Personalised medicine: Needs & barriers

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**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 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

- 1990: 5K
- 2000: 100K
- 2006: 100M
- 2010: 100G
- 2016: 1T
- 2018: 6T

Costs:
- 1990: 7000€
- 2000: 700€
- 2006: 70€
- 2010: 7€
- 2016: 0.7€
- 2018: 0.07€
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?
incidental findings:

"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 per Genome

$100M

$10M

$1M

$100K

$10K

$1K

National Human Genome Research Institute

genome.gov/sequencingcosts

Moore's Law

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

**Analytic cost per genome**

Including 1 month of storage

- Amazon: 14.30 €
- Google: 14.01 €
- WD P100: 4.62 €
- WD X100: 4.61 €
- WD P100 3SEO: 4.62 €
- WD X100 3SEO: 4.56 €

**Analytic cost per genome**

Including 60 months of storage

- Amazon: 65.84 €
- Google: 50.82 €
- WD P100: 17.55 €
- WD X100: 16.56 €
- WD P100 3SEO: 17.22 €
- WD X100 3SEO: 13.49 €
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
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 Schampelaere

Ons land gaat het DNA van tienduizenden Belgen in kaart brengen, voor een omwenteling in de geneeskunde.
Ons land is van plan meer dan 10 miljoen euro te investeren om het DNA van tienduizenden Belgen in kaart te brengen. Een onderzoeks domein dat de jongste jaren in een sterk uitgebreide groei is.
International datasharing for rare disease research

ClinGen’s Critical Questions

- Is this gene associated with a disease? (Clinical Validity)
- Is this variant causative? (Pathogenicity)
- Is this information actionable? (Clinical Utility)

Building a Genomic Knowledge Base

- ClinVar & Other Resources

Improved Patient Care Through Genomic Medicine

Matchmaker Exchange

- Gene Matcher
- Cafe Variome
- Decipher
- Undiagnosed Disease Network
- UDN

Institutions and Resources

- BROAD
- PEER
- RD Connect
- GENESIS/GEM.app
- Miami
- PEER
- GIMAPP
International datasharing for complex genetics & pharmacogenetics

As of July 2017
- 3,055 publications
- 44,619 variant-trait associations
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
Creating a longitudinal/societal based learning environment
An existing model: Estonia!
A biobank is a requirement for life-long learning for pharmacogenomics
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 $\rightarrow$ hypercholesterolemia mutation
  – Type 2 diabetes $\rightarrow$ 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

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?
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 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!
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, 2016
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

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!