

# Opportunities and challenges of implementing genomic medicine

Katrin Männik, PhD  
[katrin.mannik@health2030.ch](mailto:katrin.mannik@health2030.ch)  
EPFL, 20.02.2025

# Outline of the presentation

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- ▶ Potential and applications of genomic medicine

  - Theoretical background

  - Illustrative examples from national strategies

- ▶ Pan-European initiatives

  - Genome of Europe; GDI; 1 + Million Genomes; EP PerMed  
Genome of Switzerland; SFGN

- ▶ Discussion

# The key differences between genomic and genetic analyses

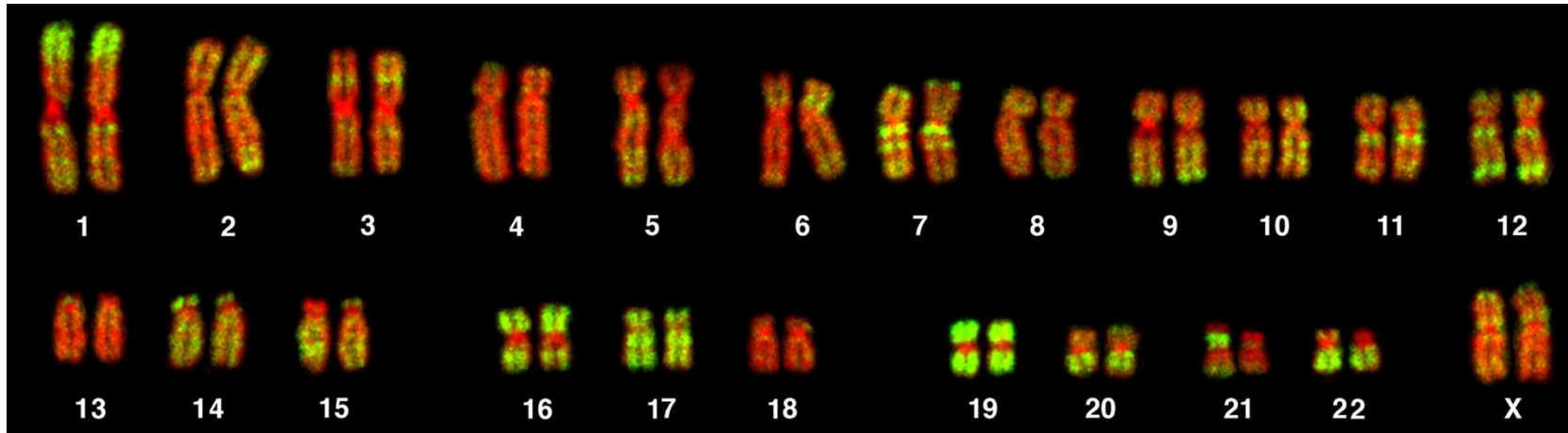
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<b>Genomics</b>	<b>Genetics</b>
The study of an organism's complete set of genetic information	The study of heredity
Analysis includes both genes (coding) and non-coding DNA	Analysis of the function and composition of single genes
Genome: The complete 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

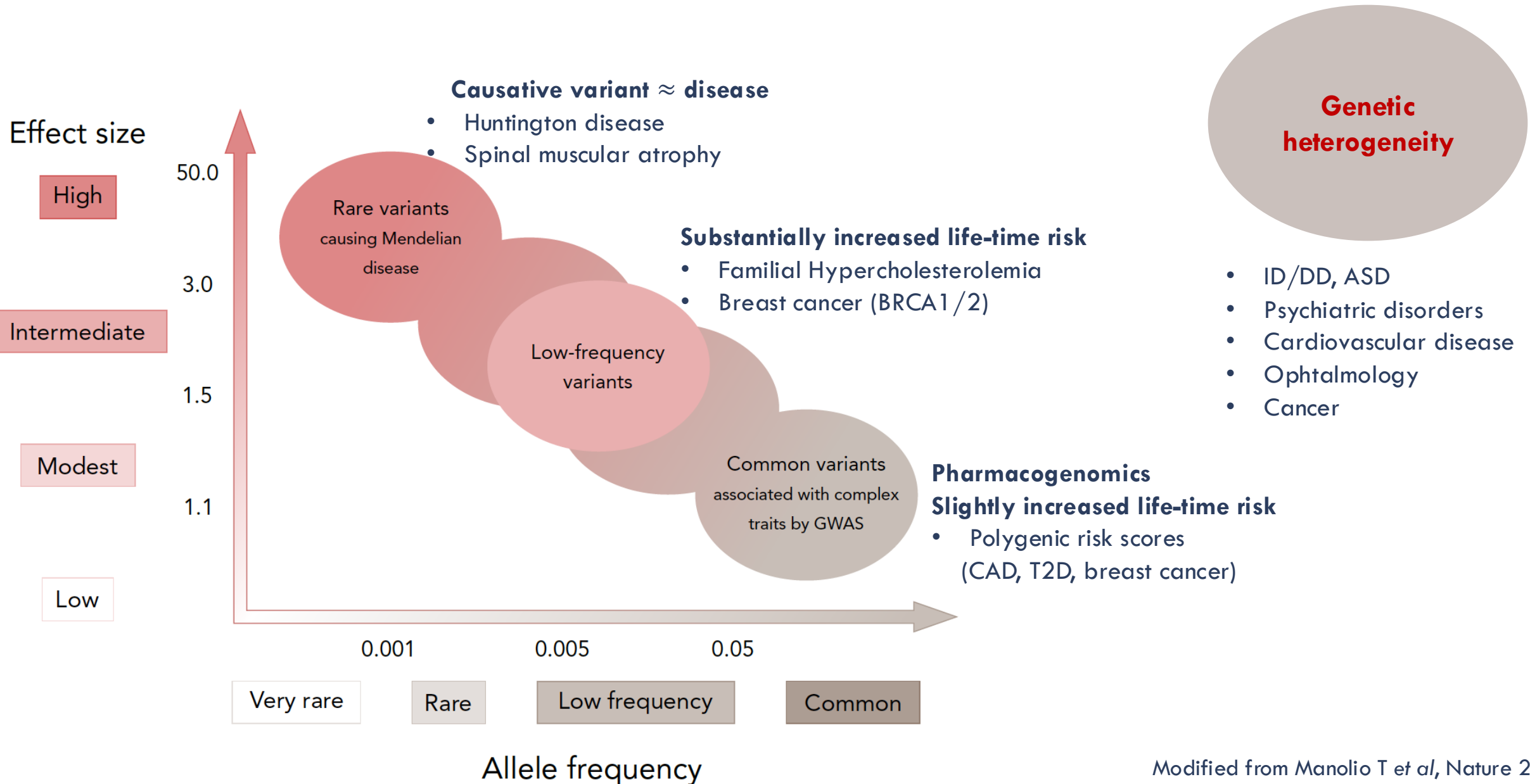


Every human genome contains approximately **4-5 million variants**, including SNVs (sequence variants) and CNVs (duplicated or deleted chromosome fragments)

**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

# Genetic variants by their frequency and effect size



# Where is genomic medicine in 2025?

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- ▶ 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**

# Plan France Médecine Génomique 2025

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Launched by the French government in 2016

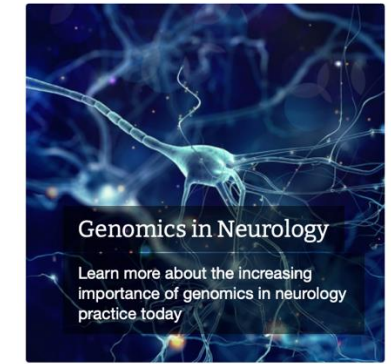
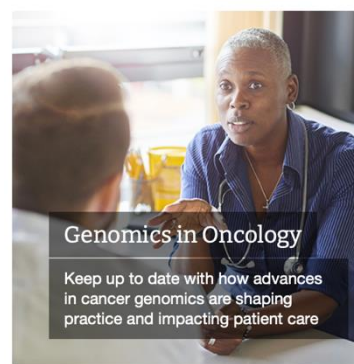
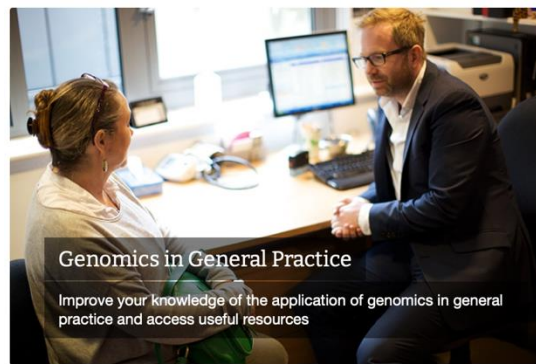
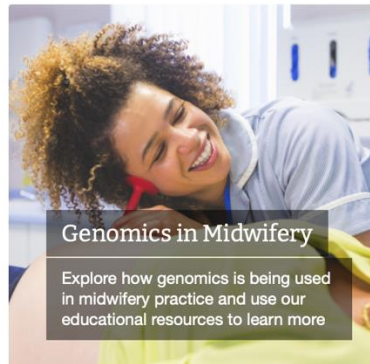
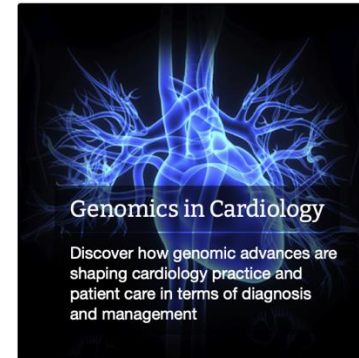
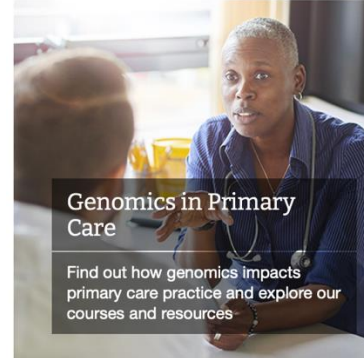
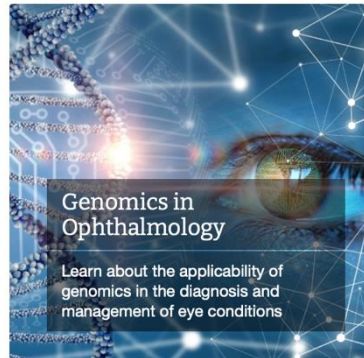
*"Genomic medicine is no longer a promise - **it is already a reality** that will transform how we prevent, diagnose, treat and predict the prognosis of disease.*

...

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

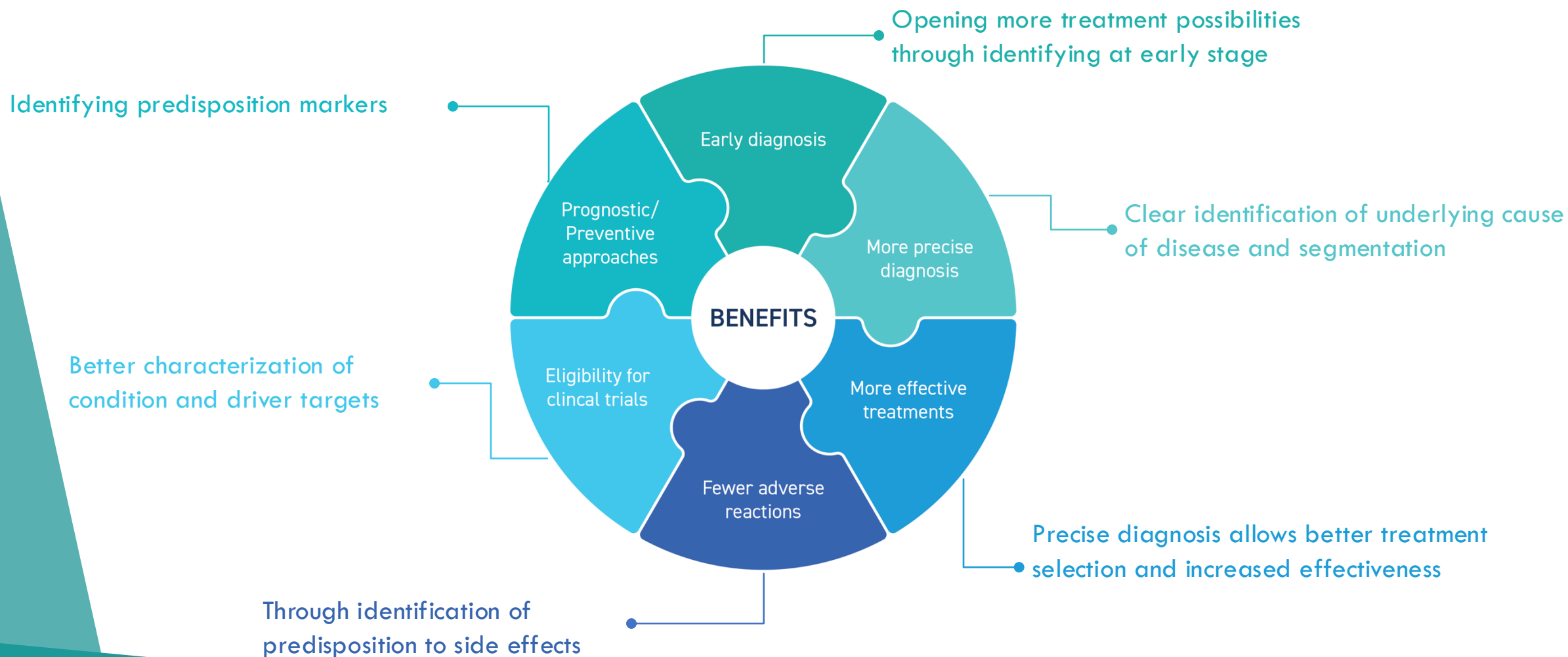


# Genomic services for healthcare providers





# Benefits provided by genomic medicine



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

# The Costs of Imprecision

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**All of Us**  
RESEARCH PROGRAM

The  
Future of  
Health Begins  
With You

*"When health care providers don't have enough information to make tailored recommendations, the costs of care can mount"*



You



1 million+ participants  
from diverse communities



Health discoveries



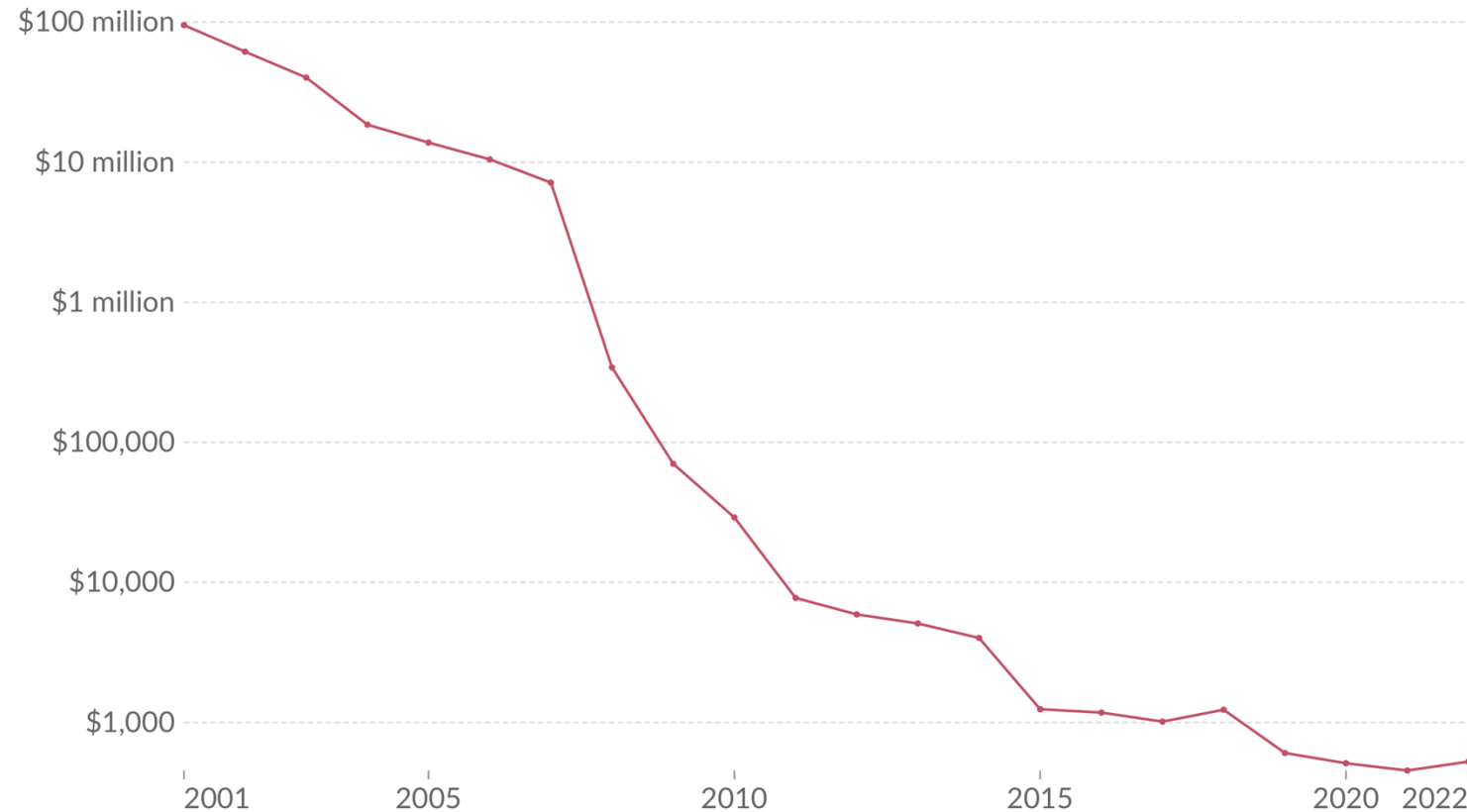
Individualized prevention,  
diagnosis, and treatment for all

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

## Cost of sequencing a full human genome

Our World  
in Data

The cost of sequencing the full genetic information of a human, measured in US\$. This data is not adjusted for inflation.



Data source: National Human Genome Research Institute (2022)

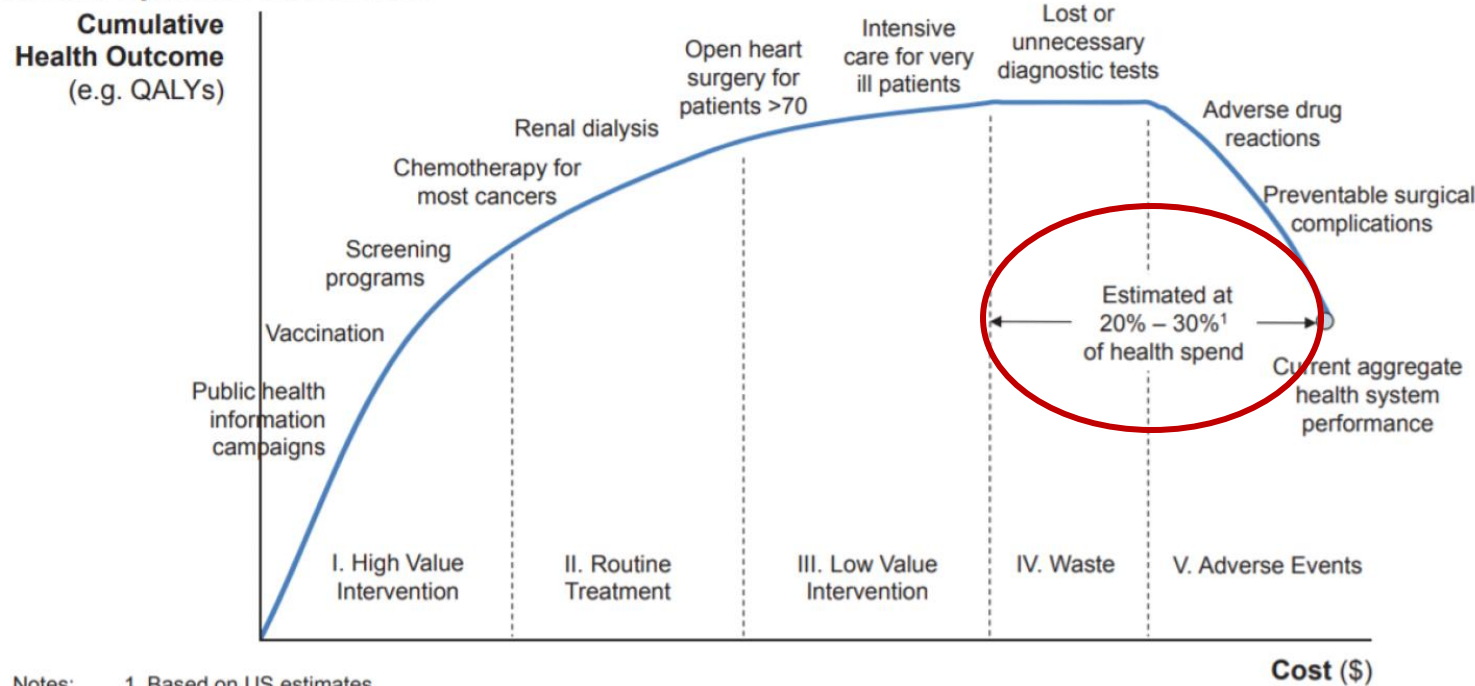
[OurWorldInData.org/technological-change](https://OurWorldInData.org/technological-change) | CC BY

# Cost-saving potential of genomic analyses



Health outcomes are driven by productivity and cost-effectiveness of interventions

## Health System Performance



Notes: 1. Based on US estimates  
Source: Pacific Strategy Partners analysis; TO Tengs, et al, 'Five-hundred life saving interventions and their cost effectiveness', *Risk Analysis*, 1995, 15(3):369– 484; Institute of Medicine of the National Academies, *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*, 2012; DM Berwick & AD Hackbarth, 'Eliminating Waste in US Health Care', *Journal of the American Medical Association*, 2012, 307(14):1513-1516; Pricewaterhouse Coopers (PWC) Health Research Institute, *The Price of Excess: Identifying Waste in Healthcare Spending*, 2008

**Source:** Commonwealth of Australia (2013). Strategic Review of Health and Medical Research in Australia – Better Health Through Research.

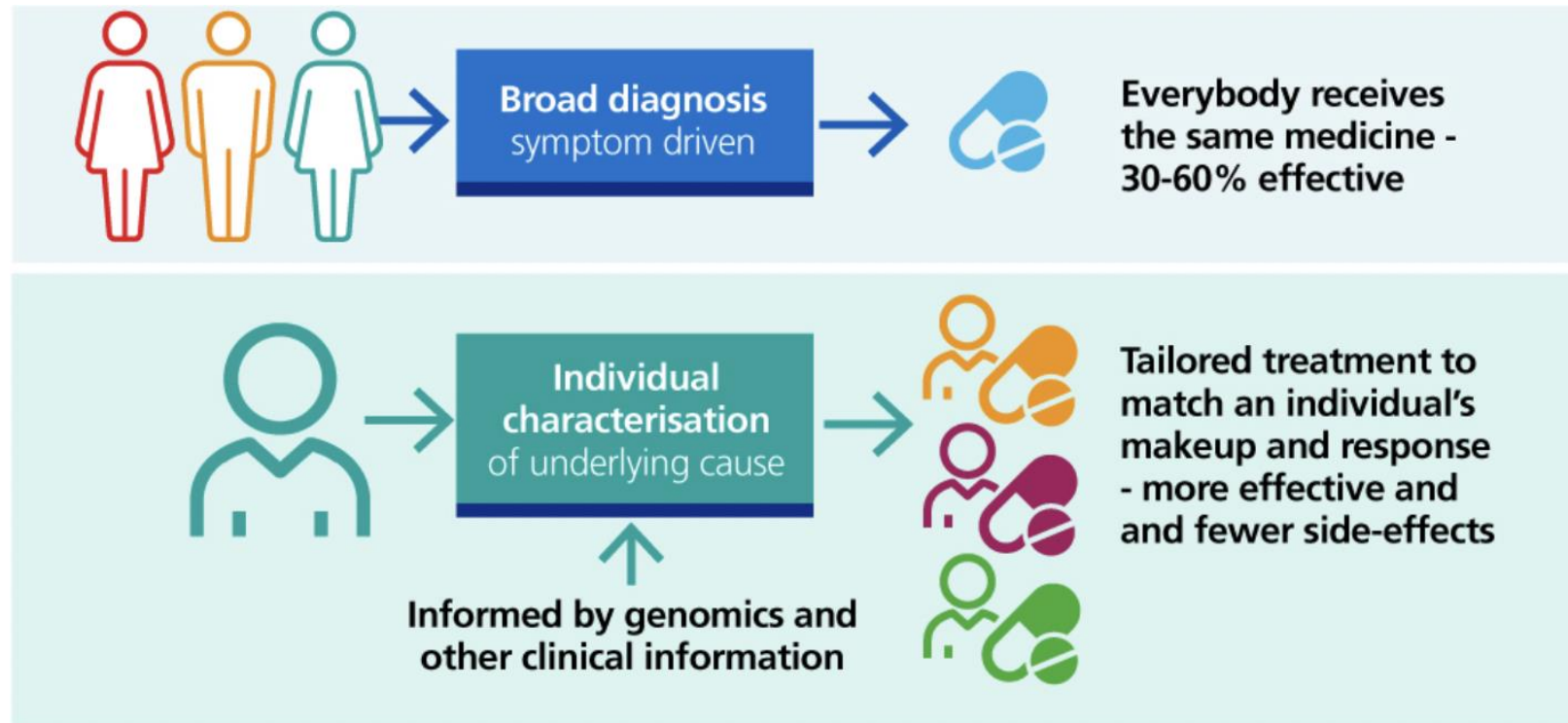
- The **ACMG 59 medically actionable genes**
  - Early interventions **3% population**
  - Better adjusted screening programs (e.g. breast cancer)
- ↓ **Unnecessary diagnostic tests**
- ↓ **Unnecessary (surgical) interventions**
- **Pharmacogenomic screens (↓↓↓cost per QALY per drug)**

**99.5% population**

# The first nation-wide PGx service



As the first nation-wide health system, the NHS Genomic Medicine Services plans to launch in 2023 PGx service providing screens for 40 compounds to all people in England





# Ultra-rapid WGS in critically ill infants



## Impact of Rapid Whole Genome Sequencing

IMPROVED  
HEALTH  
OUTCOMES

IMPROVED  
CLINICAL  
EXPERIENCE

COST  
SAVINGS

"I have never seen a diagnostic tool that's made such a huge impact in intensive care medicine in all my years of practice."

—Mario Rojas, MD  
NICU Medical Director Valley Children's Hospital



# Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System

Australian Genomics Health Alliance Acute Care Flagship

**Australian  
Genomics**



## Acute Care Genomics 2018-23: Piloting a national approach



>400 infants and  
children



Trio whole genome  
sequencing



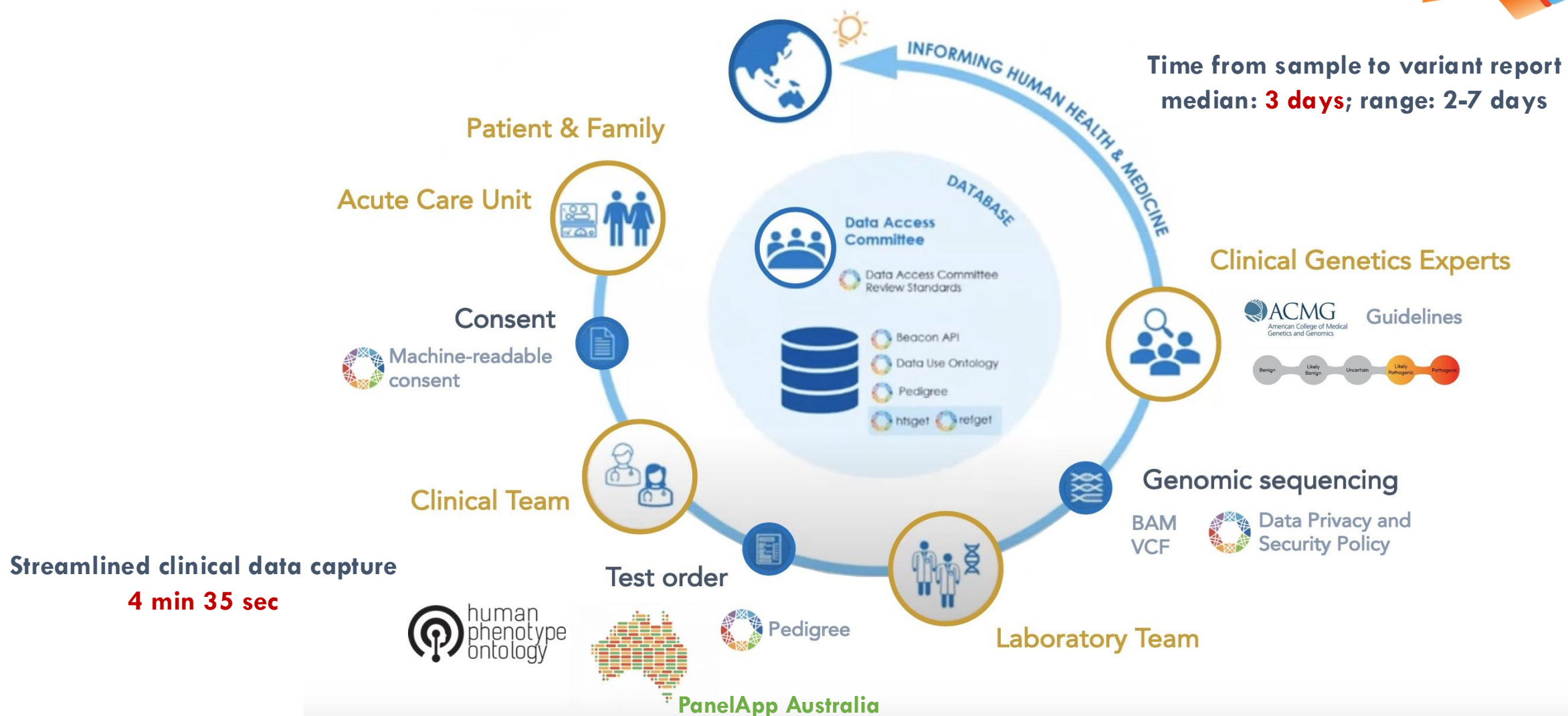
Time to report  
3.0 days



~50% diagnostic  
yield

# Automated and standardized rWGS workflow

Australian  
Genomics





# Ultra-rapid WGS in critically ill infants

PILOT SITES	# OF BABIES	BABIES DIAGNOSED	BABIES WHOSE CARE WAS CHANGED*	DAYS TO RESULTS**
CHOC CHILDREN'S HOSPITAL (ORANGE COUNTY)	23	12 (52%)	9 (39%)	2.5
RADY CHILDREN'S HOSPITAL-SAN DIEGO	59	22 (37%)	19 (32%)	3
UC DAVIS CHILDREN'S HOSPITAL ( <i>Sacramento</i> )	34	12 (35%)	8 (24%)	2
UCSF BENIOFF CHILDREN'S HOSPITAL OAKLAND	24	12 (50%)	9 (38%)	3
VALLEY CHILDREN'S HOSPITAL ( <i>Madera</i> )	38	18 (47%)	10 (26%)	3
TOTAL PROJECT BABY BEAR CASES				
178		76 (43%)	55 (31%)	3

## Healthcare spendings ↓↓

- 513 fewer days in hospital
- 11 fewer major surgeries and 16 invasive diagnostic tests
- \$2.5 million in healthcare savings; **\$4,509 per QALY gained**

# National genomic medicine initiatives (non-exhaustive list)



Background world map from:  
Vemaps.com

# Prerequisites for human health-related genomics

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Understanding of **genomic architecture** in the population

# European over-representation in genomic datasets affects the accuracy of risk prediction in other populations

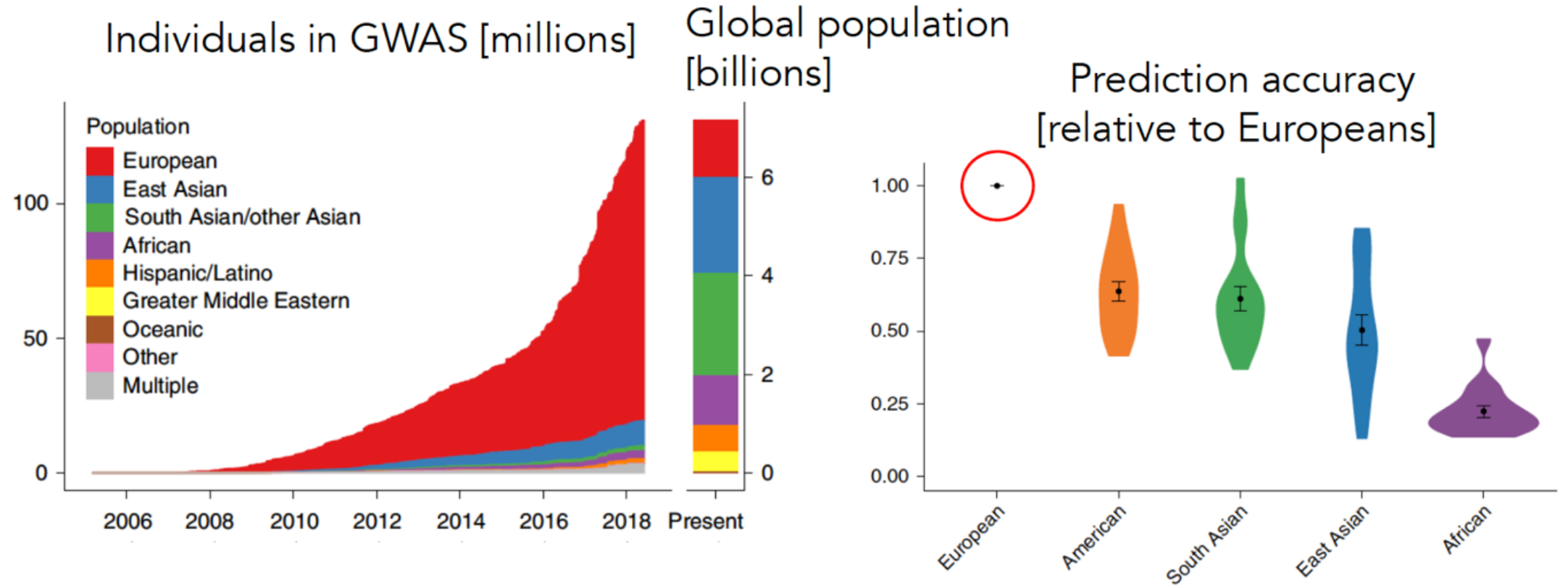


Figure adapted from Martin et al, Nature Genetics 2019



# Examples of population genomics and \*omics initiatives

Country	Pop.	Initiative	Focus area	# of WGS	# of GT	Other molecular data
USA	332 Mio	All of Us	General population	245,400	313,000	In discussion
		Trans-Omics for Precision Medicine	General population, multi-ancestry	206,000	NA	Transcriptome; Metabolome; Proteome; Methylation
UK	67.3 Mio	UK Biobank	Population, aged 40-69 years	500,000	500,000	Blood proteome; NMR-metabolites; Panel of disease-specific biomarkers
		Genomics England	Rare disease, cancer	97,000 NHS patients (increasing)	NA	In discussion
Finland	5.5 Mio	FinnGen	General population	9,000	412,000	NMR-metabolites
Estonia	1.3 Mio	Estonian Genome Center	General population	3,000 + 10,000 in progress	210,000	Transcriptome; NMR-metabolites; Metagenomics
Iceland	376,000	deCode	General population	62,240	160,000	Targeted plasma proteins
Denmark	5.9 Mio	Danish National Genome Center	Broad spectrum of clinical conditions	60,000 in progress	NA	Transcriptome

# Prerequisites for human health-related genomics

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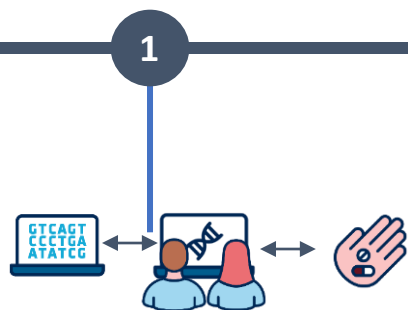
Understanding of **genomic architecture** in the population



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



# Danish National Genome Center offers three services



**1**

## **Clinical services**

- Data processing, computing power, validated pipelines
- Tools for interpretation
- Secure server capacity



**2**

## **Research services**

- Secure server capacity
- Data storage
- Powerful processing
- Tools, modules, programs and applications
- Consultancy and architectural assistance

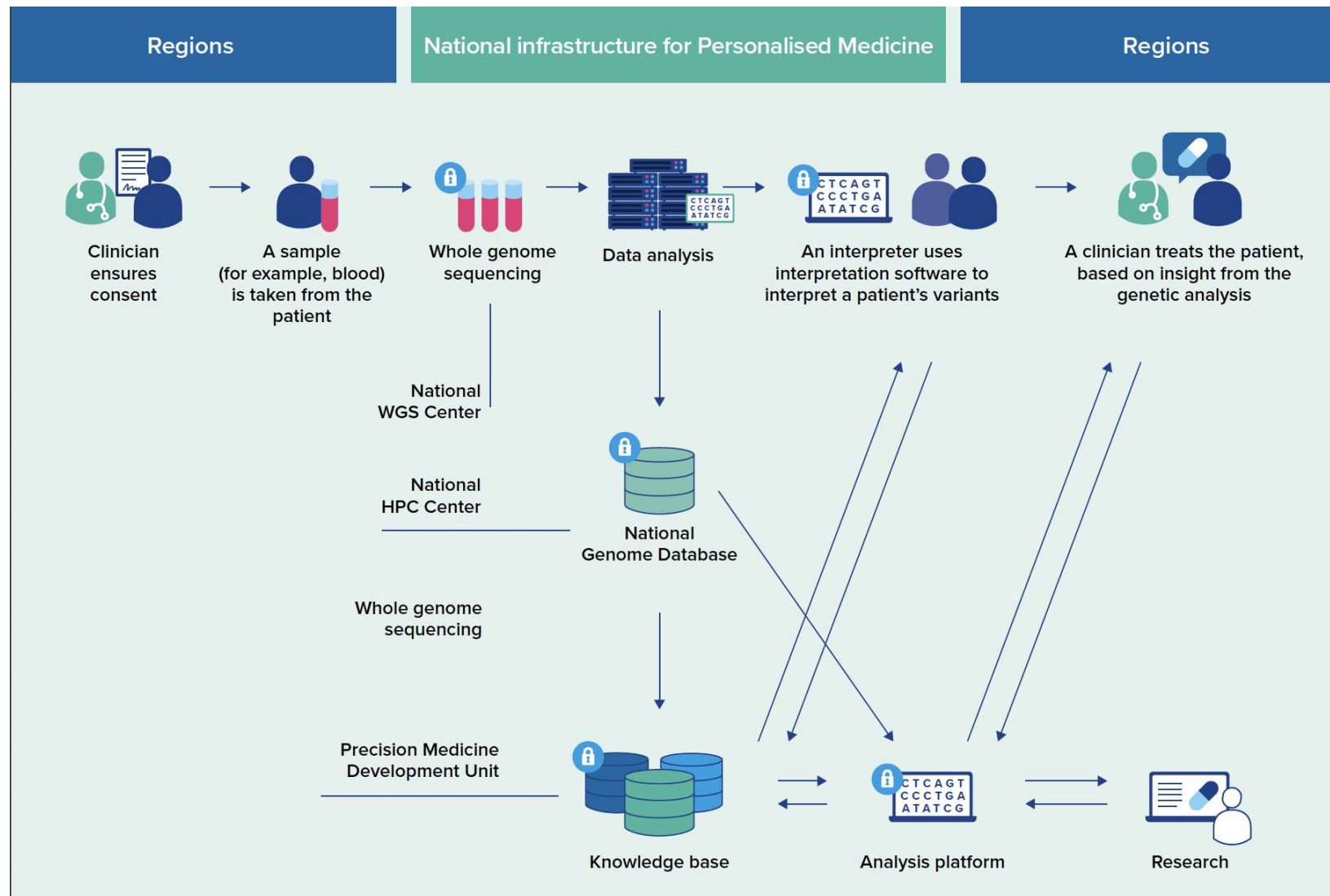


**3**

## **Strategic partners services**

- Collaboration with other authorities
- Use of infrastructure
- Data storage, secure server capacity, databases, development projects, federated systems

# National infrastructure for personalized medicine



**PERSONALISED  
MEDICINE FOR  
THE BENEFIT OF  
THE PATIENTS**

CLEAR DIAGNOSIS  
TARGETED TREATMENT  
ENHANCED RESEARCH

NATIONAL STRATEGY FOR  
PERSONALISED MEDICINE 2021-2022

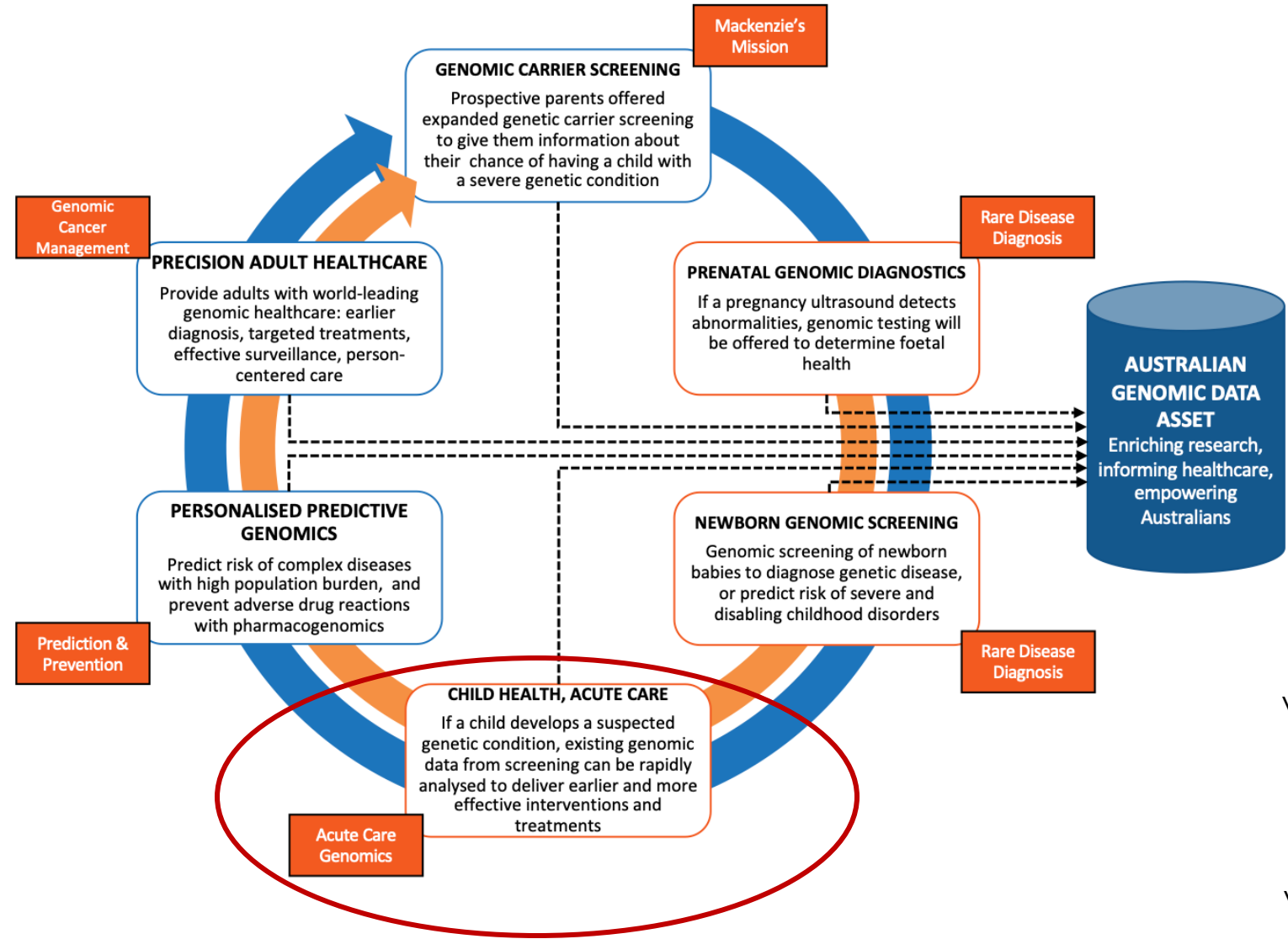


**DANISH NATIONAL  
GENOME CENTER**

- Implementation of WGS in patient treatment
- Collect and store Danish genome data in a secure national genome database
- Genome data access to health care professionals, researchers and patients

# The Australian Acute Care Genomics

Australian  
Genomics



Professor Zornitza Stark  
Victorian Clinical Genetic Services



A/Professor Sebastian Lunke  
Victorian Clinical Genetic Services



# Prerequisites for human health-related genomics

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Understanding of **genomic architecture** in the population



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



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



# What is needed for responsible implementation?



**EP PerMed**

European Partnership  
for Personalised Medicine

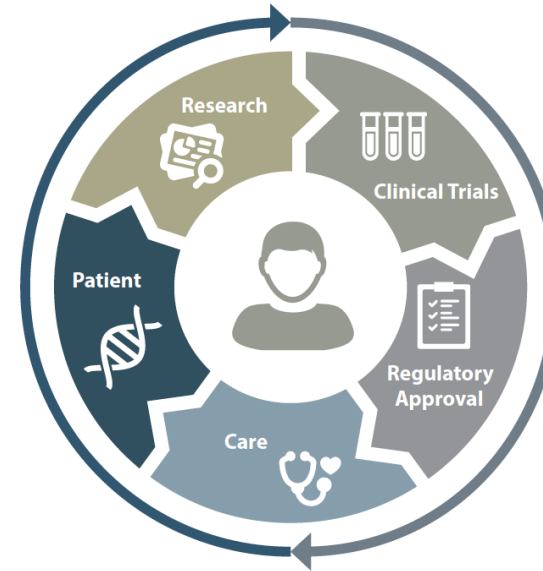
- ▶ Public and professional trust
- ▶ Modernizing and education
- ▶ Focus on inclusion and facilitating access
- ▶ IT-infrastructure and technology
- ▶ Legal and ethical framework



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

# Genomics is changing the research transition pathway

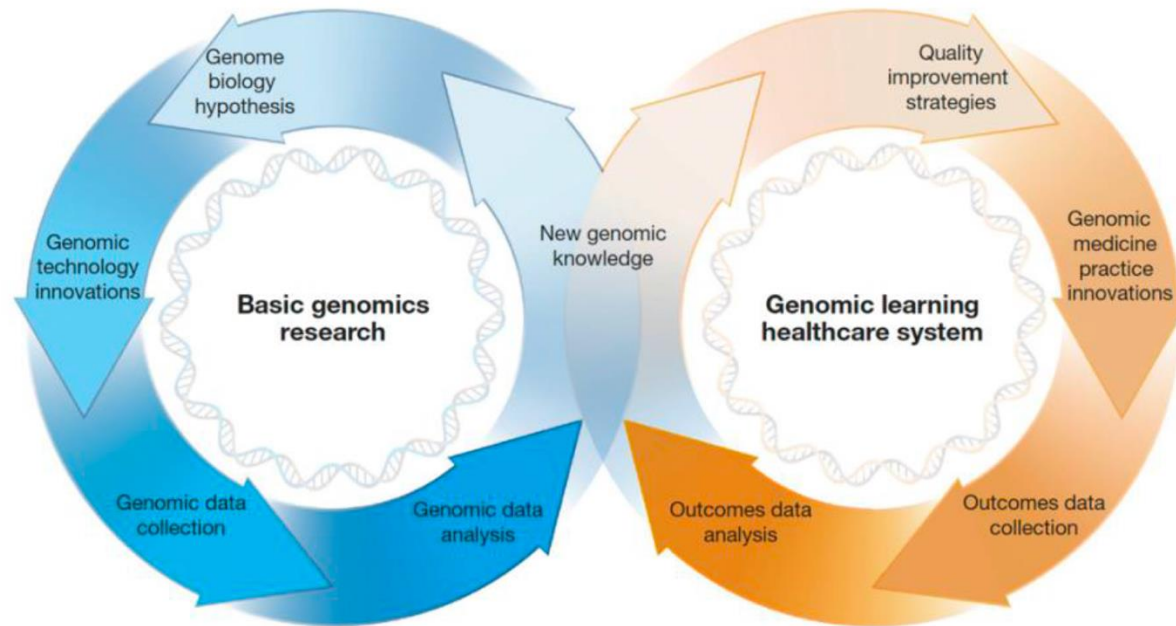
**Traditional linear genetic**  
research translation  
pathway



**Emerging cyclic genomic** research  
translation pathway  
=  
Clinically driven research

# 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

# Where does Europe stand in 2025?

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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 Competitiveness”**

Report by Mario Draghi

September 2024

# 1 + MG Declaration of Cooperation (2018)

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## Drive personalised medicine and health in Europe

- Build a cohort of at least **1 million sequenced genomes** that provides clinically impactful associations in research
- Providing **access to genomic and health data** for **secondary use**
  - **in a harmonised fashion**
  - **to cross-border datasets**

to foster **better healthcare outcome** and **economic growth**

- **Harmonised fashion** covers
  - Harmonised quality
  - Harmonised semantic
  - Harmonised information and communication systems and tools
  - Harmonised data governance

# The 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





Implementation of genomic medicine

# Where does Europe stand in 2025?



**European Commission  
Digital Europe Programme**

- Duration 2024 – 2028
- Coordinated data generation for genomic medicine across Europe
- Funding for WGS 20% of population target in each participating country
- Kick-off meeting 30.-31.10.2024, Rotterdam



# Why Genome of Europe?

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The **reference dataset** for genomic health programs of the European countries

- Documenting and quantifying **genetic diversity and heterogeneity** across European populations
- Reference for **interpreting clinical genetic variants** in comparison to disease-specific genomes
- Recalibrating genetic risk profiles to **ancestral backgrounds**, essentially important for developing polygenic risk scores
- **Reference panel for imputations** in lower resolution but cheaper and larger scale genotyped samples (low-pass WGS, SNP genotyping)

# GoE within the 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



# What is GDI setting out to do?



## **Support the EU 1+Million Genomes (1+MG) initiative (Digital Europe policy)**

**ambition** to enable secure access to high-quality genomics and the corresponding clinical data across Europe for better research, personalised healthcare and health policy making

Establishing a **federated, sustainable and secure infrastructure based on open community standards** to access genomic and related phenotypic and clinical data across Europe

Building on the Beyond 1 Million Genomes (B1MG) project outputs

Slide credit: Tommy Nyrönen, GDI and ELIXIR Finland

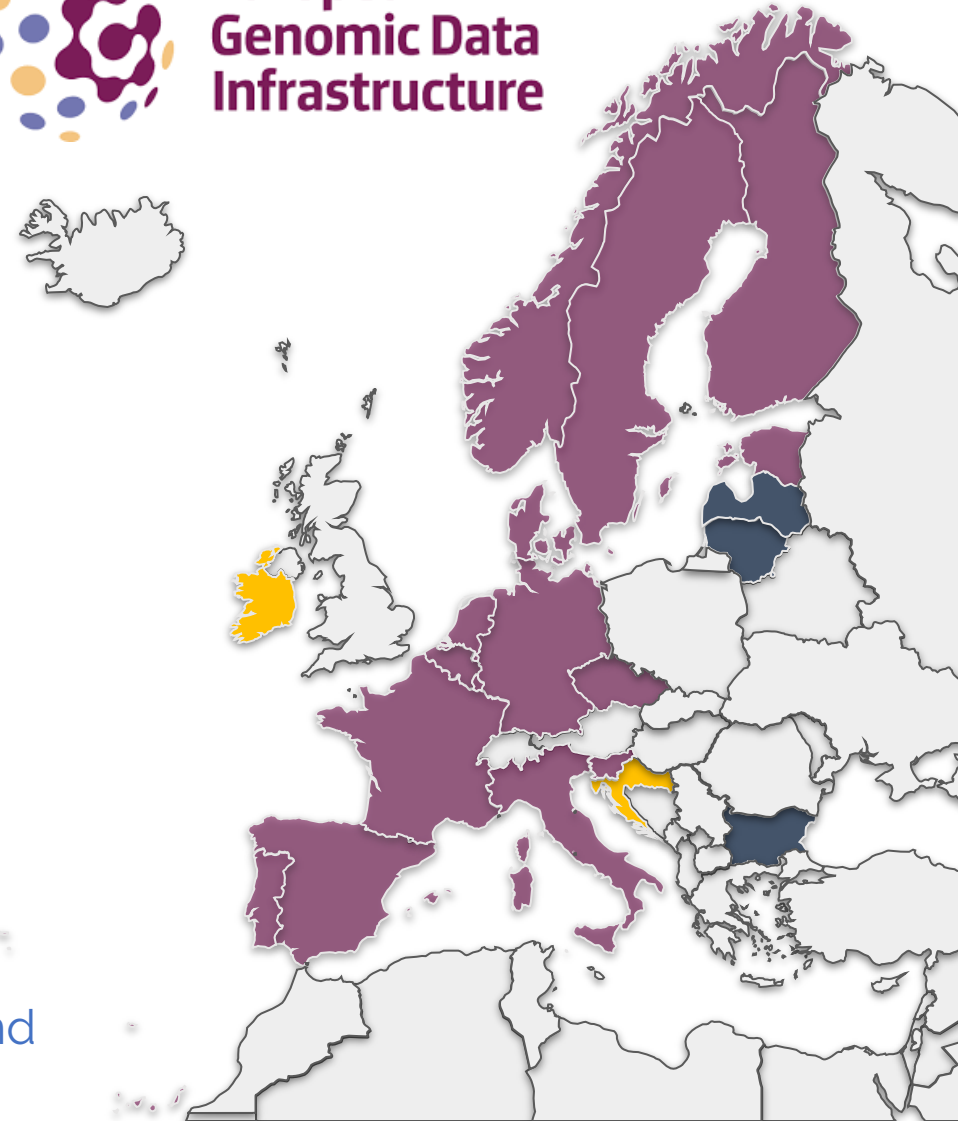
# Countries' commitment to GDI by 2026

- Fully operational and integrated into 1+MG infrastructure: **Belgium, Czechia, Denmark, Estonia, Finland, France, Germany, Italy, Luxembourg, Portugal, Slovenia, Spain, Sweden, The Netherlands, Norway**
- Fully operational national node but not yet integrated in the 1+MG infrastructure: **Bulgaria, Latvia, Lithuania**
- Onboarding: **Croatia, Ireland**

Infrastructure will exist in 2024 with at least 6 countries



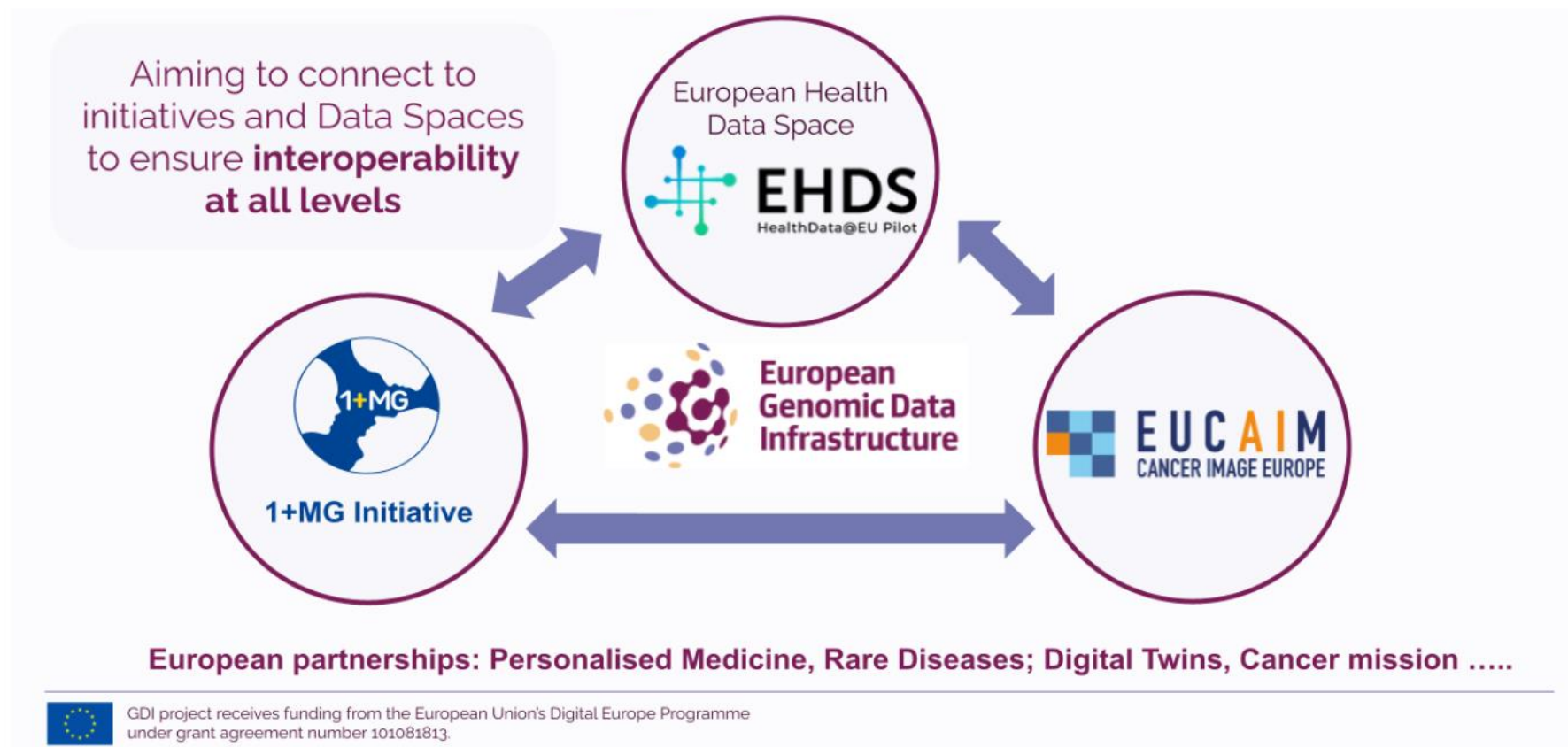
**European  
Genomic Data  
Infrastructure**



Slide credit: Tommy Nyrönen, GDI and ELIXIR Finland



# Connecting relevant EU initiatives





# Core components of the 1+ MG Framework



Components based on the output of the 1+MG projects that **provide guidance** on ELSI, data quality, data standards, and technical infrastructure standards and APIs.

## Technical framework



### Sequencing guidelines

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



### Data governance and ELSI

Guidance and recommendations on how to address data 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

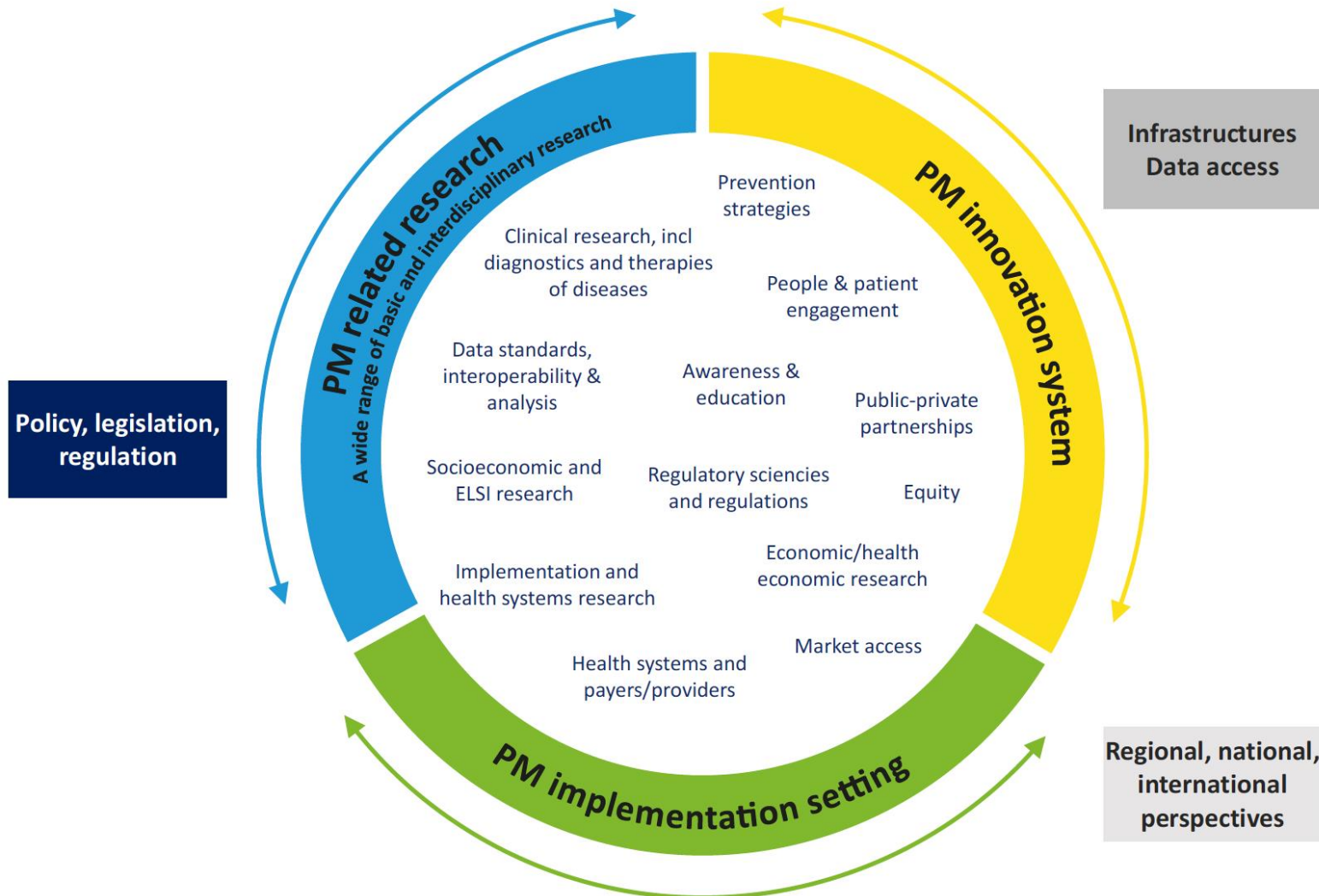
Find pointers to country specific information resources and national research data management practices.

# EP PerMed joins European personalized medicine initiatives under one roof



**EP PerMed**  
European Partnership  
for Personalised Medicine

Launched in October 2023



## Key figures of EP PerMed:

- Duration: 2023 - 2033
- Total budget: Approximately 370 Mio Euro
- Partners: More than 50, mainly funding organisations from Europe and beyond

**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 **reference data** and knowledge about the genetic structure of the Swiss population
- ▶ To serve as stepping stone for **international collaborations**

Implementation of genomic medicine

# Swiss Federated Genomics Network

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**Genome of Switzerland**



**Swiss fEGA repository**

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



**European  
Genomic Data  
Infrastructure**



# Suggested ancestral composition of the Genome of Europe



#participants in Genome of Europe	AUSTRIA	BELGIUM	BULGARIA	CROATIA	CYPRUS	CZECH REPUBLIC	DENMARK	ESTONIA	FINLAND	GERMANY	GREECE	HUNGARY	ITALY	LATVIA	LITHUANIA	LUXEMBOURG	MALTA	NETHERLANDS	NORWAY	PORTUGAL	SLOVENIA	SPAIN	SWEDEN	SUM	FRANCE	IRELAND	POLAND	SWITZERLAND
Ancestry	12%	18%	18.2%	6.8%	1.7%	17%	8.7%	2.9%	8.5%	12%	16%	15%	24%	2.2%	4.4%	1.9%	1.9%	28%	8.5%	15%	2.3%	74%	15%	100%	18%	7.8%	30%	12%
Albania	0	10	0	28	0	0	0	0	0	158	541	0	716	0	0	0	0	7	6	0	0	0	16	1,483	0	0	0	22
Austria	10,765	5	0	0	0	2	0	0	0	722	0	0	11	0	0	1	0	29	3	2	0	0	11	11,575	0	14	0	383
Belgium	0	18,304	0	0	0	0	0	0	0	94	0	0	10	0	0	24	0	223	3	8	0	91	6	16,853	199	0	0	116
Bosnia and Herz	159	3	0	50	0	2	38	0	0	837	0	0	35	0	0	0	0	71	32	0	37	0	140	1,404	0	0	0	236
Bulgaria	58	70	1,618	1	32	11	0	0	5	459	66	10	83	1	0	2	0	82	15	11	0	192	20	9,935	0	0	0	109
China	22	21	0	0	0	8	0	0	22	328	0	0	547	0	0	0	0	149	20	48	0	301	72	1,536	179	185	0	183
Colombia	0	4	0	0	0	0	0	0	0	76	0	0	33	0	0	0	0	37	4	2	0	925	25	1,106	50	0	0	42
Croatia	155	5	0	6,326	0	3	0	0	0	701	0	43	29	0	0	2	0	23	11	1	60	0	24	7,382	0	102	0	229
Cyprus	0	1	0	0	1,175	0	0	0	0	0	17	0	1	0	0	0	0	3	0	0	0	0	2	1,199	0	0	0	6
Czechia	25	6	0	15	0	17,998	0	0	0	365	0	0	9	0	0	0	0	20	4	1	0	0	5	17,733	0	95	2	75
Denmark	0	4	0	0	0	0	8,204	0	0	62	0	0	3	0	0	2	0	13	36	2	0	19	61	8,427	0	0	0	38
Estonia	0	2	0	0	0	0	0	1,478	84	37	0	0	2	3	0	1	0	4	9	0	0	0	22	1,643	0	0	0	8
Finland	0	5	0	0	0	0	0	0	14	8,423	54	0	0	3	0	0	2	11	13	2	0	21	360	8,904	0	0	0	33
France	0	282	0	0	0	2	0	0	0	415	0	0	52	0	0	59	0	92	11	38	0	375	22	1,347	99,743	226	2	1,192
Germany	353	65	0	5	2	7	57	4	9	162,711	41	297	58	4	5	15	0	631	50	24	0	329	103	104,770	188	223	119	2,537
Greece	0	30	0	0	52	1	0	0	0	785	15,691	7	12	0	0	5	0	53	6	1	0	0	44	16,610	0	0	2	137
Hungary	154	11	0	22	0	3	0	0	0	497	0	14,365	13	0	0	2	0	49	8	1	0	0	37	15,667	0	180	0	207
Iraq	22	21	0	0	0	1	56	0	42	539	0	0	10	0	0	0	0	121	60	1	0	0	365	1,237	0	0	0	72
Italy	58	252	0	28	0	4	0	0	0	1,532	0	0	89,402	0	0	28	0	112	9	42	0	277	27	91,771	474	227	3	2,667
Kazakhstan	0	2	0	0	0	5	0	0	0	1,904	0	0	4	1	0	0	0	6	2	1	0	0	5	1,928	0	0	0	9
Latvia	0	4	0	0	0	0	0	6	5	92	0	0	5	1,976	5	1	0	15	22	1	0	0	17	2,149	0	386	0	24
Lithuania	0	5	0	0	0	1	26	3	0	128	0	0	8	36	3,890	1	0	20	84	1	0	28	32	4,263	0	708	9	25
Luxembourg	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1,000	0	0	0	0	0	0	0	1,000	0	0	0	0
Malta	0	1	0	0	0	0	0	0	0	0	0	1	0	0	0	1,000	1	0	0	0	0	0	0	1,000	0	0	0	3
Morocco	0	131	0	0	0	0	0	0	6	388	0	0	709	0	0	0	0	756	19	3	0	1,414	29	3,456	1,299	0	0	65
Netherlands	0	262	0	0	0	2	0	0	0	428	0	0	17	0	0	5	0	24,022	16	17	0	89	24	24,883	58	83	0	176
Norway	0	2	0	0	0	0	28	0	0	18	0	0	2	0	0	0	0	9	7,660	1	0	23	79	7,823	0	0	0	17
Poland	108	114	0	1	5	18	62	3	9	3,461	27	11	129	62	259	6	0	382	203	5	0	104	196	5,184	144	2,371	59,53	296
Portugal	0	82	0	0	0	0	0	0	0	307	0	0	11	0	0	114	0	53	7	16,056	0	177	9	16,817	1,010	0	0	2,112
Roma (Gypsy)	0	0	509	27	0	0	0	0	0	0	329	505	0	8	5	0	0	0	0	0	0	0	0	1,382	0	0	20	0
Romania	225	181	0	1	41	9	60	0	9	1,601	44	57	1,780	1	0	7	0	79	32	51	0	973	67	5,216	218	563	0	191
Russia	55	19	0	2	14	38	0	521	16	2,058	69	0	66	771	205	0	0	61	39	8	0	168	44	4,154	117	0	13	135
Serbia	198	8	0	298	0	3	0	0	0	590	0	16	54	0	0	0	0	35	16	0	67	0	30	1,317	134	0	0	508
Slovenia	37	2	0	0	0	0	0	0	0	99	0	5	6	0	0	1	0	5	1	0	2,789	0	3	2,949	0	0	0	67
Spain	0	114	0	0	0	1	0	0	0	430	0	0	54	0	0	9	0	92	13	26	0	28,671	24	69,435	406	234	0	707
Sweden	0	6	0	0	0	1	28	0	12	49	0	0	5	0	0	2	0	14	68	8	0	38	13,962	14,193	0	35	0	68
Syria	111	0	0	0	5	1	72	0	14	1,717	13	0	11	0	0	0	0	206	65	2	0	0	403	2,622	0	0	0	192
Turkey	192	61	914	1	0	2	108	0	18	4,632	20	0	35	0	0	0	0	770	36	2	0	0	148	6,936	406	0	0	558
Ukraine	21	9	0	3	5	147	0	44	6	546	17	12	390	70	64	0	0	36	13	49	0	185	22	1,638	0	65	61	57
United Kingdom	18	30	0	0	44	5	29	0	8	296	17	0	50	0	0	6	0	178	29	57	0	541	57	1,365	241	1,996	0	350

## Switzerland

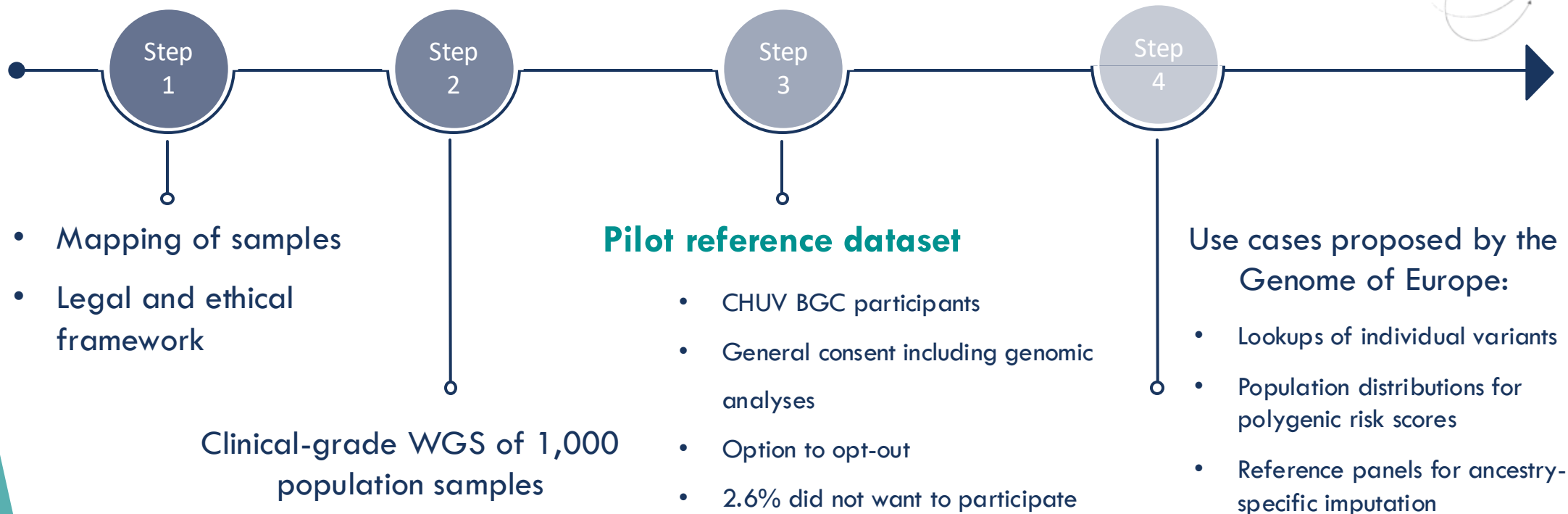
- Highly heterogeneous composition
- High benefits from GoE
- Expected "fair share"  
13,808 samples

## EU Digital Europe funds (2024-2028)

- 20% of Genome of Europe target in each country

Columns: Countries; Rows: Different ancestries in each country

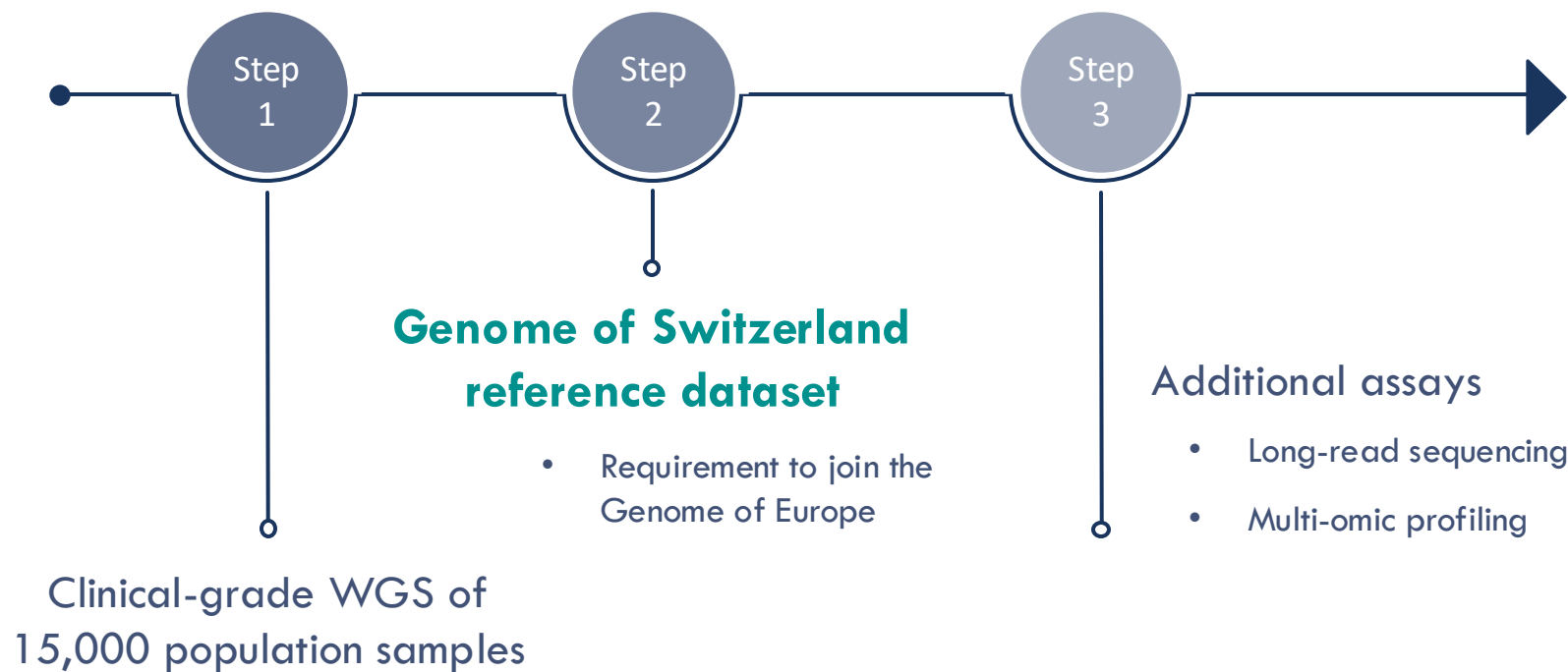
# Pilot Phase 2023-2025





# Scale-up Phase 2025 - onwards

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# Genome of Switzerland Pilot Phase

## Population genetic architecture (preliminary results)

### Principal Component Analysis

- Genome of Switzerland (n=416)
- Reference: 1000 Genomes

