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Personalised Medicine – what's in for Rare Diseases?

ICORD

Ede, October 2014

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Public Health Genomics (PHG):

translational research

„from cell to society“

“Public Health Genomics (PHG) is the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health.”

[Bellagio Statement 2005: GRAPH*Int*, GMA, PHGEN, PHGEN-NTFs, IPHG, etc.]

Personalized Medicine – what's in for RDs?

1. What evidence for informed policy-making?

2. What key policy areas for Europe and beyond?

1. What evidence for informed policy-making?

Why are our health interventions still not successful?
(only 15% are evidence-based...)

... because there is no „one size fits all“!

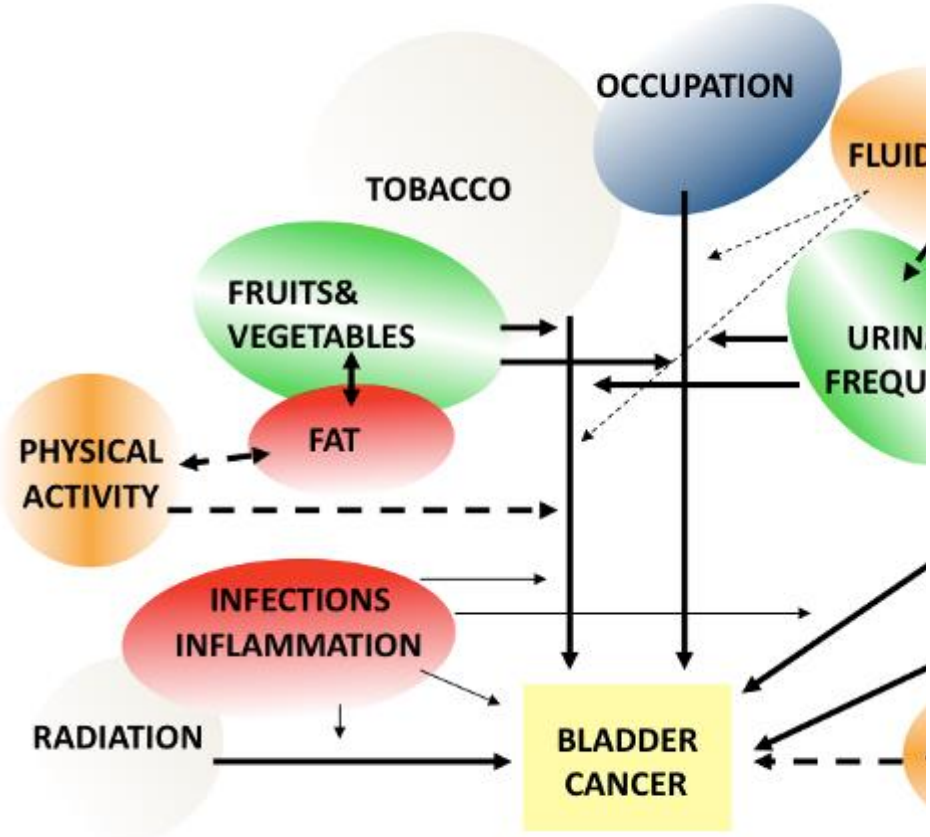
>> we need more targeted/“personalized“ interventions

>> we need complementary interventions running in parallel (population level, subpopulation level, individual level)

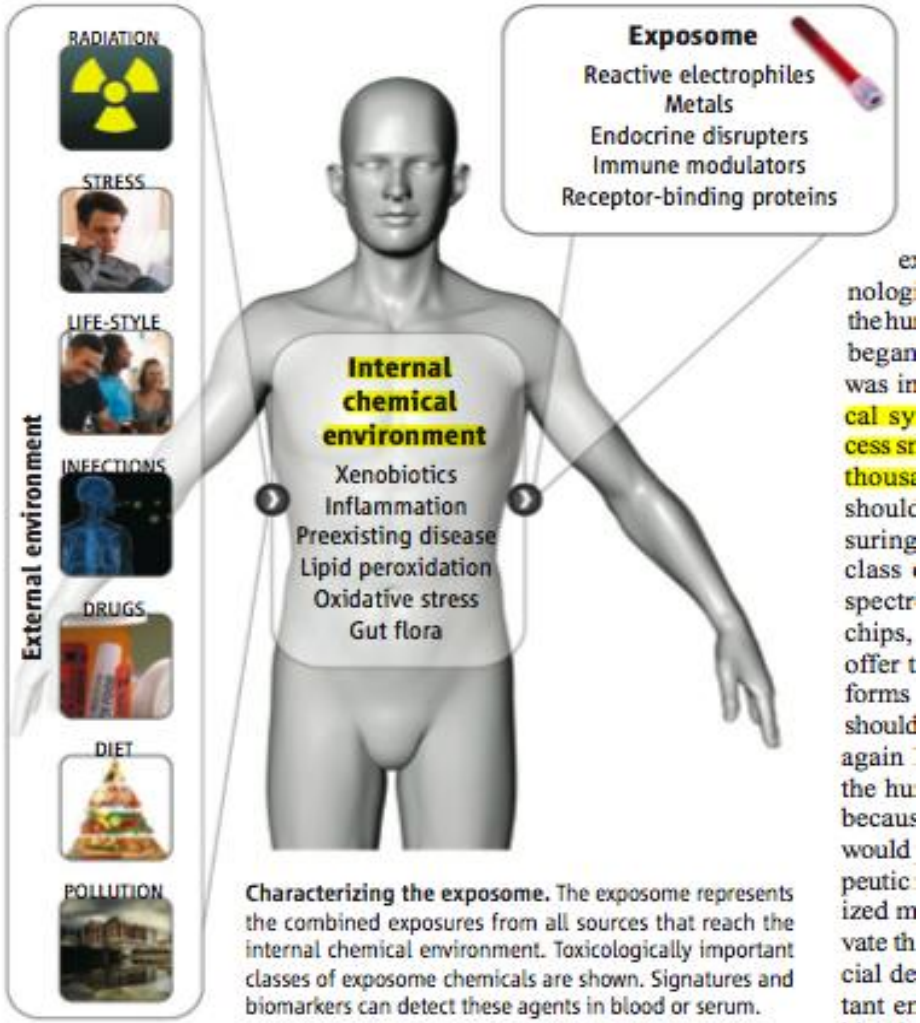
... and *basic research in genomics* is providing evidence for doing so - all diseases are due to genome-environmental interactions!

Examples: IDs, obesity, CVDs, addiction, vaccination, cancer and RDs (!)

Environmental exposures vs. Exposome
[Nuria Malats, EUPHA 2010]

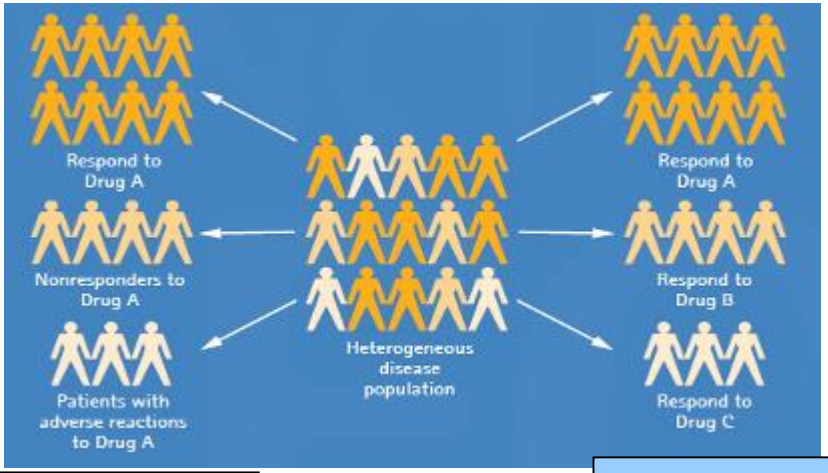


Rappaport&Smith, Science 2010



Pharmacogenomics [Ilhan Celik, EHFG, 2010]

Stratified Medicine is about <u>adapting the treatment</u> (molecule, dose, schedule,…) according to the patient's characteristics <u>for better efficacy and less adverse events.</u>



Stratified Medicine	versus	Personalized Medicine
- Patient sub-population e.g. molecular testing for tumor mutation		- Individual patients e.g. cancer vaccine made from the patient's tumor

… genomics is a „moving target“ …

… from the

Human Genome Project

to the

Personal Genome Project …

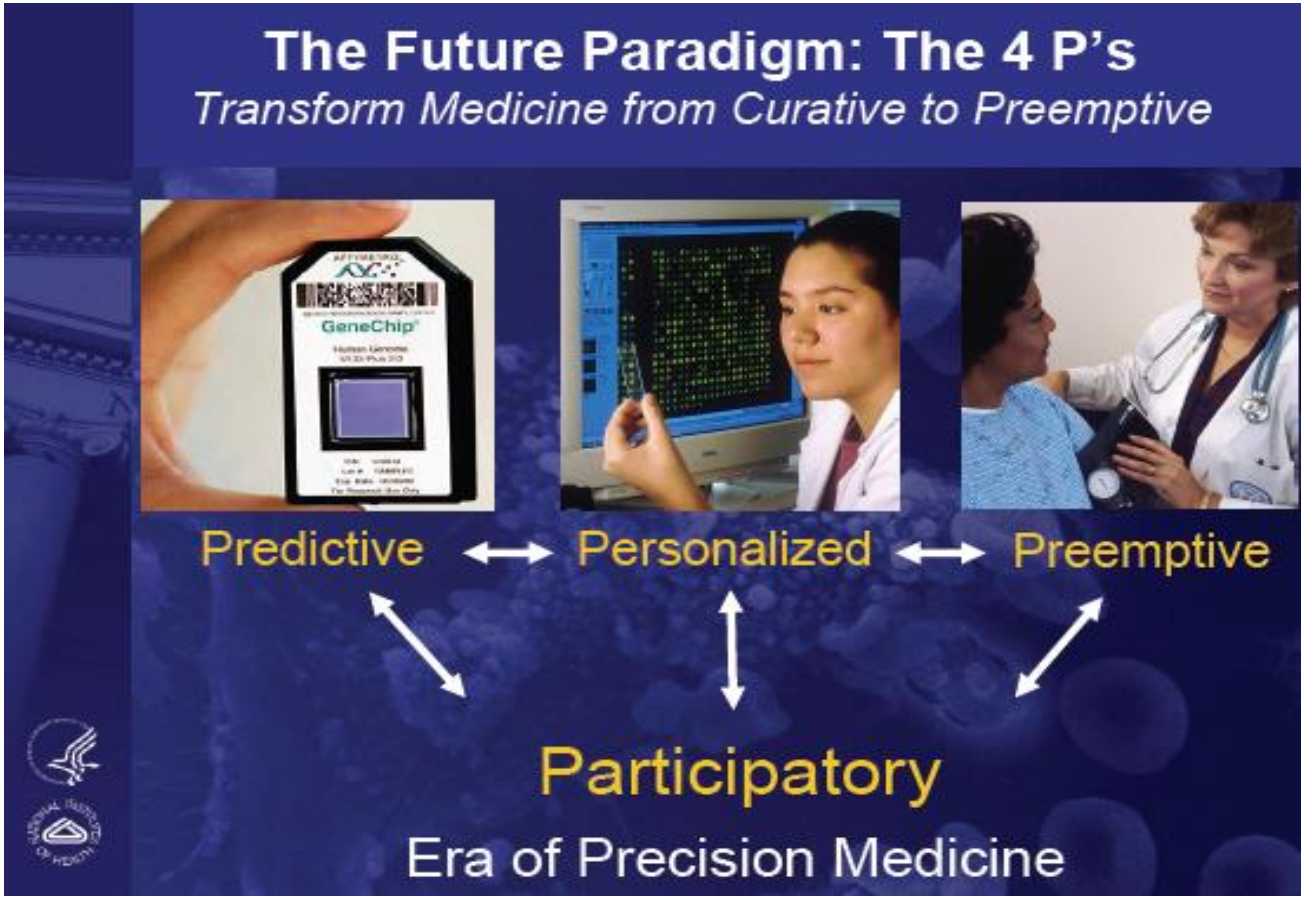
… from

single and linear systems

to

non-linear networks (e.g., in systems biology and systems medicine) …

Not only 4 P's …


The Future Paradigm: The 4 P's
Transform Medicine from Curative to Preemptive
GeneChip
Predictive
Personalized
Preemptive
Participatory
Era of Precision Medicine

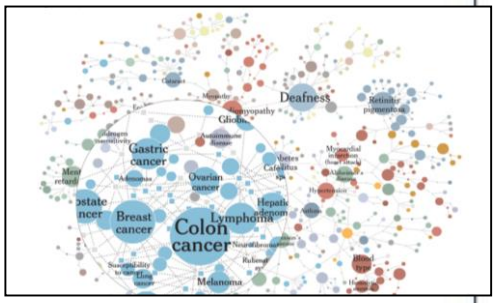
… not only beyond the 4 P's, but also (A. Brand, 2008) …

1. from common complex diseases to "multiple rare diseases"

2. from diseases to "diseasomes"

3. from risk factor to "risk pattern"

4. from clinical utility to "personal utility"



… not only beyond the 4 P's, but also (A. Brand, 2008) …

1. from common complex diseases
to "multiple rare diseases" …

sub-entities and also e.g. ….

obesity (e.g., MC4R mutation)
ca. 70% of RDs are rare cancers
"lessons learned" from Rett syndrome
rare environmental dx (e.g., mesothelioma)

Plausibility?
Two types of prediction models?

1. Will the disease occur?

<< A. hazards/health threats: incl. "inherited epigenomics", use of biomarkers and biomonitoring systems, health protection

<< B. occuring "by chance"

2. Having the disease, how will the disease develop?

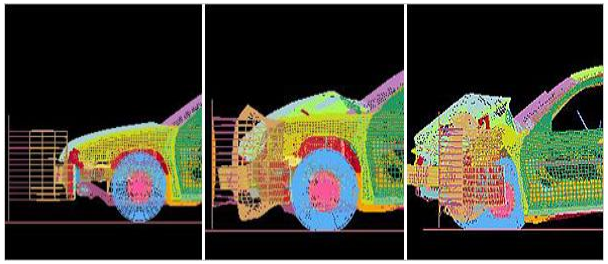
<< very accurate, "truly" individualized therapies/interventions, early secondary prevention

The Future? ….. translating into healthcare systems

(1) highly (in space & time) dynamic personal (health) information

(2) from statistical risks within groups to “individualized evidence”

(3) “virtual individual models” (simulations)



”ICT and Big Data for health & health for ICT and Big Data”:
a radically new vision for healthcare and health systems!

Epigenomics
is the missing link between environment/social sciences and biomedicine!

>> ability of all environmental factors to gene expression and phenotype change

>> ability to understand genome-environment interactions

>> ability to measure genome-environment interactions

>> ability of early diagnosis of individuals for adult-onset disease (… old Barker theory?)

>> ability of novel preventive and therapeutic approaches in an asymptomatic health status

>> need for the implementation of intraindividual monitoring & surveillance systems (individual health management)

>> need for personalized healthcare (“personal health and care”)


Joe Klein: The CIA's Afghan Disaster
Yemen: The New Center Of Terror
Why the Recession Hasn't Been Cool To Teens
TIME
WHY YOUR DNA ISN'T YOUR DESTINY
The new science of epigenetics reveals how the choices you make can change your genes —and those of your kids
BY JOHN CLOUD


The Economist
The Catholic church's unholy mess
Paul Ryan: the man with the plan
Generation Xhausted
China, victim of the Olympics?
On the origin of specie
AUGUST 18TH–24TH 2012
Economist.com
Microbes maketh man
How 90% of the cells in your body are bacteria, the benefits of faecal transplants, and other things you would rather not know before breakfast

… obesity story (21.08.2012)

International Journal of Obesity (2012), 1–8

www.nature.com/ijo

ORIGINAL ARTICLE

Infant antibiotic exposures and early-life body mass

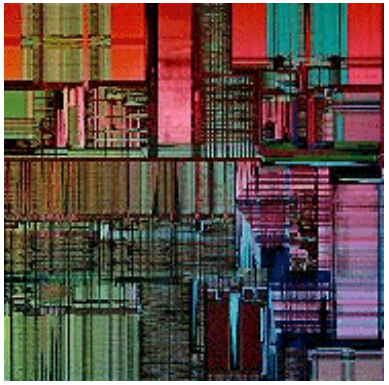
L Trasande[1,2,3], J Blustein[3,4], M Liu[2], E Corwin[3], LM Cox[5] and MJ Blaser[4,5]

OBJECTIVES: To examine the associations of antibiotic exposures during the first 2 years of life and the development of body mass over the first 7 years of life.
DESIGN: Longitudinal birth cohort study.
SUBJECTS: A total of 11 532 children born at ⩾2500 g in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based study of children born in Avon, UK in 1991–1992.
MEASUREMENTS: Exposures to antibiotics during three different early-life time windows (<6 months, 6–14 months, 15–23 months), and indices of body mass at five time points (6 weeks, 10 months, 20 months, 38 months and 7 years).
RESULTS: Antibiotic exposure during the earliest time window (<6 months) was consistently associated with increased body mass (+0.105 and +0.083 s.d. unit, increase in weight-for-length *Z*-scores at 10 and 20 months, $P<0.001$ and $P=0.001$, respectively; body mass index (BMI) *Z*-score at 38 months +0.067 s.d. units, $P=0.009$; overweight OR 1.22 at 38 months, $P=0.029$) in multivariable, mixed-effect models controlling for known social and behavioral obesity risk factors. Exposure from 6 to 14 months showed no association with body mass, while exposure from 15 to 23 months was significantly associated with increased BMI *Z*-score at 7 years (+0.049 s.d. units, $P=0.050$). Exposures to non-antibiotic medications were not associated with body mass.
CONCLUSIONS: Exposure to antibiotics during the first 6 months of life is associated with consistent increases in body mass from 10 to 38 months. Exposures later in infancy (6–14 months, 15–23 months) are not consistently associated with increased body mass. Although effects of early exposures are modest at the individual level, they could have substantial consequences for population health. Given the prevalence of antibiotic exposures in infants, and in light of the growing concerns about childhood obesity, further studies are needed to isolate effects and define life-course implications for body mass and cardiovascular risks.

International Journal of Obesity advance online publication, 21 August 2012; doi:10.1038/ijo.2012.132

Keywords: antibiotics; human microbiome; body mass; ALSPAC

Public Health Genomics (PHG) moves towards Personalised Medicine …



Public Health

Genomics

Big Data

PHG

Public Health Genomics: "bottom-up meets top-down" : approaches?

1. Rare Disease model?

2. Syndromes?

3. Very young and very old people?

4. Intraindividual follow-up?

5. Kernel-based statistical methods?

6. The "Resilience Project"?

7. "Big Data"?

How specific is the "measurement" (e.g. inflammation, lipid metabolism (pathway)) for the outcome?...

2. What key policy areas for Europe and beyond?

The BIG4HEALTH ☺
- four key policy areas …

1. decision-supporting tools

2. “big data”

3. ownership

4. health systems

1. decision-supporting tools

- HTA 3.0 (assumption non-linearity and “personal evidence”)
- systematic early dialogue/PPP (e.g. LAL model), best practice of PPP = IMI
- “just in time” interventions (JITs)
- orphan drug model & pilots (e.g. Germany: “Heilversuch” with N=25) / RoI
- drug/theranostics/CDx/IVD versus Medical Device … (use of) health information (HI)
- “virtual twin”: in silico ”try and error“ (simulations, artificial learning)

2. “big data”

- **N=1 trials: “I am my own reference point”**
- **N=all trials: mission impossible (”big data” will always be incomplete)**
- **unstructured (and structured) data for unknown future purposes (more than just data linkage or open access)**
- **validation, standardization: mission impossible (always a “momentum”)**
- **“incidental findings”/noise: all findings are important, we just cannot interpret them (yet): “junk versus garbage”**
- **health information will always be “messy”/chaotic: what (not why) is good enough in most cases! Correlation versus causality …**

3. Ownership

- "I am the owner of my data": personal ownership (property based, excluding right, paternalistic) vs. citizen ownership/control (broader, social right, shared right, democratic)

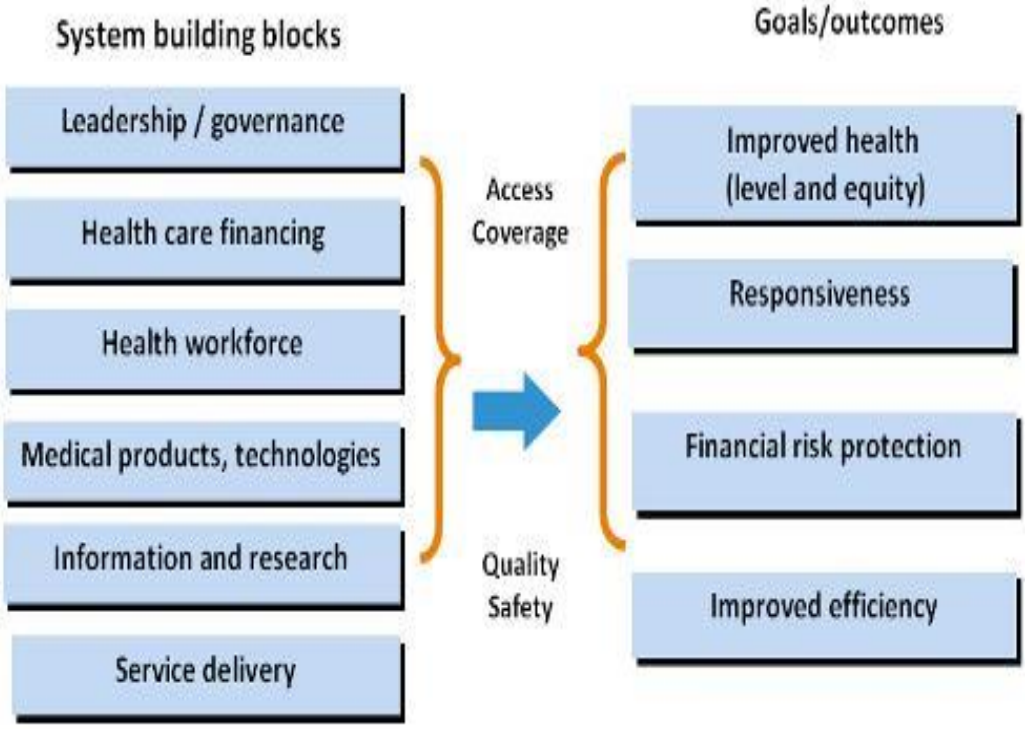
- from informed consent (blanket or broad) & privacy issues to data-users accountability: "trust & trusts"! (… to guarantee data security is dishonest!)

- "big data" meet governance of information via algorithm providers (QM): rules of impartiality, confidentiality, competence (interpretation of data) and professionalism

- Health Data Cooperatives (balance between public good – personal benefit, no monetary incentives for individuals!)

4. health systems

- "good governance" – "good" implementation of "good" health policies (e.g. in Europe cross-border directive, "bottom-up" policies)
- WHO-EU Regional office (Tallinn, 2008) : six system building blocks



Can Europe lead the global way

in Personalised Medicine?

1. Global good governance?

... global implementation of the EU common health values & principles

WHITE PAPER
Together for Health:
A Strategic Approach for the EU 2008-2013
COM(2007) 630 final

PRINCIPLE 1: A STRATEGY BASED ON SHARED HEALTH VALUES

... the Council adopted a statement on common values and principles in EU healthcare systems, listing the overarching values of **universality, access to good quality care, equity and solidarity**(1) ...

(1)Council Conclusions on Common Values and Principles in European Union Health Systems (2006/C146/01)

2. European activities in Personalised Medicine?

a. European Health Forum Gastein (EHFG)

EHFG 2006, 2010, 2011, 2012, 2013 and 2014

European Health Forum GASTEIN

PerMed

EHFG-Forum 4 "Personalised Medicine 2020"
October 2nd 2014

10.30 – 10.40 am	**Citizens' Perspective and Needs** *Kaisa Immonen-Charalambous*, European Patients' Forum (EPF), Belgium
10.40 – 10.50 am	**A Hospital's Perspective** *Antonio L. Andreu Periz*, Instituto de Salud Carlos III, Spain
10.50 – 11.00 am	**The General Practitioner's perspective** *Ferenc Hajnal*, European Union of General Practitioners (UMEO), Hungary
11.00 – 11.10 am	**Best Practice Example - Rare Diseases** *Christoph Klein*, University Munich, Germany
11.10 – 11.20 am	**Best Practice Example - Nutrition** *André Boorsma*, Netherlands Organisation for Applied Scientific Research (TNO), the Netherlands
11.20 – 12.00 am	Moderated **Discussion II & Conclusions** (Clive Cookson)

b. Public Health Genomics European Network (PHGEN)

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public health genomics
European Network

PHGEN II

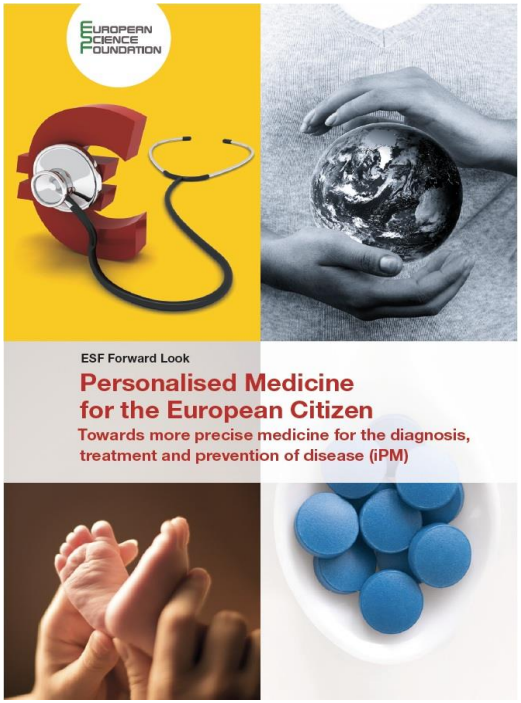
"European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies”

DE GRUYTER DOI 10.1515/dmdi-2012-0026 — Drug Metab Drug Interact 2012; x(x): xxx–xxx

Angela Brand* and Jonathan Lal for the Public Health Genomics European Network (PHGEN II)

European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies: the 2012 Declaration of Rome

c. European Science Foundation (ESF)



In-depth expert interviews

ESF Position Paper

May 2011

Technology

19-20 Sept 2011
London, UK

Disease Summit

18-20 Oct 2011
The Hague, NL

1) CV & metabolic diseases
2) Oncology
3) Rare Diseases

"Big picture" Summit on clustered issues

13-14 Feb 2012
Dubrovnik, HR

Identify grand challenges and recommendation

Stakeholder conference

18 April 2012
Rome, IT

Consensus discussion on Grand Challenges and overall recommendations

d. CSA-PerMed

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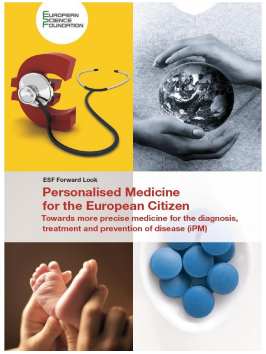
public health genomics European Network

European Alliance for Personalised Medicine



FP7 CSA - PerMed
Personalized Medicine 2020 and Beyond – Preparing Europe for Leading the Global Way

Consortium: Research and Health Ministries (funding bodies)
Connected to other key European initiatives in Personalized Medicine (e.g. ESF, PHGEN, EHFG, EAPM, EPEMED, HOPE)
Aim: strategic research and innovation agenda (SRIA) for Europe

1st Workshop of stakeholders March 27/28th 2014 in Berlin
Parallel Forum at the European Health Forum Gastein (EHFG), October 1-3, 2014
Webpage: http://www.permed2020.eu

European Health Forum GASTEIN

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Workshop Session: „Regulation, Reimbursement, Market access“

What is different? Regulatory gaps & needs?

... regulatory need: in case of safety and risk!

CSA PerMed Workshop 1, Berlin 27./28.03.2014

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„Regulation, Reimbursement, Market access“ ...

1. Assumption of non-linearity, dynamics of information, complexity

i.e. „momentum“: no prediction of risk/phenotype possible, no indication, no validation possible – regulatory need??

Exception „hazard“!!

2. product/diagnostics (medical device) versus process/tool – no regulatory need ...

3. Outcome data: feedback from market back to DSMs (conditional approvals, adaptive (social) licensing and conditional reimbursement)

e. European Alliance for Personalised Medicine (EAPM)

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European Alliance for Personalised Medicine

EAPM "Big Data" WG
(lead: Intel & Science Europe)

"European Data Value Chain Strategy – A lighthouse initiative on Personalised Medicine" (Policy paper 7 May 2014)

European Alliance for Personalised Medicine

”The European Commission is invited to focus funds to stimulate a Lighthouse Initiative on Personalised Medicine whereby computing infrastructures, data collection, storage, analytics, management, governance, security and privacy are put to work to establish a European –wide Big Data exchange for personalised medicine to spearhead research and medical decision making at the point of care.”

European Alliance for Personalised Medicine

The three sets of policy actions of big data for personalized medicine

Liberate the data but do no harm	Bring it now	Prepare the future
•Collaboration • Sharing •Public/Private partnerships •Transparency •Privacy •Ownership	•Clinical adoption •Data curation •Veracity •Security •Common standards	•Public education •Workforce skills •ICT infrastructures for life sciences •Bioinformatics •Analytics

Specialised Treatment for Europe‘s Patients – „STEPS“

informed about, and engaged in, their own healthcare. Regulators must make it possible to allow patients early access to novel and efficient treatment.

Together we can transform our healthcare system into one that delivers the best care for patients, empowers them, puts research and innovation at their service, and gives the best possible value. But the right conditions must be in place.

Empowering patents depends upon each being treated as an individual, taking into account not only the illness but also differing social and cultural backgrounds.

The patient needs to be involved in every aspect of treatment. Education and simplified, standardised information, plus full access to all relevant medical files, are cornerstones of this. The patient should have access to all possible treatments.

With the support of the European Commission and Parliament we can make this happen. It is the responsibility of all of us and all stakeholders must devise an aligned strategic research agenda, with input from all disciplines but including the patients.

All EAPM members (patients, medical professionals, healthcare planners, industry, scientists and researchers) share the vision of a Europe which inspires trust in its health systems. Unnecessary deaths of patients could be avoided via greater access to innovative treatment and diagnostics and efficiently organised research.

With this in mind, the European Alliance for

- **STEP 1: Ensuring a regulatory environment which allows early patient access to novel and efficacious personalised medicine (PM)**
- **STEP 2: Increasing R&D for PM, while also recognising its value**
- **STEP 3: Improving the education and training of healthcare professionals**
- **STEP 4: Supporting new approaches to reimbursement and HTA, required for patient access to PM**
- **STEP 5: Increasing awareness and understanding of PM**

EAPM believes that achieving these goals will improve the quality of life for patients in every country in Europe.

SIEPs

European Alliance for Personalised Medicine

An introduction to EAPM, its Policy Taskforces and STEPs campaign

SIEPs

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Personalised Medicine – what‘s in for RDs?

... A lot – a „www“ (win win win) situation!!

„Personalised Medicine for Rare Diseases

and

Rare Diseases for Personalised Medicine“!


THANK
YOU
GRACIAS
DANKSCHEEN
ARIGATO
SHUKURIA
JUSPAXAR
TASHAKKUR ATU
YAQHANYELAY
GOZAIMASHTA
EFCHARISTO
KOMAPSUMNIDA
MAAKE
GRAZIE
MEHRBANI
SUKSAMA
EKHMET
PALDIES
TINGKI
BİYAN
SHUKRIA
BOLZİN
MERCI