



# Personalised medicine: Needs & barriers

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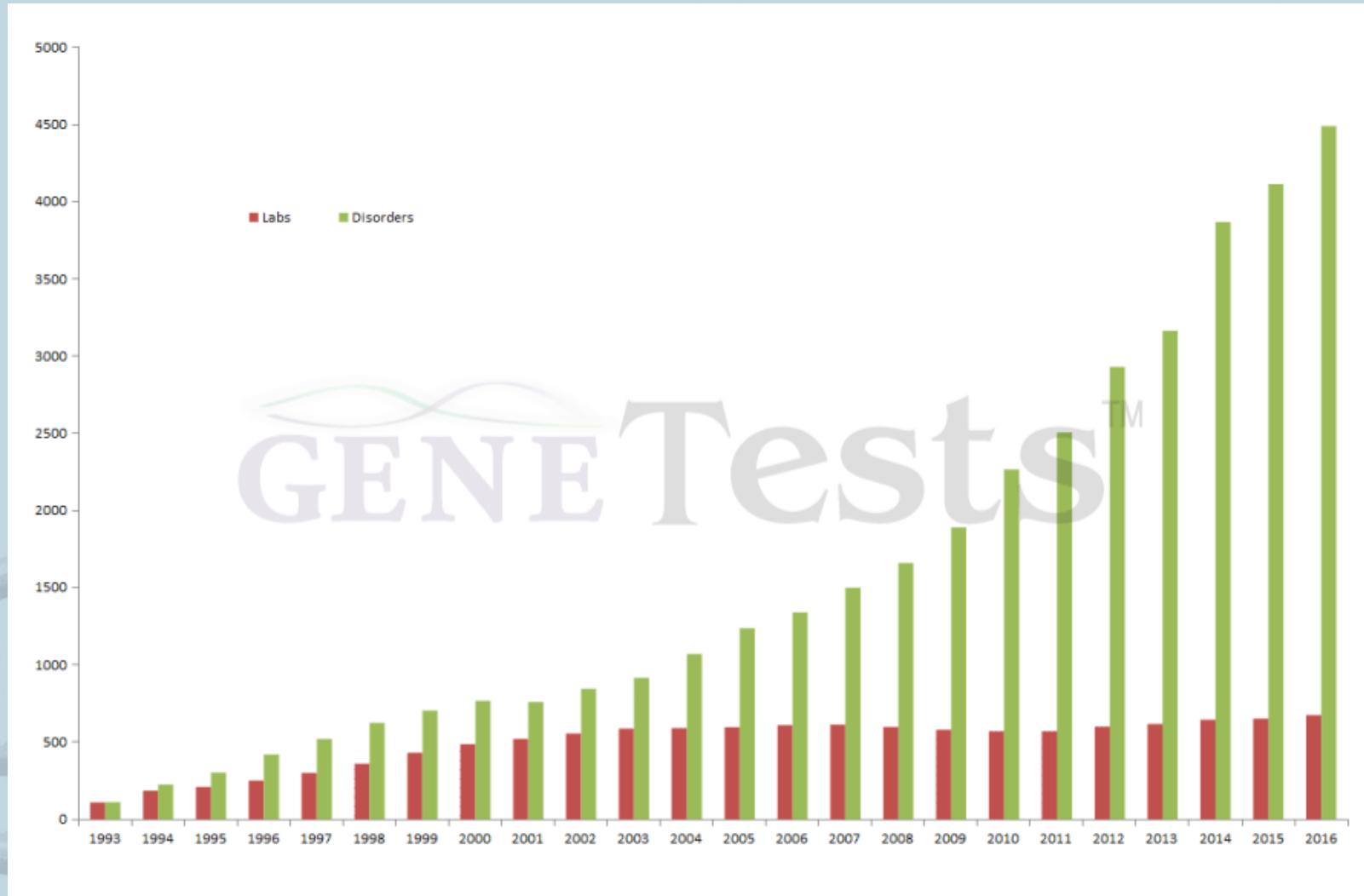
SAPHIRe Workshop  
March 13, 2019

# Personalized medicine

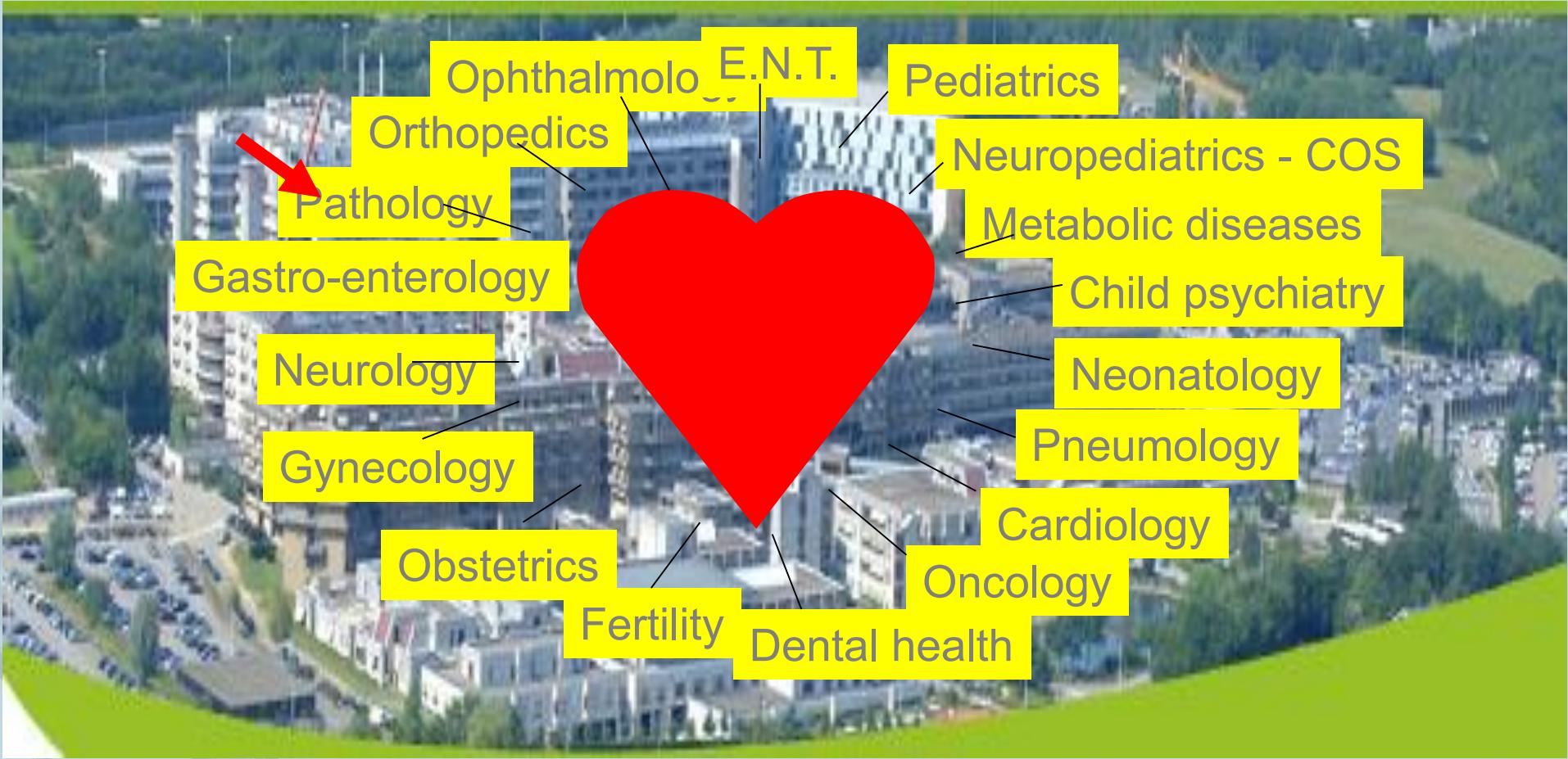
**NHS:** Personalised medicine is a move away from a 'one size fits all' approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients' health and targets therapies to achieve the best outcomes in the management of a patient's disease or predisposition to ...

**NIH:** The story of personalized medicine begins with the unique set of genes you inherited from your parents.... If doctors know your genes, they can predict drug response and incorporate this information into the medical decisions they make (Pharmacogenomics)

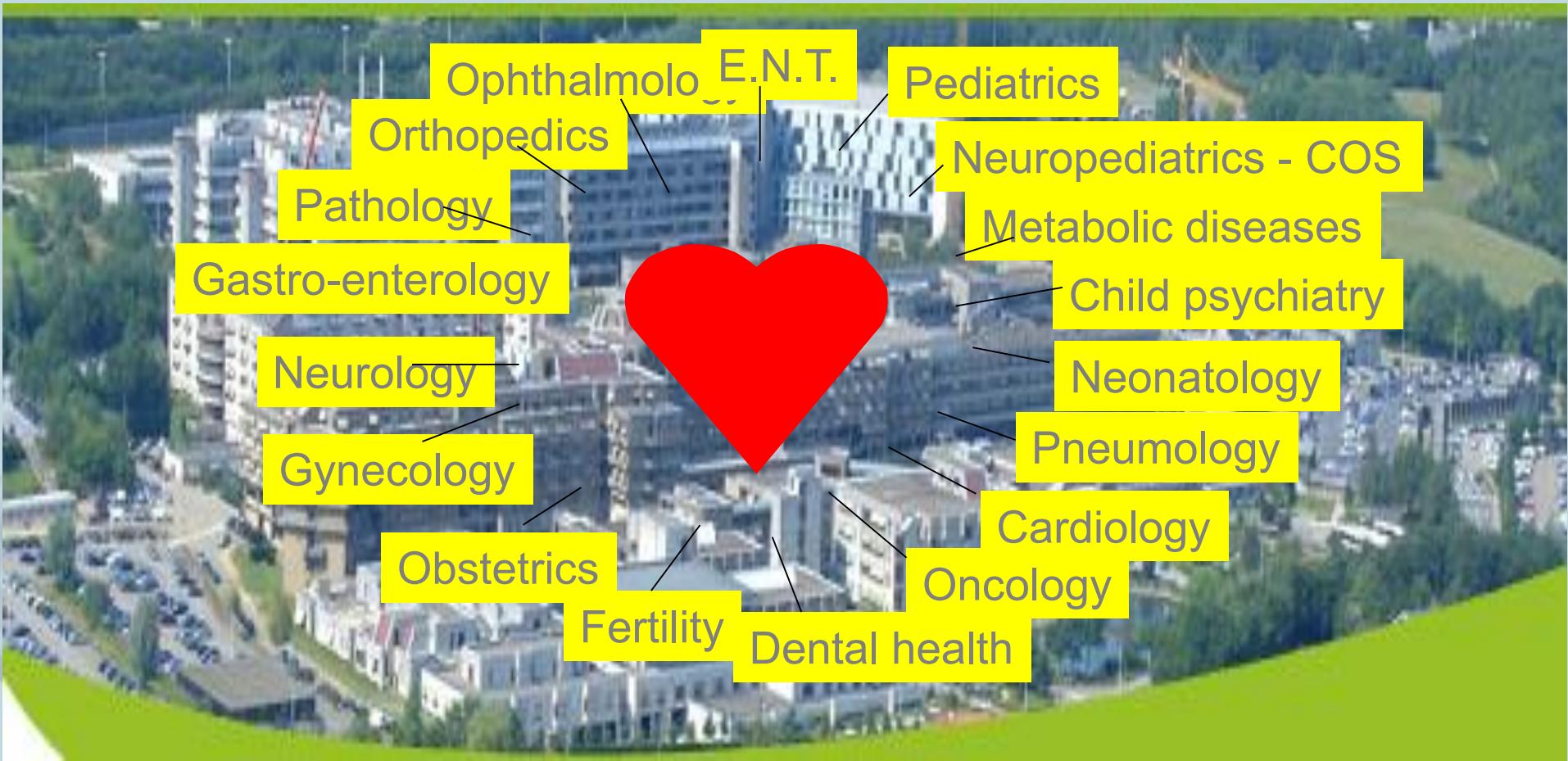
# Ever more gene variants associated with disease



# Genetics has become the heart of the hospital



# Van genetische test naar genomische geneeskunde



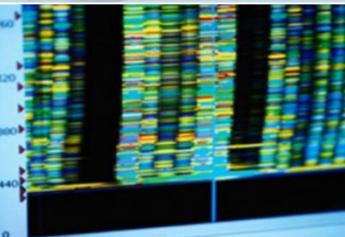
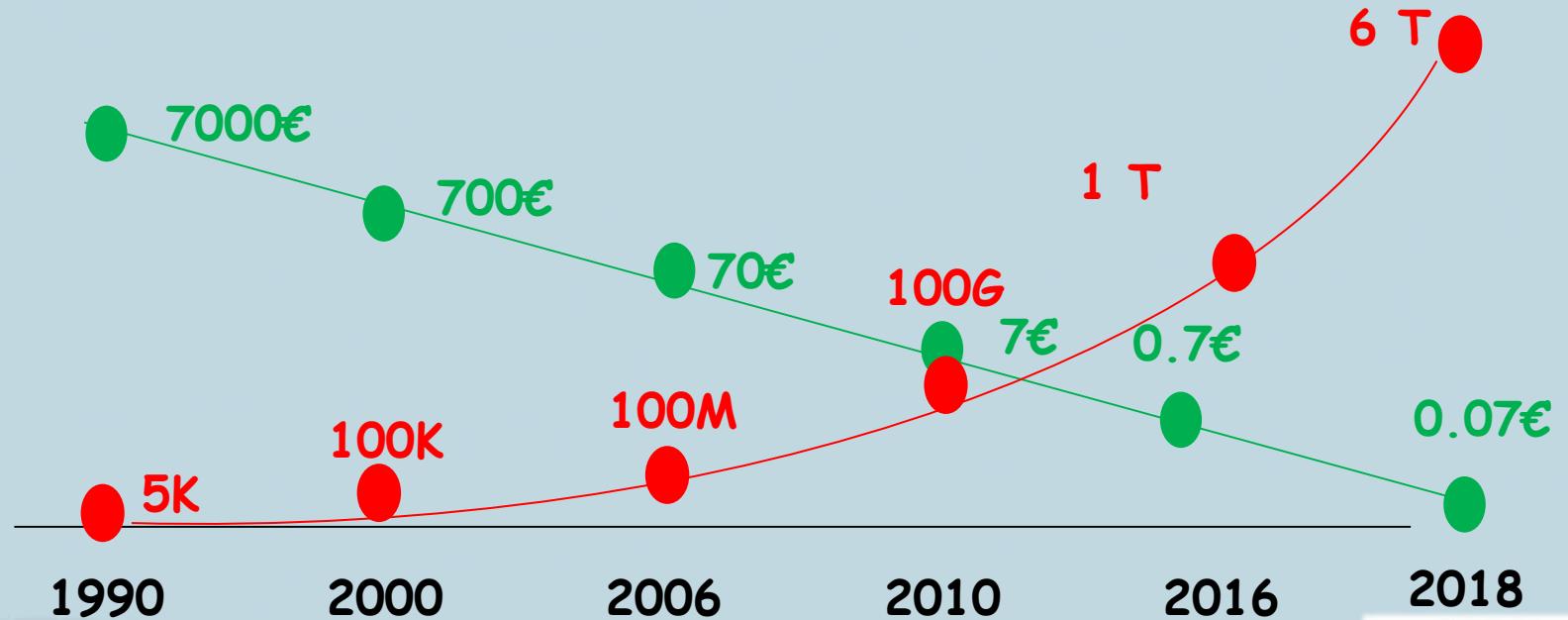
Genomic medicine is currently the main component of personalized medicine.



# Research program ‘Personalized Medicine’ in the Netherlands

- Whole genome sequencing biedt een **enorm potentieel** voor de toepassing van Personalised Medicine binnen de Nederlandse gezondheidszorg. De kwaliteit van leven van de patiënt zal toenemen door het verminderen van over- en onderbehandeling, minder ineffectieve behandelingen en uitgebreidere diagnostische mogelijkheden op basis van het genotype.
- Door verschillende actoren in de gezondheidszorg is de ontwikkeling en implementatie van whole genome sequencing al in gang gezet. ***Er zijn echter nog veel uitdagingen voordat de implementatie hiervan gerealiseerd is.*** Daarom is het onderzoeksprogramma ‘Personalised Medicine’ opgestart in samenwerking met Zilveren Kruis en KWF (zie Partners).
- Het doel van dit programma is het waarborgen van **een doelmatige implementatie van Whole genome sequencing** in de Nederlandse gezondheidszorg. Het programma bereikt dit door obstakels voor implementatie weg te nemen, bijvoorbeeld door de kosteneffectiviteit van diagnostiek en behandeling te bestuderen. Het onderzoeksprogramma richt zich tevens op projecten die efficiënt gebruikmaken van bestaande middelen en infrastructuur.

# The sequencing (r)evolution



# Not whether but when genome analysis?





*We want to stay healthy*

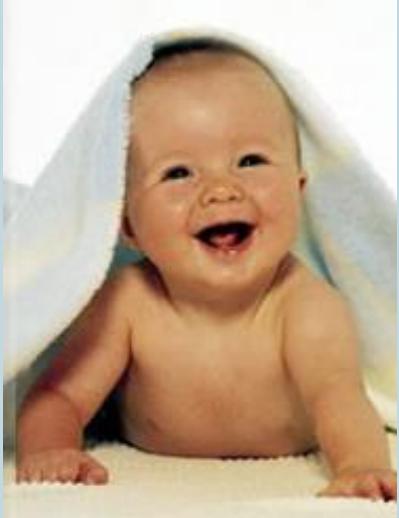




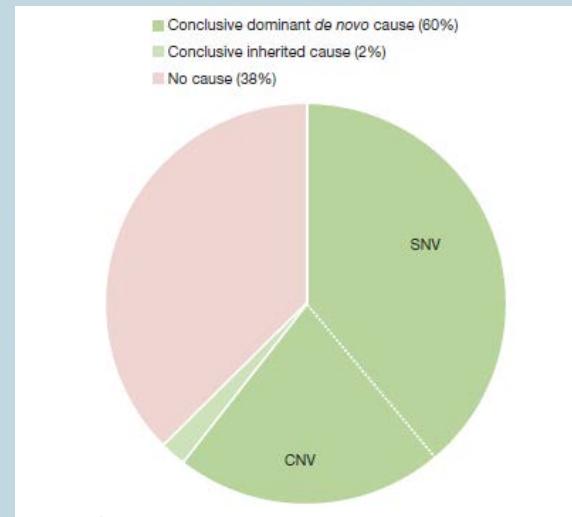
# *We want a healthy child*

## *Carrier screening*





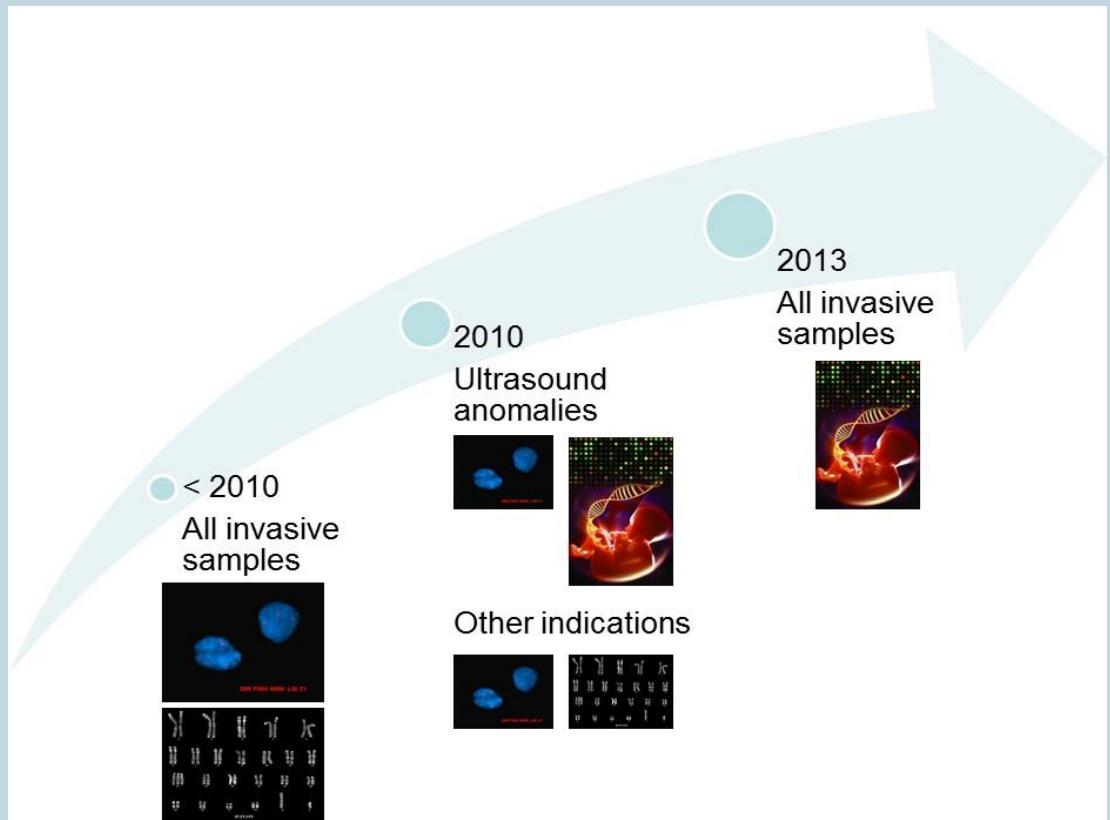
# *Is our child healthy? 1% have a rare disease*



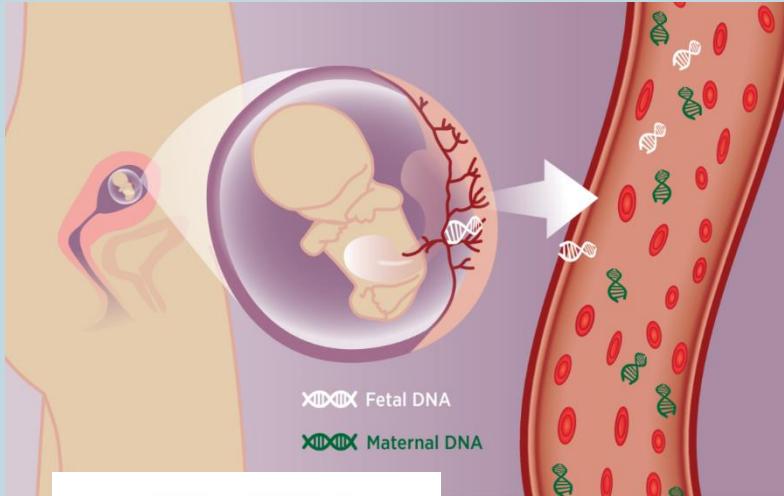
WGS can make a diagnosis for 60% of all patients  
Each of us carries 1.5 de novo mutations in genes  
Each of us is carrier of mutations in 20 recessive disease genes



# Why wait till after birth?



# Liquid biopsy for prenatal & cancer diagnosis



Potential to genotype & haplotype  
the whole population prenatally!

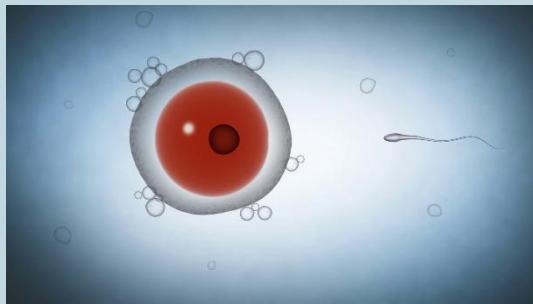


incidental findings :

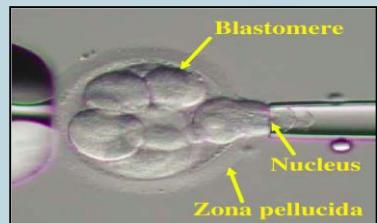
## Advies nr. 66 - niet-invasieve prenatale diagnostiek (NIPT)

Advies van 9 mei 2016 betreffende de ethische uitdagingen gesteld door de niet-invasieve prenatale diagnostiek (NIPT) voor trisomie 21, 13 en 18

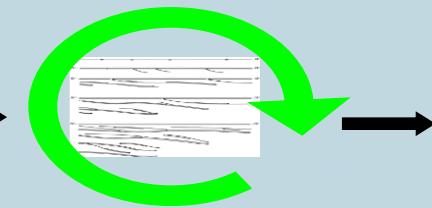
“Wanneer deze informatie kan leiden tot preventieve of therapeutische interventies is het belangrijk om deze informatie met de patiënt te delen binnen een klinisch-genetische setting. **Het niet meedelen ervan kan als een ernstige nalatigheid worden beschouwd.** ”



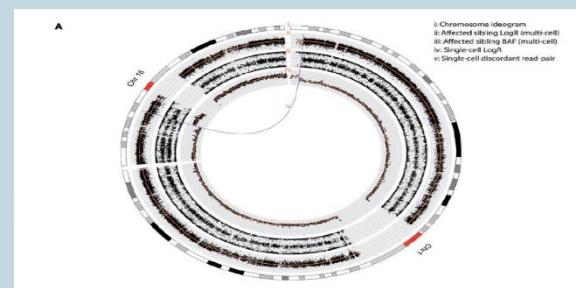
# Embryo selectie



Single  
blastomere  
7 pg DNA



WGS



# Barriers on the road towards (genomic) personalized medicine

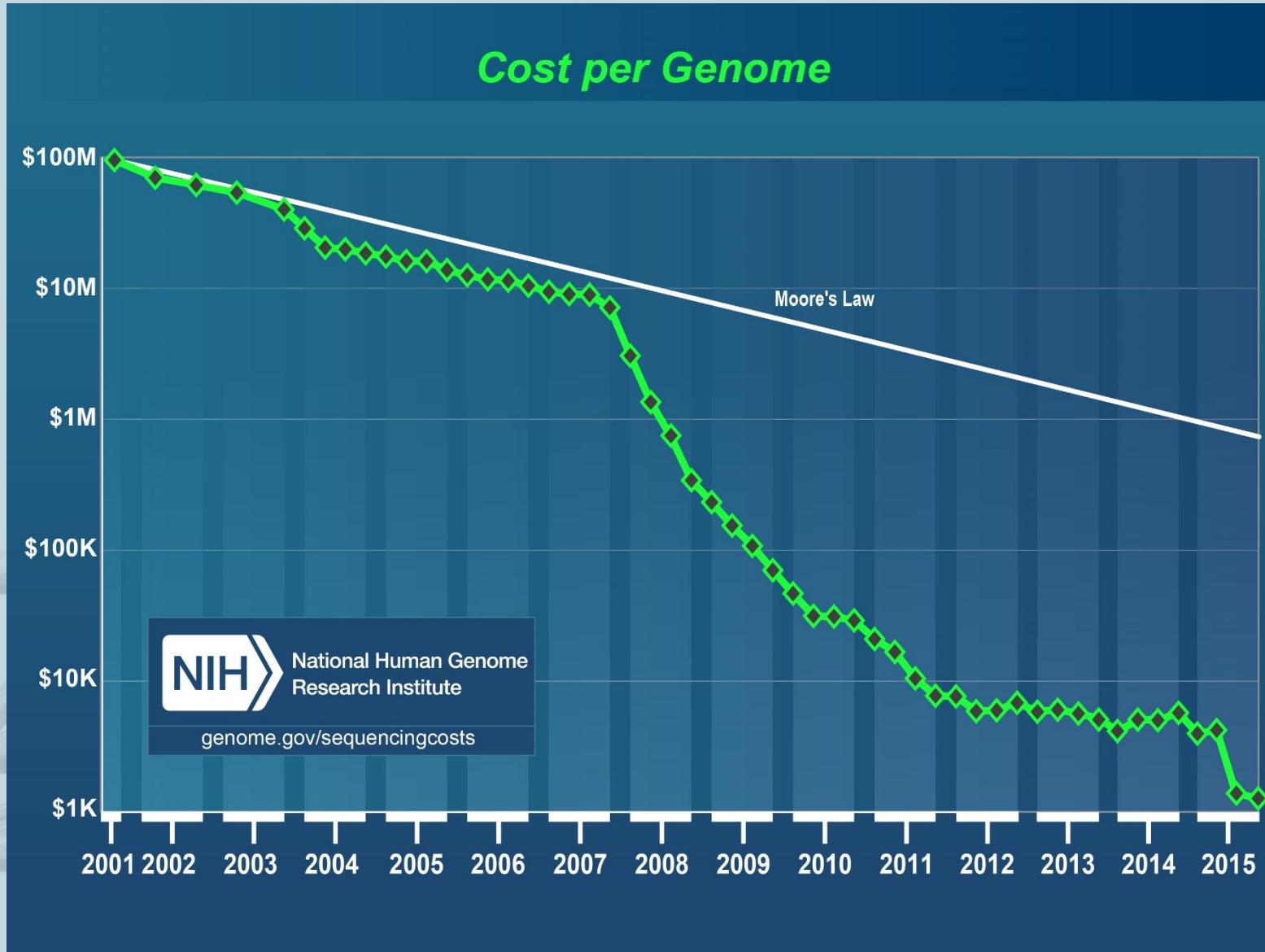


# Barriers on the road towards (genomic) personalized medicine (1)

## The IT (cost) bottleneck



# De IT bottleneck!!



# Cost of a genome analysis & storage?

THE \$1,000 GENOME,

**Active Scale X100**

578TB – 33.7PB Usable

8GB/s - 20GB/s



*Integrated  
for Petabyte-scale  
and fast growth*

**Western Digital.**

With a portfolio of leading brands

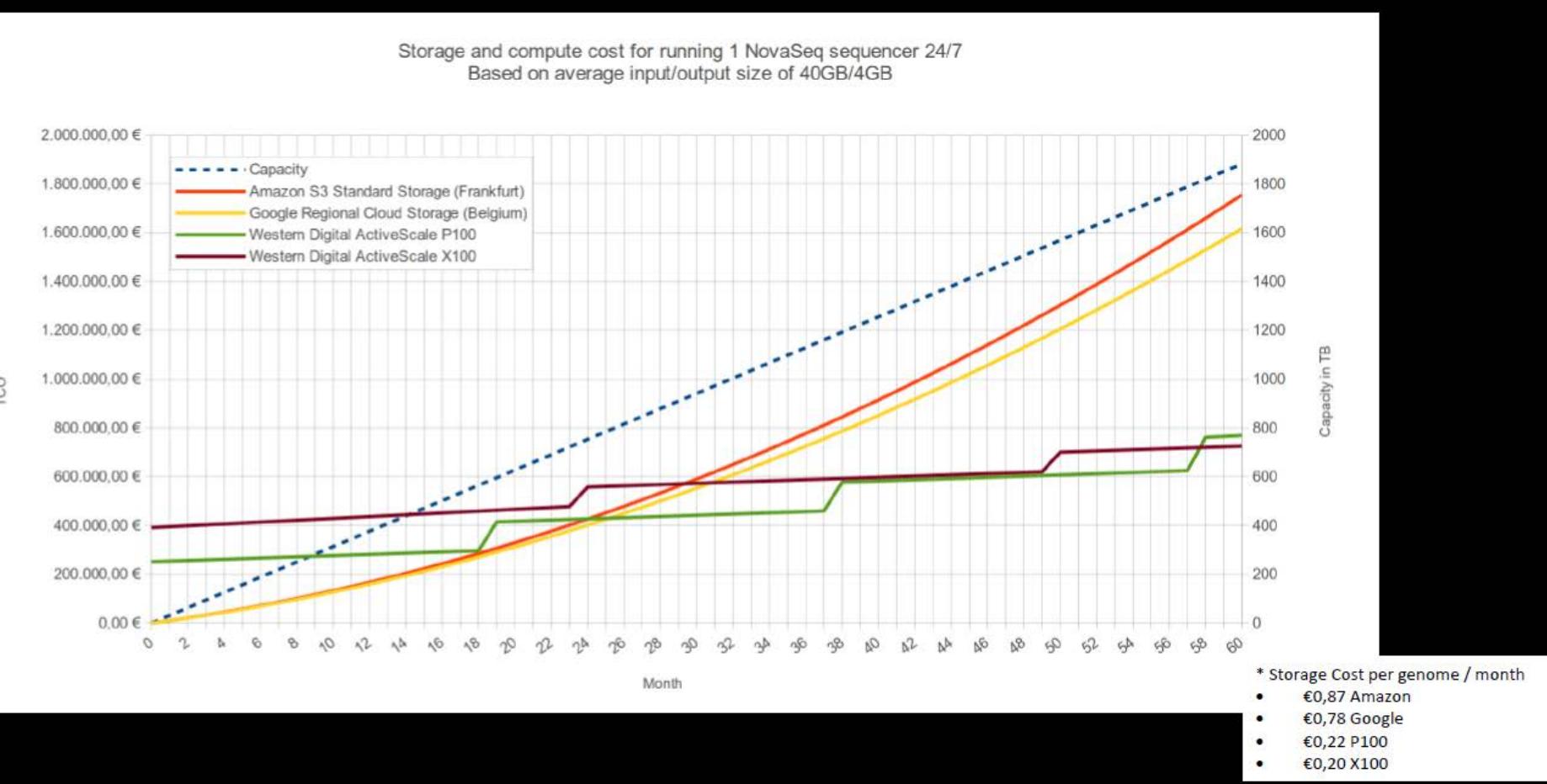
**SanDisk**

 G-Technology™

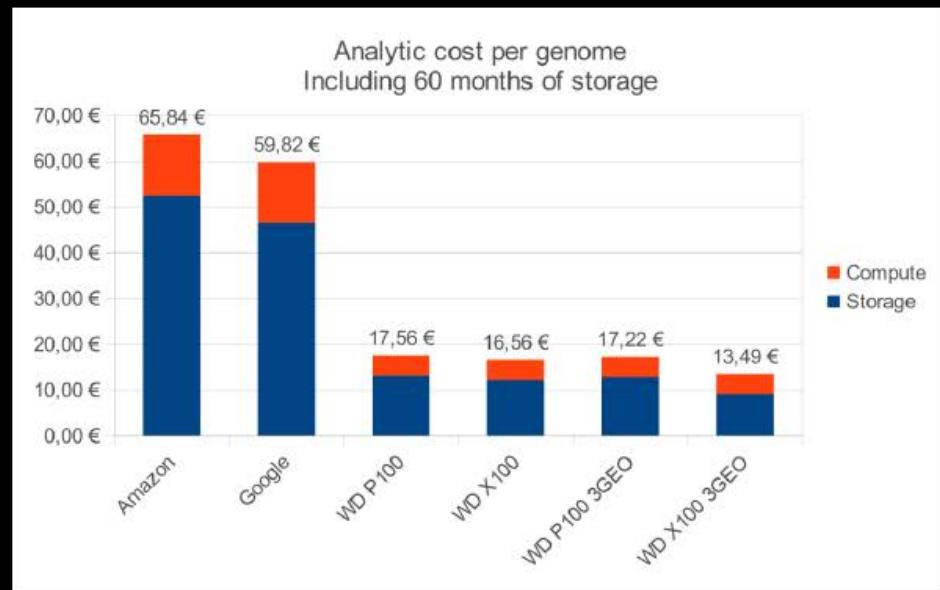
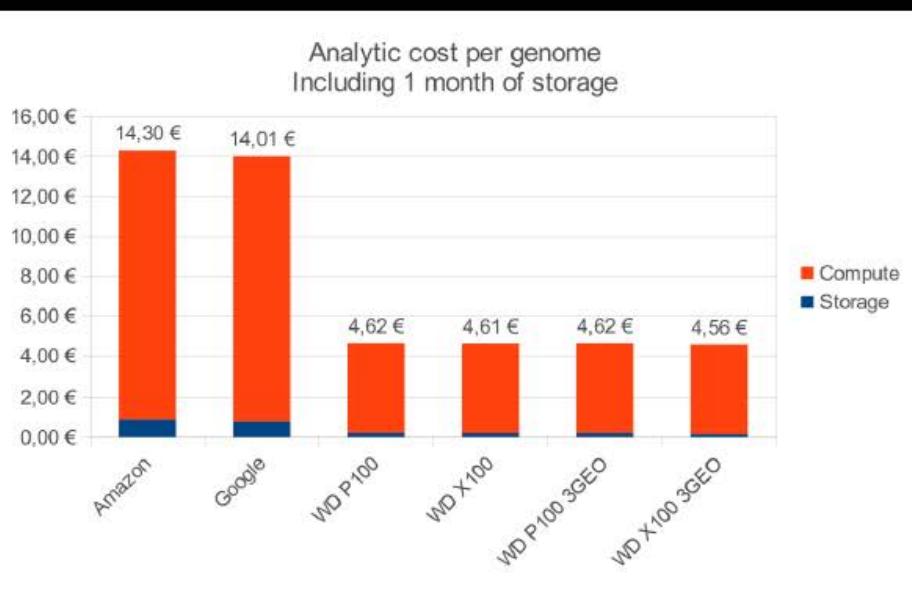
 WD

 upthere

# Cost simulation for 1 NovaSeq 24/7 (5000 genomes/year)



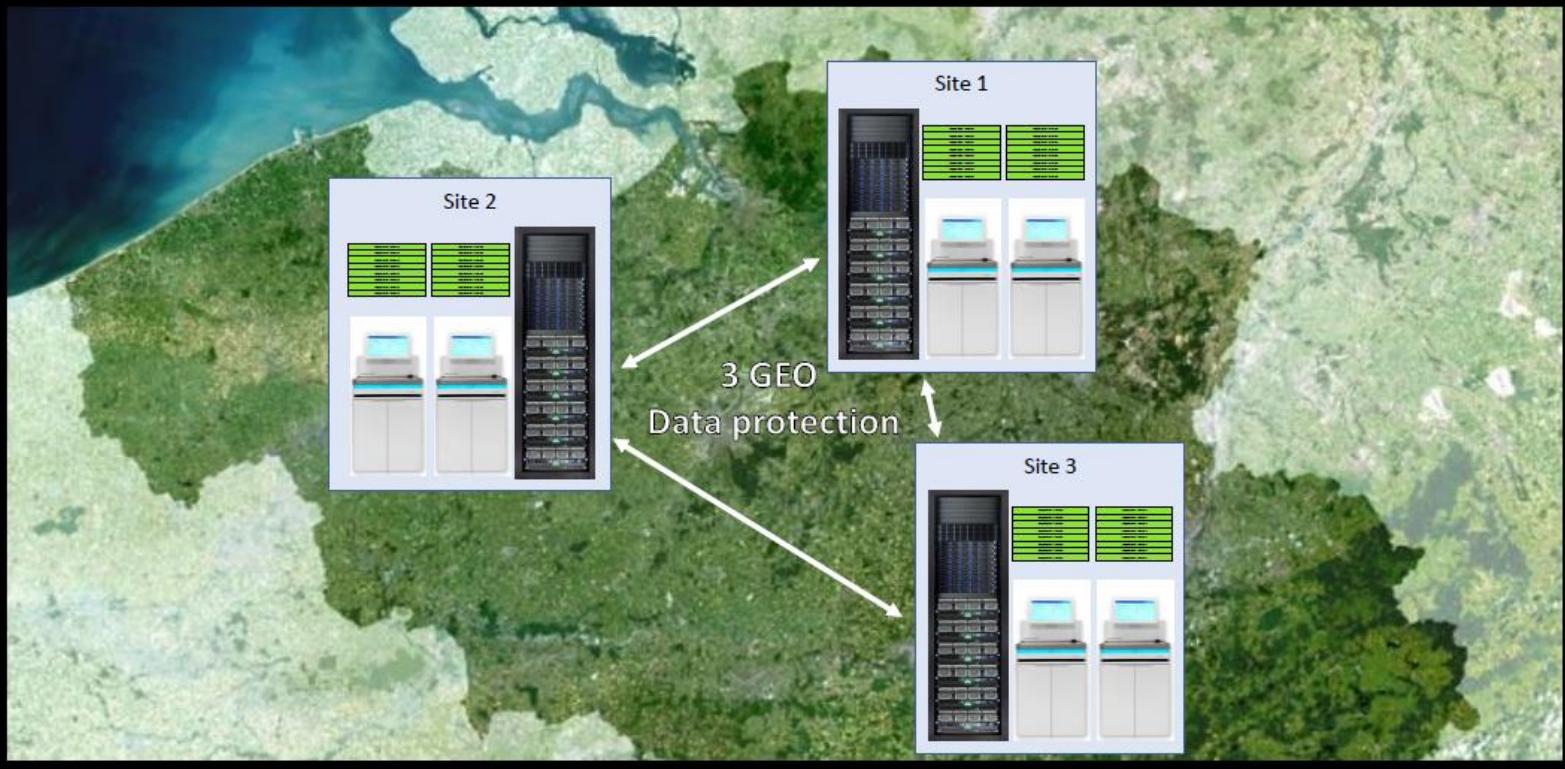
# Cost simulations



# Private cloud simulation

3 Geo:

- Data protection against 1 full site failure
- Overhead 64% (less than 3 copy)
- 1TB usable requires 0.55TB capacity per site



# Barriers on the road towards (genomic) personalized medicine (2)

Sharing the data!  
(both clinical & genomic)

# Data sharing is required!

Reuzedatabank met DNA van Belgen in de maak | De Tijd

18/10/2016, 10:24

## Reuzedatabank met DNA van Belgen in de maak

15 oktober 2016 01:00

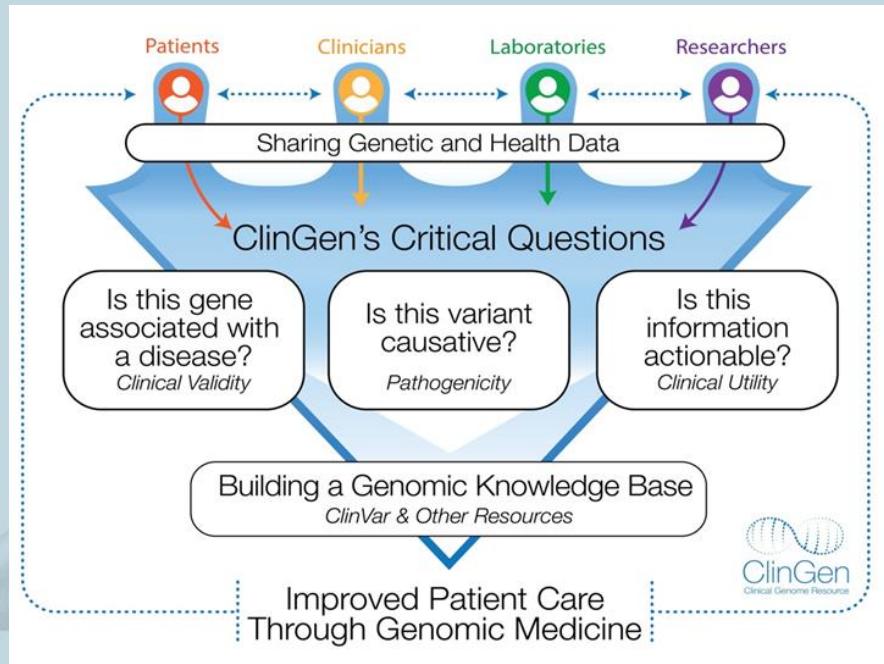
Saar Sinnaeve  
Jan De Schampheleire

**Ons land gaat het DNA van tienduizenden Belgen in kaart te brengen voor een omwenteling in de geneeskunde.**

Ons land is van plan meer dan 10 miljoen euro te investeren in de bouw van een onderzoeksdomain dat de jongste jaren in een st

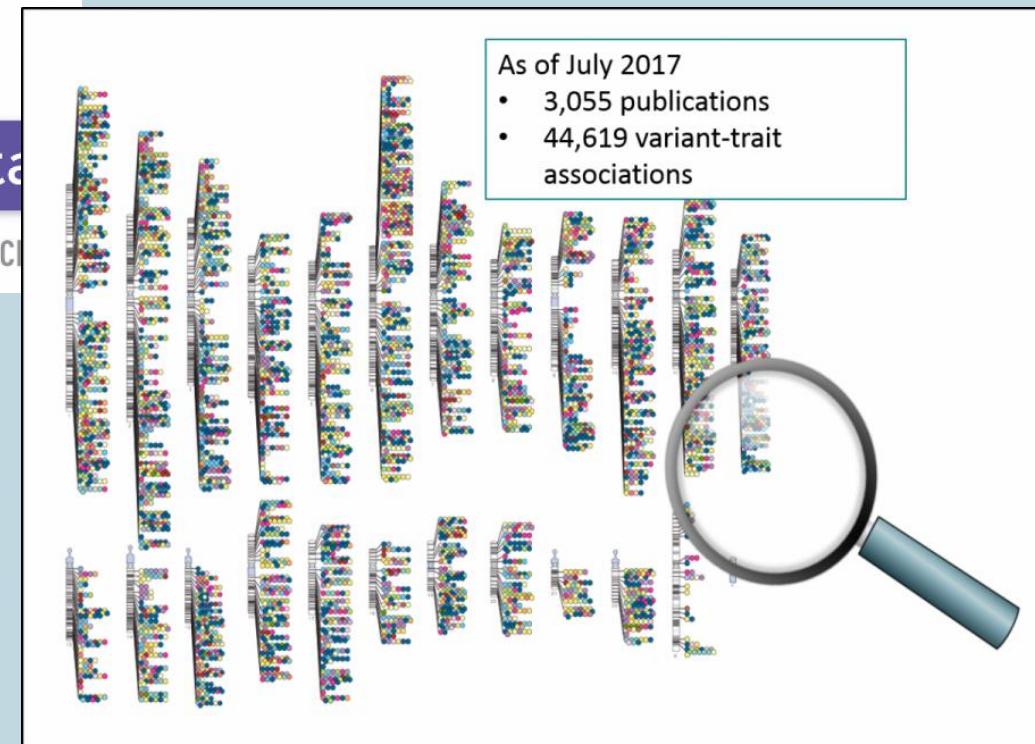


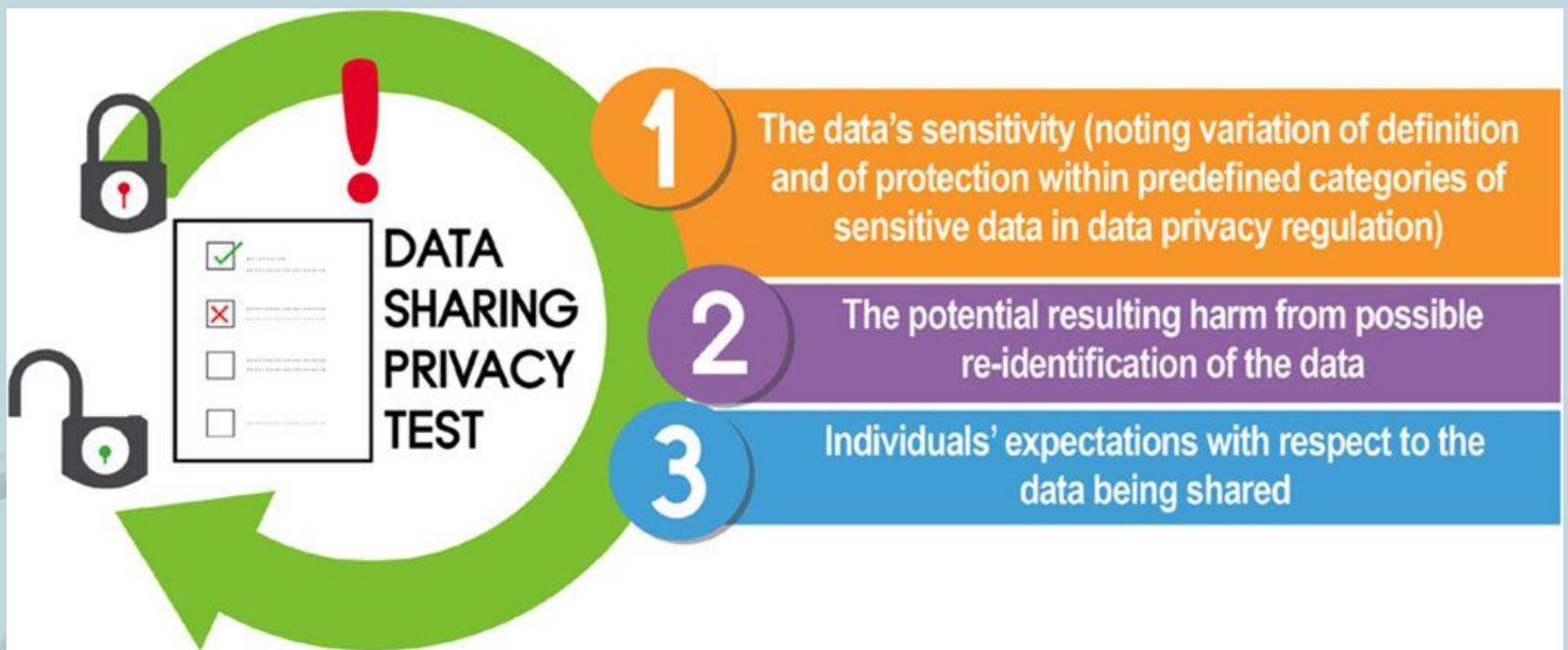
# International datasharing for rare disease research



# International datasharing for complex genetics & pharmacogenetics

## NATIONAL CANCER INSTITUTE GENOMIC DATA COMMONS



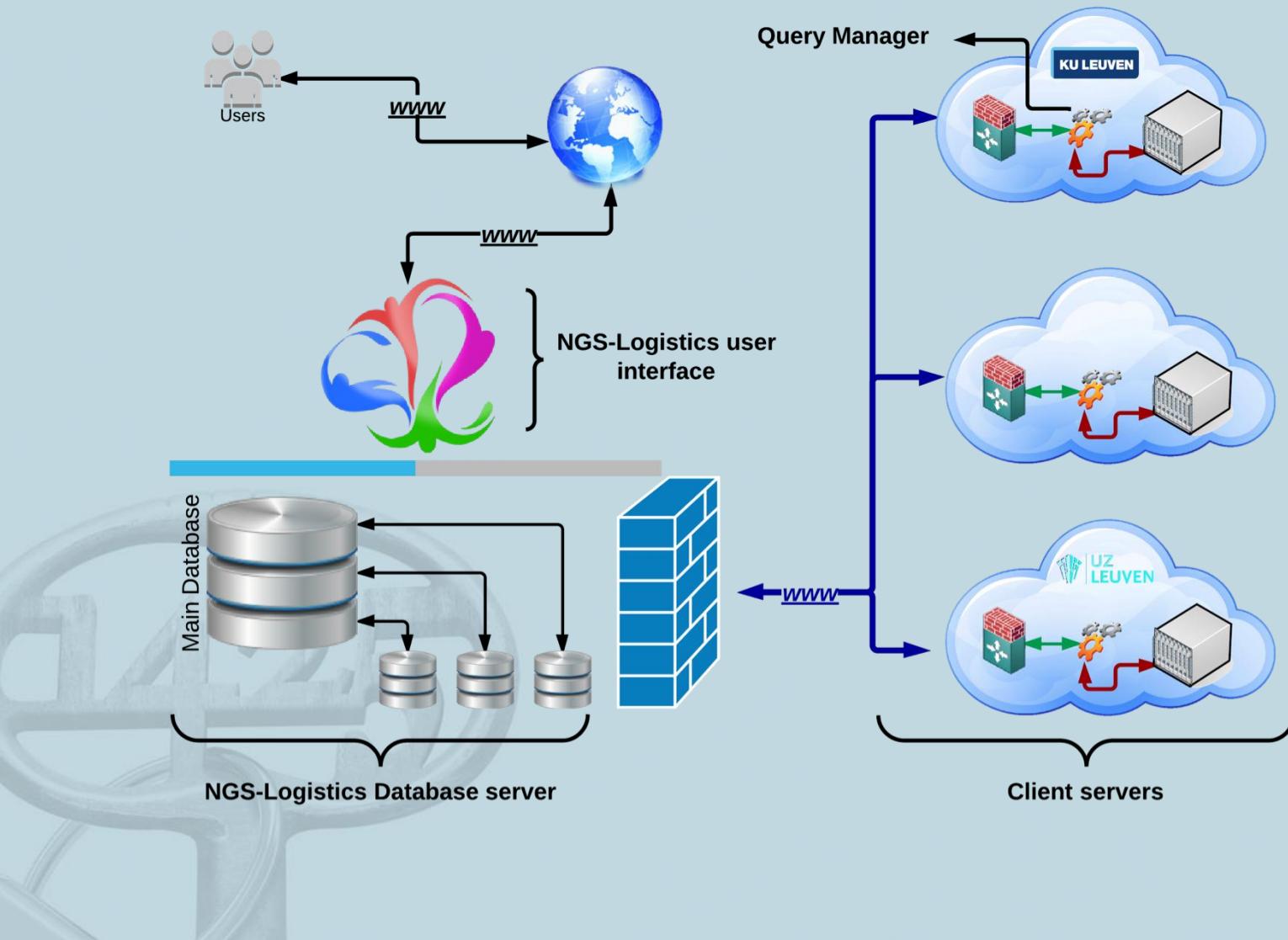


# Solutions to avoid de-anonymisation

- Centralised databases
  - Restricted access databases
  - E.g European Genome Archive (EGA)
  - eHEALTH?
- Decentralised data
  - Federated analytics



# Federated analytics



# Towards a human genome data sharing hub in Belgium & connected with the world

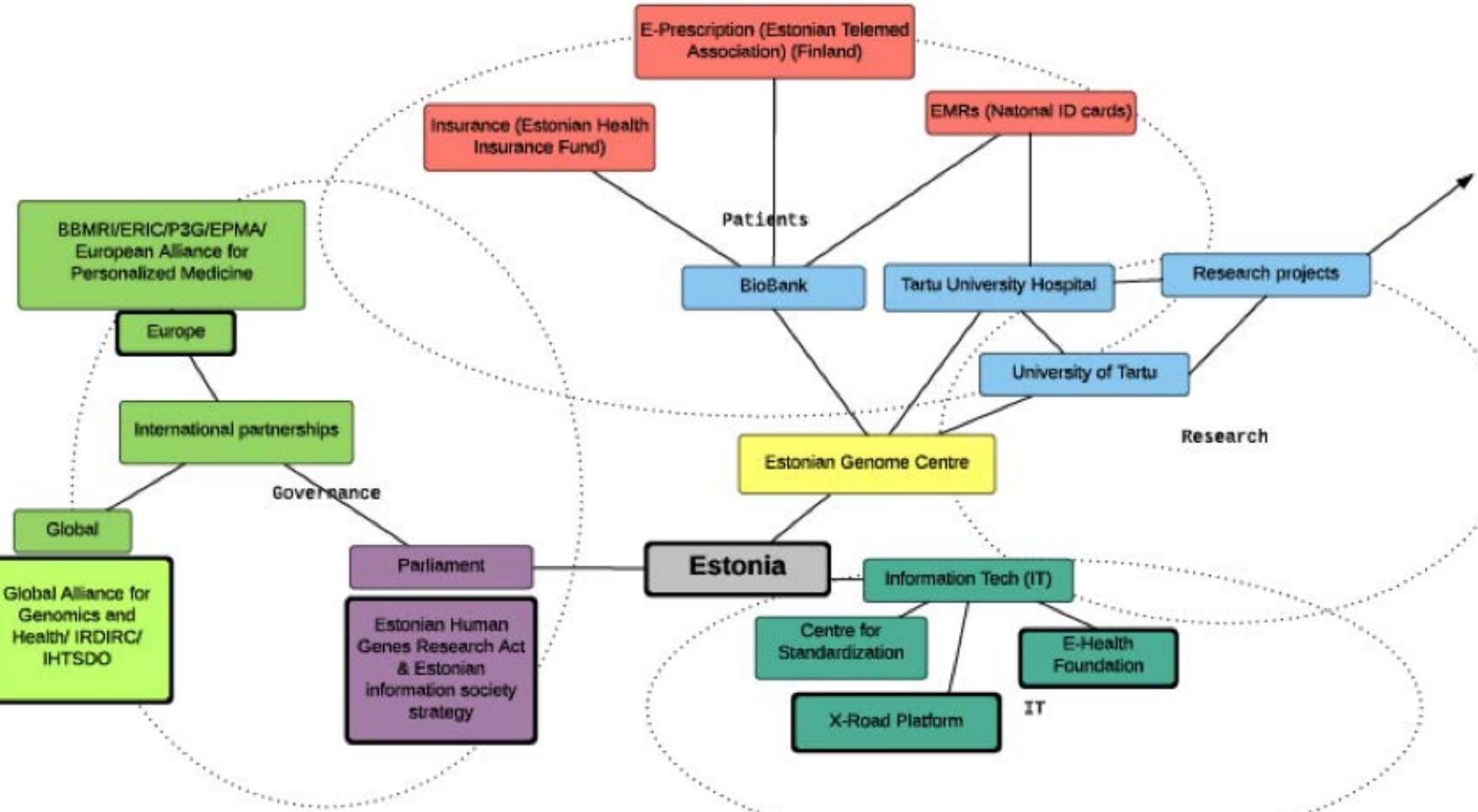


# Barriers on the road towards (genomic) personalized medicine (3)

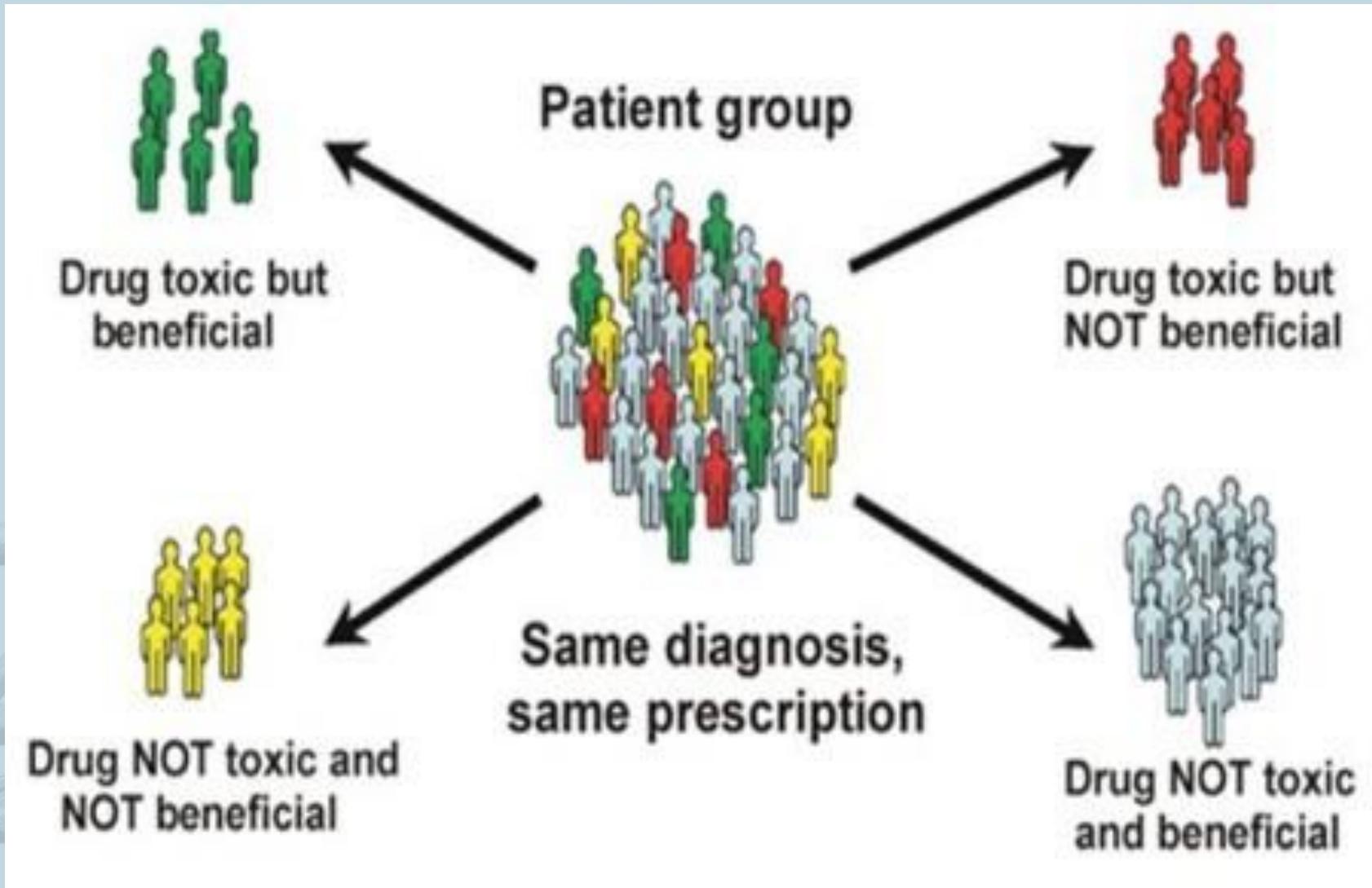
Creating a longitudinal/societal based  
learning environment



# An existing model: Estonia!



# A biobank is a requirement for life-long learning for pharmacogenomics



# Barriers on the road towards (genomic) personalized medicine (4)

Creating an evidence based  
personalized medicine research  
community



# Polygenic risk scores

- **Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations**
- For various diseases, mutations in certain genes are associated with a several-fold risk increase
  - CAD → hypercholesterolemia mutation
  - Type 2 diabetes → mutation in HNF1A
- But, the majority of diseases occur without the presence of such mutations
- Polygenic inheritance plays a greater role
  - Many common genetic variants with a small effect

# Proportions of individuals increased risks based on polygenic risk scores=> stratification of population!

- Atrial fibrillation
  - Underdiagnosed, asymptomatic
  - Increase detection in high GPS
- Type 2 Diabetes
  - Medication + lifestyle changes (but high cost + side effects)
  - Target interventions
- IBD
  - No treatment
  - GPS might help increase clinical trial population
- Breast cancer
  - Adjusting screening age recommendation

High GPS definition	Individuals in testing dataset (n)	% of individuals
<b>Odds ratio <math>\geq 3.0</math></b>		
CAD	23,119/288,978	8.0
Atrial fibrillation	17,627/288,978	6.1
Type 2 diabetes	10,099/288,978	3.5
Inflammatory bowel disease	9,209/288,978	3.2
Breast cancer	2,369/157,895	1.5
Any of the five diseases	57,115/288,978	19.8
<b>Odds ratio <math>\geq 4.0</math></b>		
CAD	6,631/288,978	2.3
Atrial fibrillation	4,335/288,978	1.5
Type 2 diabetes	578/288,978	0.2
Inflammatory bowel disease	2,297/288,978	0.8
Breast cancer	474/157,895	0.3
Any of the five diseases	14,029/288,978	4.9
<b>Odds ratio <math>\geq 5.0</math></b>		
CAD	1,443/288,978	0.5
Atrial fibrillation	2,020/288,978	0.7
Type 2 diabetes	144/288,978	0.05
Inflammatory bowel disease	571/288,978	0.2
Breast cancer	158/157,895	0.1
Any of the five diseases	4,305/288,978	1.5

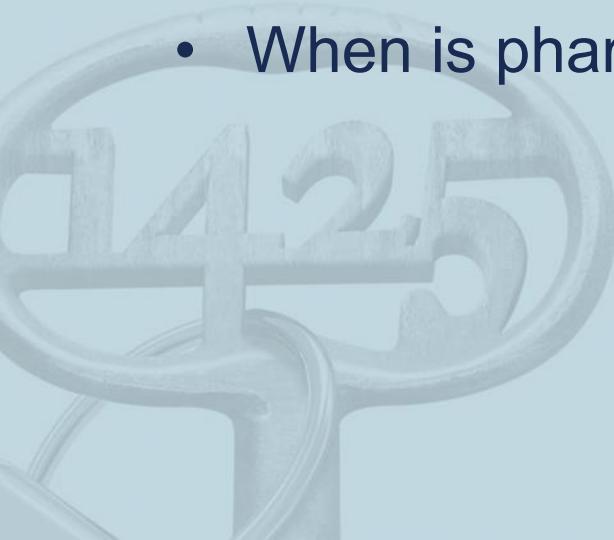
# Polygenic risk scores versus monogenic risk factors

- Monogenic mutations
  - Sequencing + interpretation of functional effects
- Polygenic risks
  - can readily be calculated
  - 19,8 % of individuals → > threefold risk for 1 disease
- Polygenic risks have the potential to:
  - identify individuals at significantly higher genetic risk
  - across a wide range of common diseases
  - at any age



# Opportunities and challenges for clinical medicine

- Prevention and early detection available?
  - Allocation of resources
- No prevention/early detection available?
  - Efficient natural history studies
- Risk communication?
  - To disclose or not? Potential harm to patient?
- When is pharmacogenomics information relevant?



# Barriers on the road towards (genomic) personalized medicine (5)

## Strengthening genetics

# Genetic centra at the forefront of personalised medicine

- Following a medical odyssey, patients with rare diseases are identified in genetic centra
- Genetic testing is advanced.
- Targeted testing for personalised cancer treatment & pharmacogenetic testing is up and running.
- Because of limited funding, Belgian genetic centra have been creative and work very efficient, compared with international peers.



# Genetic centra at the forefront of personalised medicine

- Personalised medicine is the core of clinical genetics
  - Curating rare diseases
  - Understanding different cancer profiles
- Preventive medicine is already in place (f.e. during prenatal, cancer, postnatal testing of rare diseases)
- Only specialisation which works/interacts with whole families
- Familial counseling & familial care

# Increase funding for WGS & personalised medicine

WGS for rare disease & cancer will leverage population based personal medicine



# Geneticists are needed to

Despite promises of personalised medicine,  
there is some hype!

- Frame the relevance of new findings
- Assure evidence based implementation
- Following the hype, guide the further implementation



# Barriers on the road towards (genomic) personalized medicine (6)

New organization of healthcare!

# Preventive, predictive, personal: New organisation



# Preventive, predictive, personal: New job opportunities, new needs

- More genetics training in medical curricula
- More clinical geneticists
- New discipline: genomic counselors
  - Action urgently required!



# Care framework is important!

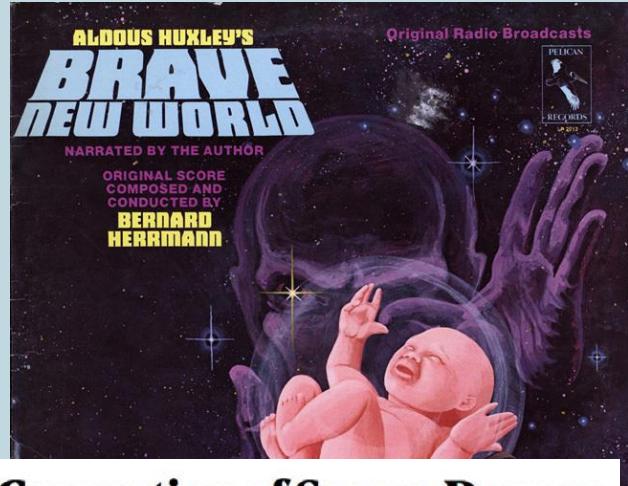
## Genetics is rarely black and white!



# Barriers on the road towards (genomic) personalized medicine (7)

**Get societal buy-in!**

# Utopia or dystopia?



## Finding the Lost Generation of Sperm Donors

Tens of thousands of donor-conceived children grew up thinking they'd never know their biological fathers. Now, they have a chance to.

ASHLEY FETTERS · MAY 18, 2018



### MORE STORIES

**Dear Therapist: I Obsess About My I From a Decade Ago**  
LORI GOTTLIEB

**The Futility of Trying to Prevent More School Shootings in America**  
BARBARA BRADLEY HANNUM

**The Enduring Appeal of the Fairy-Tale Wedding**

# KU LEUVEN

Leuven Institute for human  
Genomics and Society

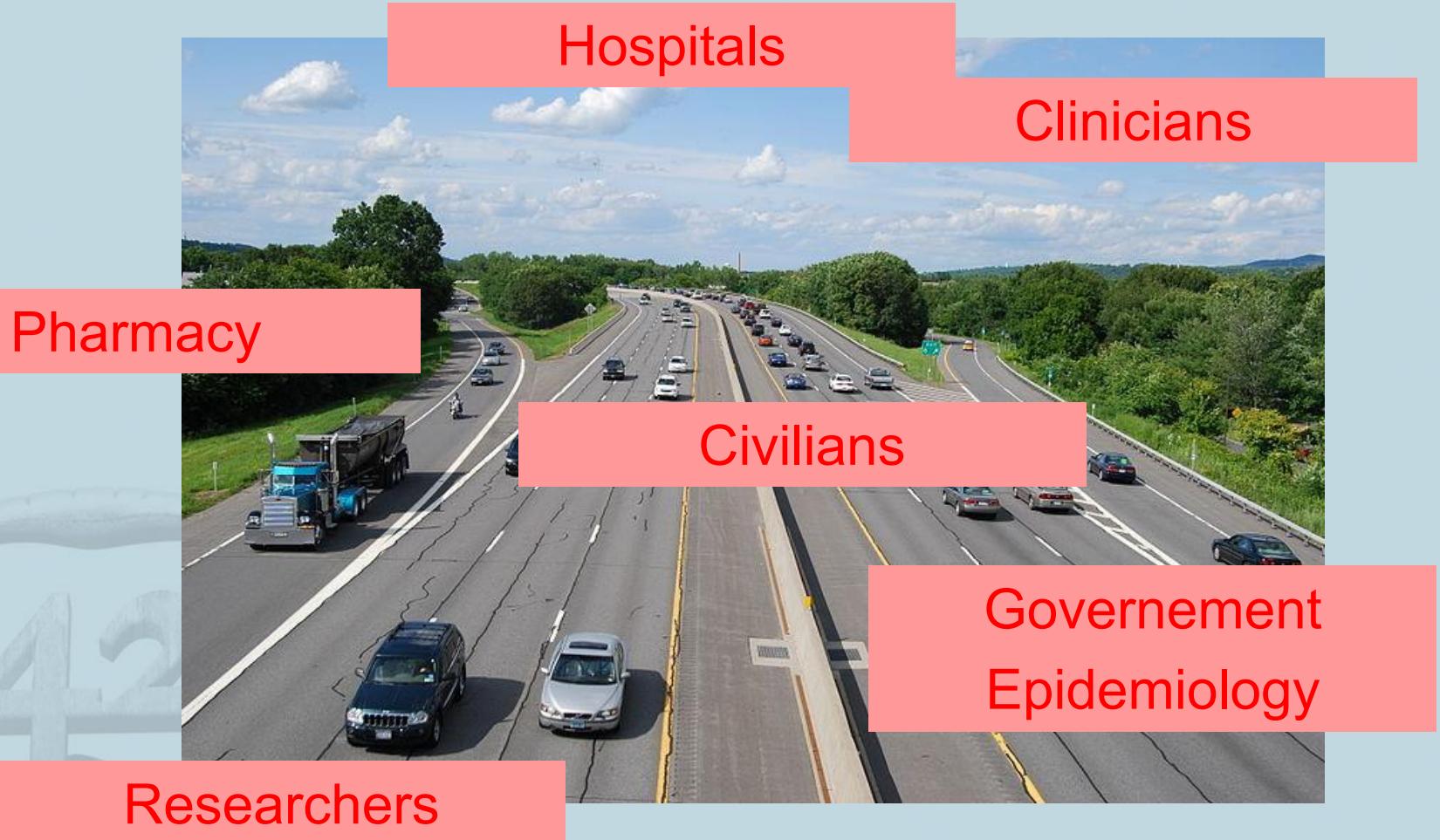
# Barriers on the road towards (genomic) personalized medicine (8)

Who is in charge?

# Who is in charge?

- Is this research YES
- Is this healthcare? YES
- Is this risk prevention? YES
- Is this economy? YES
- Is education required? YES
- Together: INFRASTRUCTURE!

# It should be infrastructure!!



# Road forward for Europe/Belgium is NOT a 1M genome project



**Declaration for delivering cross-border access to genomic database**

-  1 million **genomes accessible** in the EU by 2022
-  **Linking access** to existing and future genomic database across the EU
-  Providing a sufficient scale for **new clinically impactful** associations in research



BUT



741 M Genome Project!