Pharmacogenomics and Pharmacogenetics

Medical-Pharmaceutical Biotechnology
Master's Degree

Università di Genova

Academic year 2025-2026

The course comprises 2.5 CFU, corresponding to 20 hours of lectures

Pharmacogenetics and pharmacogenomics are pharmacological disciplines that study the genetic basis of individual variability in drug response. They are crucial for personalized medicine, an innovative approach that aims to optimize drug treatment on the basis of patient's individual characteristics in order to target therapies and thus minimize adverse reactions.

Timetable of the course

- **Monday: 11.00- 13.00**
- **Tuesday: 11.00-13.00**
- **Thursday: 11.00-13.00**

Auletta Sez. Biologia
(Via Pastore 3- piano 2°)

Teachers

Guendalina Olivero
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AULAWEB PASSWORD: Pharmacogenomics_2526

Syllabus

- Introduction to pharmacogenetics and pharmacogenomics: interindividual variability in drug response and personalized medicine.
- Genetic polymorphisms (single nucleotide polymorphisms, deletions, copy number variation) and possible impact on protein function.
- Polymorphisms in genes coding for proteins involved in drug metabolism, transport.
- Polymorphisms in genes coding for drug target proteins.
- HLA gene polymorphisms and adverse drug reactions.
- Examples of tools used in the clinic to highlight possible pharmacogenetic adverse drug reactions: PharmaGKB
- Gene therapy using *in vivo* and *ex vivo* approaches: CarT cells, ASOs, siRNAs, miRNAs, aptamers, ribozymes and DNAzymes.
- Pharmacogenomics in cancer therapy.

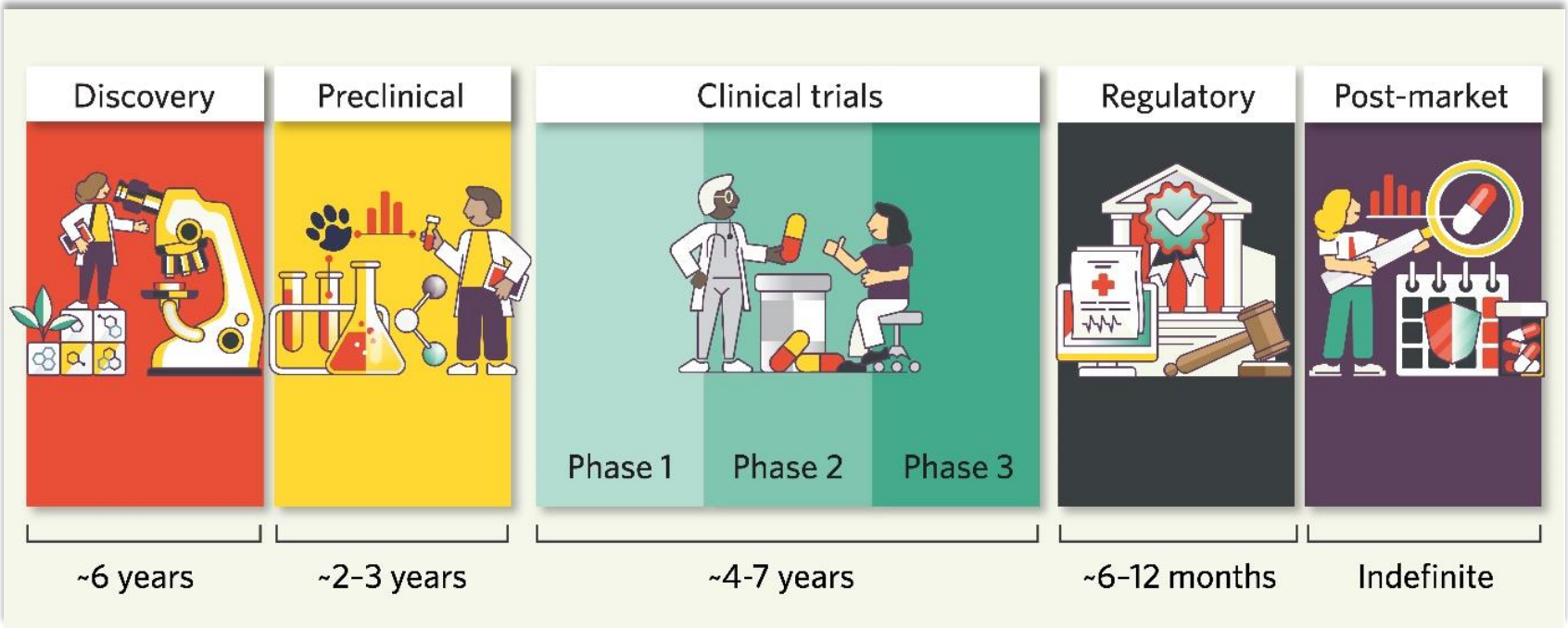
Exam

The examination will consist of an oral test. Students are required to prepare and discuss a powerpoint presentation on a topic related to the teaching. This will be the starting point for checking the level of preparation with regard to the topics addressed in the course.

Presentations will take place during the last class on Thursday June, 4th.

Pharmacogenetics and precision medicine: toward therapy personalization

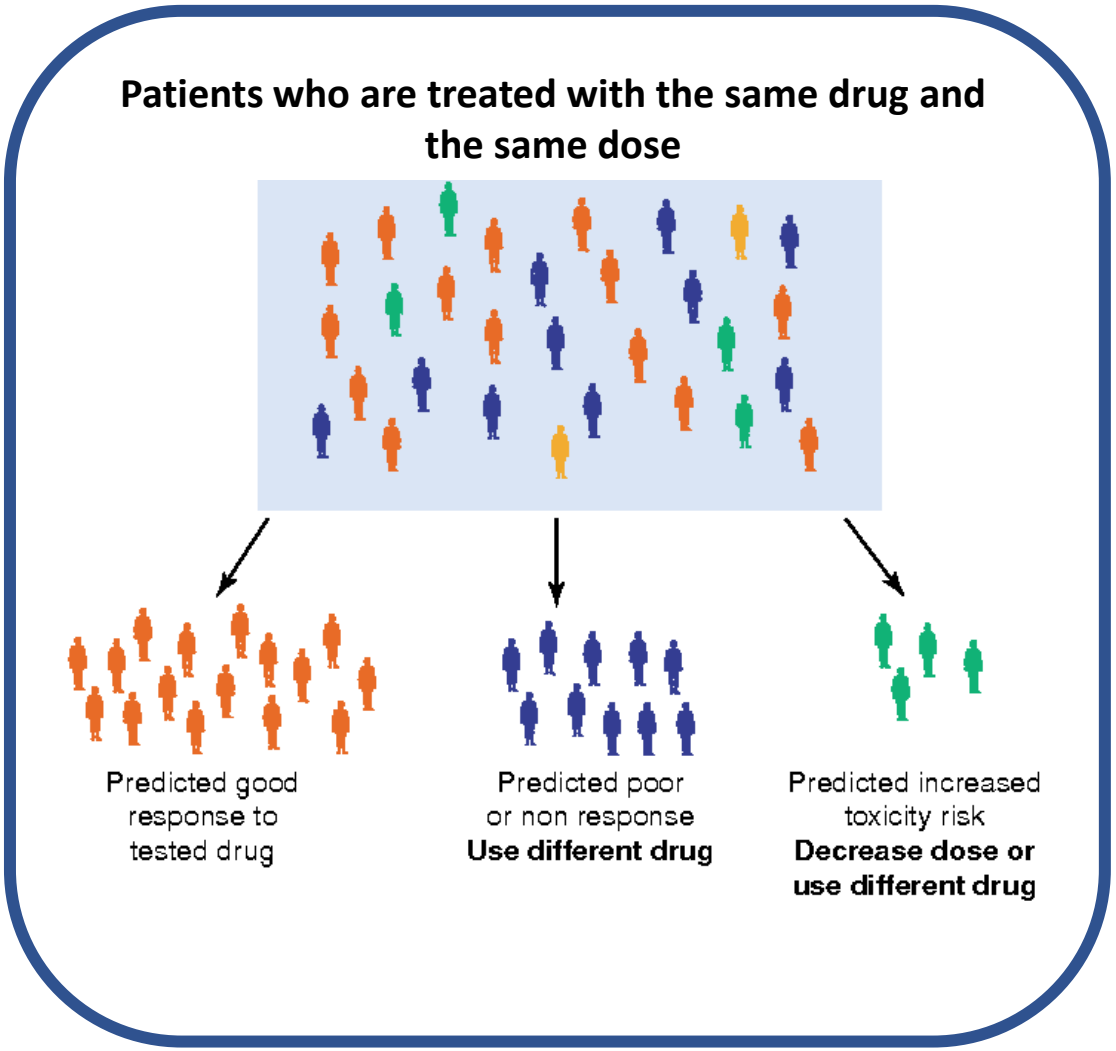
Drug development process



https://www.the-scientist.com/understanding-the-drug-development-process-72854

Drug development is the process of identifying a new drug molecule and bringing it into clinical practice. The final aim of the drug development process is to produce a new, safe, and effective medicine that has been officially approved by regulatory authorities (such as the EMA or FDA) to treat, cure, or prevent a specific disease or medical condition.

Drug response inter-individual variability



- **Therapeutic effect**
- **Therapeutic failure**
- **Side or toxic effects**

Drug treatment failure

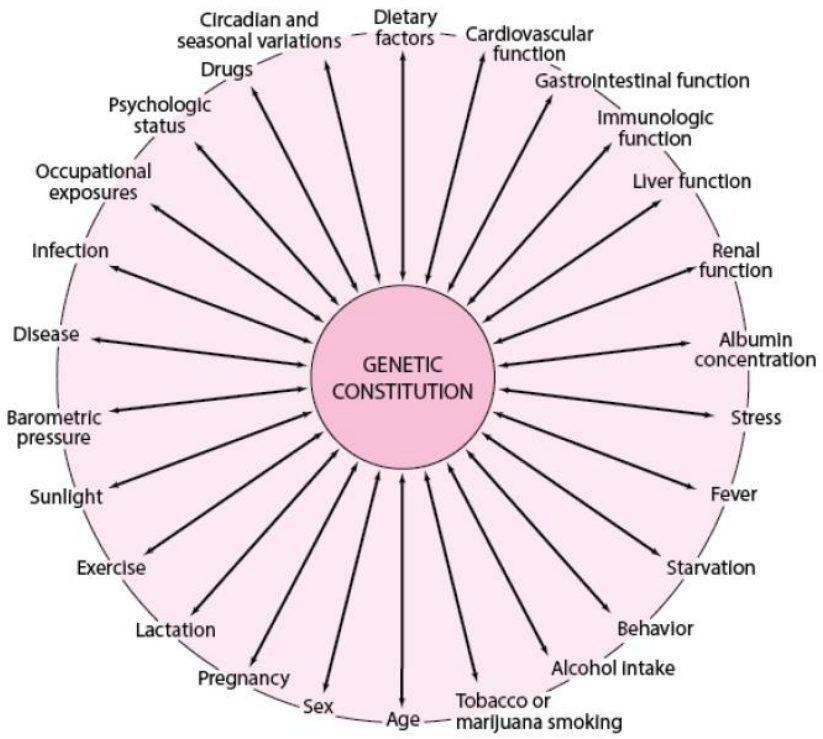
Table 1. Response rates of patients to a major drug for a selected group of therapeutic areas[1]

Therapeutic area	Efficacy rate (%)
Alzheimer's	30
Analgesics (Cox-2)	80
Asthma	60
Cardiac Arrythmias	60
Depression (SSRI)	62
Diabetes	57
HCV	47
Incontinence	40
Migraine (acute)	52
Migraine (prophylaxis)	50
Oncology	25
Osteoporosis	48
Rheumatoid arthritis	50
Schizophrenia	60

Spear, B.B., Heath-Chiozzi, M., & Huff, J. (2001). Clinical application of pharmacogenetics. TRENDS in Molecular Medicine, 7(5), 201-204.

- **20-40% of patients do not respond to antidepressant medications**
- **40% of people with asthma have no response to standard treatments**
- **Anti-ulcer drugs fail in 40% of patients**

Causes of inter-individual variability in drug response



Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

MSD MANUAL
Professional Version

Non-Genetic Factors

- age, gender
- life style (diet, alcohol, smoking)
- multiple medications
- disease states (impaired kidney and/or liver function)

Genetic factors

PHARMACOGENETICS

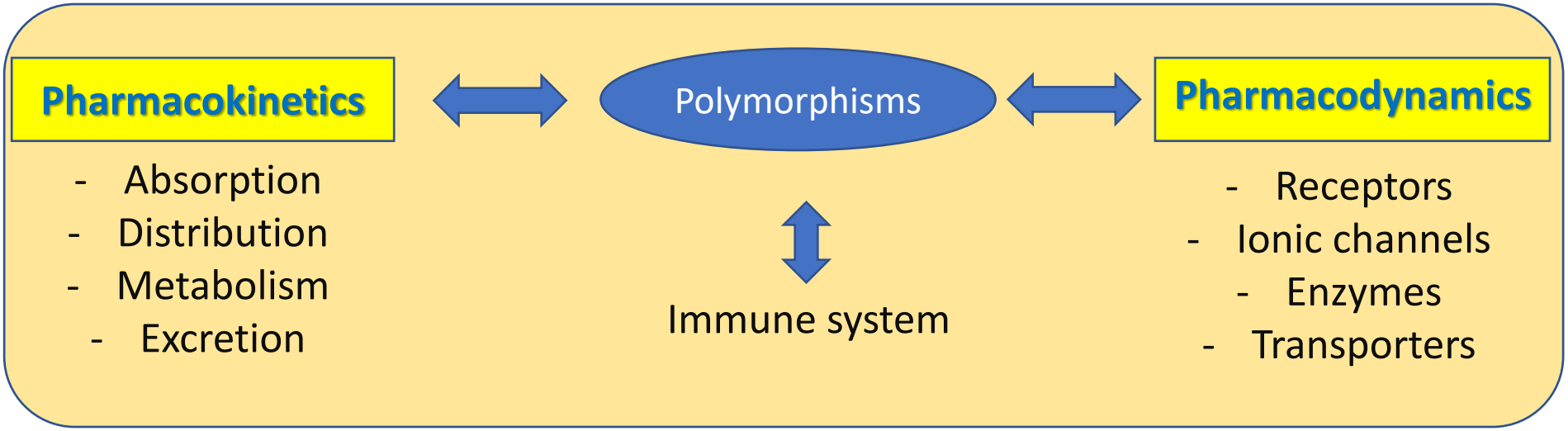
Pharmacogenetics and pharmacogenomics

Pharmacogenetics is the study of how genes affect individual variability in drug response.

Many genes encoding proteins involved in drug response are polymorphic in the population.

These genes can be divided into two classes:

- genes encoding proteins involved in drug absorption, distribution, metabolism and excretion (ADME processes)
- genes encoding drug targets (receptors, enzymes, transporters and ion channels)



Pharmacogenomics is the genome-wide evolution of pharmacogenetics: it study how the whole individual's genetic makeup affects their response to drugs.

Pharmacogenetics: gene-by-gene approach

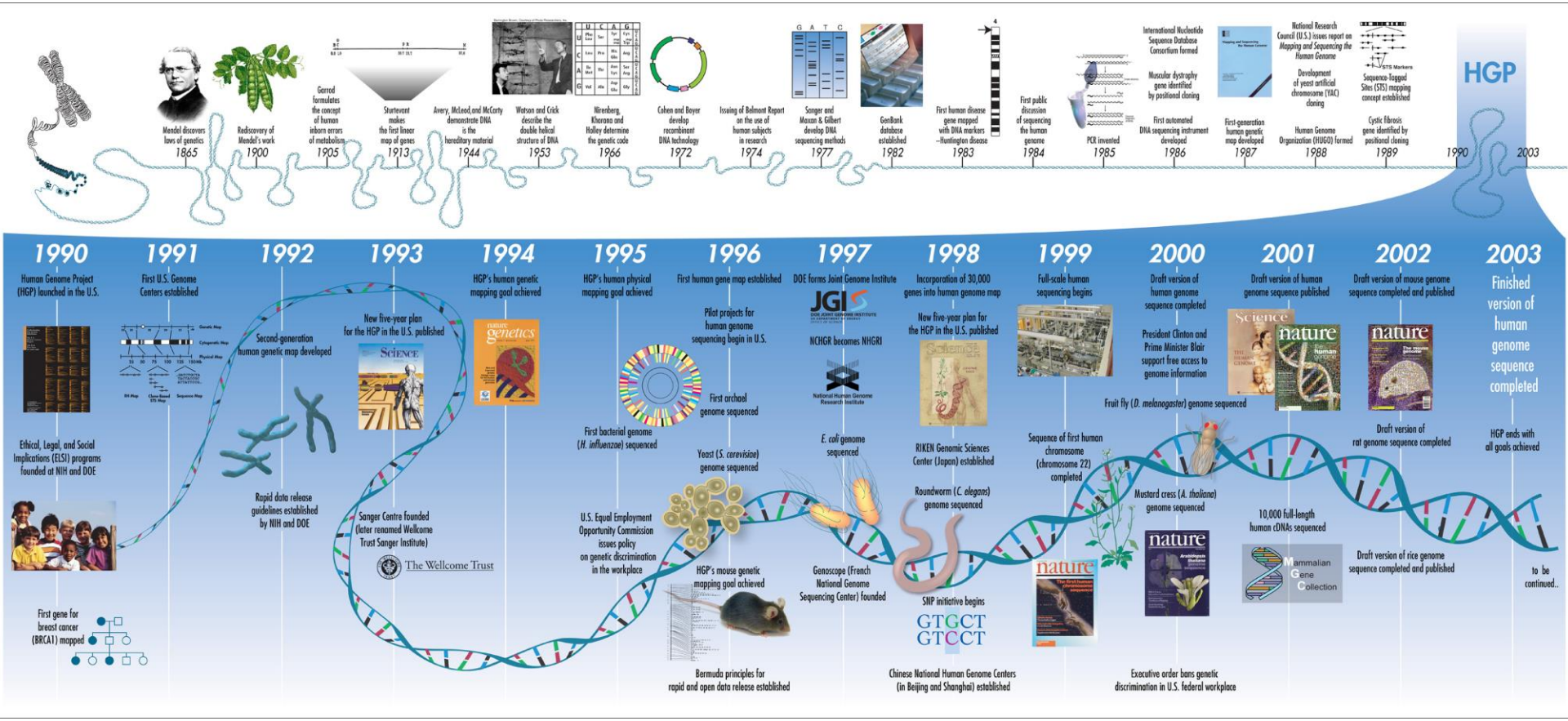
Pharmacogenomics: genome-wide approach

AIMS:

- to improve effectiveness of therapeutic intervention: correct dose selection and reduction of adverse drug reactions
- to identify new therapeutic targets and develop new drugs for individuals who do not respond to a specific treatment or who experience adverse side effects

Personalized or precision medicine

From the discovery of DNA to the sequencing of the human genome



1953 James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin provide the first description of the structure of DNA.

2003 The human genome is completely sequenced.

HOME > SCIENCE > VOL. 231, NO. 4742 > A TURNING POINT IN CANCER RESEARCH: SEQUENCING THE HUMAN GENOME

PERSPECTIVE

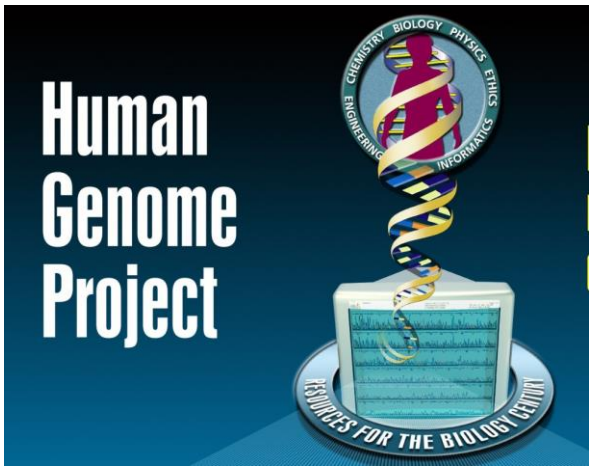
A Turning Point in Cancer Research: Sequencing the Human Genome

RENATO DULBECCO

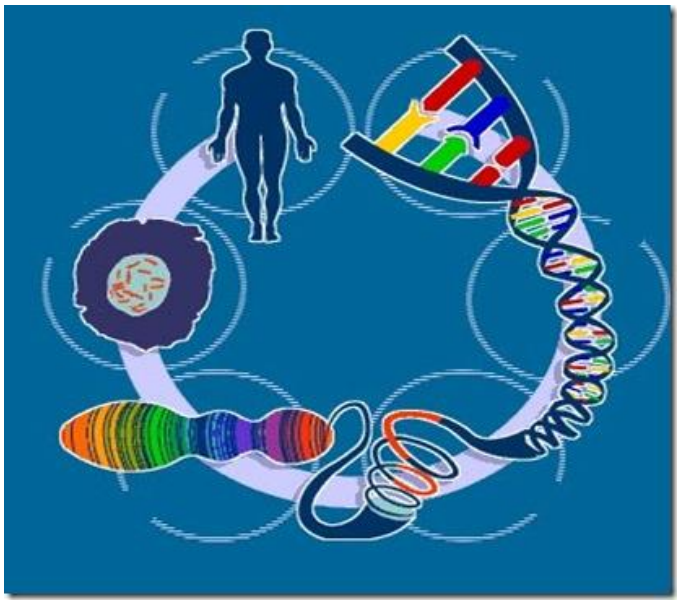
SCIENCE • 7 Mar 1986 • Vol 231, Issue 4742 • pp. 1055-1056 • DOI: 10.1126/science.3945817

Renato Dulbecco
(1914-2012)

In 1986 Renato Dulbecco, winner of Nobel Prize in Medicine in 1975, proposed the idea of sequencing the human genome.

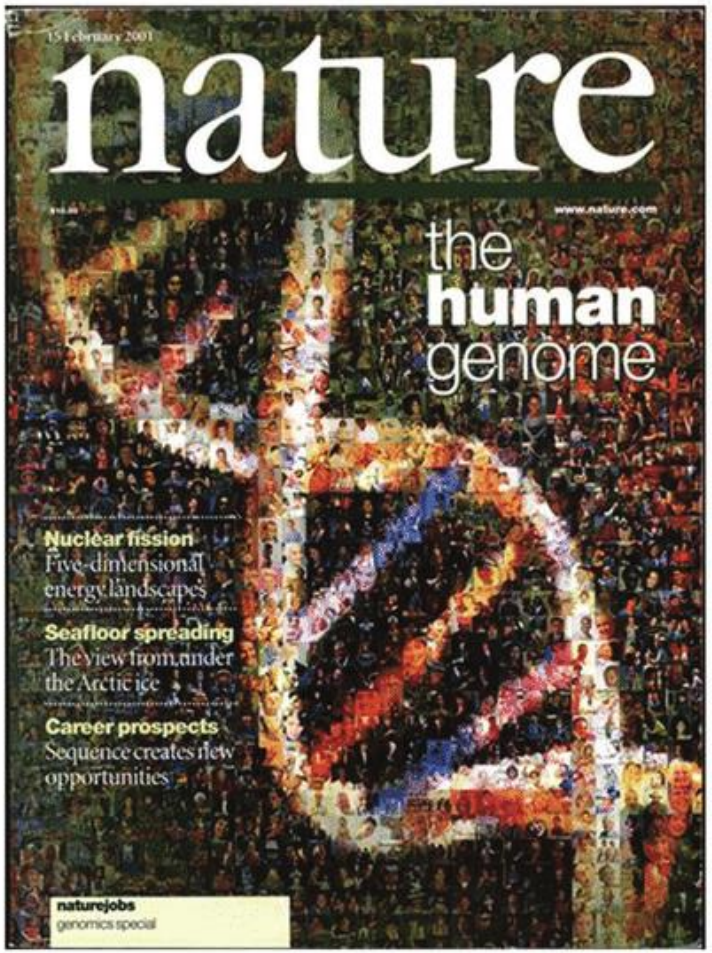


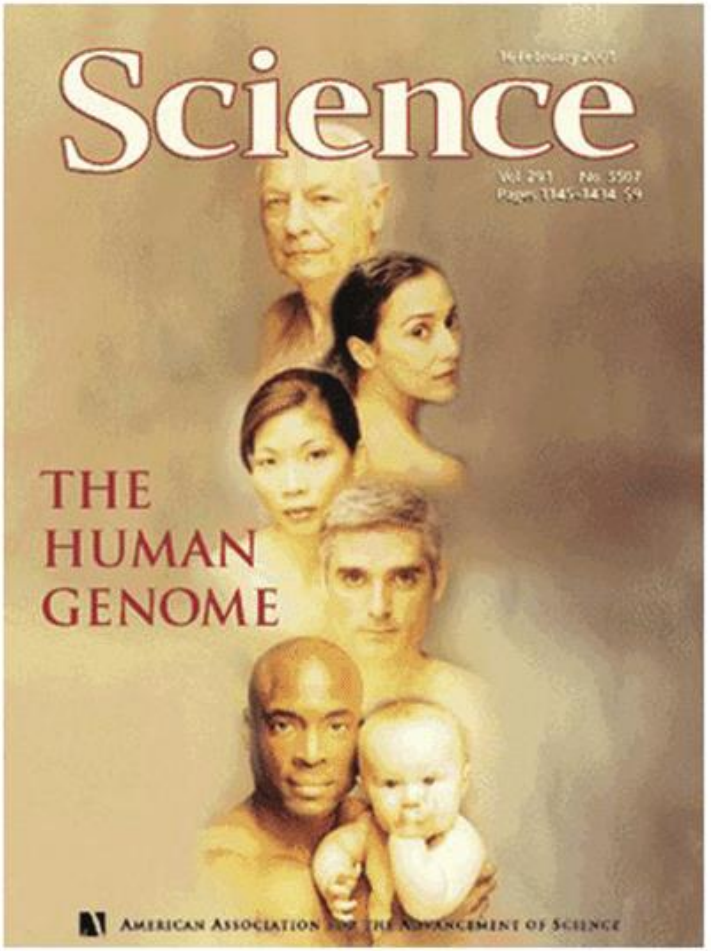
Human Genome Project (1990-2003)



Aim: to identify the sequence of genes of the human species and their location on chromosomes, building the map of the human genome.

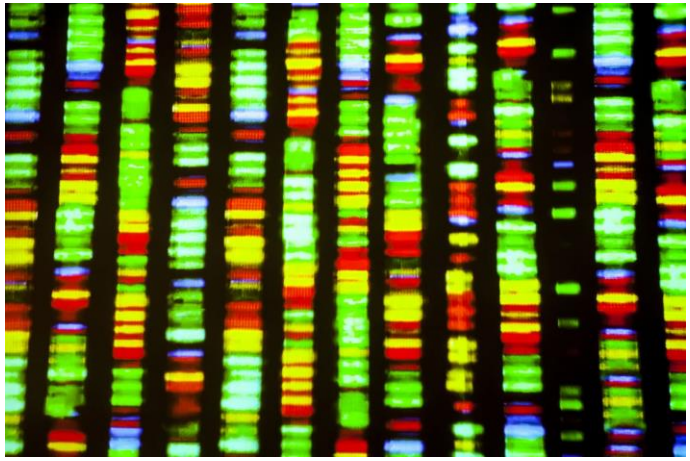
February 2001





The results of the sequencing of the human genome have been published.

Results of the Human Genome Project



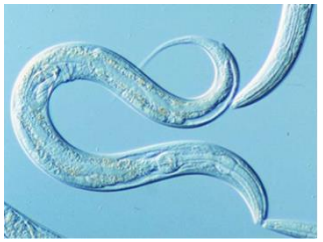
- Approximately 3 billion base pairs
- 20,000–25,000 genes
- Only 1.5% of the genome encodes proteins (exons)
- Non-coding DNA accounts for 98.5% of the genome.

It was long referred to as *"junk DNA"*. However, many of these non-coding sequences have important biological functions (e.g., chromosome protection and regulation of gene expression).

- Humans share 99.9% of their genetic code

The human genome consists of 20000-25000 genes…

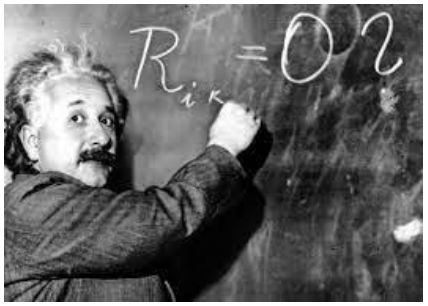
- *Caenorhabitis elegans*, nematode, 12000 genes



- *Drosophila melanogaster* , fruit fly 14000 genes

- *Oryza sativa,* rice, 40000-60000 genes

- *Homo sapiens*, 20000 genes



Once the human genome had been sequenced, the main aims shifted to:

- understanding the biological function of each identified gene and the interactions among genes;
- analyzing genomic variability.

Genomic variability

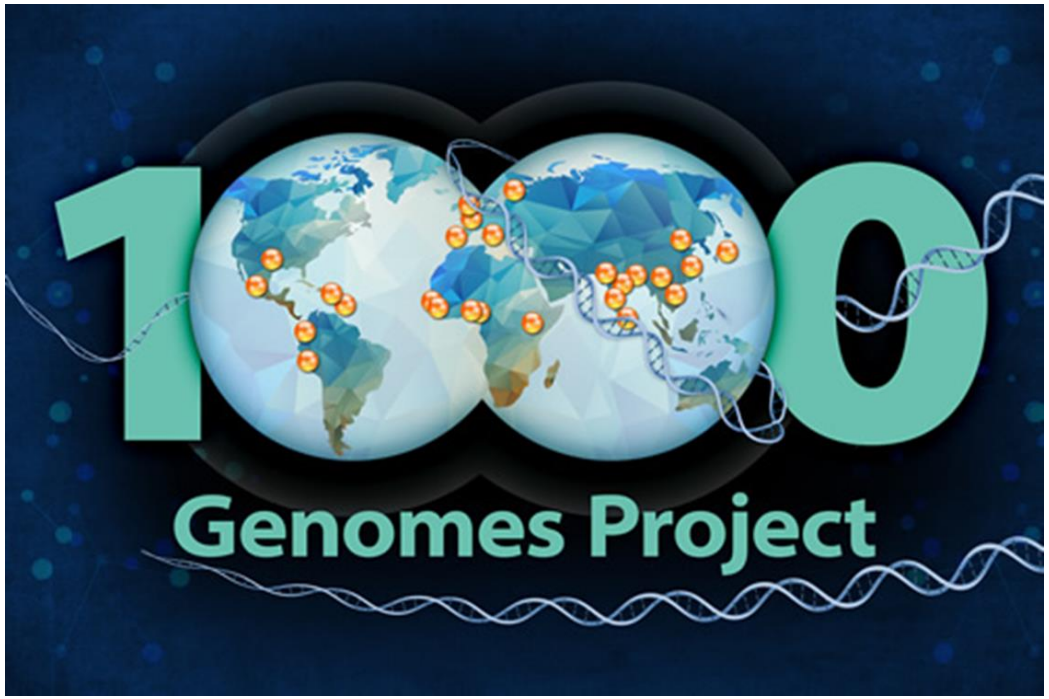
Genomic differences among individuals are minimal (about 0.1%), corresponding to an average of one nucleotide variation every 1000 base pairs (3 million every 3 billion nucleotides).
This small fraction of variable DNA account for some of the differences among people, including important aspects of their health.

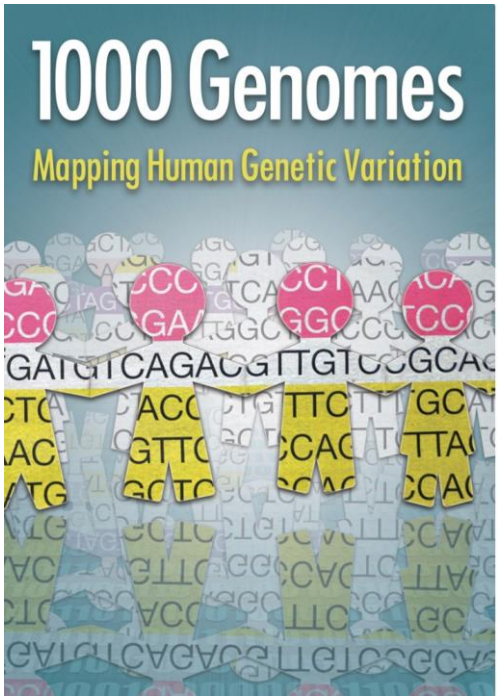
The investigation of genomic variability is essential for elucidating the genetic basis underlying interindividual differences in susceptibility to specific diseases and in responses to pharmacological treatments.

1000 Genomes Project

Project launched in 2008 by an international consortium of scientists

Aim: to sequence the genomes of at least 1000 volunteers from multiple populations worldwide in order to create a comprehensive catalog of human genetic variation (variants occurring at a frequency of 1% or lower) to improve the understanding of genetic contribution to human health and disease





Nature. 2010 Oct 28;467(7319):1061-73. doi: 10.1038/nature09534.

A map of human genome variation from population-scale sequencing

1000 Genomes Project Consortium; Gonçalo R Abecasis, David Altshuler, Adam Auton, Lisa D Brooks, Richard M Durbin, Richard A Gibbs, Matt E Hurles, Gil A McVean

2010

2015

NATURE
An open access paper www.nature.com

Nature. 2015; 526(7571): 68–74.
Published online 2015 Sep 30. doi: 10.1038/nature15393

PMCID: PMC4750478
NIHMSID: NIHMS753481
PMID: 26432245

A global reference for human genetic variation

The 1000 Genomes Project Consortium

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nature › articles › article

Open Access | Published: 30 September 2015

An integrated map of structural variation in 2,504 human genomes

Peter H. Sudmant, Tobias Rausch, ... Jan O. Korbel + Show authors

Nature **526**, 75–81 (2015) | Cite this article

The genomes of 2,504 individuals belonging to 26 different populations were sequenced and analyzed.

Main results of the 1000 Genomes Project

- ~ 88 million sites within the genome show variation among individuals, including 84.7 million single-nucleotide polymorphisms (SNPs), 2.6 million small insertions or deletions (indels), and 60,000 larger structural variants.
- Approximately one quarter of these variants are common (>1% of individuals, polymorphisms) occuring in many or all populations worldwide, while the remaining variants are rare (<1% of individuals).
- Most individuals carry between 250 and 300 genetic alterations able of disrupting the normal function of a gene, as well as up to 100 genetic variants that have been associated with an inherited disease.
- Each individual carries approximately 60 *de novo* mutations, which are not present in either parent.

internationalgenome.org/home

IGSR: The International Genome Sample Resource

Supporting open human variation data

Home About Data Help

Search IGSR

The International Genome Sample Resource

The 1000 Genomes Project created a catalogue of common human genetic variation, using openly consented samples from people who declared themselves to be healthy. The reference data resources generated by the project remain heavily used by the biomedical science community.

The International Genome Sample Resource (IGSR) maintains and shares the human genetic variation resources built by the 1000 Genomes Project. We also update the resources to the current reference assembly, add new data sets generated from the 1000 Genomes Project samples and add data from projects working with other openly consented samples.

Explore the data sets in IGSR through our data portal

View variants in genomic context in Ensembl

IGSR was set up to ensure the future usability and accessibility of data from the 1000 Genomes Project and to extend the data set produced by the 1000 Genomes Project to include new data generated from the 1000 Genomes Project samples and new populations where sampling has been carried out in line with IGSR sampling principles.

The 1000 Genomes Project ran between 2008 and 2015, creating the largest public catalogue of human variation and genotype data. As the project ended, the Data Coordination Centre at EMBL-EBI received funding from the Wellcome Trust to create IGSR with the following aims:

1. Ensure the future access to and usability of the 1000 Genomes reference data
2. Incorporate additional published genomic data on the 1000 Genomes samples
3. Expand the data collection to include new populations not represented in the 1000 Genomes Project

The 100,000 Genomes Project by numbers

Genomics england

2012-2018

100,000 genomes

70,000 patients and family members

21 Petabytes of data.
1 Petabyte of music would take 2,000 years to play on an MP3 player.

13 Genomic Medicine Centres, and **85** NHS Trusts within them are involved in recruiting participants

1,500 NHS staff
(doctors, nurses, pathologists, laboratory staff, genetic counsellors)

2,500 researchers and trainees from around the world

What it is all about?

Patients who take part in the project may be able to get diagnosis.

For some, genome sequencing may mean a specific treatment can be recommended.

But for most, taking part means knowing they are helping medical research for future generations.

Research on genomes will help us understand diseases and what's causing them.

It can help researchers develop treatments and new diagnosis.

Who is involved?

It is estimated half of all Britons will get some form of cancer at some point in their lives.

A rare diseases is one that affects 1 in 2,000 or less of the UK population. There are up to 8,000 rare diseases – affecting a total of 3 million people in the UK.

8,000 rare diseases affecting **3,000,000** people in the UK

There are over 100 rare diseases included in the Project and 7 common cancers.

7 common cancers
100+ rare diseases

Sequencing of the genomes of patients affected by rare diseases, cancer, and their family members.

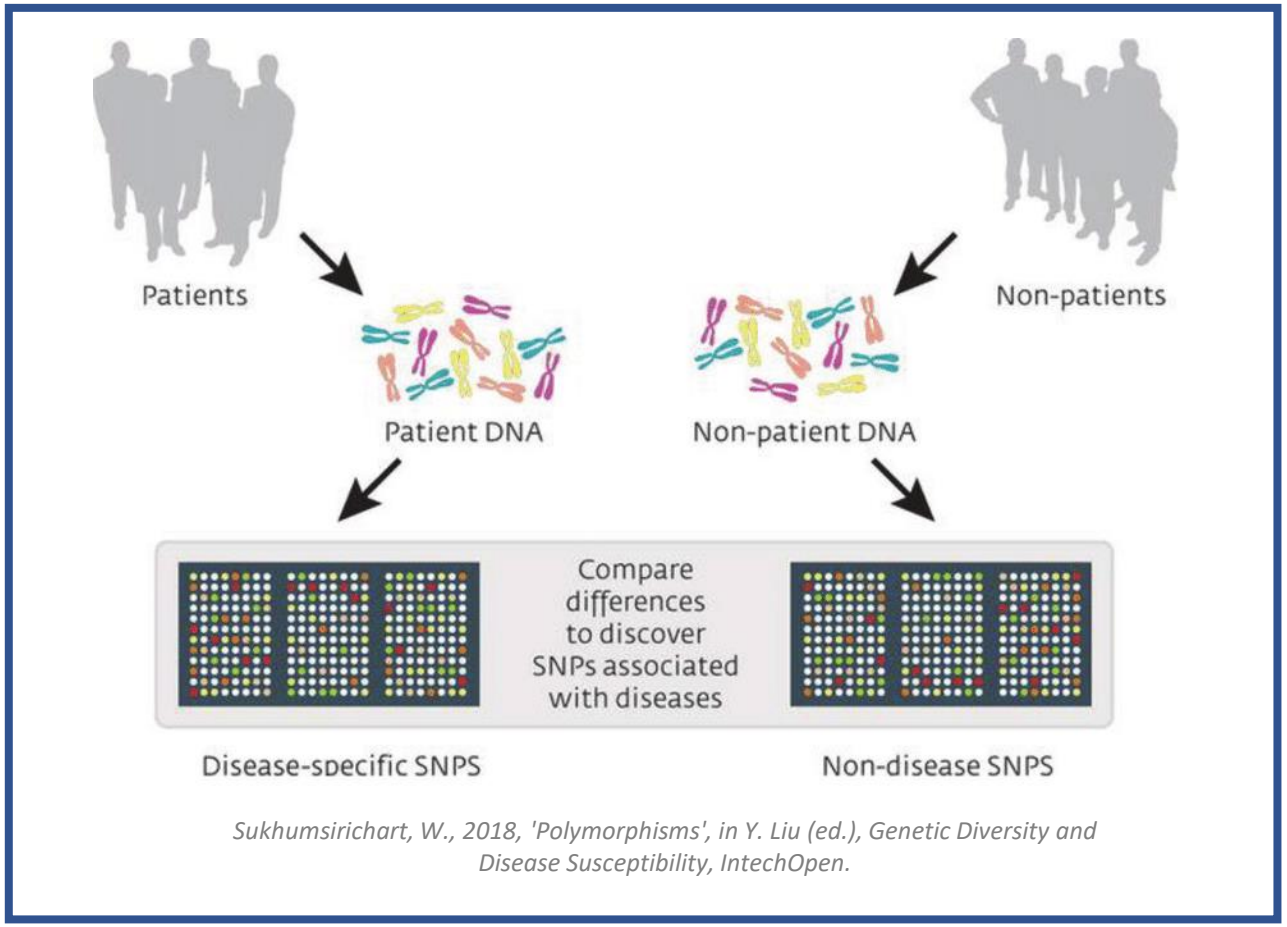
Main results of the 100000 Genomes Project

- **New Diagnoses:** About 25% of rare disease patients received a diagnosis for the first time.

- **Targeted Treatment:** Around 50% of cancer cases revealed genetic findings that could potentially change how the patient was treated or allow them to join clinical trials.

- **The Genomic Medicine Service:** The project's success led to the creation of the world's first national genomic medicine service integrated into a public healthcare system

Genome-Wide Association Studies (GWAS)



Sukhumsirichart, W., 2018, 'Polymorphisms', in Y. Liu (ed.), Genetic Diversity and Disease Susceptibility, IntechOpen.

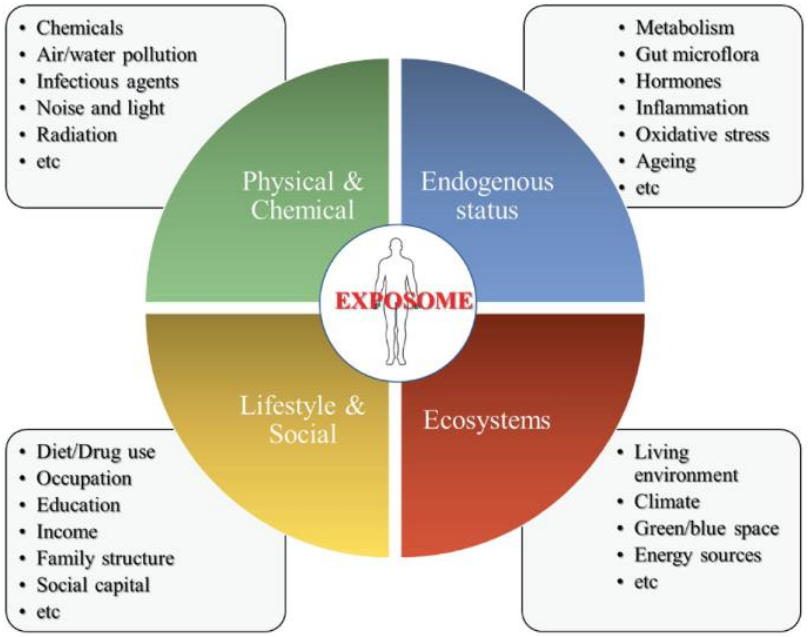
GWAS are observational research approaches that scan the DNA of large populations to identify genetic variants, typically single nucleotide polymorphisms (SNPs), associated with specific traits or diseases.

GWAS and missing heritability

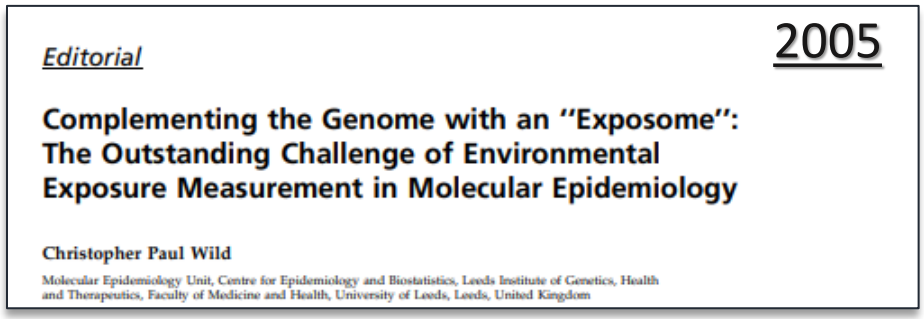
Disease	Number of loci	% of heritability explained
Age-related macular degeneration	5	50%
Crohn's sidease	32	20%
Systemic Lupus heritematosus	6	15%
Type 2 diabetes	18	6 %
HDL cholesterol	7	5.2%
Myocardial infarction	9	2,8%
Fasting blood glucose	4	1,5%

For most of the associations between polymorphisms and diseases, genetic variants explain only a limited proportion of overall heritability. This issue, known as "*missing heritability*", is likely attributable to low-frequency allelic variants or rare variants that are not detected by GWAS.

The contribution of environmental factors to interindividual variability: the exposome



Tan and Chen (2022). Advances in Exposome. Advances in Toxicology and Risk Assessment of Nanomaterials and Emerging Contaminants. Springer.



Editorial

2005

Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom

The **exposome** is defined as the totality of environmental and internal exposures individuals experience from conception throughout their lifetime and how these factors impact health. It comprises the exposure to environmental and lifestyle factors, social interactions and endogenous processes (inflammation, metabolism, oxidative stress, gut microbiota…).

Gene-environment interaction

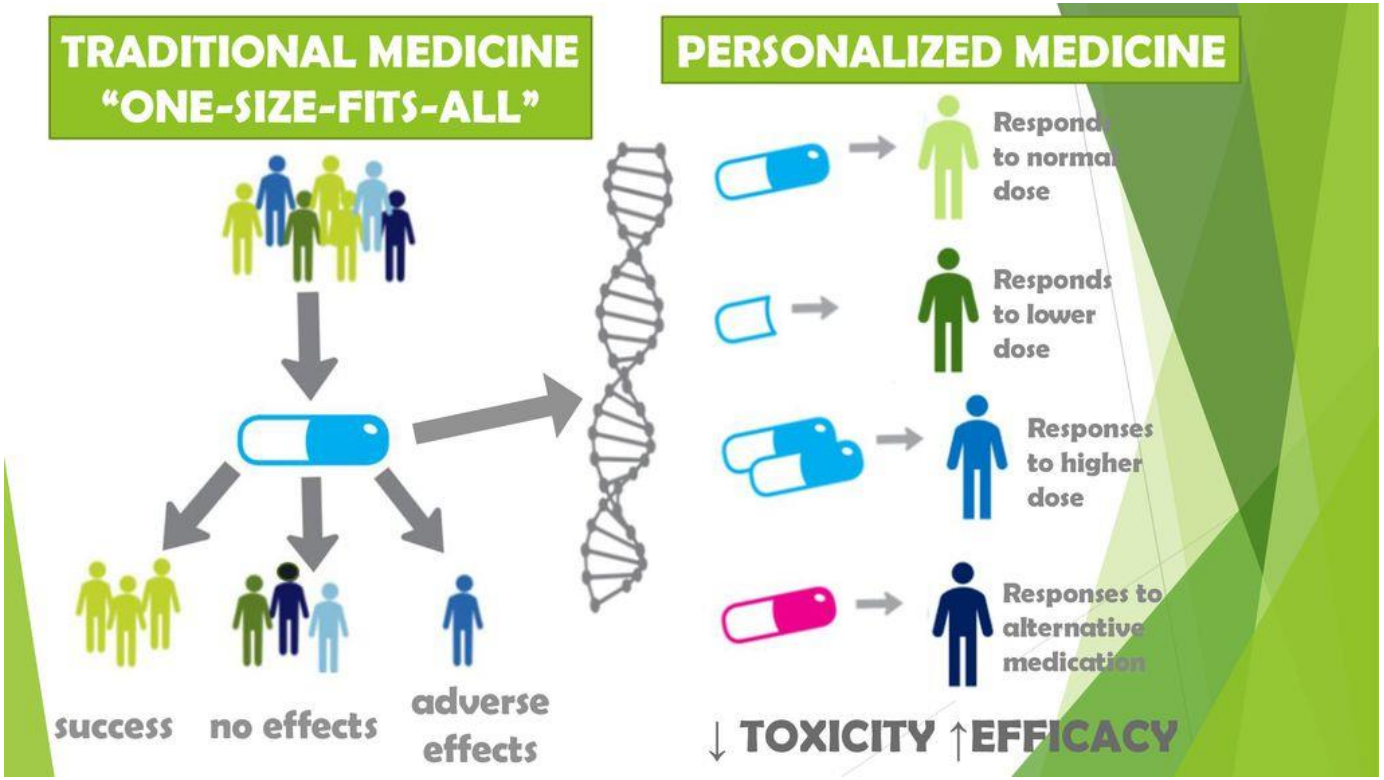
Many multifactorial diseases originate from a genetic predisposition but are also regulated by environmental factors.

Gene–environment interaction (**Gene × Environment, GxE**) can be defined as:

- a different effect of an environmental exposure on disease risk in individuals with different genotypes
- a different effect of a genotype on disease risk in individuals with different environmental exposures

GxE is a fundamental risk factor of developing a disease.

Precision medicine



Emerging approach for the treatment and prevention of diseases that takes into account individual variability from a genetic, environmental and lifestyle perspective. Its goal is to personalize prevention, diagnosis and treatment tailored on the individual characteristics of a patient.

Maximize therapeutic effects

Reduce adverse reactions

Reduce costs

NATURE | COMMENT

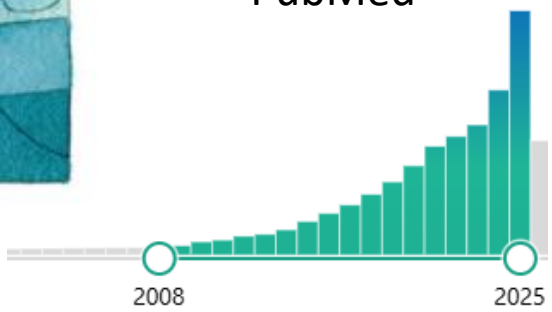
Personalized medicine: Time for one-person trials

Nicholas J. Schork

29 April 2015

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says Nicholas J. Schork.

PubMed



All of Us℠

THE FUTURE OF HEALTH BEGINS WITH YOU

The Precision Medicine Initiative®

"health care tailored to you".

The initiative was launched by Barack Obama in 2015 and involves the U.S. National Institutes of Health (NIH) along with many other research centers. Its aim is to gain a deeper understanding of how an individual's genetics, environment, and lifestyle influence health to set the most effective strategies for disease prevention and/or treatment.

NEAR-TERM GOALS

Intensify efforts to apply precision medicine to **cancer.**

Innovative **clinical trials** of targeted drugs for adult, pediatric cancers

Use of **combination therapies**

Knowledge to overcome **drug resistance**

LONGER-TERM GOALS

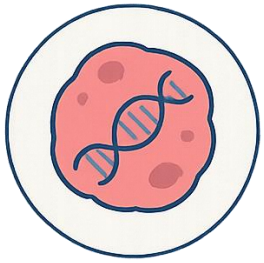
Create a research cohort of **> 1 million American volunteers** who will share genetic data, biological samples, and diet/lifestyle information, all linked to their electronic health records if they choose.

Pioneer **a new model for doing science** that emphasizes **engaged participants, responsible data sharing, and privacy protection.**

Research based upon the cohort data will:

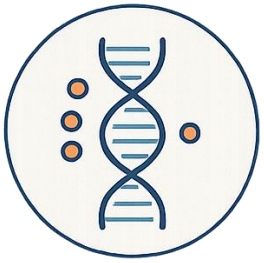
- Advance **pharmacogenomics,** the right drug for the right patient at the right dose
- Identify new targets for **treatment and prevention**
- Test whether **mobile devices** can encourage healthy behaviors
- Lay **scientific foundation** for precision medicine for **many diseases**

Precision medicine today



Oncology

Pharmacogenomics



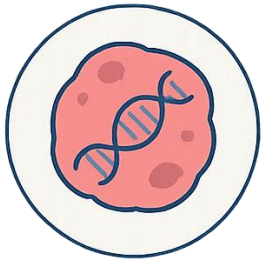
Rare and Genetic Diseases

Inherited Cancer Risk and Preventive Medicine

Oncology

- **Targeted Therapies**: drugs designed on the basis of specific genetic, molecular, and cellular profile of a patient's tumor to target mutated protein which drives tumor’s growth or resistance.
- **Personalized immunotherapy:** treatment that help the immune system to fight cancer based on individual biomarkers

Precision medicine today



Oncology

Pharmacogenomics

Rare and Genetic Diseases

Inherited Cancer Risk and Preventive Medicine

Pharmacogenomics

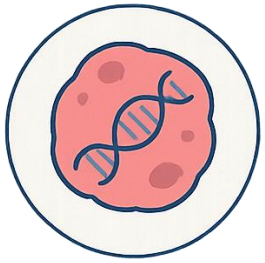
Genetic tests are used in clinical practice to tailor drug choice and dosing according to genetic variants affecting drug pharmacokinetics and response: to prevent adverse reaction and therapeutic failure.

Precision medicine today

Rare and genetic diseases

Whole-genome or whole-exome sequencing is used for diagnosis and treatment selection. Precision medicine enables accurate diagnosis of previously unexplained disorders and, in some cases, **gene-based or enzyme-replacement therapies**.

Precision medicine today



Oncology

Pharmacogenomics

Rare and Genetic Diseases

Inherited Cancer Risk and Preventive Medicine

Preventive medicine

Genetic testing is used to assess disease risk. Results guide surveillance strategies, preventive interventions, or prophylactic treatments.