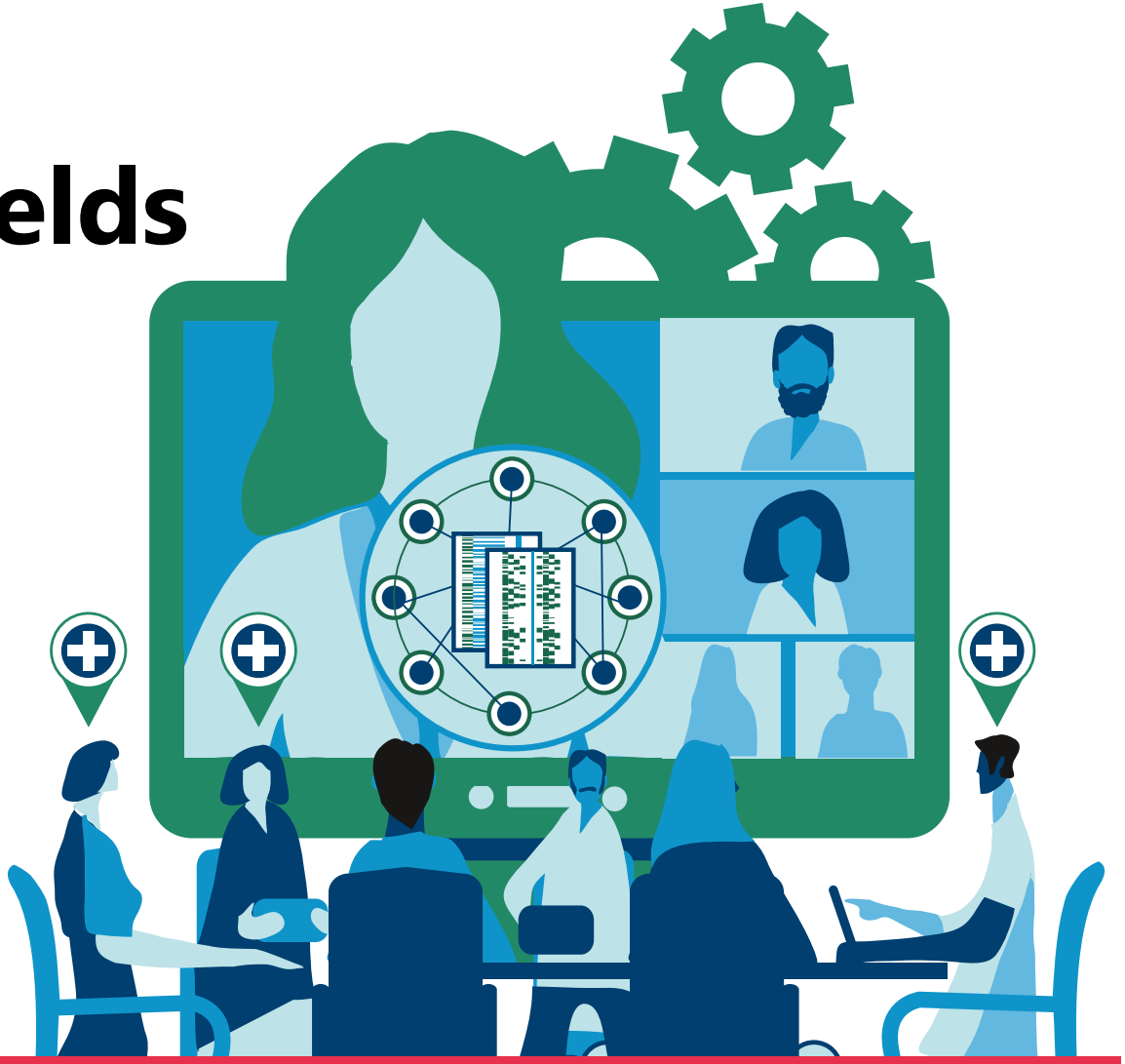
Precision Medicine: Lessons from the Fields

Prof. Dr. Mark A. Rubin, MD



UNIVERSITÄT BERN

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HÔPITAL UNIVERSITAIRE DE BERNE

Precision Medicine: Lessons from the Fields

Disclosures

Nature of the Financial Relationship	Name of the Ineligible Company
Grant/Research Support	Genentech
Grant/Research Support	Novartis
Grant/Research Support	Roche
Honoraria/ Scientific Advisory Board	NeoGenomics Laboratories
Stock Holder/ Scientific Advisory Board	OWKIN
Patents	U6atac and SMARCA4 for diagnostics and therapy in prostate cancer (Uni. Bern); ETS fusion and SPOP Pca (Harvard and Cornell)

Is precision, precision medicine?

PRECISION MEDICINE

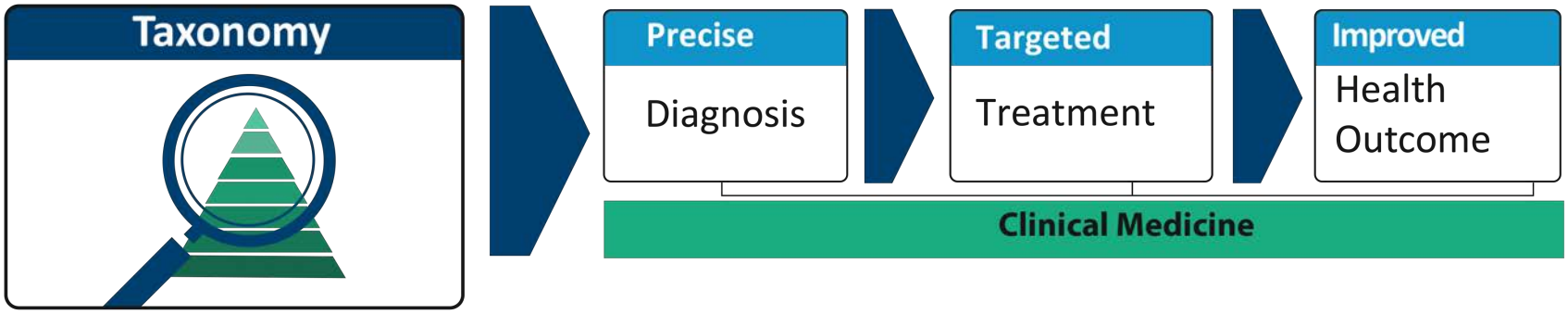
PRECISION MEDICINE

Precision medicine is a personalized approach in modern medicine. Individual characteristics such as genetic predisposition, environmental factors, or lifestyle of patients are accounted for in the treatment.

PRECISION MEDICINE

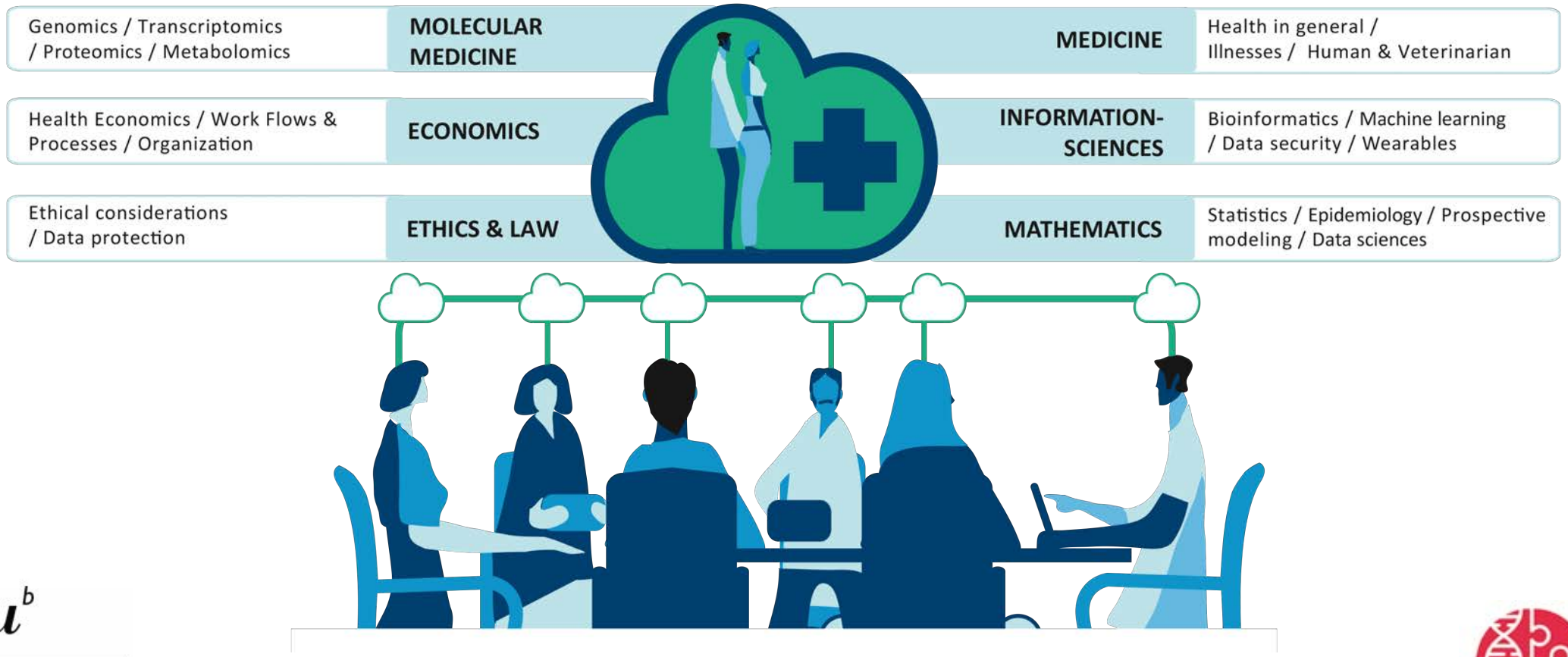
Right treatment for the right patient at the right time.

The Promise and Future of Precision Medicine



Critical components required for Precision Medicine

Towards a truly Interdisciplinary Collaboration



TRADITIONAL MEDICINE

Same treatment for all

PRECISION MEDICINE

Best treatment per patient


Precision Medicine across the globe

Genomics England

Genomic Medicine | Our Initiatives | Patients and Participants | Research and Partnerships | News and Events | About Us

Genomics England

Powering genomic medicine, together

We partner with the NHS to provide whole genome sequencing diagnostics. We also equip researchers to find the causes of disease and develop new treatments – with patients and participants at the heart of it all.

About us

SPHN

Menu

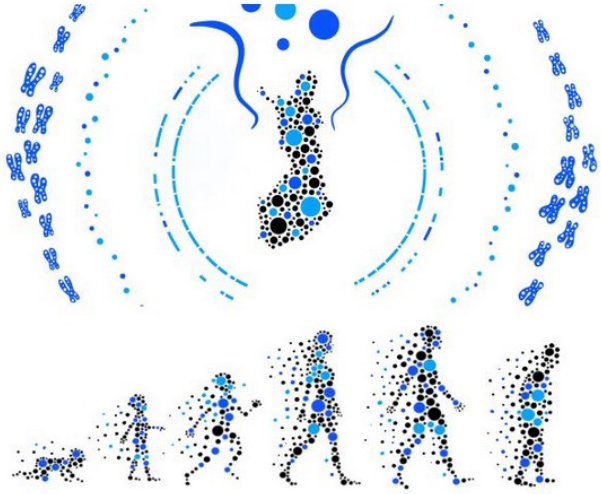
Swiss Personalized Health Network (SPHN)

Infrastructure building to enable nationwide use and exchange of health data for research

THE POWER OF A GENETIC ISOLATE: HUNDREDS OF NOVEL GENETIC DISCOVERIES FROM THE FINNGEN STUDY

New results from the FinnGen research consortium demonstrate the undeniable benefits of Finnish health research environment for genomic research. Among the wealth of novel genetic discoveries are previously unknown genetic risk factors for many debilitating diseases. These findings have potential to facilitate the development of new therapies.

FINNGEN



Credits: Alex Cagan

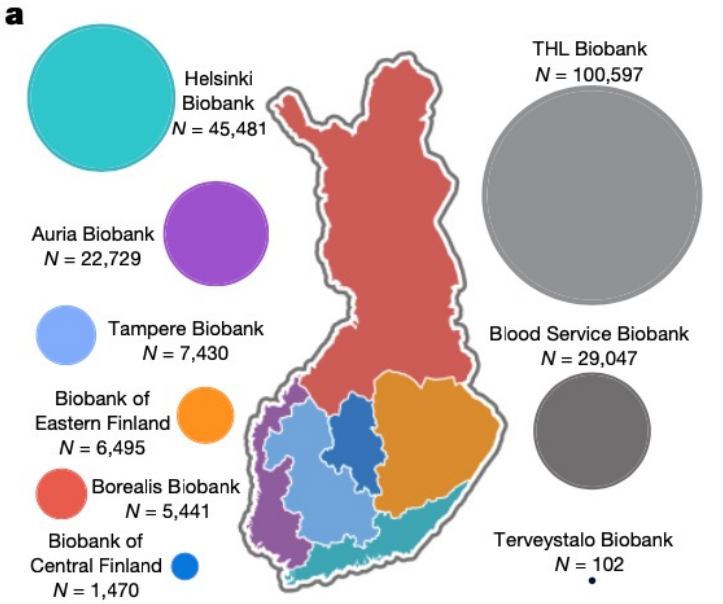
Since initiation in 2017, the FinnGen study has developed into one of the world's leading biobank-based genomic research projects. Currently FinnGen is completing the construction of a resource that integrates genomic information from 500,000 Finns with more than half a century of national health registry data.

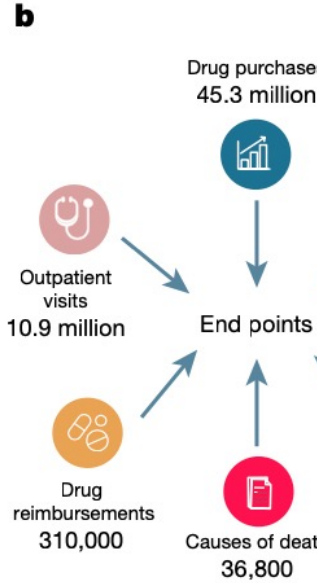
Article

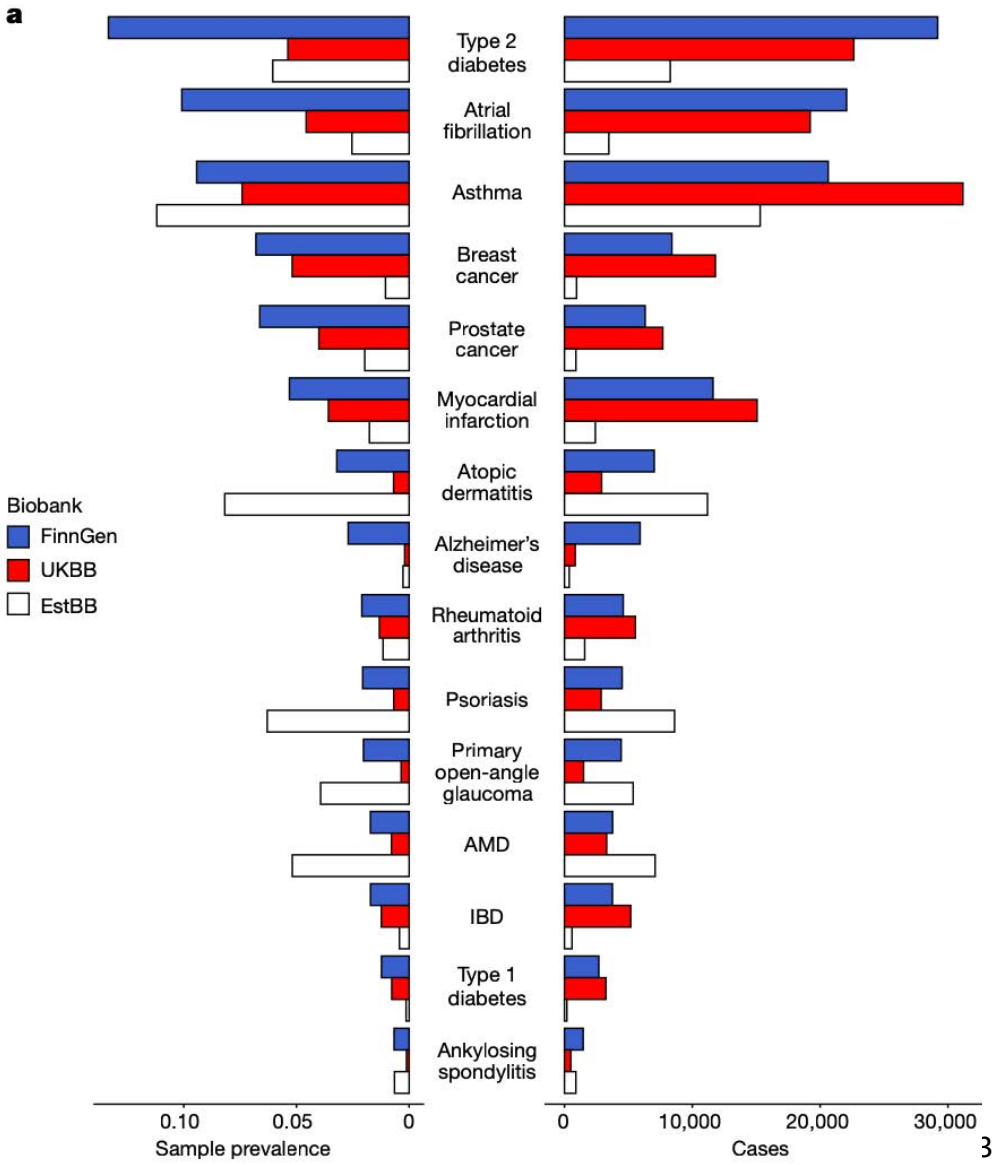
FinnGen provides genetic insights from a well-phenotyped isolated population

https://doi.org/10.1038/s41586-022-05473-8
Received: 10 January 2022
Accepted: 21 October 2022
Published online: 18 January 2023
Open access
Check for updates

Population isolates such as those in Finland benefit genetic research because deleterious alleles are often concentrated on a small number of low-frequency variants (0.1% ≤ minor allele frequency < 5%). These variants survived the founding bottleneck rather than being distributed over a large number of ultrarare variants. Although this effect is well established in Mendelian genetics, its value in common disease genetics is less explored[1,2]. FinnGen aims to study the genome and national health register data of 500,000 Finnish individuals. Given the relatively high median age of participants







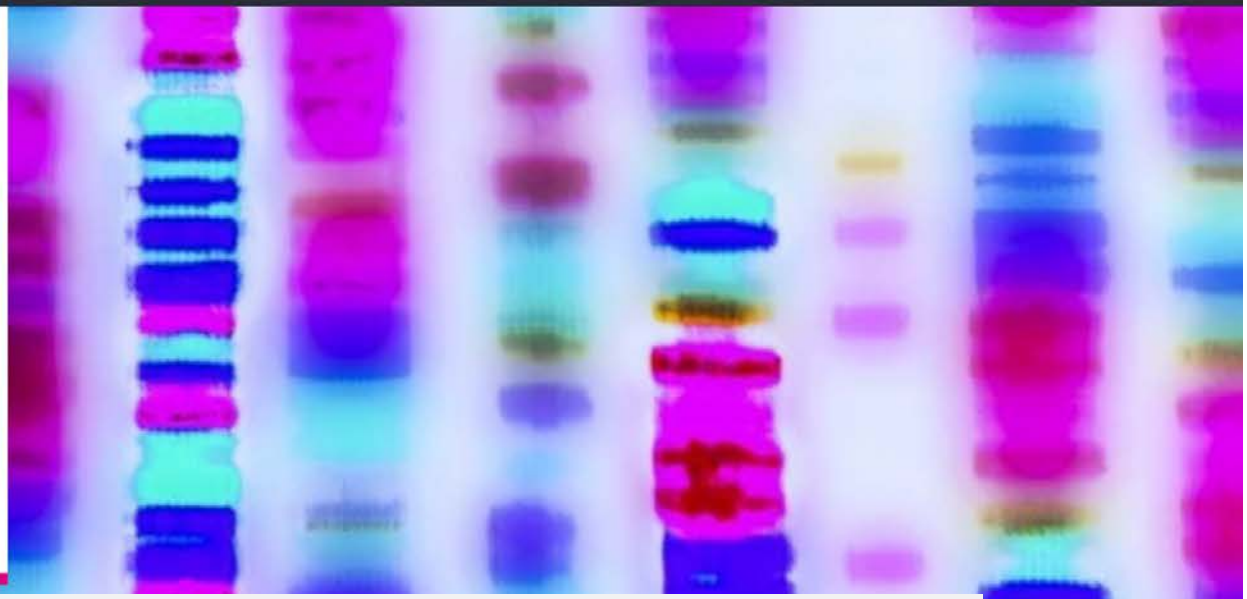
Genomics England

Genomic Medicine | Our Initiatives | Patients and Participants | Research and Partnerships | News and Events | About Us

Our initiatives > 100,000 Genomes Project

100,000 Genomes Project

Genomics England's very first initiative – sequencing 100,000 genomes from around 85,000 NHS patients affected by rare disease or cancer – is leading to groundbreaking insights and continued findings into the role genomics can play in healthcare.



Aims of the 100,000 Genomes Project

Make genomics part of routine healthcare

by working closely with the NHS to integrate whole genome sequencing

Enhance genomic healthcare research

by creating the largest genomic healthcare data resource in the world

Uncover answers for participants

both now and in the future through genomic-level analysis conditions

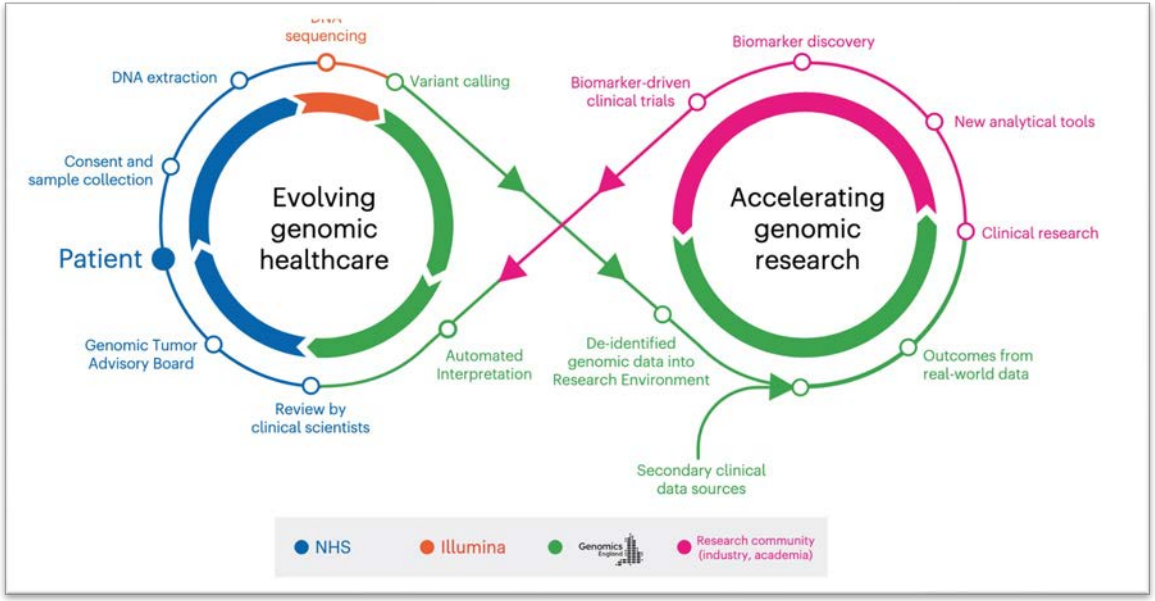
Genomics England

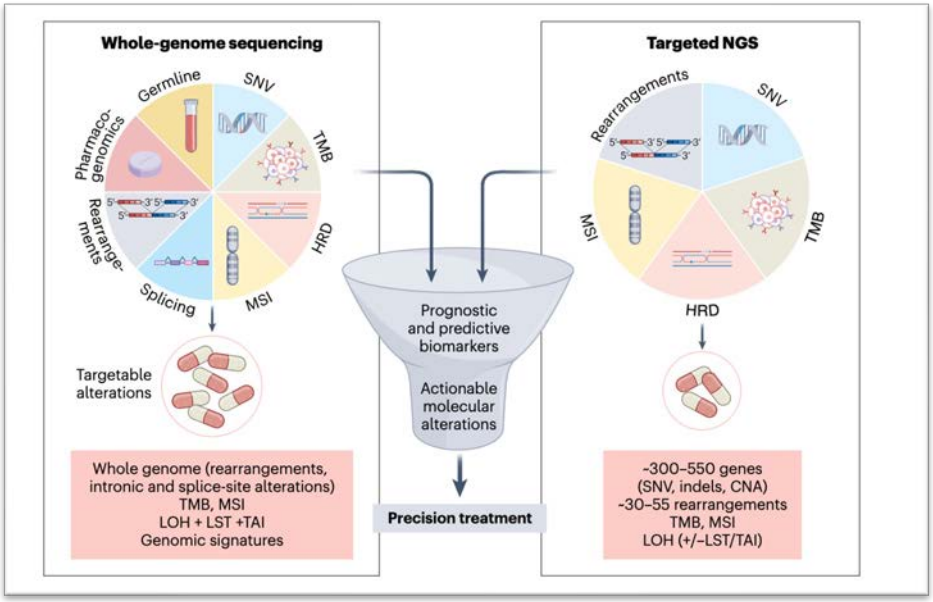
nature medicine

Analysis

https://doi.org/10.1038/s41591-023-02682-0

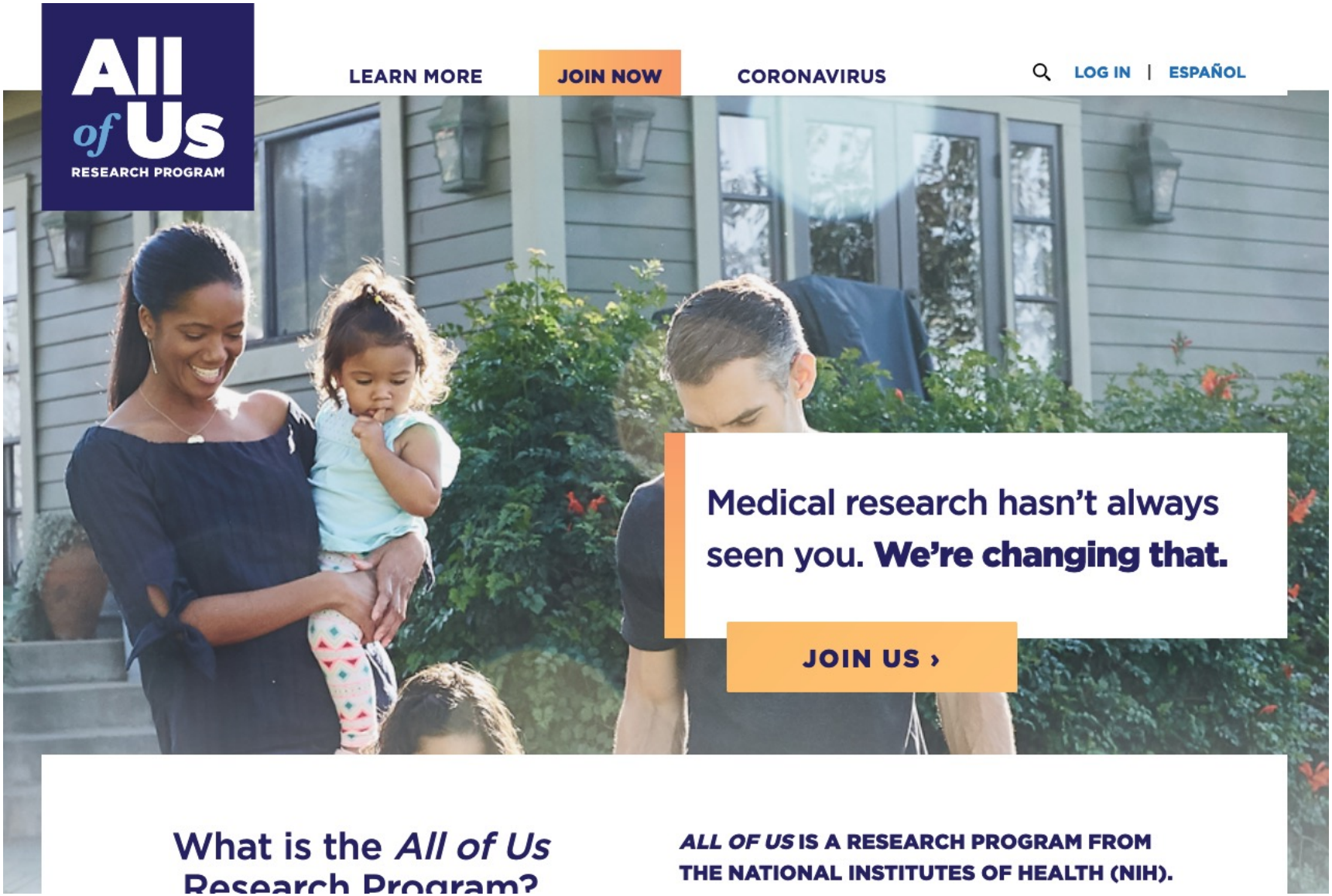
Insights for precision oncology from the integration of genomic and clinical data of 13,880 tumors from the 100,000 Genomes Cancer Programme



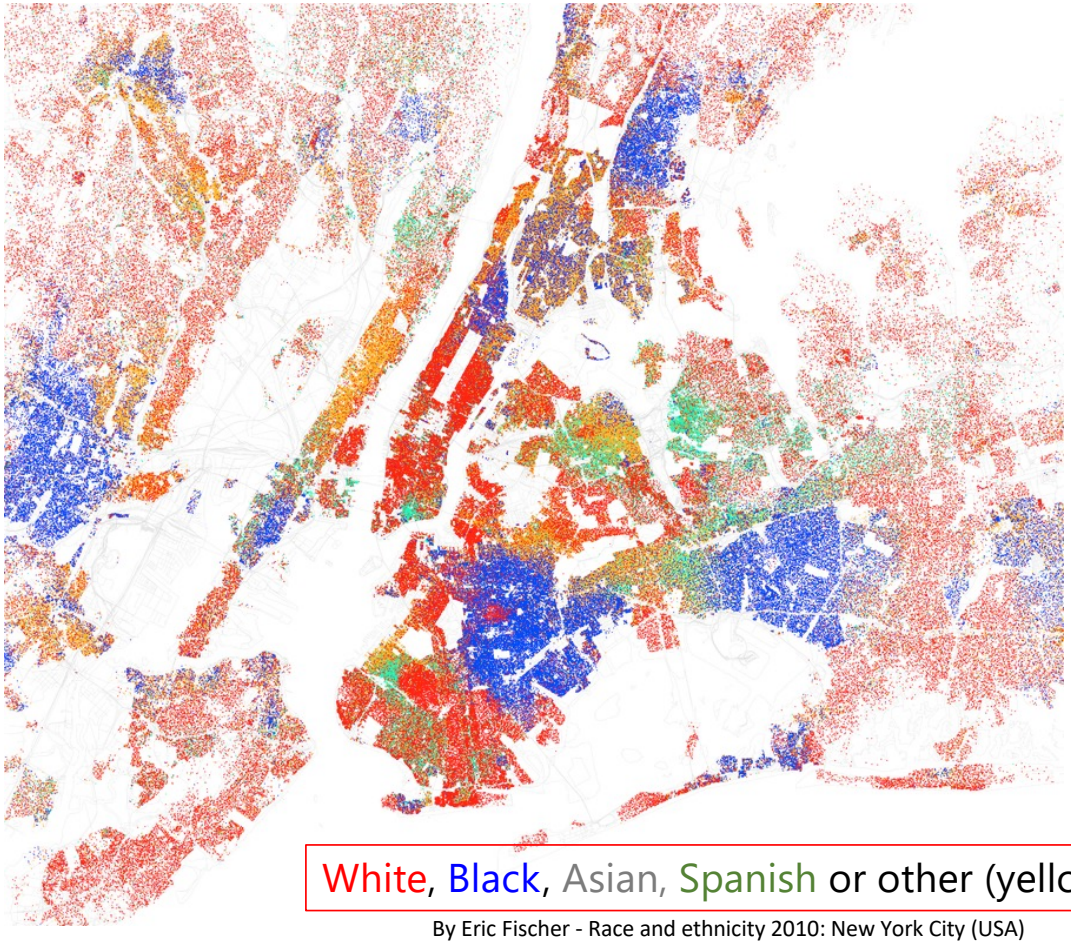


Read More

Nat. Med 2024

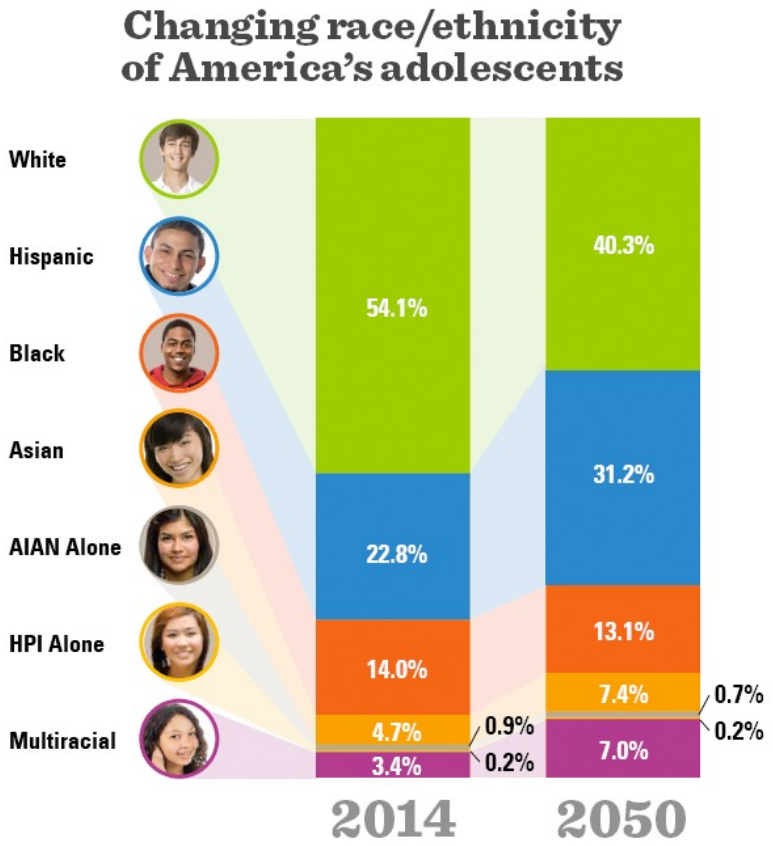

All of Us
RESEARCH PROGRAM
LEARN MORE
JOIN NOW
CORONAVIRUS
LOG IN | ESPAÑOL
Medical research hasn't always seen you. We're changing that.
JOIN US ›
What is the All of Us Research Program?
ALL OF US IS A RESEARCH PROGRAM FROM THE NATIONAL INSTITUTES OF HEALTH (NIH).

Columbia-Cornell All of Us:
Demographic Development in New York City



White, Black, Asian, Spanish or other (yellow)

By Eric Fischer - Race and ethnicity 2010: New York City (USA)



AIAN American Indian and Alaska Native

By Mugeek Vidalondon

Article

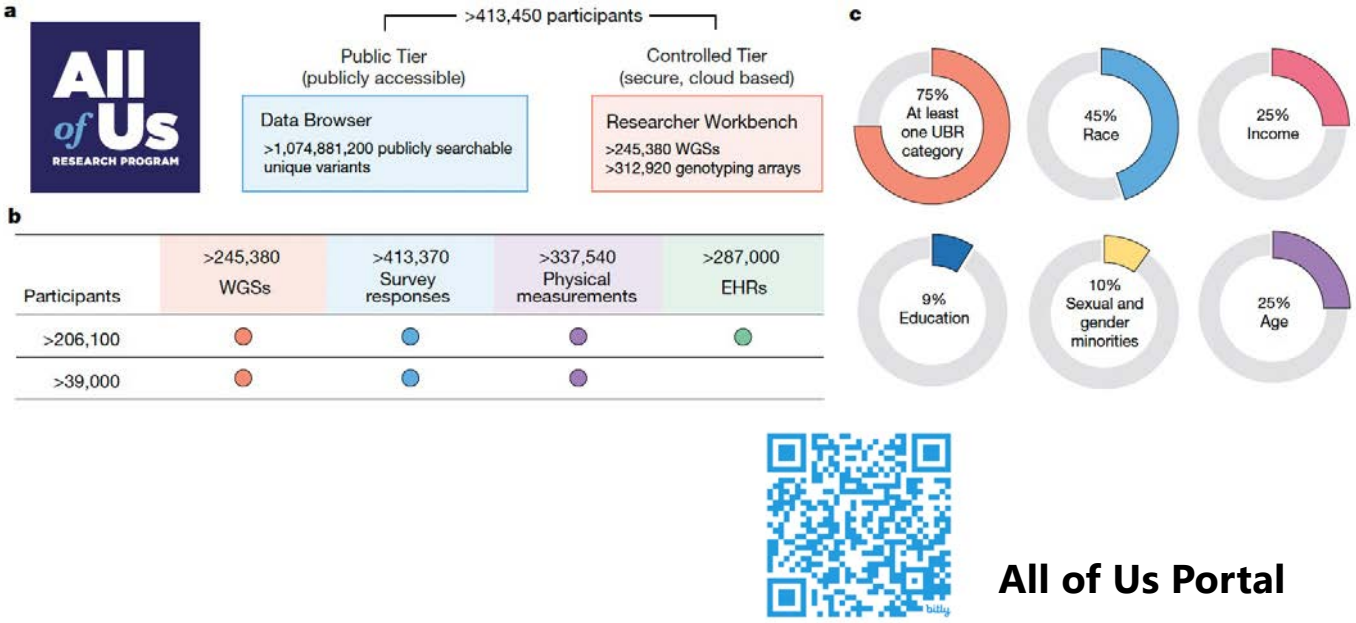
Genomic data in the All of Us Research Program

https://doi.org/10.1038/s41586-023-06957-x
Received: 22 July 2022
Accepted: 8 December 2023
Published online: 19 February 2024

The All of Us Research Program Genomics Investigators*

Comprehensively mapping the genetic basis of human disease across diverse individuals is a long-standing goal for the field of human genetics[1–4]. The All of Us

Nature, Feb 2024



All of Us Portal

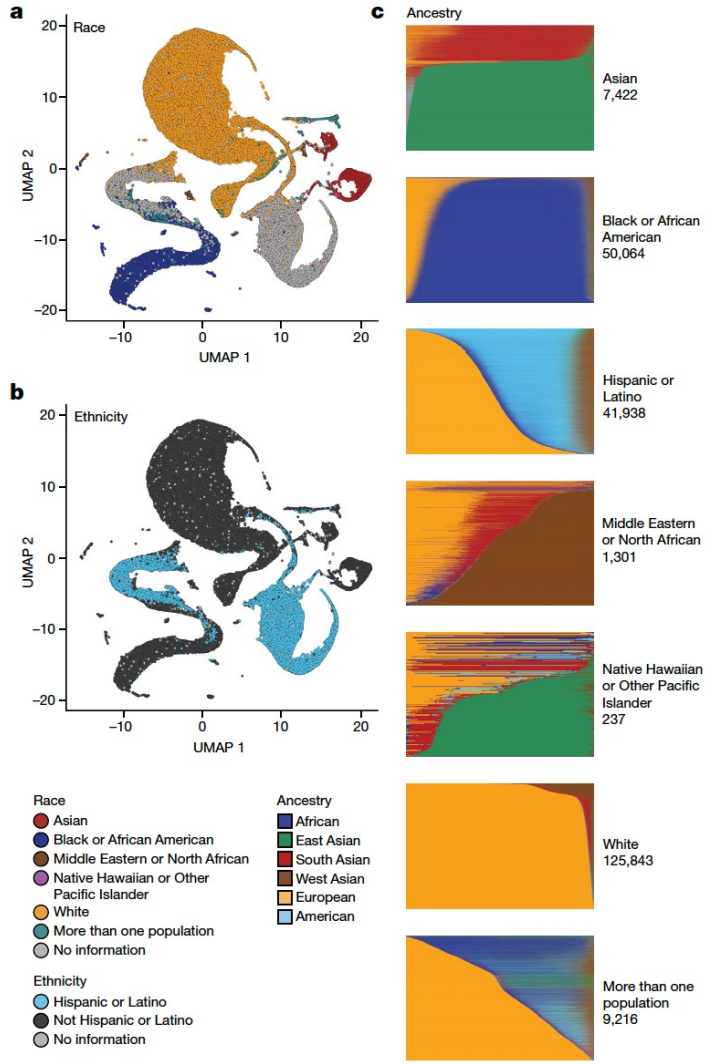
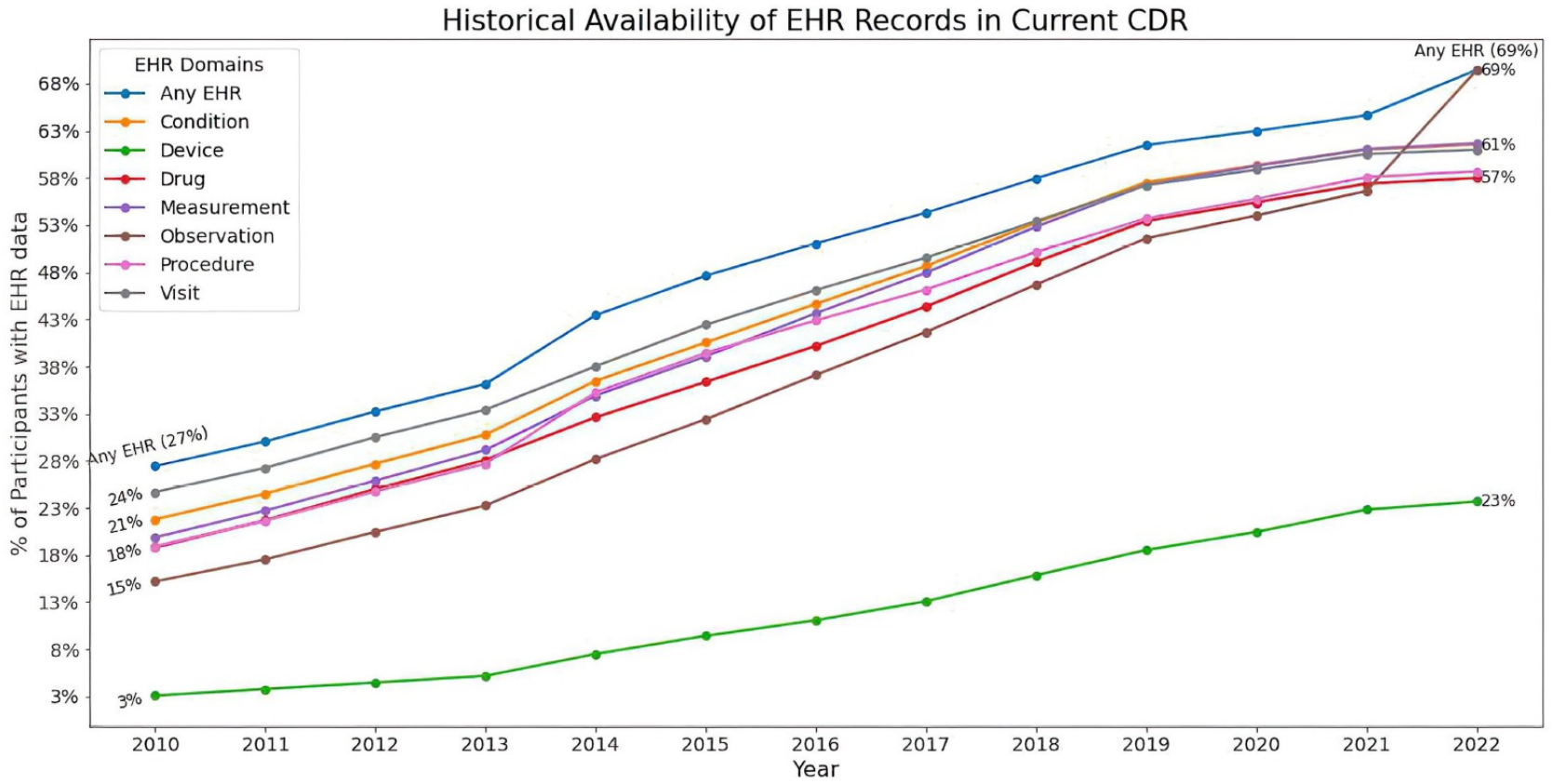


Fig. 2 | Genetic ancestry in All of Us. a, b Uniform manifold approximation and

Genomic data in the All of Us Research Program

https://doi.org/10.1038/s4158
Received: 22 July 2022
Accepted: 8 December 2023
Published online: 19 February 2

Article

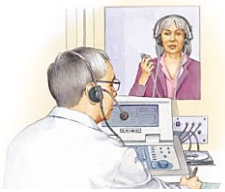


Extended Data Fig. 1 | Historic availability of EHR records in All of Us v7 Controlled Tier Curated Data Repository (N = 413,457). For better visibility, the plot shows growth starting in 2010.

Investments vs. Gains

Precision Medicine at what cost?

F (PM)=Social and economic PM Model



None

Weeks

Months

Years

$100

$1000

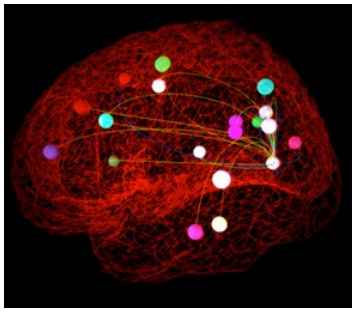
$10,000

$100,000

Condition Diagnosis Treatment Benefit Cost

Big Data transforms the Economy

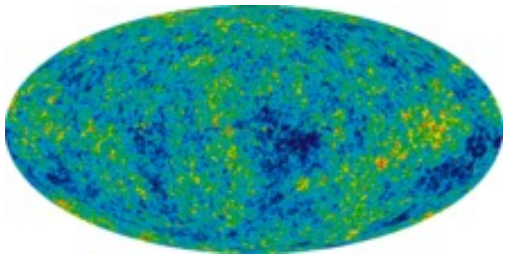
High energy physics -
Large Hadron Collider



Neuroscience -
The Human Connectome Project

Ecology - Fluxnet

Genomics
DNA sequencer



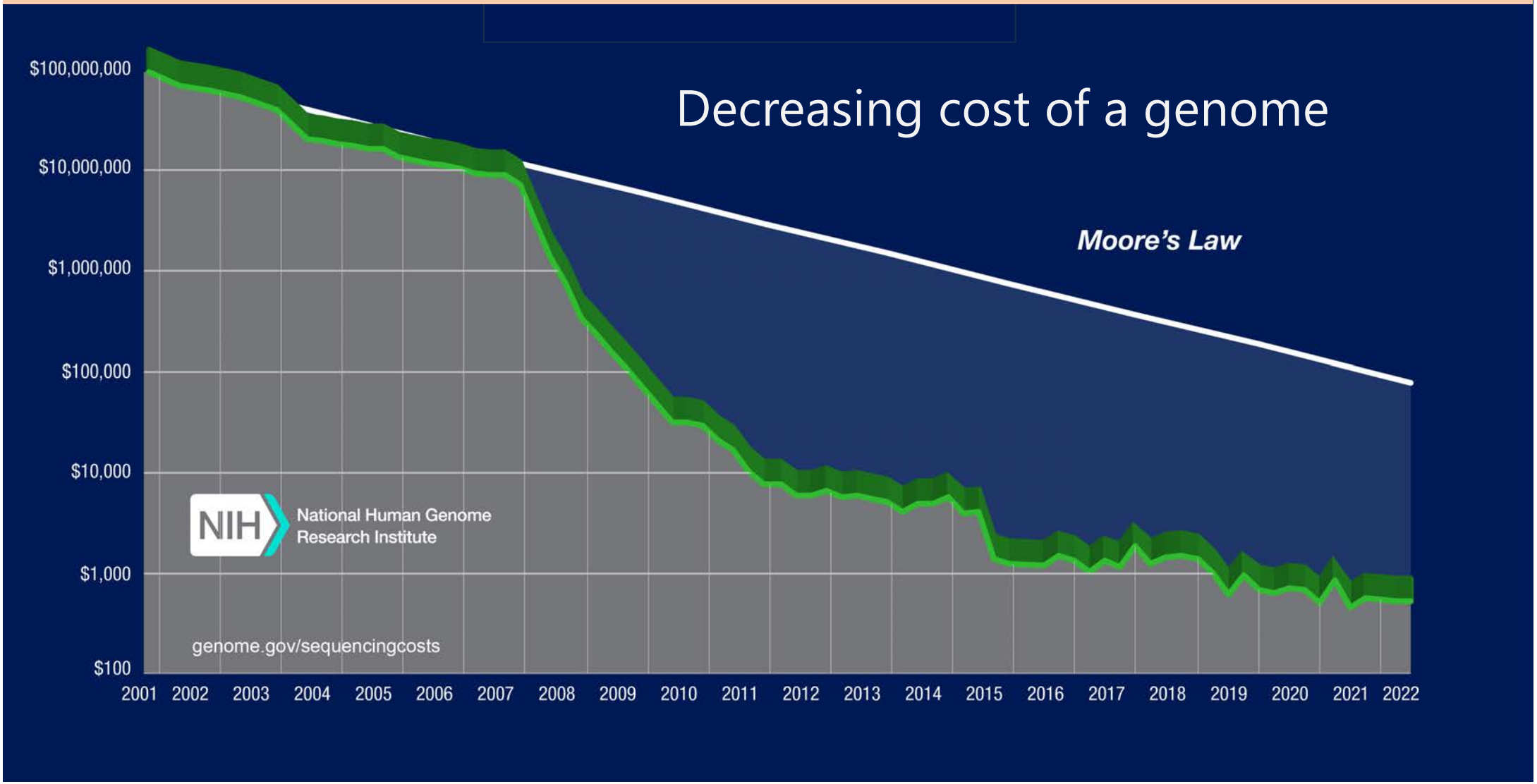
Astronomy -
Sloan Digital Sky survey

Knowledge of knowledge
Meta-data of scientific documents

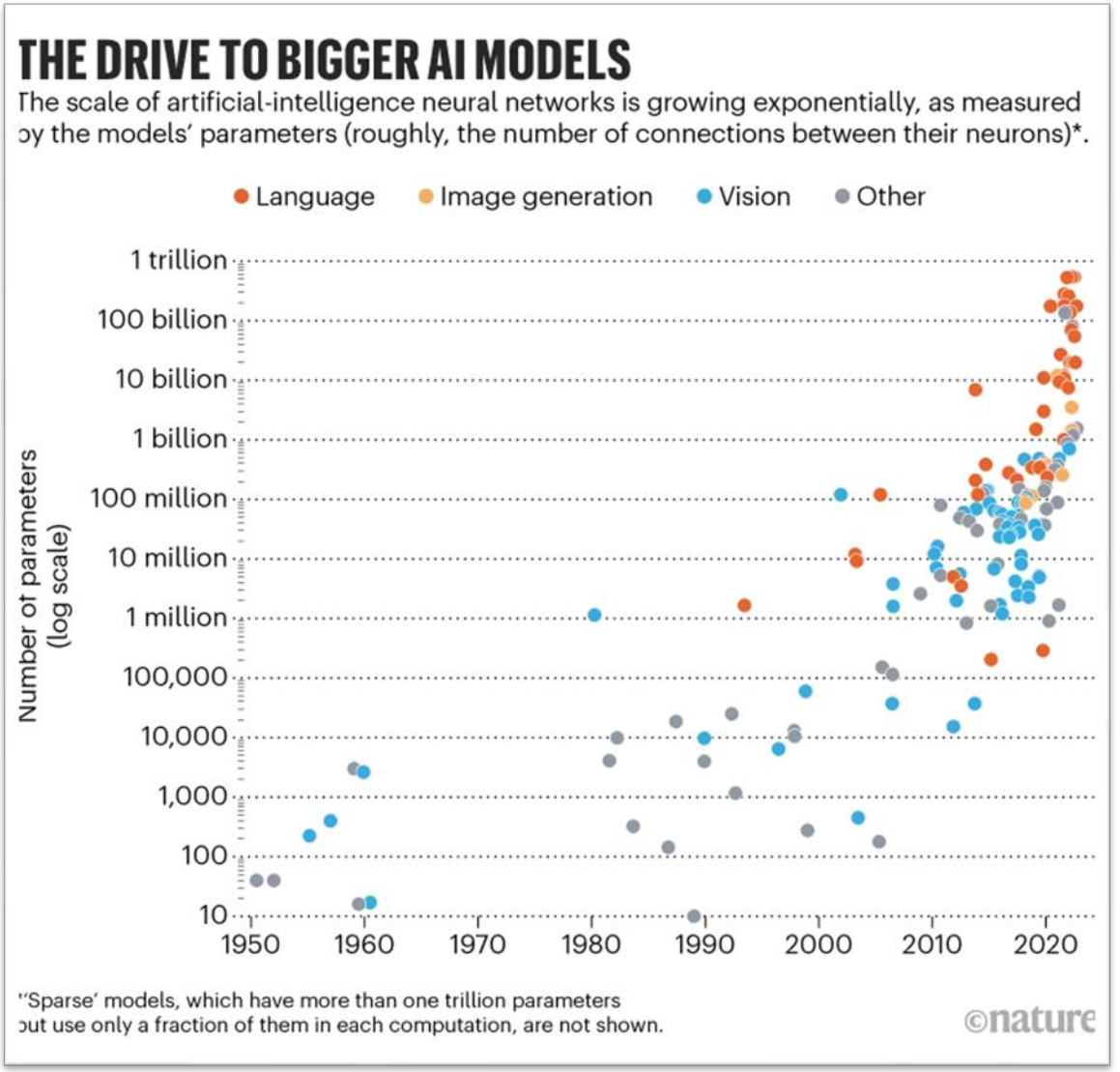
ISI Web of KNOWLEDGE
Transforming Research

Yale Lectures.GersteinLab.org

Big Data transforms the Economy

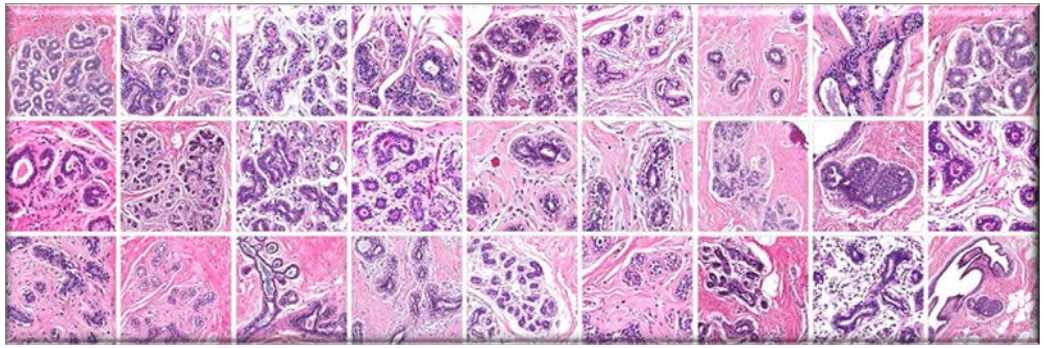


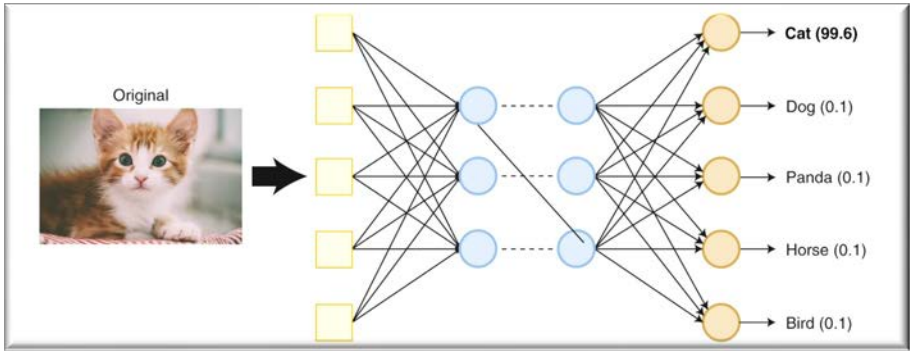
The explosion of available data and AI data content

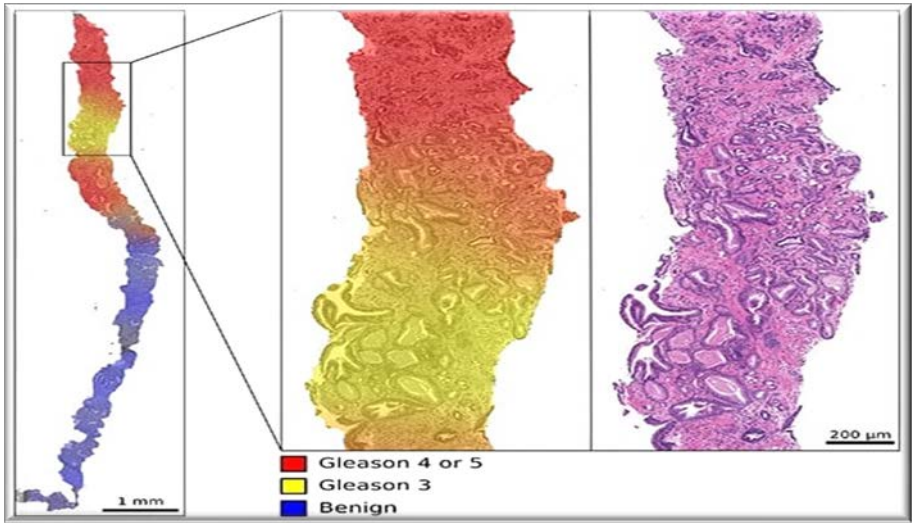


Nature 2023

AI will Change How Medicine is Practiced: example pathology







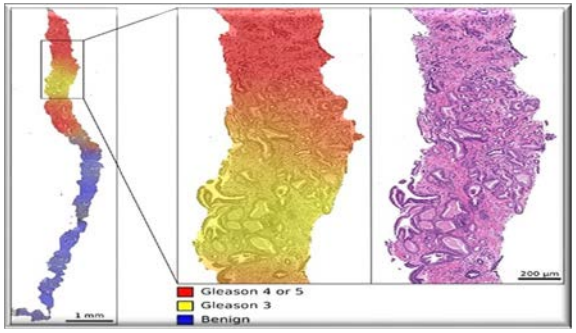
Big Data transforms the Economy

Phase 1

Assisting Pathologists

Costly systems provide help in daily workflow of diagnosis and reporting

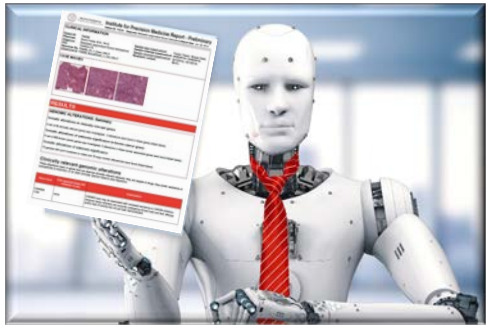
Phase 2



Democratizing Pathology

Costly systems replace the need for expert pathologists assisting non-expert pathologists

Phase 3



Redefining Diagnostic Profession

Costly systems replace costly pathologists using massive data sources

SMALL DATA

Where are you?

Where have you been?

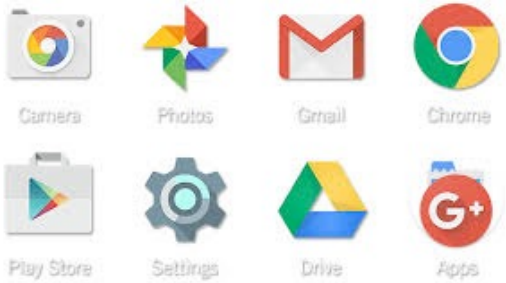
What do you buy?

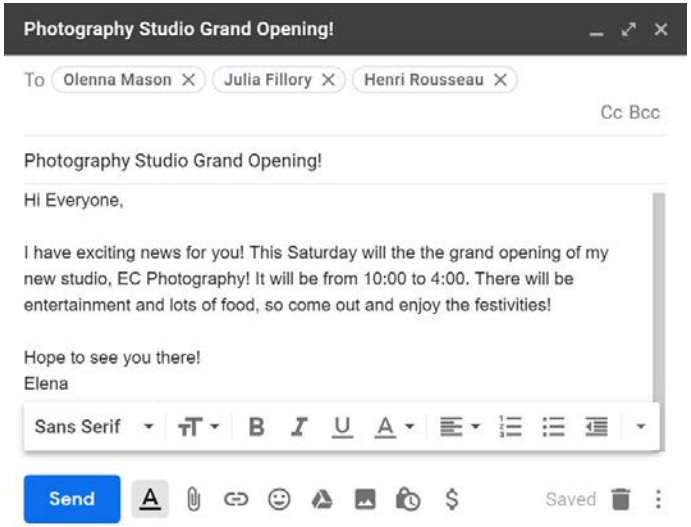
How often do you write e-mails?

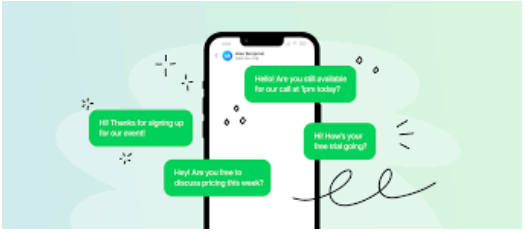
How many people do you live with?

What do you look for in the Internet?
When? How often?

But small data, too…








Are you worried?


NETFLIX
STRANGER THINGS
WEDNESDAY
NIGHT AGENT
ONE PIECE
HEARTSTONE
THE WITCHER
Glass Onion
EXTRACTION 2
THE LINCOLN LAWYER
SQUID GAME


Google Maps


Spotify


Good morning
Recently played
Your top mixes
Chaise Lounge

Genomic Data Protection

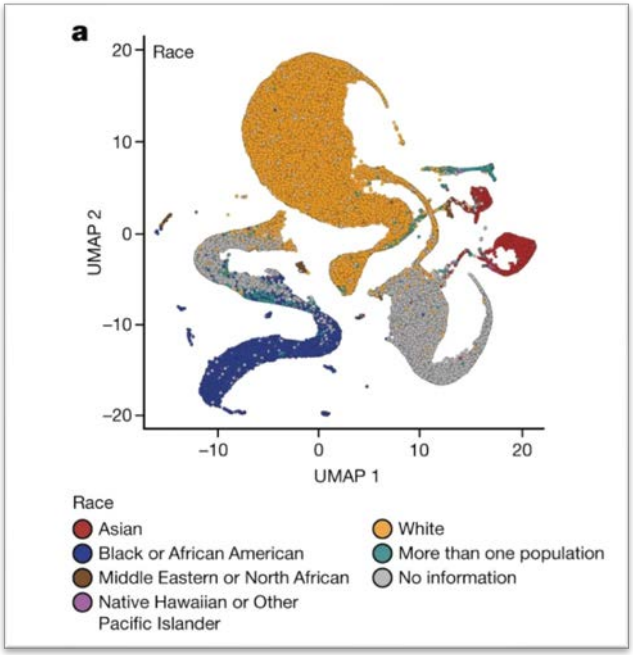
The dilemma of genomic research: Information sharing is against data privacy, but society benefits from medical research.

Balance: Risk/Benefits

NEWS | 23 February 2024

‘All of Us’ genetics chart stirs unease over controversial depiction of race

Debate over figure connecting genes, race and ethnicity reignites concerns among geneticists about how to represent human diversity.

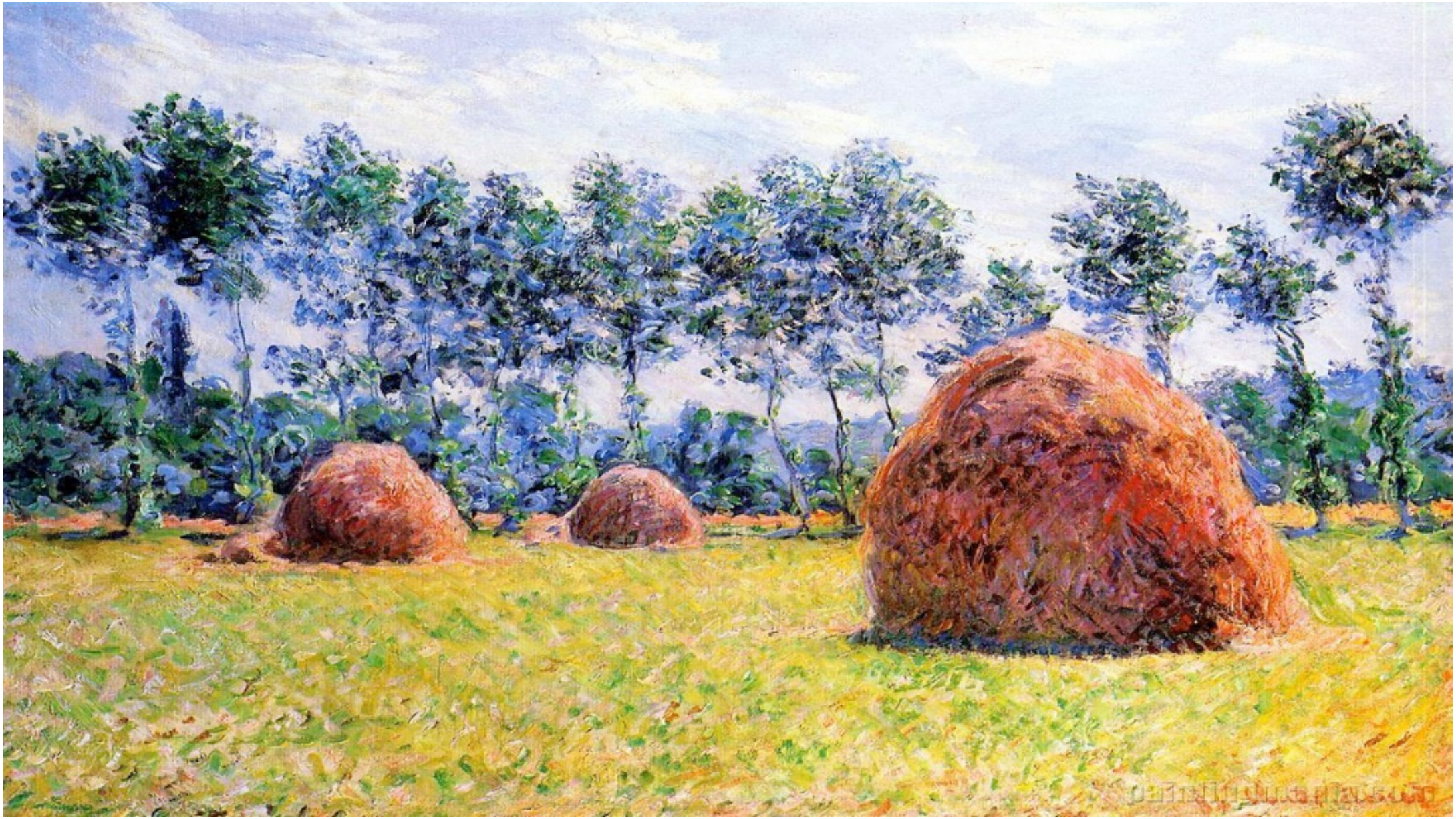


“genetic variation is a **continuum**, and thus **genetic ancestry cannot be objectively carved out into discrete groups**”, says Roshni Patel, a statistical geneticist who works with Pritchard at Stanford University.

To a layperson, the chart shows **several distinct colourful blobs** that could be misinterpreted as supporting genetic essentialism — the pseudoscientific belief that racial or ethnic groups are distinct genetic categories, and that individuals of the same group are genetically similar, Birney says. That is the opposite of what the data show, Bick says. “**Our analysis reaffirms that race and ethnicity are social constructs that do not have a basis in genetics”.**

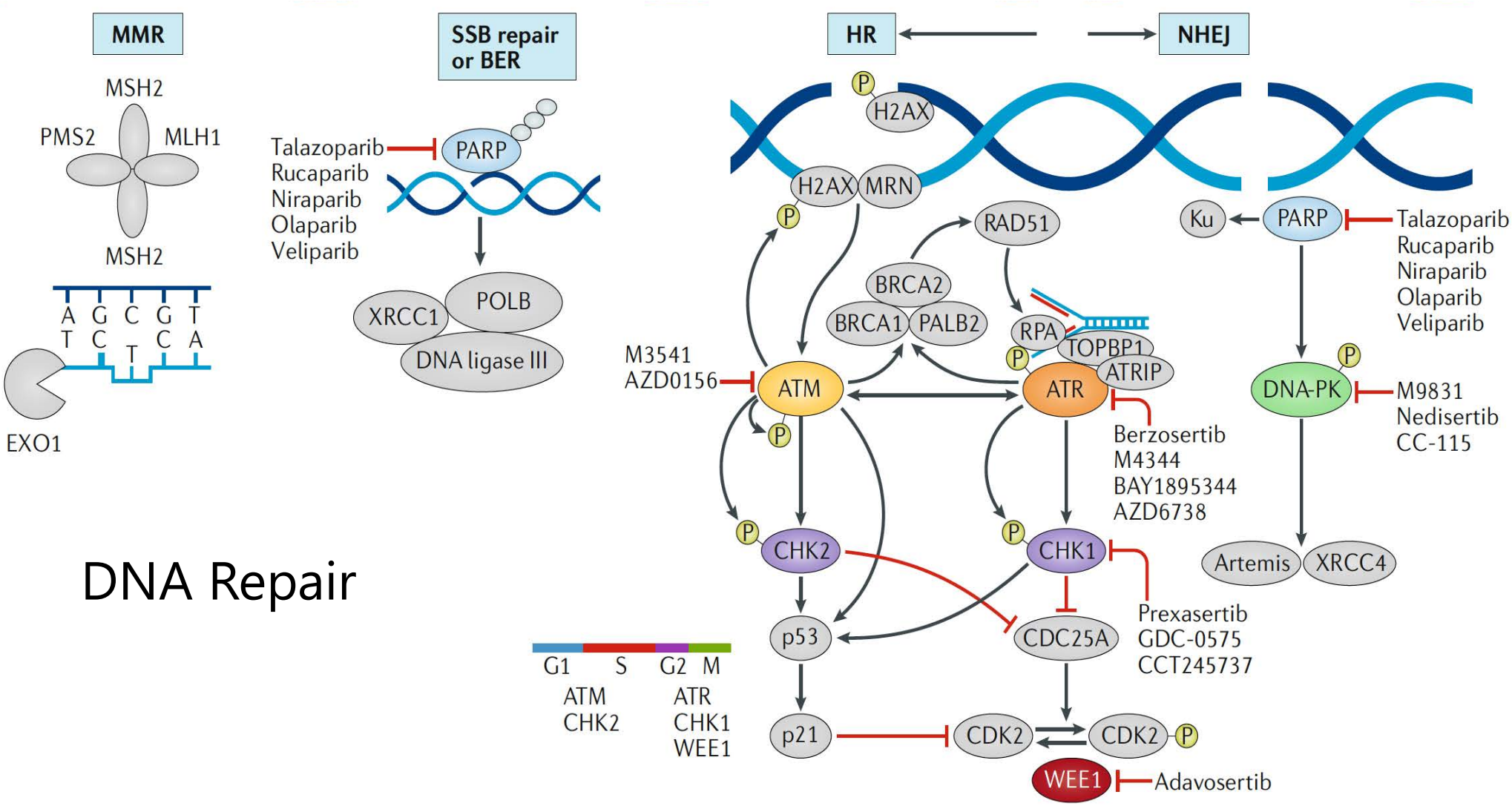
Learning Solutions for the Health System

- **Continuous** improvement of standard of care treatment.
- **Integrative dynamic analysis** of patient data and "omics" data nominate novel treatment strategies.
- **Individualize** treatment to patient's specific circumstances (e.g., genome, lifestyle, environment)
- Bedside to Bench **scientific findings will improve training, education, and care.**

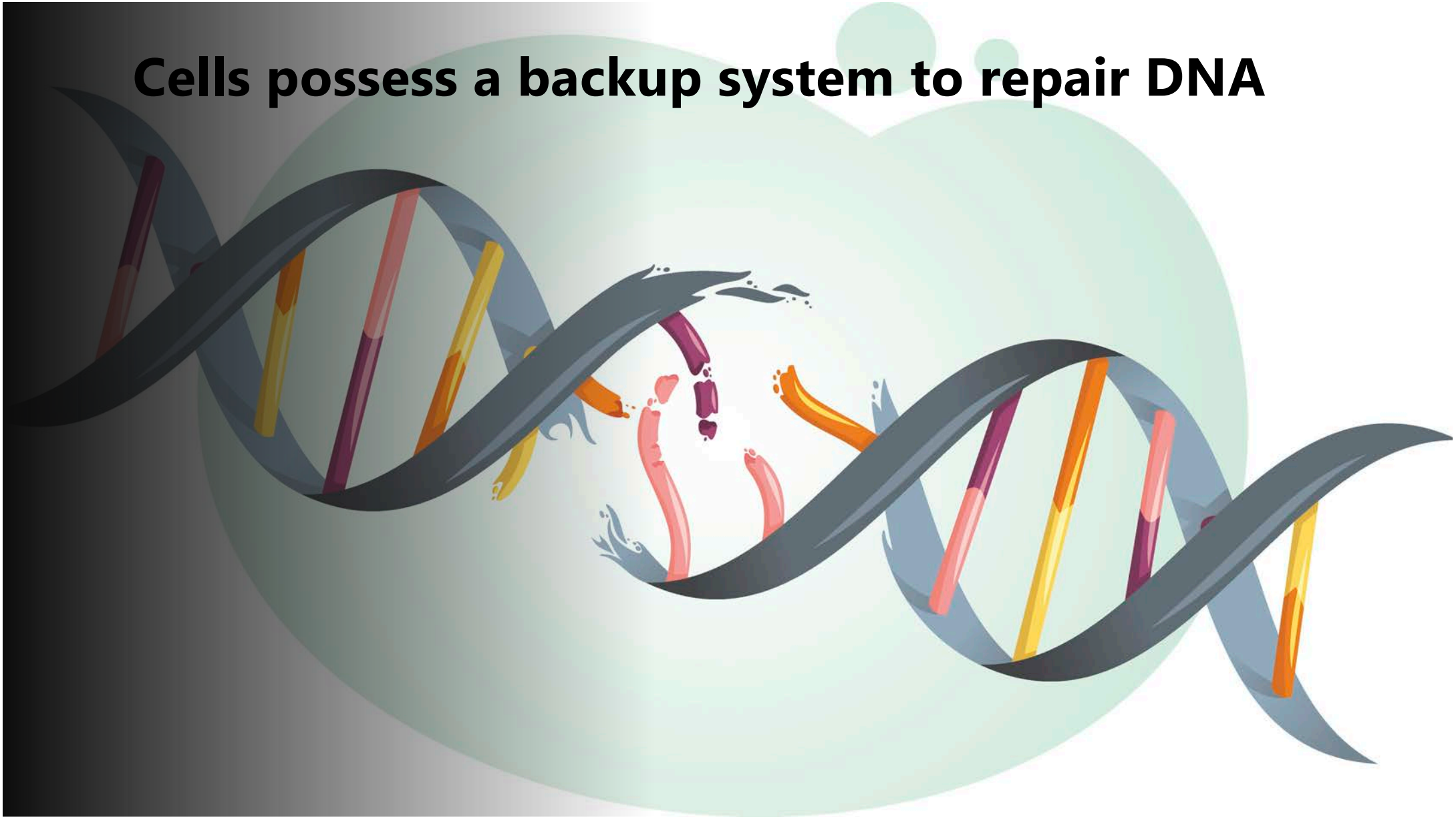


Basic Understanding. New Treatments

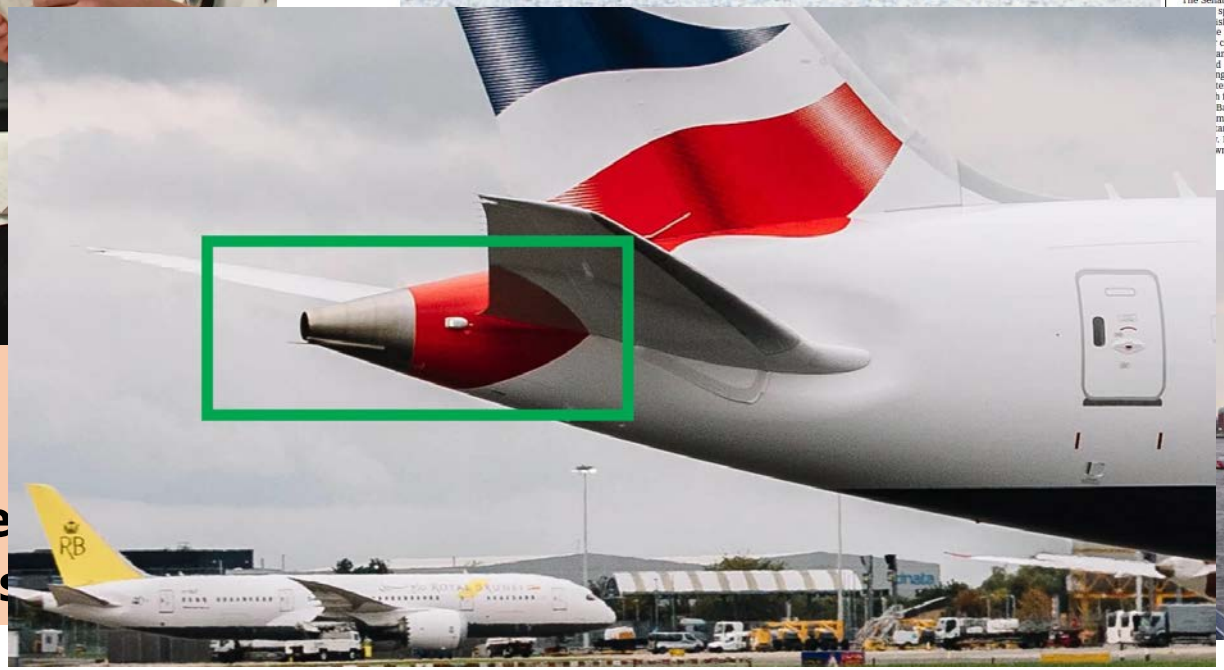
DNA Repair

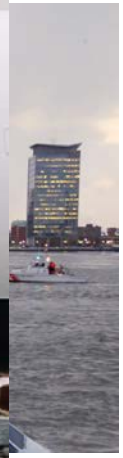

MMR
MSH2
PMS2
MLH1
MSH2
A G C G T
T C T C A
EXO1
SSB repair or BER
Talazoparib
Rucaparib
Niraparib
Olaparib
Veliparib
PARP
XRCC1
POLB
DNA ligase III
HR
NHEJ
P
H2AX
H2AX
MRN
RAD51
Ku
PARP
Talazoparib
Rucaparib
Niraparib
Olaparib
Veliparib
BRCA2
BRCA1
PALB2
RPA
TOPBP1
ATRIP
M3541
AZD0156
ATM
ATR
DNA-PK
M9831
Nedisertib
CC-115
Berzosertib
M4344
BAY1895344
AZD6738
CHK2
CHK1
Artemis
XRCC4
Prexasertib
GDC-0575
CCT245737
p53
CDC25A
G1
S
G2
M
ATM
CHK2
ATR
CHK1
WEE1
p21
CDK2
CDK2
WEE1
Adavosertib

Cells possess a backup system to repair DNA



Captain Chesley "Sully"
Sullenberger
and First Officer Jeff Skile
knew how to use backup s





"All the News That's Fit to Print"

The New York Times

Late Edition

Today, bitterly cold, partly sunny, high 17. Tonight, frigid, clearing, lighter winds, low 8. Tomorrow, still cold, sunshine, snow late at night, high 19. Weather map, Page B10.

VOL. CLVIII . . No. 54,557 ©2009 The New York Times NEW YORK, FRIDAY, JANUARY 16, 2009 $1.50

SENATE RELEASES SECOND PORTION OF BAILOUT FUND

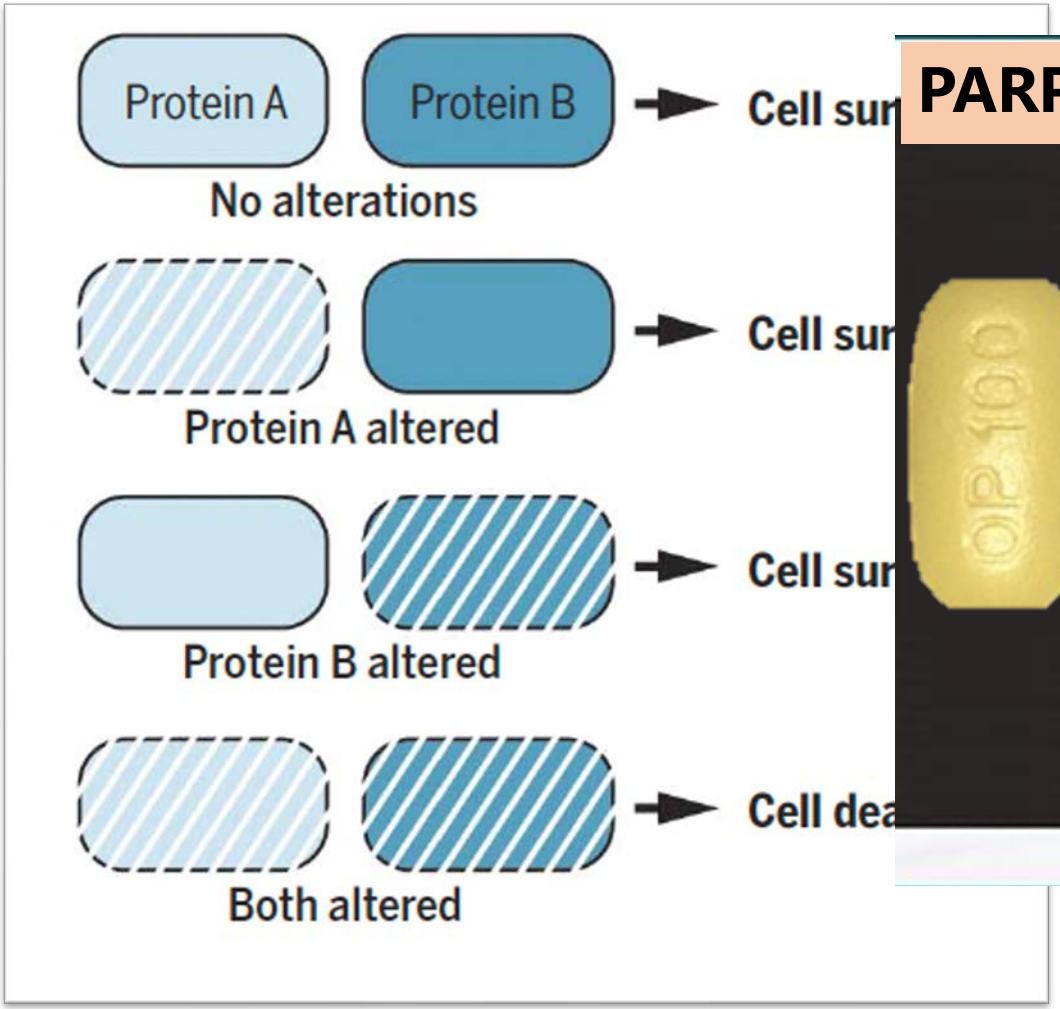
A VICTORY FOR OBAMA

Democrats in the House Offer an $825 Billion Recovery Plan

By DAVID M. HERSZENHORN

WASHINGTON — President-elect Barack Obama's economic agenda advanced rapidly in Congress on Thursday as the Senate voted to release the second half of the financial industry bailout fund and House Democrats unveiled an $825 billion fiscal recovery plan aimed at putting millions of unemployed Americans back to work.

The Senate action, by a vote of spares Mr. Obama a slative fight just as he e and gives him a $350 chest to further stabil- ancial sector. The vote d renewed distress in ng industry, including terioration of Citigroup h for more government Bank of America. ma had personally lob- ant senators to release . His top economic ad- wrence H. Summers,



PARP inhibitor

Lord and Ashworth, Science 2017

Read More

Redundant engineering or synthetic lethality

Peter Nelson, MD
Dream Team Principal
University of Washington /
Fred Hutchinson Cancer Research Center

FRED HUTCHINSON CANCER RESEARCH CENTER

Arul Chinnaiyan, MD, PhD
Dream Team Co-Leader
University of Michigan

BROAD INSTITUTE

Levi Garraway, MD, PhD
Dream Team Principal
The Broad Institute

DANA-FARBER CANCER INSTITUTE

Philip Kantoff, MD
Dream Team Principal
Dana Farber Cancer Institute

STAND UP TO CANCER

UNIVERSITY OF MICHIGAN

Mark Rubin, MD
Dream Team Principal
Weill Cornell

Johann de Bono, MD, PhD
Institute of Cancer Research/
Royal Marsden Hospital

PROSTATE CANCER FOUNDATION
Accelerating the world's most promising research

Charles Sawyers, MD
Dream Team Co-Leader
Memorial Sloan Kettering Cancer Center

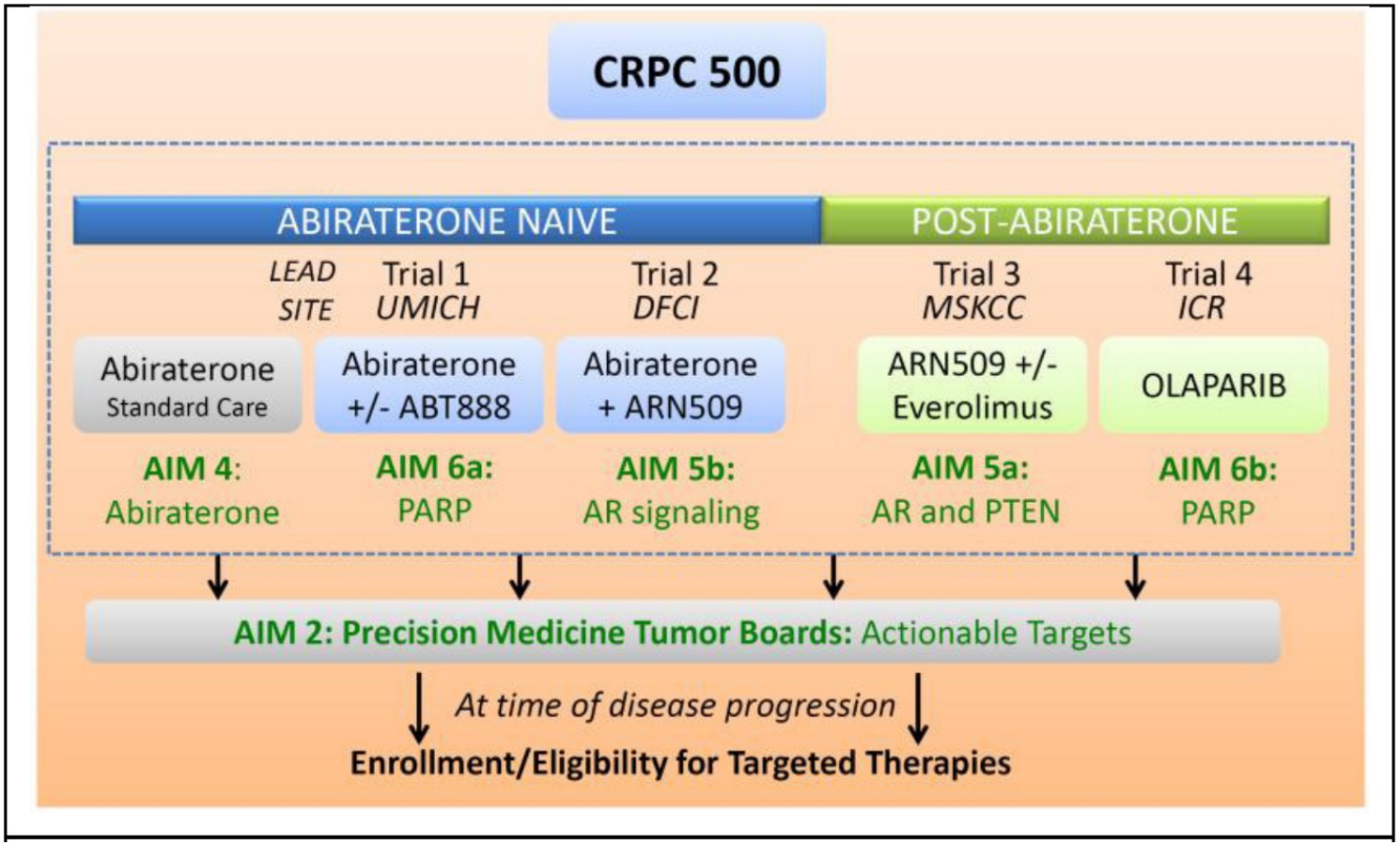
MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

ICR The Institute of Cancer Research

THE ROYAL MARSDEN

Read more

SU2C/PCF Precision Oncology Trial 2013: Prostate Cancer

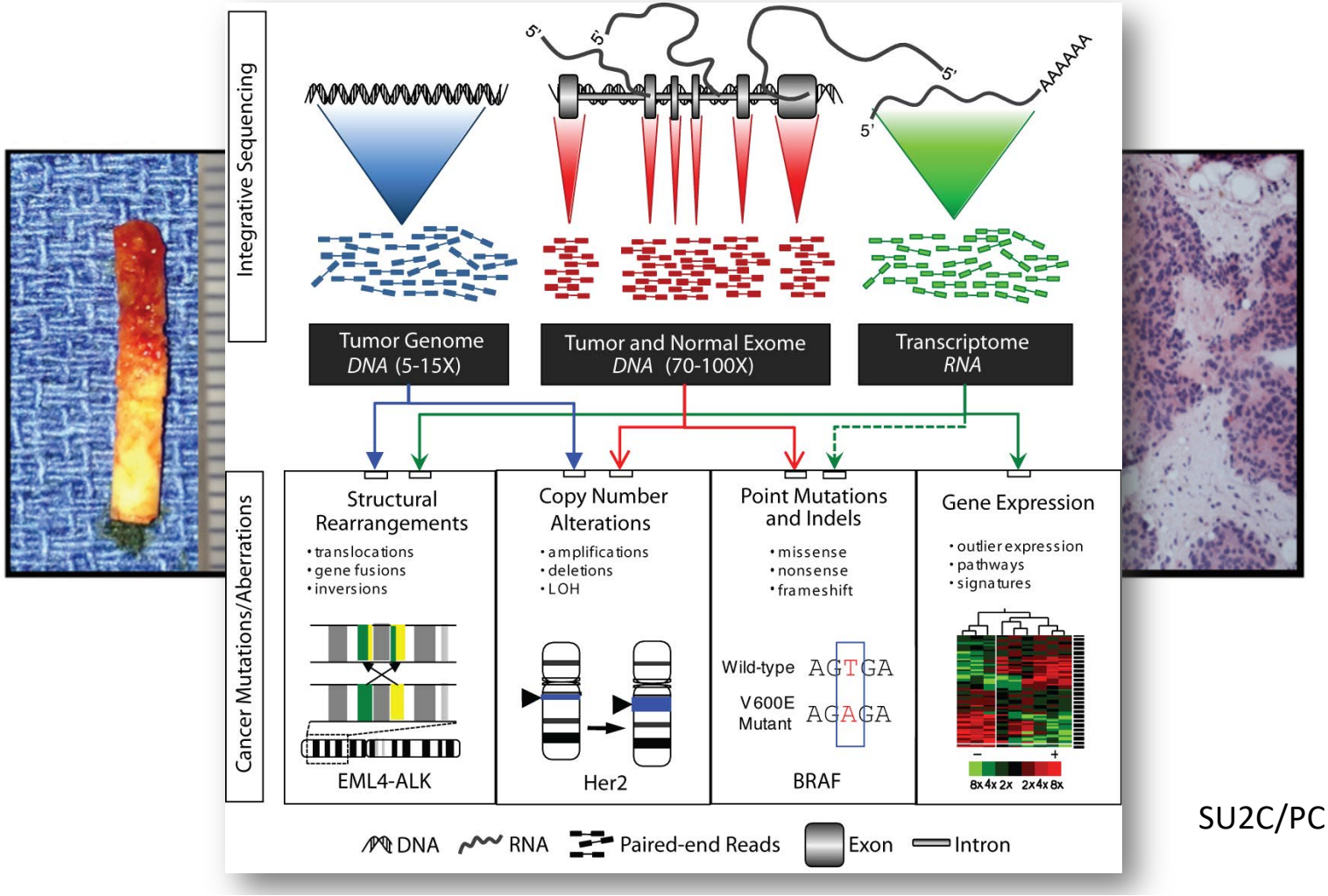


Goals:

1) Enroll 500 Men with metastatic prostate cancer.
2) Perform comprehensive "omics" analysis of their metastatic tumor during treatment.
3) Provide information to guide the next treatment option.
4) Discover new treatments through basic science and translation research.

SU2C/PCF Precision Oncology Trial 2013: Prostate Cancer

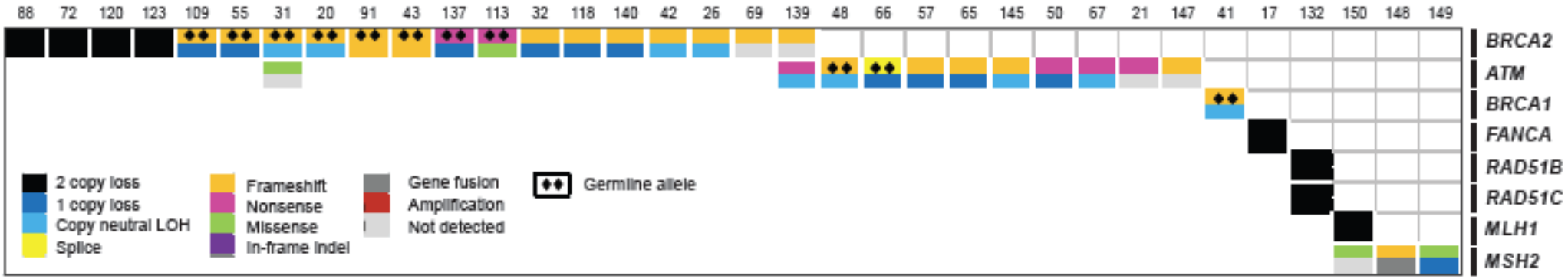
Processing metastatic samples for pathology, RNAseq and WES



Read more

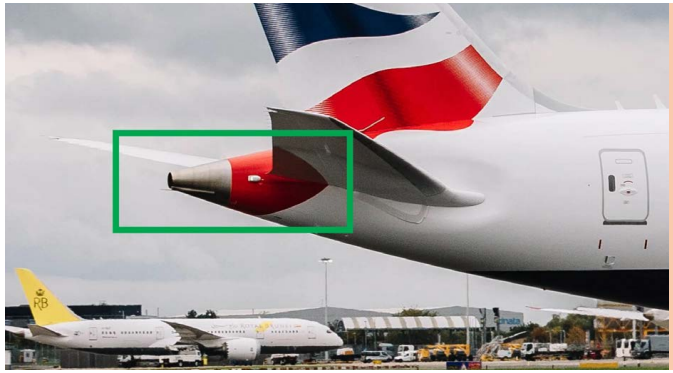
SU2C/PCF., Cell 2015

Significant Alterations in DNA Repair Genes:



Robinson et al, Cell 2015

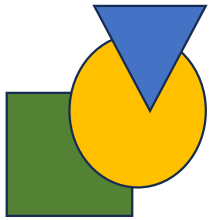
Read more



BRCA1/2 and other DNA Backup System genes disrupted in 20-30% of Tumors

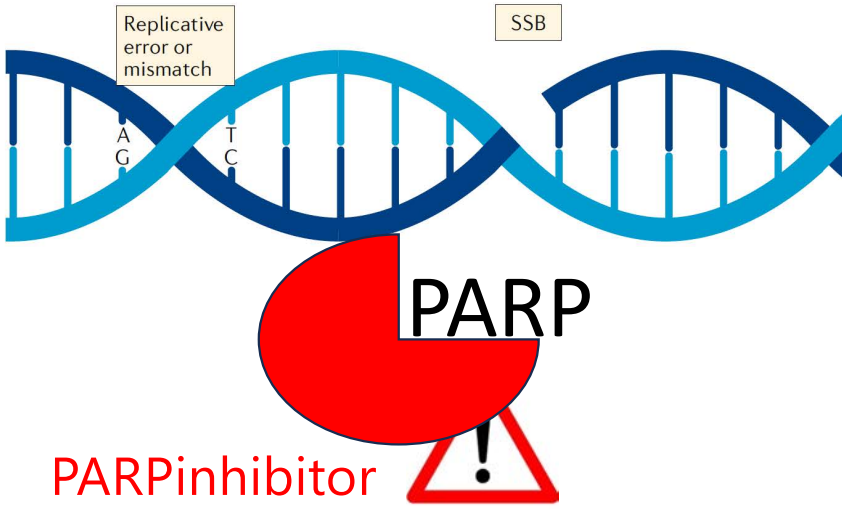
DNA repair backup systems are being exploited for precision medicine

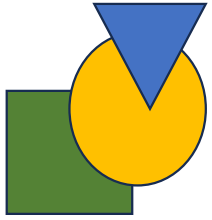
PARP



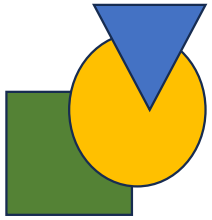
DNA Repair Machinery

DNA repair backup systems are being exploited for precision medicine

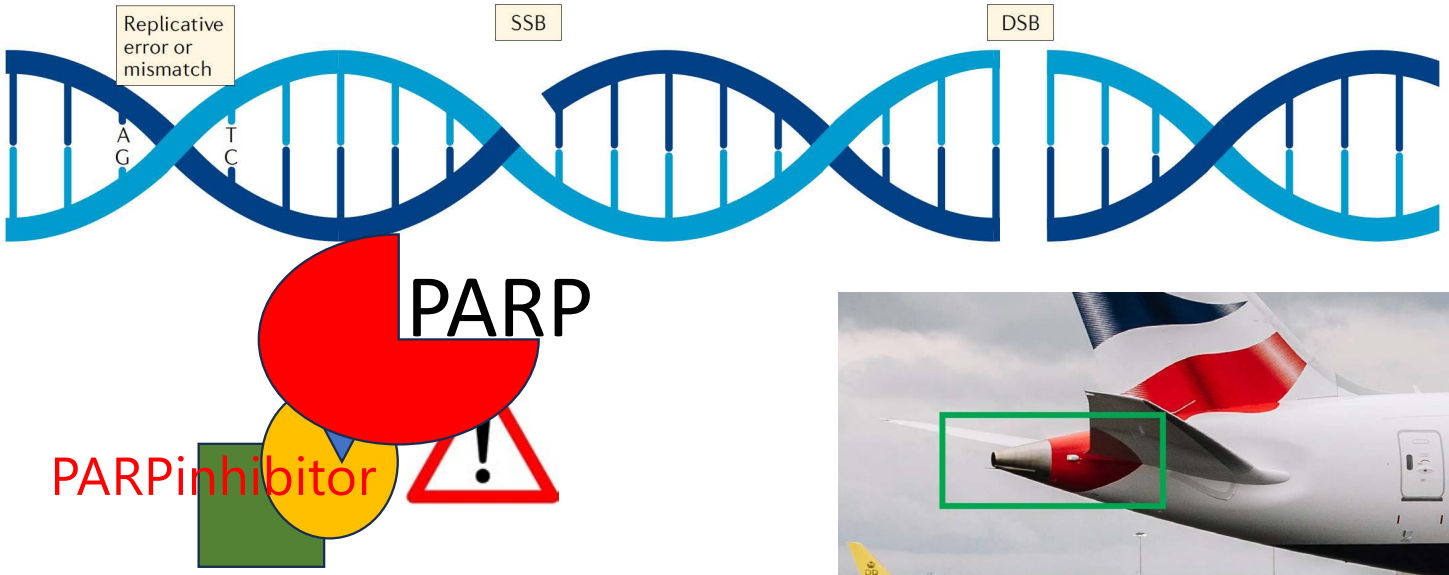




DNA Repair Machinery



DNA repair backup systems are being exploited for precision medicine



BRCA1/2 and other DNA Backup System genes disrupted in 20-30% of Tumors

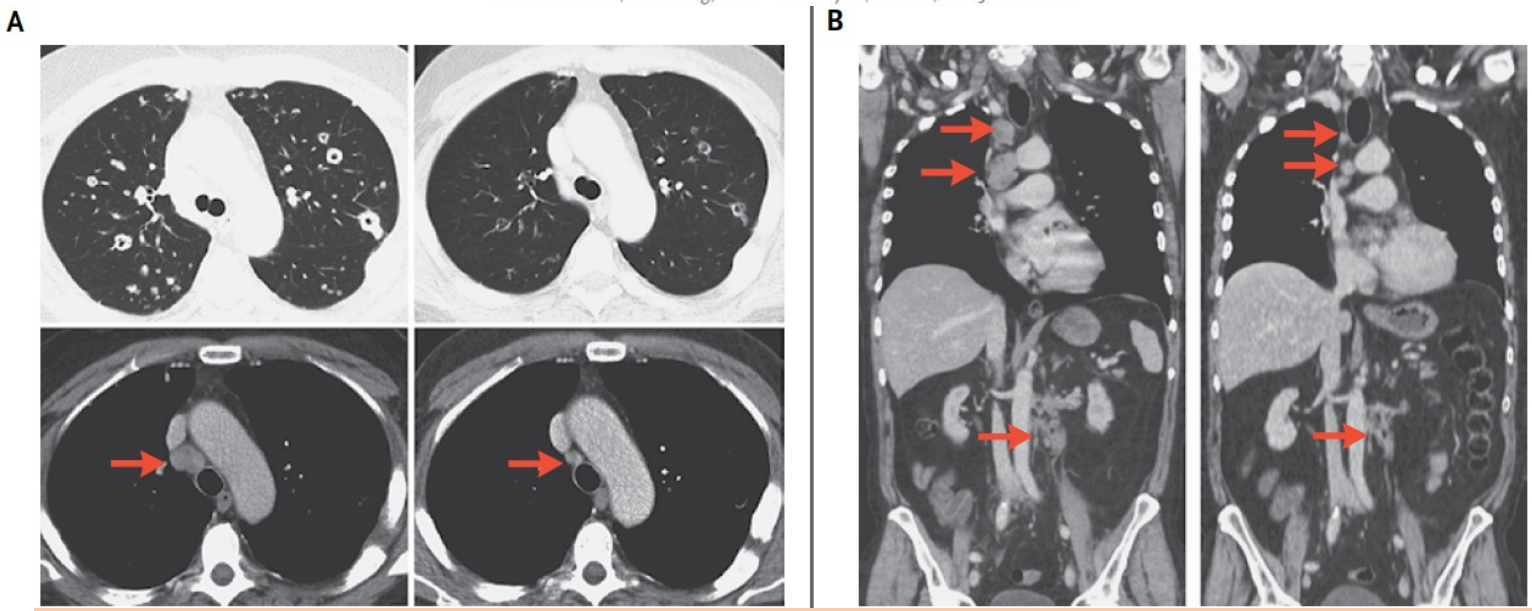
DNA Repair Backup Machinery

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono



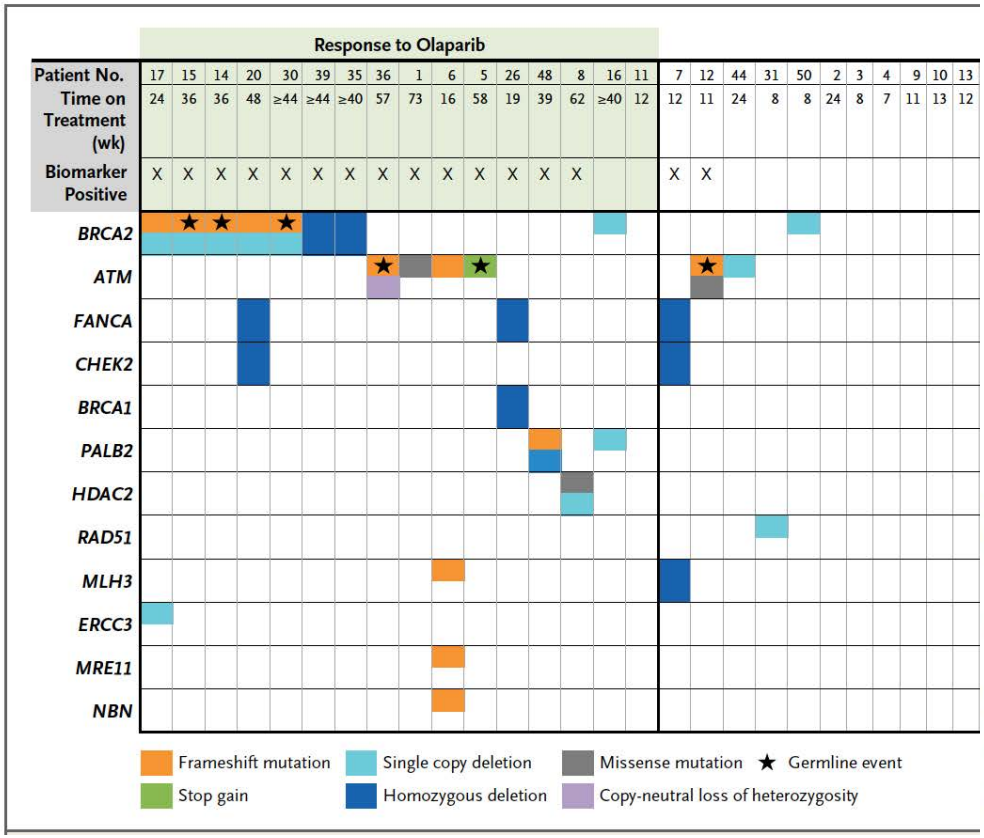
Johann de Bono, MD, PhD
Institute of Cancer Research/
Royal Marsden Hospital

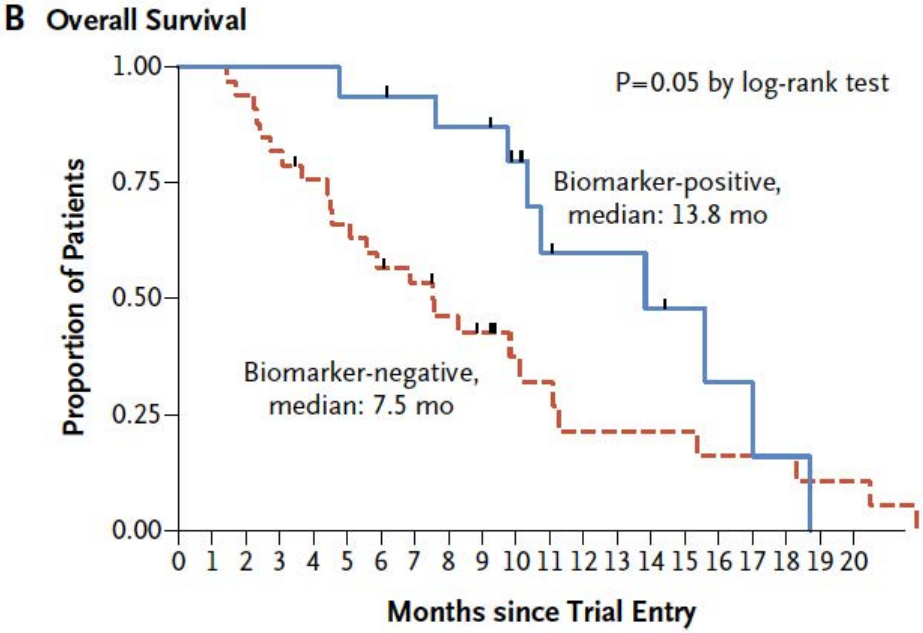
ICR The Institute of Cancer Research

THE ROYAL MARSDEN

TOPARP Trial shows 30% Long Term Responders

NEJM, Oct 29 2015





No. at Risk

Biomarker-negative	33	33	31	27	24	21	18	16	13	11	7	6	4	4	4	4	3	3	3	2	2
Biomarker-positive	16	16	16	16	16	15	15	14	13	13	10	6	5	5	4	3	2	2	1	0	0

No. of Events

Biomarker-negative	0	2	4	2	3	3	1	2	1	1	1	2	0	0	0	1	0	0	1	0	–
Biomarker-positive	0	0	0	0	1	0	0	1	0	1	2	0	0	1	0	1	0	2	0	0	–

NEJM, Oct 29 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer

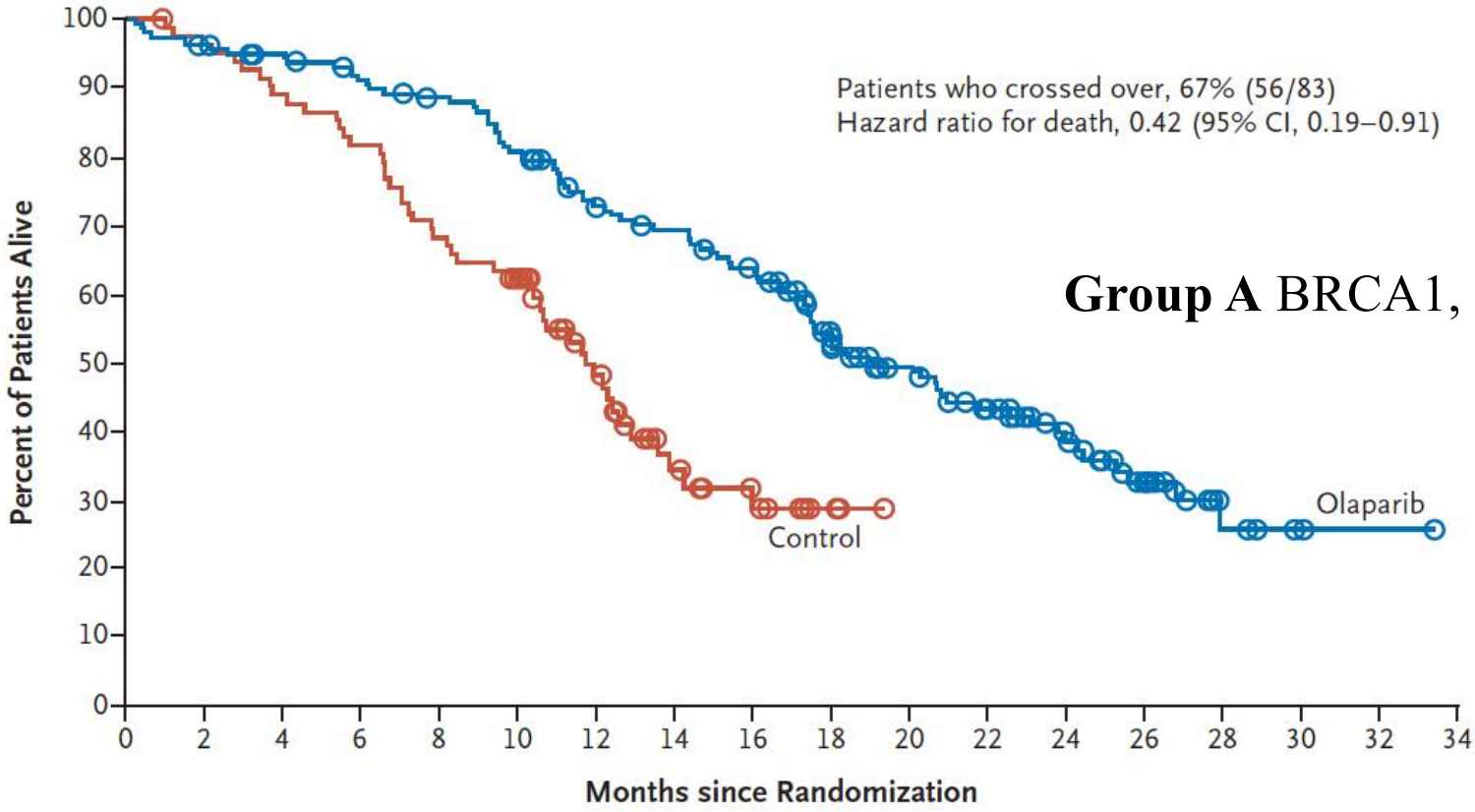
M. Hussain, J. Mateo, K. Fizazi, F. Saad, N. Shore, S. Sandhu, K.N. Chi, O. Sartor, N. Agarwal, D. Olmos, A. Thiery-Vuillemin, P. Twardowski, G. Roubaud, M. Özgüroğlu, J. Kang, J. Burgents, C. Gresty, C. Corcoran, C.A. Adelman, and J. de Bono, for the PROfound Trial Investigators*

Group A BRCA1, BRCA2, ATM

Group B: BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L

NEJM 2020

B Crossover-Adjusted Analysis of Overall Survival in Cohort A



Group A BRCA1, BRCA2, ATM

No. at risk																		
Olaparib	162	155	150	142	136	124	107	101	91	71	56	44	30	18	6	2	1	0
Control	83	79	73	67	56	47	29	15	9	3	0	0	0	0	0	0	0	0

NEJM 2020

Cells possess a backup system to repair DNA

Exploiting the weakness of cancer cells can lead to new **precision medicine** approaches…

How can precision medicine help resolve the pain?

Sickle Cell Anemia: Symptoms usually appear around 6 months.

<u>Common SSD Symptoms</u>

Anemia

Episodes of pain

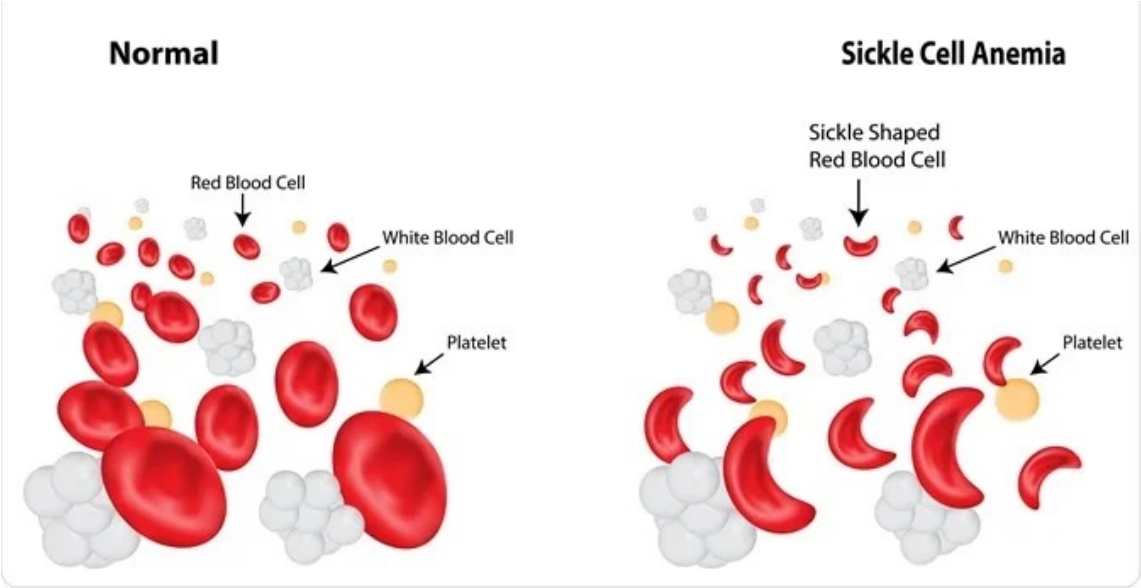
Swelling of hands and feet

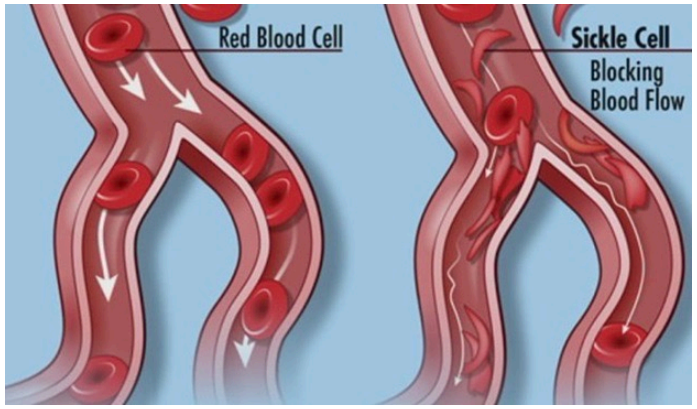
Frequent infections

Delayed growth or puberty

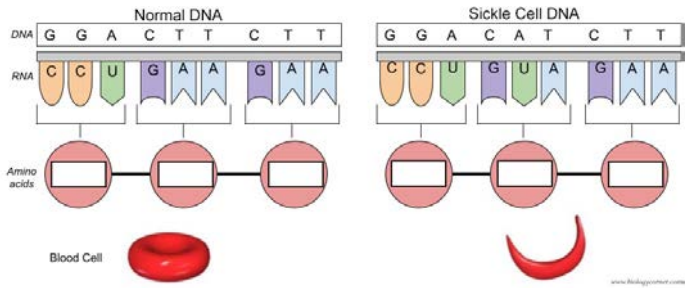
Vision problems

Sickle Cell Anemia: One base-pair mutation-
A spelling mistake that leads to chronic disease

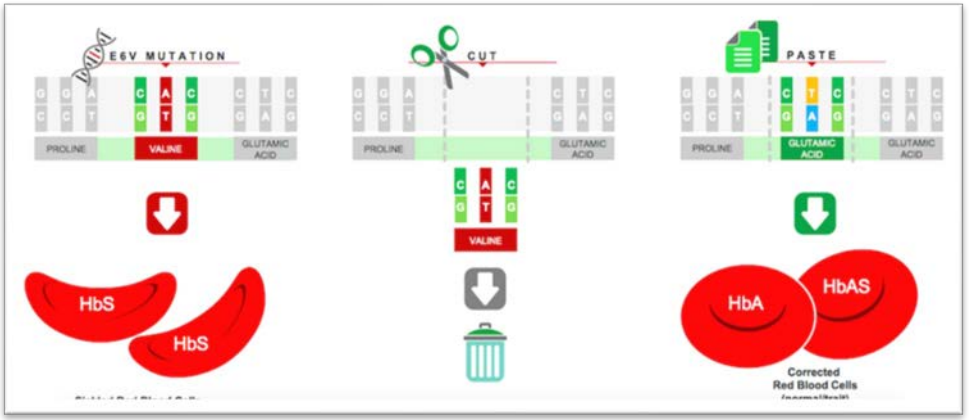




Monogenic Disease



Gene Editing through CRISPR-cas9 can correct defective red blood cells



VERTEX

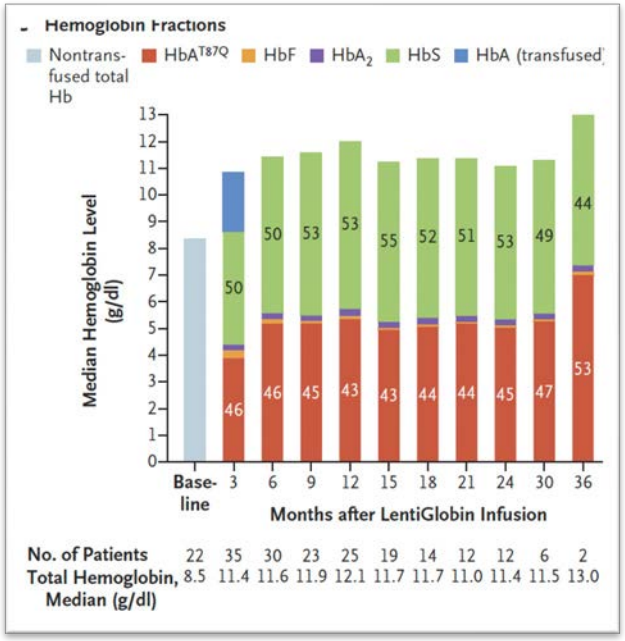
LentiGlobin

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 17, 2022 VOL. 386 NO. 7

Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

J. Kanter, M.C. Walters, L. Krishnamurti, M.Y. Mapara, J.L. Kwiatkowski, S. Rifkin-Zenenberg, B. Aygun, K.A. Kasow, F.J. Pierciey, Jr., M. Bonner, A. Miller, X. Zhang, J. Lynch, D. Kim, J.-A. Ribeil, M. Asmal, S. Goyal, A.A. Thompson, and J.F. Tisdale

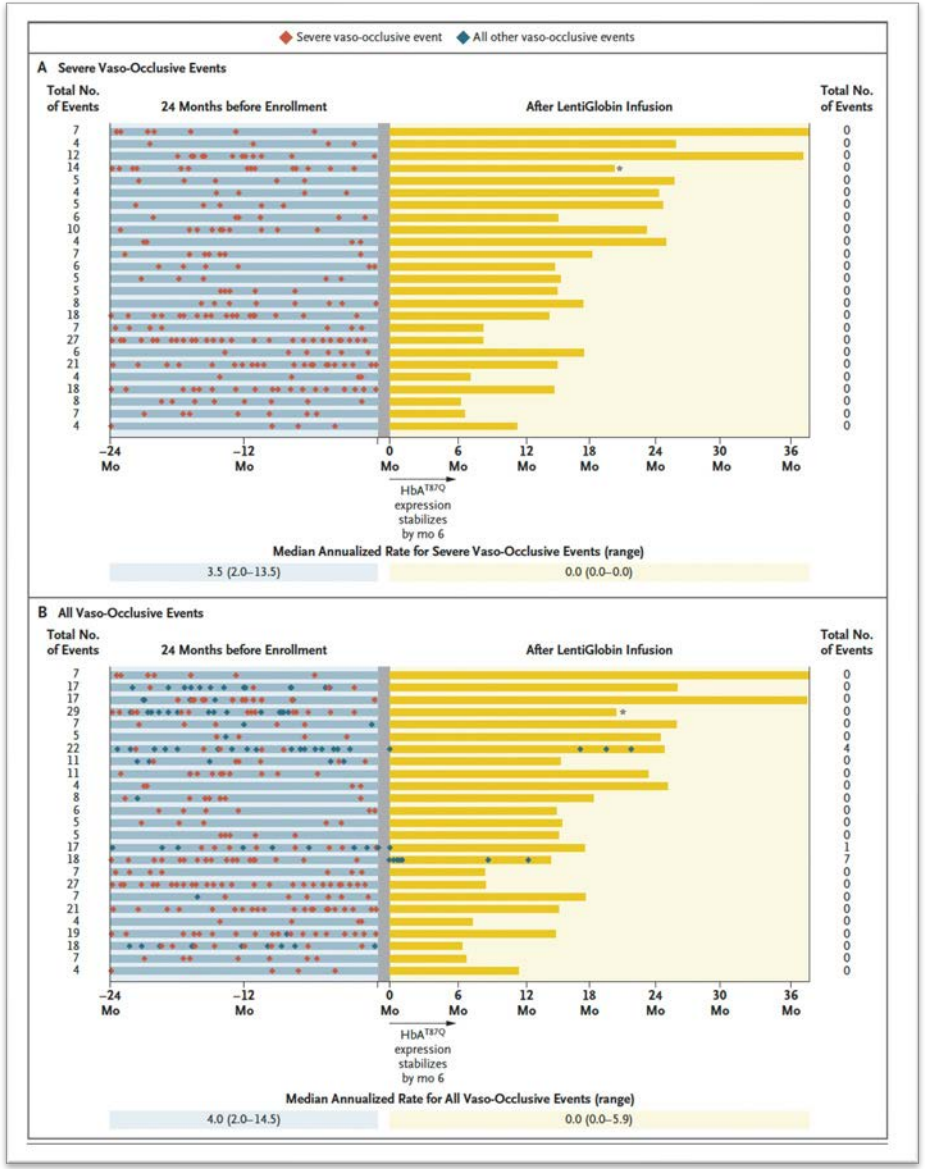


Feb 2022

LentiGlobin produces antisickling hemoglobin, Hb^{AT87Q}

After bone marrow transplantation, greater than 40% of red blood cells have non-sickling Hb

Read More




Sickle Cell Anemia: Cure in hand
Costly and complex but feasible

How does our DNA past fit into our precision medicine future ?

Article

Elevated genetic risk for multiple sclerosis emerged in steppe pastoralist populations

https://doi.org/10.1038/s41586-023-06618-z

Received: 21 September 2022

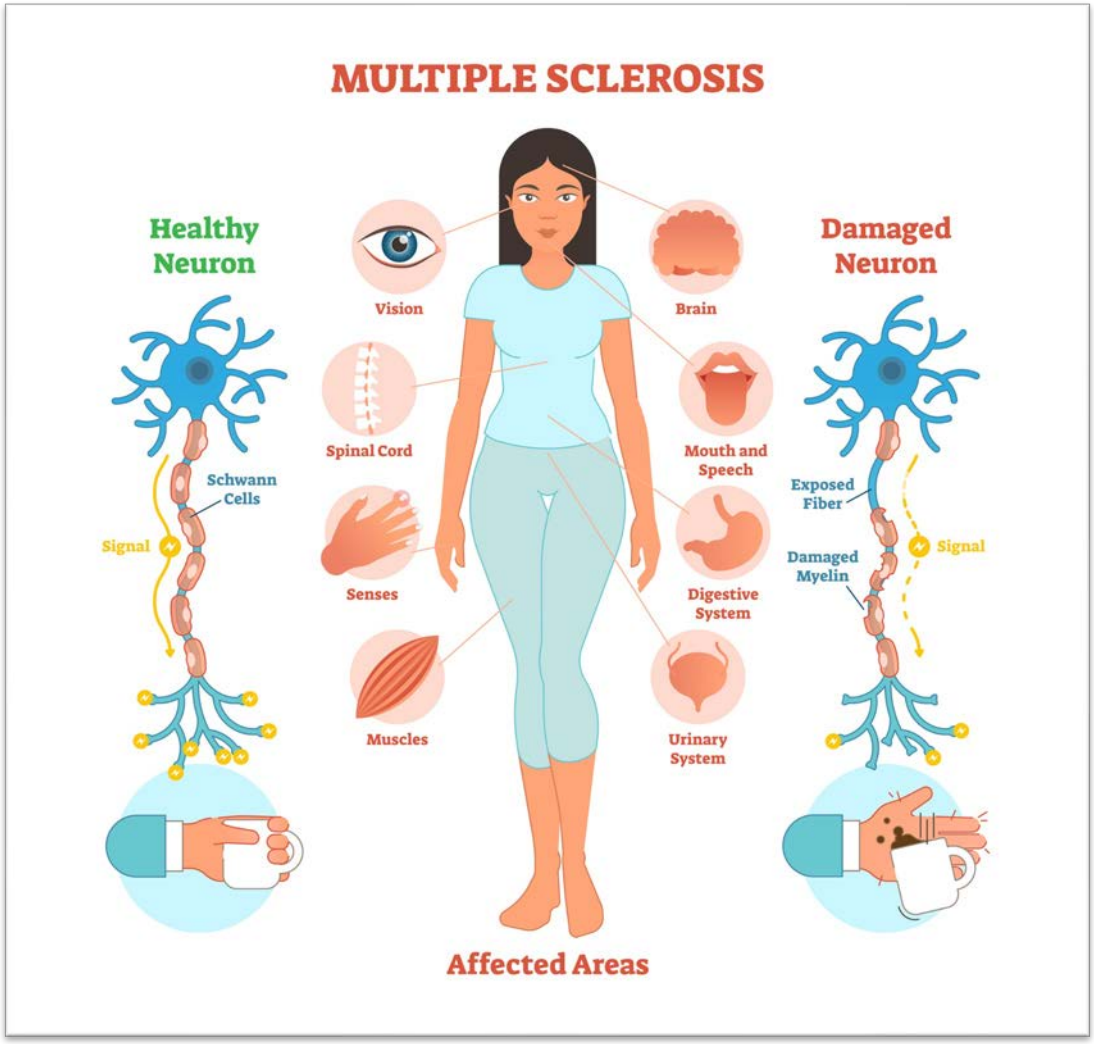
Accepted: 6 September 2023

Published online: 10 January 2024

Open access

Check for updates

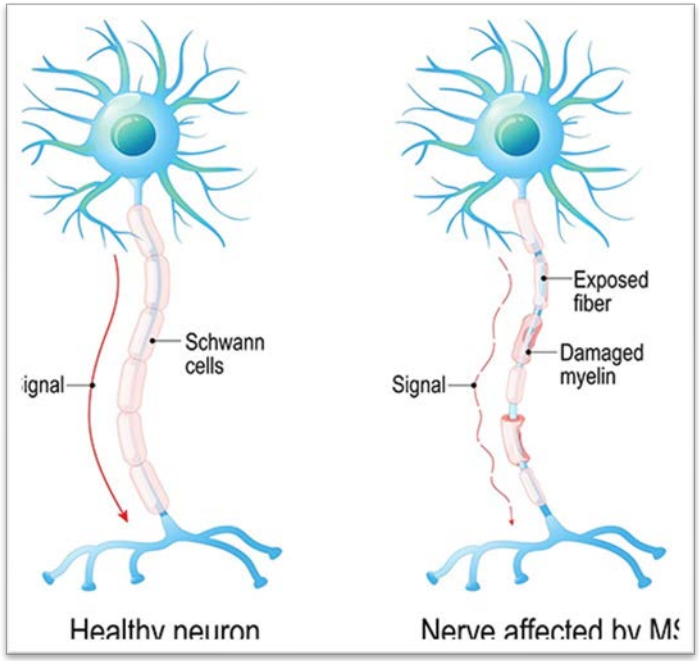
William Barrie[1,20,21], Yaoling Yang[2,3,21], Evan K. Irving-Pease[4,21], Kathrine E. Attfield[5,21], Gabriele Scorrano[4,21], Lise Torp Jensen[5,6,21], Angelos P. Armen[5], Evangelos Antonios Dimopoulos[7], Aaron Stern[8], Alba Refoyo-Martinez[4], Alice Pearson[9], Abigail Ramsøe[4], Charleen Gaunitz[4], Fabrice Demeter[4,10], Marie Louise S. Jørkov[11], Stig Bermann Møller[12], Bente Springborg[12], Lutz Klassen[13], Inger Marie Hyldgård[13], Niels Wickmann[14], Lasse Vinner[4], Thorfinn Sand Korneliussen[4], Morten E. Allentoft[4,15], Martin Sikora[4], Kristian Kristiansen[4,16], Santiago Rodriguez[3], Rasmus Nielsen[4,8], Astrid K. N. Iversen[5,17,22]✉, Daniel J. Lawson[2,3,22]✉, Lars Fugger[5,6,18,22]✉ & Eske Willerslev[1,4,19,22]✉



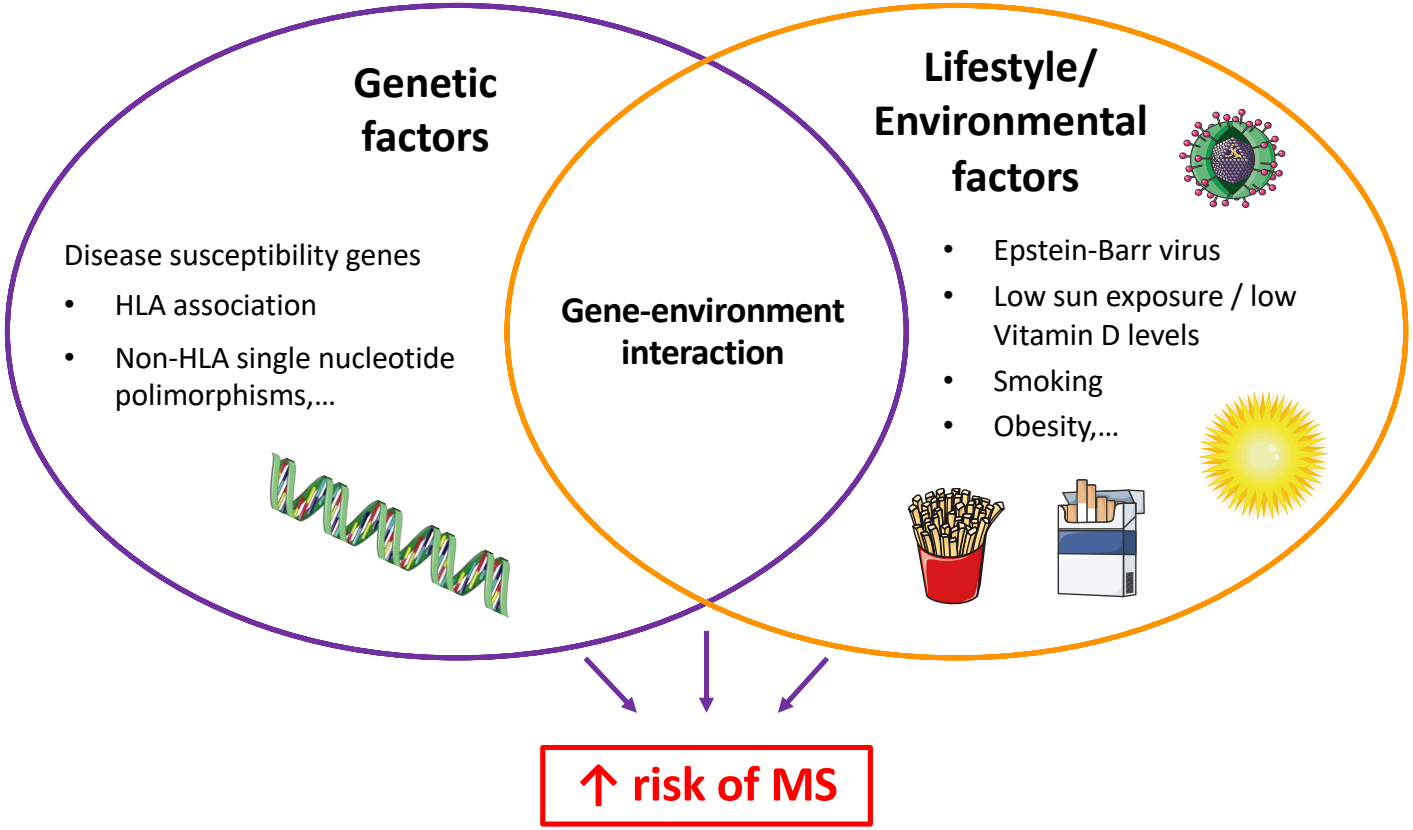
Source: Oragon Health and Science University-Brain Institute

Multiple sclerosis is an **autoimmune disease.**

The immune system attacks the body's own tissues. In MS, immune system cells attacks myelin, the sheath that covers nerve fibers in the brain and spinal cord (the central nervous system).

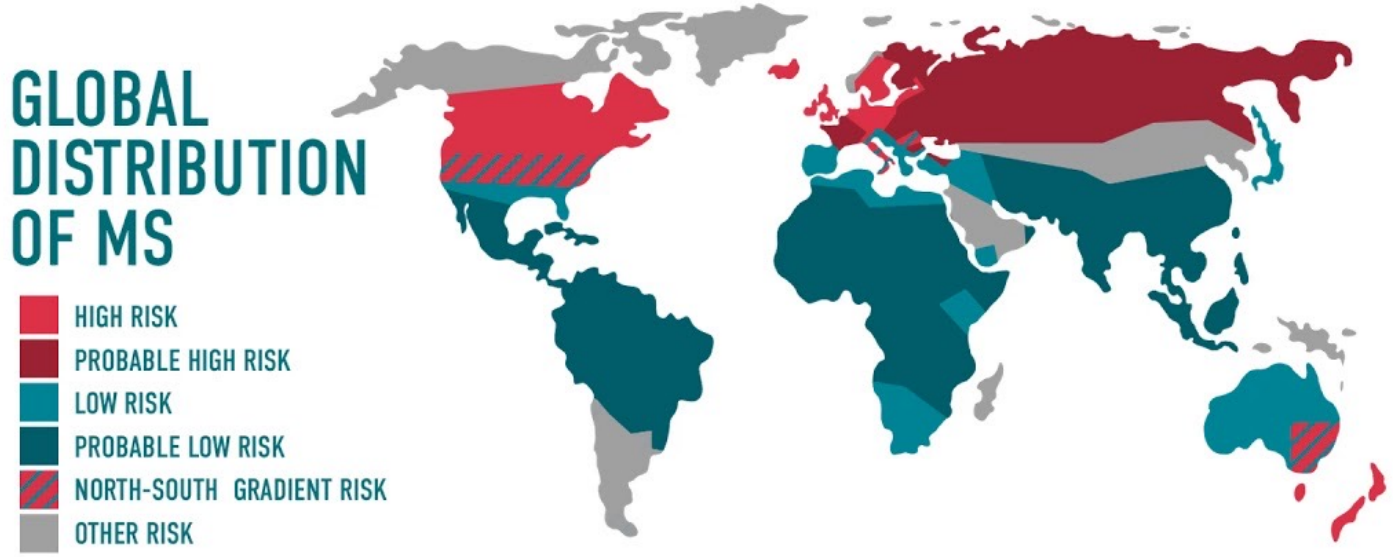


MS risk factors

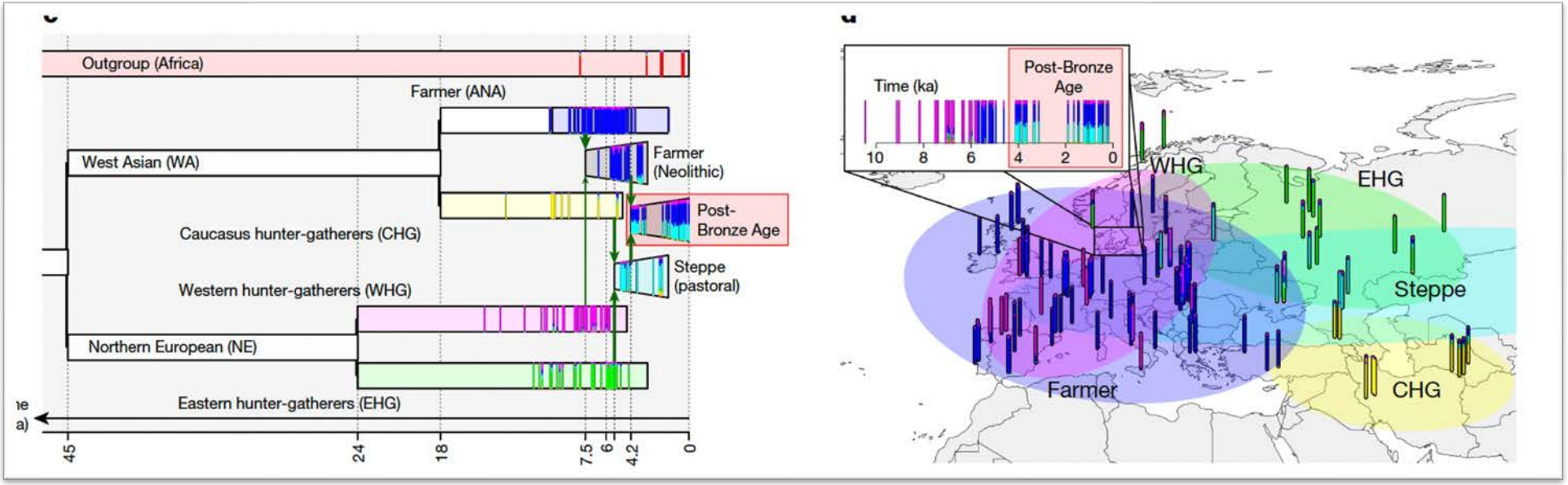


Oksenberg JR & Baranzini SE (2010), *Nat Rev Neurol*

Epidemiology



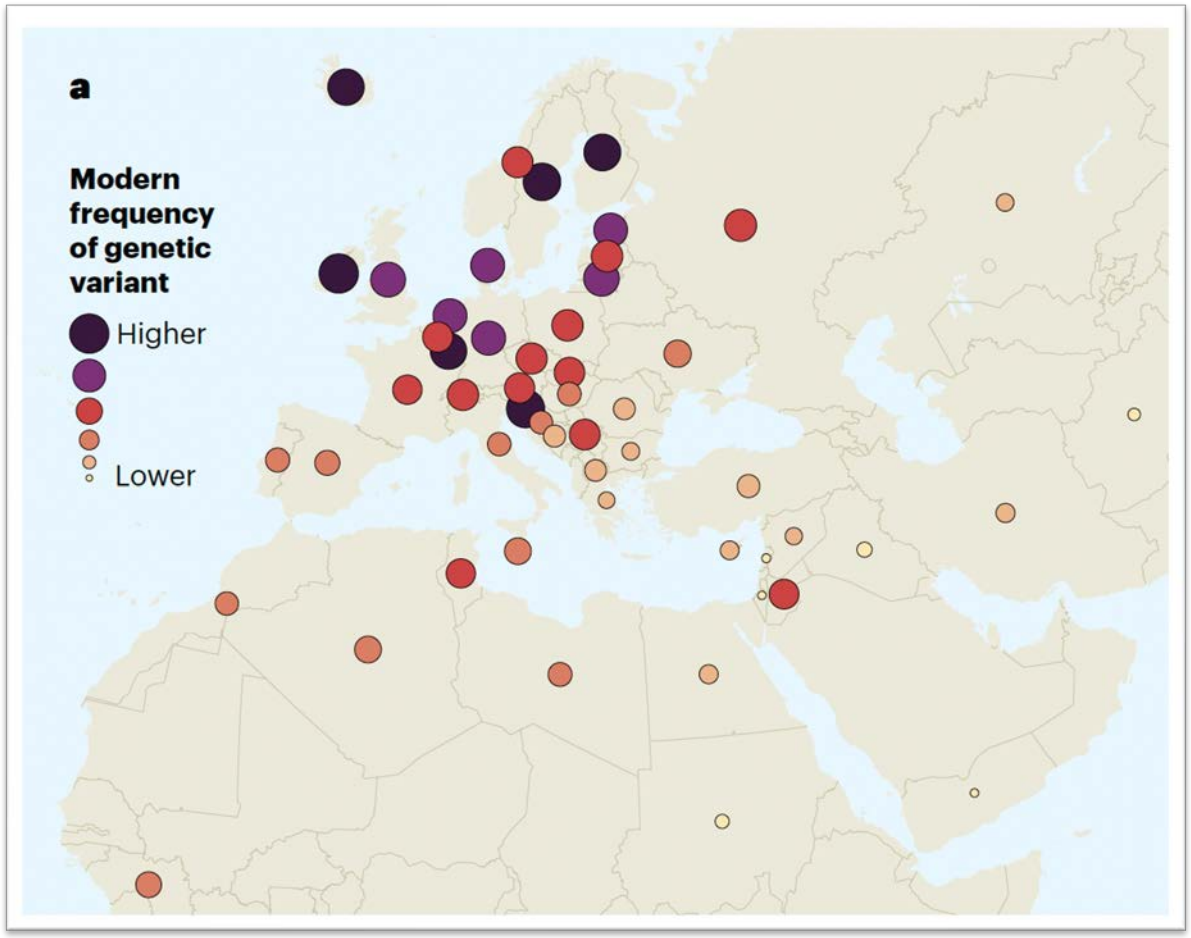
http://www.wehearthealth.org/what-is-multiple-sclerosis/. Accessed September 1, 2016.



Hunter/Gatherers

Farmers

Pastoralists



Over 1600 Ancient Eurasian Genomes Sequenced

HLA-DRB1*15:01 variant associated with three-fold risk of MS

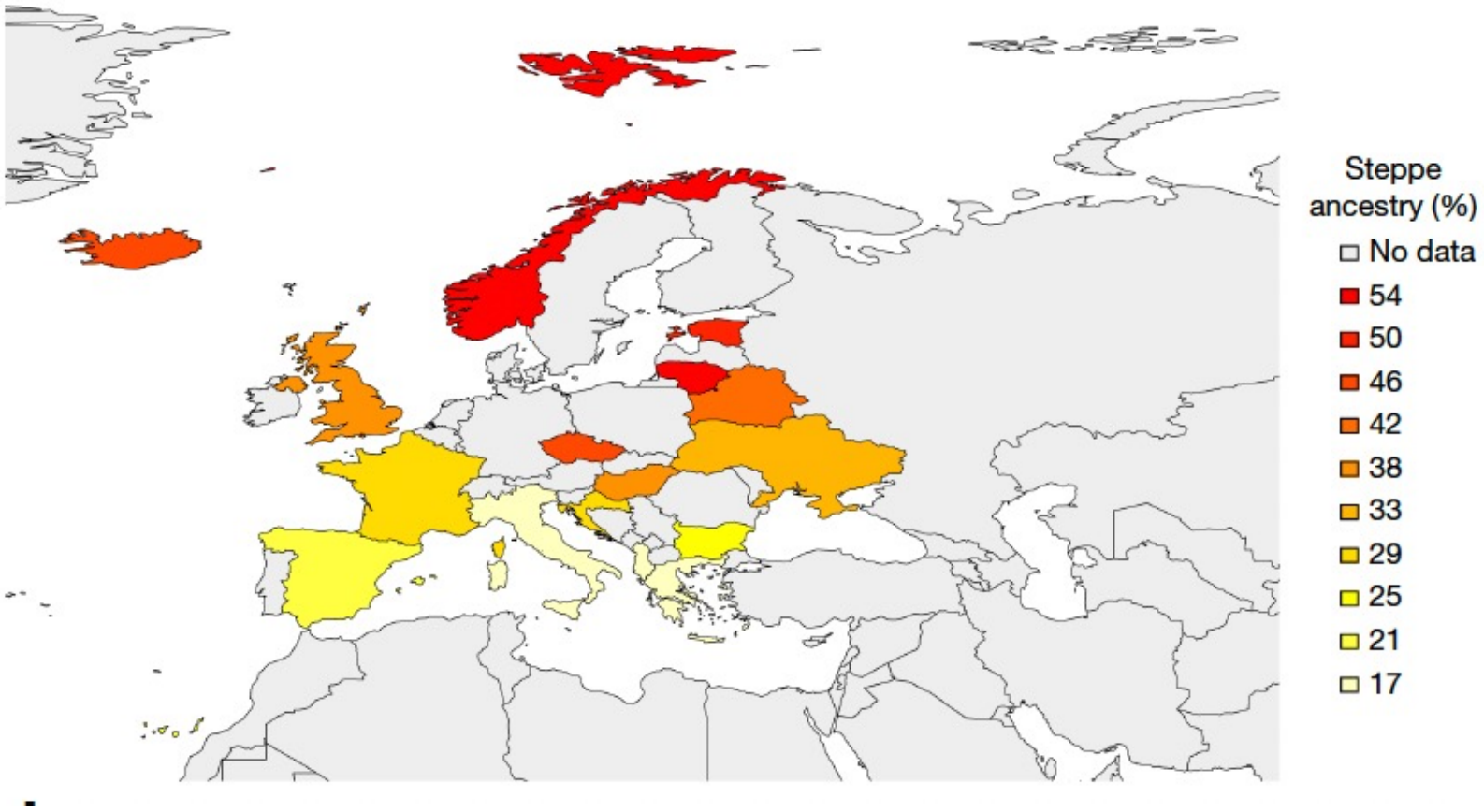
HLA-DRB1*15:01 variant is much less common in southern European populations and populations with non-European ancestry

Used over 400K **UK Genome** to ask where were ancient genes located from the hunter gatherers, farmers, and pastoralist

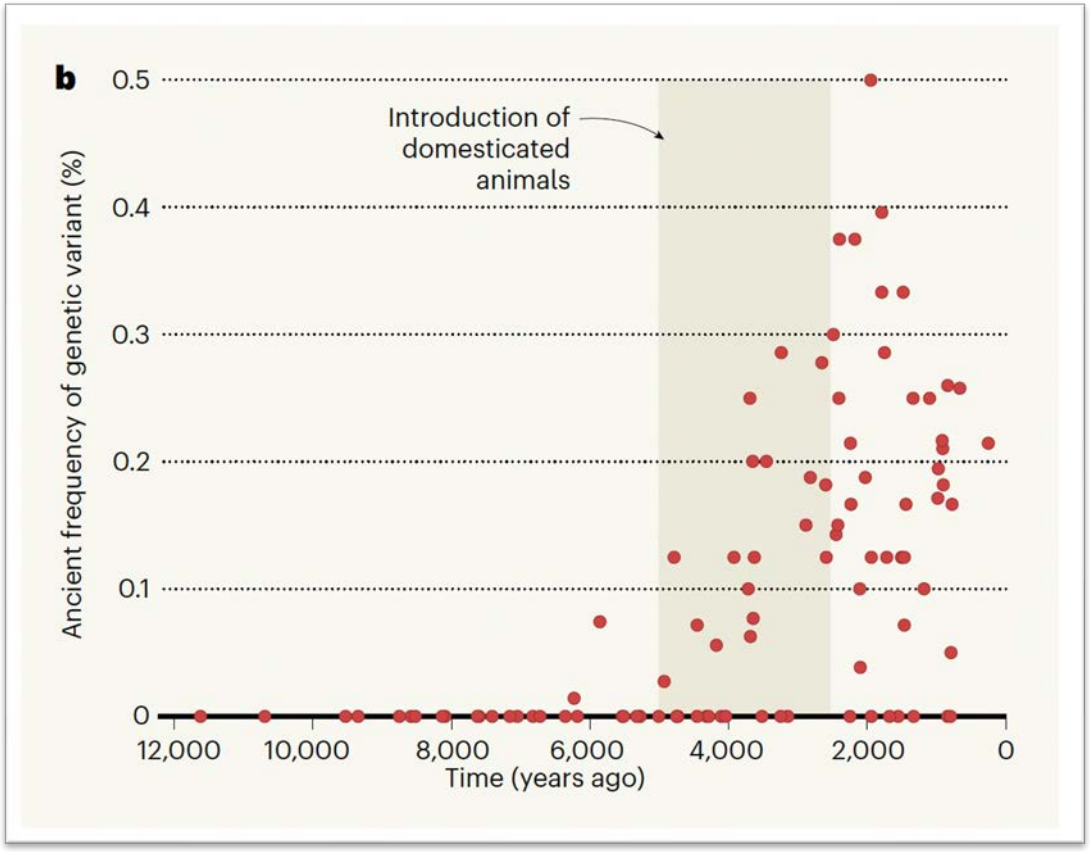
Nature, News and Views, Samira Asgari & Lionel A. Pousaz, Jan 2024

Nature, Jan 2024

HLA-DRB1*15:01



The prehistoric origins of a genetic variant that elevates multiple sclerosis risk in northern Europeans.



Nature, News and Views, Samira Asgari & Lionel A. Pousaz, Jan 2024

Why have the HLA-DRB1*15:01 variant if it is associated with MS?

Turning up the immune system to protect against infection may be a benefit if you are around animals

..but puts you at risk for autoimmune diseases

Hunter/Gatherers

Farmers

Pastoralists

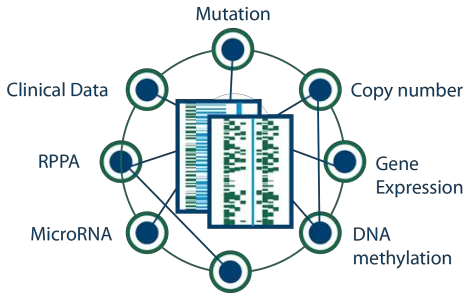
The Promise and Future of Precision Medicine

Discover disease vulnerabilities

New Knowledge

Taxonomy

Knowledge Network



Precise Diagnosis

Targeted Treatment

Improved Health Outcome

Clinical Medicine

Observational Studies During clinical care (EHR)

Basic, Translational, & Population Sciences

Bold Therapies

Grazie per l'attenzione