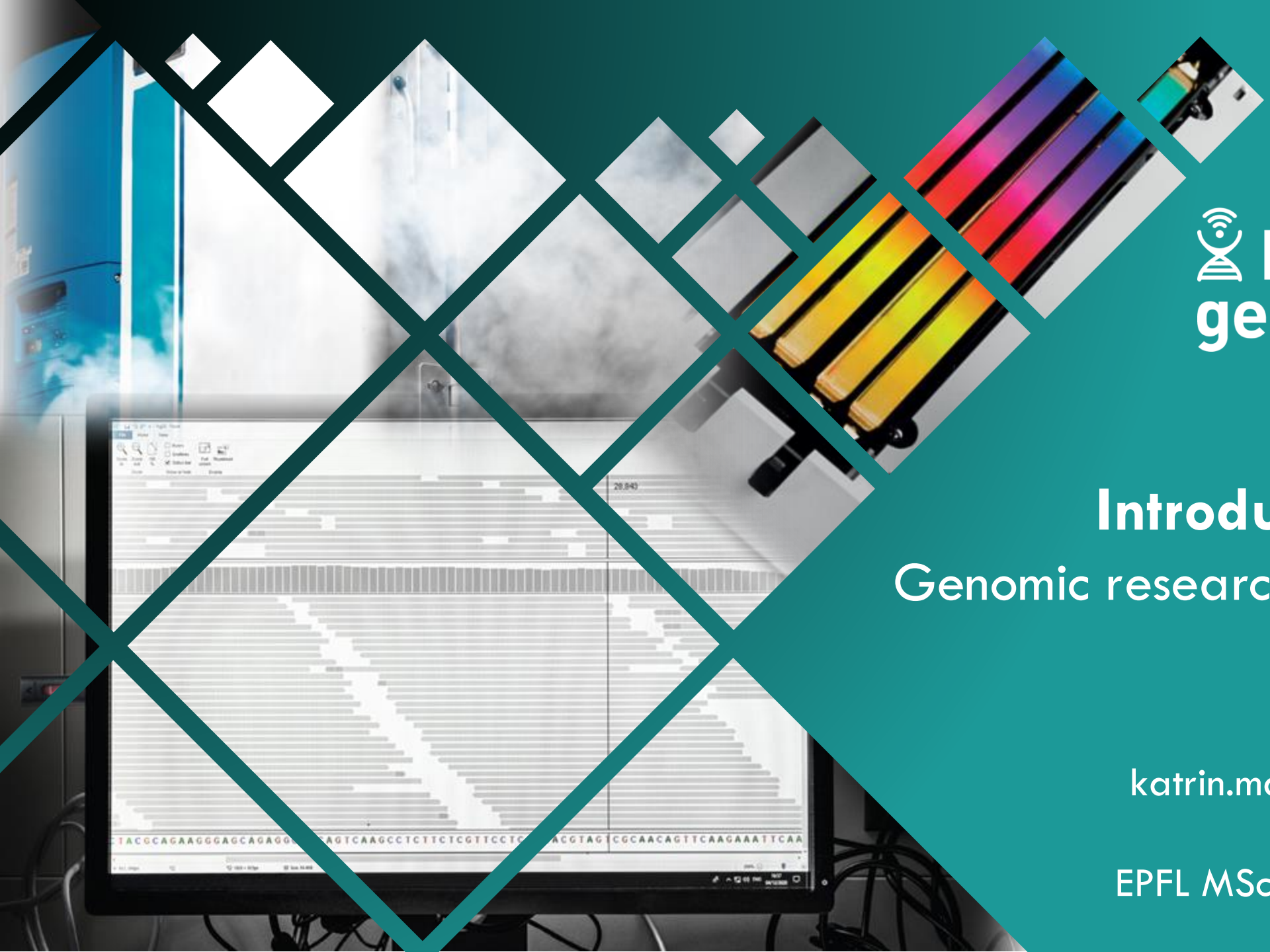

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Introduction

Genomic research and medicine

Katrin Männik, PhD
katrin.mannik@health2030.ch

EPFL MSc seminar, 26.11.2024

Where is genomic medicine in 2024?

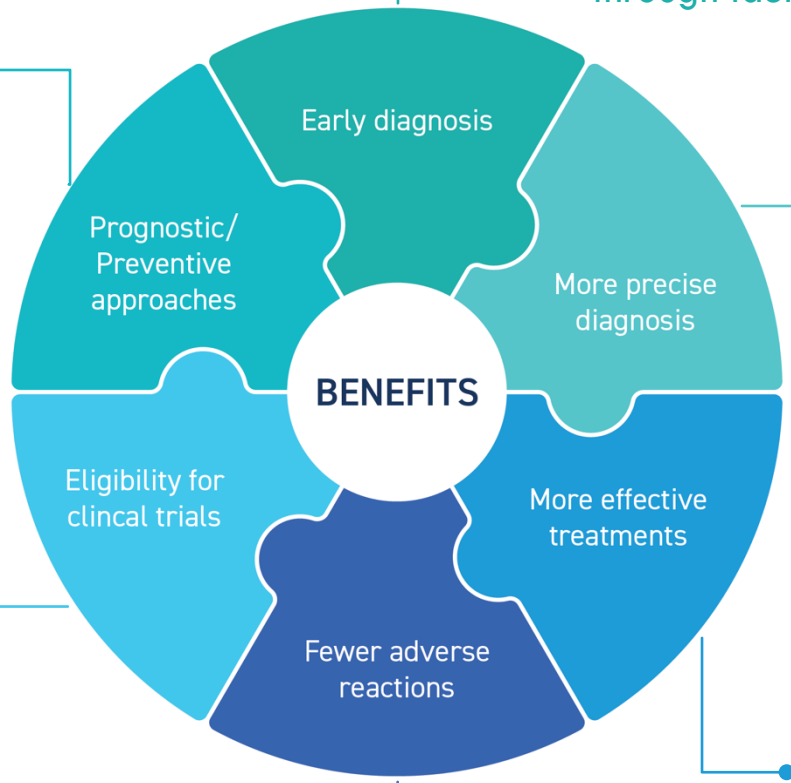
- Genetic factors play a role, to a greater or lesser extent, in **all human diseases**

- Genomic research and medicine are **central for biomedical research and healthcare**

Benefits provided by genomic medicine

Opening more treatment possibilities through identifying at early stage

Identifying predisposition markers



Clear identification of underlying cause of disease and segmentation

Better characterization of condition and driver targets

Precise diagnosis allows better treatment selection and increased effectiveness

Through identification of predisposition to side effects

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NHS Genomic Medicine Five-Year Strategy (UK), October 2022

Plan France Médecine Génomique 2025

Launched by the French government in 2016

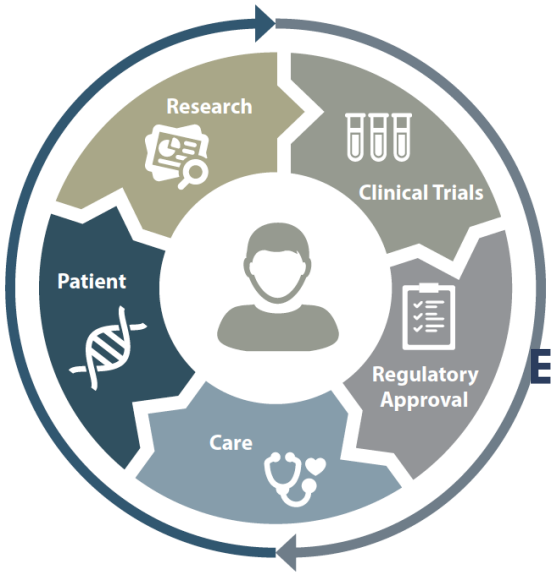
*"Genomic medicine is no longer a promise - **it is already a reality** that will transform how we prevent, diagnose, treat and predict the prognosis of disease.*

...

***It is a public health issue.** Genomic medicine is revolutionizing the care pathway and therefore how the public health system is organized."*

Genomics is changing the research transition pathway

Traditional linear genetic research translation pathway



Emerging cyclic genomic research translation pathway

=

Clinically driven research

Australian Government "The National Health Genomics Policy Framework 2018–2021"

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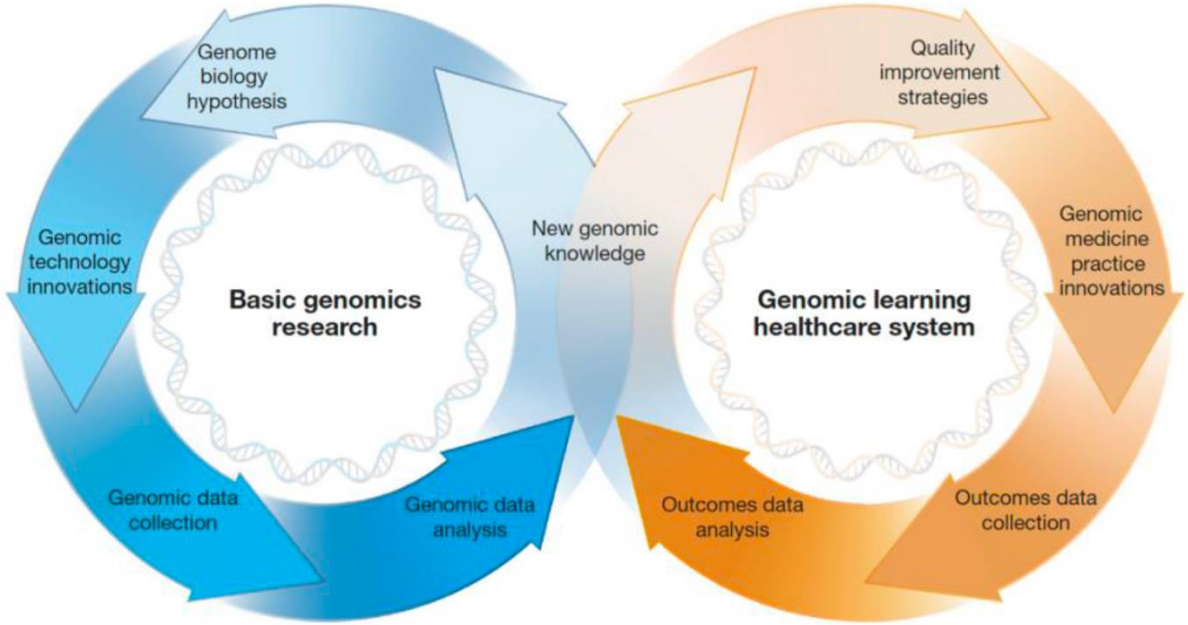
Genomic learning healthcare systems

Positive cycles driven by new knowledge and technological innovation
in human genomics research and clinical care



"Strategic vision for improving human health at The Forefront of Genomics"
Green ED *et al*, Nature 2020

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Clinical *versus* Research Genetic Testing

Clinical genetic testing

- Medical need, recommended by MD
- Informed consent for testing
- Clinical accreditation of the testing protocol
- Targets gene(s) relevant to a particular disease
- Evidence-based interpretation
- Results shared with the patient
- Information for individual diagnosis, treatment
- **Individual benefits**

Research genetic testing

- Voluntary decision by participant
- Informed consent for research, sharing
- Approval of the research protocol by IRB
- Broad analysis, screening of genetic variation
- Exploratory interpretation, novelty
- Results shared with the community
- New scientific knowledge
- **Collective benefits**

Modified from the Michigan Medicine, University of Michigan; healthblog.uofmhealth.org

Will societies be able to afford genomic medicine as a routine service?

WORLD ECONOMIC FORUM

Governance gaps related to equitable and widespread implementation of genomic medicine tools and services, by the WEF

- International data sharing and interoperability
- Ethical use of technologies
- Patient and public engagement and trust
- Access and delivery of the services, their pricing and reimbursement
- Responsive regulatory systems

Precision Medicine Vision Statement:
A Product of the World Economic Forum Global Precision Medicine Council, 2020

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What is needed for responsible implementation?

EP PerMed
European Partnership
for Personalised Medicine

- Public and professional trust
- Modernizing and education
- Focus on inclusion and facilitating access
- IT-infrastructure and technology
- Legal and ethical framework

The EP PerMed "The Strategic Research & Innovation Agenda for Personalised Medicine", 2023

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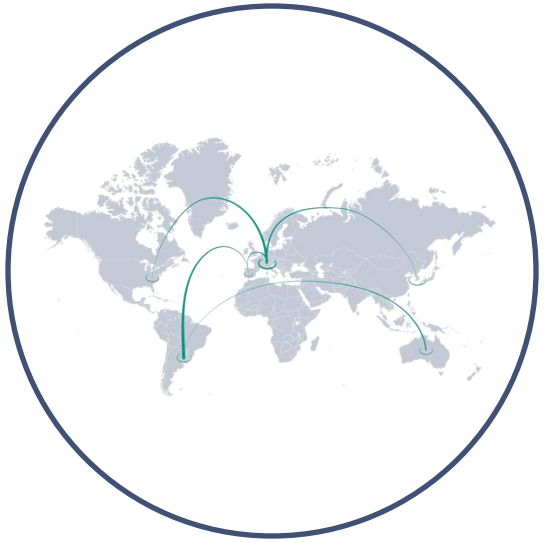
Prerequisites for human health-related genomics

Understanding of **genomic architecture** in the population

Infrastructure and policies for data exchange and analysis, optimized for large-scale genomic data



Readiness to participate in **international collaborations** and data exchange ecosystems

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National genomic medicine initiatives (non-exhaustive list)

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Vemaps.com

Implementation of genomic medicine

Where does Europe stand?

THE FUTURE OF EUROPEAN COMPETITIVENESS – PART | SECTION 1 | CHAPTER 9

1. Maximise the impact of the European Health Data Space (EHDS)

Further scale up genome sequencing capacities in the EU and present a strategic blueprint beyond 2026. Building on the European 1+ Million Genomes (1+MG) initiative and complementing Beyond 1 Million Genomes (B1MG), there is a continued need to strengthen the infrastructure for whole-genome sequencing, including to enhance data sharing across borders under the EHDS. This action, to be set up under a private-public partnership, should build on the European Genomic Data Infrastructure, delivered by a project that will conclude by 2026.

"The Future of European Competitivness"
Report by Mario Draghi
September 2024

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The European Union 1+MG Roadmap

Cross-border access to genomic data, implementation of genomics-based health

2018 2019 2020 2021 2022 2023 2024 2025 2026 2027

Design & Testing

Scale-up & Sustainability

European Genomic Data Infrastructure

Population Genomics

Funded by
the European Union's Digital Europe Program
Grant agreement #101168231
Part of 1+MG Initiative

GENOME OF EUROPE

Slide courtesy Valentina Oberti, EC officer

1+MG Framework

Core 1+MG Framework

Technical framework

Data quality & inclusion

Sequence data generation and quality requirements for WGS/WES data to be labelled as 1+MG compliant

Data models, standards & ontologies

1+MG minimal data models for different use cases and recommendations on ontologies and data standards

Technical infrastructure

Stack of standards, open source references implementations, synthetic data and proof of concepts that can be used to establish a 1+MG node

Implementation

Governance and ELSI

Guidance and recommendations on how to address governance and ELSI aspect to ensure data can be made available

Genomics into healthcare

Assessment Maturity Level Model to guide healthcare systems on their journey to implement genomic medicine

National implementation

Find pointers to country specific information resources and national research data management practices

Implementation of genomic medicine

Where does Europe stand?

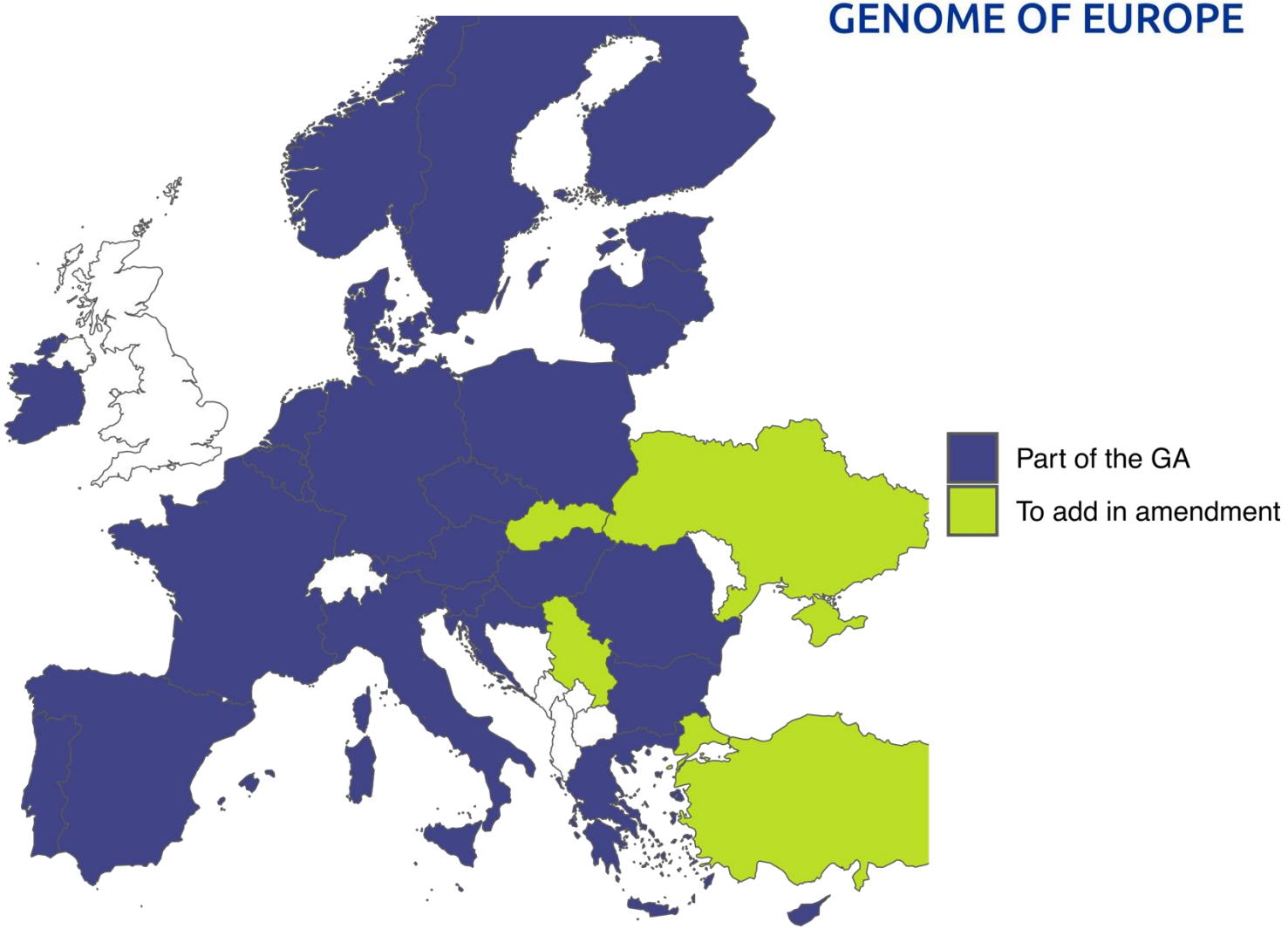
GENOME OF EUROPE

Current grant agreement:

- 27 EU and EEA countries

Additional consortium members

- Amendment in preparation: Turkey, Slovakia, Serbia, Ukraine

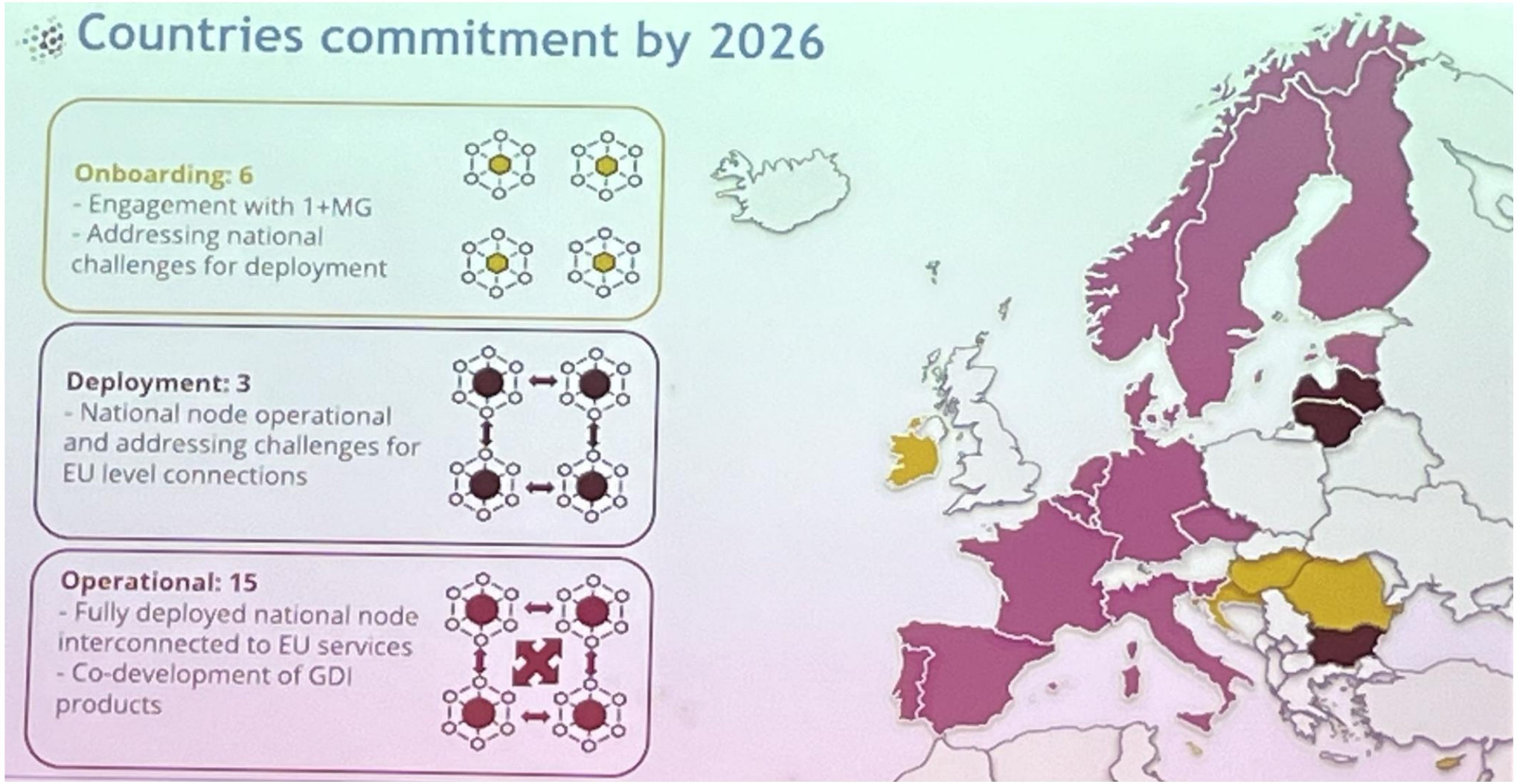


Slide courtesy André Uitterlinden and Helen Ray-Jones, GoE

Implementation of genomic medicine

Where does Europe stand?

European Genomic Data Infrastructure



Swiss Federated Genomics Network

Swiss Personalized Health Network

Strategic Focus Area
Personalized Health and Related Technologies

National genomic strategy to facilitate genomic research and accelerate the integration of genomics into healthcare practice

- To develop a streamlined infrastructure supporting collaborative genomic research
- To provide researchers and clinicians with secure and efficient access to genomic information
- To collect data and knowledge about the genetic structure of the Swiss population
- To serve as stepping stone for international collaborations

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Implementation of genomic medicine

Swiss Federated Genomics Network

Genome of Switzerland

Swiss fEGA repository

Aim to align with the parallel ongoing genomics initiatives at European level

GENOME OF EUROPE

European Genomic Data Infrastructure

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General ethical principles in biomedical research

Respect for persons

- Respect for individual's autonomy and self-determination
- Persons with diminished autonomy are entitled to protection, should be afforded security against harm or abuse

Beneficience

- Do not harm (nonmaleficience)
- Ethical obligation to maximize possible benefits and to minimize possible harms

Justice

- Treat each person in accordance with what is morally right and proper
- Equitable distribution of both the burdens and the benefits (fairness in distribution)

The CIOMS "International Ethical Guidelines for Biomedical Research Involving Human Subjects", 2002; The Belmont Report, 1979

What are the emerging problems in „Genethics“?

Genetic paternalism
Balance between professional opinion and individual autonomy

Control over personal data
Data ownership, sharing and re-use for common good

Re-identification of individuals
Finding family members, matching tissue donors

Right to know and to not know
In the context of abundant, heterogeneous genomic risk information

The shared nature of genomic information
Implications of disclosure, avoiding harm to relatives

Incidental findings
Clinically relevant information, non-paternity, unexpected ancestry

Secondary findings
Opprotunistic screening of clinically relevant genomic variants

Equal access to benefits
Costly, but life-saving experimental therapies

Who need special care in the context of population-scale genomics?

Minors
Subordination of children's autonomy to that of their parents

Individuals with limited capacity
Lack of inclusion and equal access to benefits

Diverse ethnicities
Genomic knowledge is largely biased towards Europeans

Minority populations
The effects of being underrepresented, equal acces to benefits

Close relatives, twins, siblings
Restricted freedom to choose and decided to know or not to know

People with disabilities
Elimination or marginalization of disabilities (severe disease)

Neuropsychiatric diseases
Genetic determinants of vulnerability, risk for stigmatism

Examples of vulnerability in clinical care

Source	*Cited examples of vulnerability in health care*
Agency for Healthcare Research and Quality	• Populations less able than others to safeguard their own needs and interests adequately. • Populations who may incur different health outcomes traceable to unwarranted disparities in their care or stemming from special needs for care of barriers to care.
Aday	• Social status ○ Age: infants, children, adolescents, elderly ○ Gender: females ○ Race and ethnicity: African Americans, Hispanics, native Americans, Asian Americans • Social capital ○ Family structure: living alone, female head ○ Marital status: single, separated, divorced, widowed ○ Voluntary organizations: non-member ○ Social networks: weak • Human capital ○ School: less than high school ○ Jobs: unemployed, blue collar ○ Income: poor, low income ○ Housing: substandard
Danis and Patrick	• Those at risk at any particular point in time for unequal opportunity to achieve maximum possible health and quality of life because of differences in intrinsic and extrinsic resources that are associated with good health. ○ Financial circumstances ○ Place of residence ○ Cultural background and ethnicity ○ Age ○ Health conditions (such as terminal illness or mental illness, impairments, including psychological and cognitive ones, and functional status or disability, such as inability to communicate effectively)

Hurst SA, Bioethics 2008

Potential impact of genetic analysis for insurance

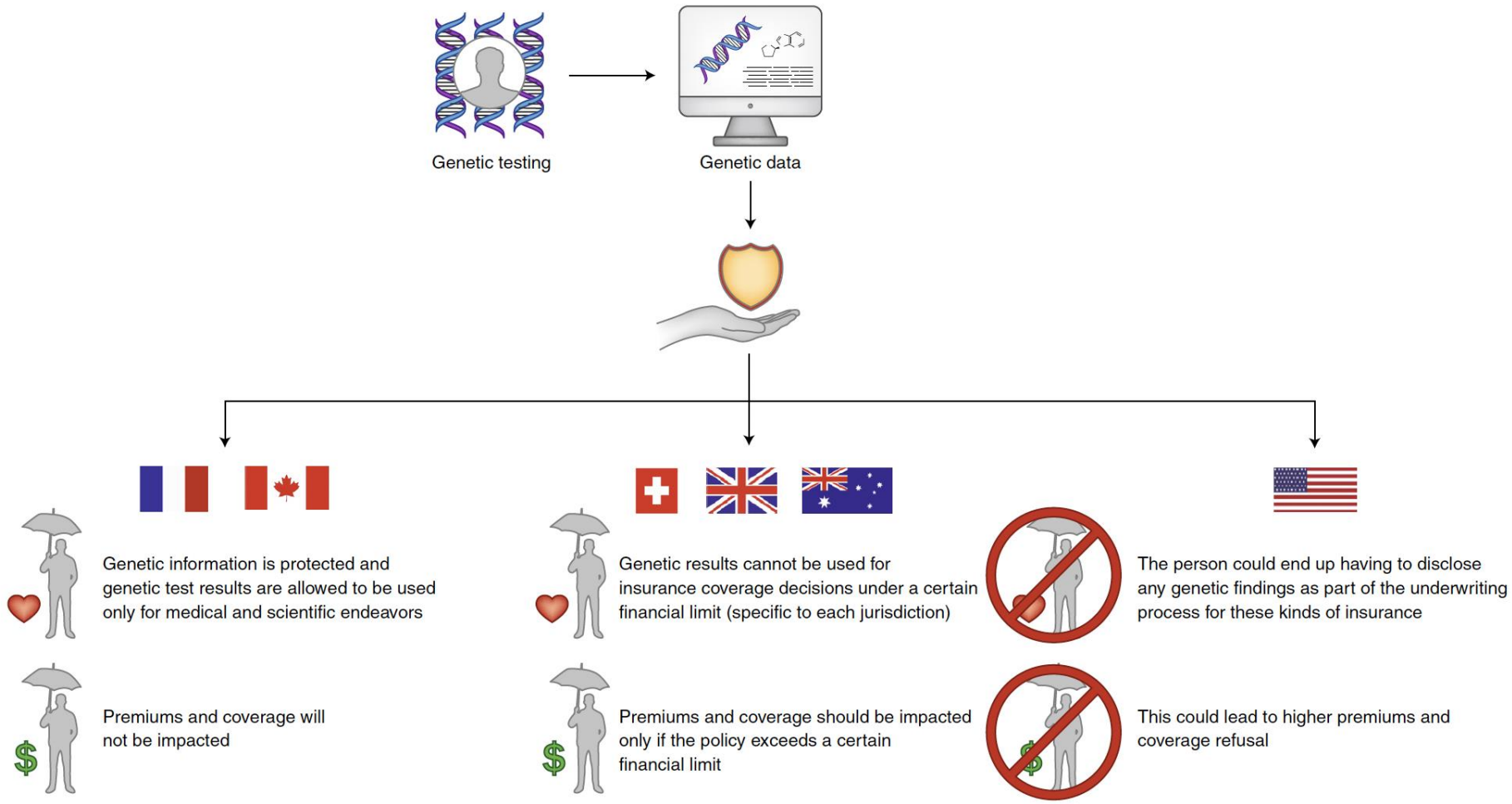


Figure from Bélisle-Pipon *et al*, Nat Med 2019

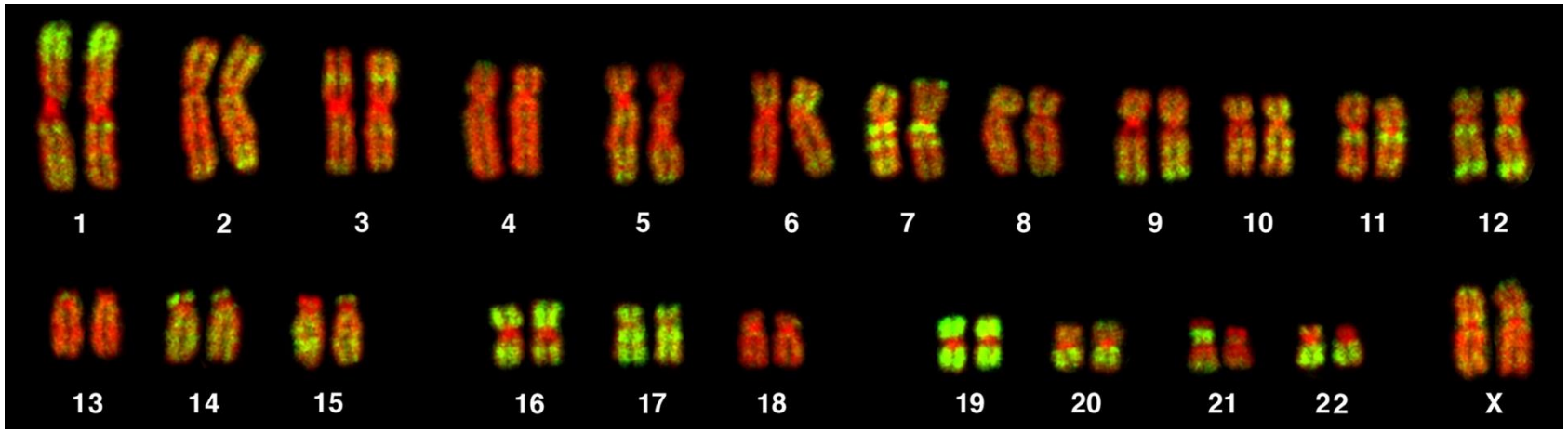
The key differences between genomic and genetic analyses

Genomics	Genetics
The study of an organism's complete set of genetic information	The study of heredity
Analysis includes both genes (coding) and non-coding DNA	Analysis of the function and composition of single genes
Genome: The complete genetic information of an organism	Gene: Specific sequence of DNA that encodes for a functional molecule

Source: adapted from the NHS Genomics Education Programme
https://genomicseducation.hee.nhs.uk

Genetic variation - Random changes in our genome

The total length of diploid human genome is 6.5 billion nucleotides



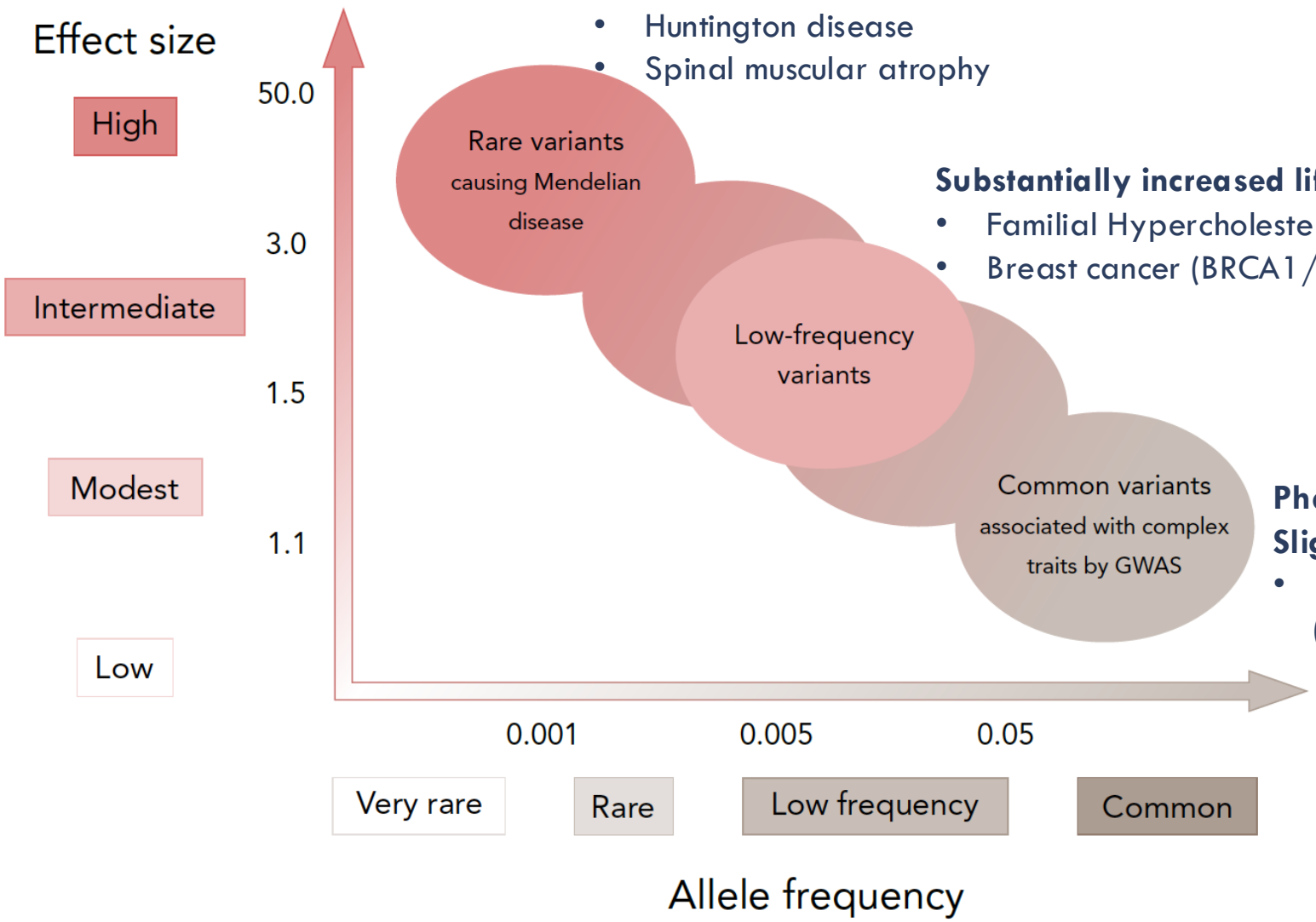
Every human genome contains approximately **4-5 million variants**, including single-nucleotide (sequence) variants and DNA copy-number variants (duplicated or deleted chromosome fragments)

An average newborn has acquired **50 *de novo*** mutations ("random errors of nature")

About 100 genuine LoF variants, with ca **20 genes** completely inactivated in every human genome

Firth & Hurst, „Oxford Desk Reference Clinical Genetics and Genomics"; 2017; Figure from Bolzer *et al*, PLoS Biol 2005

Genetic variants by their frequency and effect size



Causative variant ≈ disease

- Huntington disease
- Spinal muscular atrophy

Substantially increased life-time risk

- Familial Hypercholesterolemia
- Breast cancer (BRCA1/2)

Pharmacogenomics
Slightly increased life-time risk

- Polygenic risk scores (CAD, T2D, breast cancer)

Genetic heterogeneity

- ID/DD, ASD
- Psychiatric disorders
- Cardiovascular disease
- Ophtalmology
- Cancer

Modified from Manolio T *et al*, Nature 2009