KATHOLIEKE UNIVERSITEIT LEUVEN

Personalised medicine: Needs & barriers

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KULeuven, Belgium

SAPHIRe Workshop
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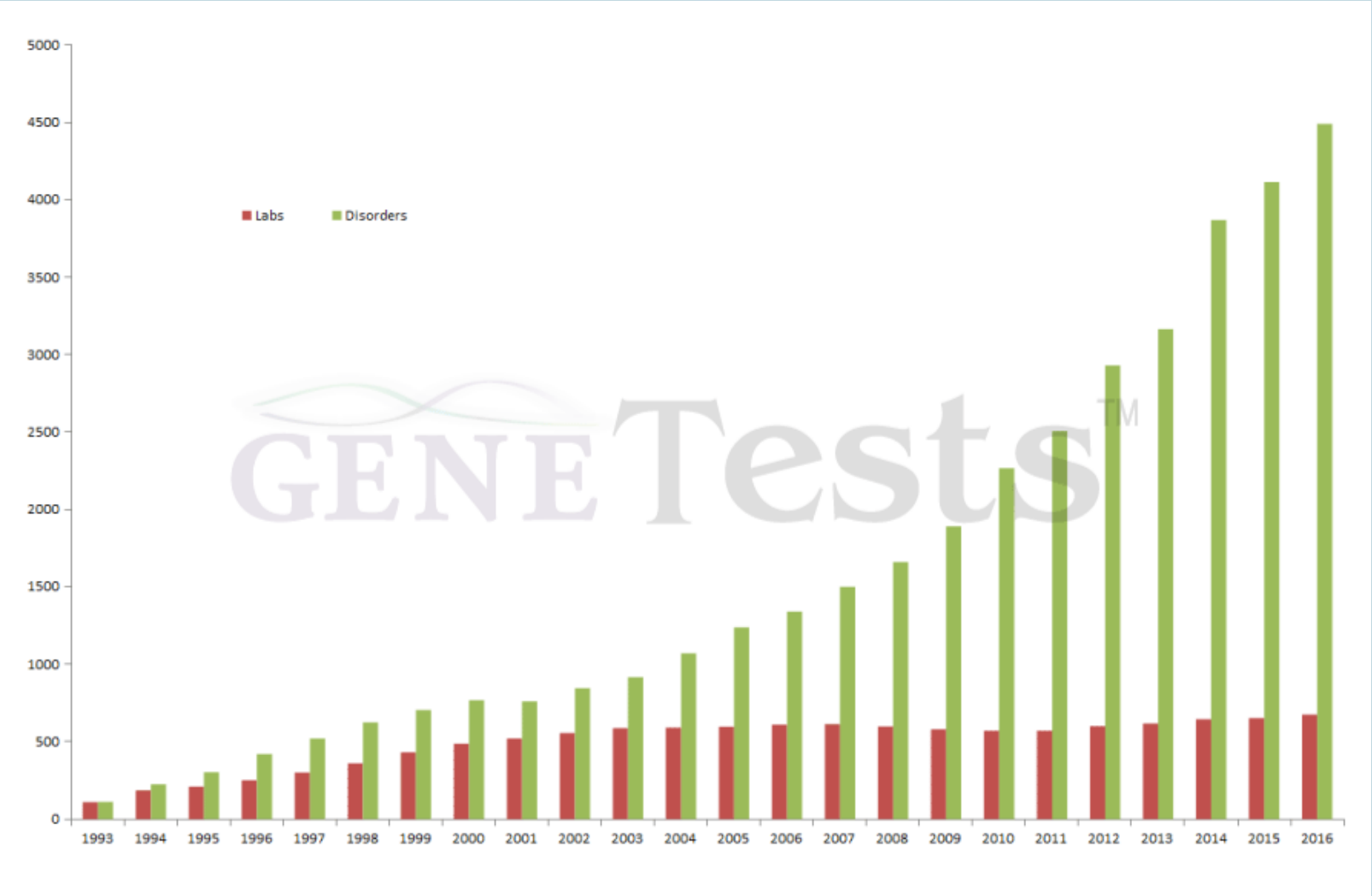
Personalized medicine

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 ...

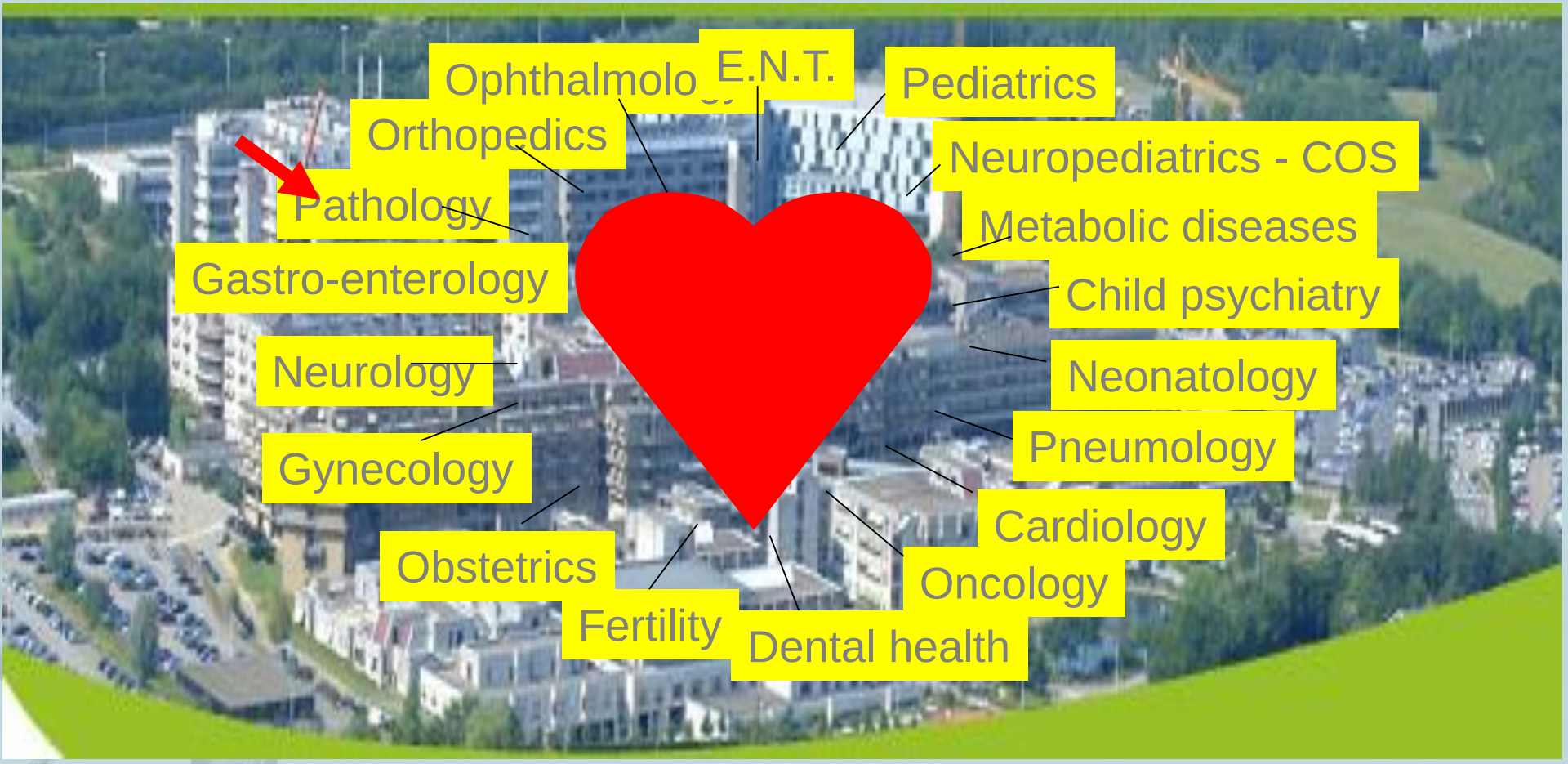
NIH: The story of personalized medicine begins with the unique set of genes you inherited from your parents.... If doctors know your genes, they can predict drug response and incorporate this information into the medical decisions they make (Pharmacogenomics)

Ever more gene variants associated with disease

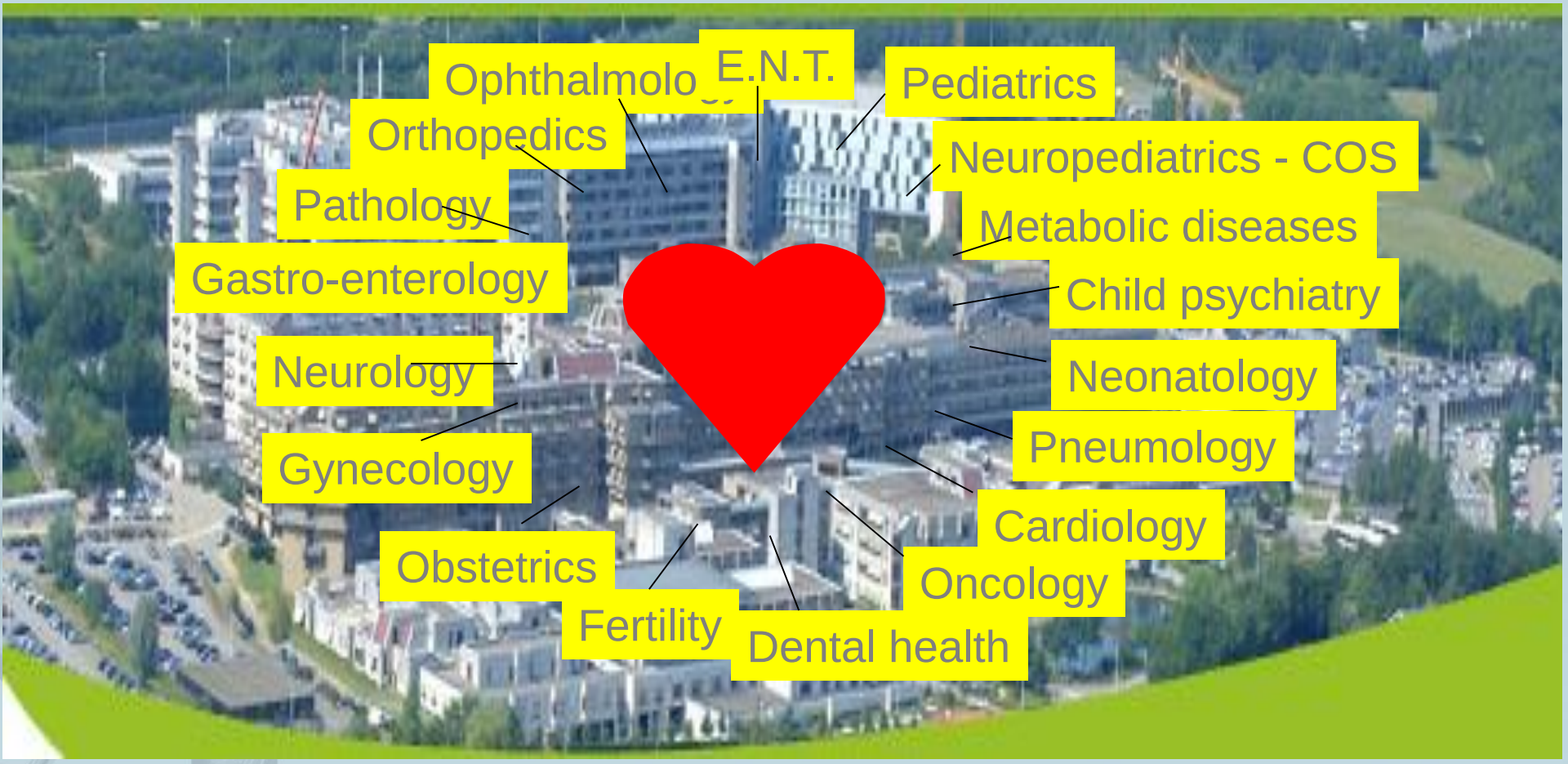


Source: Genetests Database 2016 www.genetests.org

Genetics has become the heart of the hospital



Van genetische test naar genomische geneeskunde

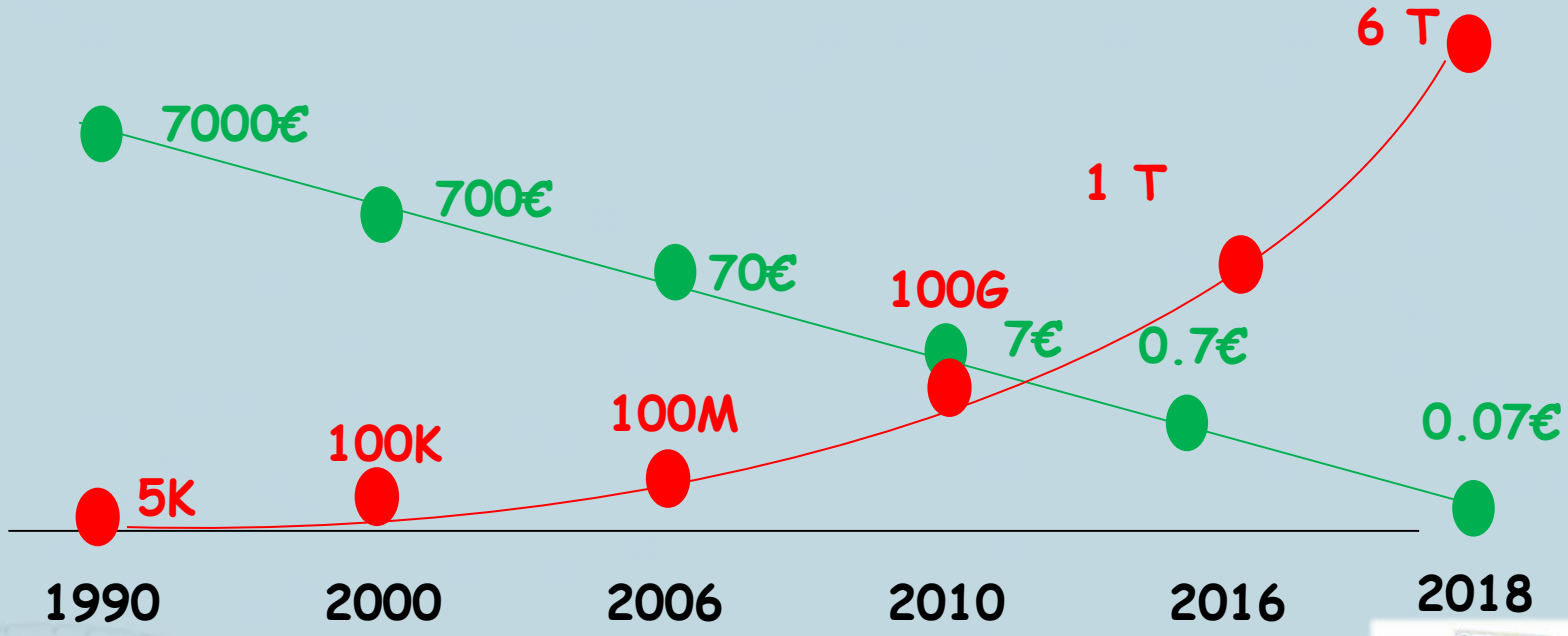


Genomic medicine is currently the main component of personalized medicine.

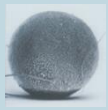
Research program ‘Personalized Medine’ in the Netherlands

- **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



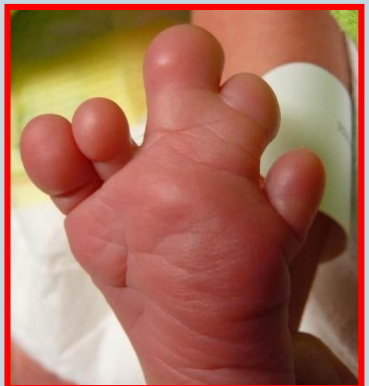
Not whether but when genome analysis?



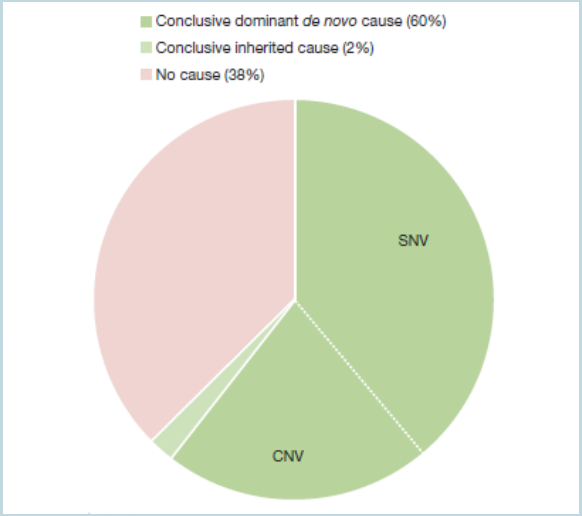


We want to stay healthy

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

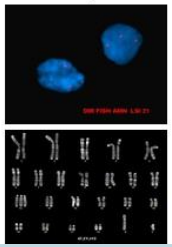
Each of us carries 1.5 de novo mutations in genes

Each of us is carrier of mutations in 20 recessive disease genes

Why wait till after birth?

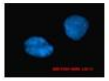
< 2010

All invasive samples

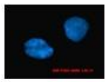


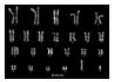
2010

Ultrasound anomalies



Other indications

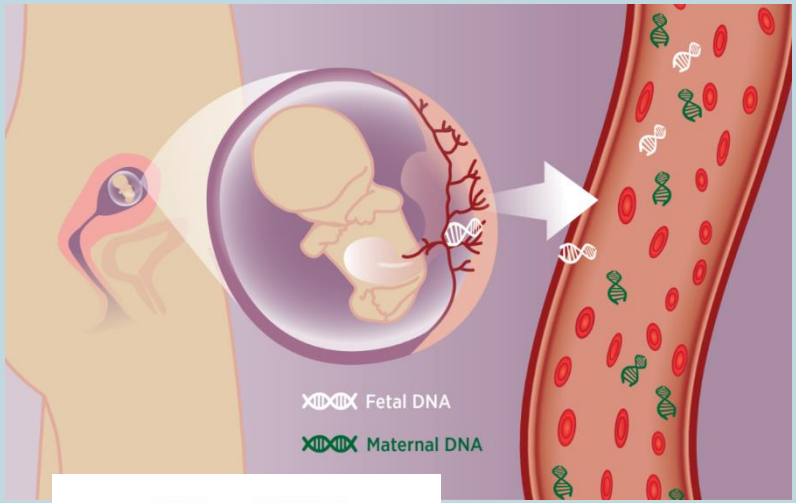




2013

All invasive samples

Liquid biopsy for prenatal & cancer diagnosis



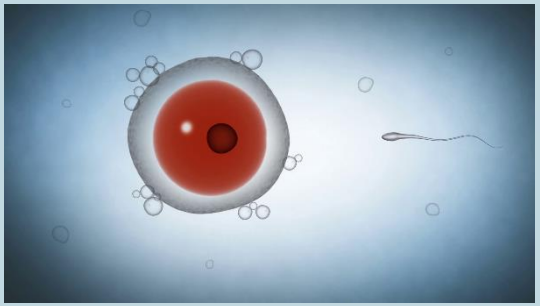
Potential to genotype & haplotype the whole population prenataly!

incidental findings :

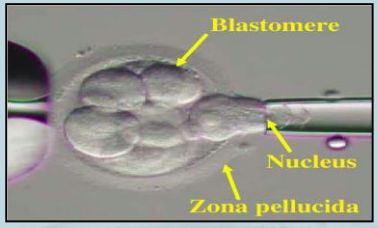
Advies nr. 66 - niet-invasieve prenatale diagnostiek (NIPT)

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

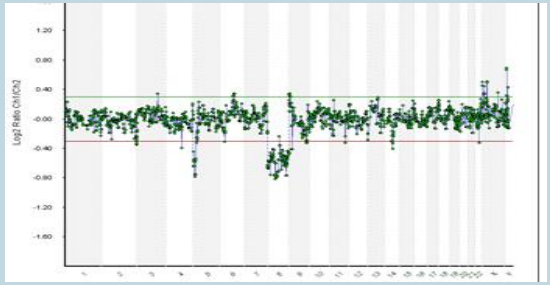
"Wanneer deze informatie kan leiden tot preventieve of therapeutische interventies is het belangrijk om deze informatie met de patiënt te delen binnen een klinisch-genetische setting. **Het niet meedelen ervan kan als een ernstige nalatigheid worden beschouwd.** ".



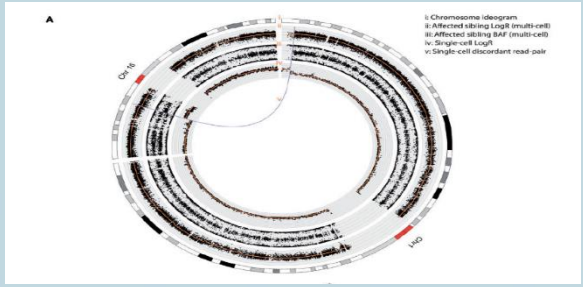
Embryo selectie



Single blastomere
7 pg DNA



WGS



Barriers on the road towards (genomic) personalized medicine

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

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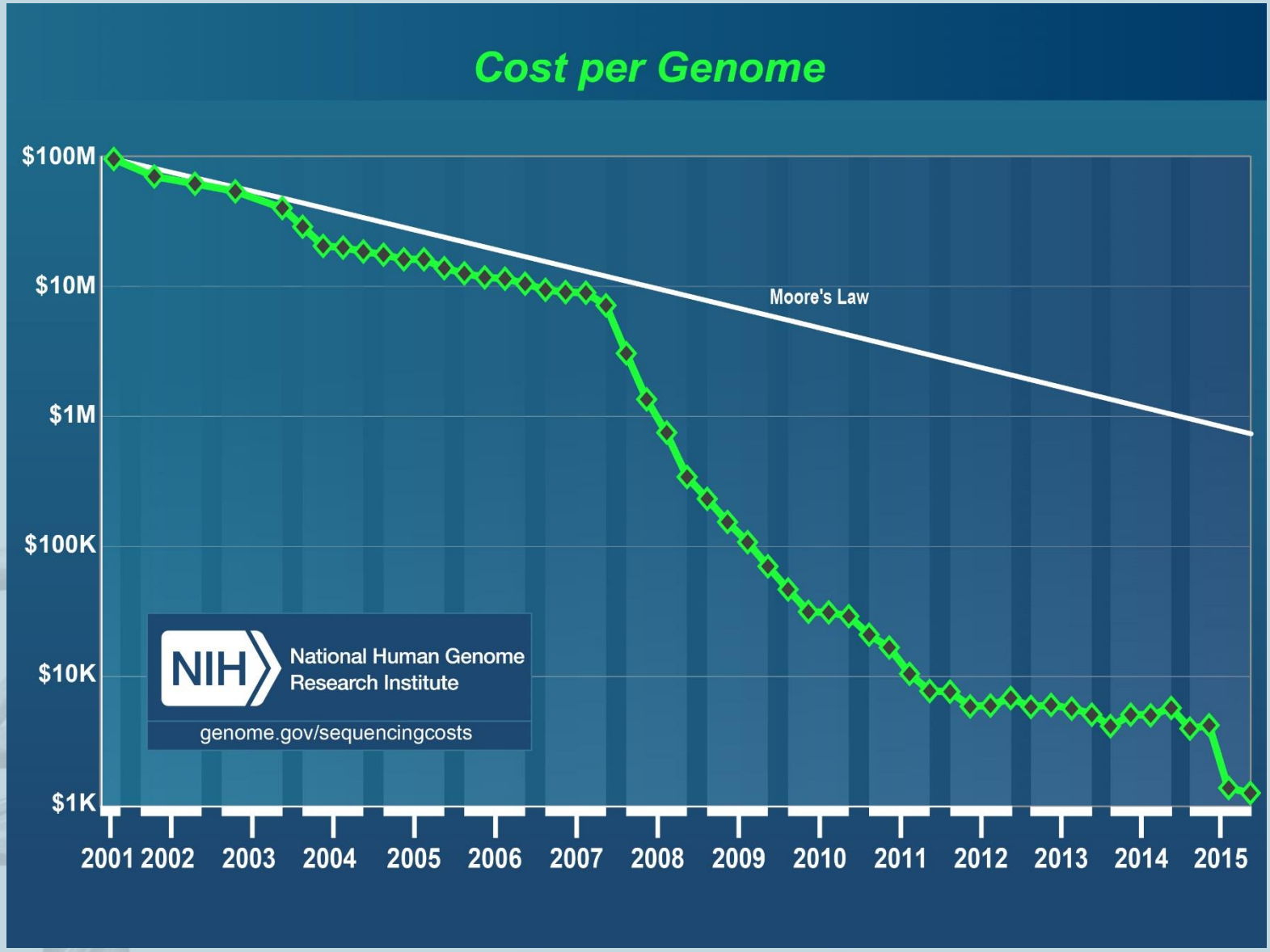
The IT (cost) bottleneck

De IT bottleneck!!



Cost of a genome analysis & storage?

THE $1,000 GENOME,

Active Scale X100

578TB – 33.7PB Usable

8GB/s - 20GB/s

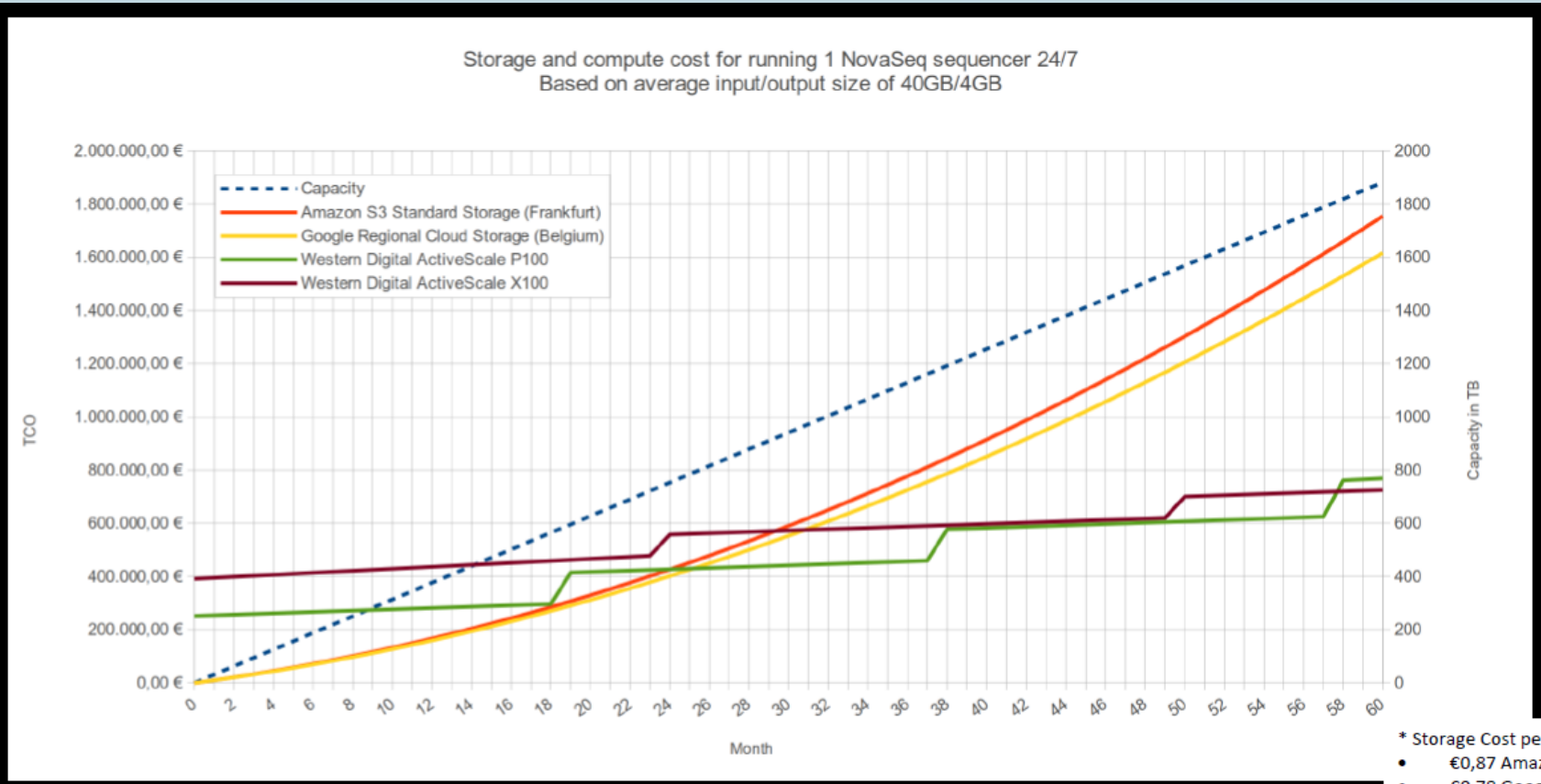
Integrated
for Petabyte-scale
and fast growth

Western Digital.

With a portfolio of leading brands

SanDisk · G-Technology · WD · upthere

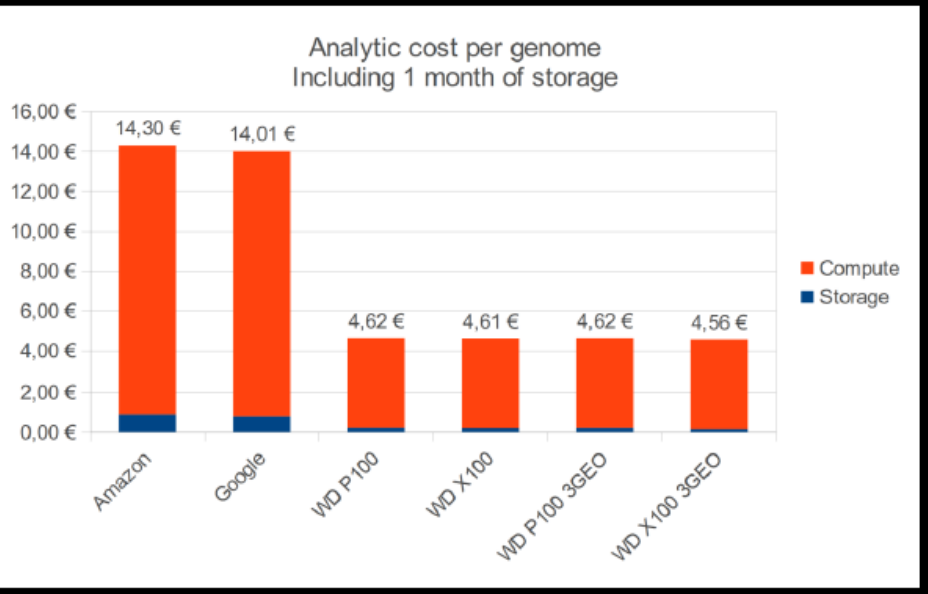
Cost simulation for 1 NovaSeq 24/7 (5000 genomes/year)

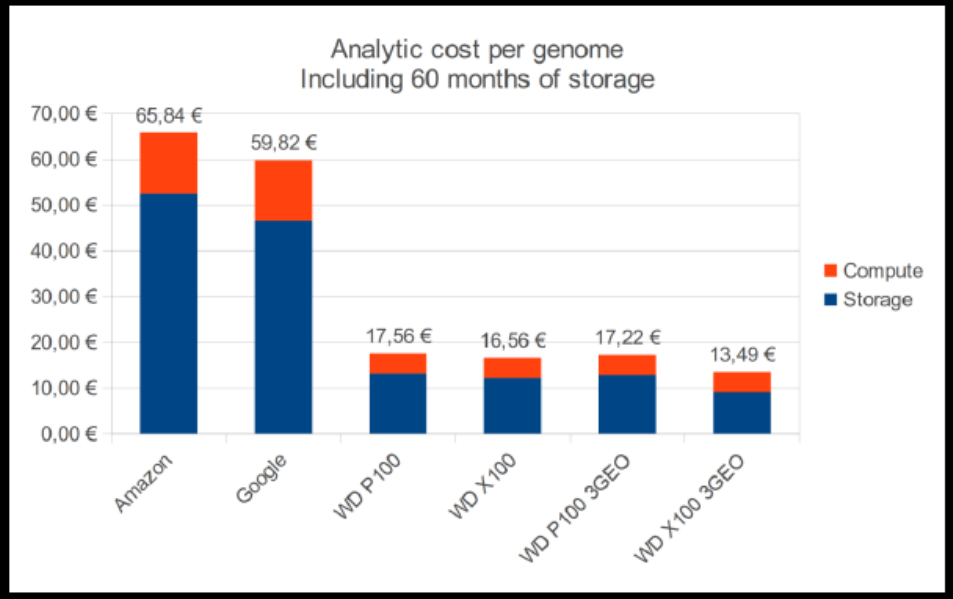


* Storage Cost per genome / month

- €0,87 Amazon
- €0,78 Google
- €0,22 P100
- €0,20 X100

Cost simulations

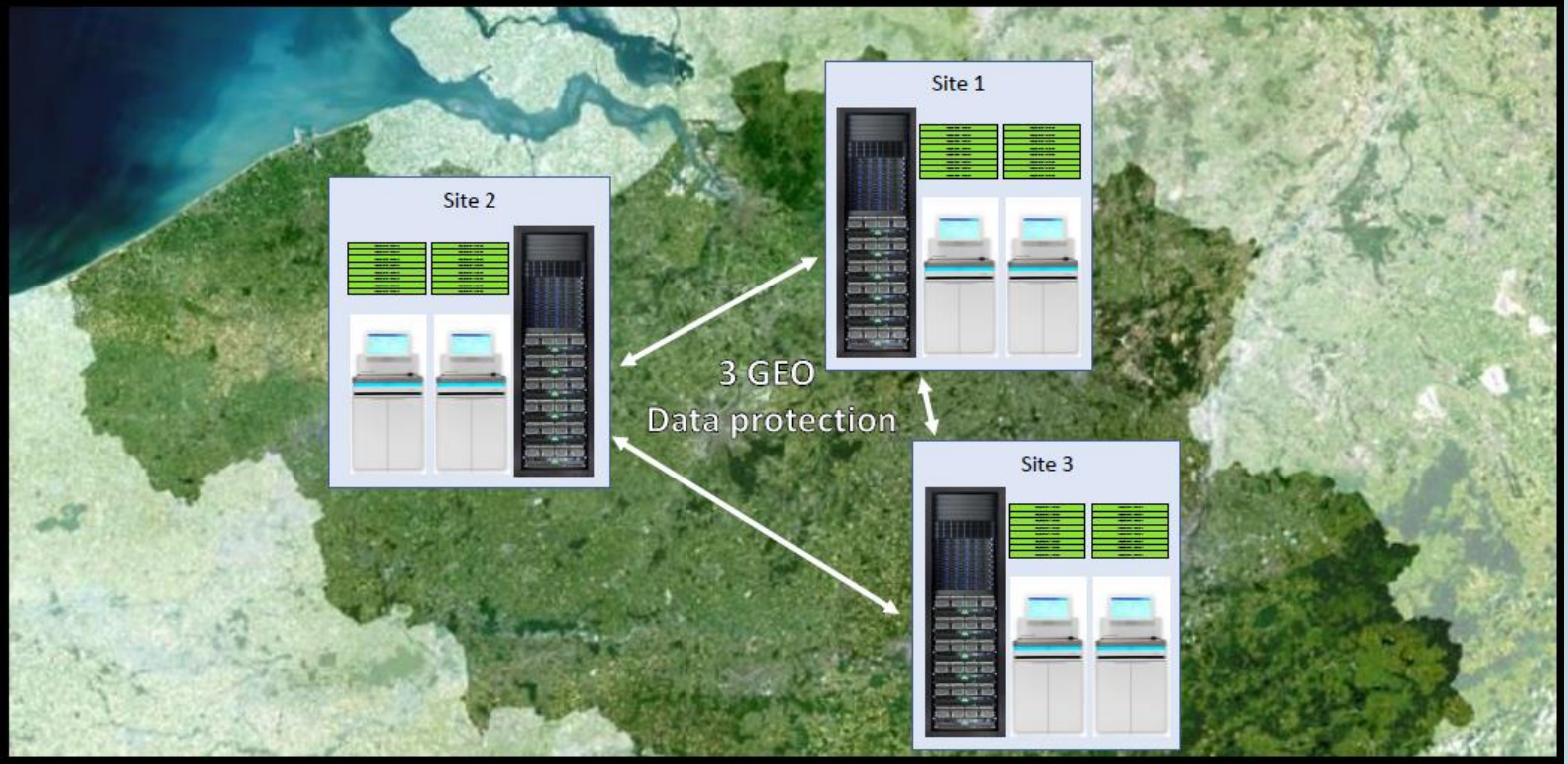




Private cloud simulation

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!

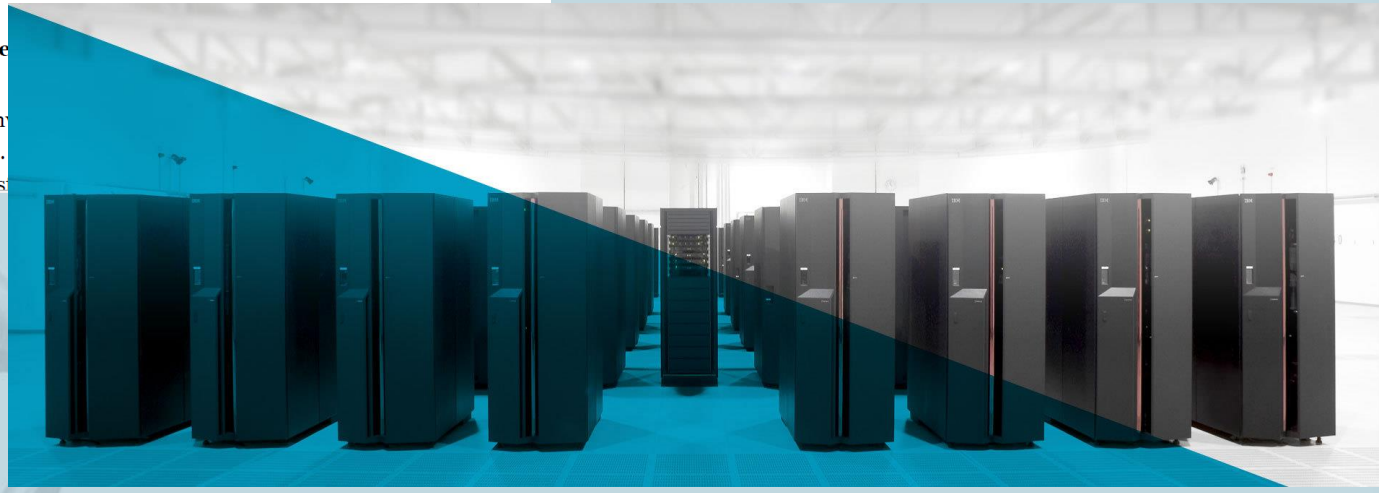
Reuzedatabank met DNA van Belgen in de maak

15 oktober 2016 01:00

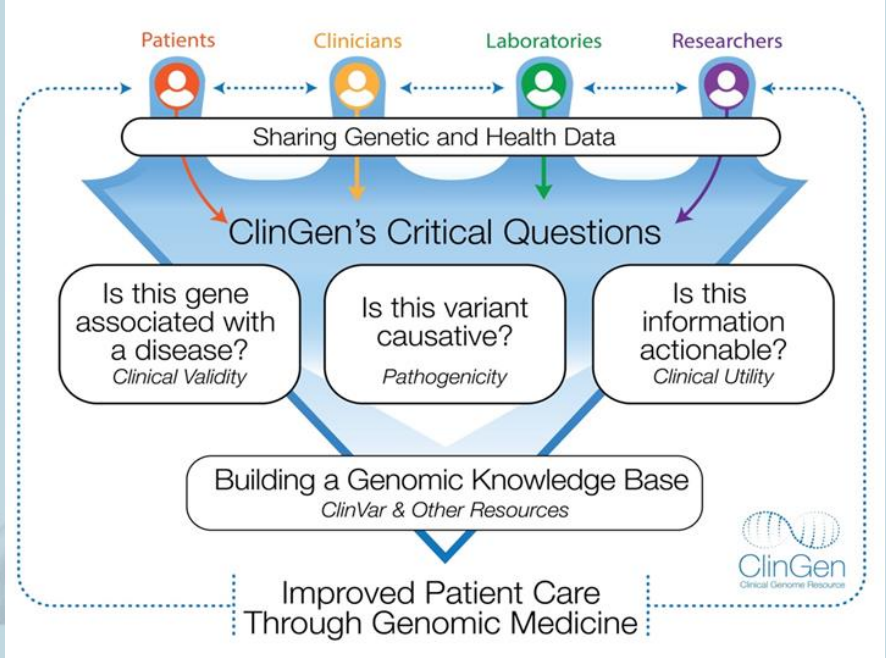
Saar Sinnaeve
Jan De Schamphelaere

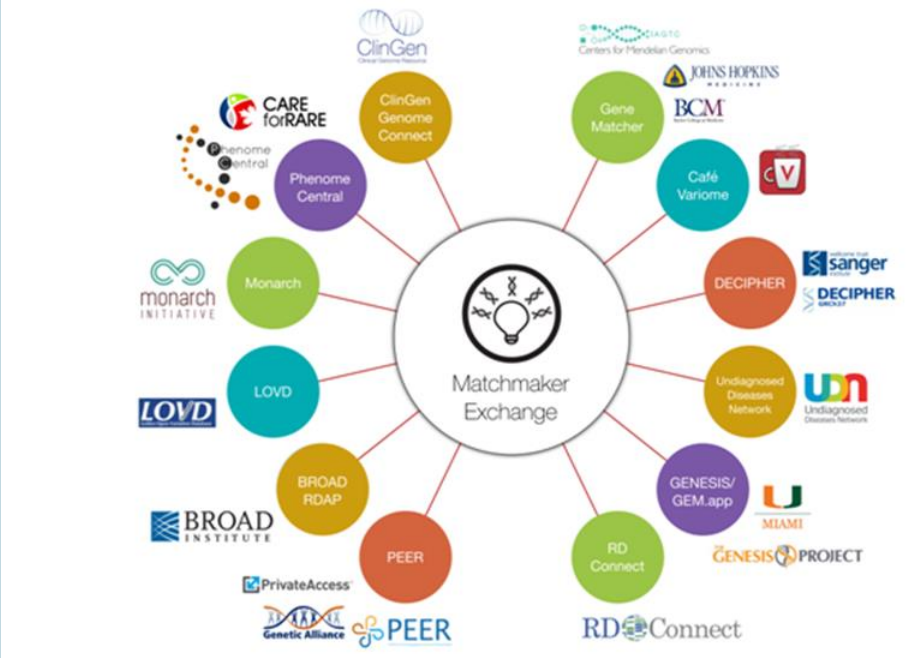
Ons land gaat het DNA van tienduizenden Be
voor een omwenteling in de geneeskunde.

Ons land is van plan meer dan 10 miljoen euro te in
DNA van tienduizenden Belgen in kaart te brengen.
een onderzoeksdomein dat de jongste jaren in een s

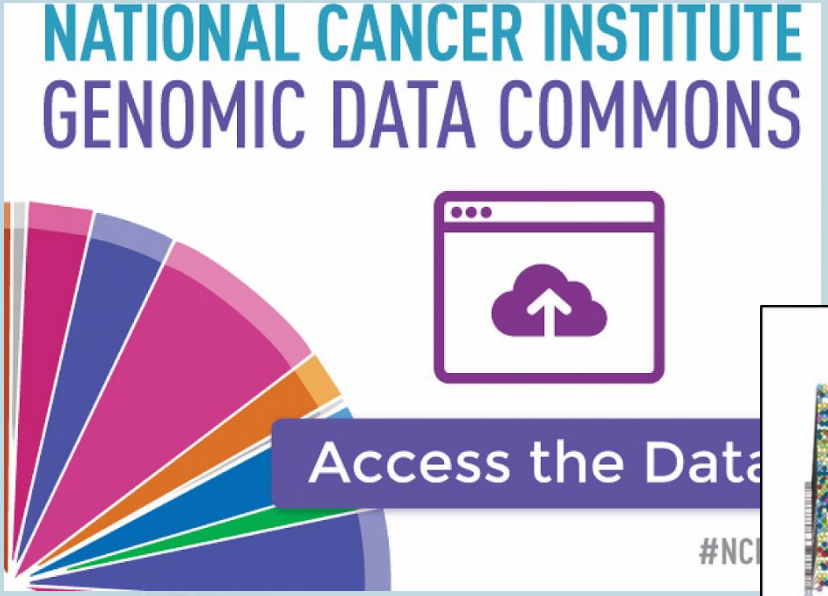


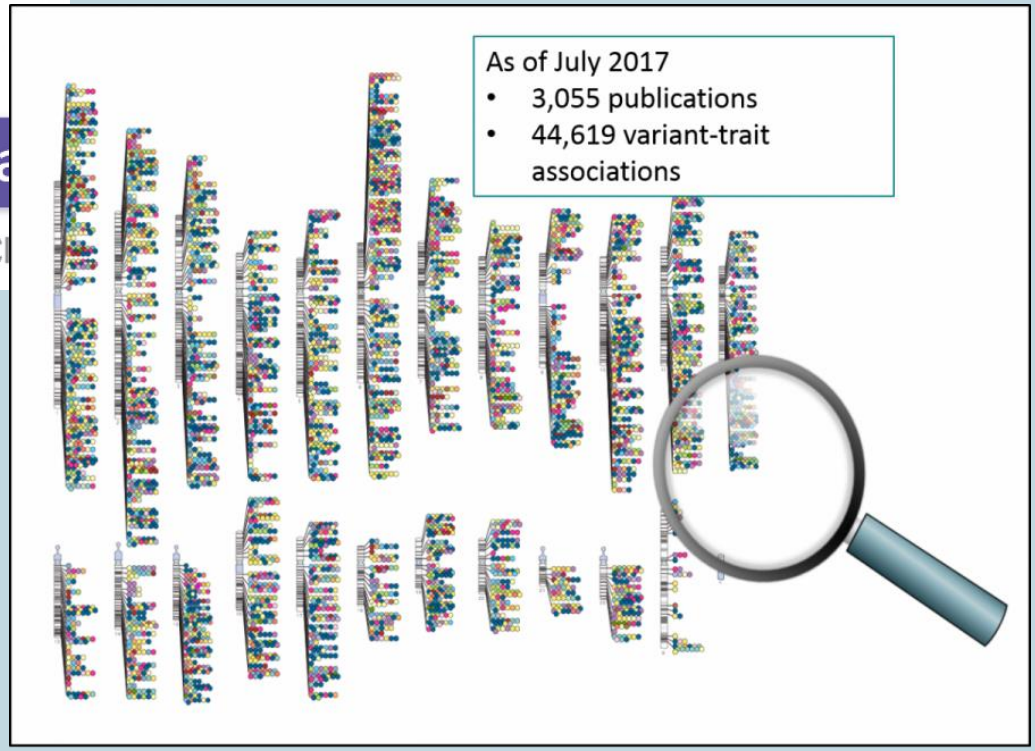
International datasharing for rare disease research

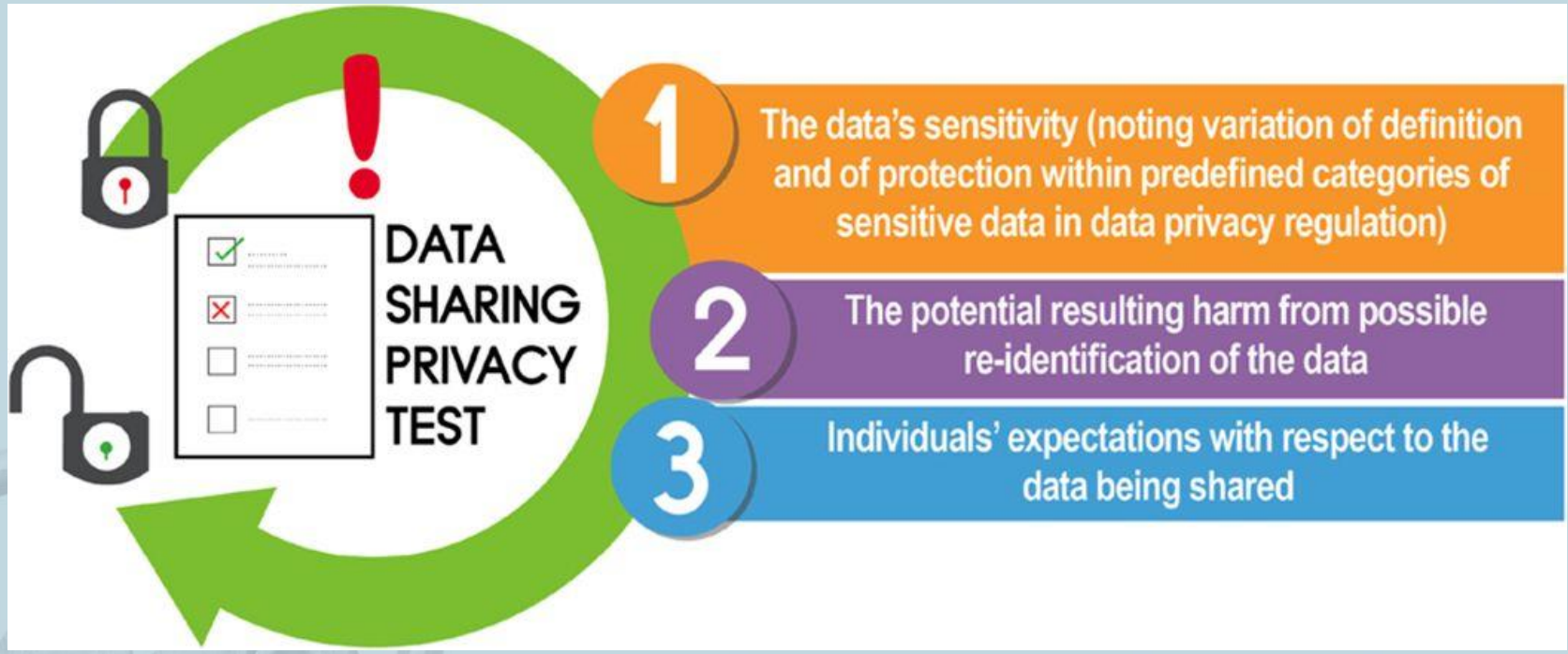




International datasharing for complex genetics & pharmacogenetics



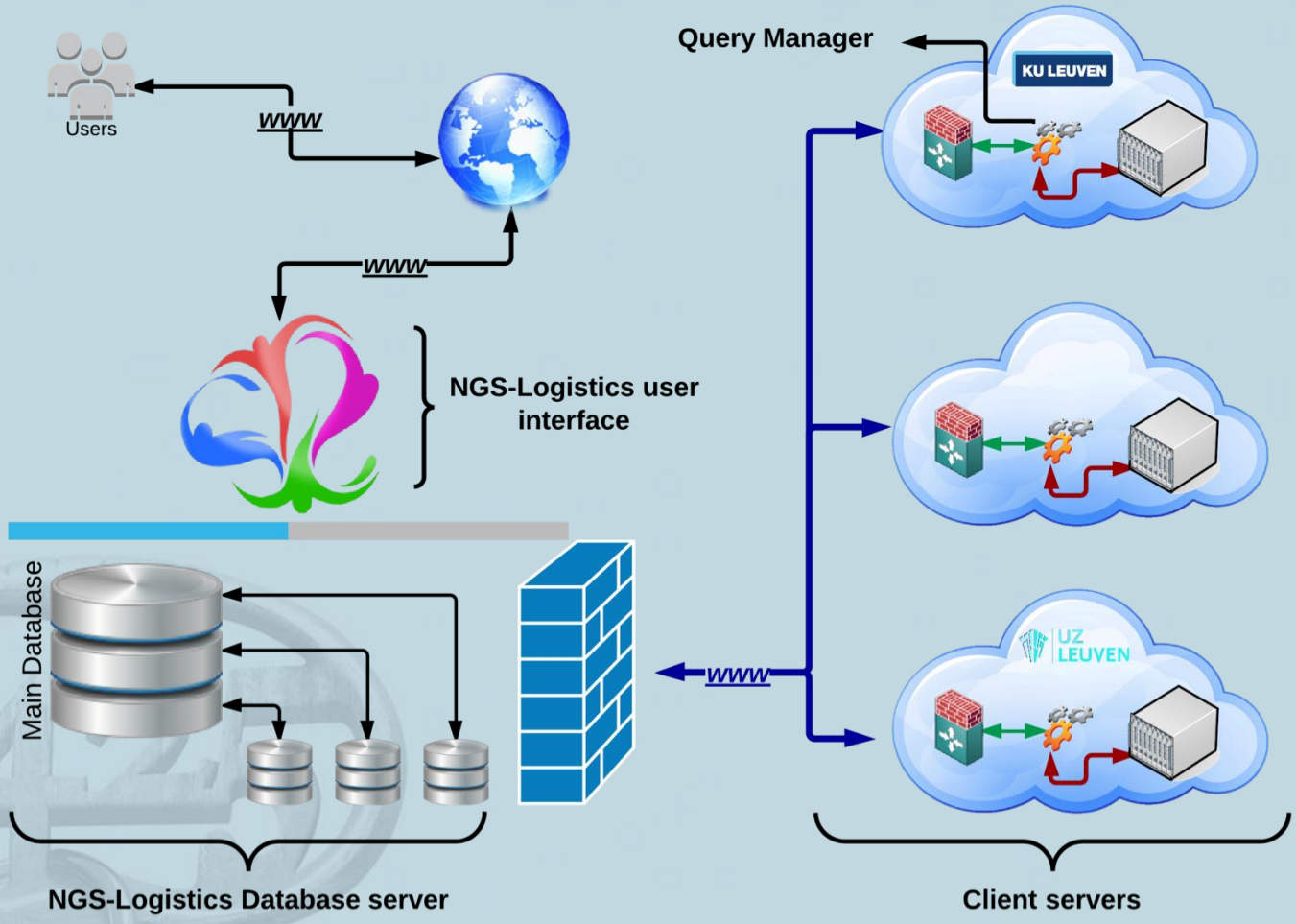



DATA
SHARING
PRIVACY
TEST
1
The data's sensitivity (noting variation of definition and of protection within predefined categories of sensitive data in data privacy regulation)
2
The potential resulting harm from possible re-identification of the data
3
Individuals' expectations with respect to the data being shared

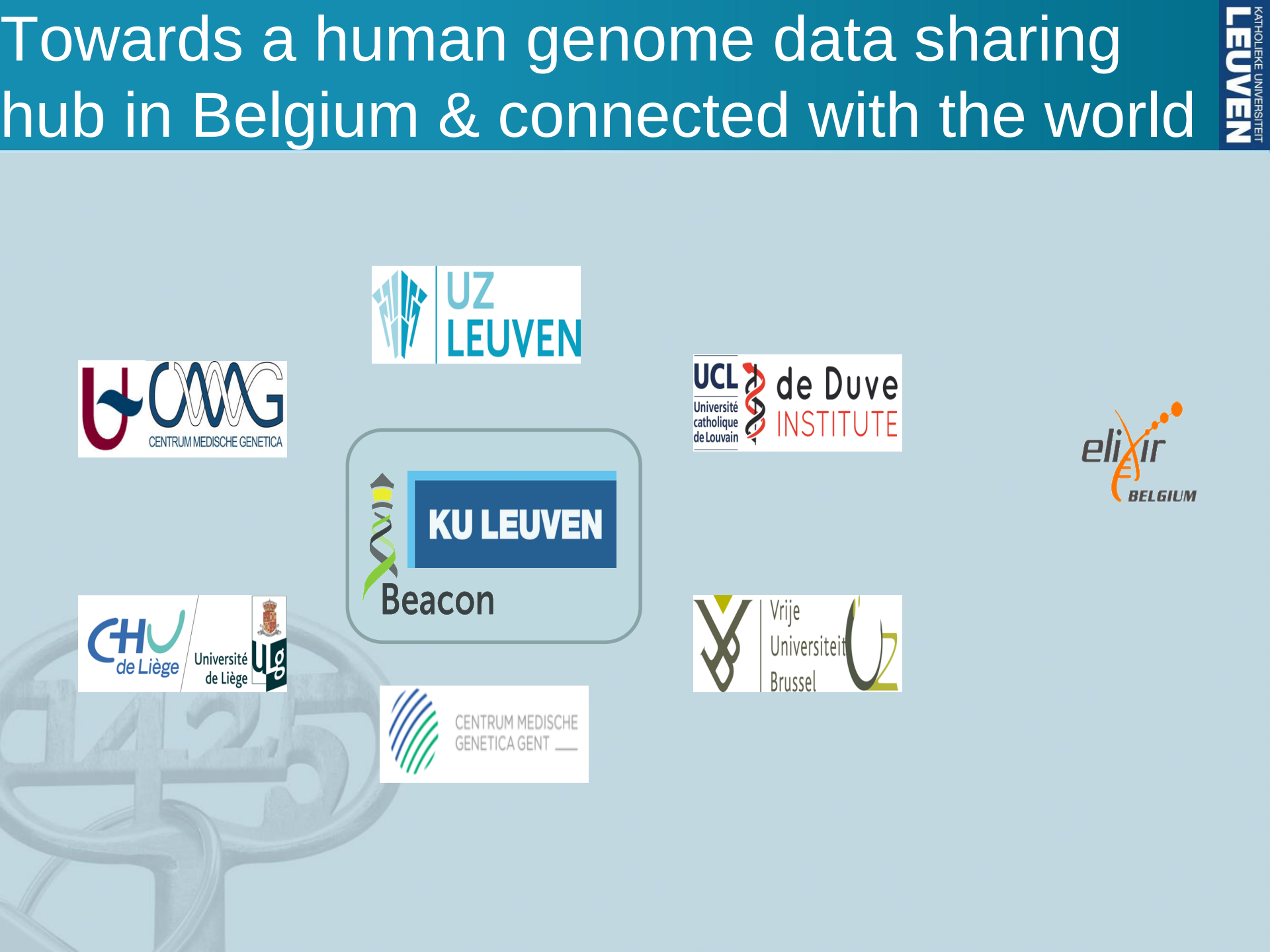
Solutions to avoid de-anonymisation

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

Federated analytics



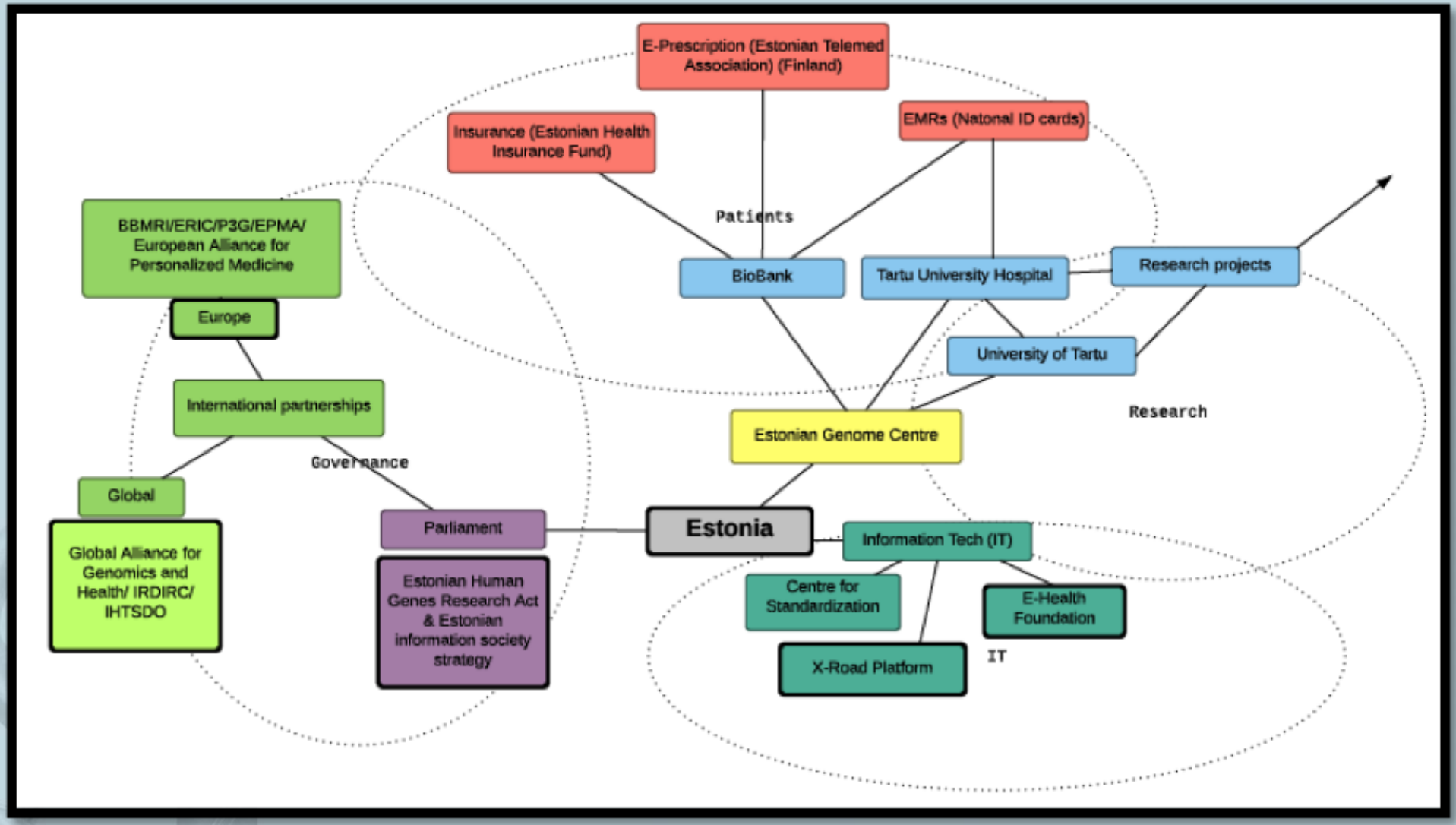
Towards a human genome data sharing hub in Belgium & connected with the world



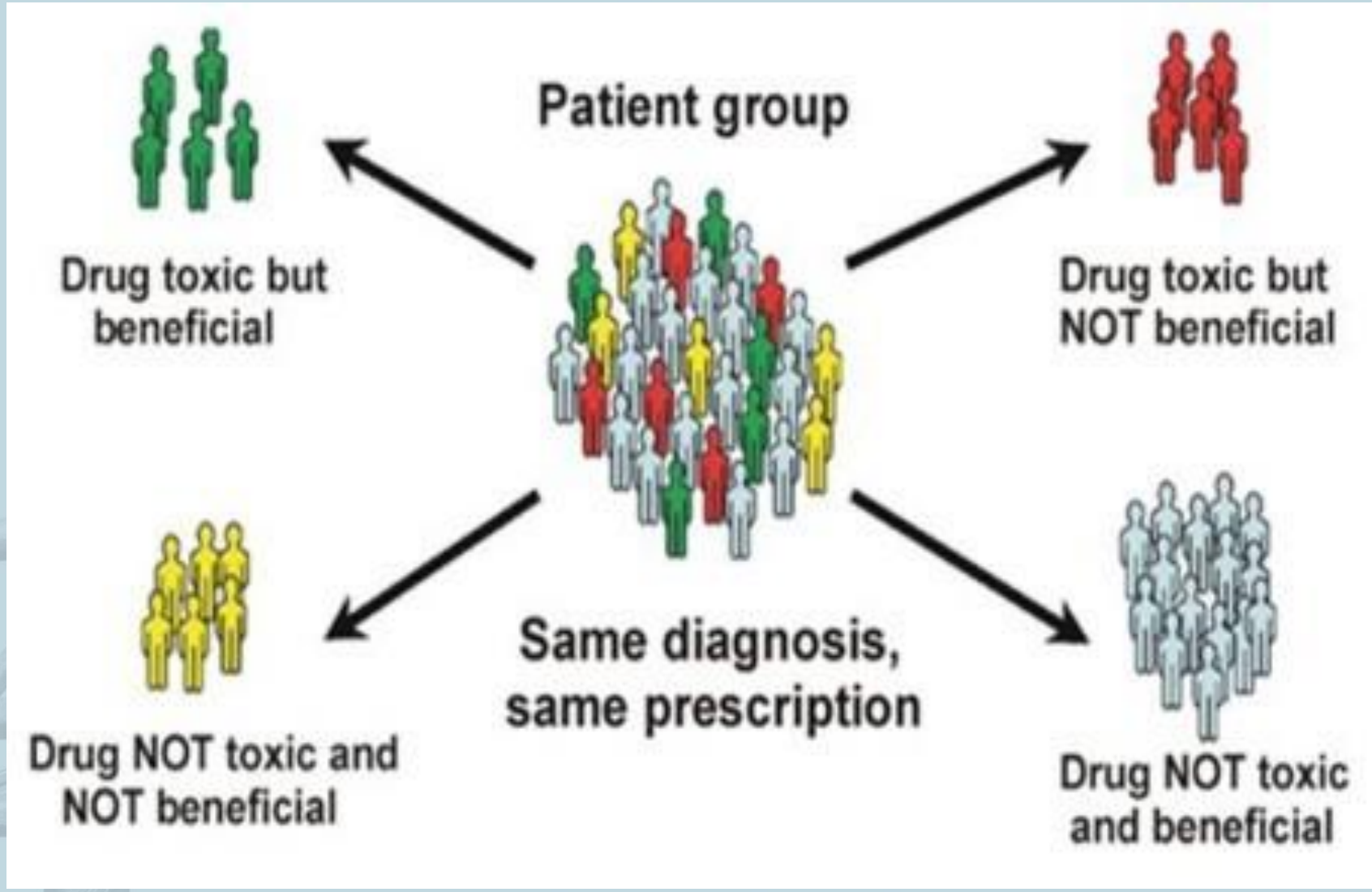
Barriers on the road towards (genomic) personalized medicine (3)

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
Odds ratio ≥3.0		
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
Odds ratio ≥4.0		
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
Odds ratio ≥5.0		
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

Khera *et al.* Nature Genetics 2018

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

Khera *et al.* Nature Genetics 2018

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)

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Strengthening genetics

Genetic centra at the forefront of personalised medicine

- Following a medical odissay, 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 neeed 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

Huidig ziekenhuis

Nieuwbouwprojecten ziekenhuis

Huidig O&N

Toekomstig O&N

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

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

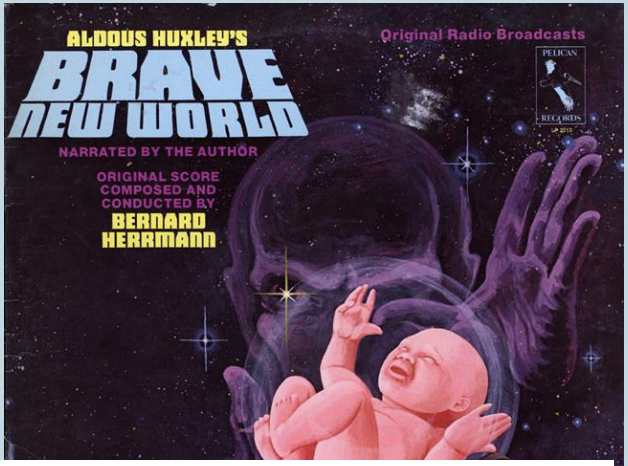
Care framework is important!

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 S
Obsess About My I
From a Decade Ag
LORI GOTTLIEB

The Futility of Try
Prevent More Sch
Shootings in Amer
BARBARA BRADLEY HA

The Enduring App
the Fairy-Tale We

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KU LEUVEN

Leuven Institute for human Genomics and Society

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

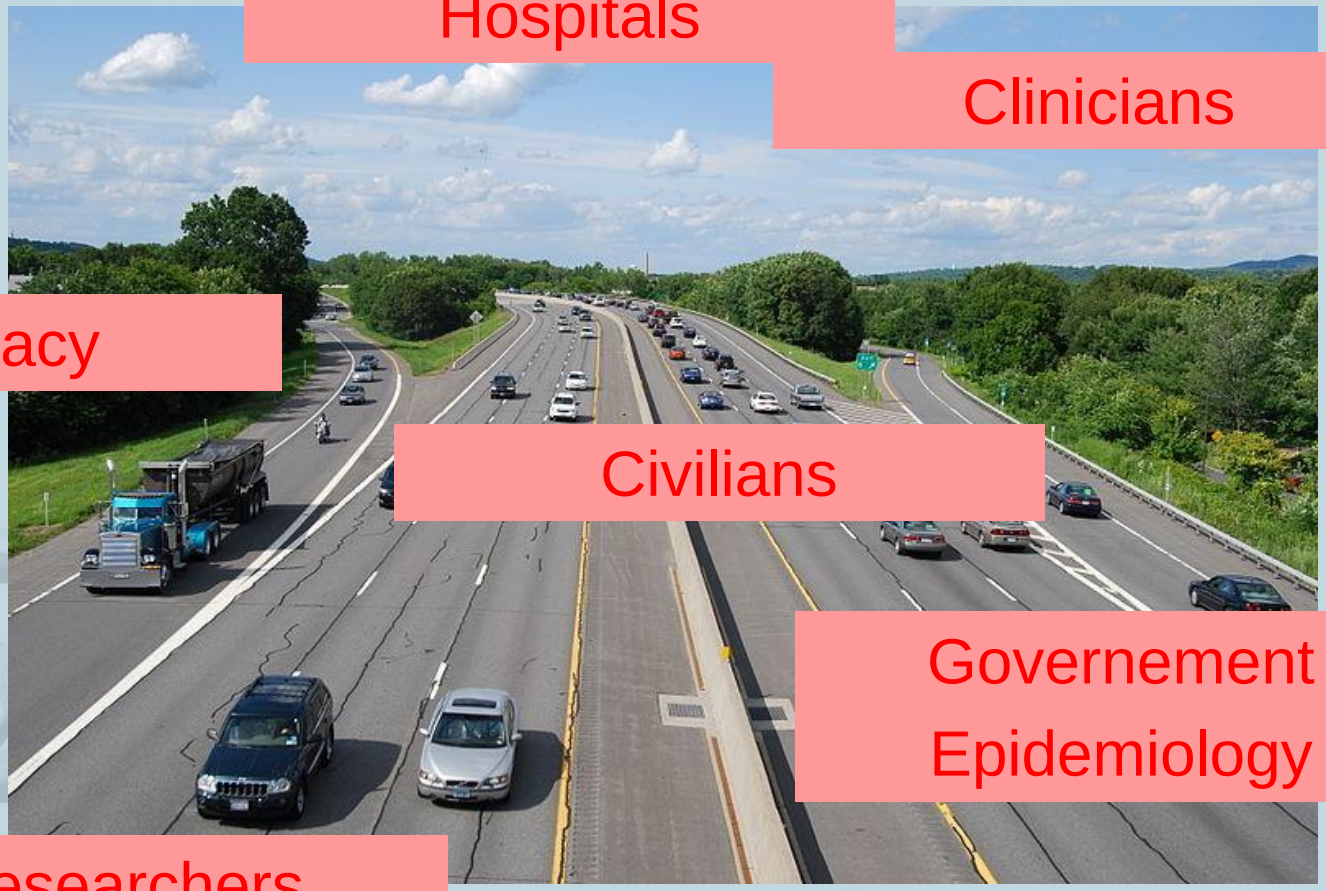
Who is in charge?

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!!



Hospitals

Clinicians

Pharmacy

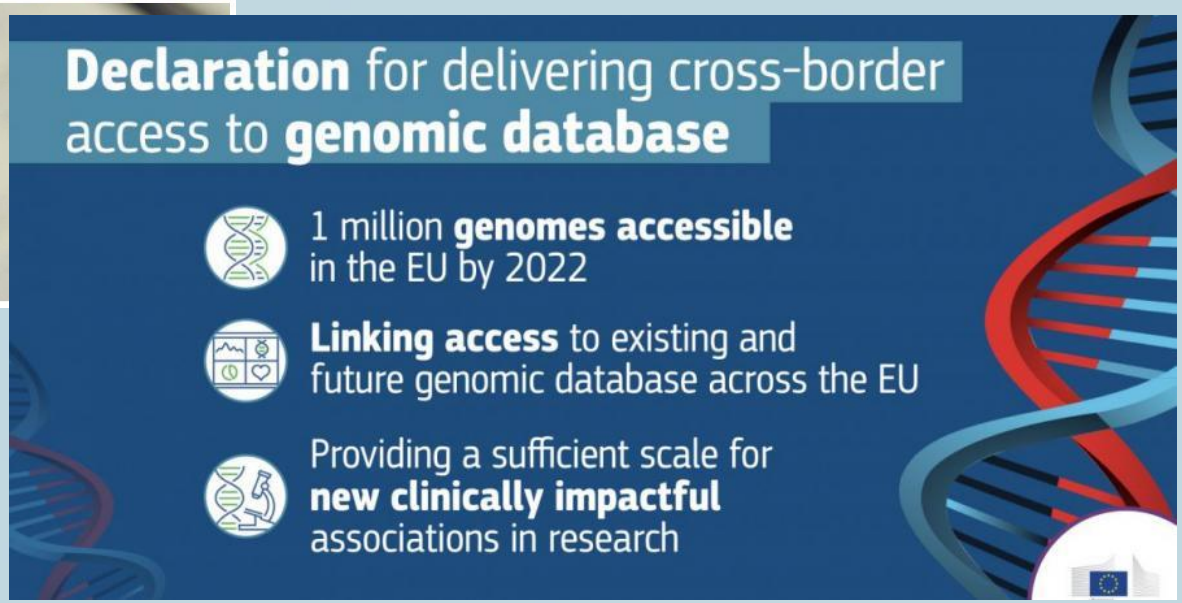
Civilians

Governement

Epidemiology

Researchers

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



BUT

741 M Genome Project!