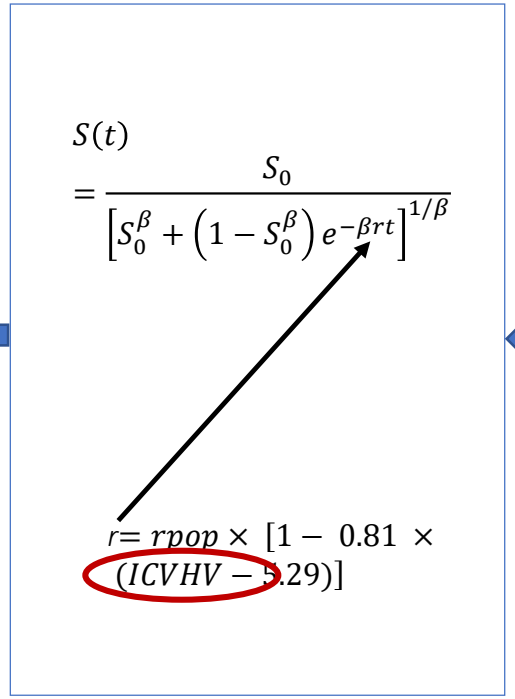
Tying the biomarker together with the model

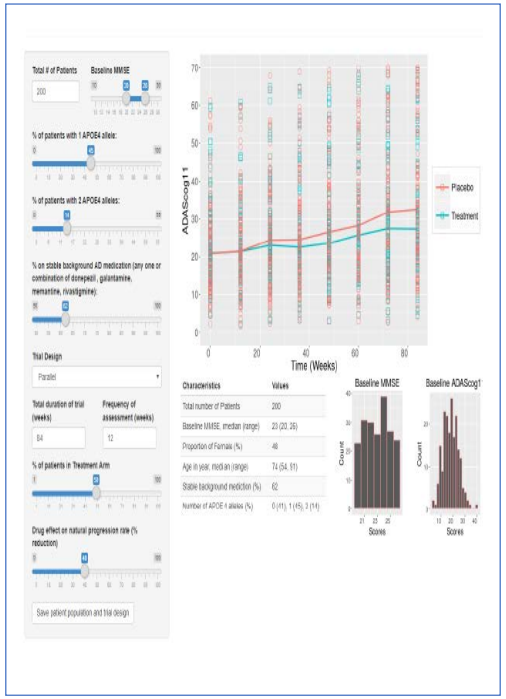
- Start with the envisioned model-based tool that can practically address a drug development need and reverse engineer the steps to develop such a tool.





	IDp	TIME	AGE_prim	SEX	IDp	CAG_prim	CAP	IDp	PIN_thres	TMS	TFC	SDMT
1	1	0	0.05518	1	0.15214	107.177	-1	0.23333	11	0.23333
2	1	1.01644	0.05518	1	0.15214	107.177	-1	0.26667	11	0.13333
3	1	2.01096	0.05518	1	0.15214	107.177	-1	0.375	11	0.1
4	2	0	1.84991	1	-0.72739	124.561	-1	0.1	12	0.42222
5	2	0.82192	1.84991	1	-0.72739	124.561	-1	0.18333	12	0.4
6	3	0	-1.58348	0	0.15214	60.2871	-1	0	13	0.62222
7	4	0	-0.10088	1	-0.72739	80.7018	-1	0.05	12	0.58889
8	4	1.11233	-0.10088	1	-0.72739	80.7018	-1	0.05	12	0.73333
9	4	2.32055	-0.10088	1	-0.72739	80.7018	-1	0.1	10	0.74444
10	5	0	1.61582	1	-0.43421	130.144	-1	0.23333	12	0.14444
11	5	2.13973	1.61582	1	-0.43421	130.144	-1	0.24167	9	0.15556
12	5	2.91233	1.61582	1	-0.43421	130.144	-1	0.31667	9	0.22222
13	6	0	1.0696	0	-1.02056	97.2887	-1	0.04167	13	0.58889
14	6	0.9589	1.0696	0	-1.02056	97.2887	-1	0.05833	13	0.6
15	7	0	0.60141	1	-0.72739	96.4912	-1	0	13	0.58889
16	7	1.01096	0.60141	1	-0.72739	96.4912	-1	0.05	13	0.63333
17	7	2.0137	0.60141	1	-0.72739	96.4912	-1	0.025	13	0.6
18	8	0	0.13322	1	-0.43421	93.7799	-1	0.01667	13	0.46667
19	8	0.98904	0.13322	1	-0.43421	93.7799	-1	0.00833	13	0.5
20	8	1.98904	0.13322	1	-0.43421	93.7799	-1	0.025	13	0.48889
21	8	2.90685	0.13322	1	-0.43421	93.7799	-1	0.01667	13	0.53333
22	8	5.07945	0.13322	1	-0.43421	93.7799	-1	0.025	13	0.47778
23	8	6.2	0.13322	1	-0.43421	93.7799	-1	0	13	0.54444
24	8	7.50685	0.13322	1	-0.43421	93.7799	-1	0.05833	13	0.54444
25	8	9.13973	0.13322	1	-0.43421	93.7799	-1	0.04167	13	0.41111
26	9	0	0.52337	0	-0.43421	108.349	-1	0.175	13	0.46667
27	10	0	-1.50545	0	0.44531	66.9856	-1	0	13	0.61111
28	10	0.99726	-1.50545	0	0.44531	66.9856	-1	0	13	0.67778
29	11	0	0.13322	0	-0.43421	93.7799	-1	0.29167	9	0.24444
30	12	0	-0.6471	0	-0.14104	80.8612	-1	0.03333	12	0.54444
31	12	2.51233	-0.6471	0	-0.14104	80.8612	-1	0.03333	10	0.52222
32	13	0	-1.27135	0	0.44531	74.1627	-1	0.09167	10	0.52222
33	14	0	1.38172	0	-1.90008	72.5678	-1	0.175	8	0.32222
34	14	0.86301	1.38172	0	-1.90008	72.5678	-1	0.18333	8	0.28889
35	15	0	0.05518	0	-0.14104	99.5215	-1	0.41667	12	0.14444





Execution

DAT clinical trial simulator: DAT biomarker enrichment (EMA Qualification opinion)

CRITICAL PATH INSTITUTE

CPP PARKINSON'S CONSORTIUM CRITICAL PATH INSTITUTE

DAT Neuroimaging-Informed Early PD Clinical Trial Simulator - Version 1.0

Simulate clinical trials on patients with early-stage Parkinson disease

Click here for more information on this application.

Number of Subjects per Arm:

200

Duration of Subjects Follow-up (Months):

1 — 24

Assessment Interval (Months):

1 — 3 — 12

Proportion of Subjects with SWEDD (%):

0 — 8 — 28

Effect of Drug on Rate of Disease Progression (% Reduction):

0 — 50 — 100

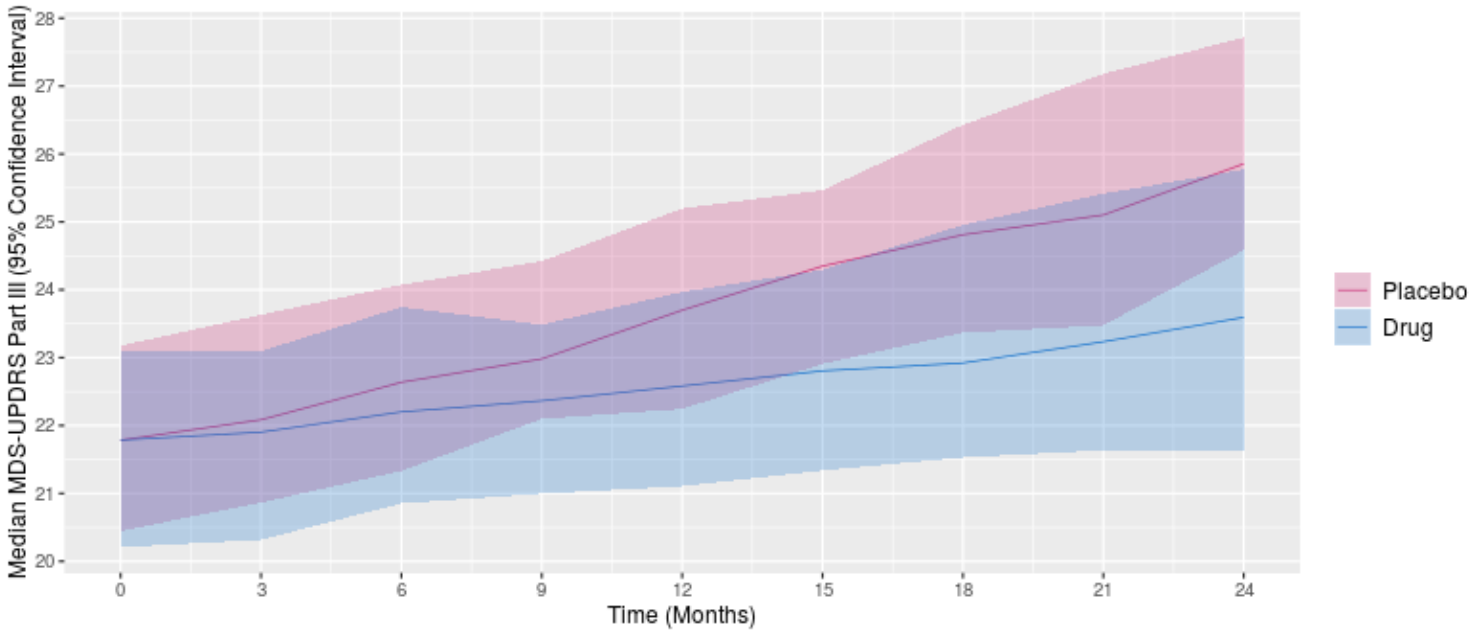
Effect of Digital Measure on Noise of MDS-UPDRS Part III (% Reduction):

0 — 99

Number of Simulations:

100

Simulate



Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	400
Study Duration (Months)	24
Assessment Interval (Months)	3
Effect of Drug on Rate of Disease Progression (% Reduction)	50

MCI clinical trial simulator: HV biomarker enrichment (Letter of support – EMA)

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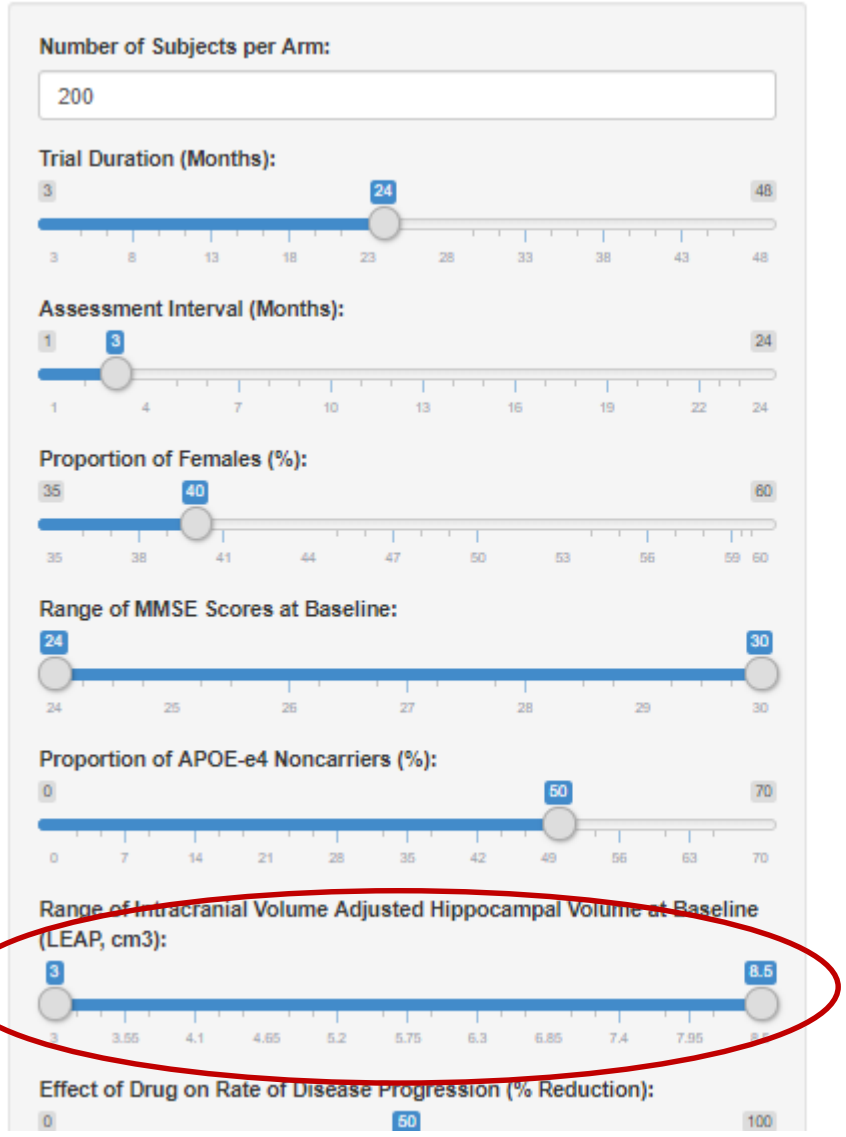

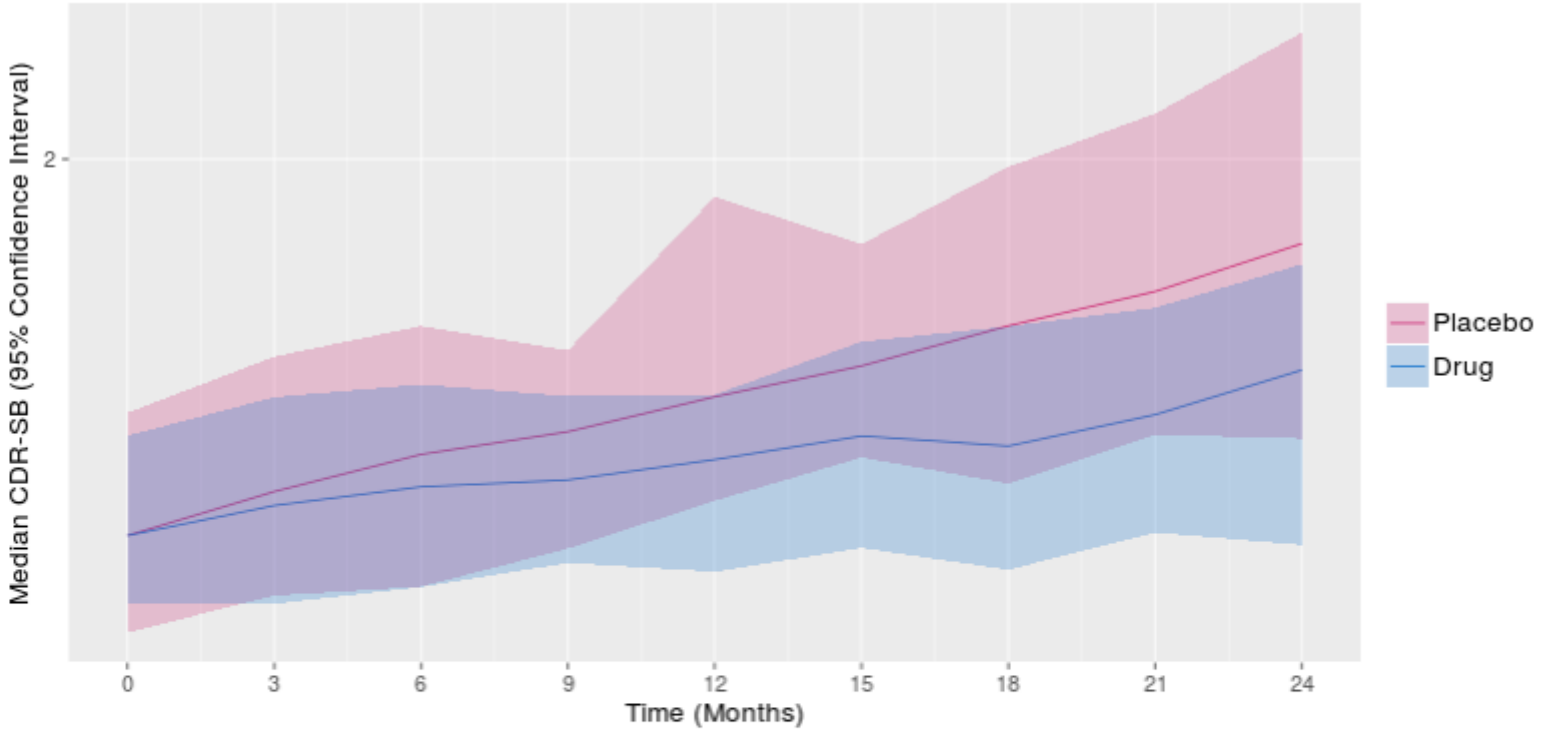

Characteristics	Values
Study Design	Placebo-Controlled Parallel Group
Total Number of Subjects	400
Study Duration (Months)	24
Assessment Interval (Months)	3
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Proportion of Female (%)	40
Range of MMSE Scores at Baseline	[24, 30]

Some concluding thoughts

- Biomarker validity vs. utility → models focus on utility
- The role of models to ‘extract’ biomarker information depends on the intended application of the biomarker in drug development
- Regulatory pathways to endorse biomarkers / models have one goal – instill confidence for sponsors

Thank you!

Backups

Example of data refinement – T1D

	Longitudinal		>= 2 AAs		Derived Baseline	
	TEDDY	TN01	TEDDY	TN01	TEDDY	TN01
Subjects	693	202,461	441	4,462	274	2,094
Timepoints	16,404	345,221	5,848	15,917		
Diagnoses	216	1,696	201	1,170	100	727
Data	% of subjects	% of timepoints for subjects w/ tests run	% of subjects	% of timepoints for subjects w/ tests run	% of subjects	
Autoantibody Tests						
GADA	100%	99.4%	100%	95%	100%	
IA2A	100%	99.4%	100%	95%	100%	
IAA	100%	99.4%	100%	95%	100%	
Blood						
OGTT (0,120 min)	3.5%	50.2%	71.5%	63%	100%	
HbA1c	3.6%	58.6%	74.1%	75%	100%	
Risk factors						
HLA	3.5%		72%		95.5%	
FDR	87%		87%		92%	

2 or more islet AAs driven by sponsor needs

Refine

Challenges with modeling using time-varying covariates

Refine

***Derived baseline = the first record for each individual with any 2 or more islet AAs and complete information for OGTT and HbA1c**