BIO-312
Genomic Solutions to Sustainable Development

Personalized Medicine: The Future of Sustainable Healthcare?

Laboratory of Human Genomics of infection and immunity

CHUV Precision Medicine Unit

Unité de médecine de précision

Precision Medicine

This group, led by Prof. Jacques Fellay, focuses on translational genomics research and on demonstrating the clinical value of human genome analysis in medicine. The group also aims to set up and to operate a new personalized health clinic. The group's research focuses on: the development and application of polygenic risk scores for complex diseases, pharmacogenomics, the integration of genome analysis in healthcare, and societal acceptance of genomics and artificial intelligence in medicine.

Defining Personalized Medicine

Defining Personalized Medicine

Personalized medicine is an approach that tailors healthcare to individuals, considering their unique genetic makeup, environmental influences, and lifestyle factors. This approach aims to provide better prediction of disease risk, earlier prevention, more targeted and effective treatments, and patient empowerment.


The human genome

The human genome(s)

3.2 billions base pairs (**A**T**G**C)

20,000 genes

4 million DNA variants per individual

1865: Mendel

Heredity laws


MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what would hold the structure together. In particular, the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has been suggested by Fraser (in the press). In this model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the nearby atoms is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached phosphate group.

This figure is purely diagrammatic. The two ribbons symbolize the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

1953: Watson / Crick

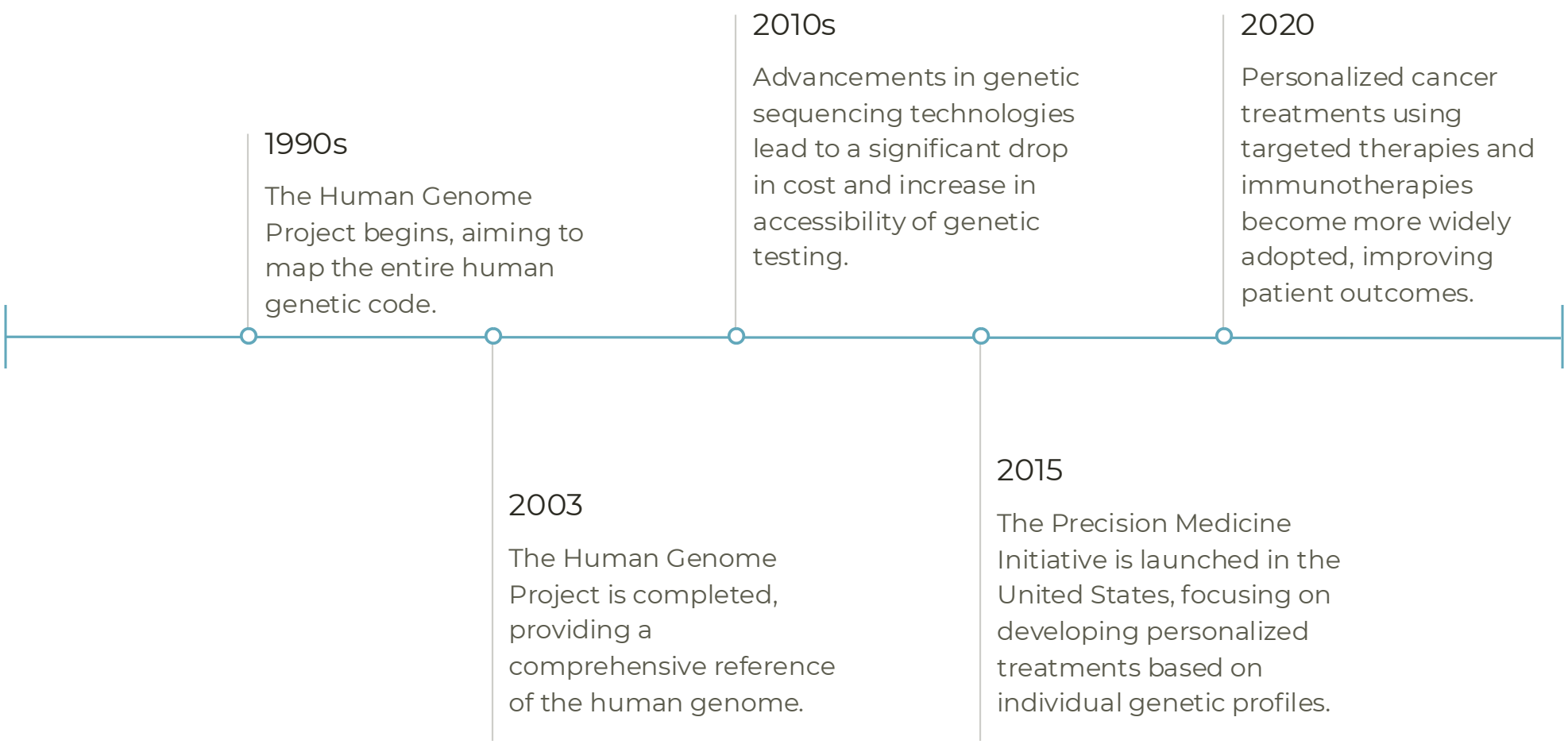
DNA structure

2001:

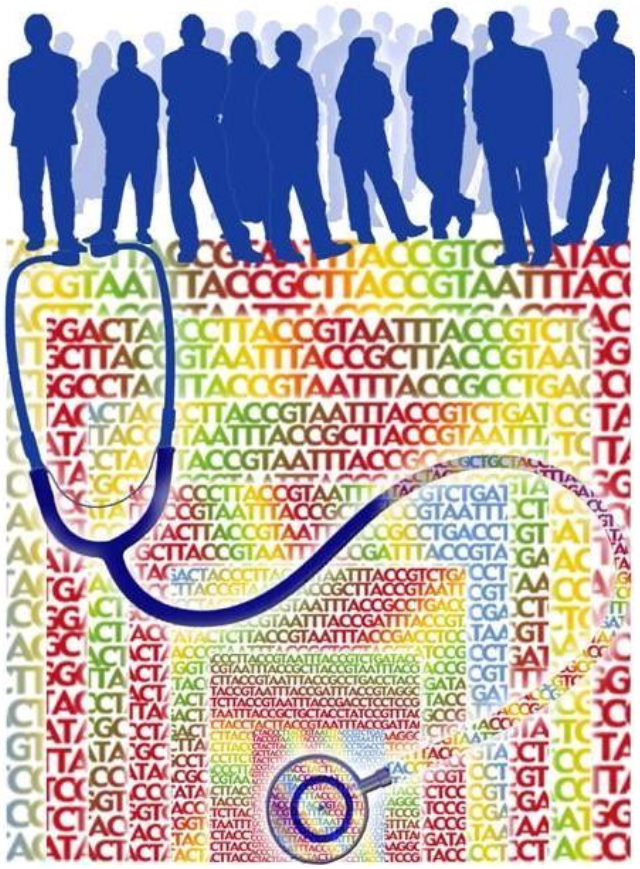
Human genome project

First genome sequenced

Entering the Era of Personalized Medicine



We are all different…



4 million DNA variants / individual

- Single nucleotide polymorphisms (SNPs)
- Small insertions/deletions (indels)
- Larger structural variants
  - copy number variants (CNVs)
  - inversions
  - translocations


Entrée dans l'ère
du génome discount
ADN
Budget
VOTRE GENOME
entièrement décodé
prêt à l'emploi
46 chromosomes
999.-
ADN
995
© ALAIN HERZOG

Understanding of biological mechanisms

Models of individualized prediction

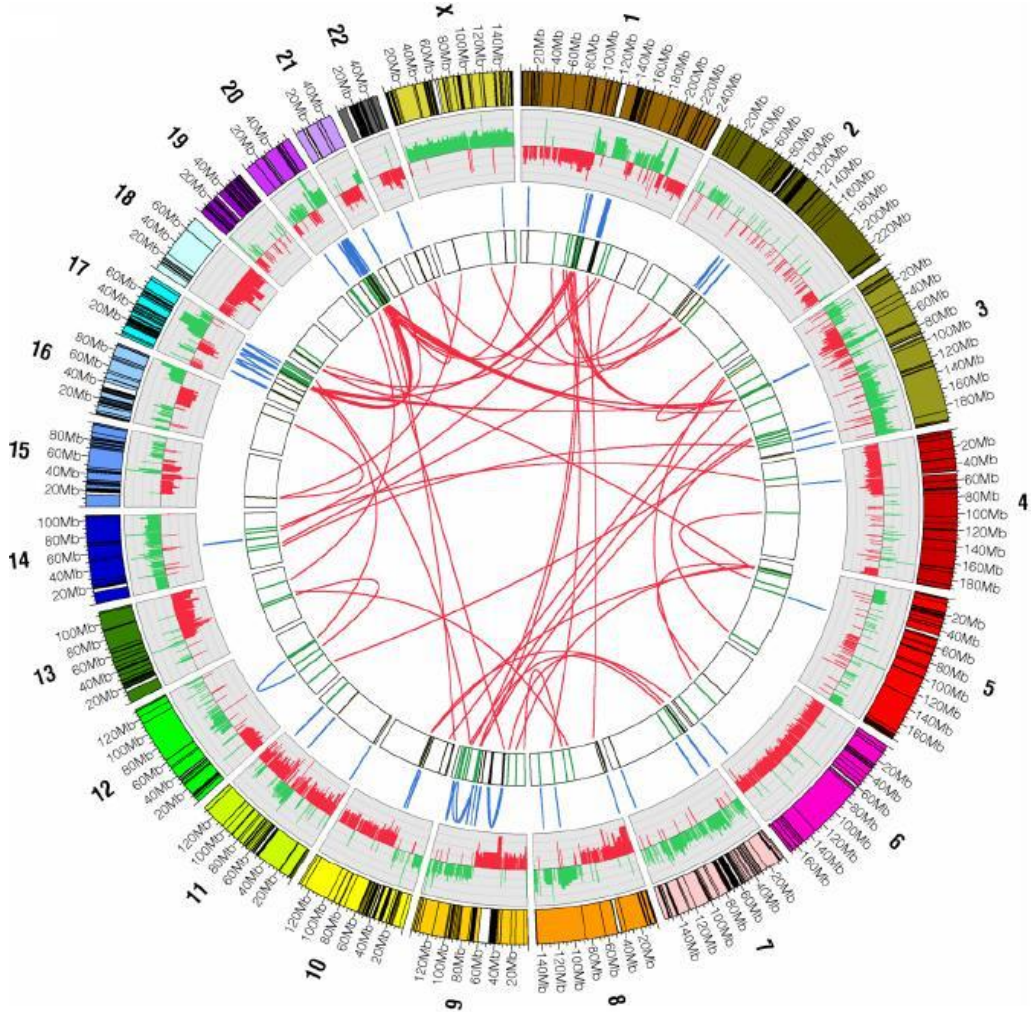
Innovative diagnostics and treatments

Predictive and preventive medicine

Genomic medicine

- Today
  - Oncology
  - Pharmacogenetics
  - Rare disease diagnostic
  - (Gene therapy)
- Tomorrow
  - Genomics for complex diseases: polygenic risk scores
  - Pivot from reactive medicine to preventative healthcare

Oncogenomics



Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women

Ranjit Manchanda, Shreeya Patel, Vladimir S Gordeev, Antonis C Antoniou, Shantel Smith, Andrew Lee, John L Hopper, Robert J MacInnis, Clare Turnbull, Susan J Ramus Simon A Gayther, Paul D P Pharoah, Usha Menon, Ian Jacobs, Rosa Legood

JNCI: Journal of the National Cancer Institute, djx265,
https://doi.org/10.1093/jnci/djx265
Published: 18 January 2018 **Article history**

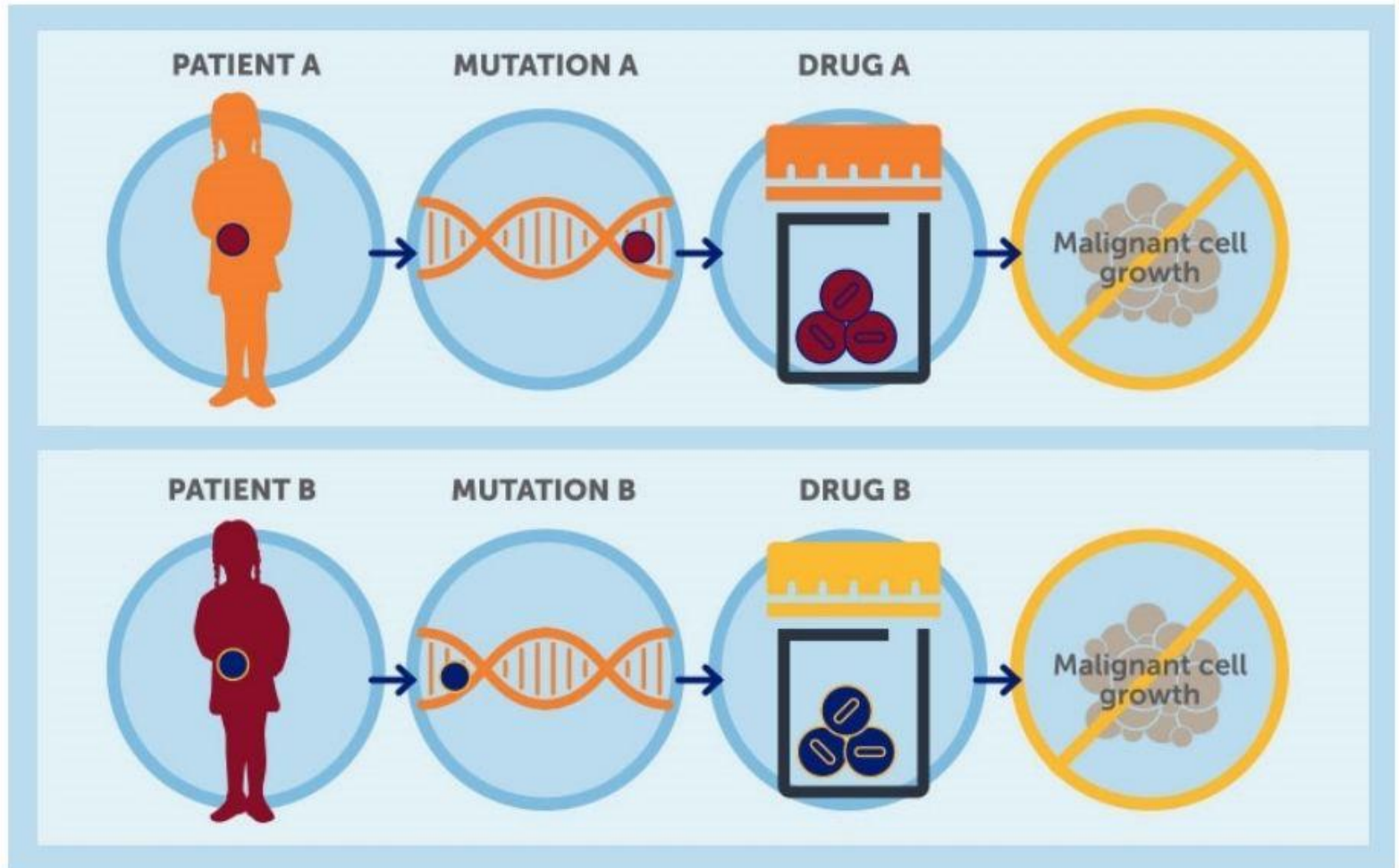
All women over 30 should be tested for faulty cancer gene, researchers say

Barts Cancer Institute research estimates around 83,000 cancers could be prevented if all women over 30 were screened.

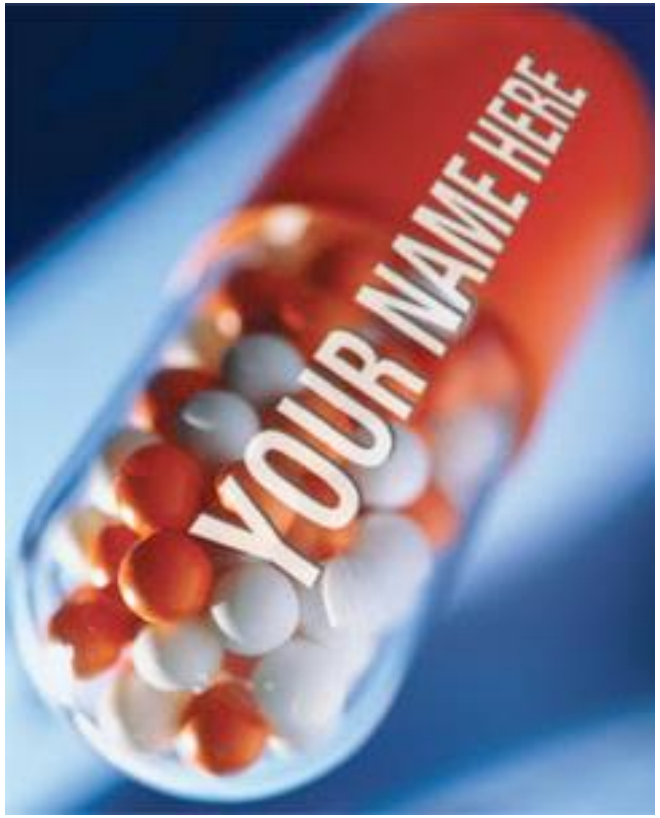
SCREENING TO SAVE LIVES

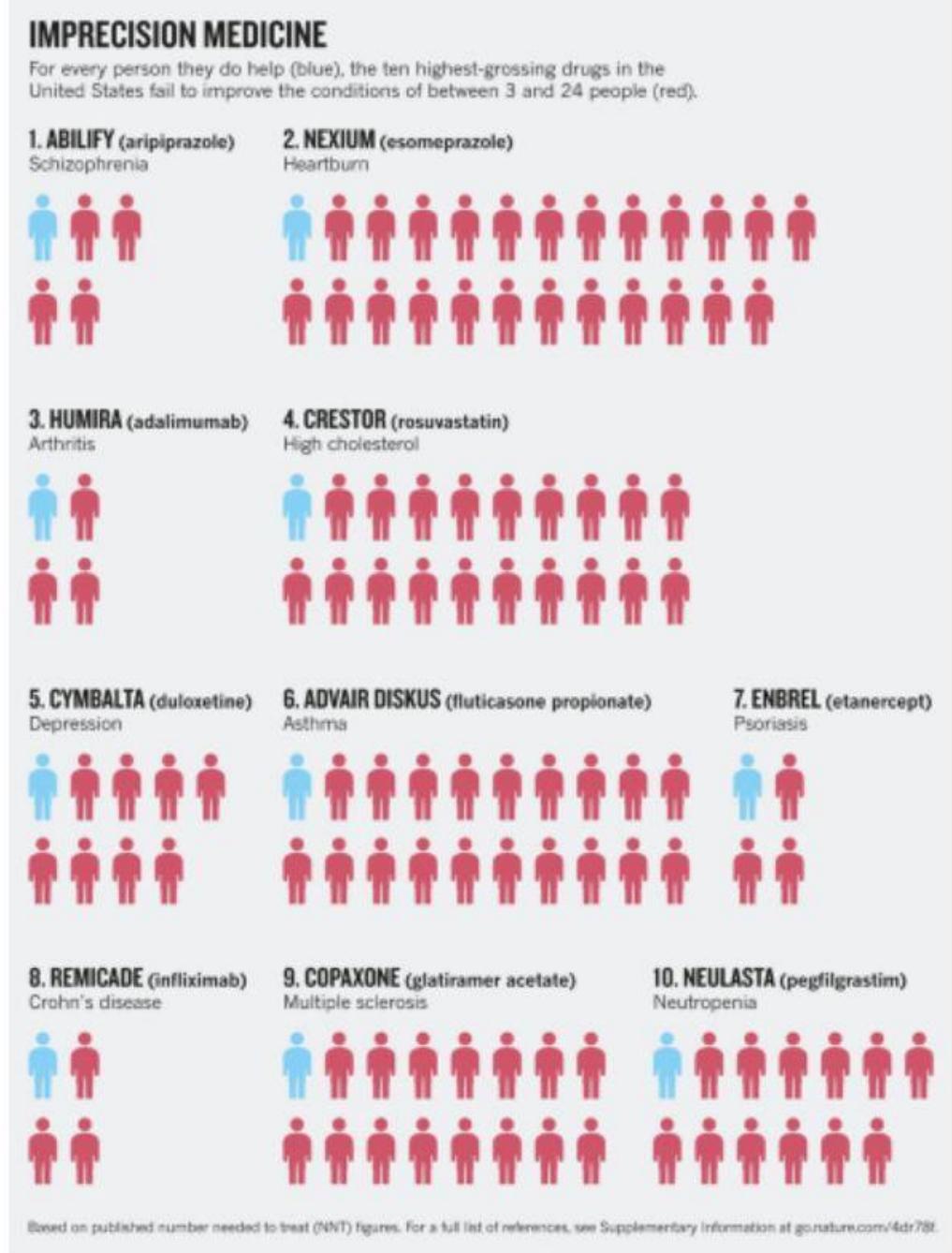
Screening all women over 30 for cancer could lead to 64,000 fewer breast cancers, study reveals

Studies at Queen Mary University London found that screening all women over 30 could lead to 17,000 fewer ovarian cancers


PATIENT A
MUTATION A
DRUG A
Malignant cell growth
PATIENT B
MUTATION B
DRUG B
Malignant cell growth

Pharmacogenomics




IMPRECISION MEDICINE
For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).
1. ABILIFY (aripiprazole)
Schizophrenia
2. NEXIUM (esomeprazole)
Heartburn
3. HUMIRA (adalimumab)
Arthritis
4. CRESTOR (rosuvastatin)
High cholesterol
5. CYMBALTA (duloxetine)
Depression
6. ADVAIR DISKUS (fluticasone propionate)
Asthma
7. ENBREL (etanercept)
Psoriasis
8. REMICADE (infliximab)
Crohn's disease
9. COPAXONE (glatiramer acetate)
Multiple sclerosis
10. NEULASTA (pegfilgrastim)
Neutropenia
Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at go.nature.com/4dr78t.

The effect of more than 100 drugs is influenced by genetic variation

codeine

carbamazepine

azathioprine

warfarin

flucloxacillin

Pharmacogenomics

Examples of successful implementation in the clinic

- **Abacavir hypersensitivity**: Genetic testing for the HLA-B*5701 allele is used to identify patients at risk for a severe hypersensitivity reaction before starting abacavir for HIV treatment.
- **Warfarin dosing**: Genotyping of *CYP2C9* and *VKORC1* helps adjust warfarin doses to reduce the risk of bleeding or clotting complications.
- **Clopidogrel metabolism**: Screening for *CYP2C19* variants guides the use of alternative antiplatelet therapies in patients who may not effectively metabolize clopidogrel.
- **Thiopurine therapy**: Testing for *TPMT* variants informs dosing decisions for thiopurines used in conditions like inflammatory bowel disease or leukemia.
- **Targeted therapy in oncology**: *EGFR* testing in non-small cell lung cancer patients helps determine suitability for EGFR inhibitors.

Rare diseases

1/05/2011 @ 4:57PM | 30,076 views

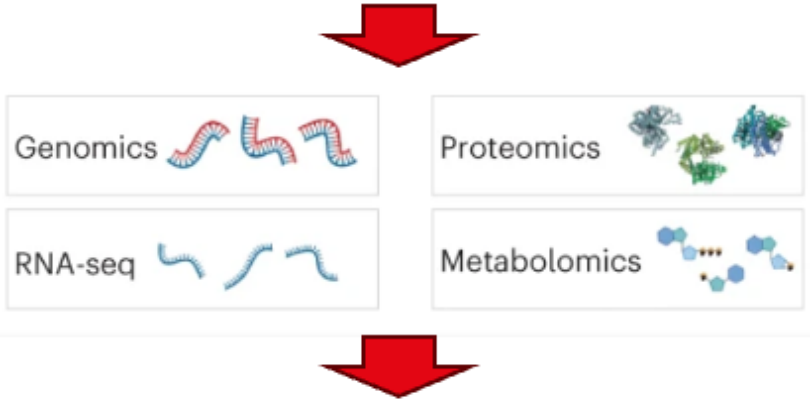
The First Child Saved By DNA Sequencing

+ Comment Now + Follow Comments

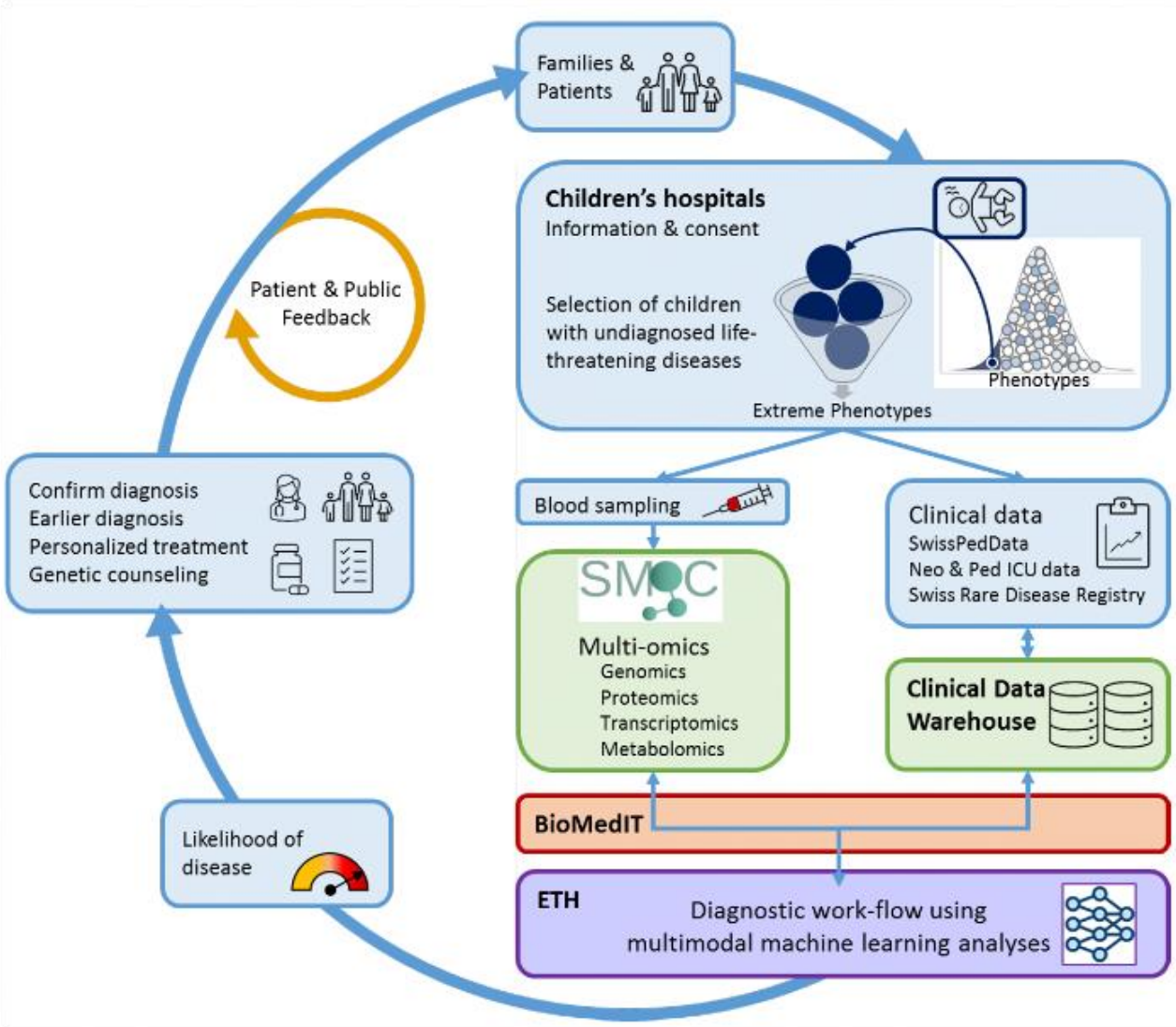
“Genome sequencing provides tangible clinical benefit for individuals with idiopathic genetic disease”

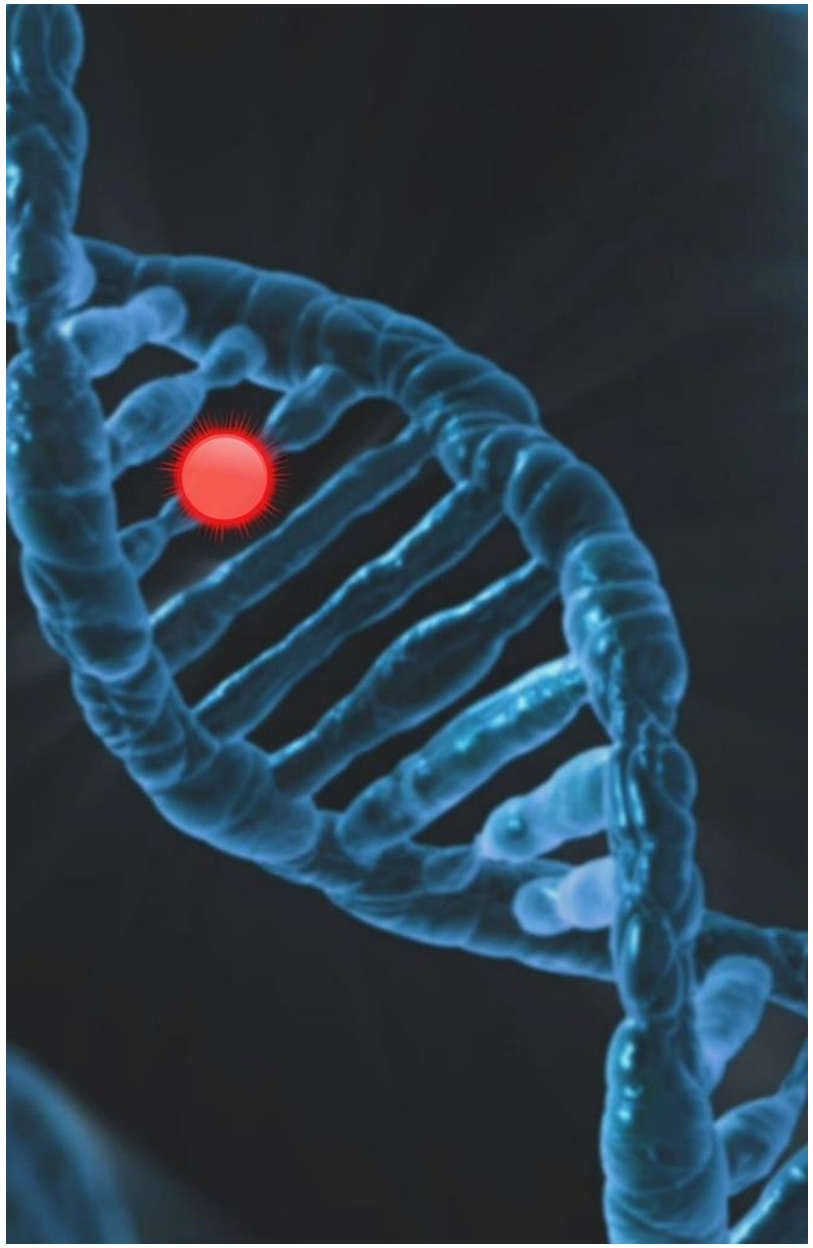
SwissPedHealth

Children in ICU with undiagnosed disease



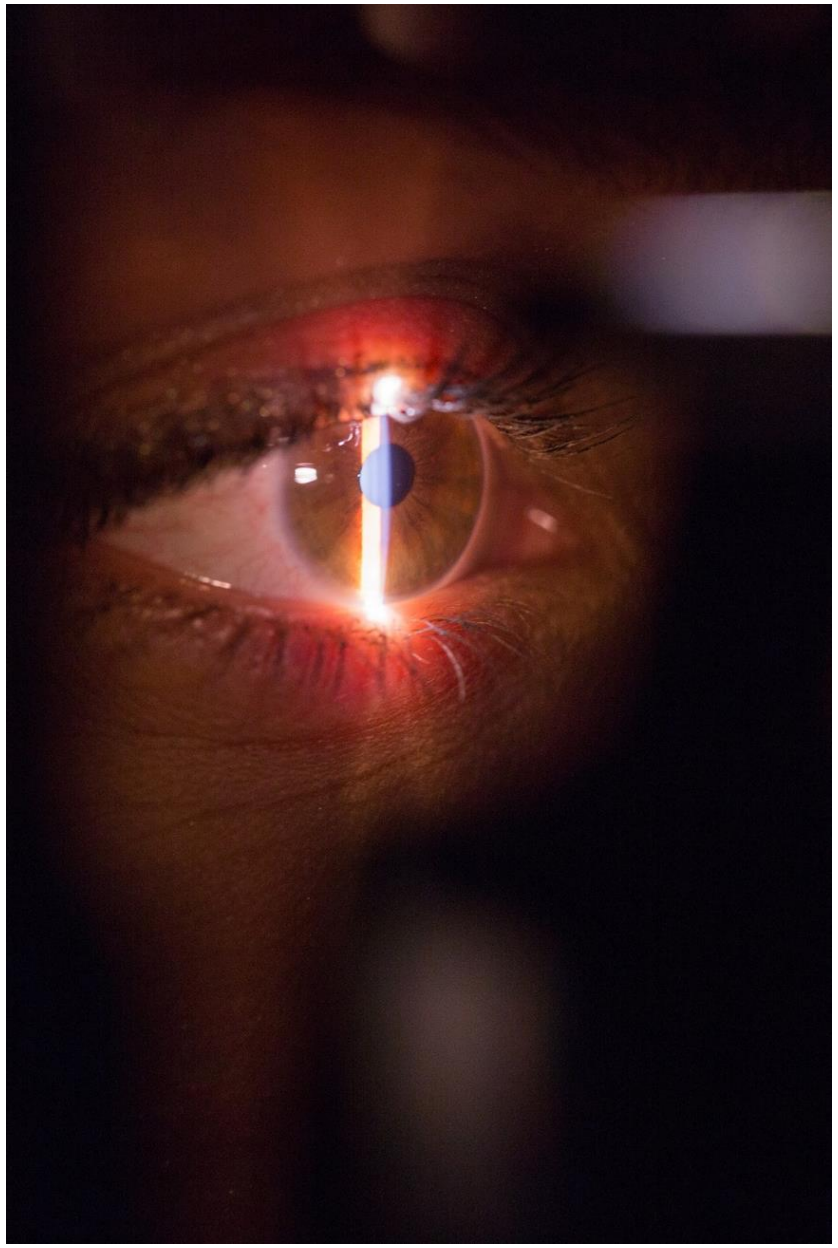
Data integration and analysis





Gene Therapy

Modification of genes to treat or prevent diseases. Works by replacing, removing, or introducing genetic material into patient DNA to address the underlying cause of a genetic disorder.



Gene therapy for Leber congenital amaurosis

Retinal dystrophy caused by mutations in RPE65, which is essential for the function of photoreceptors.

Voretigene neparvovec (Luxturna™) = AAV2 vector containing human RPE65 cDNA.

The gene therapy is injected underneath the retina through vitrectomy (by an eye surgeon), delivering a functional copy of RPE65 to retinal cells.

First gene therapy approved by the FDA in 2017 and by SwissMedic in 2020.

Gene therapy for spinal muscular atrophy

Spinal muscular atrophy (SMA) is caused by mutations in SMN1 resulting in the loss of motor neurons and progressive muscle wasting.

Zolgensma: AAV9 vector with SMN1 transgene, administered intravenously.

Risdiplam: oral small-molecule drug that modulates splicing of the gene SMN2, increasing the level of the protein SMN.

CORRESPONDENCE

Risdiplam for Prenatal Therapy of Spinal Muscular Atrophy

Published February 19, 2025 | DOI: 10.1056/NEJMc2300802 | Copyright © 2025

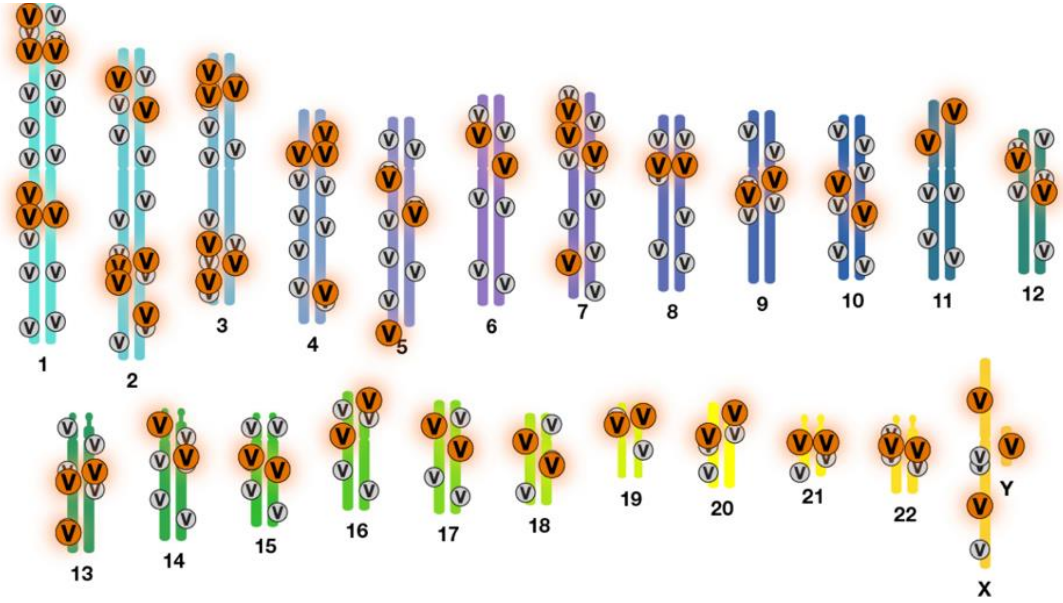
Risdiplam was administered to a fetus with SMA by means of oral administration to the mother, with subsequent administration to the child through 30 months of age. No features of SMA, such as hypotonia, weakness, areflexia, or fasciculation, have appeared to date. Motor-function, muscle ultrasonographic, and electrophysiological studies have been performed every 6 months and have shown normal peripheral-nerve and muscle development for age.

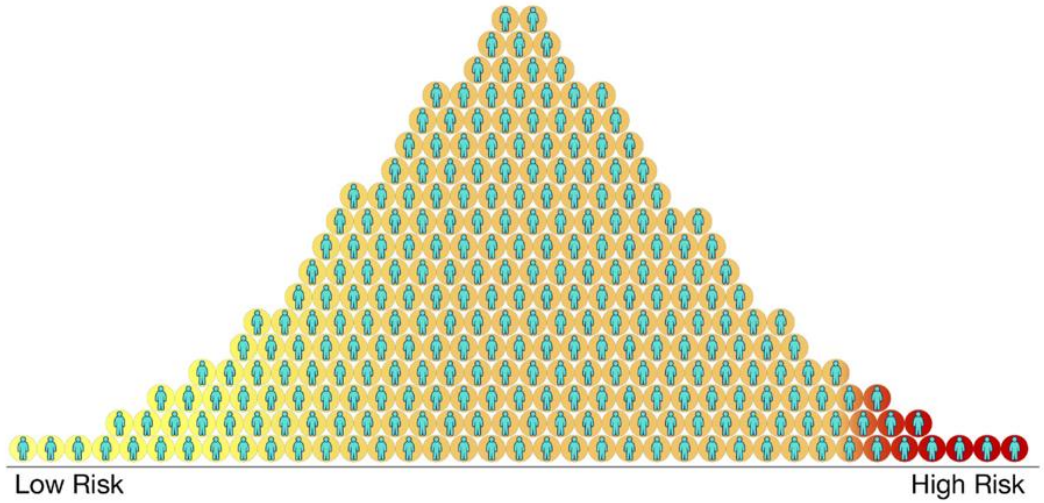
Genomic medicine - tomorrow

Polygenic risk scores

A polygenic score or polygenic risk score (PRS) is an estimate of an individual’s genetic liability to a trait or disease, calculated according to their genotype profile and relevant genome-wide association study (GWAS) data

Polygenic risk scores





https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

Polygenic risk scores

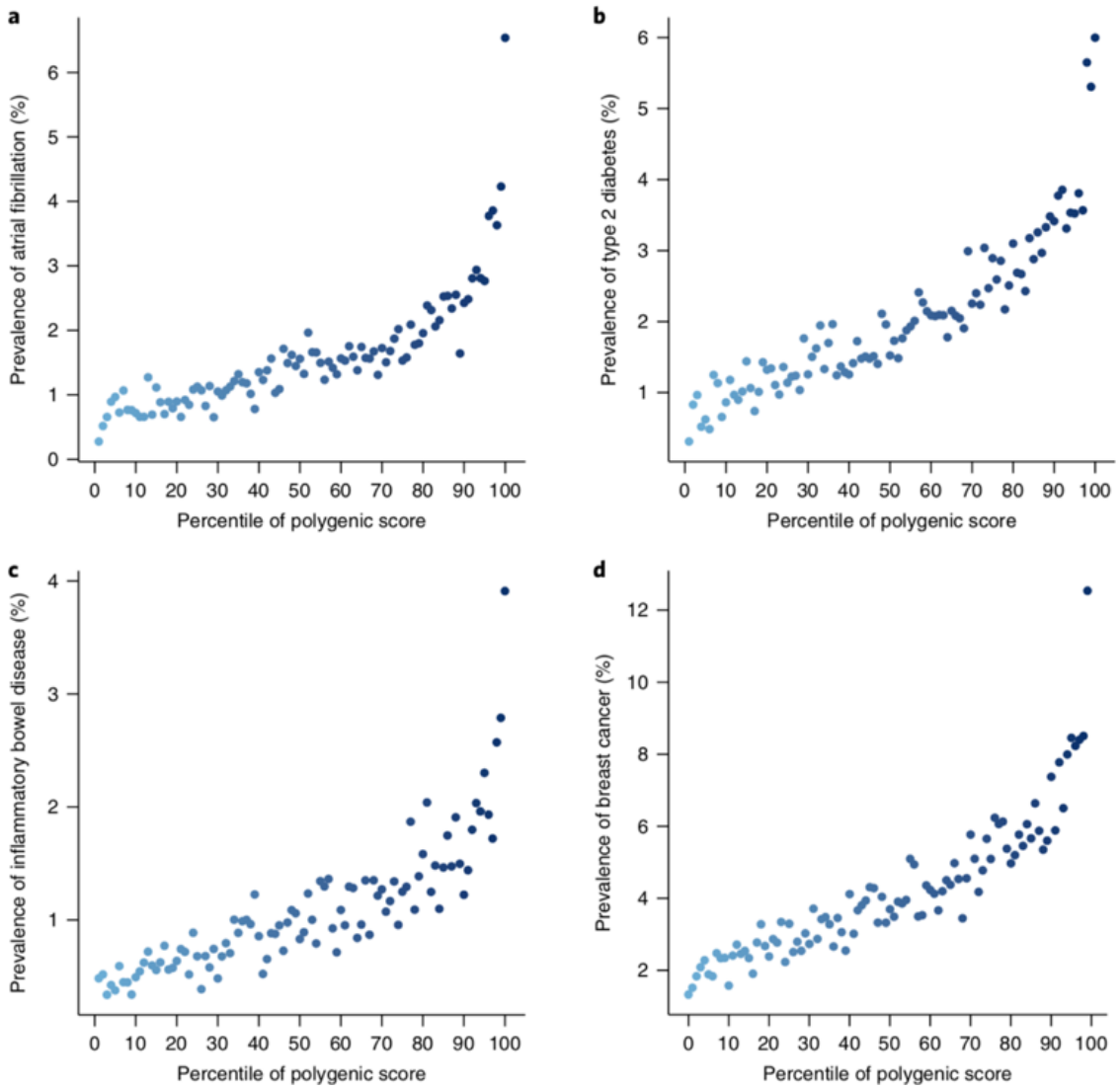
nature genetics

Letter | Published: 13 August 2018

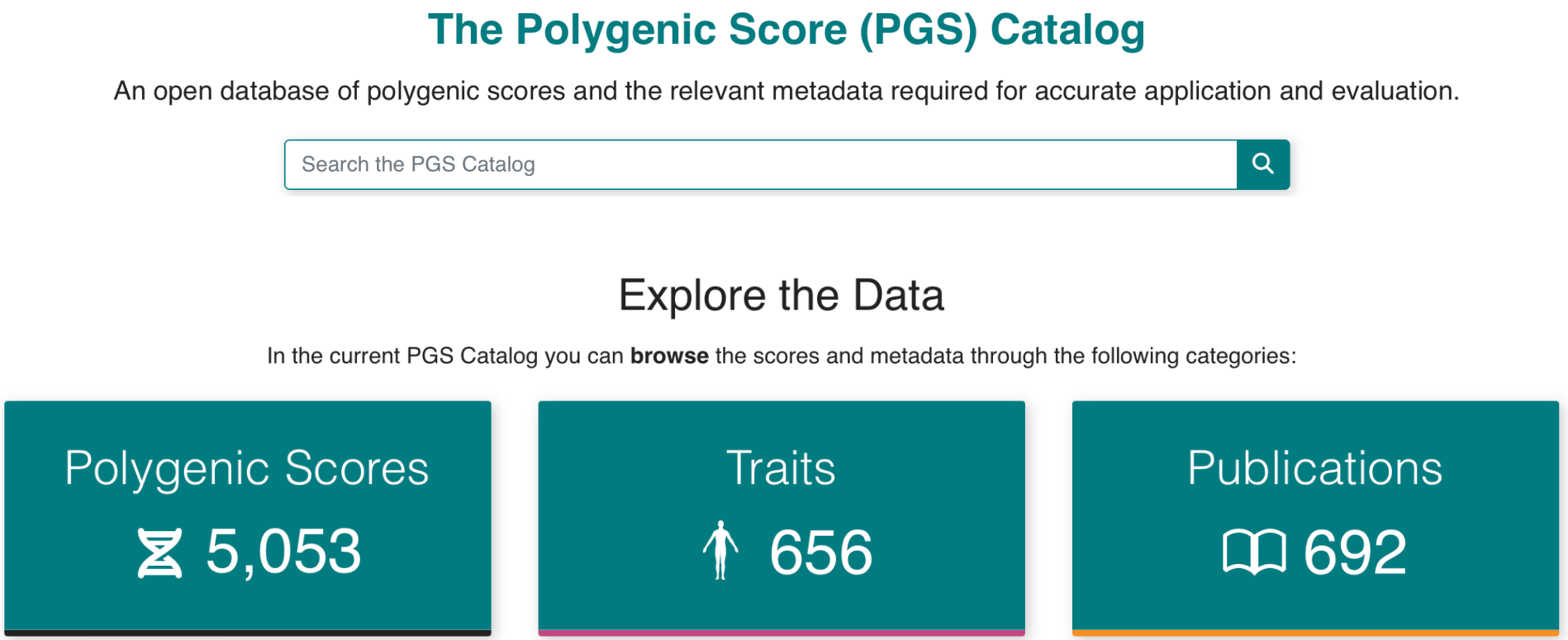
Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera, Mark Chaffin, Krishna G. Aragam, Mary E. Haas, Carolina Roselli, Seung Hoan Choi, Pradeep Natarajan, Eric S. Lander, Steven A. Lubitz, Patrick T. Ellinor & Sekar Kathiresan

Nature Genetics **50**, 1219–1224 (2018) | Download Citation



Polygenic risk scores



https://www.pgscatalog.org

Challenges to clinical implementation of PRS

- Demonstration of clinical utility
  - Integration with non-genetic risk
  - Calculation of PRS as age-based absolute risk
  - Implementation of effective prevention strategies based on the results
- Return of results to healthcare providers & to patients
- Regulatory and ethical compliance
- Generalizability across populations

Polygenic risk scores

Genomics plc and MassMutual's program enables more policyowners to understand health risks through innovative genetic testing

April 10th, 2024

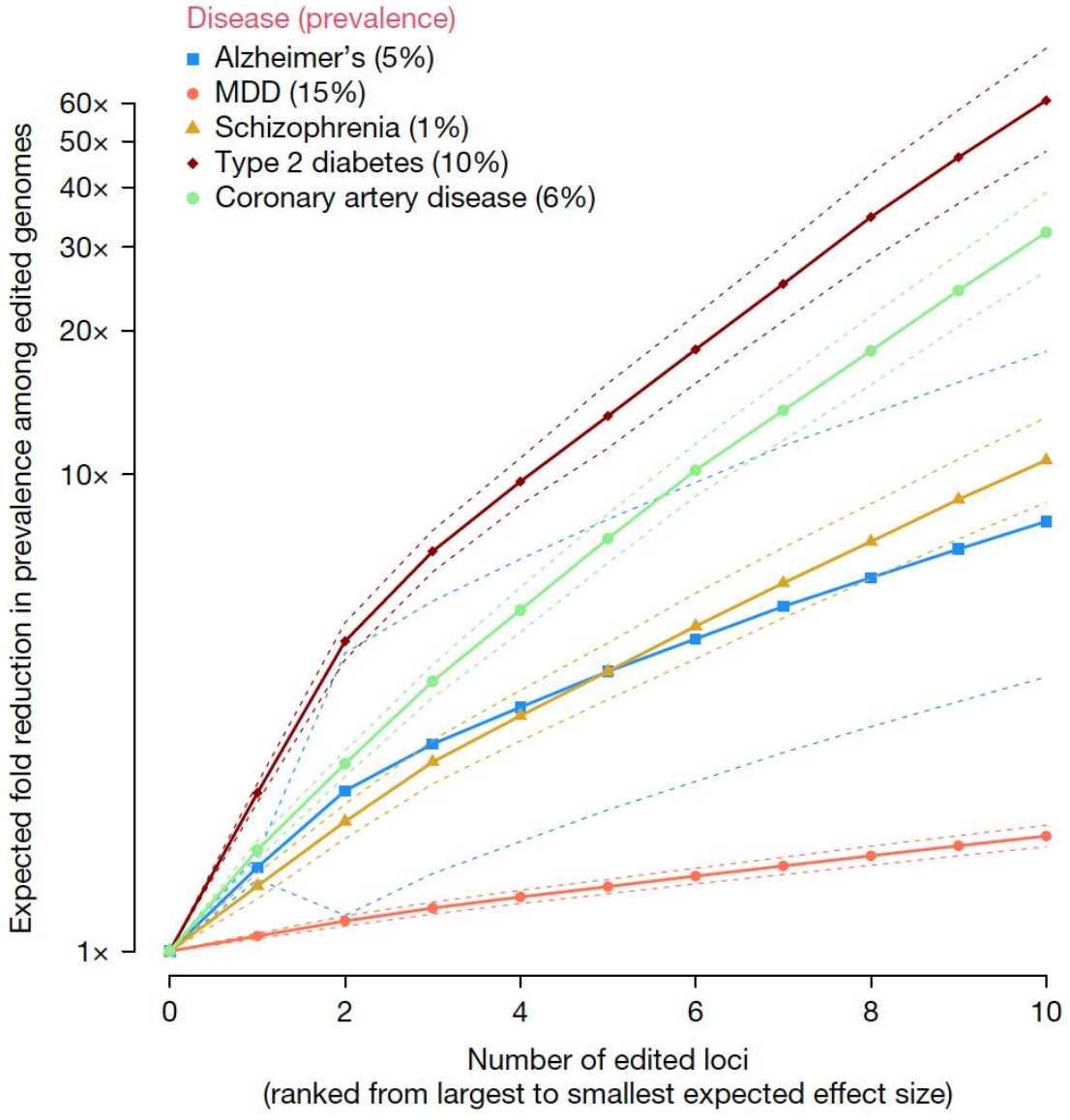
The program offers eligible MassMutual policyowners aged 35-70 access to polygenic risk testing via a saliva test that identifies hidden risk for eight common conditions: atrial fibrillation, breast or prostate cancer, cardiovascular disease, high blood pressure, high low-density lipoprotein cholesterol, low bone density and type 2 diabetes.

In addition to learning about their risk for each of the conditions, policyowners also receive actionable, tailored health advice and a report they can review with their doctor to reduce the chances of developing the condition.

Heritable polygenic editing: the next frontier in genomic medicine?

Visscher et al, Nature 2025

"Editing a relatively small number of genomic variants could make a substantial difference to an individual's risk of developing coronary artery disease, Alzheimer's disease, major depressive disorder, diabetes and schizophrenia."



Embryo editing for disease is unsafe and unproven

Carmi et al, Nature 2025

"Given how far scientists are from understanding and mitigating the associated risks, we wonder whether describing its prospects so confidently is responsible"

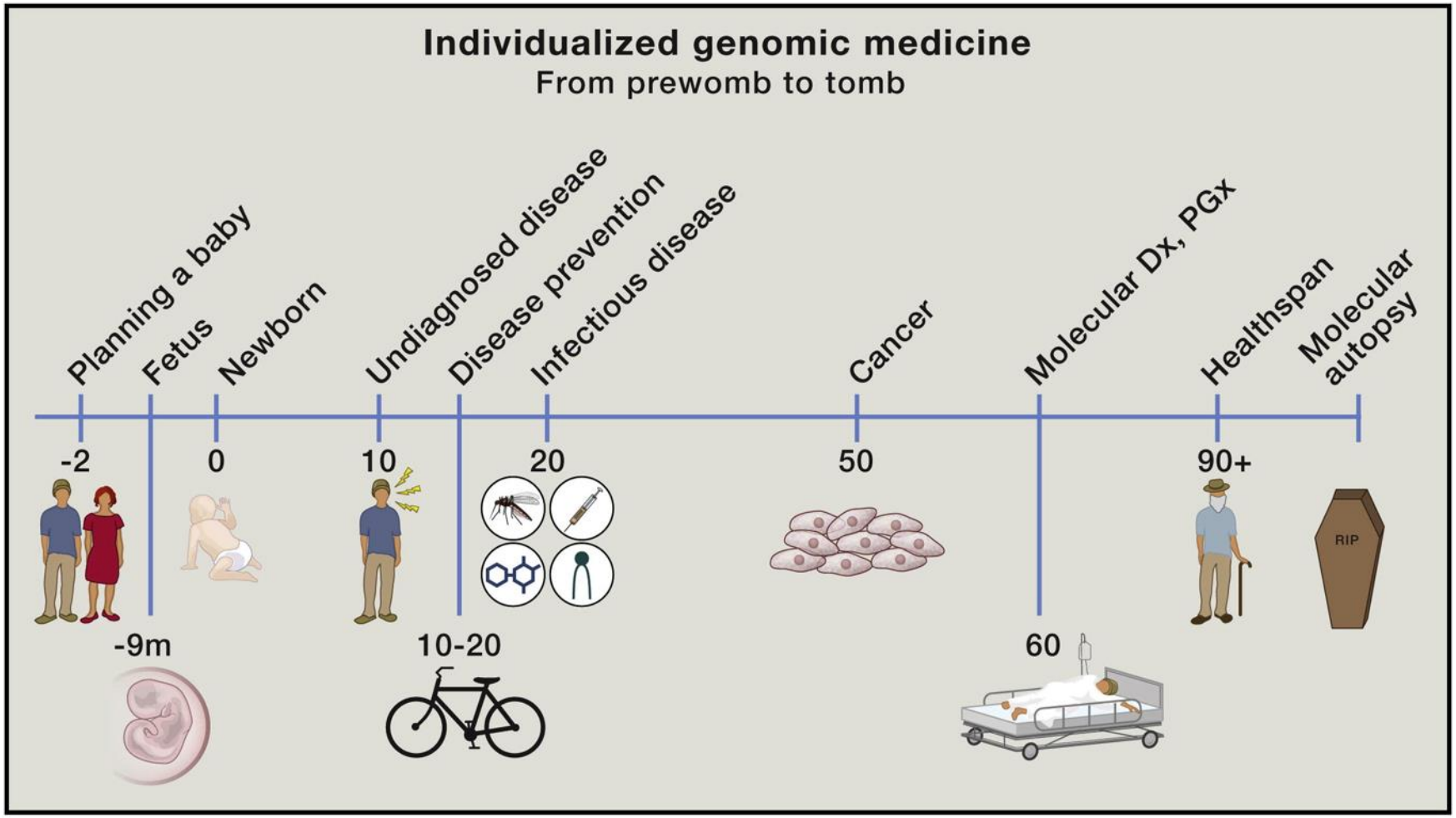
Editorials

nature

We need to talk about human genome editing

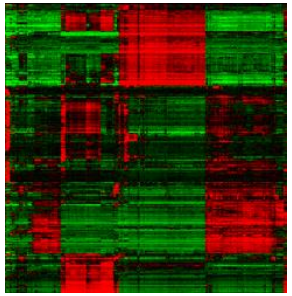
In a few decades, gene-editing technologies could reduce the likelihood of common human diseases. Societies must use this time to prepare for their arrival.

Toward life-long genomics

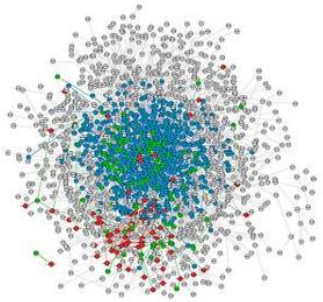


Eric Topol. *Individualized Medicine from Prewomb to Tomb*. Cell 2014

Epigenome



Transcriptome



Proteome

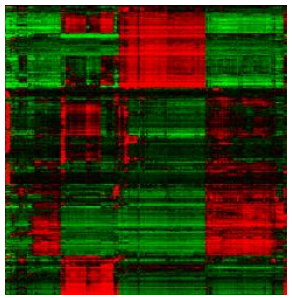
Genome

Metabolome

Metagenome

Exposome

Epigenome



Transcriptome

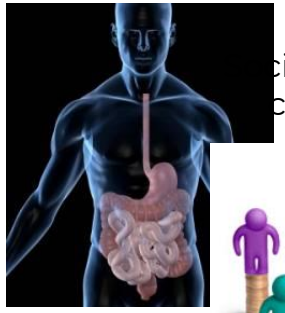
Social networks

Proteome

Genome

Life style

abolome



cio-economic
conditions

Metageno

From Genomic Medicine to AI-Based Healthcare

- Genomics in only part of precision health
- Must be integrated with electronic health record, imaging data, info from wearables, etc.
- Need for advanced biomedical data science
- AI-fueled revolution is coming for health

SCIENTIFIC AMERICAN

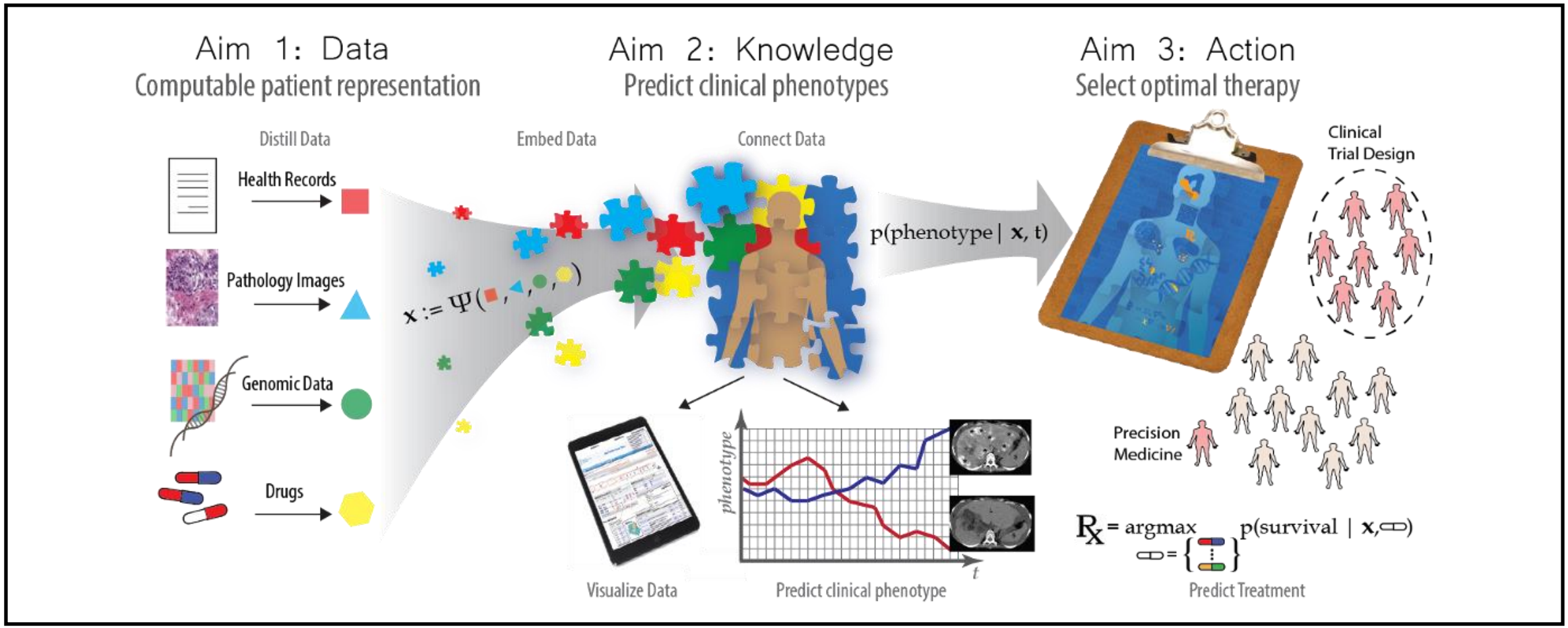
ARTIFICIAL INTELLIGENCE | OPINION

AI in Medicine Is Overhyped

The Boston Globe

This time, the hype about AI in medicine is warranted

Swiss AI Initiative - Health vertical



Goal = multimodal integration of health data

Examples of AI Applications in Healthcare

Disease Diagnosis

Stanford's AI system diagnoses skin cancer as accurately as dermatologists

Microsoft's InnerEye helps radiologists precisely measure tumors

Google Health's AI system detects lung cancer in CT scans

Clinical Decision Support

Mayo Clinic's AI CDS system use CT images to improve lung cancer diagnosis

Epic's Deterioration Index predicts health decline in hospitalized patients

Babylon Health's AI triage recommends appropriate care levels in the ER

Examples of AI Applications in Healthcare

Surgical Applications

Medtronic's GI Genius intelligent endoscopy module helps detect colorectal polyps

Surgical robots like Da Vinci use AI to enhance surgeon precision

Theator's AI platform uses AI and computer vision to improve surgical techniques

Mental Health

Woebot, an AI chatbot, provides mental support using cognitive behavioral therapy

CompanionMx's AI system analyzes voice patterns to detect mental health changes

Spring Health's AI platform matches patients with mental health treatment plans

Examples of AI Applications in Healthcare

Medical Imaging Analysis

Google DeepMind's AI detects breast cancer in mammograms

IDx-DR, an FDA-approved AI system, detects diabetic retinopathy using retinal images

Arterys' cardiac imaging AI creates 4D heart flow models from MRI

Drug Discovery

Atomwise used AI to identify potential treatments for Ebola

Insilico Medicine's AI platform discovered a drug for pulmonary fibrosis

BenevolentAI identified a potential anti-COVID-19 drug, later validated in clinical trials

Examples of AI Applications in Healthcare

Patient Monitoring

Current Health's AI-powered wearable monitors vital signs and can sends alerts

AiCure's smartphone app uses AI to confirm medication adherence through video

Cardiogram's heart rate monitoring AI can detect sleep apnea

Administrative Tasks

Natural language processing systems convert doctor's voice into structured records

AI scheduling systems optimize hospital staffing and operating room utilization

Many AI-based algorithms predict length of stay and readmission risk based on EHR

Is personalized health doable?

Challenges in Implementing Personalized Medicine

- Increased complexity in healthcare delivery
- Limited scalability due to the individualized nature of care
- Need to change the business model of health
- Data management and privacy protection requirements
- Acceptability / health literacy of the population
- Education of healthcare providers

Is personalized health sustainable?

Towards a Sustainable Healthcare System

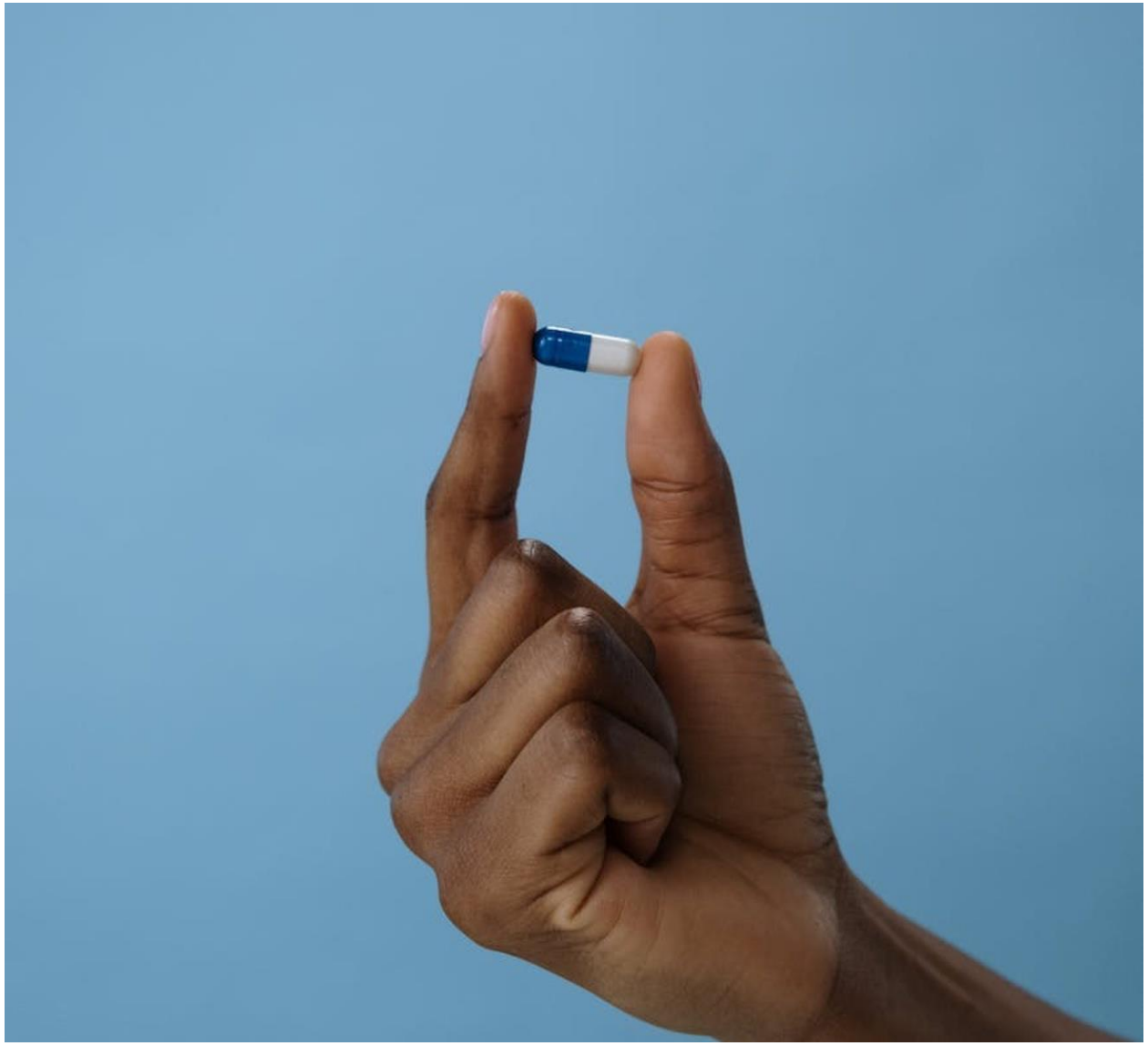
Better prediction and prevention

Personalized medicine enables a more proactive, preventive approach to healthcare by identifying individual risk factors and predispositions, allowing for early interventions and the implementation of targeted prevention strategies.

Towards a Sustainable Healthcare System

Improved Patient Outcomes

By tailoring therapies and interventions to individual patient needs, personalized medicine can lead to better treatment responses, reduced adverse effects, and improved overall health outcomes.



Towards a Sustainable Healthcare System

Optimized Resource Allocation

Personalized medicine can help allocate healthcare resources more efficiently, reducing waste and ensuring that the right care is provided to the right patient at the right time.

Towards a Sustainable Healthcare System

Cost Savings

Personalized medicine can help reduce healthcare costs by minimizing the use of ineffective treatments, reducing hospitalization rates, and preventing complications and adverse events, ultimately lowering the overall burden on the healthcare system.

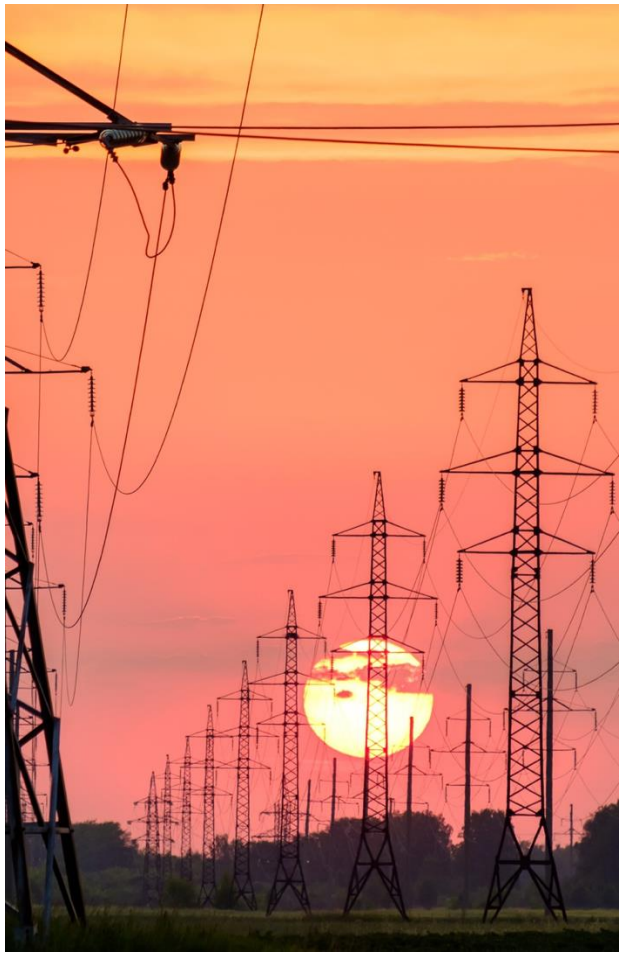
Towards an **Un**sustainable Healthcare System

High cost

Data management systems
Longitudinal, multimodal testing
Drugs

Name	Price (USD)	Indication
Lenmeldy	4250000	Metachromatic leukodystrophy in children
Hemgenix	3500000	Hemophilia B in adults
Elevidys	3200000	Duchenne Muscular Dystrophy in children
Lyfgenia	3100000	Sickle cell disease
Zolgensma	2125000	Spinal muscular atrophy in children
Myalept	1260000	Leptin deficiency in patients with lipodystrophy
Zokinvy	1070000	Hutchinson-Gilford Progeria Syndrome
Danyelza	1010000	Neuroblastoma in bone or bone marrow
Kimmtrak	975520	Uveal melanoma
Folotyn	842585	Peripheral T-cell lymphoma

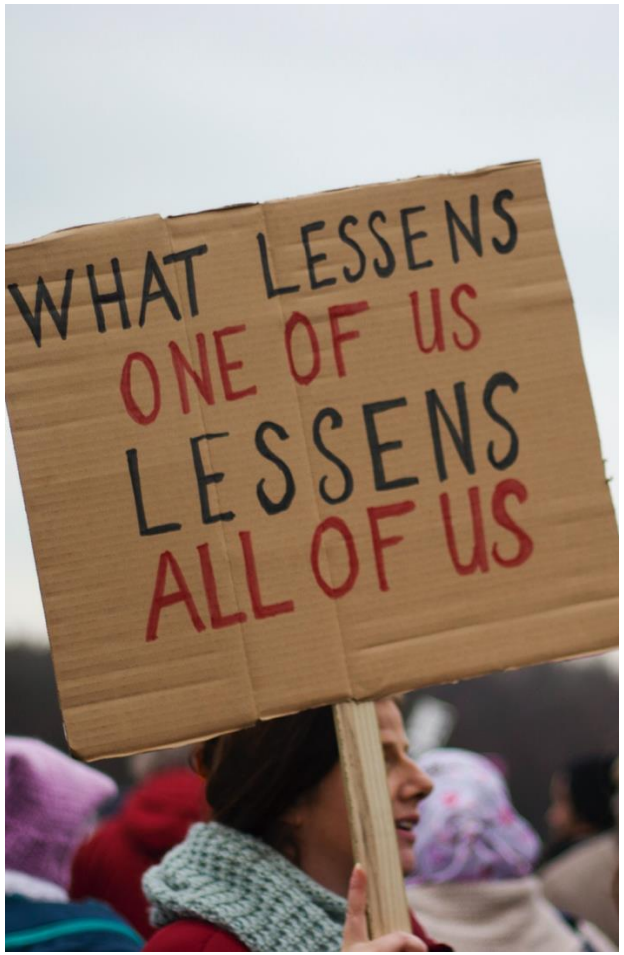
Towards an **Un**sustainable Healthcare System



Limited resources

Trained healthcare professionals
Advanced laboratory equipment
Energy for AI centers

Towards an **Un**sustainable Healthcare System



Inequalities