

AITIA



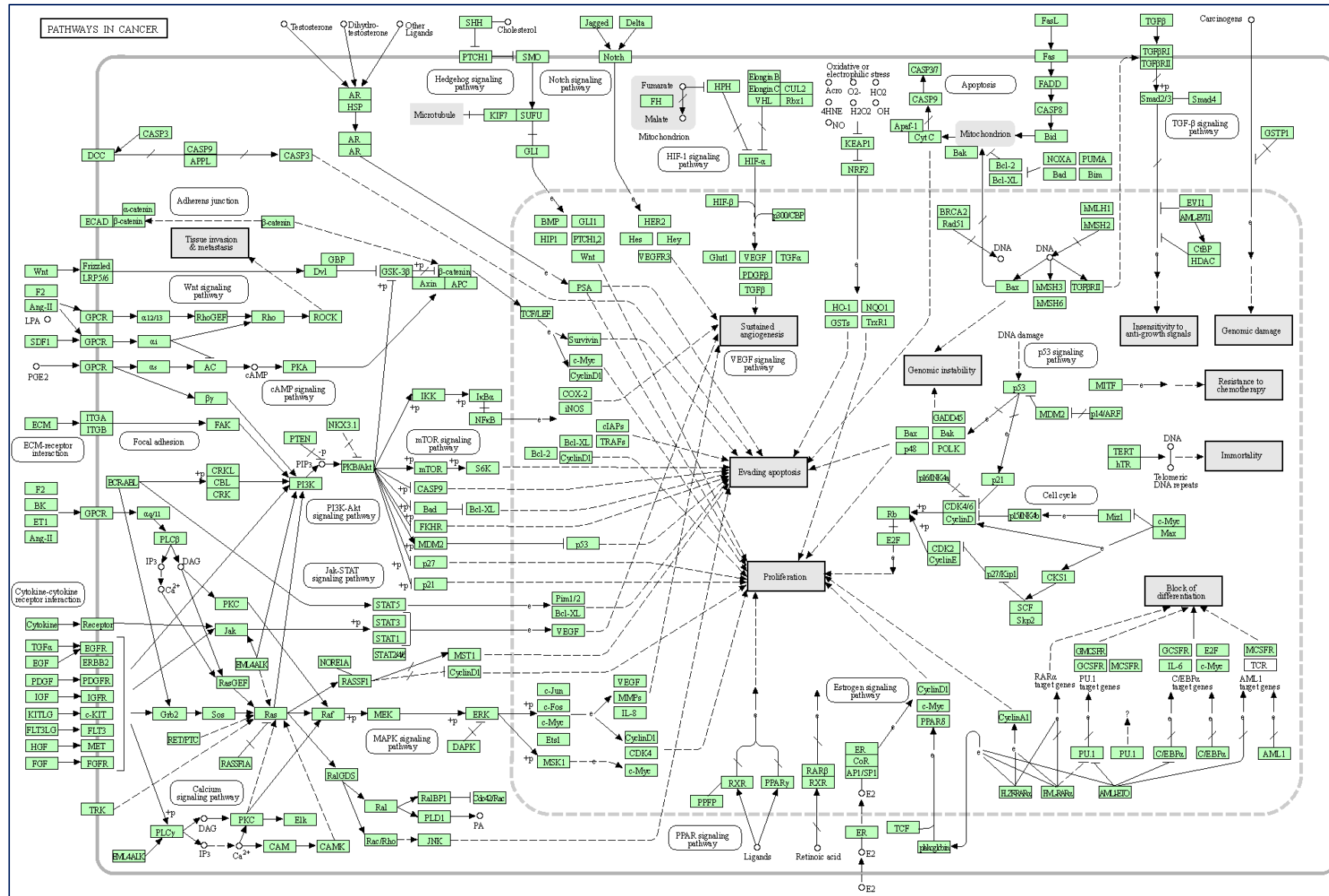
**Causal AI for Learning “Gemini Digital Twins” from Human
Multi-Omic Data for Drug Discovery and Clinical Development:**

A Cardiovascular Disease Case Study

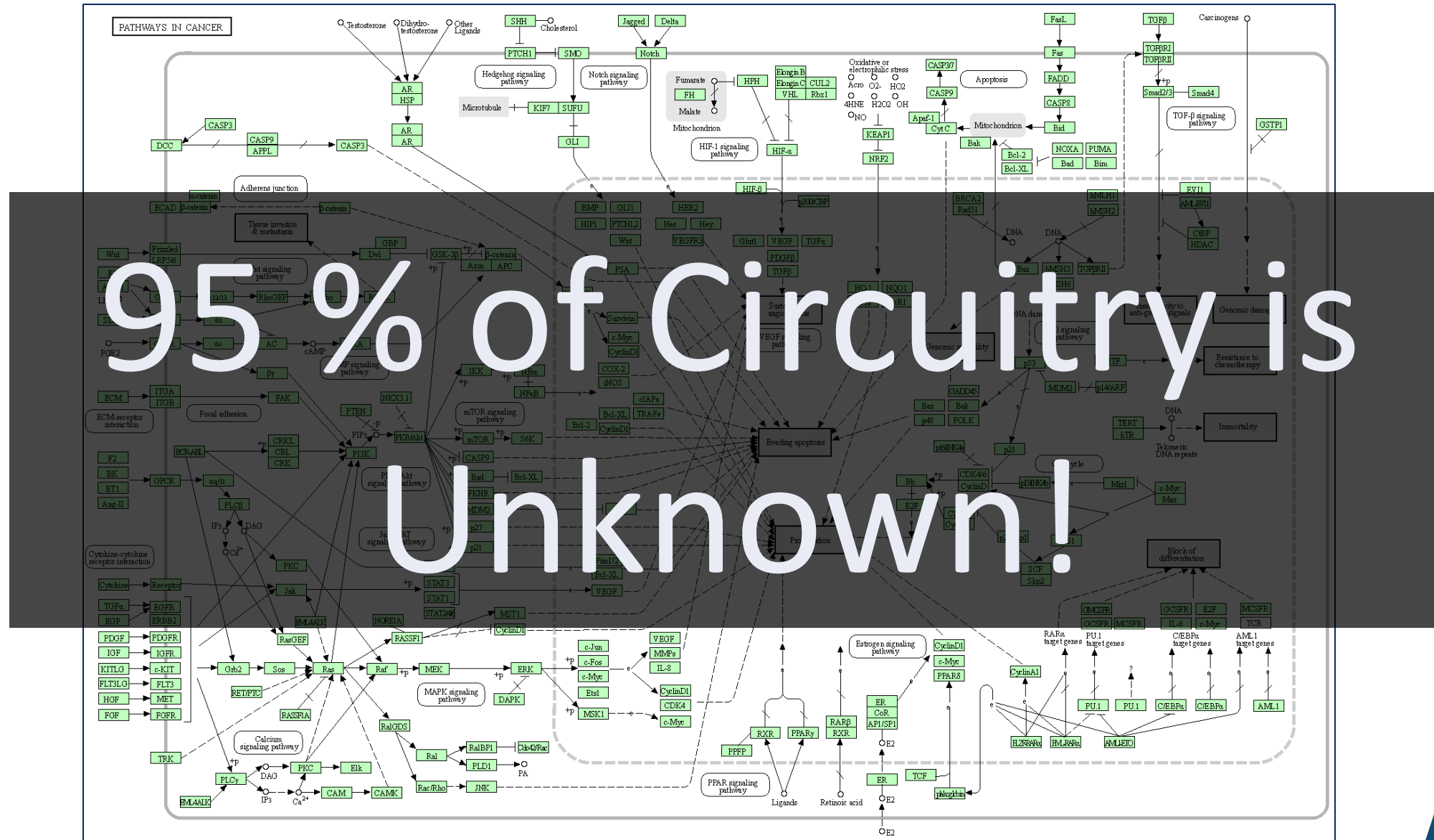
Bruce W. Church PhD

Feb 29th, 2024

Genetic Circuitry in Cell Replication of Cancer



Genetic Circuitry in Cell Replication of Cancer



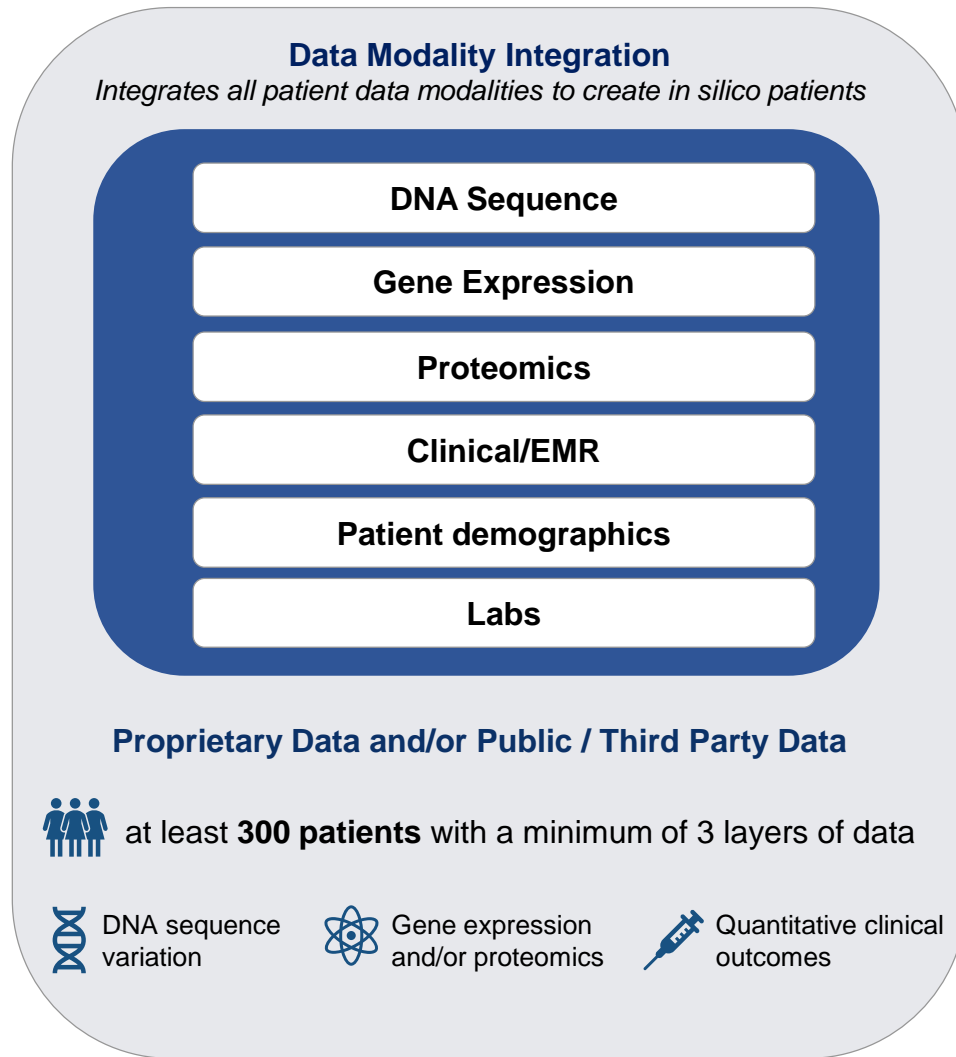
What is Causal Learning?

Correlation: Answers the question
“What happens when I see”

Causation: Answers the question
“What happens when I do”

Unlike correlation, which asks ‘is A related to B?’, causal inference tests – in parallel – a vast number of hypotheses of the form ‘does A cause B?’

Multi-omic Data



Aitia Data Partners Include

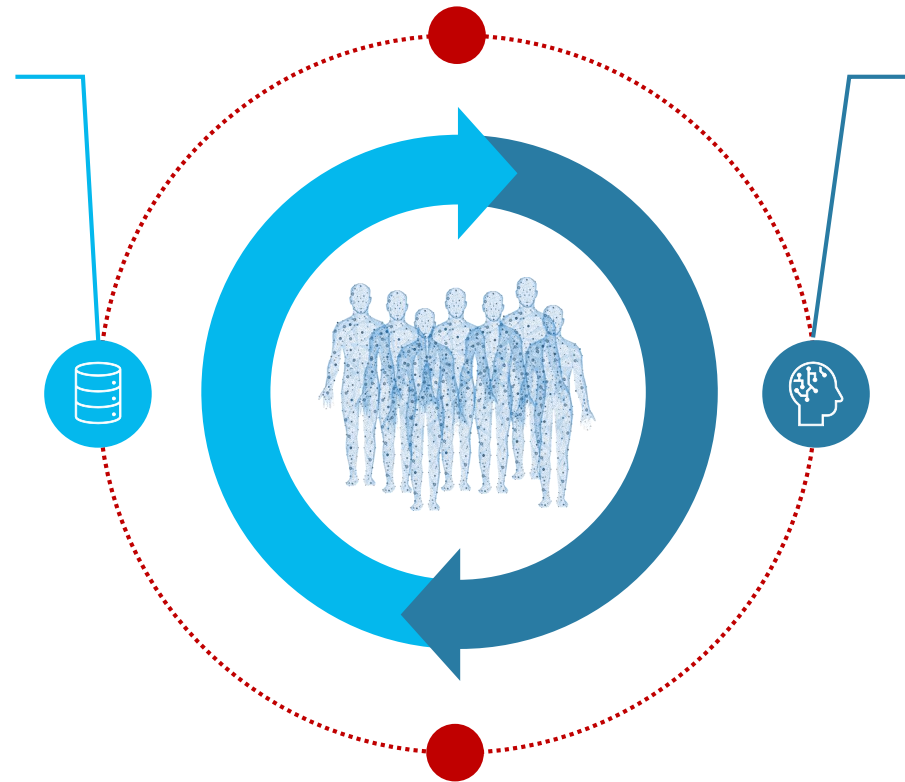
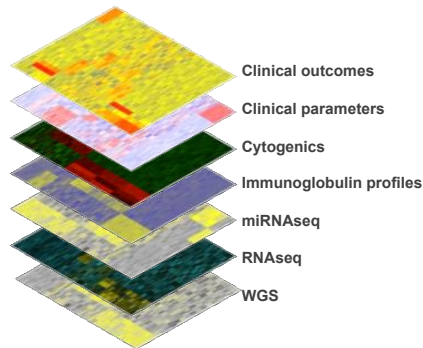


The Gemini Digital Twins

Aitia's *Gemini Digital Twins* are *computational representations of disease that capture genetic and molecular interactions that causally drive clinical and physiological outcomes*

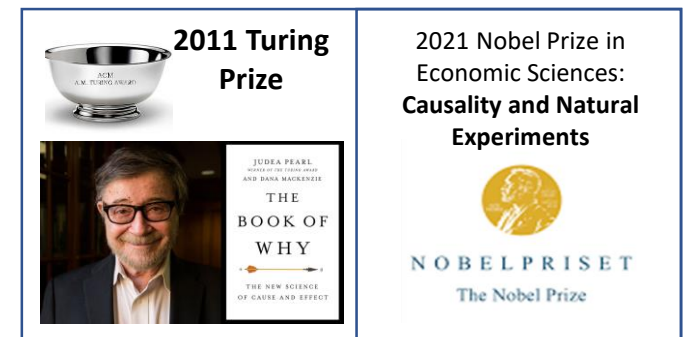
Scaled Multi-Omic Human Datasets

With a large and growing set of deep data partnerships across oncology, neurodegeneration, immunology and cardiology, Aitia has achieved the critical mass of human-derived multi-omic data necessary to build Gemini Digital Twins at scale



Causal Artificial Intelligence

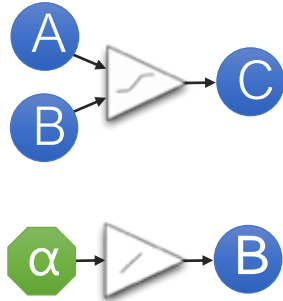
Gemini Digital Twins are built on top of REFS, Aitia's proprietary causal AI platform, opening the door for analyses beyond statistical correlation to a true, fully-digital representation and simulation of underlying biological mechanisms



How REFS™ Works

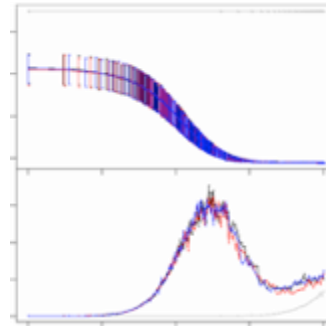
REFS™ proceeds in three steps: enumeration, optimization, and simulation. From an ensemble of network models, simulation results predict which variables and relationships in the data drive the outcomes.

Enumeration



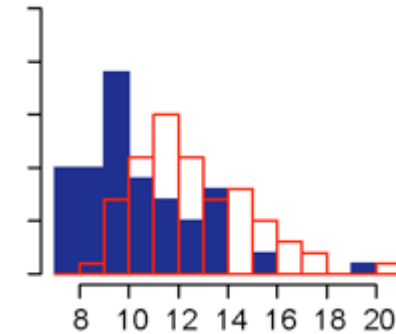
Individual network fragments are scored based on the full distribution of parameter values

Optimization



A globally optimal ensemble of networks is found by the Metropolis Monte Carlo algorithm

Simulation



Simulations are run across the ensemble of networks to discover the causal drivers of response

[Transparent Mathematical Methods](#) The mathematics behind REFS™ are well-documented in the literature. What sets REFS™ apart is its proprietary, efficient and scalable supercomputer implementation.

How Aitia Creates Gemini Digital Twins

Rich Data
(Real Example)



The single most comprehensive multi-omic CVD dataset, anchored in genomics

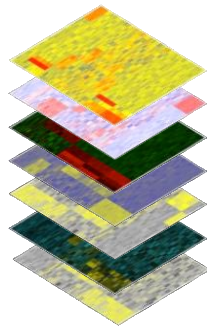
7,700+
Patients



from



48
Clinical Sites



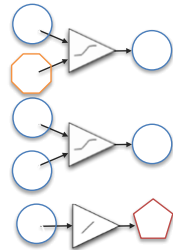
WGS
DNA
RNA-Seq
Proteomics
Metabolomics
Lipidomics
Blood Biomarkers

Genes & molecules	Patients						
	P1	P2	P3	P4	P5	...	PN
A	2.0	3.6	4.6	1.2	8.9	4.6	
B	6.0	3.1	2.6	4.7	6.3	3.9	
C	4.4	4.7	7.9	3.5	6.6	4.6	
D	3.0	2.9	2.0	3.6	4.6	2.6	
E	2.6	4.7	6.3	2.0	2.0	2.5	
F	9.0	2.9	2.0	3.6	5.0	2.6	
G	4.4	4.7	7.9	3.5	6.6	6.6	

Data Frame

Causal AI
(REFS Platform)

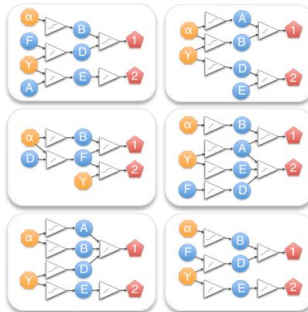
Enumeration



Trillions of individual network fragments are scored based on the full distribution of parameter values

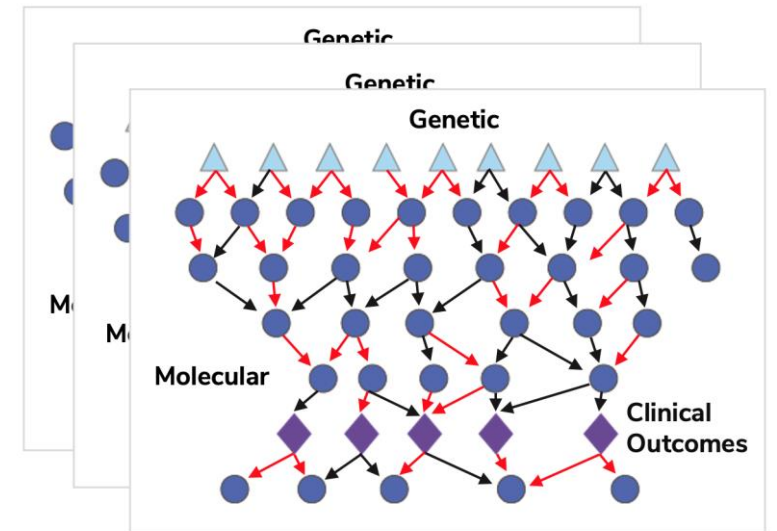
REFS

Optimization



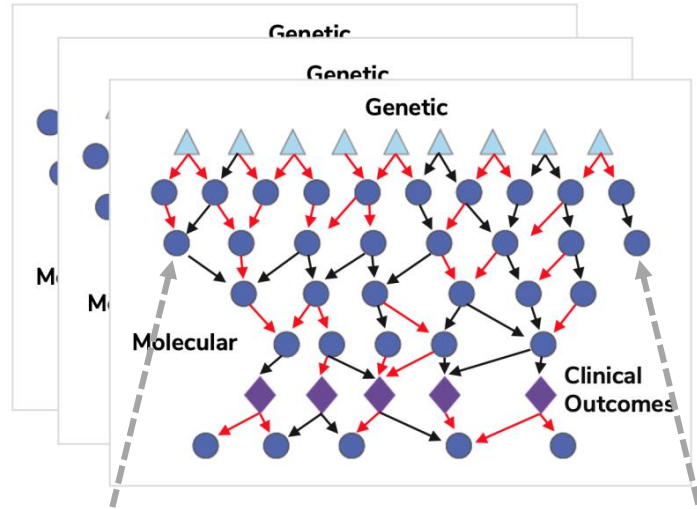
A globally optimal ensemble of networks (1000) is sampled by Metropolis Monte Carlo

Digital Twins

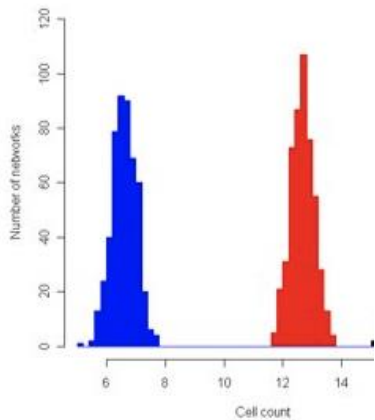


Using the Gemini Digital Twins

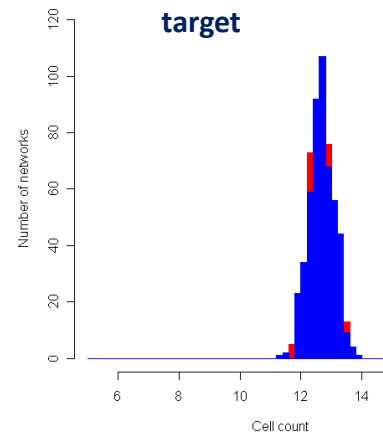
Discovery of Novel Drug Targets & Drugs



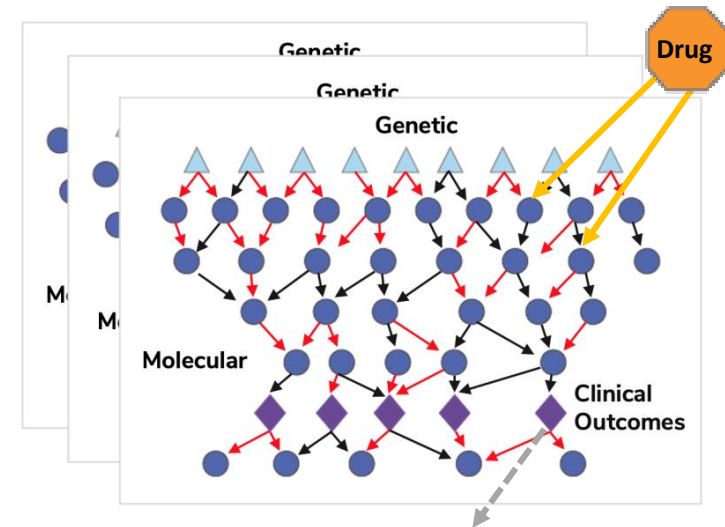
Good potential drug target



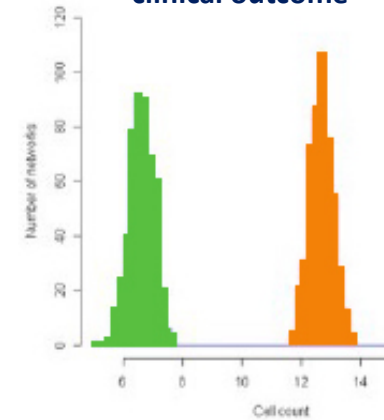
Poor potential drug target



Simulating Drug Treatment to Discover Responding vs Non-Responding Patients



Impact of drug on clinical outcome



Validated Results From Gemini Digital Twins



Deep dive into select case studies

Target and Drug Discovery Case Studies

Drug Simulation Case Studies

Neurology



Alzheimer's Disease Target and Drug Discovery

- Nine (9) Aitia-predicted targets validated with pre-clinical assays by partner Merck



Biomarker Identification in Parkinson's Disease

- Aitia models classified patients as having slow, moderate, or fast progression rates, which could reduce enrollment need by up to 20%

Oncology



Prognostic Markers in Multiple Myeloma

- Causal inference of biology surrounding PHF19 identifies potential drug targets



Head-to-Head In Silico Multiple Myeloma Trials

- In silico trial Drug X vs Velcade in first line reveals superiority of Drug X over Velcade with 51/2 mos PFS & 6 mos OS benefit

Cardiovascular Disease



Atherosclerotic Disease Drug Target Discovery & Validation

- Gemini models discovered a novel target in the elimination of larger Lp(a) particles
- Results validated in a knockout model of the receptor



Discovery of Biomarkers of Coronary Atherosclerosis

- Identified LDL-TG as a causal driver in CAD
- Hepatic lipase is directly upstream and represents a new target for CAD



Identified Novel Predictors of Major Adverse Cardiovascular Events (MACE)

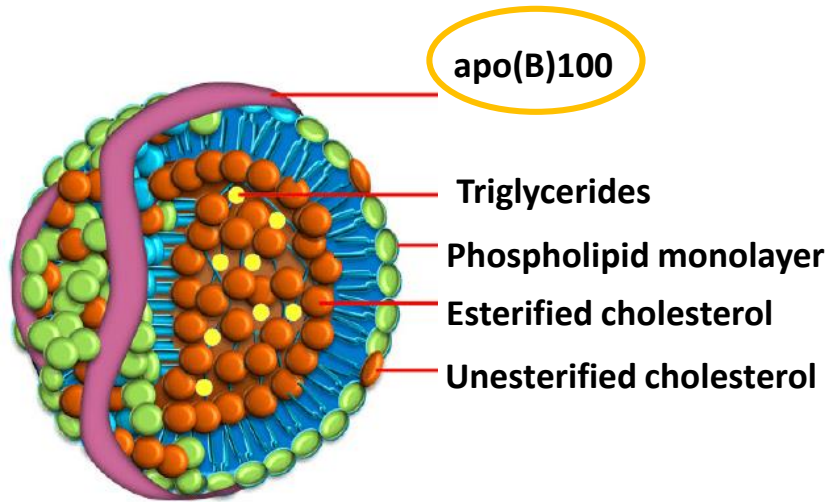
- Using REFS, Amgen predicted causal drivers of MACE and identified Inflammatory and CV dysfunctions as key drivers
- Identified prognostic biomarkers that were superior to current risk prediction

Gemini Digital Twins in Cardiovascular Disease

Application of Gemini Digital Twins in Cardiovascular Disease to Discover Breakthrough Drug Targets and Drivers of Disease

Discovery & Validation of Breakthrough Drug Target Driving Atherosclerotic Disease

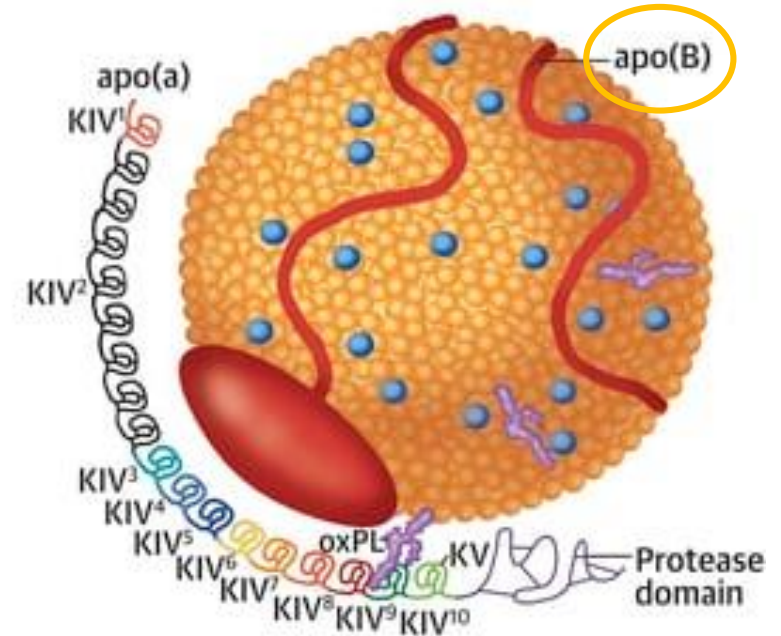
TG Rich LDL Particle



Atherosclerosis



Lp(a)

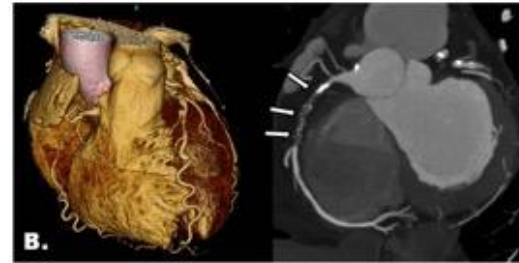


Data Fueling the Gemini Digital Twins in Cardiovascular Disease from Aitia Partner G3 and The GLOBAL Study

Control

Case

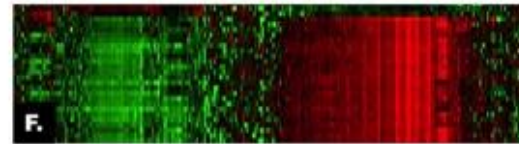
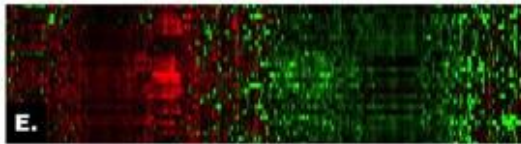
Phenotyping
Cardiac CT



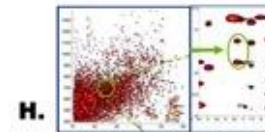
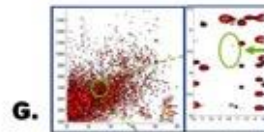
DNA
Whole Genome Sequencing



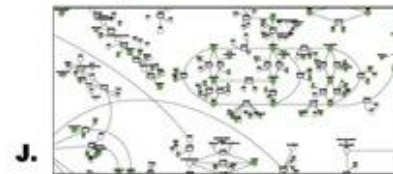
RNA
Transcriptome Sequencing



Proteome
Proteomic Profiling

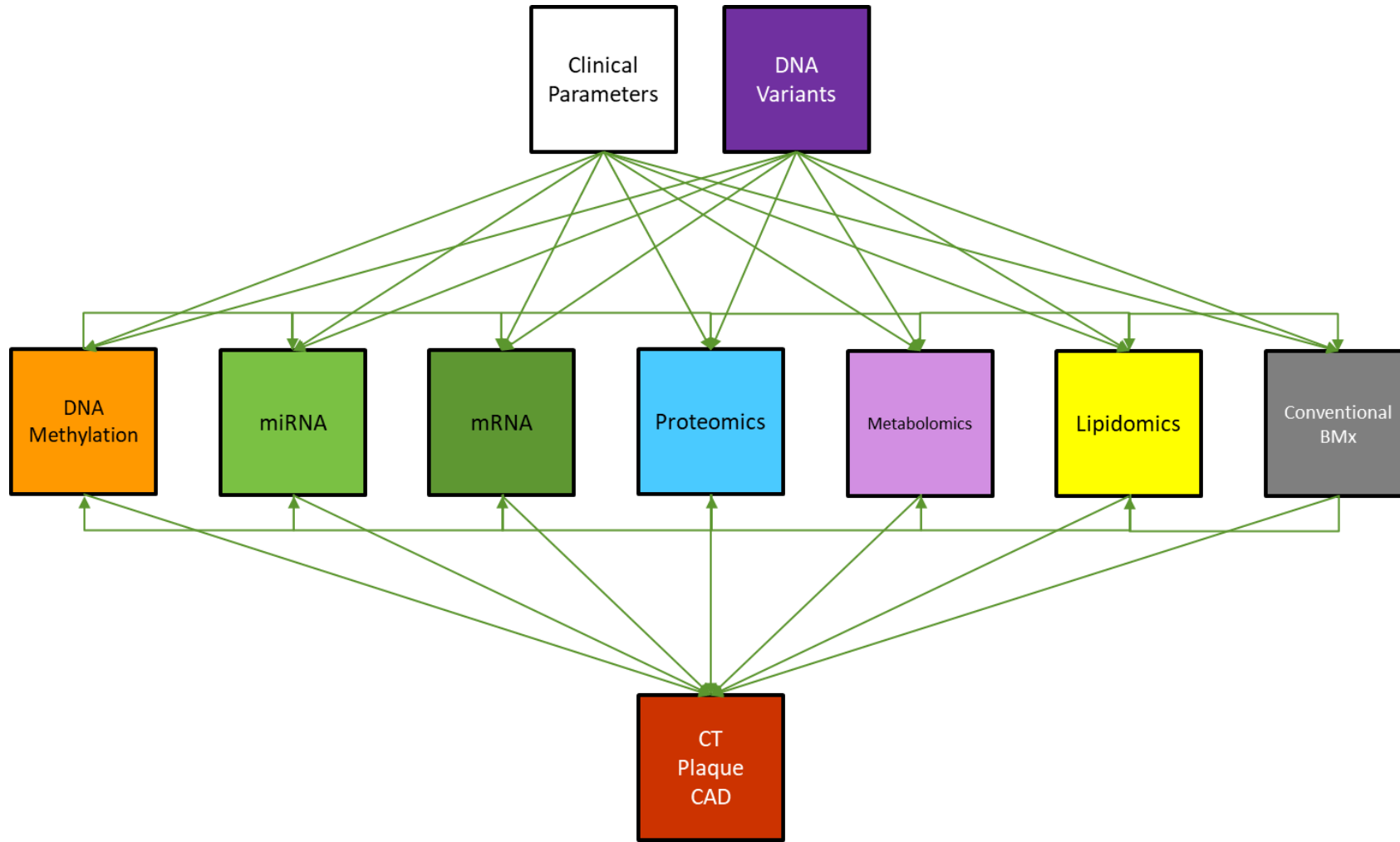


Metabolome and Lipidome



Method	Number of Data Points Per Person
Whole Genome Sequencing	3.2 billion
DNA Methylation	500,000
RNA Sequencing (miR, mRNA)	130,000
Proteomics	3,000-4,000
Metabolomics	1,000-2,000
Lipidomics	500-1,000
Blood Biomarkers	300-400
Cardiac Imaging	4,000-5,000 voxels

Reverse-Engineering the Gemini Digital Twins in Cardiovascular Disease



Data Frame

- 10^5 Variables
- 300 Patients

Reverse Engineering

- 10^{18} Network Fragments
- $(10^{13})^{(10^5)}$ Networks
- 6×10^{11} Networks Sampled

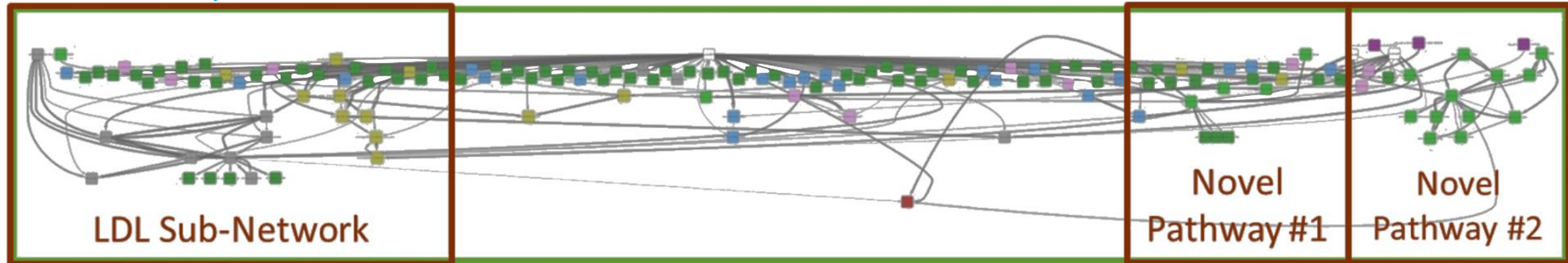
Forward Simulation

- 10^{10} pairwise causal connections evaluated

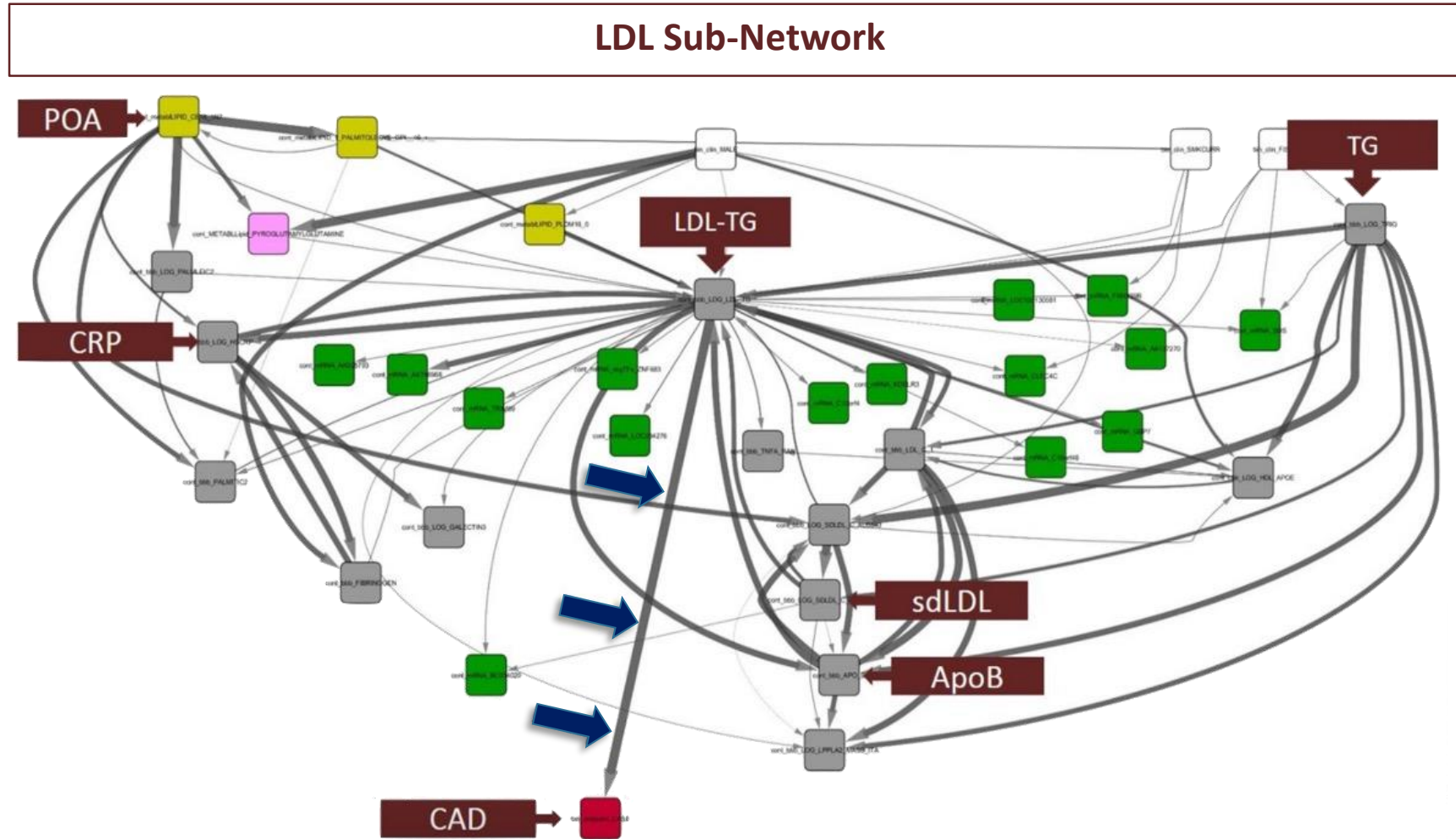
Cloud Scaled Computation

- 256 cores (AWS C3.8xLarge)
- 6 days end-to-end run time

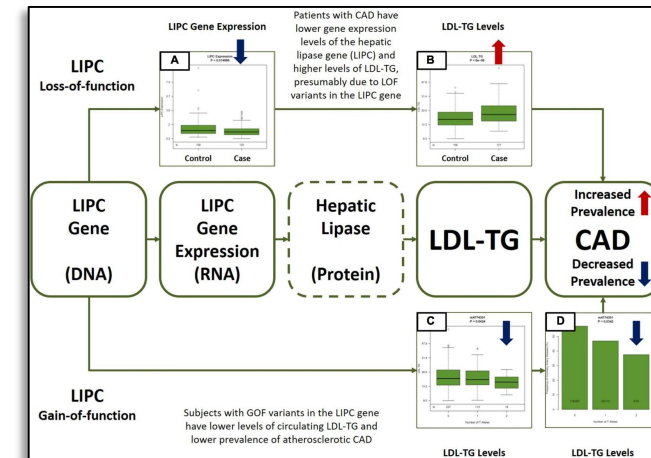
Gemini Digital Twins Reveal Known and Novel Biological Pathways of Atherosclerosis



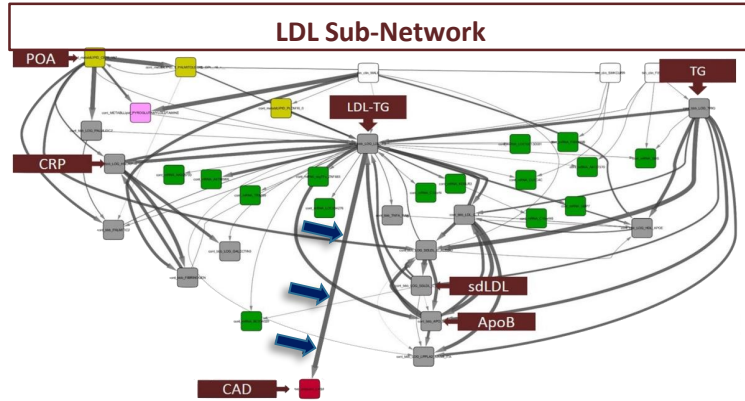
Gemini Digital Twins Identify Hepatic lipase and LDL-TG axis as an important pathway in ASCAD



- Clinical Parameters
 - Lipidomics
 - Metabolomics
 - RNA-Seq
 - Conventional Biomarkers
 - Outcome
- ▬ Edge frequency

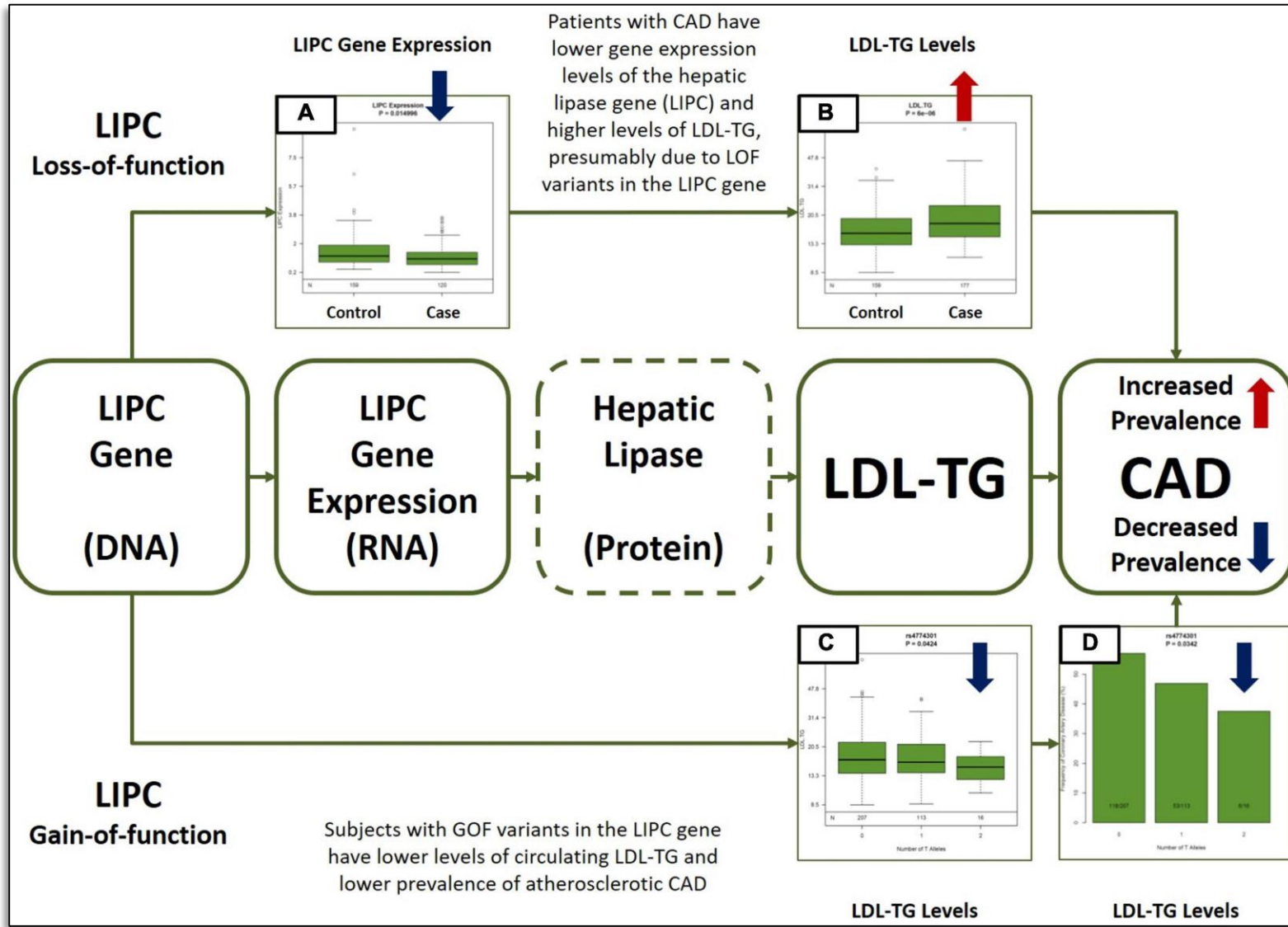


Gemini Digital Twins Identify Hepatic lipase and LDL-TG axis as an important pathway in ASCAD

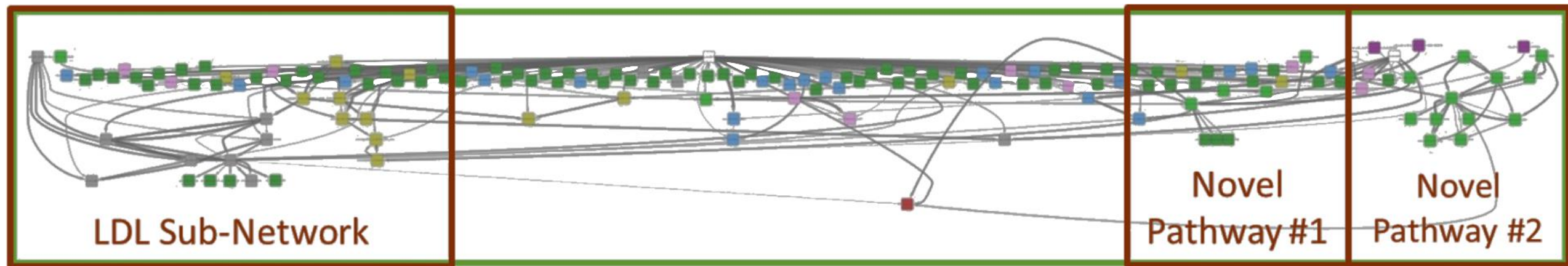


- Clinical Parameters
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- Outcome

Edge frequency



Gemini Digital Twins Reveal Known and Novel Biological Pathways of Atherosclerosis

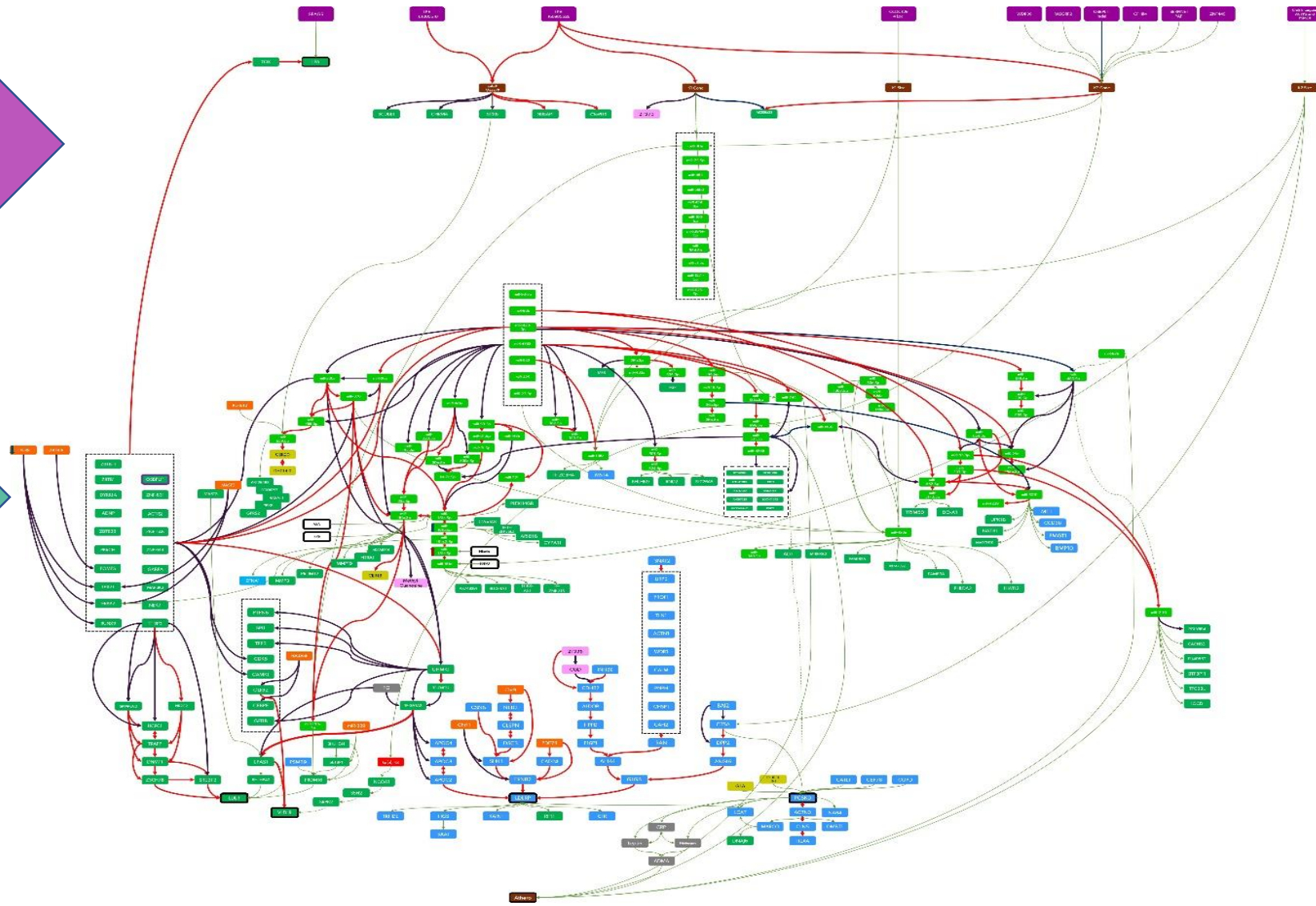


Gemini Digital Twins Network Explaining the Regulation of Serum Lp(a)

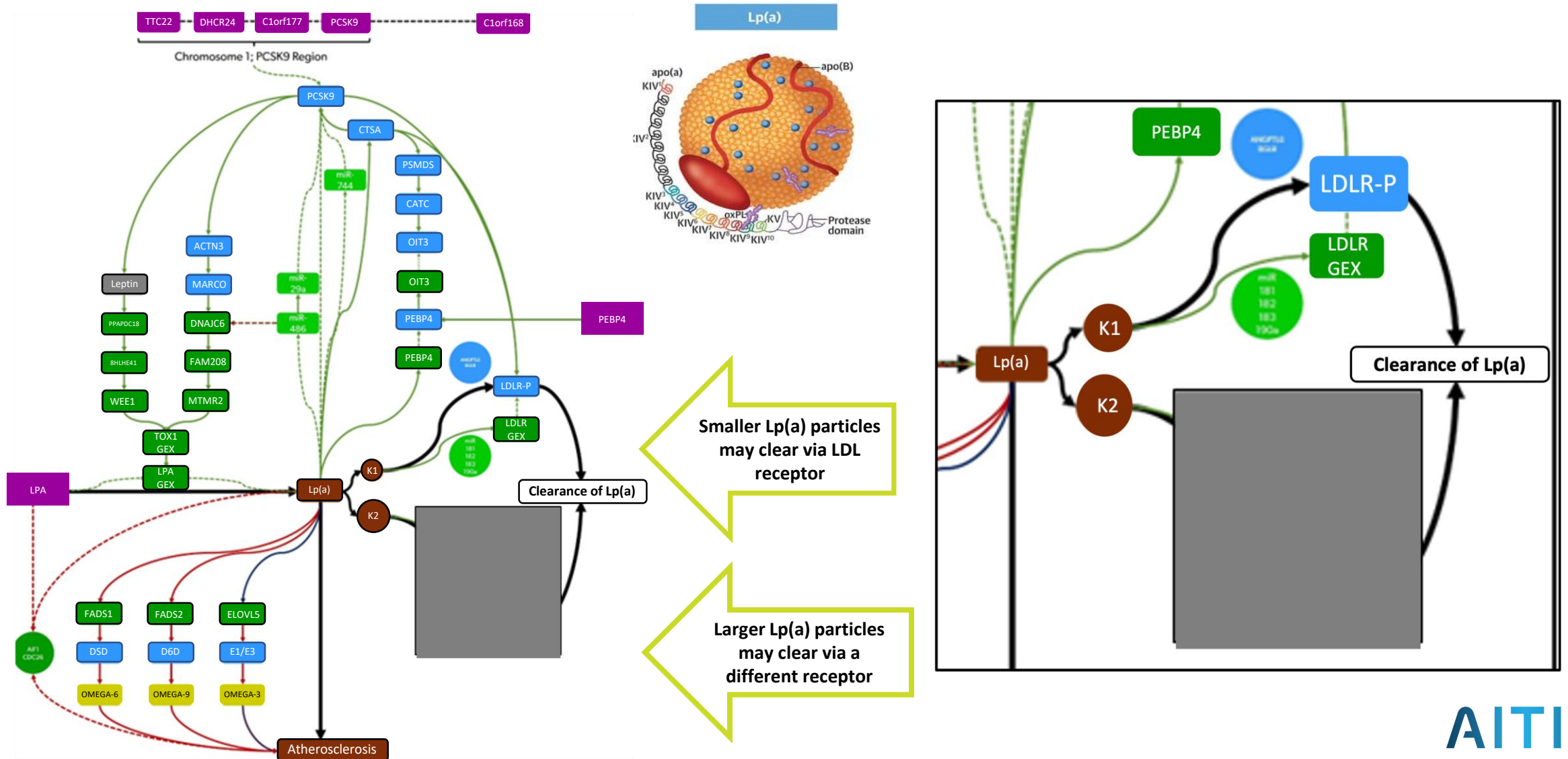
LPA, LDLR, PCSK9 and RECX genes drive network

Multi-omic causal network

Atherosclerotic Phenotype

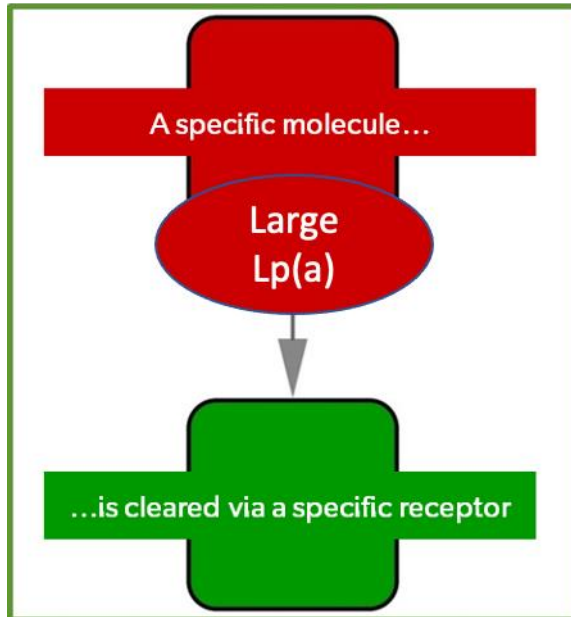


Gemini Digital Twins Network Suggests that Elimination of Lp(a) is Size Dependent

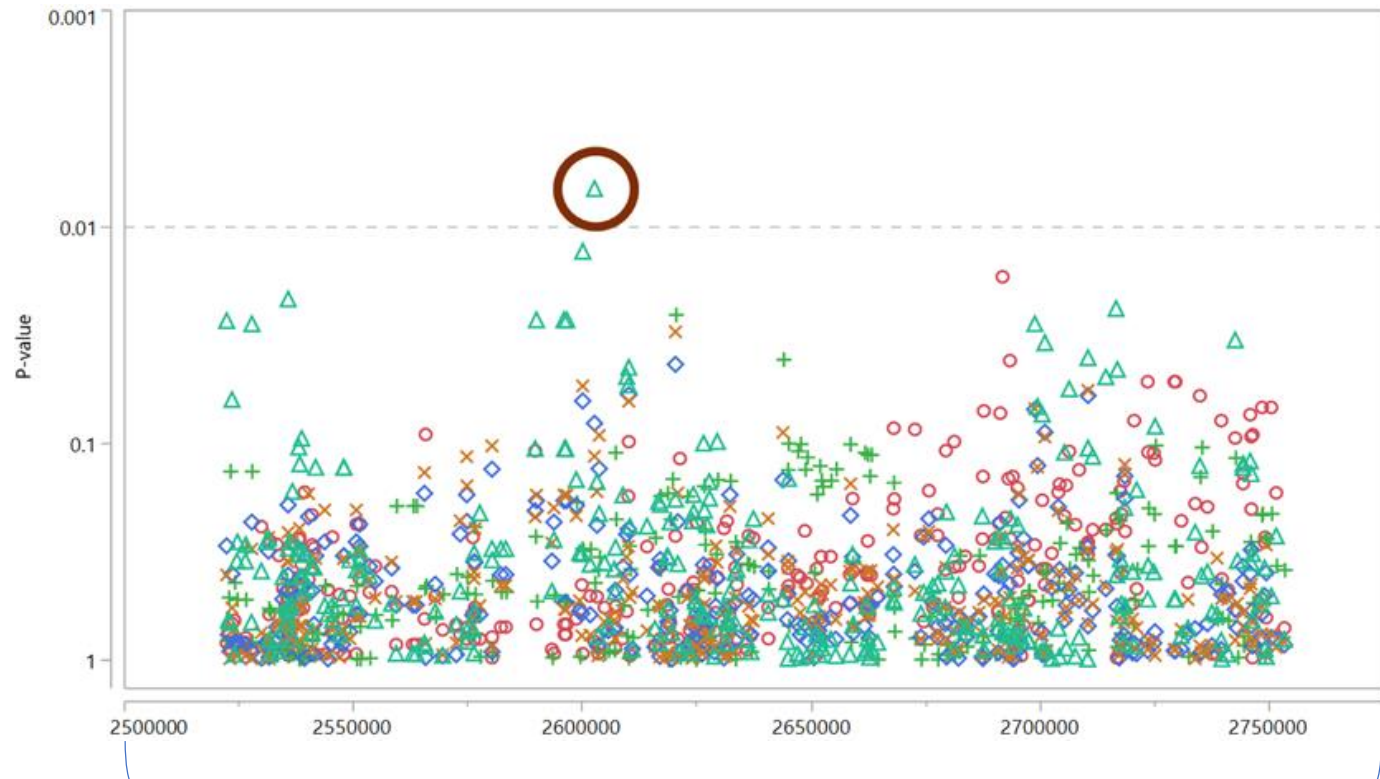


Discovery of Novel Potential Target for Lp(a) Regulation

Gemini Digital Twin in Cardiovascular Disease pointed to the role of a specific receptor in the elimination of larger Lp(a) particles at the *mRNA level*



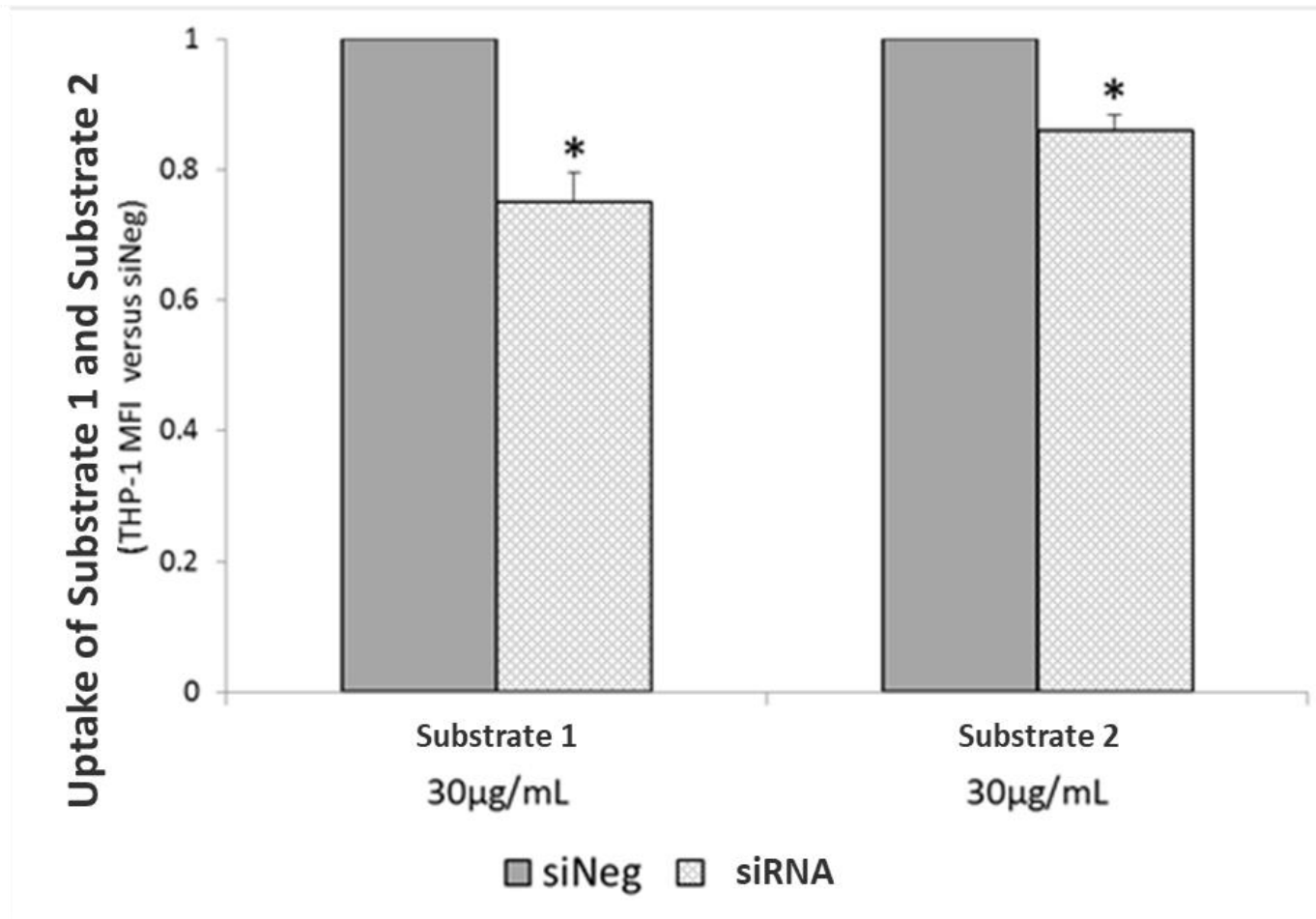
Then, based on the *whole genome sequencing data*, it was demonstrated that circulating levels of large Lp(a), but not small Lp(a), were associated with the gene encoding the novel receptor



Gene encoding the novel target

in vitro Validation by siRNA Knockdown

Inhibition of Target Receptor by siRNA Confirms the Reduction of Uptake of its Substrates, as Predicted by Aitia-G3

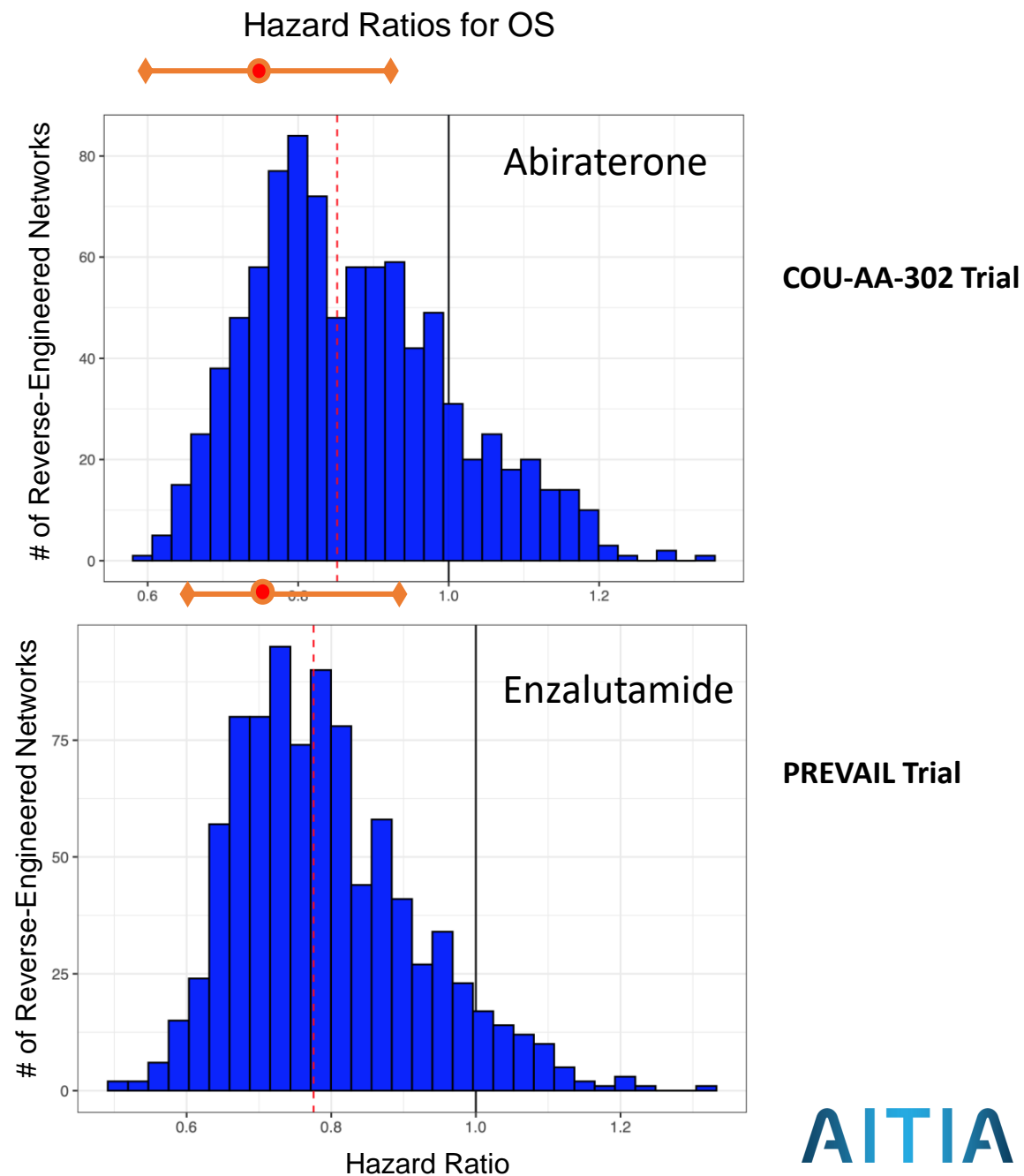


Gemini Digital Twins: Towards Trial Simulation and Patient Selection

Application of Gemini Digital Twins in Prostate Cancer
to simulate clinical trials and identify patient

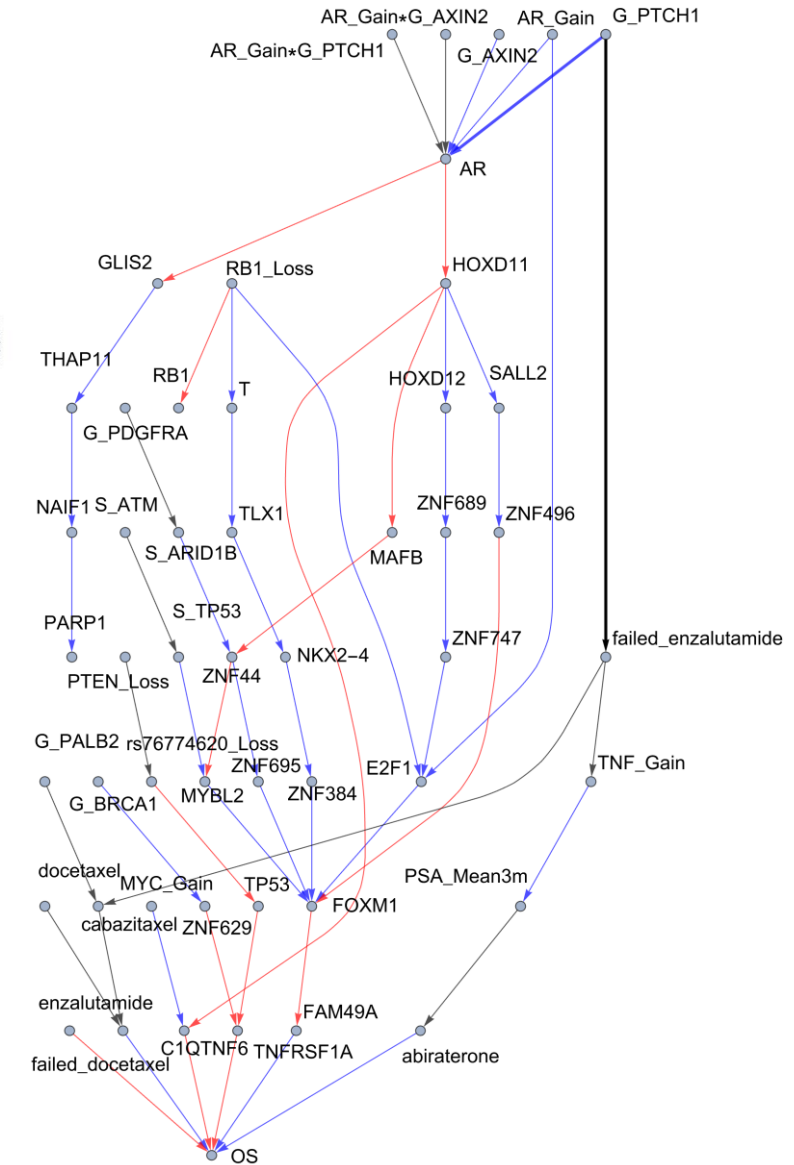
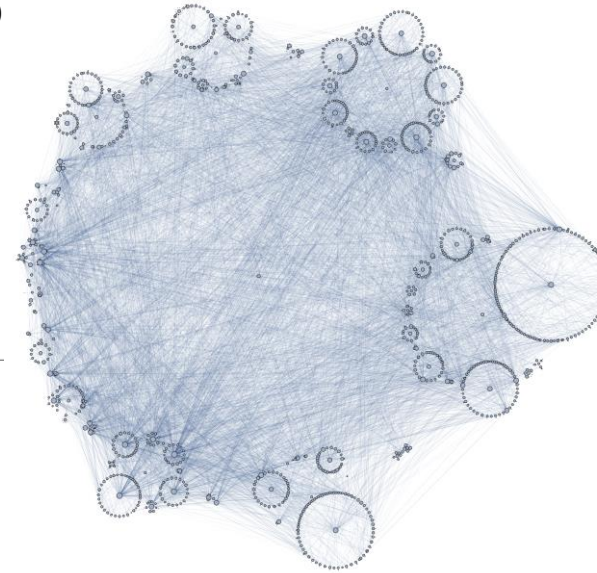
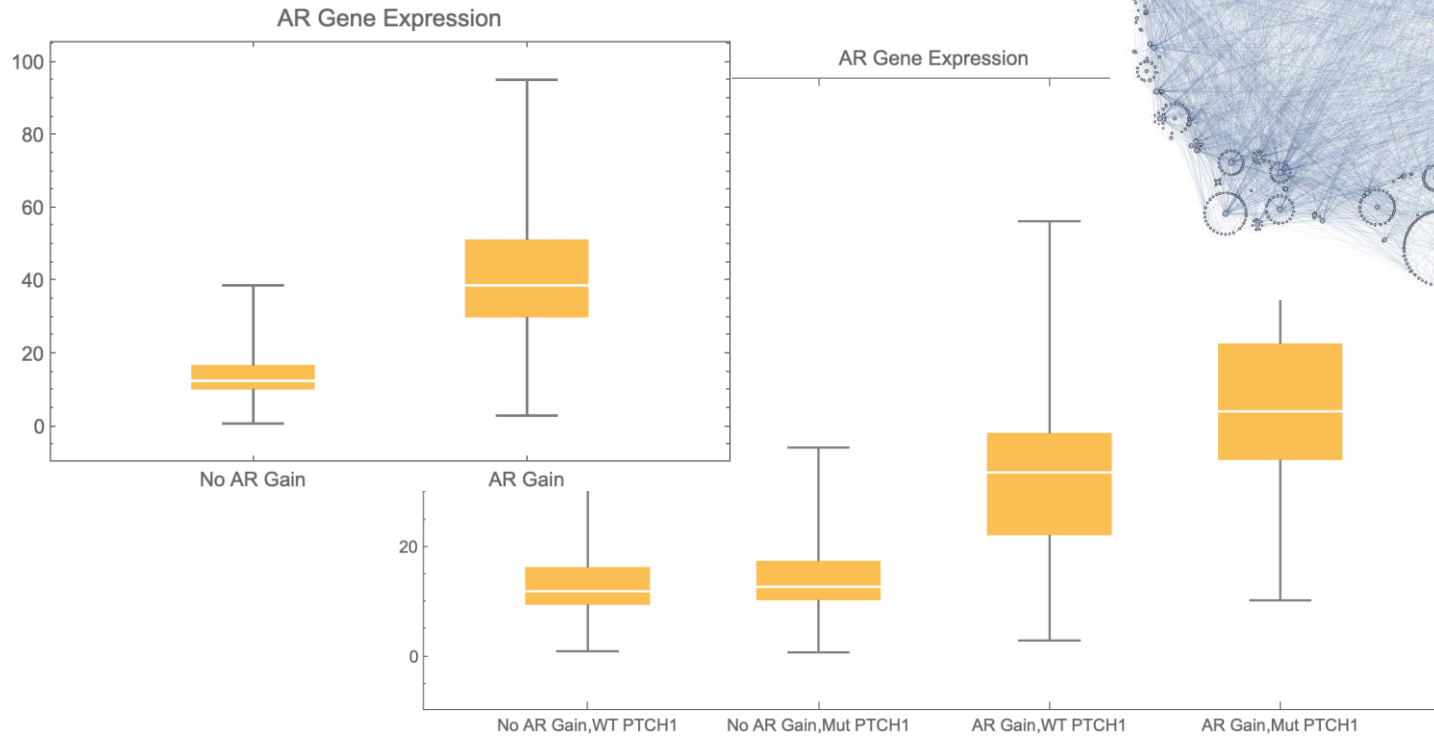
PC Gemini Digital Twin Validation

- *In Silico* Head to Head Trials
Reproduce Metastatic Castrate Resistant trials for
 - Abiraterone -- COU-AA-302 Trial
 - Enzalutamide – PREVAIL Trial
- Digital twin – counterfactual simulations of 300 patient pairs on treatment vs ADT
- Reproduced direction and magnitude of both trials



PTCH1 germline mutation predicts enzalutamide resistance

“PTCH1 and AXIN2 Modulation of AR Copy Numb Effects on AR Gene Overexpression in Metastatic Castration-Resistant Prostate Cancer (mCRPC)”



AITIA

Thank you!

- Unlock the Biological Complexity of Human Disease
- Drive Creation of the Next Wave of Breakthrough Drugs

For questions, please contact:
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