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Digital Twins and the Discovery of New Drugs for Rare Diseases

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What problems do we have to solve to cure rare and other diseases?

"What is the **right drug target**?"

"What is the **right drug** against the right target?"

"Which **patients** will respond to this drug?"

Where can AI play a transformative role in solving these problems?

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AI has made significant strides in drug design, including the optimization of small molecule and antibody design

"DALL-E 2 of biology" designs proteins for new drugs

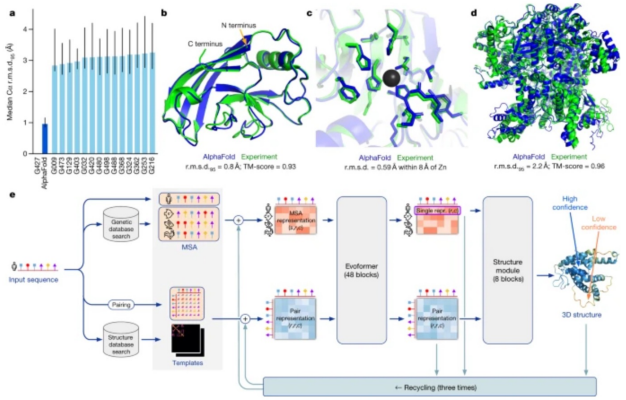
"Now that we have this ability, the possibilities of what we can produce are endless."

nature

Article | Open Access | Published: 15 July 2021

Highly accurate protein structure prediction with AlphaFold

Fig. 1: AlphaFold produces highly accurate structures.



MIT Technology Review

Google DeepMind's new AlphaFold can model a much larger slice of biological life

AlphaFold 3 can predict how DNA, RNA, and other molecules interact, further cementing its leading role in drug discovery and research. Who will benefit?

By James O'Donnell — May 8, 2024

Google The Keyword — Latest stories | Product updates | Company news

AlphaFold 3 predicts the structure and interactions of all of life's molecules

May 08, 2024
6 min read

Introducing AlphaFold 3, a new AI model developed by Google DeepMind and Isomorphic Labs. By accurately predicting the structure of proteins, DNA, RNA, ligands and more, and how they interact, we hope it will transform our understanding of the biological world and drug discovery.

FIERCE Biotech

New AI drug discovery powerhouse Xaira rises with $1B in funding

By **Annalee Armstrong** · Apr 24, 2024 6:00am

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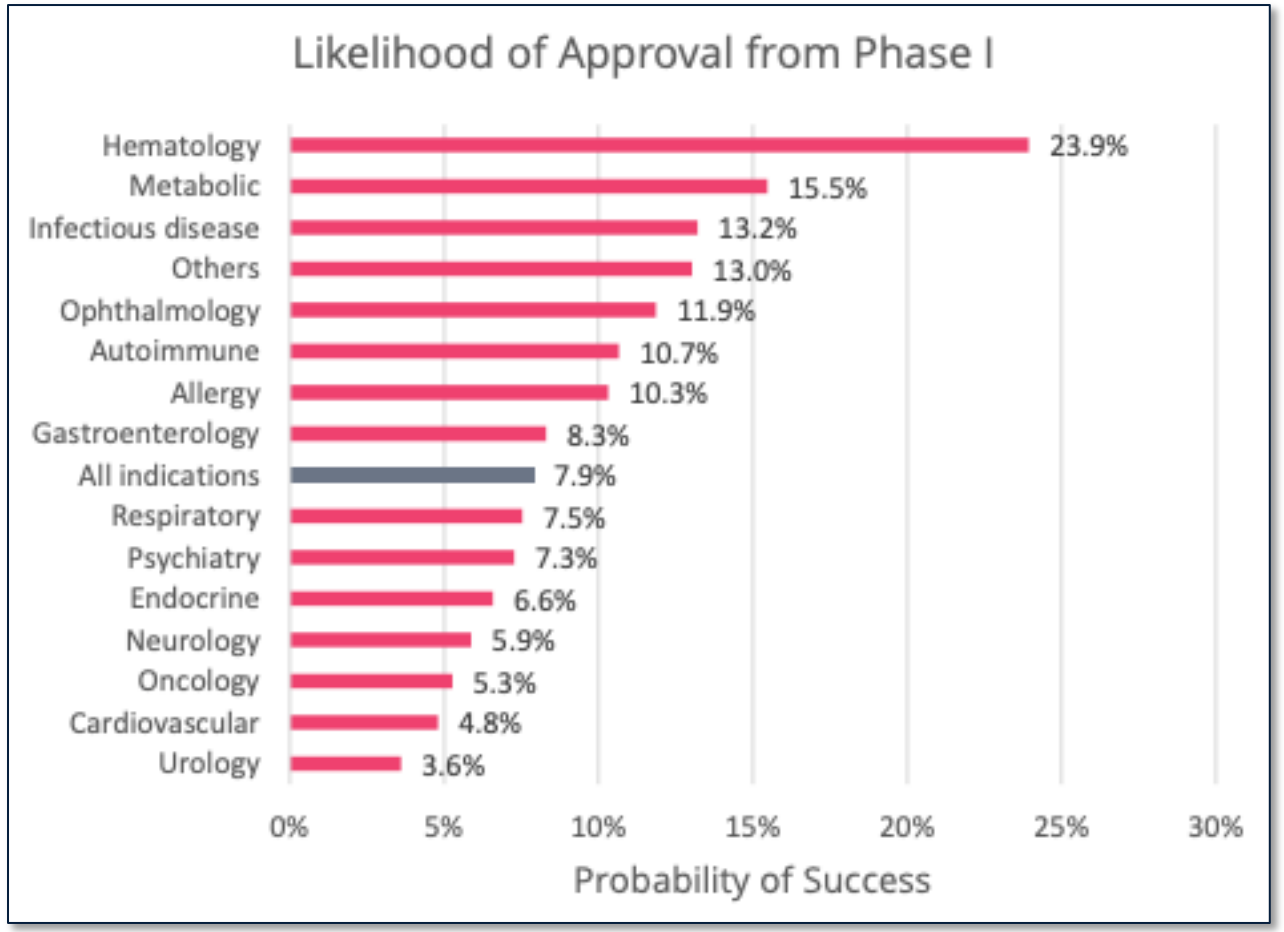
… but has struggled to make progress in discovering the right drug target and finding the right patient populations



Clinical trials success rates are ~8% across all indications

Source: Nature

Why has so little progress been made
in using AI to discover and validate novel targets
and better select patients for clinical trials?

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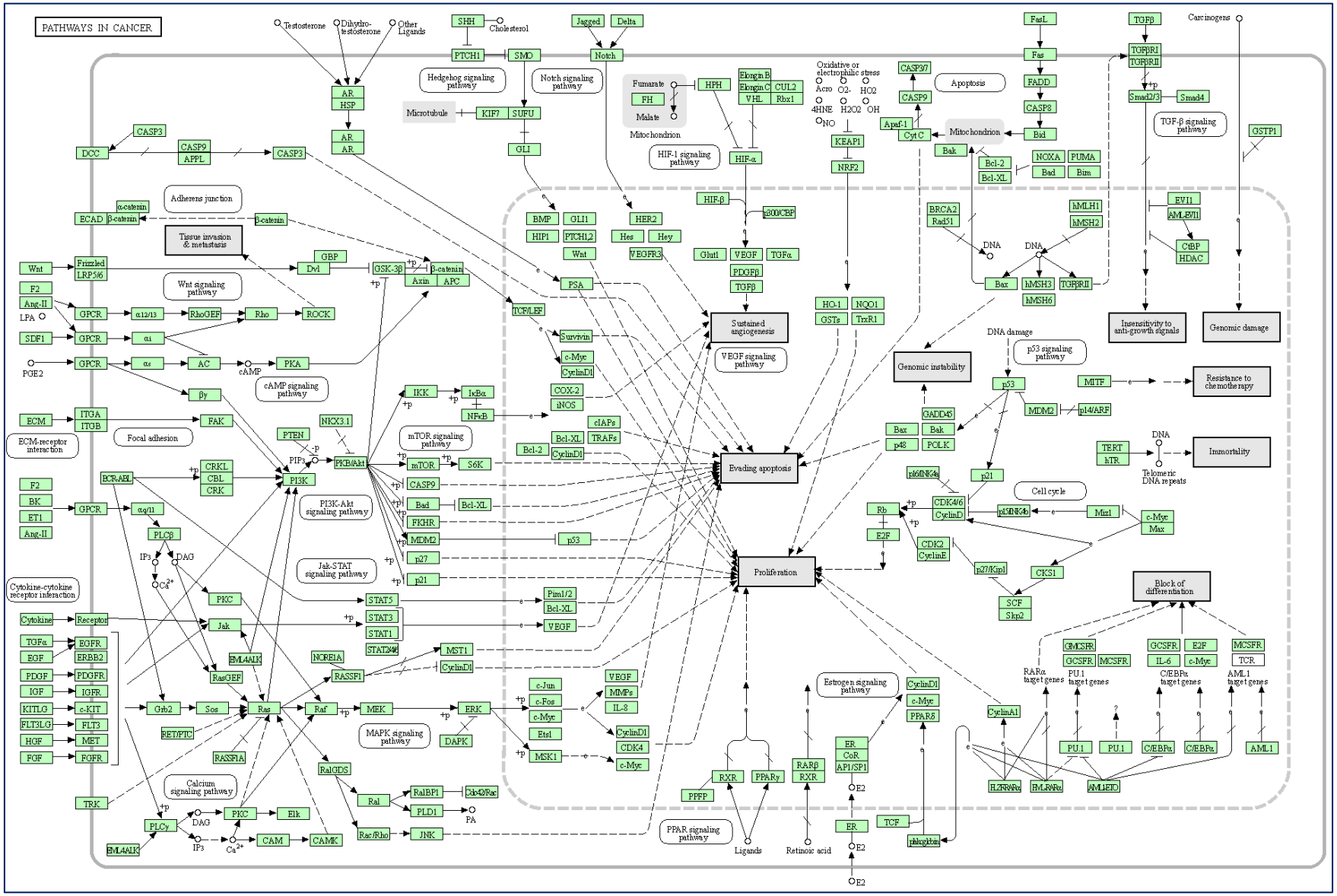
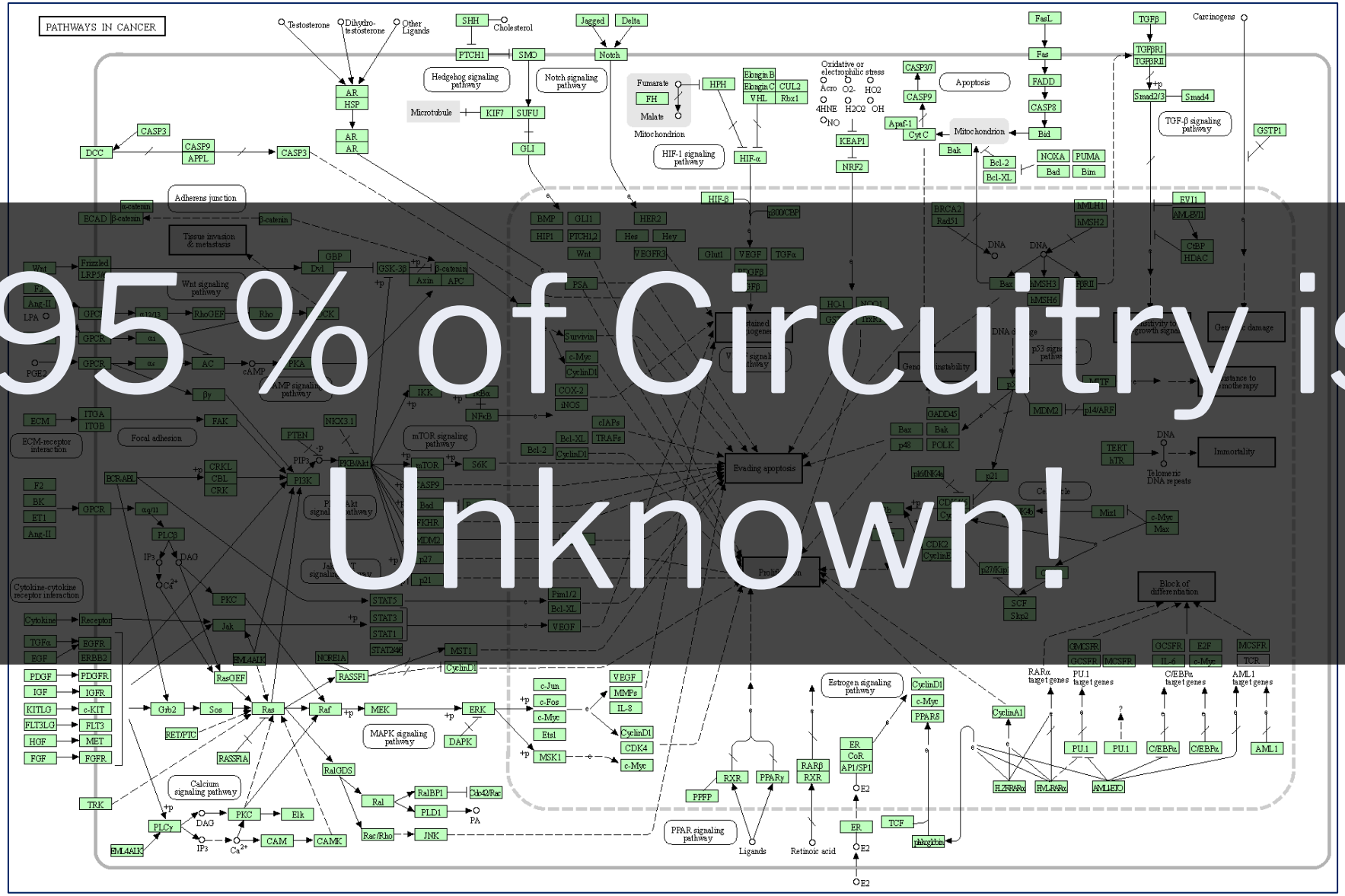
Genetic circuitry in cell replication of cancer



Genetic circuitry in cell replication of cancer



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Trends in human multi-omic data have reached a tipping point

FNIH
Foundation for the National Institutes of Health

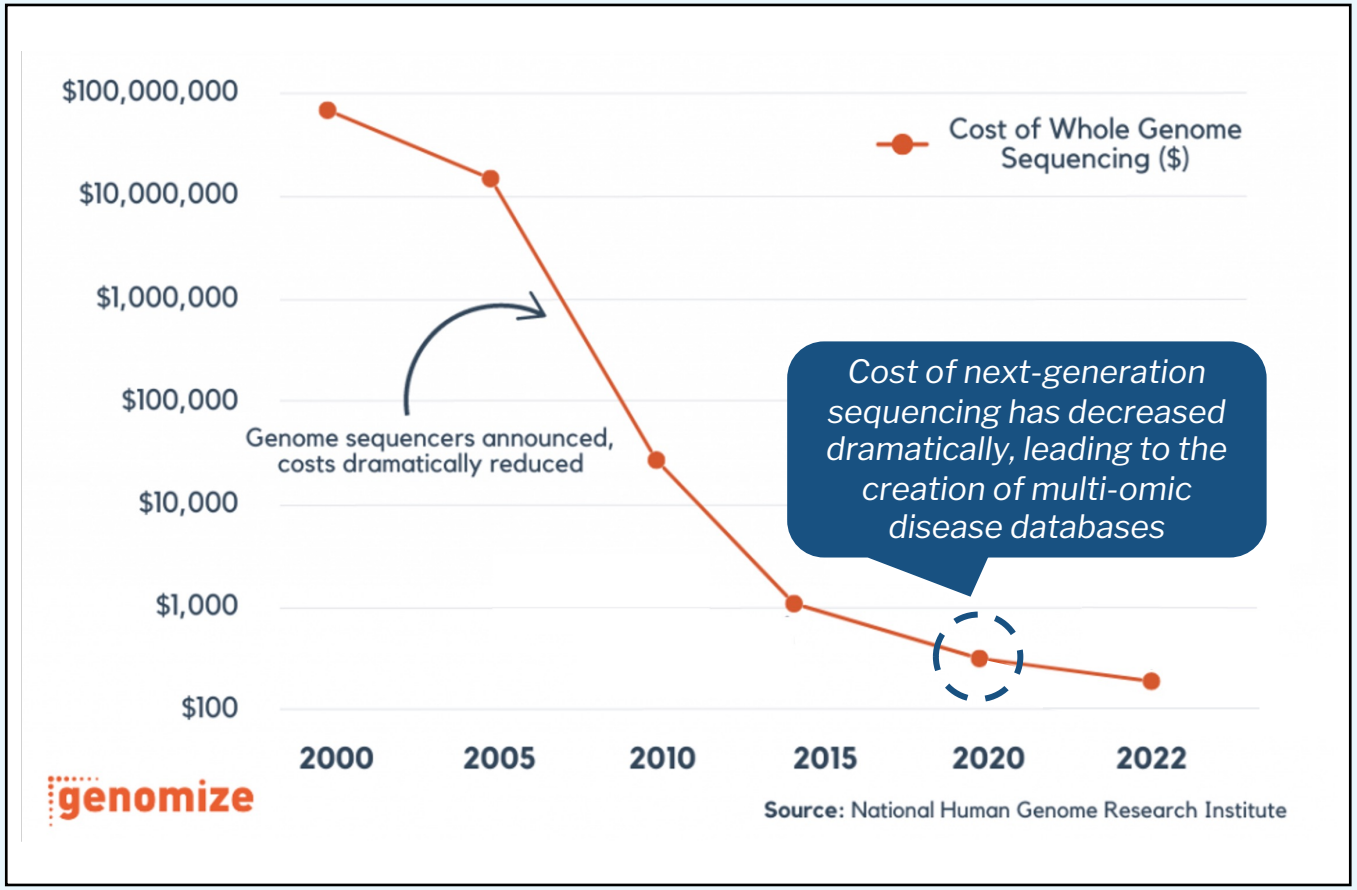
Bio-Hermes

CHDI

10x GENOMICS®

All of Us RESEARCH PROGRAM

Decreasing Genome Sequencing Costs



THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

ADNI
Alzheimer's Disease Neuroimaging Initiative

biobank uk

somalogic®

Metabolon
SMALL MOLECULES, BIG INSIGHTS™

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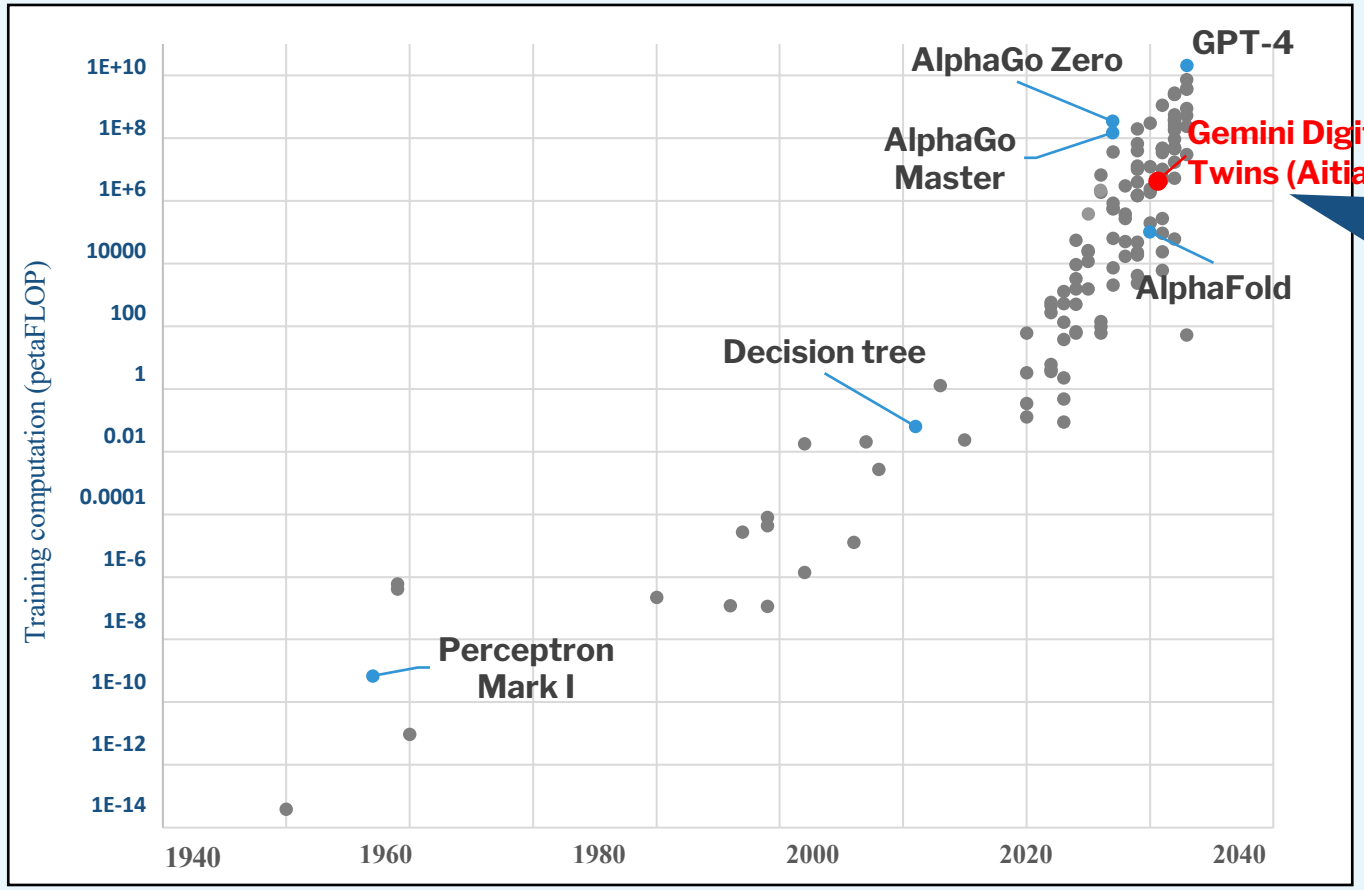
Likewise, there's been an exponential increase in computing power

Rise in Computing Power over Time



Computing power has reached critical efficiency to support roughly 3000 exaFLOPs

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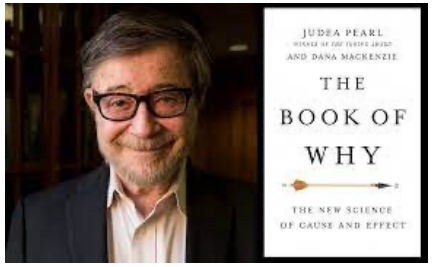
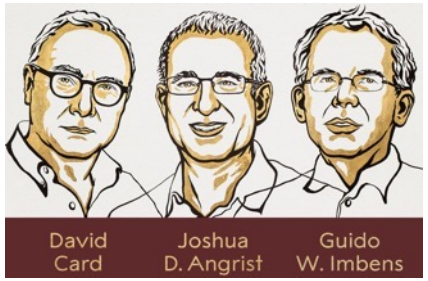
AI shifts gear with the emergence of causal AI

AI Shifts Gear with the Emergence of Causal AI



2011 Turing Prize

*"To reach the higher fruit, AI needs a ladder, which we call the Ladder of **Causation**"*
-Judea Pearl



Causality and Natural Experiments:
the 2021 Nobel Prize in Economic Sciences

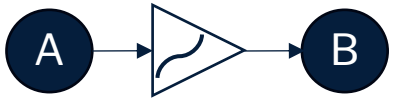
Causal AI has emerged as the **next frontier in AI**, marking a pivotal shift as the importance of **understanding causal relationships** becomes evident

Causal AI to Reverse Engineer the Hidden 95% of the Biological Circuitry

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?'



Aitia has created **REFS**, the **most powerful causal AI** and **simulation platform** for drug discovery and development; and holds the founding issued patents

Causal AI creates increasingly accurate replicas of human disease that learn directly from human multi-omic data, instead of outdated animal models and *in vitro* systems

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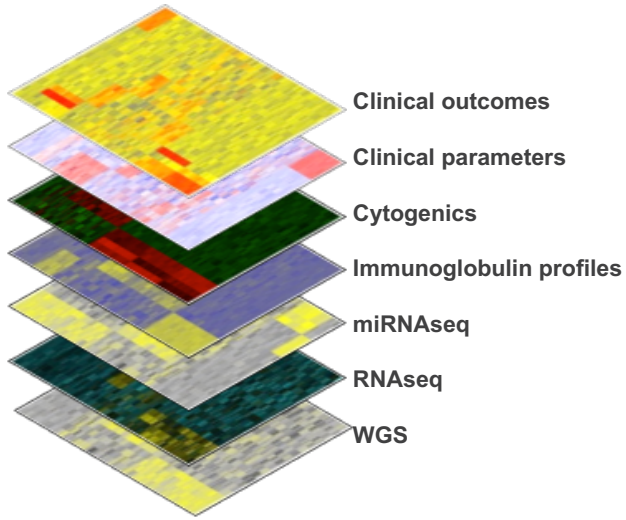
Nobel Prize Illustration by Niklas Elmehed

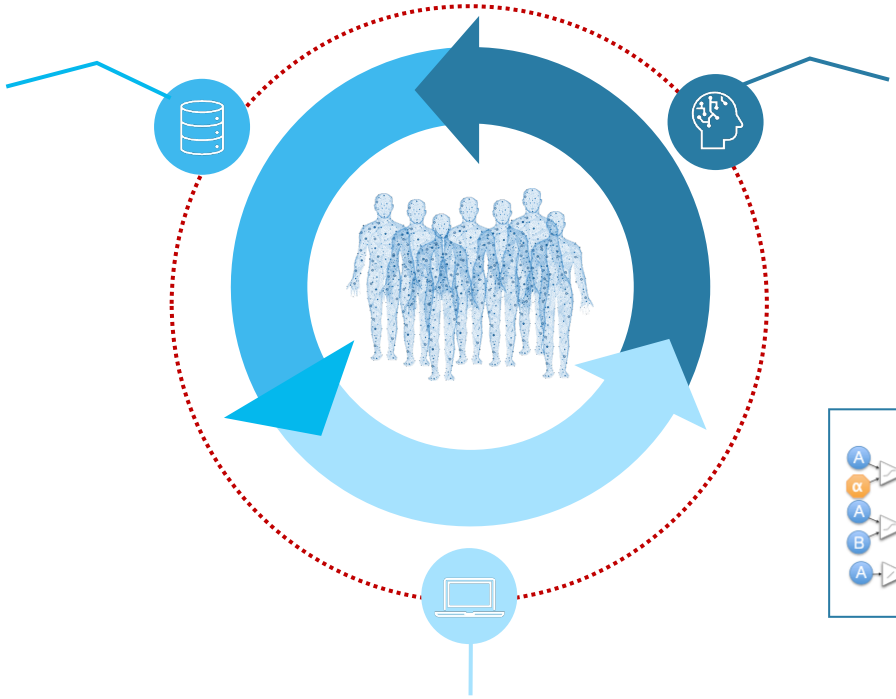
What are Gemini Digital Twins?

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

Multi-Omic Human Datasets

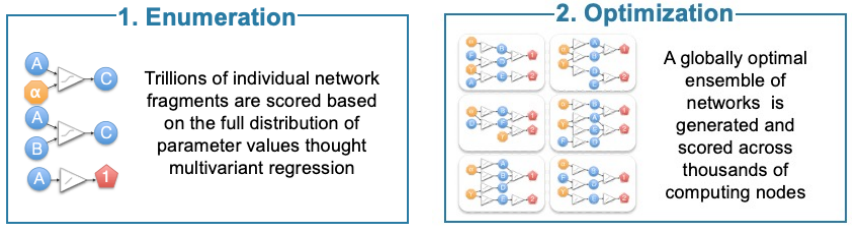
Human model systems for human therapeutics





Causal Artificial Intelligence

REFS, Aitia's proprietary causal AI and simulation platform identifies the true drivers and underlying biological mechanisms of human disease



Advances in Supercomputing

Run more computational experiments faster and more accurately
(5x greater than AlphaFold levels)

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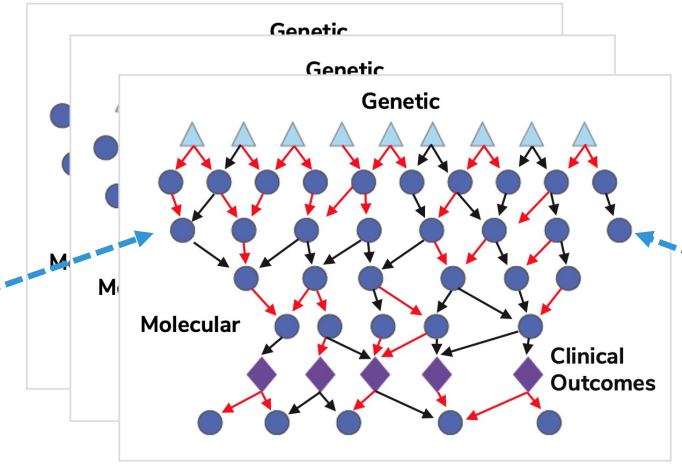
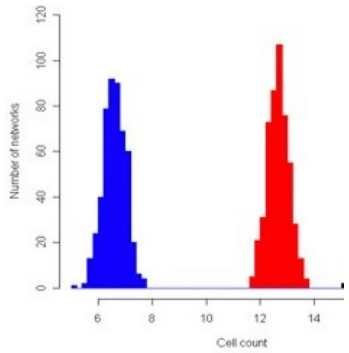
How Aitia uses the Gemini Digital Twins to simulate billions of 'experiments' to discover novel drug targets and biomarkers of response

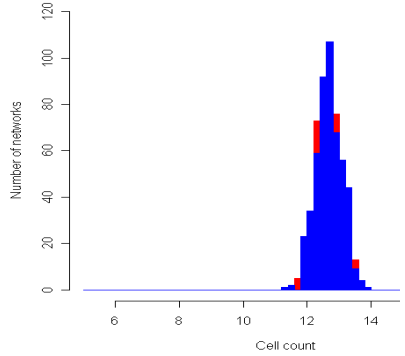


Good potential drug target



Performing *In Silico* Gene and Protein Knockdowns

Poor potential drug target



- Performs interventions in a **proxy of human patients** that has become more accurate than animal models or cell lines
- Discovers novel drug targets and biomarkers of response **orders of magnitude faster** and **cheaper** than in wet labs
- **Cross validates** novel drug targets and biomarkers in other **patient data-derived Gemini Digital Twins**

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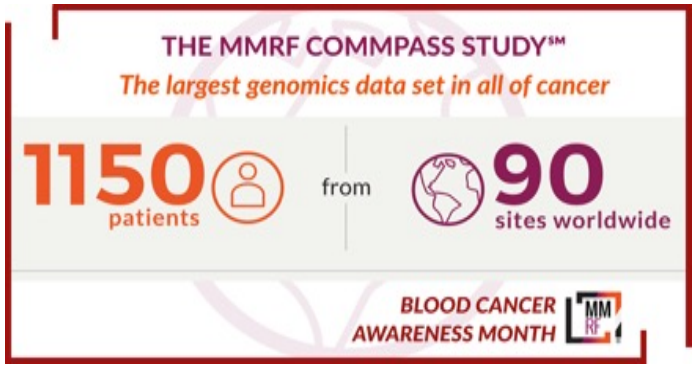
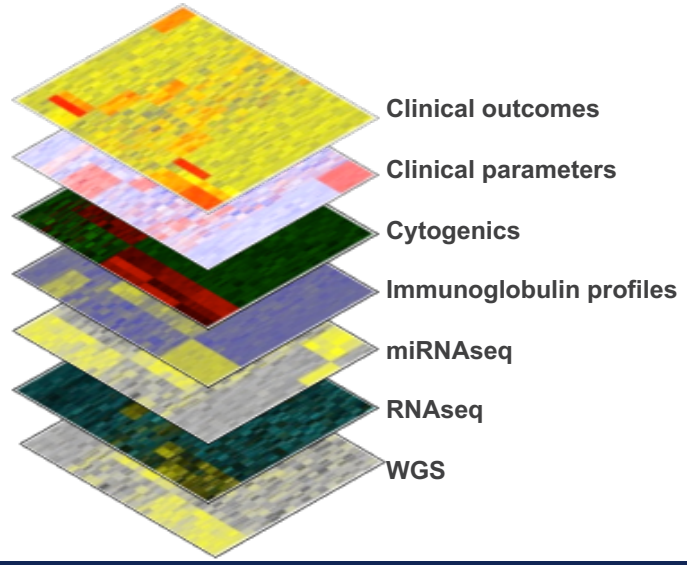
Building a Multiple Myeloma Gemini Digital Twin from multi-omic patient data

Rich Data

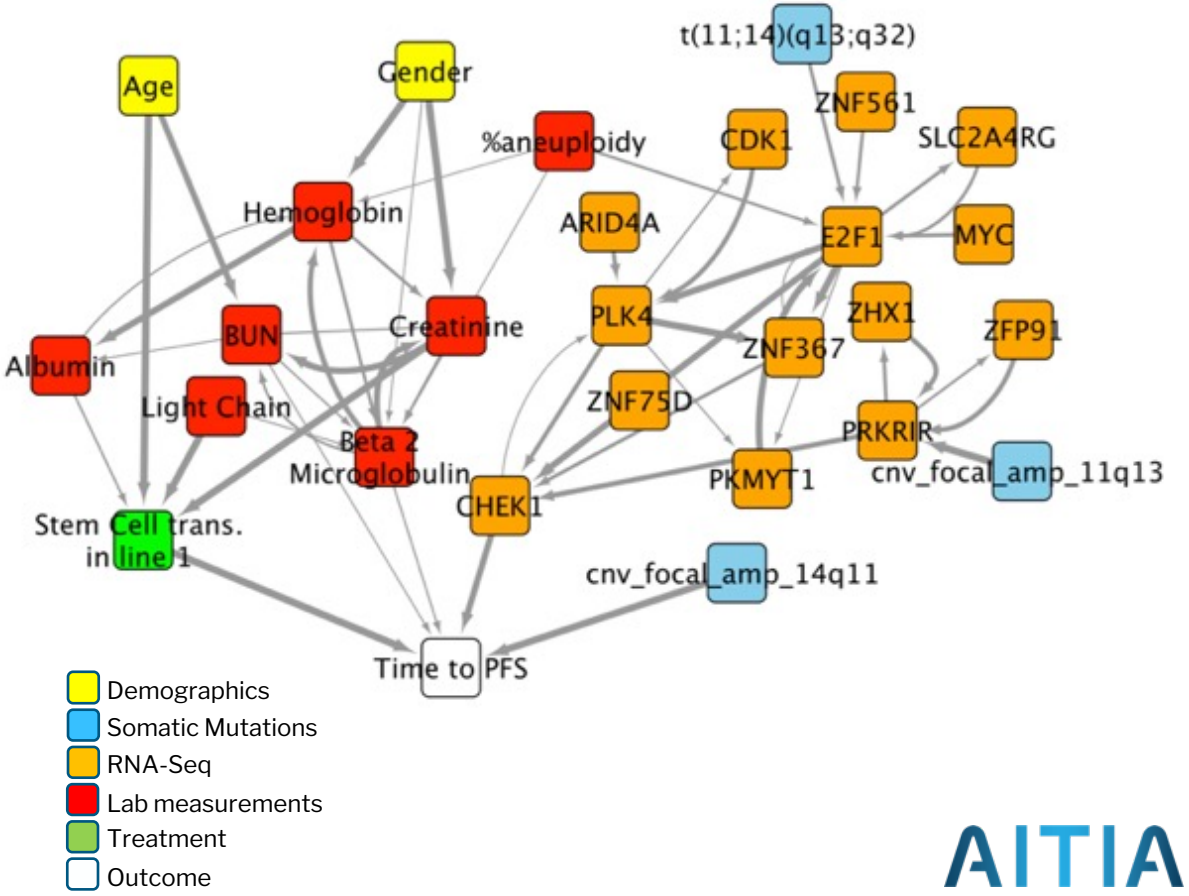


MMRF CoMMpass Study Data



Multiple Myeloma Digital Twin

Multiple Myeloma Subnetwork



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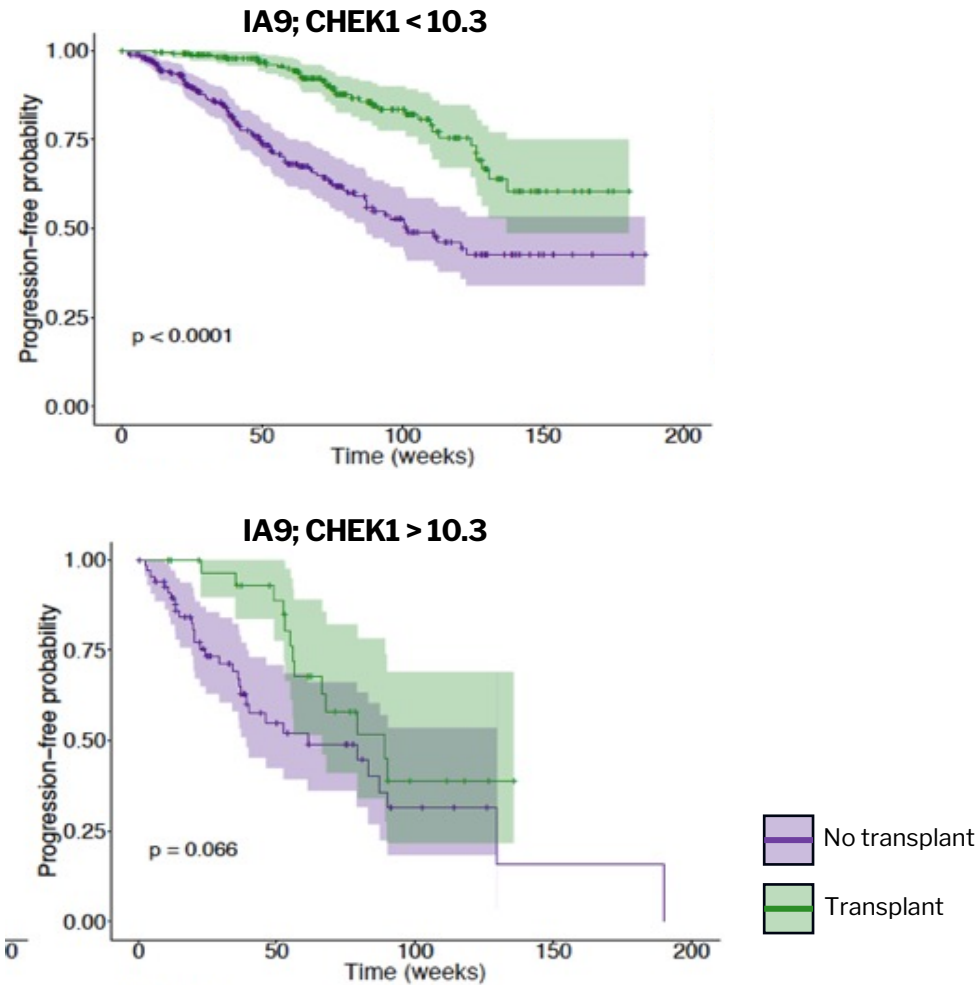
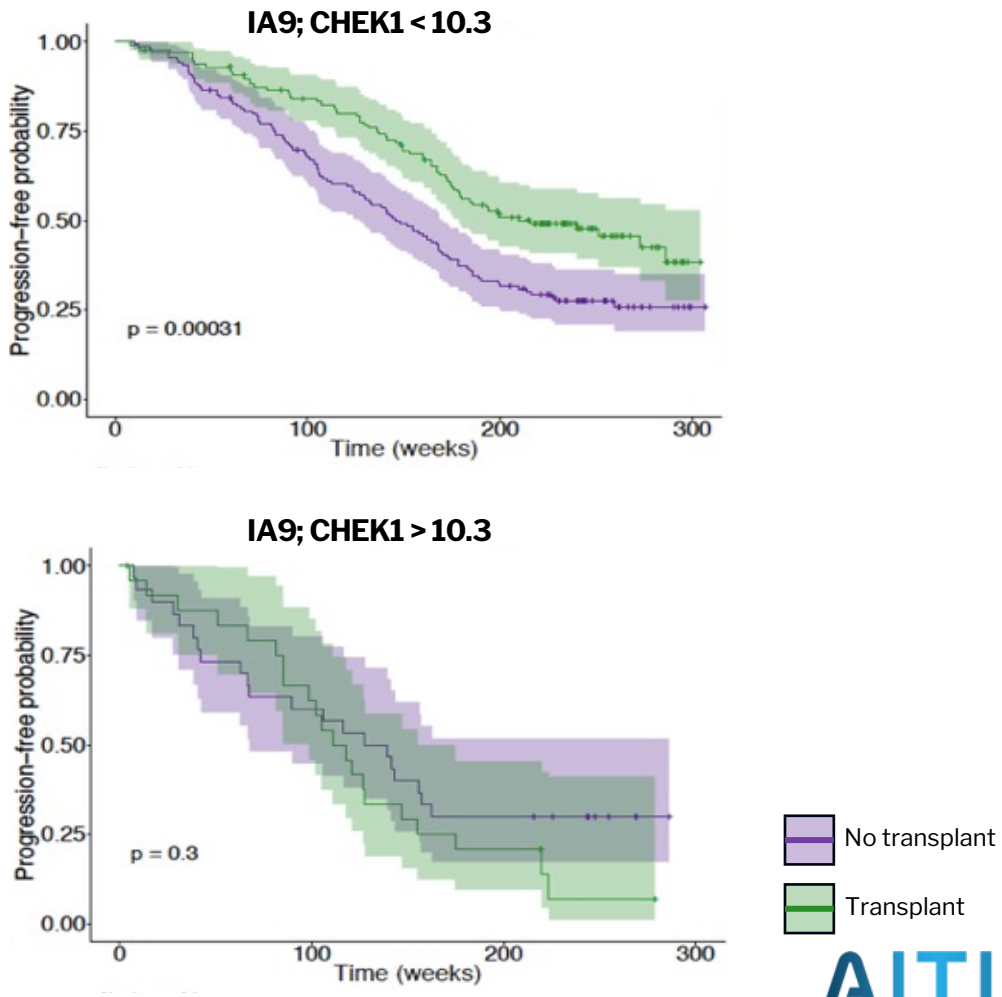
Discovering patient populations for SCT that extends PFS by 20 months

CHEK1 as the **top driver** predicting progression-free survival **(PFS) benefit from Stem Cell Therapy (SCT)**



Results were validated out of cohort in a randomized control trial at Dana Faber



Results published at the 59th ASH Annual Meeting

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Rare Diseases:
With single gene causes, can we determine the cures?

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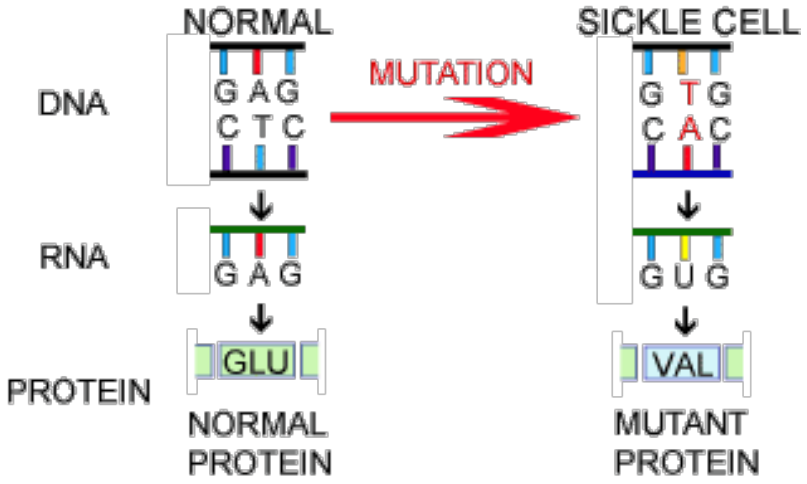
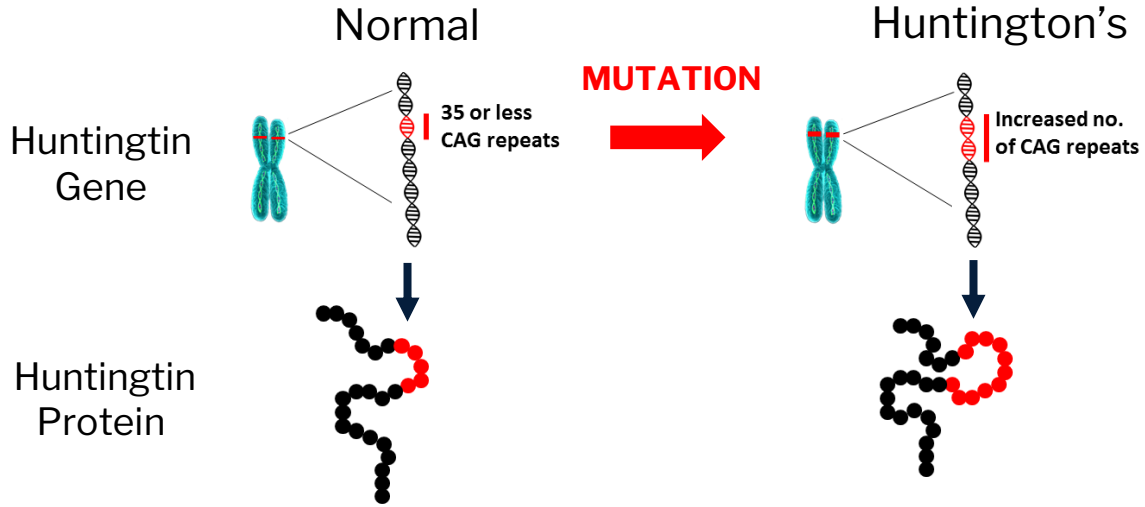
Example of rare diseases and their single gene causes

Sickle Cell Disease



Huntington's Disease



While the cause of these rare diseases with single gene mutations is relatively straightforward, treatment has been elusive

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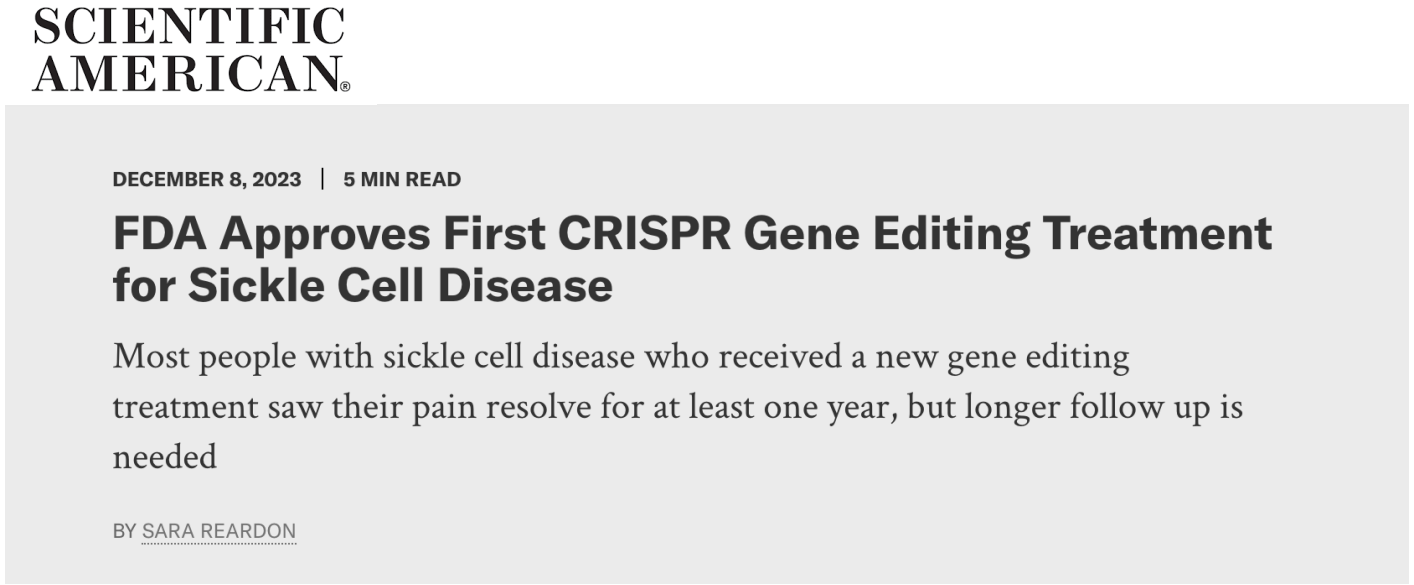
The cause is not always the cure



SCIENTIFIC AMERICAN®

DECEMBER 8, 2023 | 5 MIN READ

FDA Approves First CRISPR Gene Editing Treatment for Sickle Cell Disease

Most people with sickle cell disease who received a new gene editing treatment saw their pain resolve for at least one year, but longer follow up is needed

BY SARA REARDON

Gene therapy has shown promise, but in most rare diseases, intervention is more challenging due to the complex mechanisms of disease

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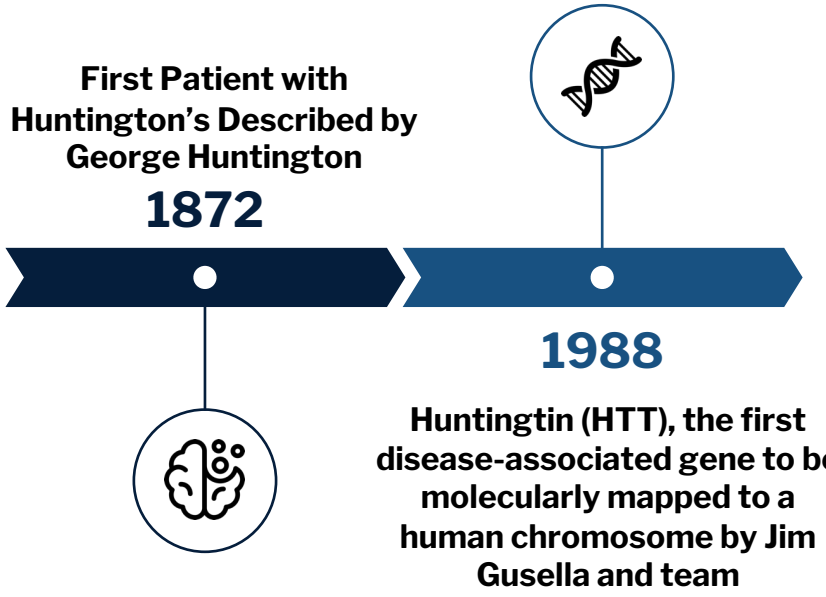
From the first Huntington's patient to the discovery of the causal gene mutation, our understanding of Huntington's disease has advanced



Mapping the Huntingtin gene to human chromosome 4

In 1983, Jim Gusella and team mapped Huntingtin (HTT) as the first disease-associated gene to be molecularly mapped to a human chromosome

Jim Gusella

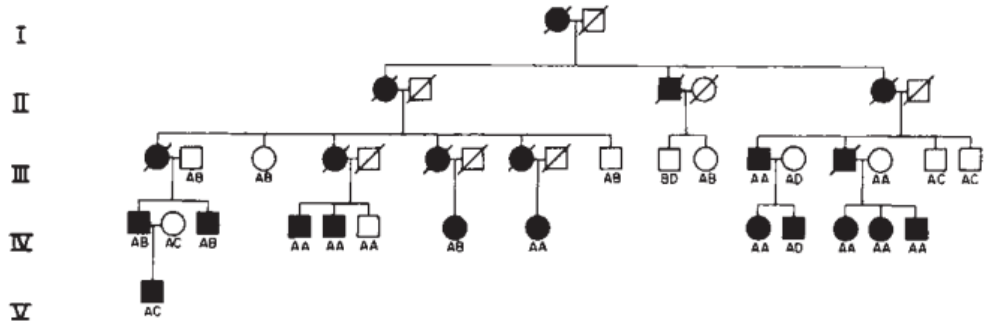
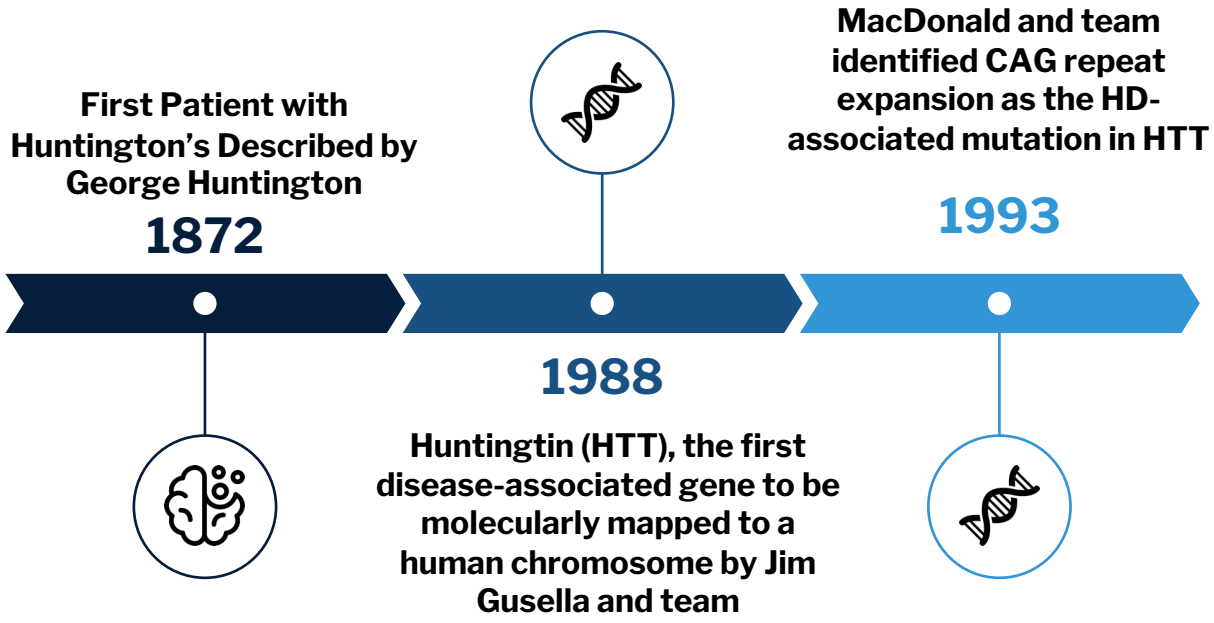


Figure: Pedigree of an American Huntington's Disease Family (Gusella et al., 1983). Provided the statistical support for the mapping of HTT to human chromosome 4

Family studies showed that the HTT gene is linked to a polymorphic DNA marker that maps to human chromosome 4

Source: Gusella et al. 1983

From the first Huntington's patient to the discovery of the causal gene mutation, our understanding of Huntington's disease has advanced



Identifying the HD gene

After determining that the HD gene is located on chromosome 4, researchers spent the next 10 years to **identify the HD gene** and to determine the **nature of the HD-associated mutation**

- They focused on the genes on **chromosome 4** and **identified IT15**, which they showed was transcribed into mRNA
- They then determined the **DNA sequence of the IT15 gene** and identified a region of the gene that contained a **repeated DNA element consisting of three nucleotides, CAG**, repeated multiple times near the beginning of the gene

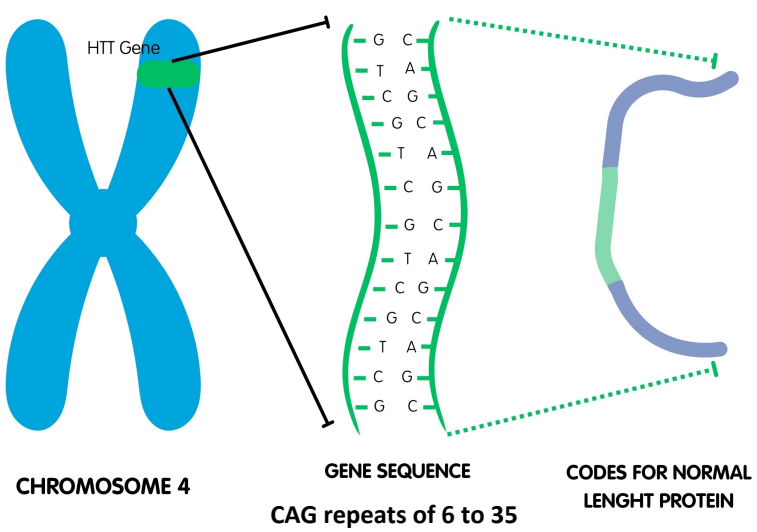
Table 1. Comparison of HD and Normal Repeat Length

Range of Allele Sizes (Number of Repeats)	Normal Chromosomes		HD Chromosomes	
	Number	Frequency	Number	Frequency
⩾48	0	0	44	0.59
42–47	0	0	30	0.41
30–41	2	0.01	0	0
25–30	2	0.01	0	0
⩽24	169	0.98	0	0
Total	173	1.00	74	1.0

CAG repeat on HD chromosomes is expanded relative to normal chromosomes

Source: MacDonald et al. 1993

Discovering the causal HTT mutation



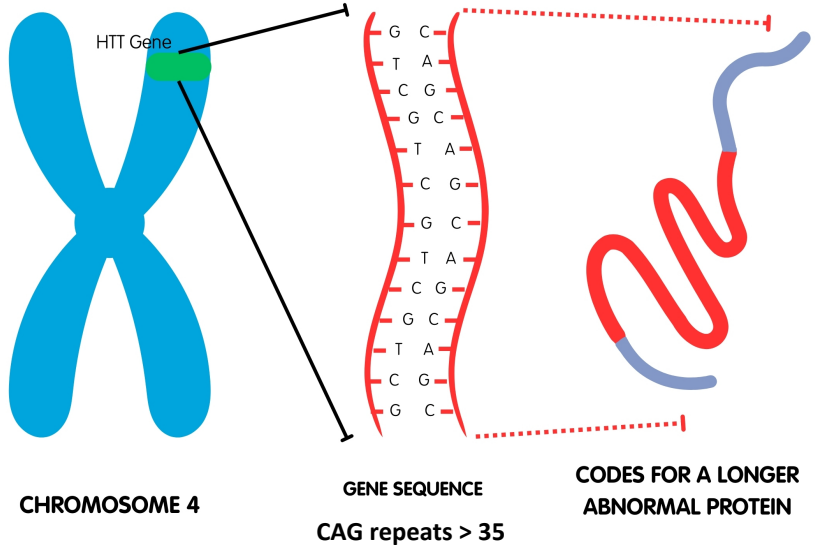


Image Source: Huntingtonsvic.org

- When researchers examined the same region of IT15 in other **non-HD controls**, they found that the **number of CAG repeats varied from six to 35**

- Analysis of this same region in the IT15 gene in **individuals with HD** showed that these people always had **40 or more CAG repeats**
- The researchers thus concluded that the **trinucleotide repeat expansion** in the IT15 gene was responsible for HD, and IT15 is now called **HTT (huntingtin)**

Source: MacDonald et al. 1993

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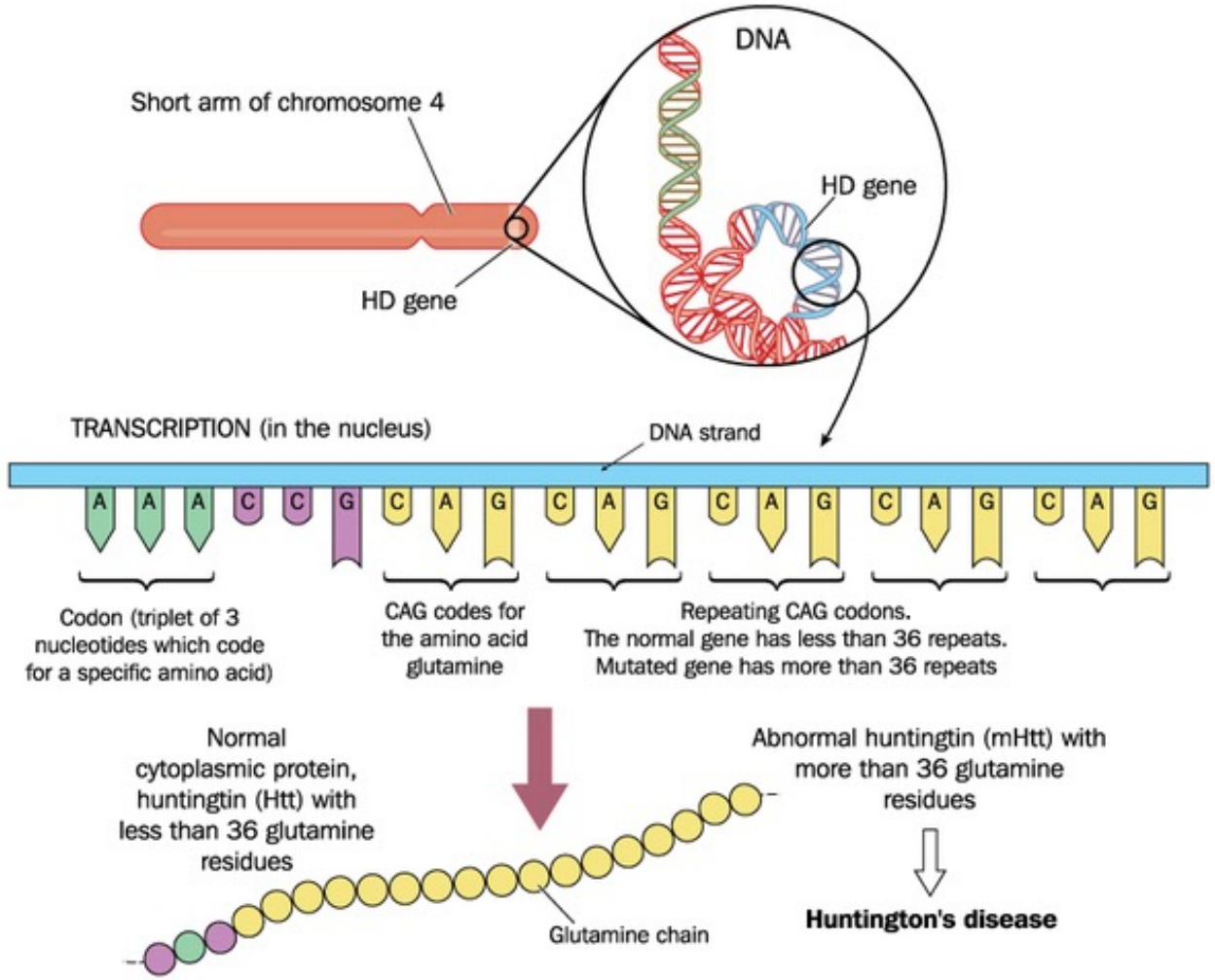
CAG repeat expansion greater than 36 eventually lead to development of the disease

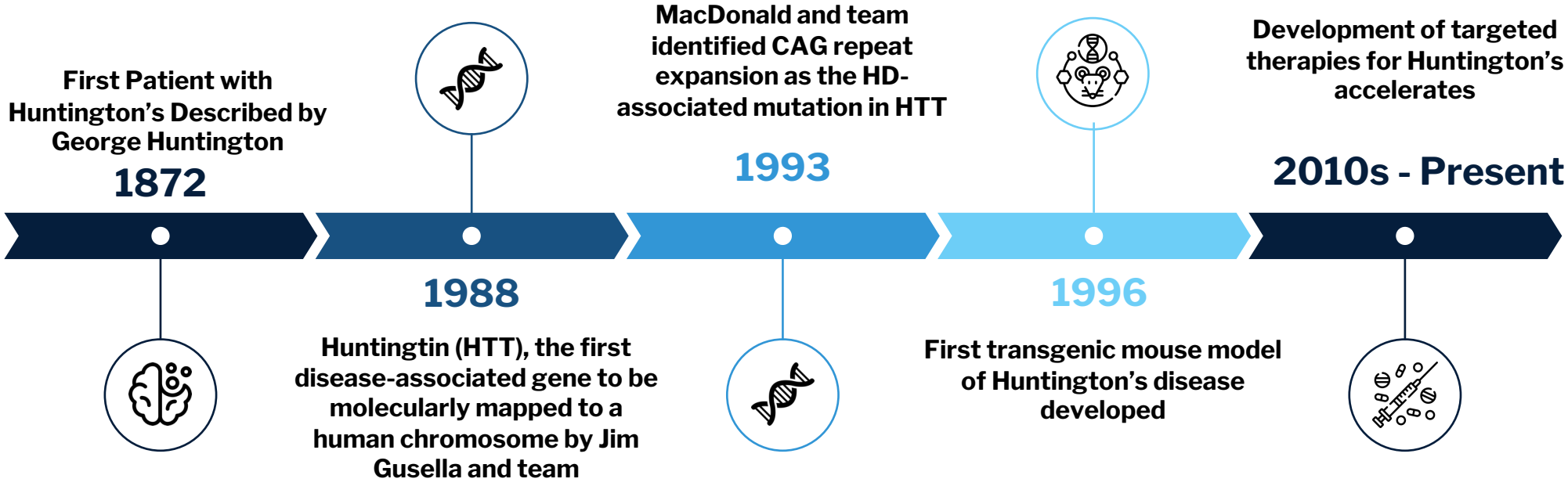
- This **repeat expansion** leads to the production of an **abnormal form of the huntingtin protein**, which is central to the neurodegenerative process in HD

- **Higher degree** of CAG repeat is linked to **faster somatic expansion** which is linked to **worse** clinical outcomes

- **Faster somatic expansion** rate leads to an earlier onset and rapid disease progression



From the first Huntington's patient to the discovery of the causal gene mutation, our understanding of Huntington's disease has advanced



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With the cause of Huntington's Disease discovered over 30 years ago, why is the treatment so elusive?

Despite being a single-gene disease, the complexity of the interacting network is high and most is unknown

Can the Gemini Digital Twin approach lead to the discovery and development of a new breakthrough treatment in Huntington's Disease?

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Huntington's Disease: *Discovery of a novel target and development of a novel treatment*

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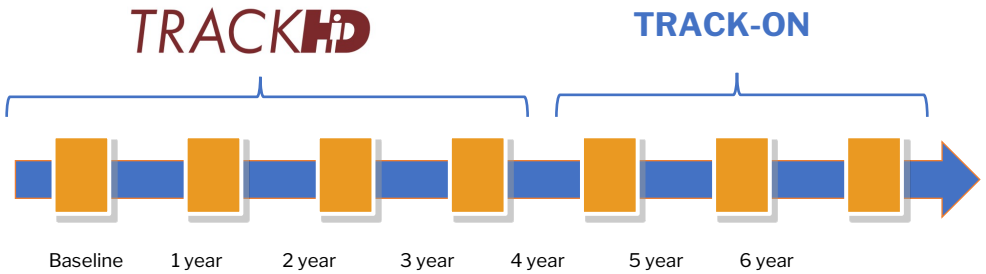
Huntington's disease multi-omic human data

CHDI FOUNDATION



Track-HD & Track-ON: Multi-national, longitudinal study in premanifest and early HD individuals and healthy controls

Enroll-HD → HDClarity

Enroll-HD: Clinical research platform and the world's largest HD observational study with n>20,000

Track-HD / Track-ON

- Ongoing prospective observational biomarker study in participants with premanifest and early HD (Current n~360)
- Data modalities include **clinical, genomics, RNAseq, imaging** and **biomarker** data

HDClarity

- Multi-site longitudinal CSF and blood collection initiative with phenotypic data from Enroll-HD (Current n~940)
- Data modalities include **genomics, proteomics** (from *SomaLogic*) **and biomarkers** (NfL, HTT)

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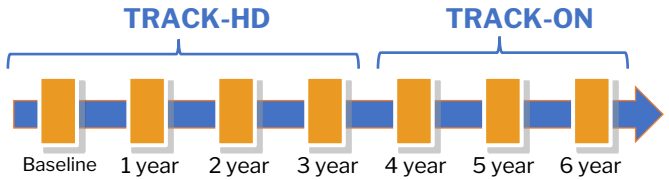
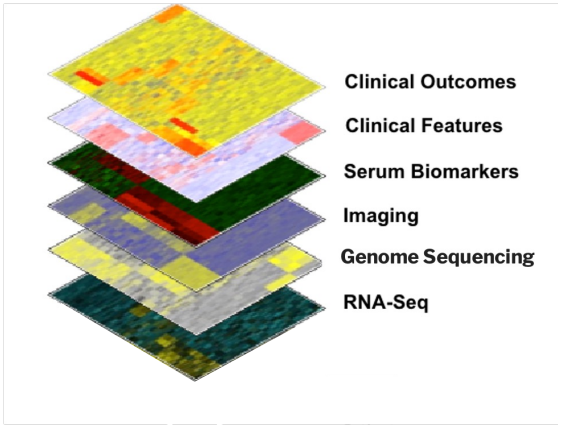
Creating HD Digital Twins from human multi-omic and clinical data

Rich HD Patient Data

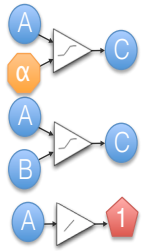


Multi-national, longitudinal study in premanifest and early HD individuals and healthy controls with around 120 patients with all layers of data available



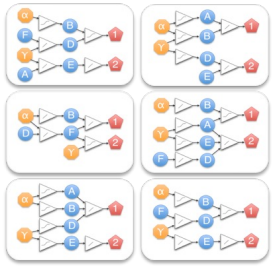
Causal AI (REFS Platform)

Enumeration



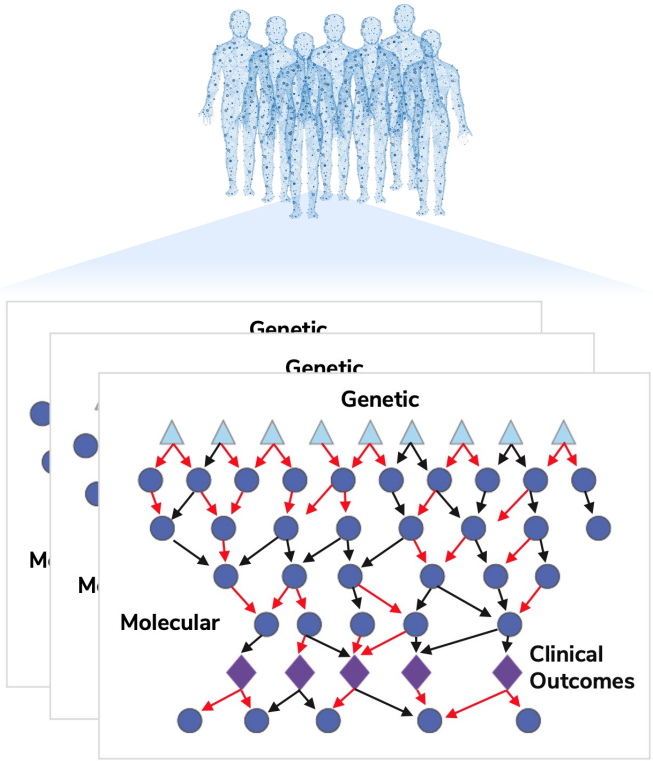
Trillions of individual network fragments are scored based on the full distribution of parameter values

Optimization



A globally optimal ensemble of networks (1000) is generated and scored across thousands of computing nodes

HD Gemini Digital Twin



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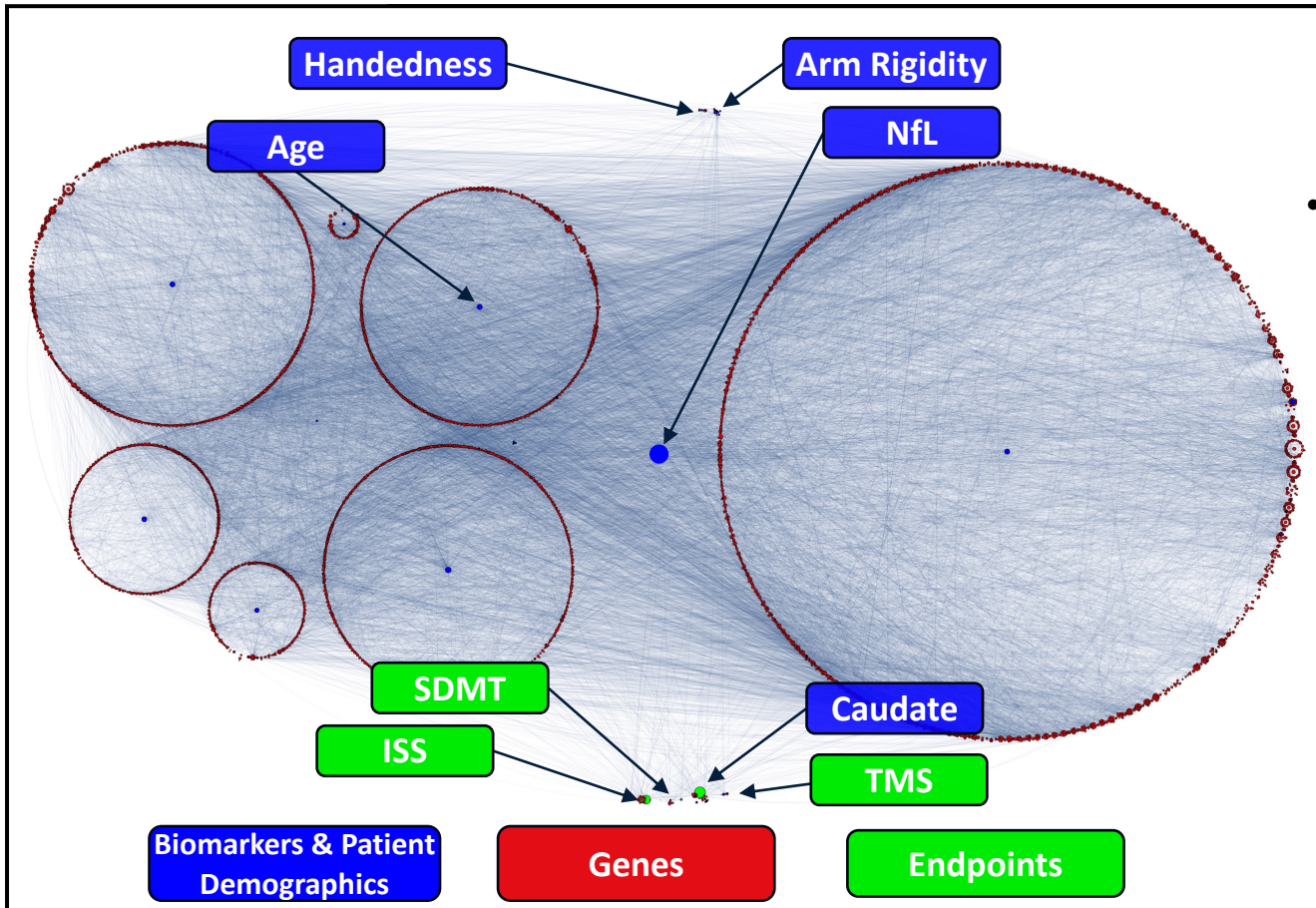
Using HD Digital Twins to discover novel drug targets

HD Gemini Digital Twin



- The HD Digital Twin is a complex, interconnected network with 128 networks, 22,770 nodes, and 5,383,791 edges*
  - Incorporates the human multi-omic data alongside motor and cognitive progression outcomes and other common parameters in HD to reconstruct known and unknown mechanisms

**Nodes represent random variables and edges represent causal relationship between variables*

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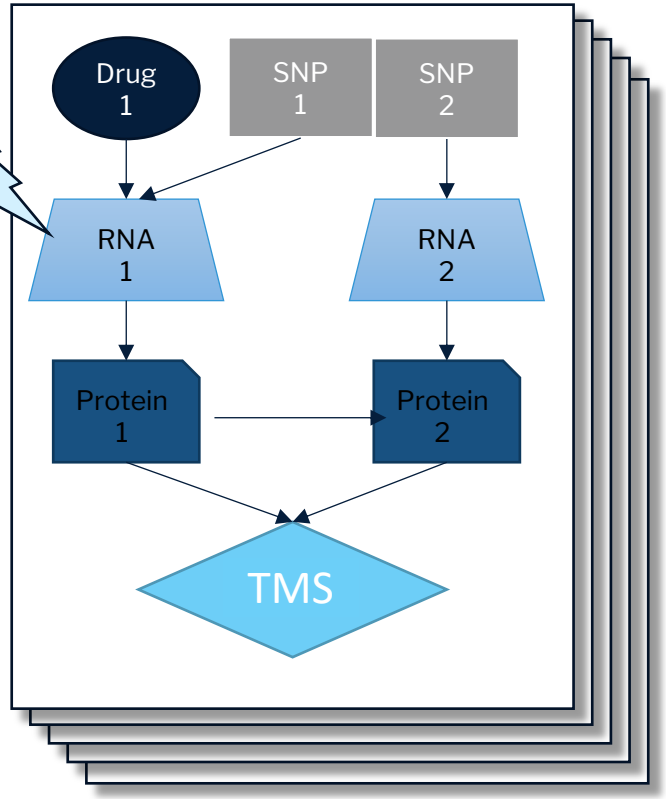
Abbreviations: SDMT: Symbol Digit Modality Test; ISS: Integrated Staging System; TMS: Total Motor Score

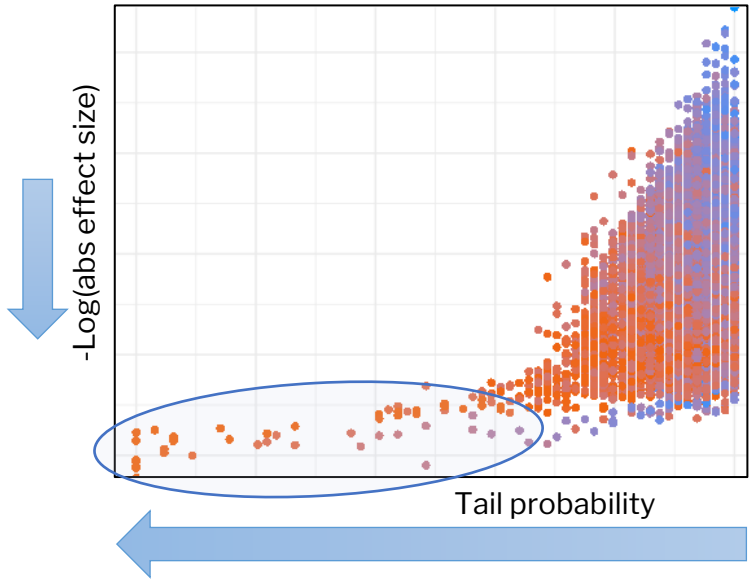
Using HD Digital Twins to discover novel drug targets

in silico Experiments

Compare two simulations setting:
$RNA1 = High$
$RNA1 = Low$



Causal Effect Evidence



Individual gene-outcome pairs

- Absolute Cohen's D↑ → Stronger effect
- Path Frequency↑ → Stronger effect
- Tail Probability↓ → Stronger effect

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Target prioritization and refinement

Target Identification and Prioritization

Mendelian Randomization

- Orthogonal evidence for HD Targets
- To infer causality between the gene and disease

Druggability

- Is there chemical matter?
- Is it expressed in target tissue?
- Is it a member of the known target families?

Biological Relevance

- Essential in cell lines?
- Functional pathways driving the gene
- Functional pathways the gene drives

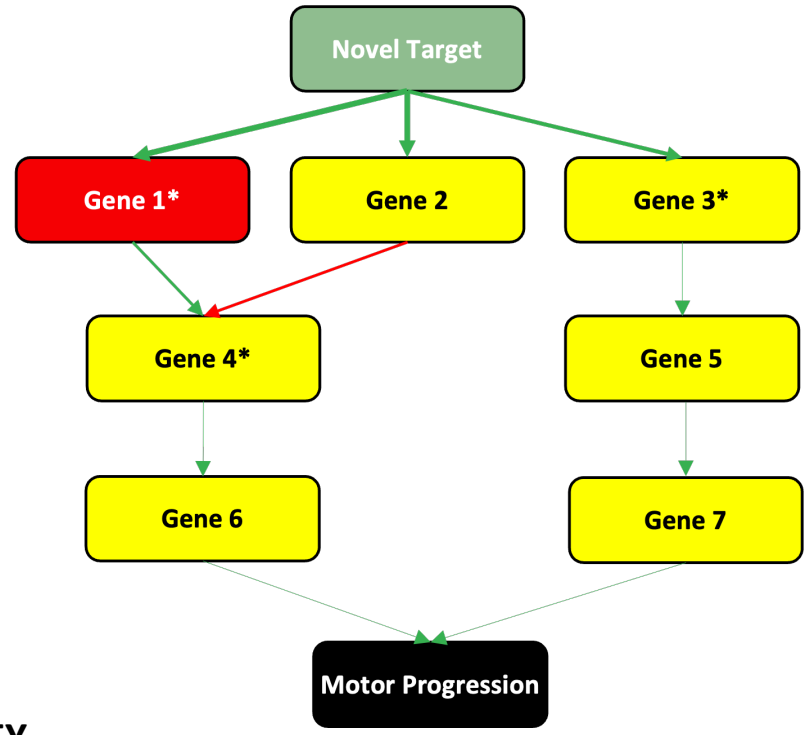
Novelty

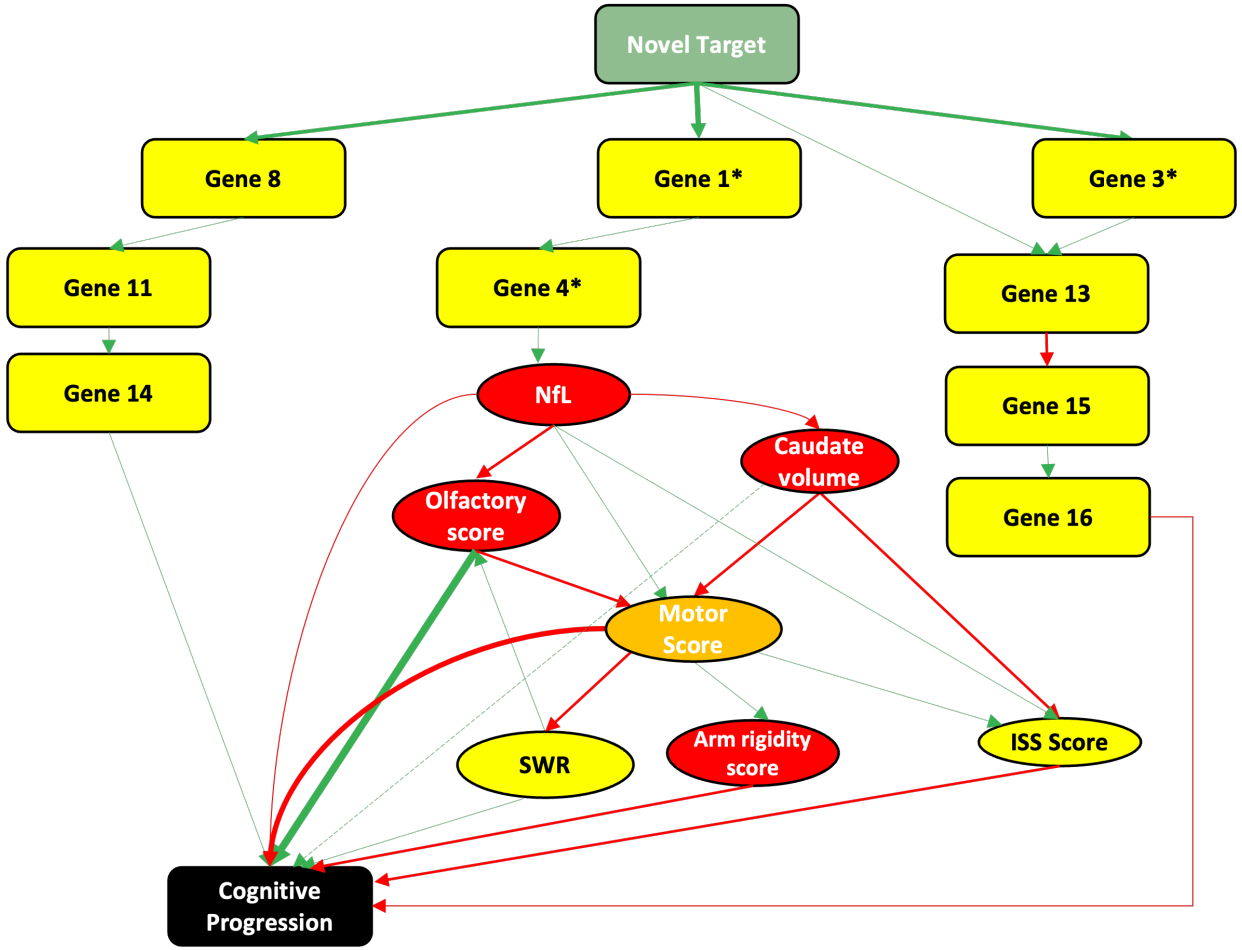
- Limited literature in the indication but scientific rational in disease progression

AITIA

Lead program in Huntington's disease with novel target impacting cognition and motor function

Network Model From HD Digital Twin





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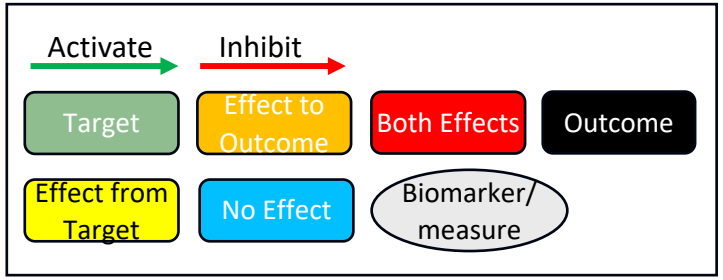

***Same genes across the models**

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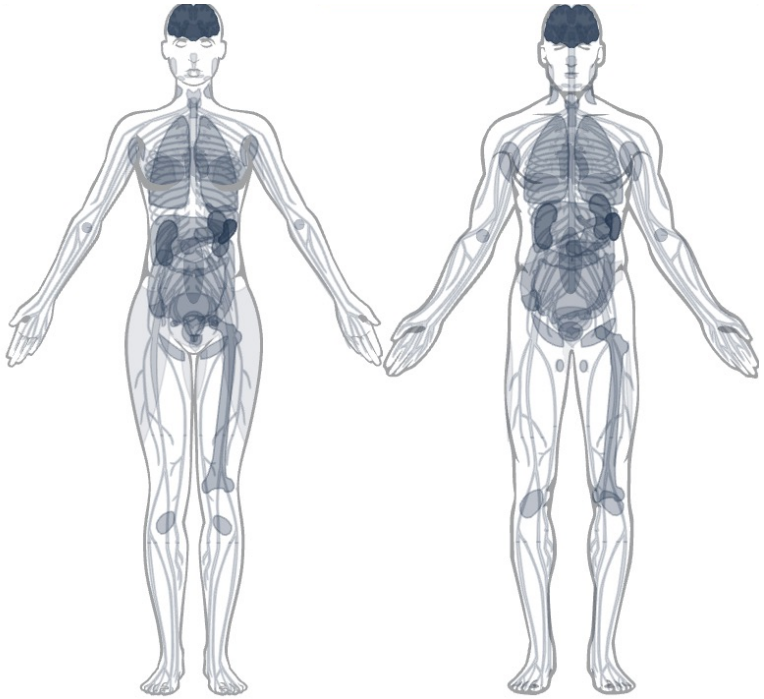
Novel target in HD has been genetically validated and is expressed in brain tissue

- Genetic validation via Mendelian Randomization – significant effect in Mendelian Randomization in brain; testing the gene effect on HD age of onset
  - Here, a two-Sample MR approach was used, utilizing the summary statistics from
    - Meta Brain eQTL[de Klein et al., Nature Genetics, 2023]
    - GWAS study for HD Age of onset [GeM-HD, Cell, 2019].

Gene Expression in Tissues



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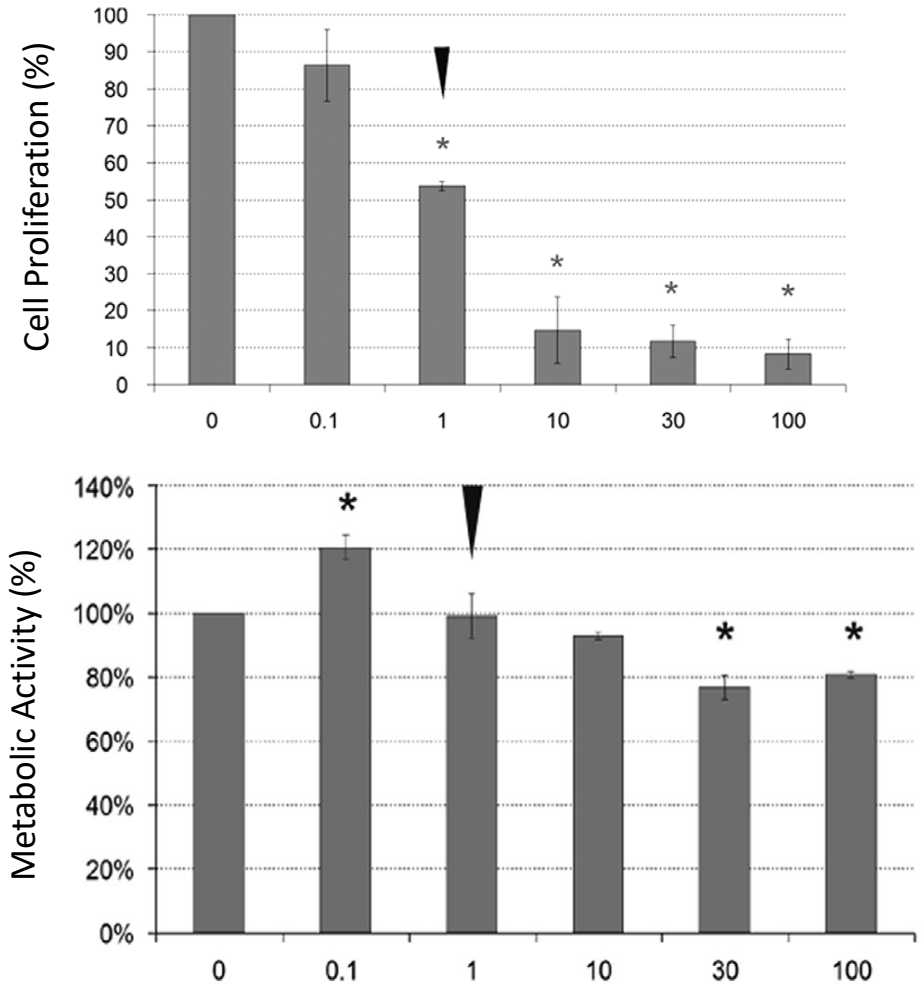
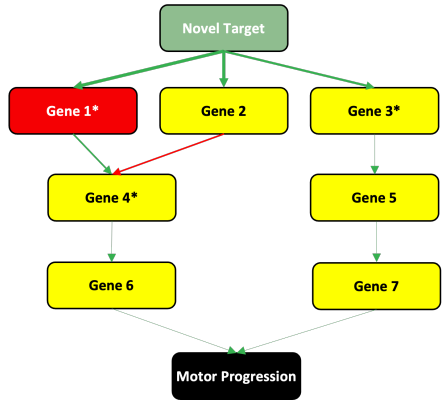
Lead program against novel target in Huntington's disease – novelty, genetic validation, and biomarkers

Similar class of drugs affect hNPC proliferation and influence metabolic activity



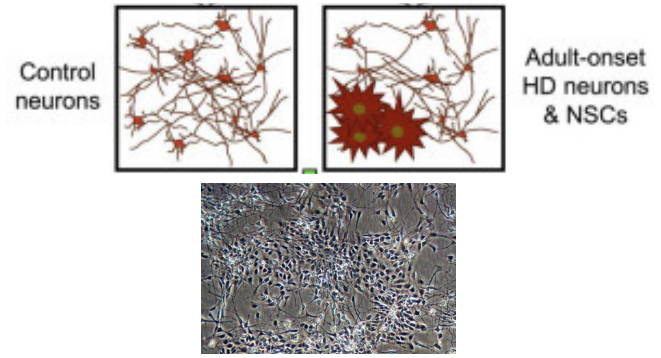
Evaluation of lead target in cell-based assays and mouse models

Model Validation Assays



- Causal network analysis with compound inhibition and/or ASO knockdown
- PK study with 2-3 tool compounds focusing on in vivo brain penetration with free fraction of molecules

Cell-based Assays for CAG Somatic Expansion



IPSC-derived HD Neural Stem Cells

- Various specific cell-based assays such as tetranucleotide expansion / contraction assay, CAG repeat cell lines, and HD iPSC-programmed striatal cells
- Develop HD-patient iPSC derived striatal cell line

HD Mouse Models

Hdh^{Q111} Knock-In Mice

Q175 Knock-In Mice

- Two mouse models resembling HD phenotype (motor deficit, pathology, etc.) and genotype with CAG repeats

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The discovery of novel therapies through the use of Digital Twins

The cause is not always the cure. Despite being defined by a single gene mutation, rare diseases often do not lend themselves to simple intervention

Advances in multi-omics, supercomputing, and causal AI have allowed us to begin to unravel the hidden mechanisms of rare diseases by creating Gemini Digital Twins

This enables us to conduct *in silico* experiments to discover the true drivers of clinical outcomes

We have used it to discover a novel drug target and we are advancing a small molecule against the novel target towards the clinic

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Gemini Digital Twins are driving the creation of the next generation of breakthrough drugs for rare diseases

Human multi-omic datasets

Causal AI Platform (REFS)

Therapeutics against novel human biology, de-risked with causal human mechanisms

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We are committed to using AI to bring life-changing therapies to improve patient lives

Thank You!

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