Biomarkers in Personalized Health(care): time for quality, not quantity

BBMRI BIOS symposium

Opening up the BBMRI genomics infrastructure in the Netherlands

21 September 2016, Amsterdam

Prof Alain van Gool

Radboudumc university medical center

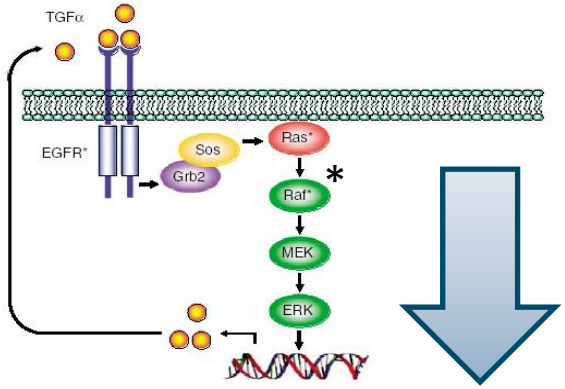
TNO innovation for life

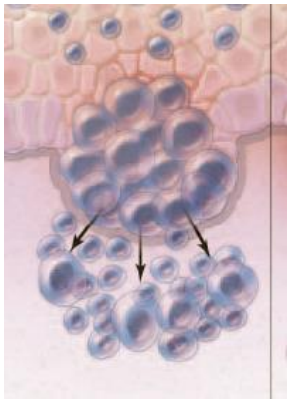
DTL

eatris

European infrastructure for translational medicine

A short story: Personalized medicine in melanoma



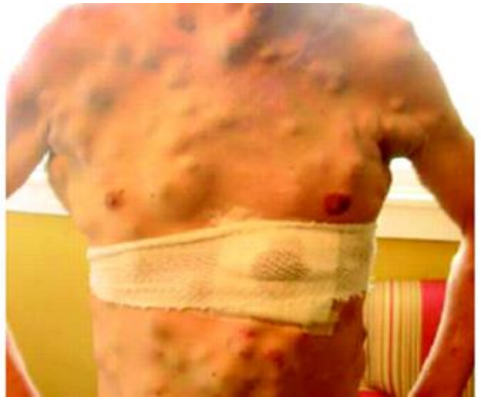


B-RAF^{V600E} mutation

Strong growth of cell

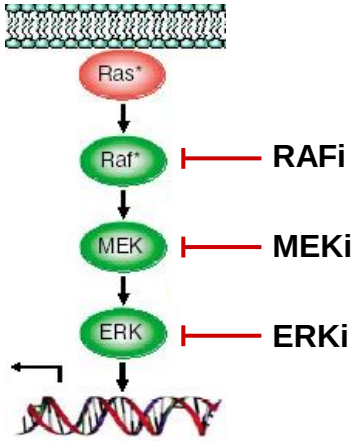
Growth of tumor

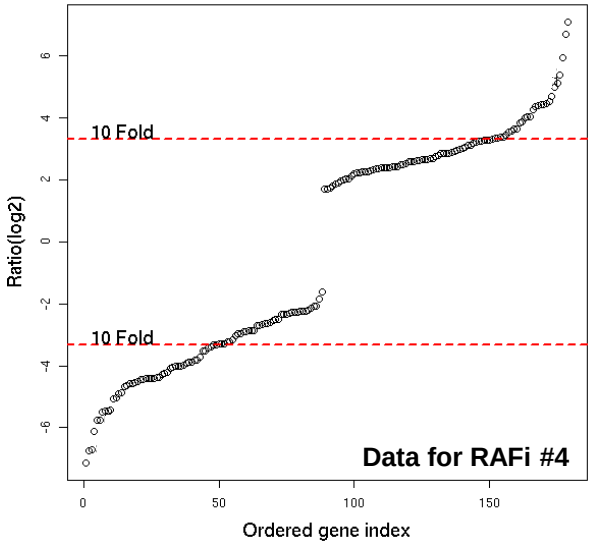
- B-RAF^{V600E} cells always grow and become cancer cells
- RAF inhibitors will block pathway, block cell growth and inhibit cancers that have a B-RAF^{V600E} mutation
- 60% of melanoma patients have B-RAF^{V600E} mutation
- Basis for a personalized medicine !

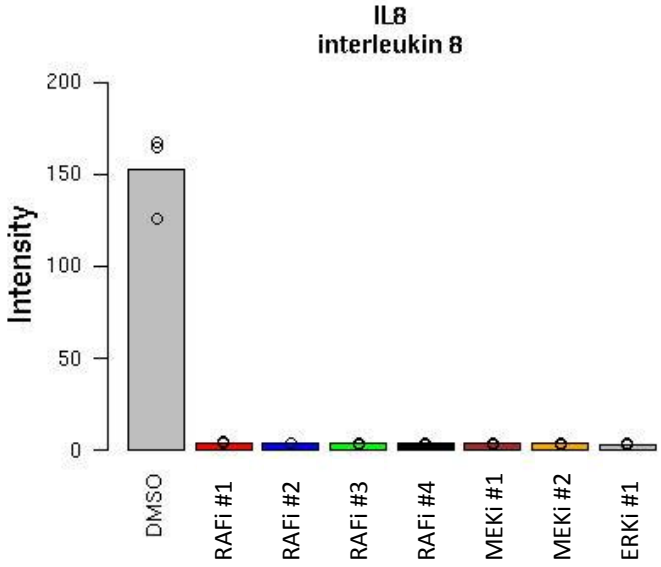


Biomarkers to support clinical development

- Within Schering-Plough 4 Lead Optimisation programs in ERK pathway (2009)
- Need for blood-based biomarker that indicated downstream effects of drugs:
  - Inhibition ERK pathway (pharmacodynamic)
  - Tumor inhibition (efficacy)
- Extensive transcriptomics profiling: **IL-8** as promising candidate biomarker

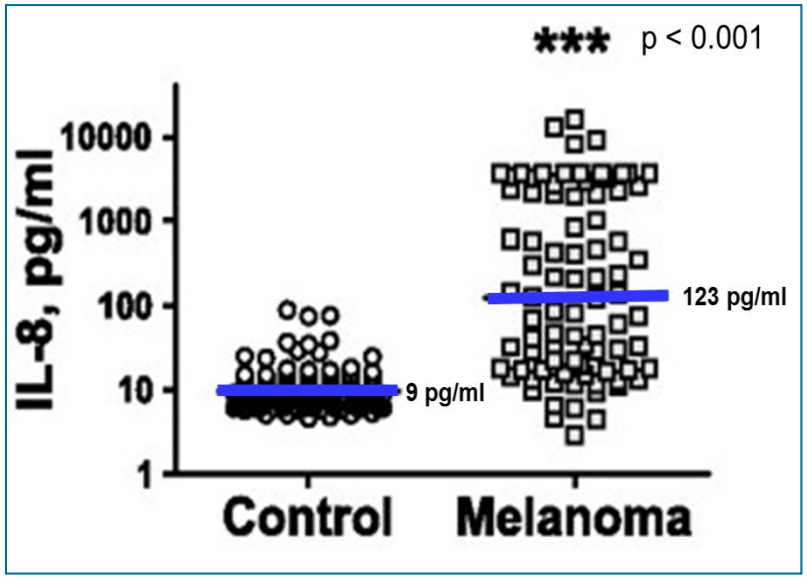






Validation study to confirm IL-8 in melanoma

Literature



Cancer Therapy: Clinical

Multiplex Analysis of Serum Cytokines in Melanoma Patients Treated with Interferon-α2b

Zoya R. Yurkovetsky,[1,2] John M. Kirkwood,[1,2] Howard D. Edington,[1,3] Adele M. Marrangoni,[1] Lyudmila Velikokhatnaya,[1] Matthew T. Winans,[1] Elieser Gorelik,[1,4,5] and Anna E. Lokshin[1,2]

{Yurkovetsky, et al. Clin Cancer Res, 2007}

Objectives:

- Confirm elevated IL-8 in melanoma
- Develop IL-8 assays for clinical use

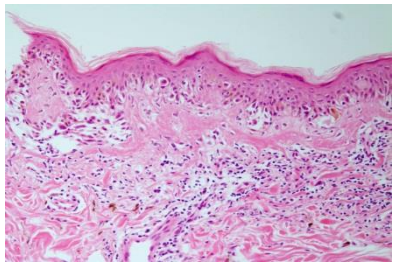
Organon Schering-Plough MERCK

Validation study to confirm IL-8 in melanoma

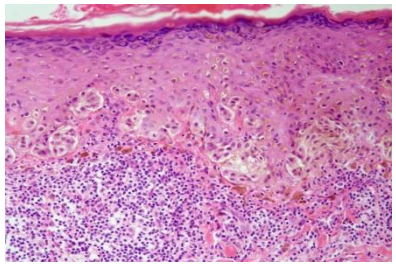
59 melanoma samples (tumor tissue (ffpe) + matching serum & plasma, stage I-IV, from two independent biobanks) + 40 healthy serum & plasma samples

1. **Genetic analysis** for $BRAF^{V600E/D}$ mutation in genomic DNA from tissue samples — **partial**
2. **IL-8 mRNA analysis** in tissue samples by in situ hybridisation using bDNA probes (multiplexing with 12 ERK pathway response transcripts) — **OK**
3. **IL-8 protein analysis** in tissue samples by immunohistochemistry (in parallel with 4 other ERK pathway response proteins, Ki67, Tunnel) — **OK**
4. **IL-8 protein analysis** in matching plasma and serum by IL-8 immunoassay (3 formats: ELISA, Luminex, Mesoscale; singleplex and multiplex) — **?**

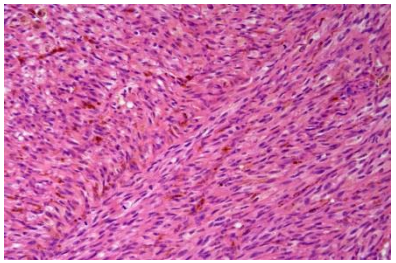
H&E staining; 20x



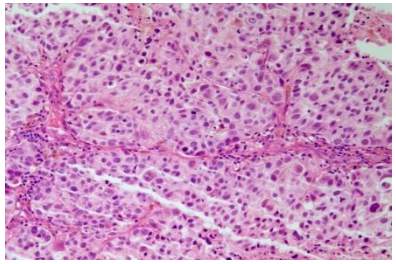
Stage 1



Stage 2



Stage 3

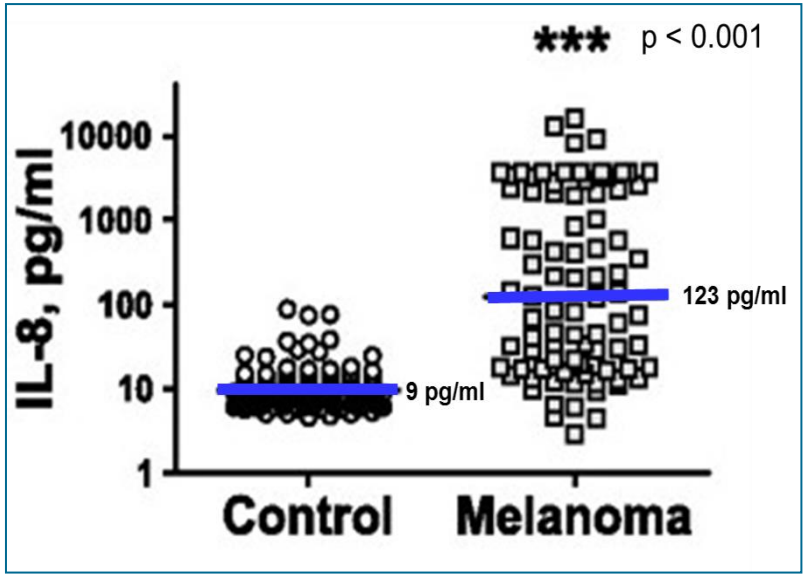


Stage 4

Organon Schering-Plough MERCK

Validation study to confirm IL-8 in melanoma

Literature



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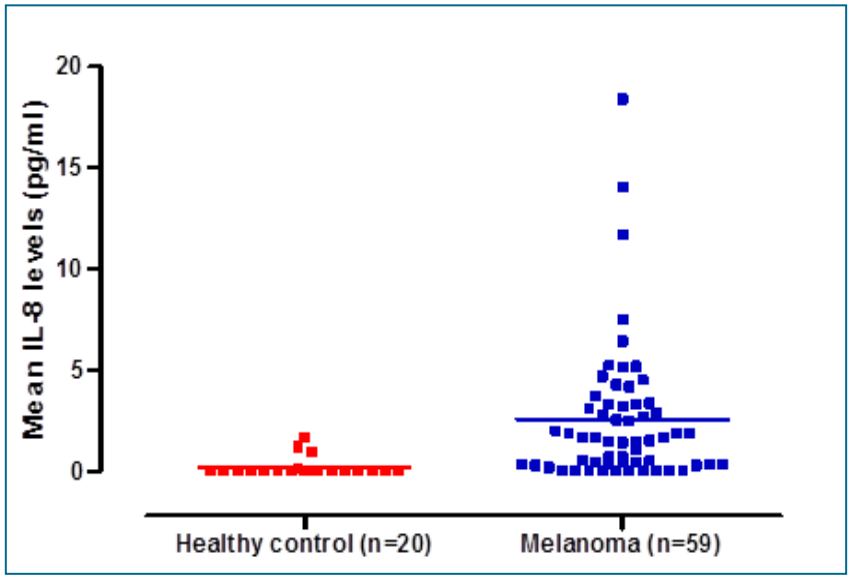
{Yurkovetsky, et al. Clin Cancer Res, 2007}

Own data



*{**Unpublished**, 2010}*

(6 months, 4 fte, USD 1.000.000)

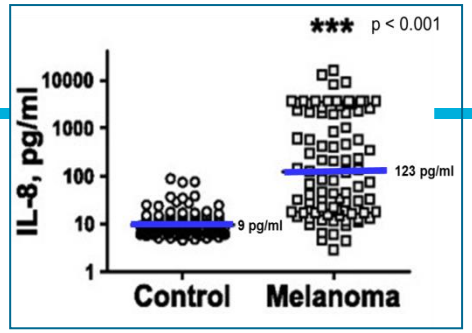
Cause?

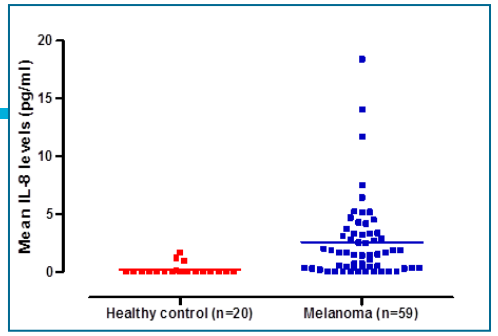
Organon Schering-Plough MERCK

Lessons learned?

Source: Youtube - Burn after reading ending}

Lessons learned?





Particularly for this case:

1. Know sample history
   - IL-8 protein appeared sensitive to freeze-thawing

2. Know all relevant information from the source (patient)
   - Tumor load may be too low for our patients

3. Do these type of expensive validation studies together !
   - For most pharma, biomarkers are precompetitive tools

We need a biomarker community that shares knowledge, ambitions, capabilities, successes, failures and best practice.

Organon Schering-Plough MERCK

Alain's path 1989-now

Universiteit Leiden

Erasmus MC
Universitair Medisch Centrum Rotterdam

Imperial Cancer Research Fund

Organon

Schering-Plough

Radboud Universiteit Nijmegen

MERCK
Be well

Radboudumc

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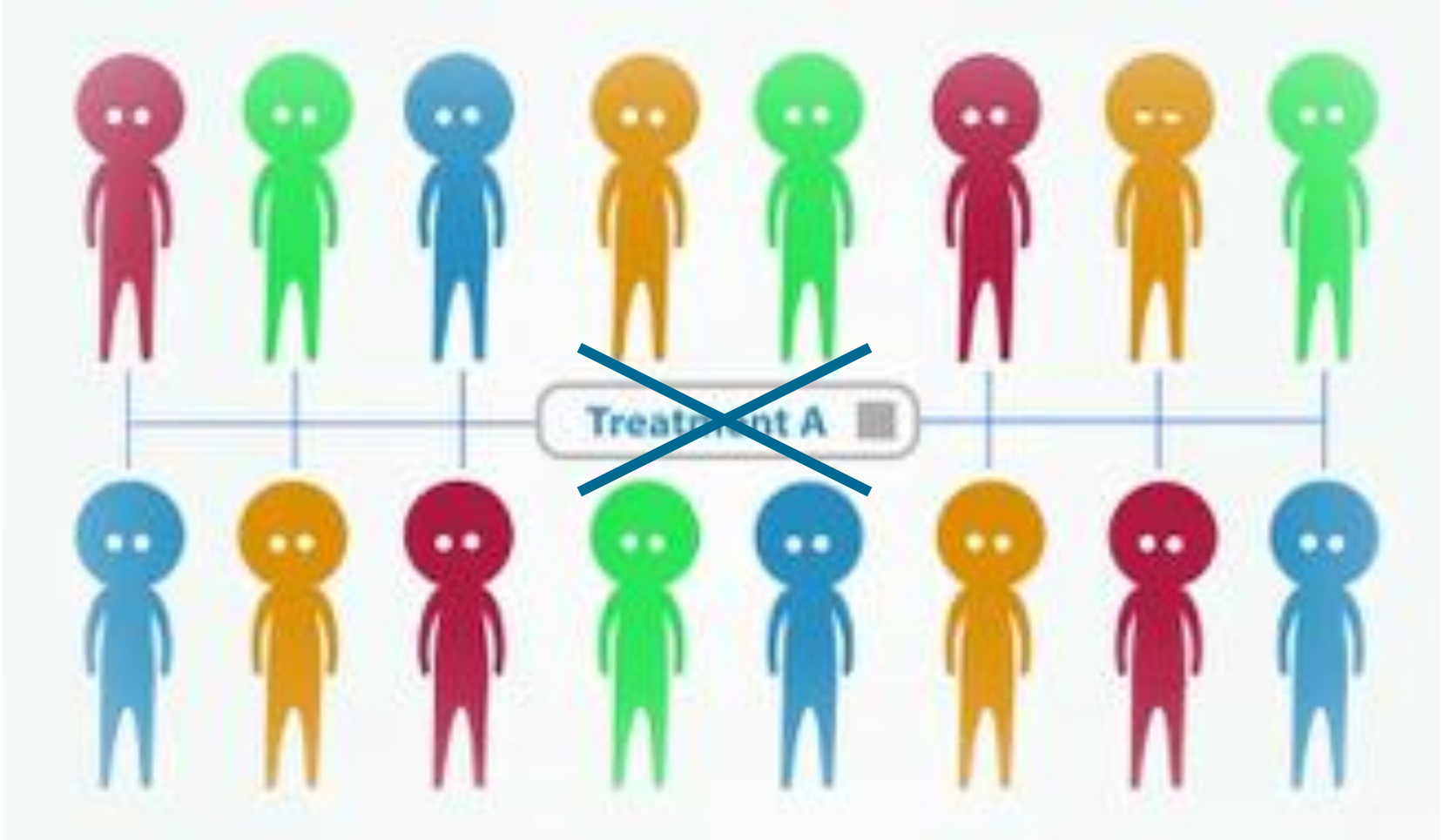
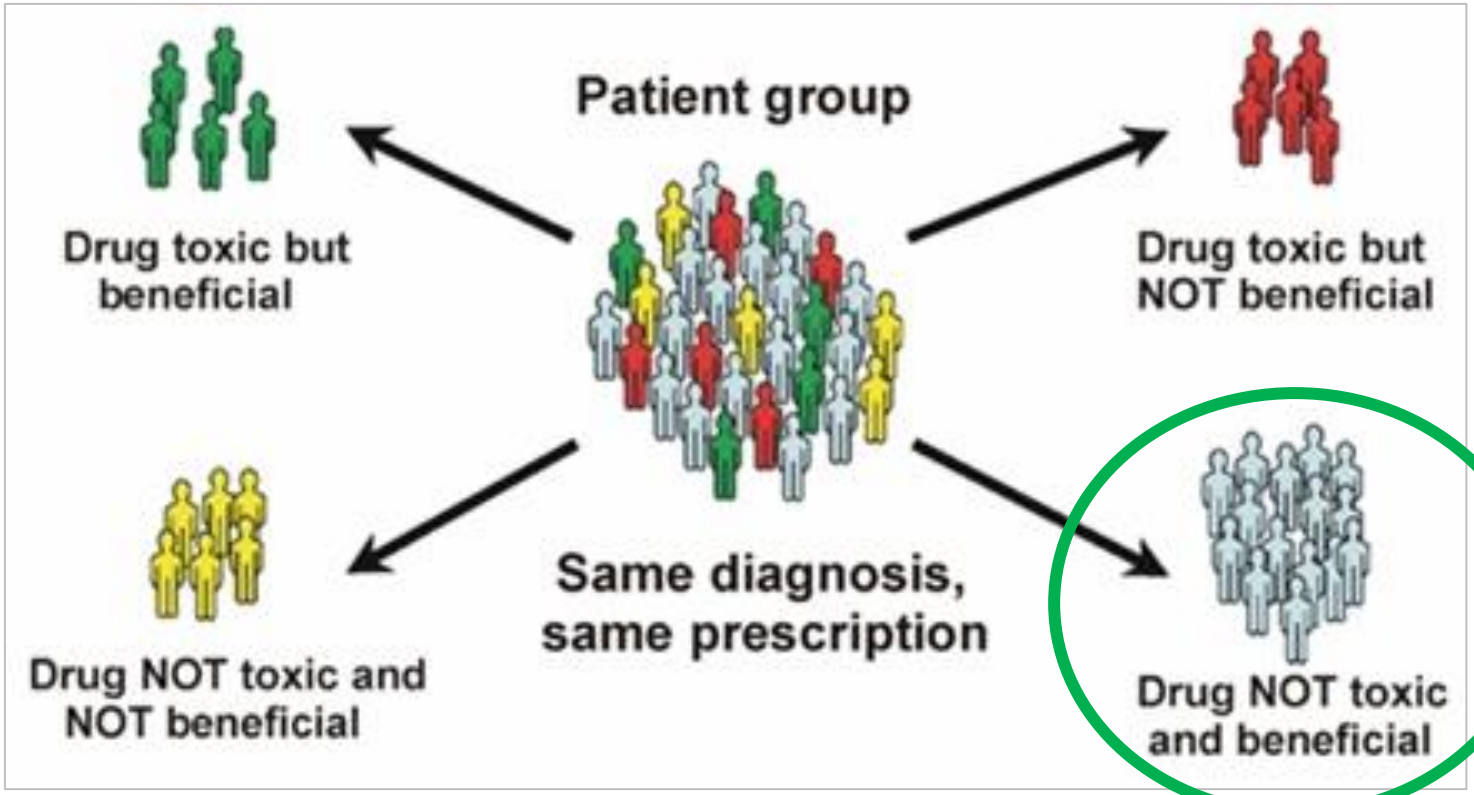
Consider individual differences in life science research



Principle of Personalized Medicine



Source: Chakma, Journal of Young Investigators, 16, 2009

- The **right drug** for **right patient** at **right dose** at **right time**
- Molecular biomarkers as key drivers of patient selection
- = Precision medicine or Targeted medicine

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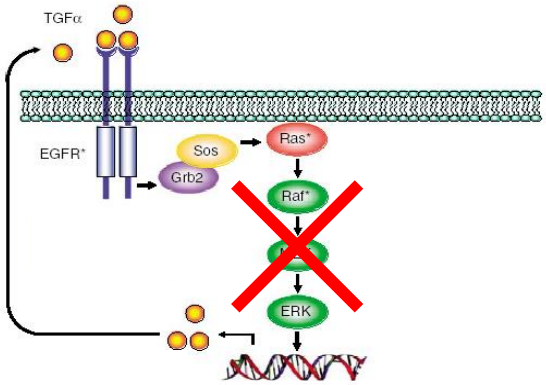
Personalized medicine in melanoma

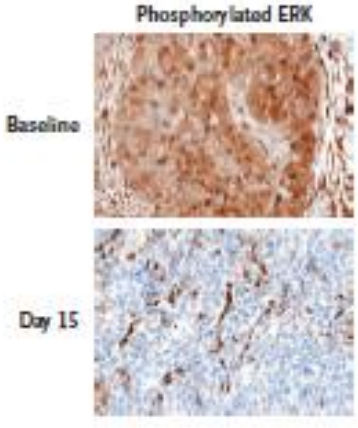
ZELBORAF (vemurafenib) tablets

B-RAF inhibitor

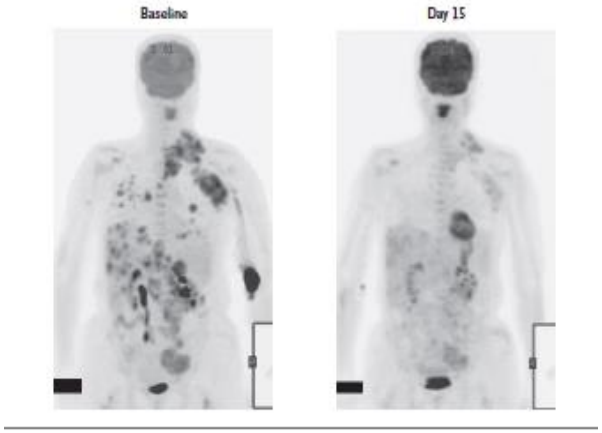
Treat patients with B-RAF^{V600E} mutation



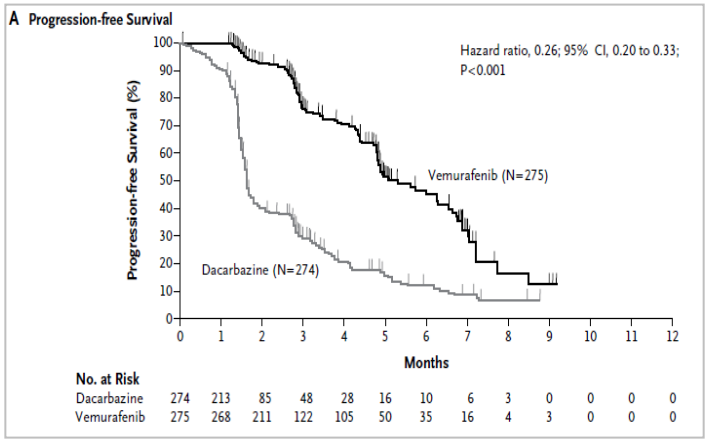
Inhibit growth of cell



Cells stop growing



Tumors disappear



Patients live longer

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Emerging Personalized / Precision / Targeted Medicine

2010:

5% of drugs in pipeline had companion diagnostic biomarker test

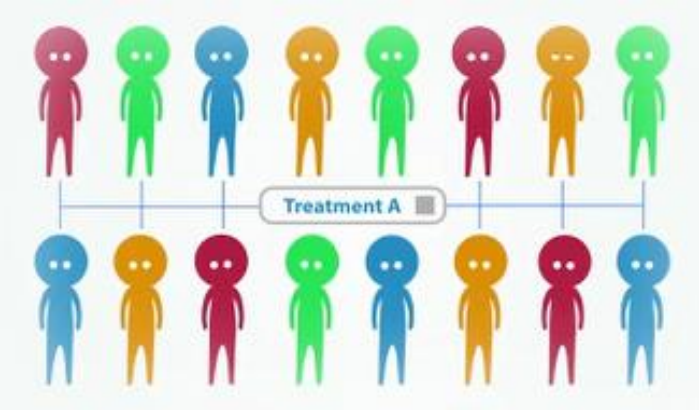
2015:

AstraZeneca 80%

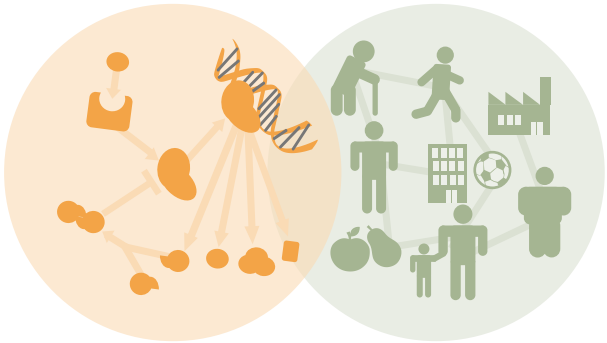
Roche 50%

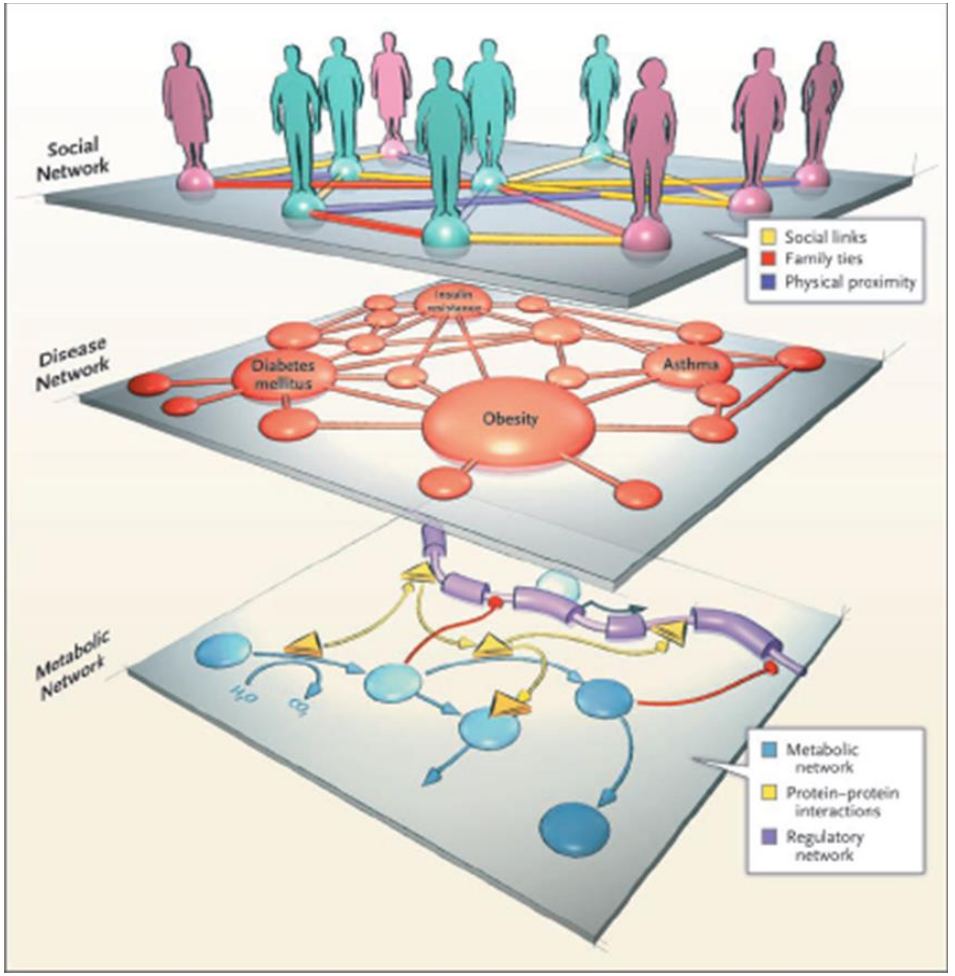
Optimal Personalized / Precision / Targeted Medicine

Moving to personalized health(care)



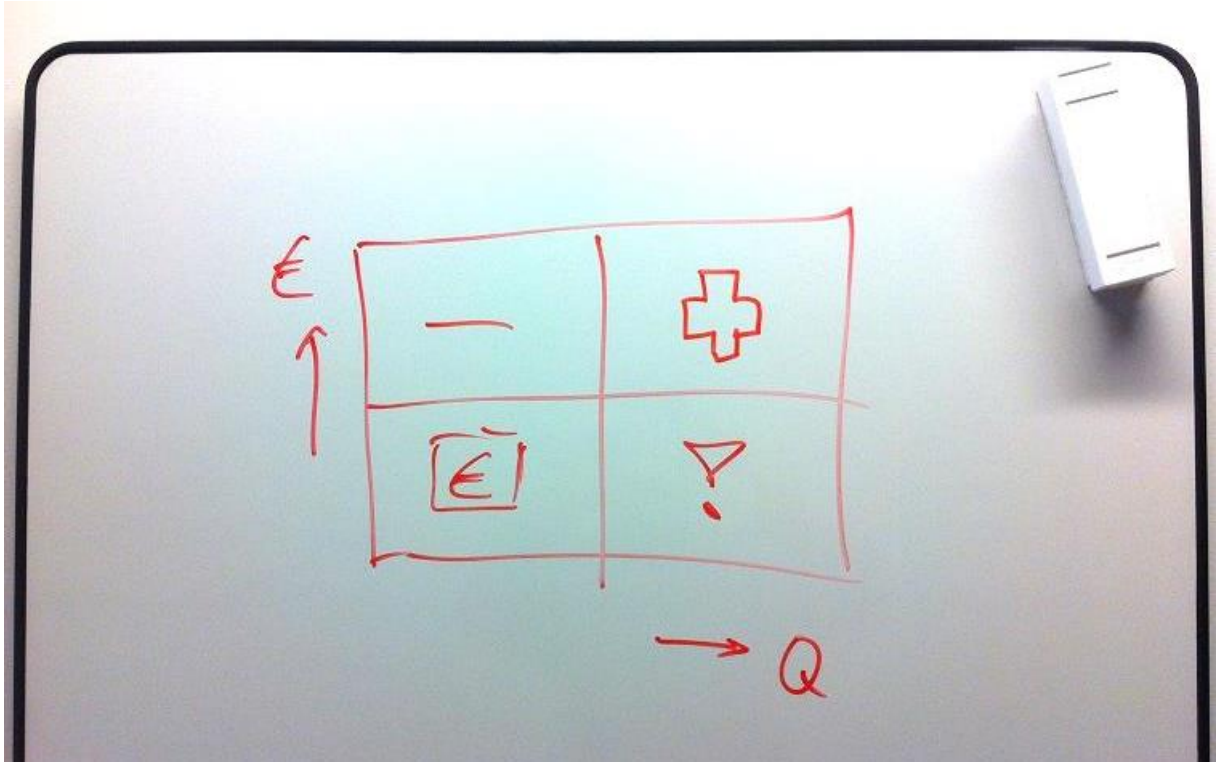
- People are more than linear pathways
- Different systems and networks
- Different risk factors
- Different preferences





{Source: Barabási 2007 NEJM 357; 4}

Societal need in efficient personalized health(care)



{Source: prof Jan Kremer}

Towards cost effective care, less cure

Highest need in efficient personalized health(care)

It's personal !

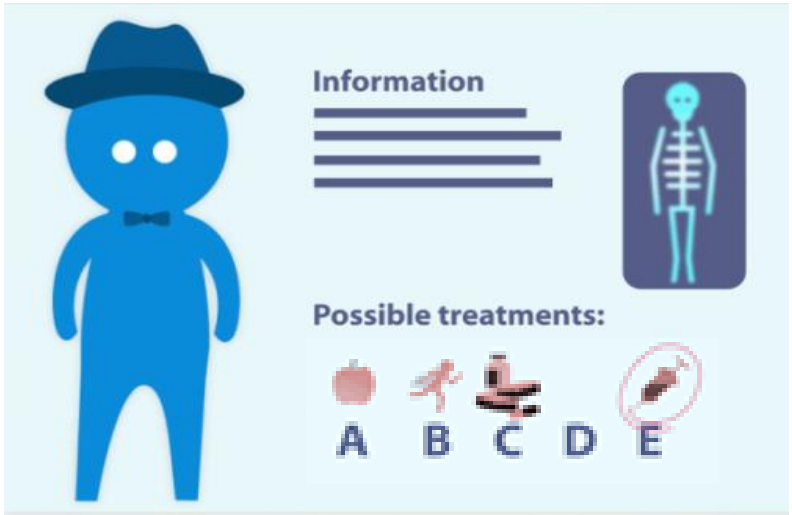
'**I** want to stay healthy.'

'If not, how do **I** get healthy?'

Translating Personalized Health(care) in society

We need a personalized data-driven GPS for health

- Monitor (biomarkers) on background
- Alert when you are at risk
- Advice what to do



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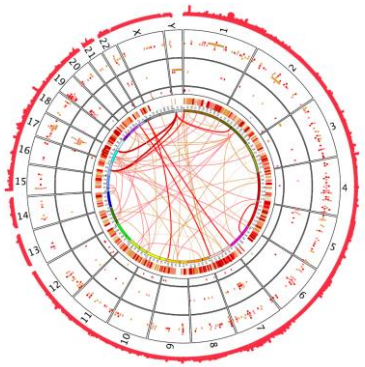
3 key aspects of personalized health(care)

'**I** want to stay healthy. If not, how do **I** get healthy?'

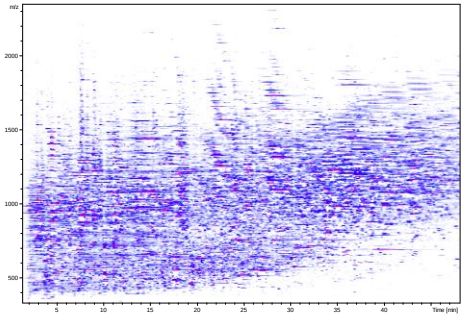
1. What to measure?
2. How much can it change?
3. What should be the follow-up for me?

Exponential technological developments

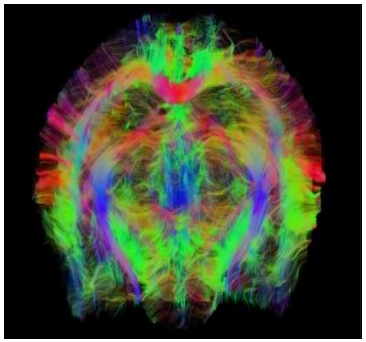
- Next generation sequencing
  - DNA, RNA
  - Risk analysis and therapy selection



- Mass spectrometry
  - Proteins, metabolites
  - Monitoring of disease and treatment effects

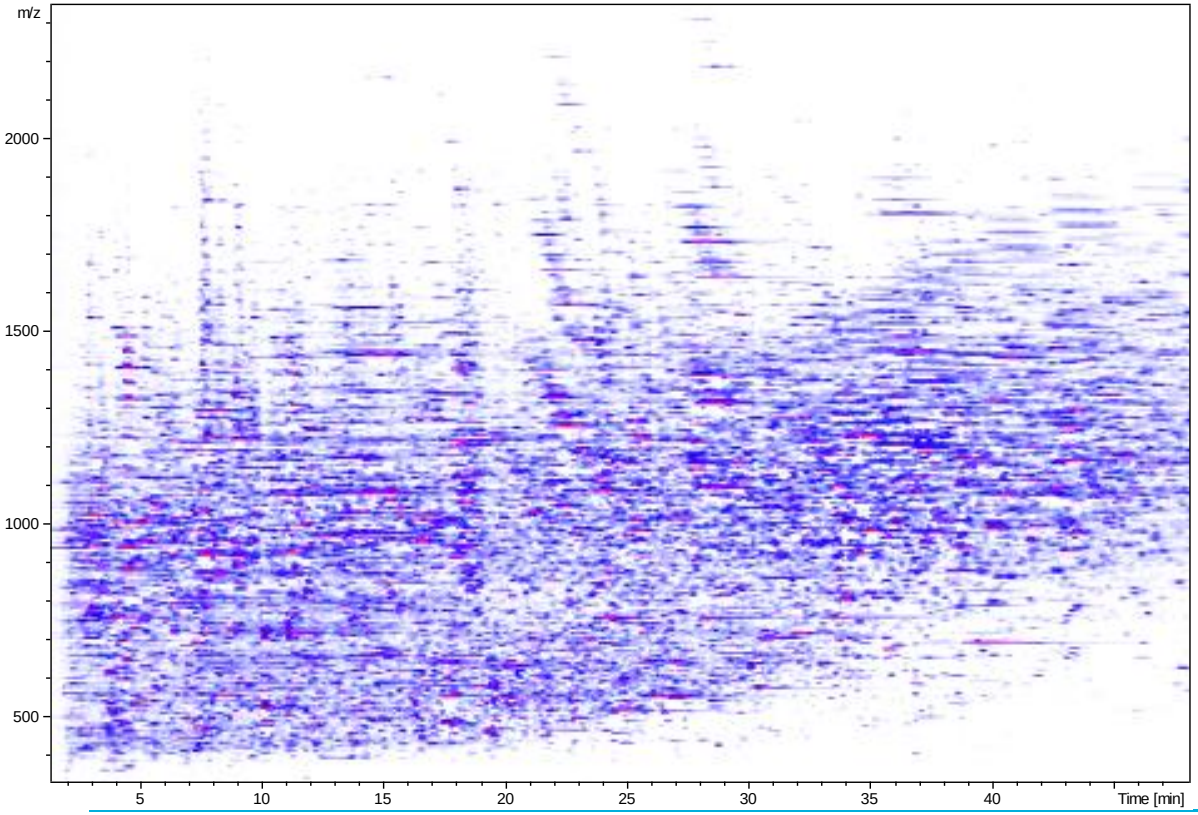


- Imaging
  - Non invasive images, real time
  - Spatial view of intact organs and organisms

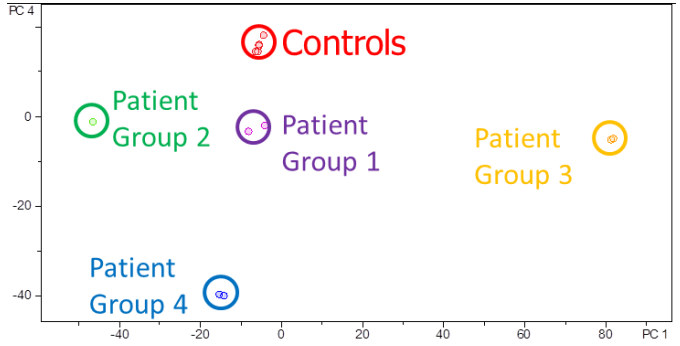


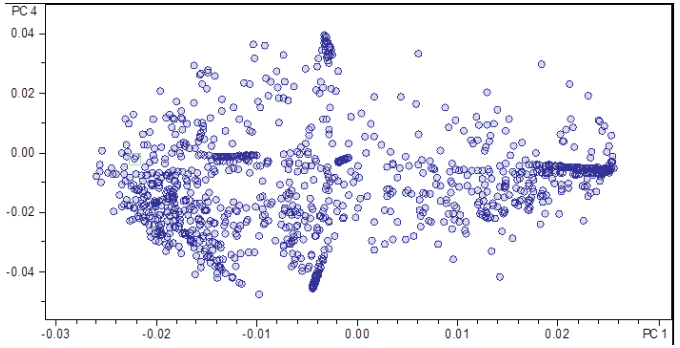
Output from a proteomics biomarker lab

- Mass spectrometry analysis of glycoproteins in human plasma
- 0,05 microliter analysis: detection of 1.000.000 signals in one scan
- ~40.000 peptides of which >80% contain sugar modification
- Diagnose patients and identify new biomarkers



Proof of principle study:





{Translational Metabolic Laboratory, Radboudumc, unpublished data}

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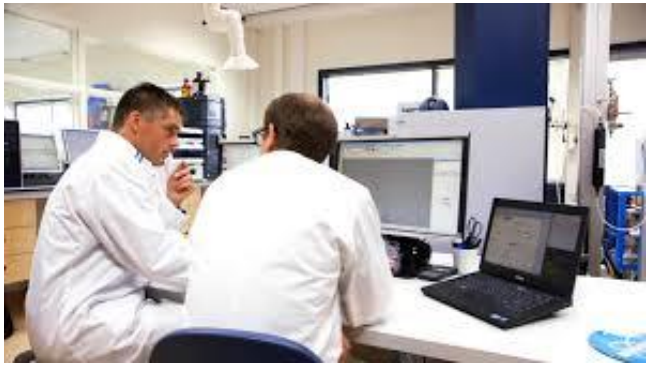
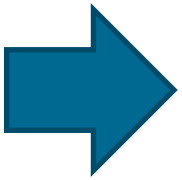
Challenge: translate laboratory to society



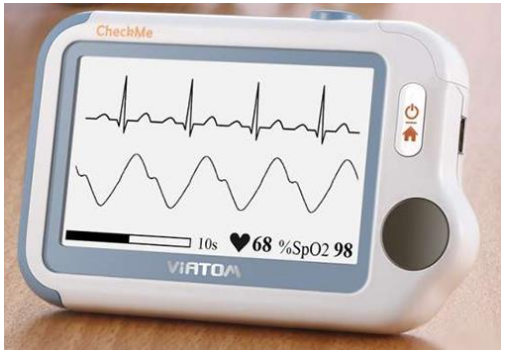
- 1.000.000 molecules per analysis



- Heart beat
- Steps / movement
- Glasses water/coffee

‘Self’ data

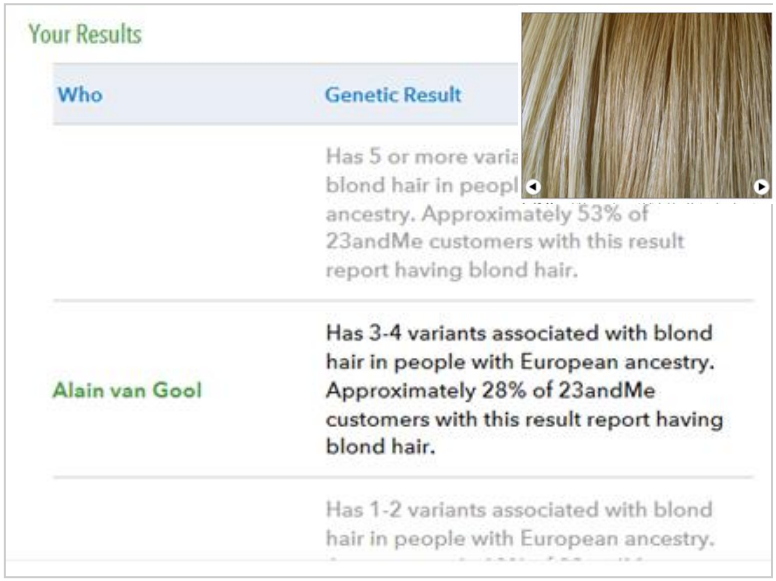
(generated by patients, citizens)



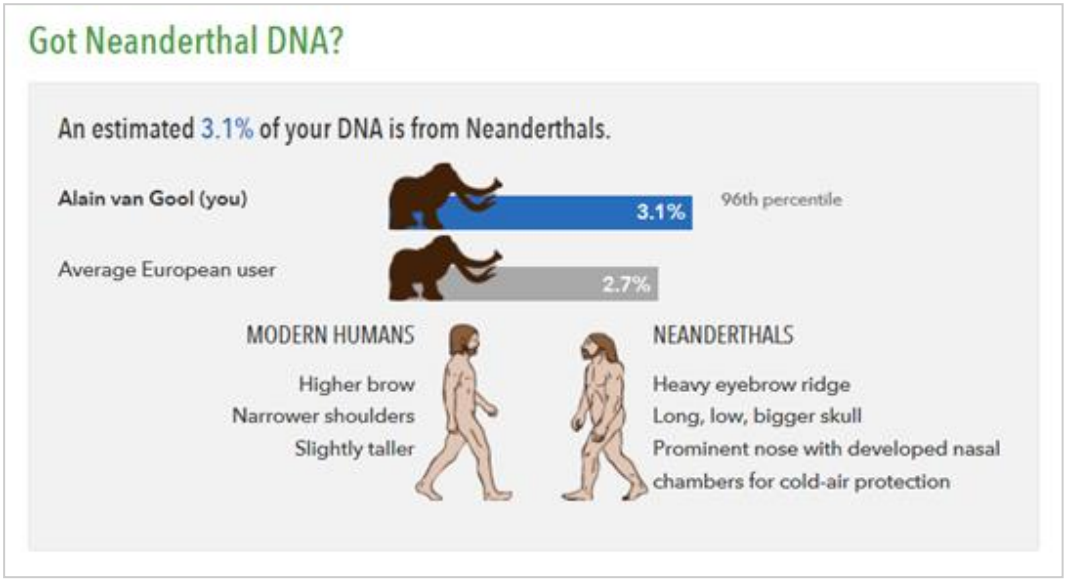
23andMe

Technology Centers
Radboudumc

What does my DNA tell me?



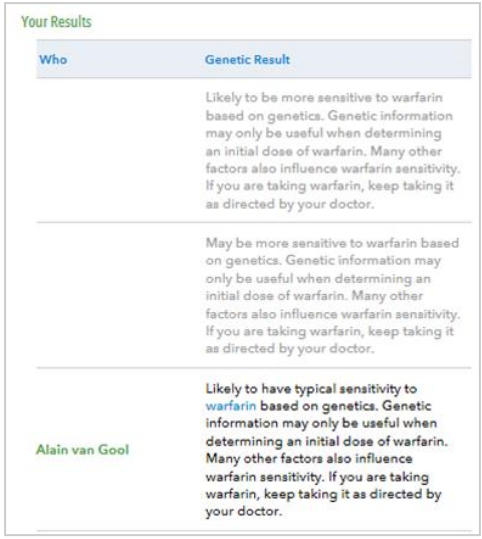
23% chance blond hair



3.1% Neanderthaler DNA

What does my DNA tell me?

Genetic risk lung cancer
→ don't smoke !



No expected adverse reaction
to Warfarin

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App-icalisering

De belangrijkste drager van de digitale revolutie in de gezondheidszorg is de smartphone. De DigitaleZorgGids – waar medische apps worden gereviewd – vermeldt momenteel meer dan 9000 medische apps. De gemiddelde waardering is 1,4 op 5. Kwalitatief is er dus nog wel een slag te maken. **(www.DigitaleZorgGids.nl)**


Big Data
… but not all data is useful data !

Need for optimal quality in health biomarker analyses

theranos

Test, interpret, advice

"Post-traumatic Test Syndrome" ?

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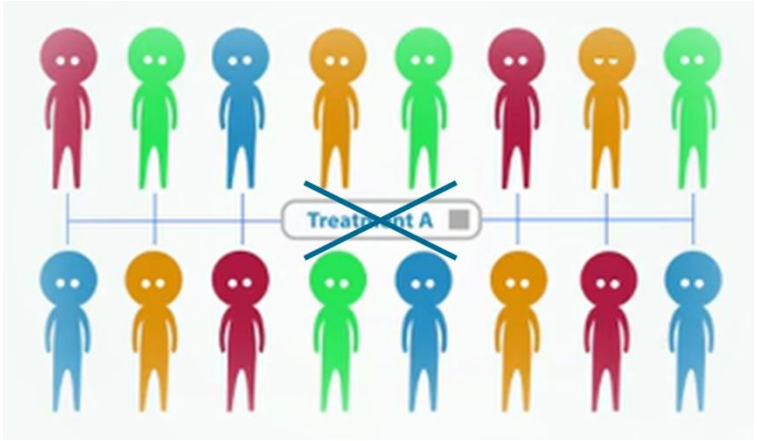
3 key aspects of personalized health(care)

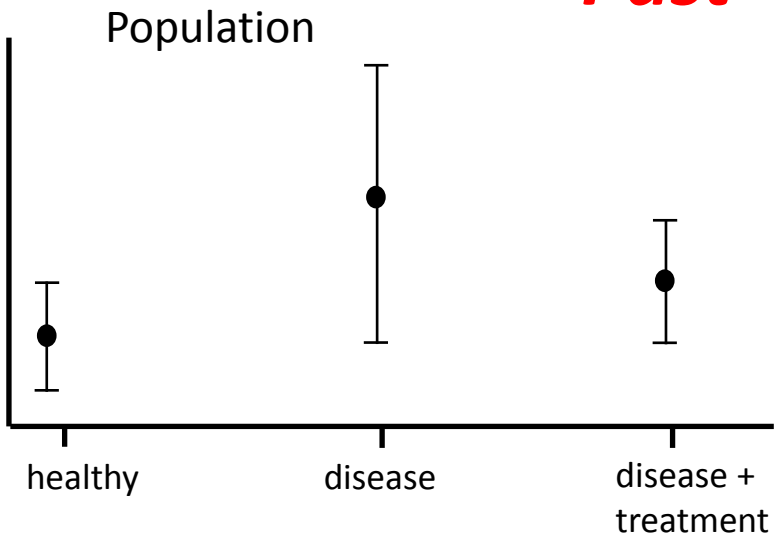
'**I** want to stay healthy. If not, how do **I** get healthy?'

1. What to measure?
2. How much can it change?
3. What should be the follow-up for me?

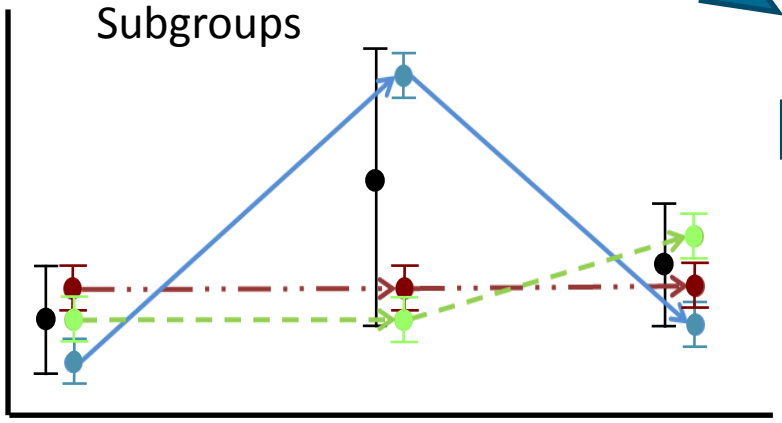
2. How much can it change?

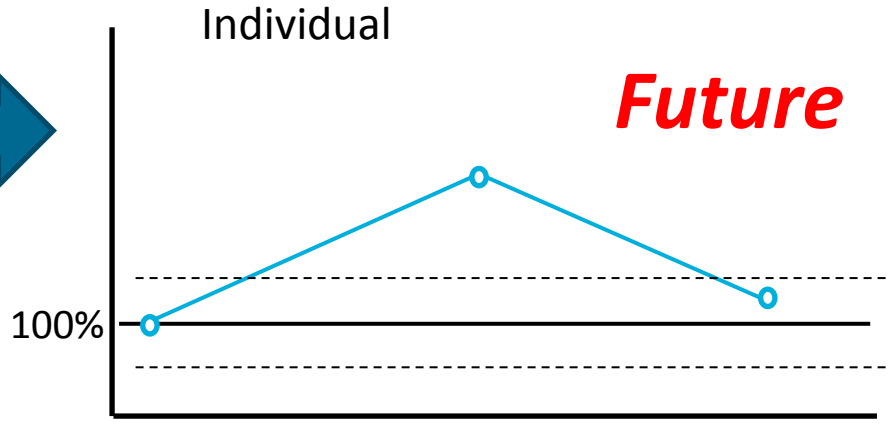


Past



Present





Future

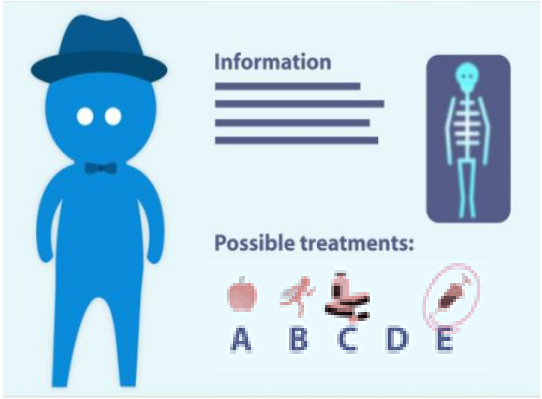
3 key aspects of personalized health(care)

'**I** want to stay healthy. If not, how do **I** get healthy?'

1. What to measure?
2. How much can it change?
3. What should be the follow-up for me?

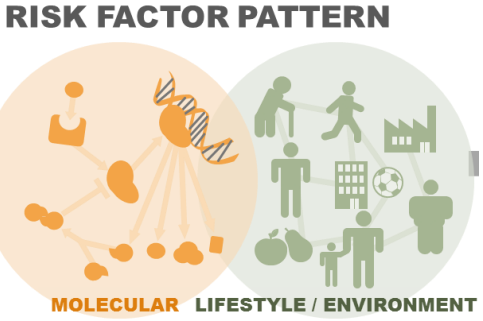
3. What should be the follow-up for me?

Personal profile data

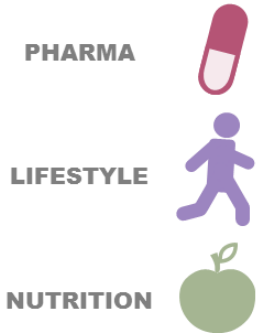


Knowledge

Understanding

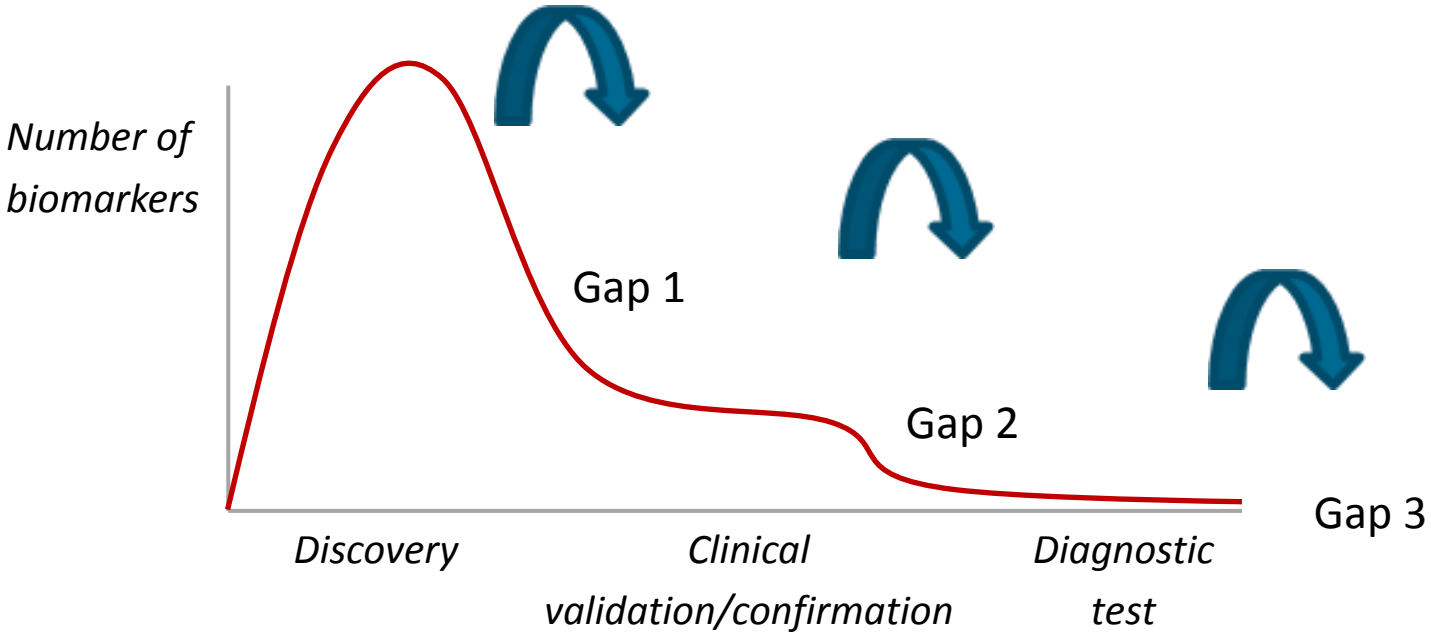


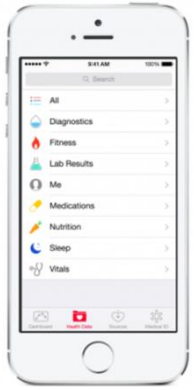
(Shared) Decision



Action

Biomarker innovation gaps !



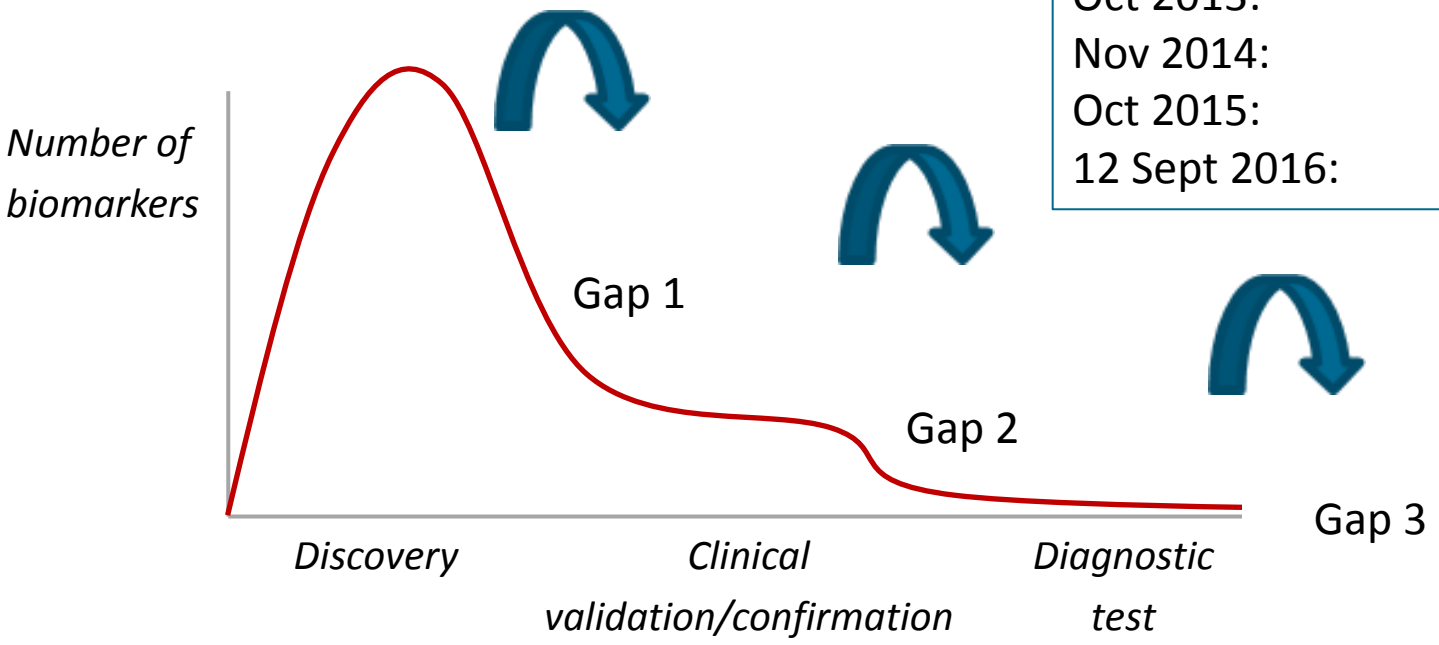


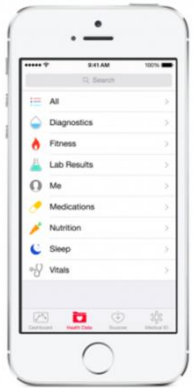
- Too much biomarker discovery
- Too little development to application

Biomarker innovation gaps: some numbers

Eg Biomarkers in time: Prostate cancer

May 2011:	**2,231** biomarkers
Nov 2012:	**6,562** biomarkers
Oct 2013:	**8,358** biomarkers
Nov 2014:	**10,350** biomarkers
Oct 2015:	**11,856** biomarkers
12 Sept 2016:	**13,888** biomarkers





5 biomarkers/ working day

1 biomarker/ 1-3 years

1 biomarker/ 3-10 years

?

Slide from:
Alain van Gool, Eur Commission advice, 11 Sept 2012

Reasons for biomarker innovation gap

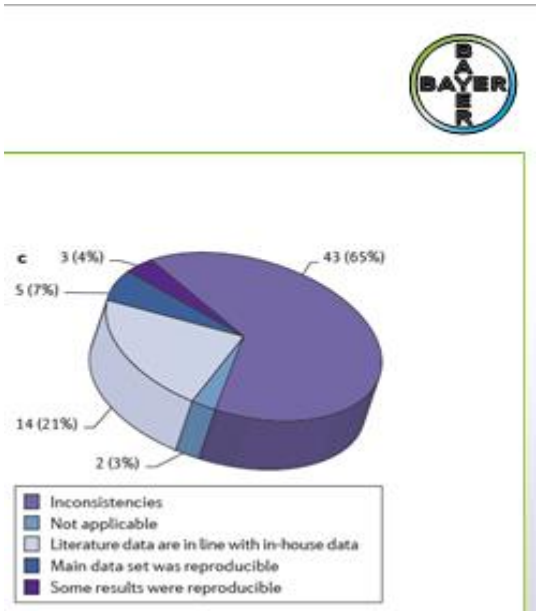
- Not one integrated pipeline of biomarker R&D
- Publication pressure towards high impact papers
- Lack of interest and funding for confirmatory biomarker studies
- Hard to organize multi-lab studies
- Biology is complex on organism level
- Data cannot be reproduced
- Publishing bias towards extreme results
- Biomarker variability
- …

Comparison of Effect Sizes Associated With Biomarkers Reported in Highly Cited Individual Articles and in Subsequent Meta-analyses

John P. A. Ioannidis, MD, DSc
Orestis A. Panagiotou, MD

Context Many biomarkers are proposed in highly cited studies as c
disease risk, prognosis, or response to treatment, but few eventually tr
practice

{Source: John Ioannidis, JAMA 2011}



{Source: Prinz, Schlange, Asadullah, Nat Rev Drug Disc 2011}

Irreproducibility of data

PLOS | BIOLOGY

PERSPECTIVE

The Economics of Reproducibility in Preclinical Research

Leonard P. Freedman[1]*, Iain M. Cockburn[2], Timothy S. Simcoe[2,3]

1 Global Biological Standards Institute, Washington, D.C., United States of America, 2 Boston University School of Management, Boston, Massachusetts, United States of America, 3 Council of Economic Advisers, Washington, D.C., United States of America

{Freedman et al, PLOS Biology, 2015}

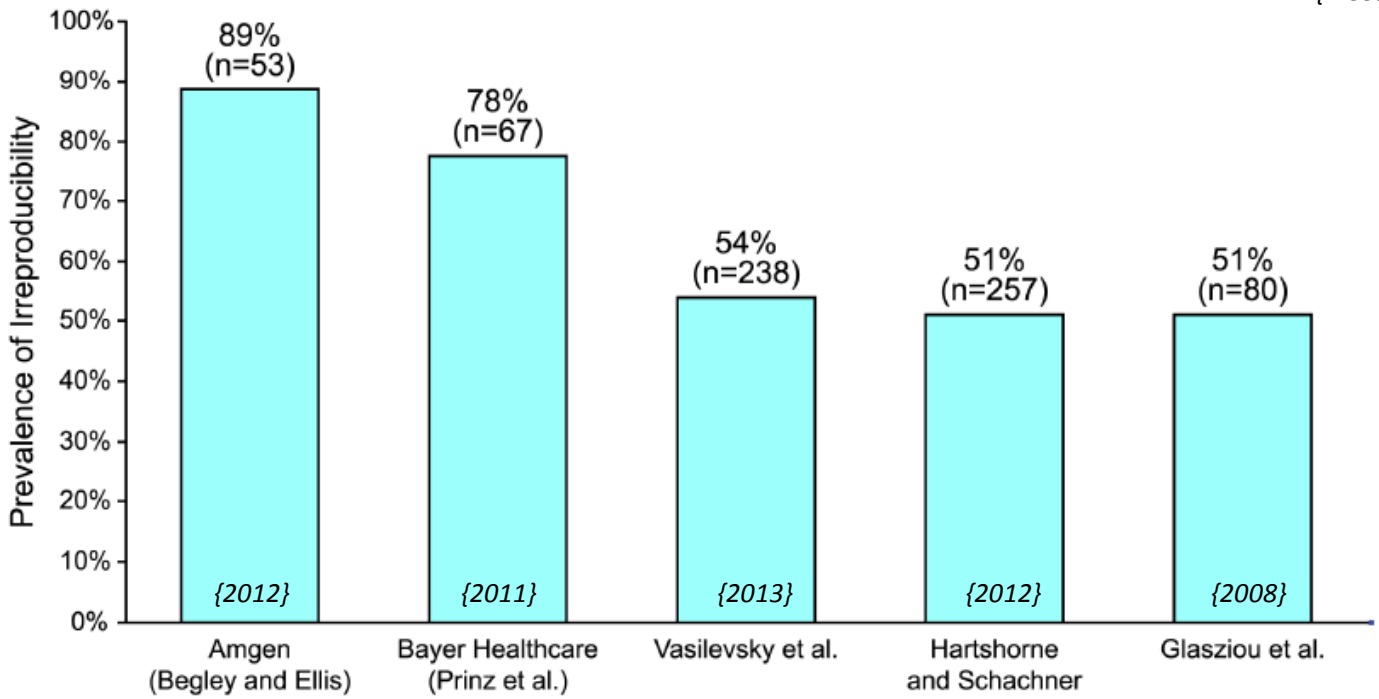


Fig 1. Studies reporting the prevalence of irreproducibility. Source: Begley and Ellis [6], Prinz et al. [7], Vasilevsky [8], Hartshorne and Schachner [5], and Glasziou et al. [9].

doi:10.1371/journal.pbio.1002165.g001

Categories of errors leading to irreproducibility

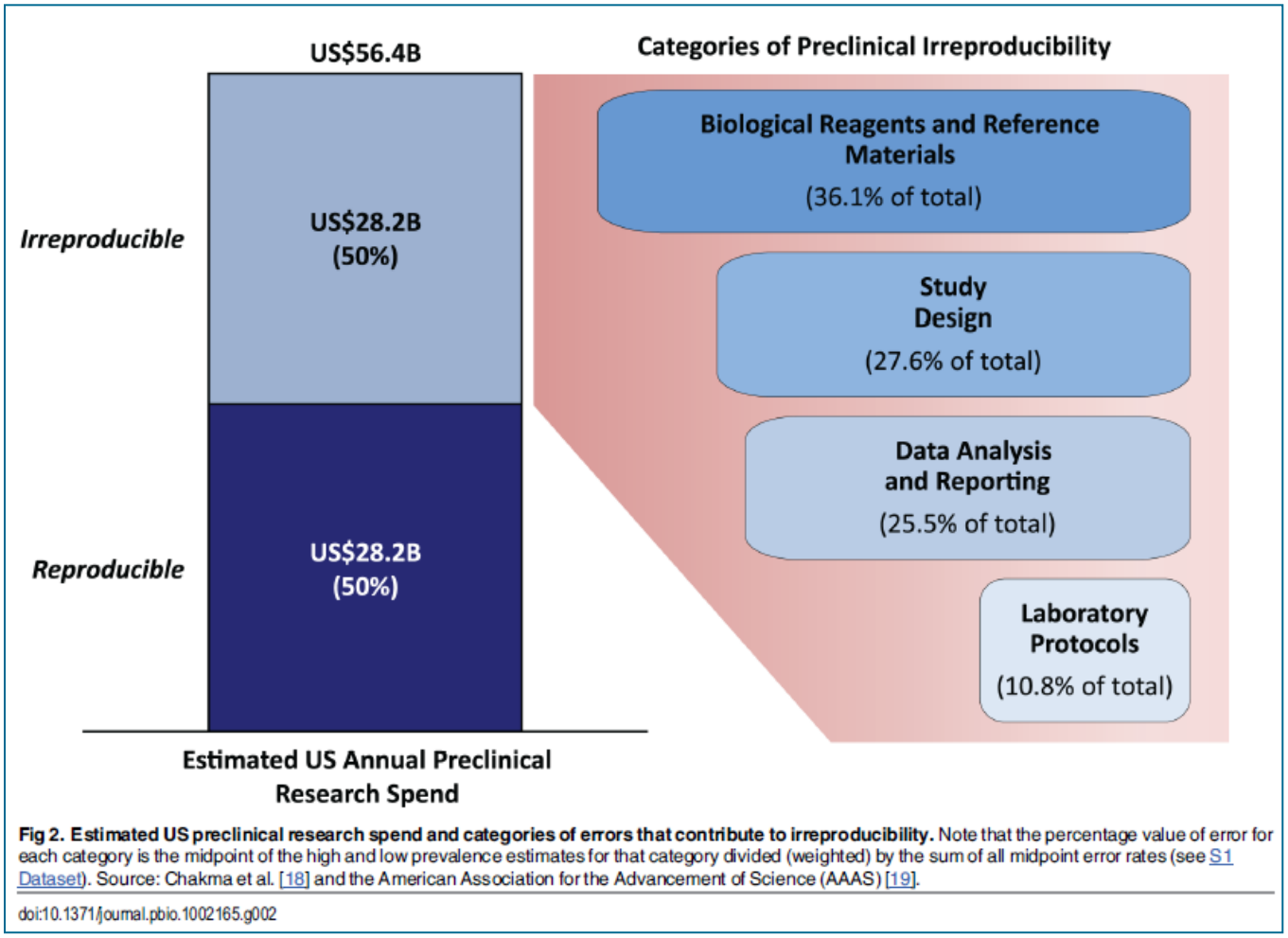


Fig 2. Estimated US preclinical research spend and categories of errors that contribute to irreproducibility. Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates (see S1 Dataset). Source: Chakma et al. [18] and the American Association for the Advancement of Science (AAAS) [19].

doi:10.1371/journal.pbio.1002165.g002

{Freedman et al, PLOS Biology, 2015}

Add to this: bad Data Stewardship

www.nature.com/scientificdata

SCIENTIFIC DATA

OPEN

SUBJECT CATEGORIES

» Research data

» Publication characteristics

Comment: The FAIR Guiding Principles for scientific data management and stewardship

Mark D. Wilkinson *et al.*#

{Wilkinson et al, Nature Scientific Data, 2016}

>80% of data is not FAIR:

Findable, **A**ccessible, **I**nteroperable, **R**eusable

Way forward

Quote Freedman paper:

The economics literature on standardization posits that unless there is a clearly dominant platform leader willing to impose a solution, complex challenges such as irreproducibility that require a coordinated response are best solved by internally organized and driven, dynamic, and self-regulating collaborations of key stakeholders who establish and enforce their respective rules of engagement [32,33]. What is needed is not another list of unfunded mandates, but rather community consensus on priorities for improvement and commitment for the additional funding for implementation.

{Freedman et al, PLOS Biology, 2015}

Departmental community

Radboudumc

Research → **Biomarkers** → **Diagnostics**

Specialities:
- Proteomics, glycomics, metabolomics
- Enzymatic assays
- Neurochemistry
- Cellulair immunotherapy
- Immunomonitoring

Areas of disease:
- Metabolic diseases
- Mitochondrial diseases
- Lysosomal /glycosylation disorders
- Neuroscience
- Nefrology
- Iron metabolism
- Pediatric oncology
- Immunodeficiency
- Transplantation

In development:
- ~500 Biomarkers
- Early and late stage
- Analytical development
- Clinical validation

Assay formats:
- Immunoassay
- Turbidicity assays
- Flow cytometry
- DNA sequencing
- Mass spectrometry
- Experimental human (-ized) invitro and invivo models for inflammation and immunosuppression

Validated assays*:
- ~ 1000 assays
- 3.000.000 tests/year

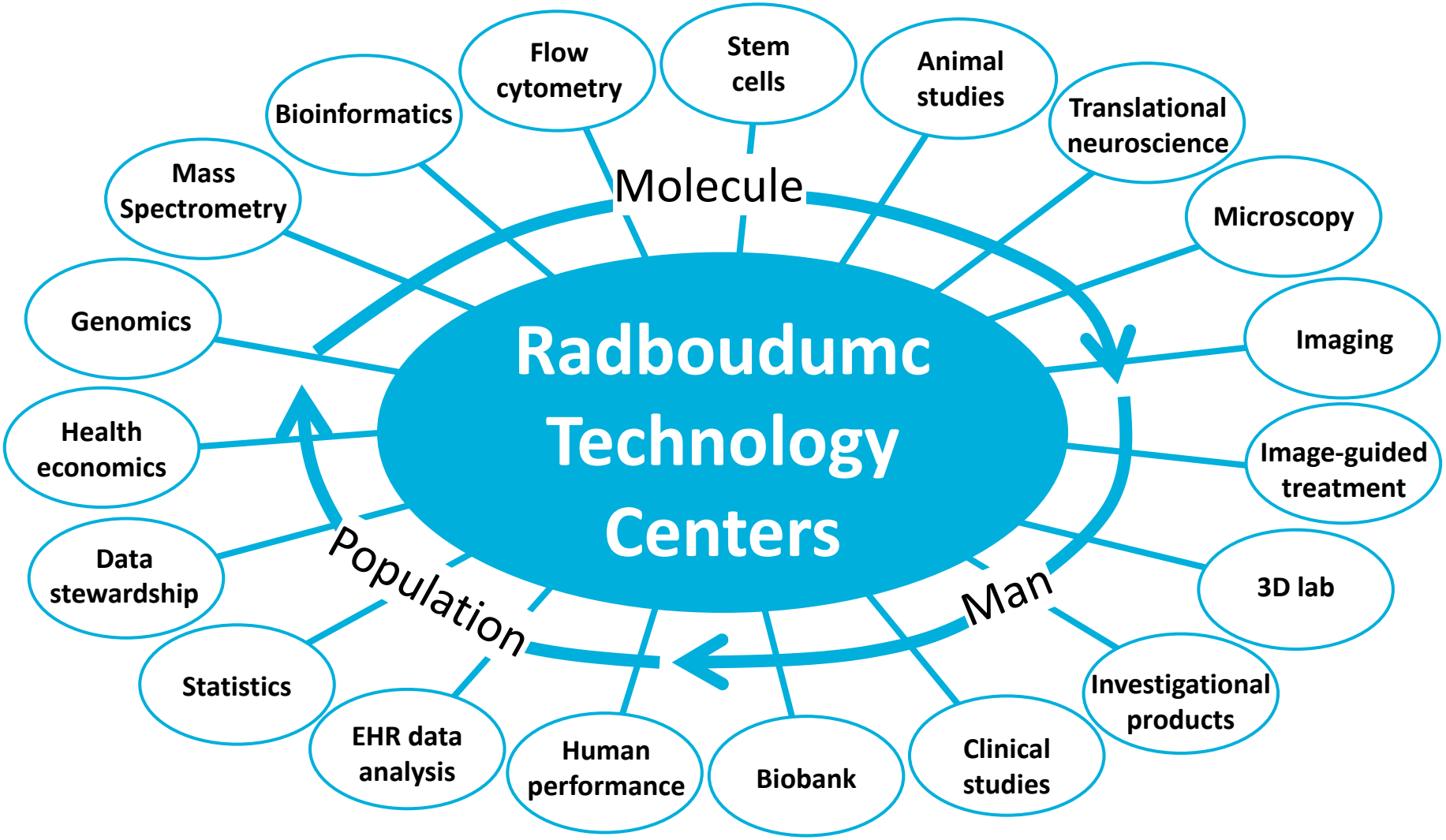
Areas of application:
- Personalized healthcare
- Diagnosis
- Prognosis
- Mechanism of disease
- Mechanism of drug action

**CCKL accreditation/RvA/EFI*

Department of Laboratory Medicine

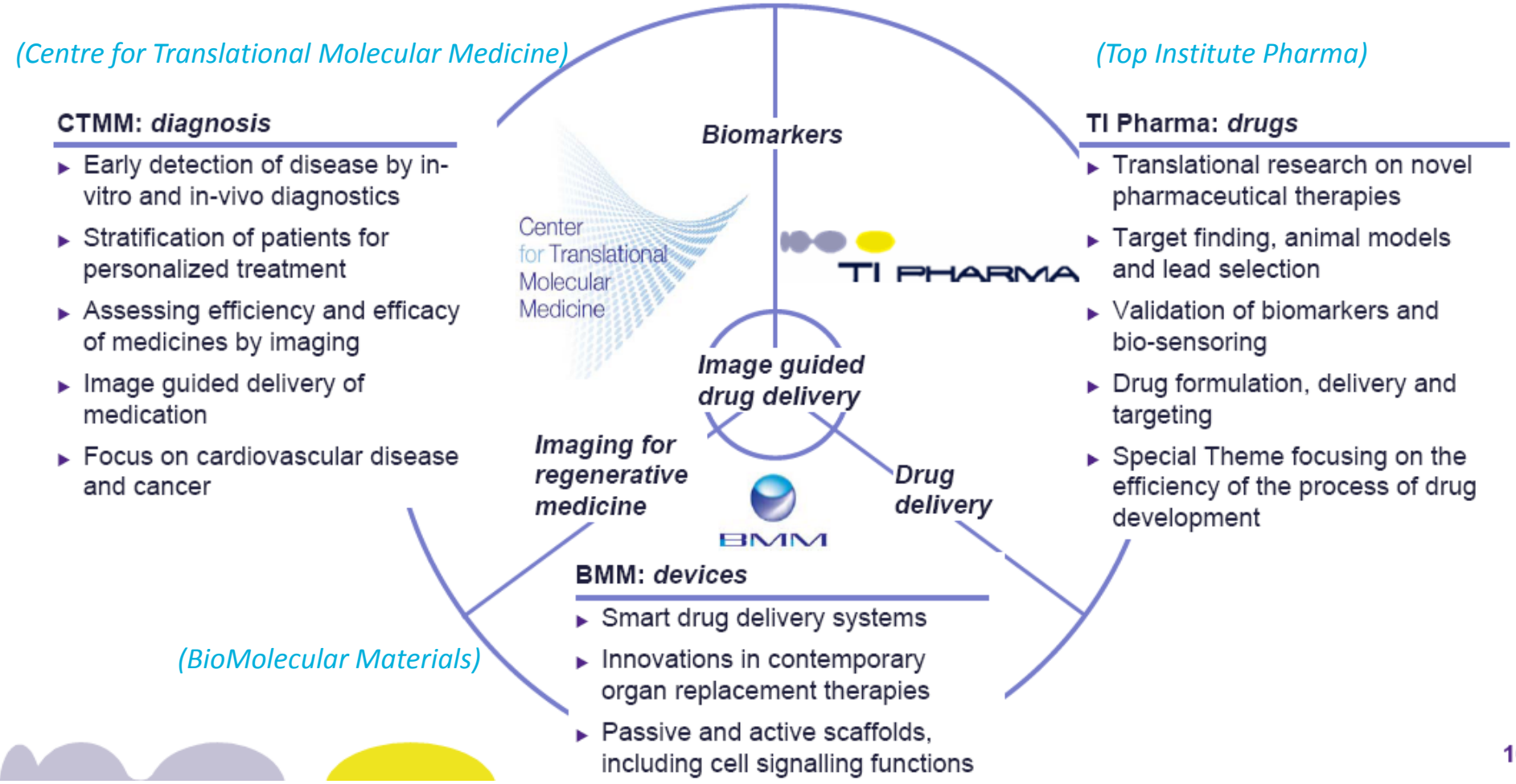
Integrated Translational Research and Diagnostic Laboratory, 250 fte, yearly budget ~ 28M euro.
Close interaction with Dept of Genetics, Pathology, Pharmacy and Medical Microbiology

Institutional community



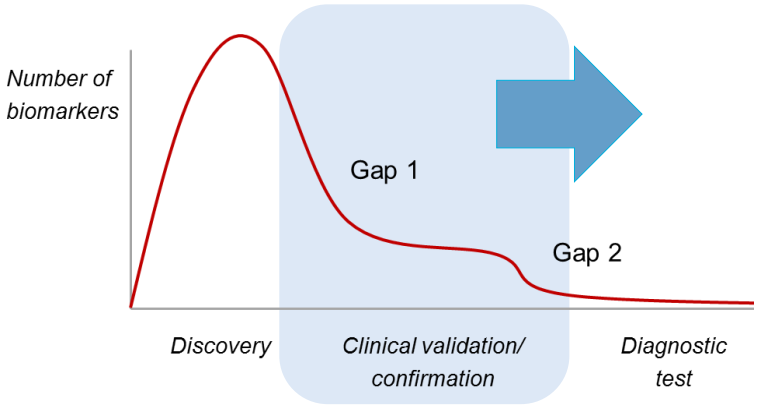
National communities

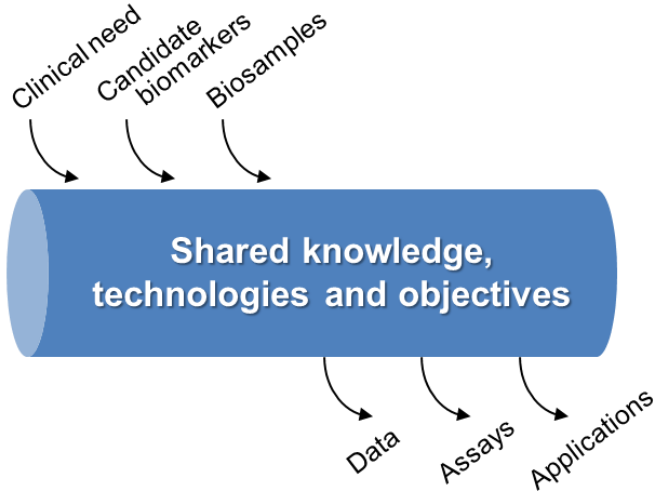
A rich history of public-private collaboration on diagnosis, drugs, devices (2006-2015)



NL Biomarker validation pipelines

Biomarker Development Center

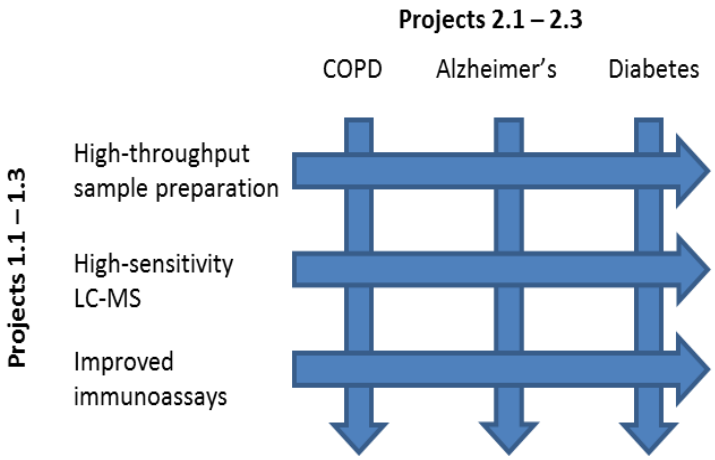




university of groningen · Radboudumc · umcg · Erasmus MC · TNO innovation for life · Waters · BRUKER · Cell Signaling Technology · PEPSCAN Therapeutics · Singulex · Avacta Life Sciences

Standardisation, harmonisation, knowledge sharing in:

1. **Assay development**
2. **Clinical validation**



Life Sciences Health → STW Perspectief (Nieuwe technologie mogelijk maken in de topsectoren)

NL Roadmap Molecular Diagnostics (2012) NL Grant 4.3M Eur (2014)

Radboudumc · TNO innovation for life · DTL · eatris European infrastructure for translational medicine

Ongoing independent biomarker activities

Europe

Innovative Medicines Initiative

HORIZON 2020
LE PROGRAMME DE RECHERCHE ET D'INNOVATION DE L'UNION EUROPÉENNE

Biomarker Development Center

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BBMRI-ERIC
Biobanking and BioMolecular Resources Research Infrastructure


COMMENT

Industry–academia collaborations for biomarkers

Khusru Asadullah[1,2], Andreas Busch[1], Matthias Gottwald[1], Petra Reinke[2] and Lilla Landeck[2,3]

Several types of collaboration are being pursued to identify, validate and apply new biomarkers. Here, we highlight examples of such initiatives and discuss the challenges, approaches to address these challenges and key factors for success.

{Asadullah et al, Nature Reviews Drug Discovery, Dec 2015}

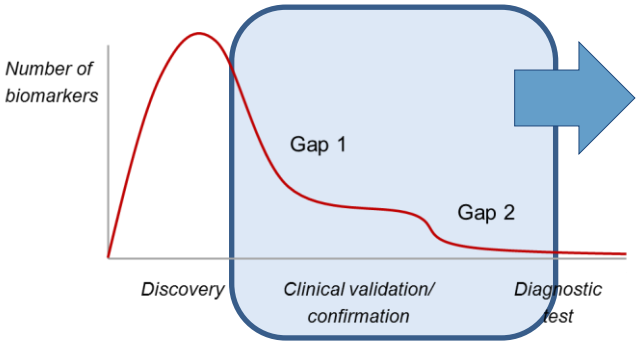
USA

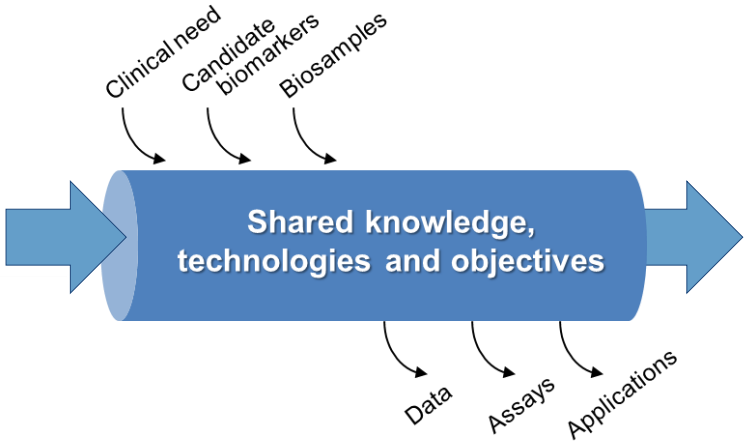
THE biomarkers CONSORTIUM

CRITICAL PATH INSTITUTE

PDBP
Parkinson's Disease Biomarkers Program

The Good Biomarker Practice initiative





Join forces among Europe's major academic infrastructures + industry to:

1. **Establish "Good Biomarker Practice" guidelines**

   - on translational research, biomarker technologies, biobanking, data stewardship.

2. **Efficiently execute high quality biomarker projects**

   - work together in clinical validation and development of probable biomarkers.

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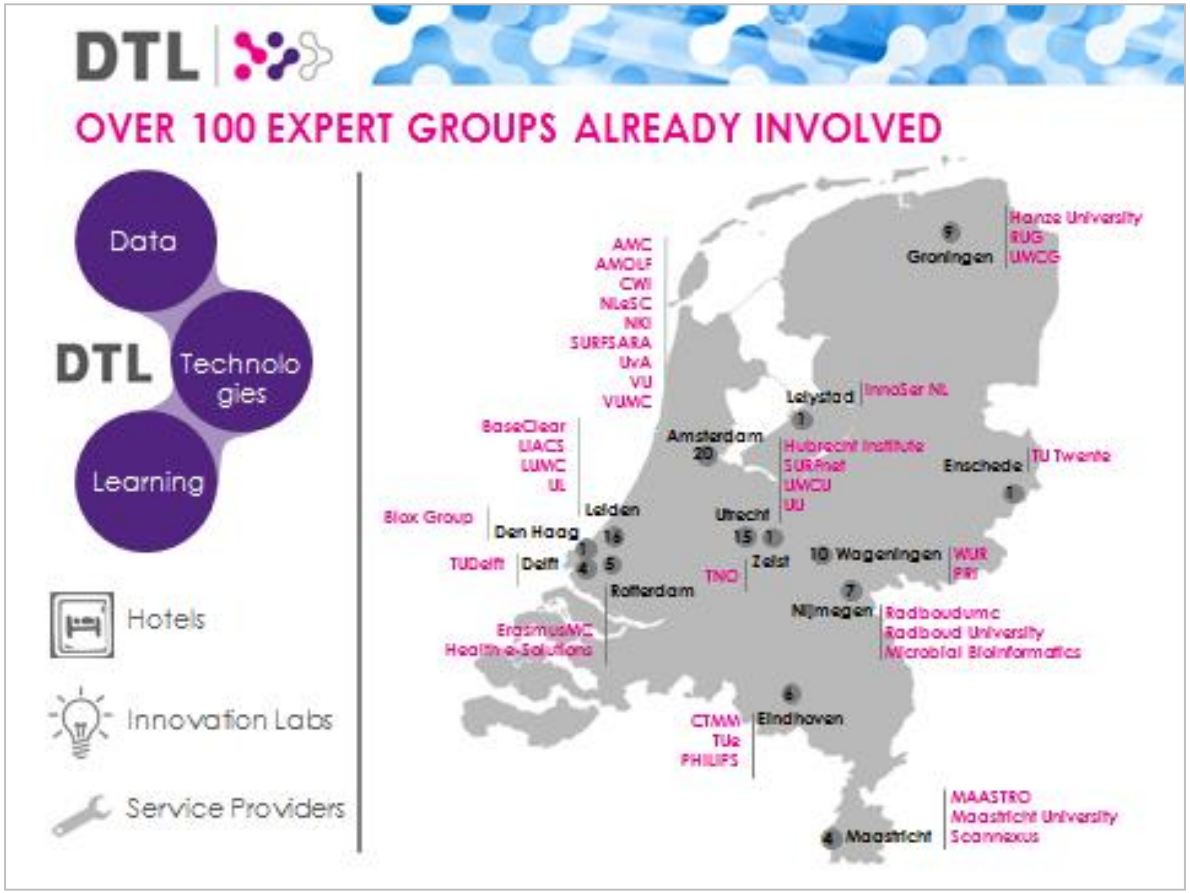
elixir

lygature
pioneering medicine.

National communities



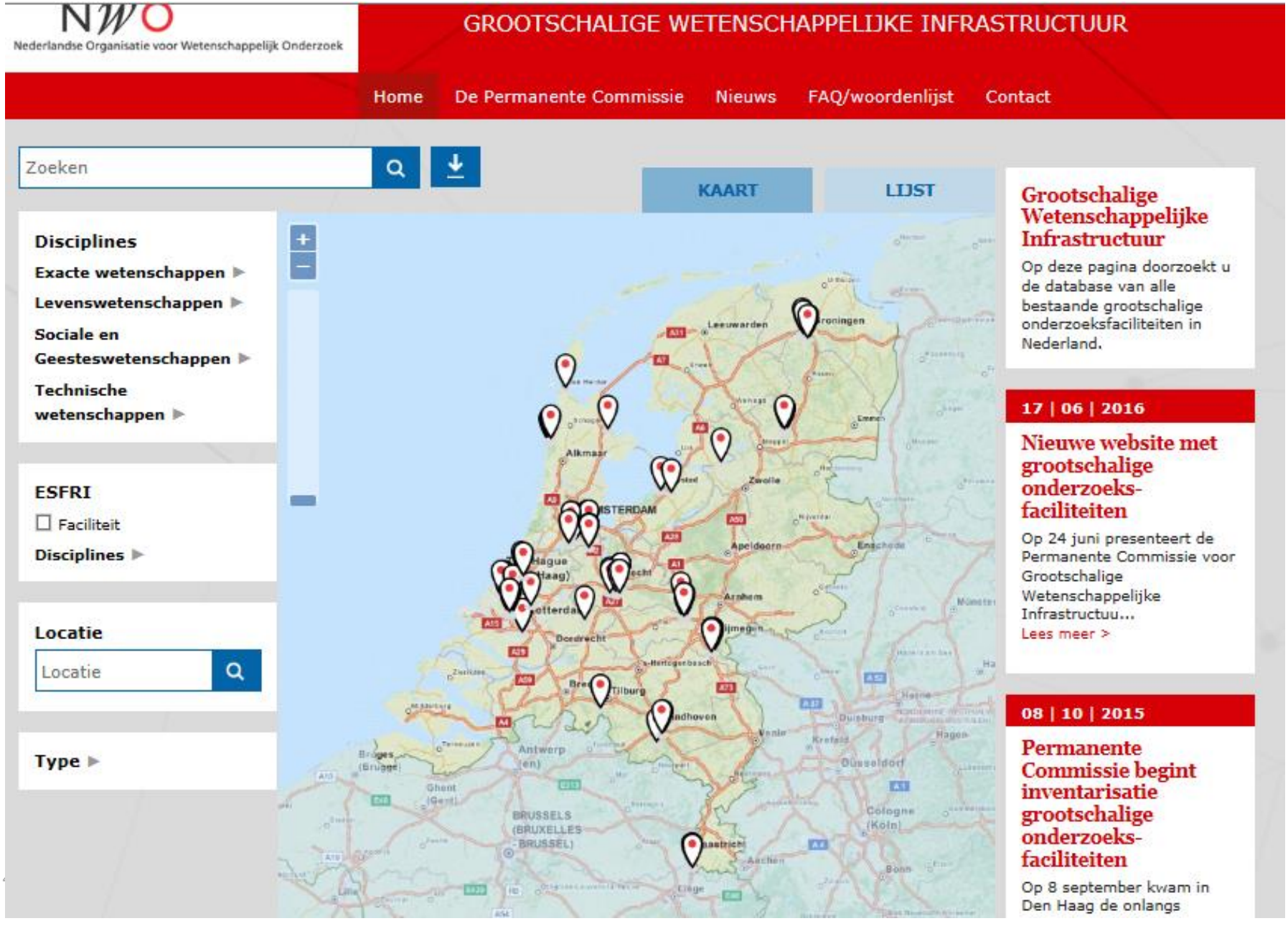
National Technology Infrastructure (from 40+ partners in DTL)

Data4LifeSciences (organising biomedical data in academic hospitals)

Funding of Large scale Scientific Infrastructures (>10M euro)

National Science Agenda (originated from citizens)

www.onderzoeksfaciliteiten.nl



Nationale wetenschaps agenda

nationale wetenschaps agenda

Nederlands English

Digitale agenda | Actueel | Routeworkshops | Achtergrond | Organisatie | Scholieren

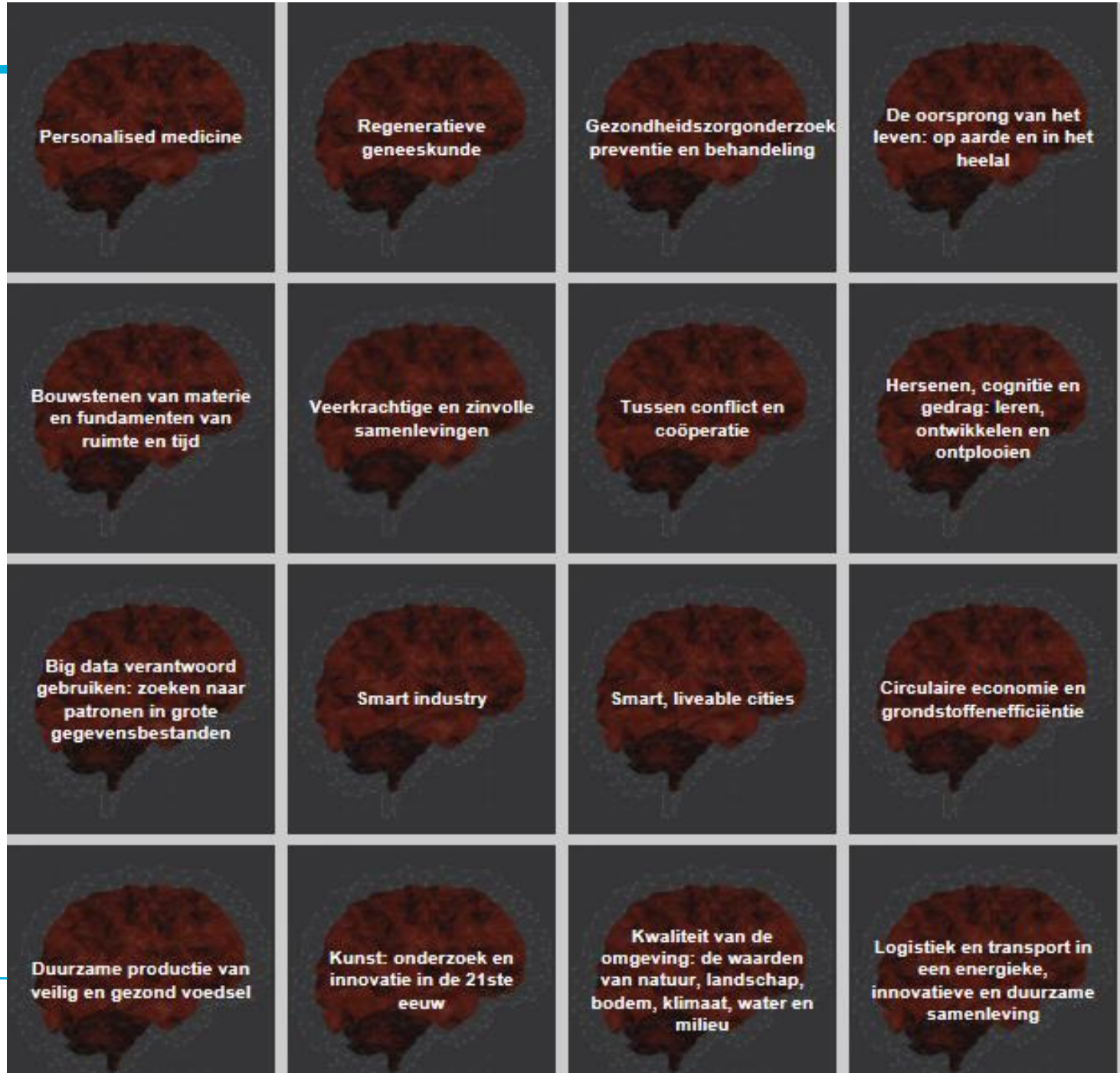
Algemene informatie

Eind vorig jaar is de NWA gepubliceerd met 140 clustervragen en 16 exemplarische routes door die vragen. De routes vormen het instrument waarmee de NWA belangrijk wetenschappelijke, maatschappelijke en

16 routes

Workshops
March/April 2016

Output all routes presented as investment agenda
to parliament
15 Sept 2016



Central thoughts Personalized Medicine route

De route naar personalised medicine.

Het ideaalbeeld:

Niet het gemiddelde, maar de variatie centraal.

Benodigd: (verbindingen tussen) heel veel betrouwbare data...

... en gericht wetenschappelijk onderzoek;

goede communicatie en educatie,

nieuwe allianties tussen onderzoekers, bedrijven en zorgaanbieders,

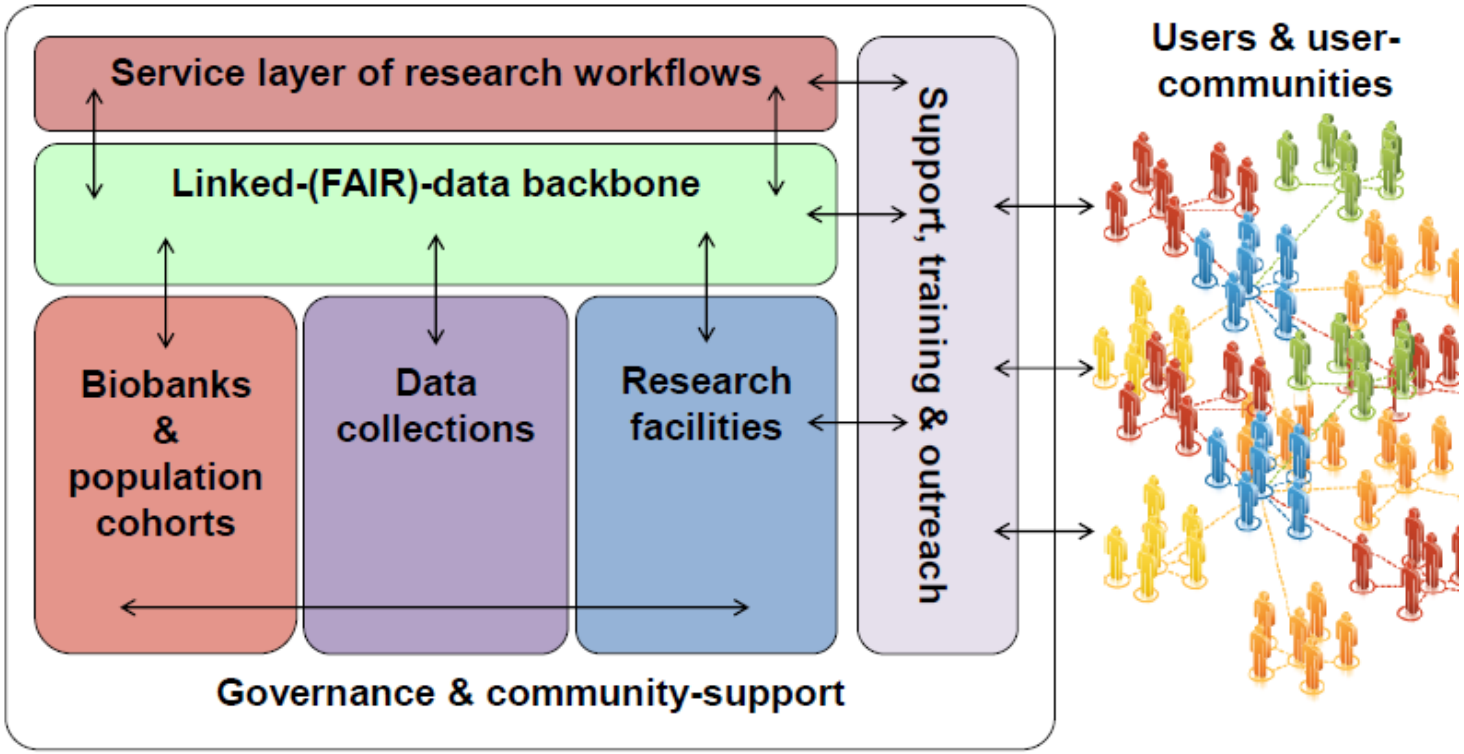
publiekvoorlichting, dialoog, ethische toetsing en juridische randvoorwaarden.

Met heldere financiering en vergoeding...

op weg naar personalised medicine.

Emerging Health Research Infrastructure

HealthRI: driving personalized medicine & health research in the Netherlands



health RI research infrastructure

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Rijksoverheid
MRDM
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organizes & visualizes your bioinformatics data
VitaValley
FHI
LABORATORY TECHNOLOGY
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CYSTIC FIBROSIS
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Voor een gezond onderzoeksklimaat
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December 1st, 2016
Starts at 09:00

Flint Theater Amersfoort
Coninckstraat 60, 3811 WK Amersfoort,
The Netherlands

Attendance fee € 95,- excluding VAT

Register here for a visit

Health-RI Conference

Connecting Researchers, Patients and Enabling Technologies

Worldwide, personalized medicine is recognized as the next big dot on the horizon for health care. The programme of the Health-RI conference, on December 1st, will give an insight into current and future developments of health research as well as initiatives to connect biomedical scientists, informaticians, clinicians, patientcare and industry.

EMPOWERED BY:

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1 December 2016
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health RI research infrastructure

Acknowledgements

Many collaborators and funders

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Hans Wessels, Roel Tans, Maurice van Dael, Dirk Lefeber, Jolein Gloerich, Esther Willems, Jenneke Keizer, Monique van Scherpenzeel, Leo Kluijtmans, Ron Wevers, Marcel Verbeek, Lucien Engelen, Jan Kremer, Bas Bloem, Nathalie Bovy, Paul Smits
the Radboudumc Technology Centers
and many others

TNO innovation for life

Jan van der Greef, Ben van Ommen, Ivana Bobeldijk, Hans Princen, Lars Verschuren, Marjan van Erk, Suzan Wopereis, Heleen Wortelboer, Wessel Kraaij, Ronald Mooi, Peter van Dijken, Cyrille Krul
and many others

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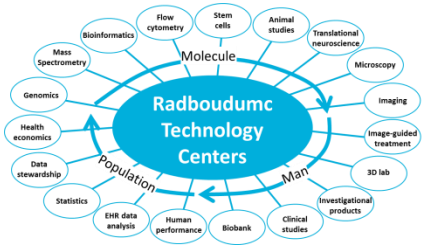
European infrastructure for translational medicine

Anton Ussi, Florence Bietrix, Laura Bermejo, Andreas Scherer, Sulev Koks, Marian Hajduch, Giovanni Migliaccio
and many others

DTL

Ruben Kok, Barend Mons, Jaap Heringa, Merlijn van Rijswijk
and many others



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