Precision Medicine and Personalized Health

Concepts, Opportunities and Challenges

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September 24-27, 2018

Agenda

Challenges to healthcare

Variability in disease risk and response to treatment

Strategies: Personalized Medicine / Precision Medicine

Tools and Technologies

Pharmacogenomics

The digital transformation of medicine, BIG DATA, AI

Translational challenges

Challenges to Healthcare

Demographic changes

Scientific and technological advances

Digitalization

Greater patient expectations

Increasing healthcare expenditures

More Challenges to Healthcare

There are no effective drugs for many chronic diseases

Existing drugs do not work in all patients

Adverse drug events the 4th leading cause of death

Health

How should we define health ?

WHO 1948: « A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity »

Alternative: « Ability to adapt and self manage in the face of social, physical and emotional challenge »

Huber M et al, BMJ 343: 253-237 (2011)

Lifespan versus Healthspan

Healthspan or Healthy Life Expectancy : The period of one's life that one is healthy, or free of serious disease (number of years of good health that a newborn can expect)

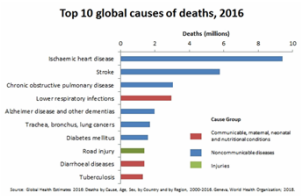
Life expectancy (LE) at birth
Global: **72 years** (74.2 ♀ / 69.8 ♂)
Range: 87.1 (♀ Japan) to 51 (♂ Lesotho)
Increase global 5.5 years since 2000

Healthy life expectancy (HALE) at birth*
Global**: 63.3 years** (64.8 ♀/ 62.0 ♂)
Range: 76.2 (Singapore) to 44-48 (Subsahara)

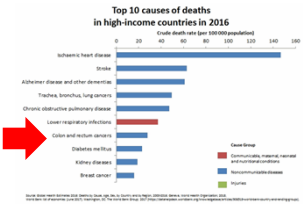
Sustained Development Goals for 2030

~ 9 years difference between Lifespan and Healthspan
Huge differences between low-income & high-income countries

Lifespan versus Healthspan



Serious diseases global



Serious diseases High income countries

Lifespan versus Healthspan Switzerland

This means that we, in Switzerland, now live ~10 years of our lives «unhealthy». This is a long and costly time

Lifespan versus Healthspan

Obvious Questions

How can we shorten the gap between healthspan and lifespan ?

What are the causes of diseases and how can we prevent them or better treat them ?

How can we extend the healthy life expectancy of an individual by designing the best prevention and treatment for this individual ?

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A major problem

Why me ?
Why you ?

Interindividual or person-to-person variability in disease risk, severity & course of disease, and response to treatment

Diseases are heterogeneous as are their hosts

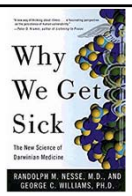
The Origins of Variability

Each individual: Unique set of genes (GENOTYPE)
Each individual: Unique features (PHENOTYPE)

Each individual is unique and differs in disease risk, course of a disease and response to treatment

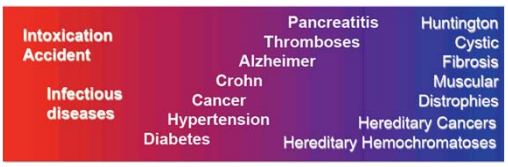
Genetic and acquired causes of diseases

Anamnestic facts	Personal «Omics»	Environment Lifestyle
Age Gender Family history Previous Diseases Medications	Genome Transcriptome Proteome Metabolome Epigenome Microbiome	Ethnic background Nutrition Drugs (DDIs) Chemical exposure Socioeconomic status Microbiome



Genotype and Phenotype

How much is genetic, how much is acquired?

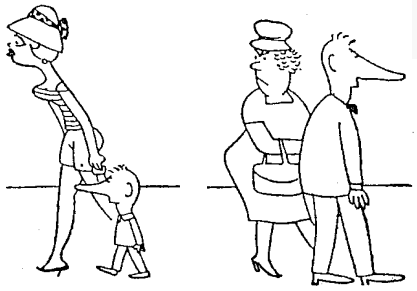


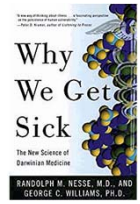
acquired combined monogenic

Courtesy **Stylianos Antonarakis**

Gregor Mendel's curse

How much is genetic, how much is environmental ?

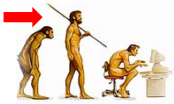




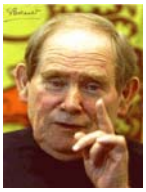
Genotype and Phenotype

Lifestyle or behavioural risk factors

Tobacco use
Unhealthy diet
Beeing overweight
Physical inactivity
Alcohol
Drugs



The Big Questions



Sydney Brenner:„Science is about making predictions"

How much of the variability in disease risk and in response to treatment is due to genetic variation ?

How much is contribution by environmental and other factors ?

How much of this variability is measurable and predictable ?

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The Strategies

Initiatives to accelerate progress in medical research and health care

- Personalized Medicine / Individualized Medicine
- Genomic Medicine (use of genome information)
- Stratified Medicine (groups with shared findings)
- Translational Medicine (bench to bedside)
- Precision Medicine

Shared Tools: Biomarkers – Molecular Diagnostics
Genome Sequences – Omics Data

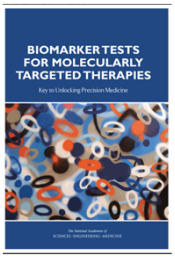
Biomarkers – Molecular Diagnostics

Biomarkers

Genomic
Epigenomic
Transcriptomic
Proteomic
Metabolomic

Where ?

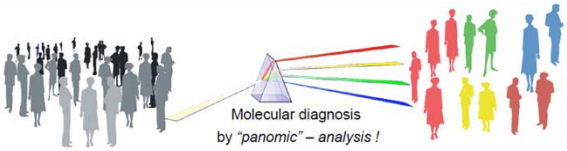
Body fluids
«Liquid biopsy»
Tissue
Imaging
Avatars



National Academic Press 2016

(More on Biomarkers in lecture Denis Hochstrasser)

From «average» to «personal» / «individual» or »precise»



Medicine Today
Reactive, population-based, one-size-fits-all model of care

Personalized Medicine / Precision Medicine
Predictive, preventive, increasingly patient-centric model of care

Personalized Medicine

Definition in EU Horizon 2020 documents

#ICPerMed

Personalized medicine refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or deliver timely and targeted prevention

„Personalized medicine is a strategy to prevent, diagnose, and treat disease so as to achieve an optimal result for the individual."
Meyer UA, Clin Pharmacol Ther 91, 373, 2012

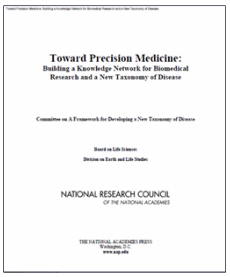
The Strategies

Initiatives to accelerate progress in medical research and health care

- Personalized Medicine / Individualized Medicine
- Genomic Medicine (use of genome information)
- Stratified Medicine (groups with shared findings)
- Translational Medicine (bench to bedside)
- **Precision Medicine**

Shared Tools: Biomarkers – Molecular Diagnostics
Genome Sequences – Omics Data

High-profile endorsement



www.nap.edu

"Tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier."

— President Barack Obama, State of the Union Address, January 20, 2015

A New Initiative on Precision Medicine
Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.
N Engl J Med 2015; 372:793-795 | February 26, 2015 | DOI: 10.1056/NEJMp1500523

What is Precision Medicine ?

Precision = more accurate, precise

President Obama's Precision Medicine Initiative is developing better approaches to preventive care and medical treatments by:

Helping patients gain access to their health information so they can collaborate in their own care

Consider each individual's specifics, like genes, environment, lifestyle

Bringing new, effective medical technologies to the market faster

Building a research network of 1 million or more U.S. volunteers

wh.gov/PMI

Personalized Medicine, Individualized Medicine, Stratified Medicine, Precision Medicine

What's in a Name ?

Precision Medicine and Personalized Medicine / Health are not strictly defined and have common goals. Conflation of the two terms leads to the situation that they are used ***interchangeably***

«one size fits all» average patient model is out

To take interindividual variability into account is the common concept of all these strategies

Precision / Personalized Medicine in Practice Today

Driver mutations in cancer cells predicting efficacy

Imatininb, gefitinib, trastuzumab, vemurafenib, crizotinib…. (~30 drugs, but only ~ 15 % of patients eligible, only 6.6 % benefit ; *Science 360:365 (2018)*

Predictors of non-response

K-ras mutations and anti-EGFR , ***CYP2C19*** variants and clopidogrel

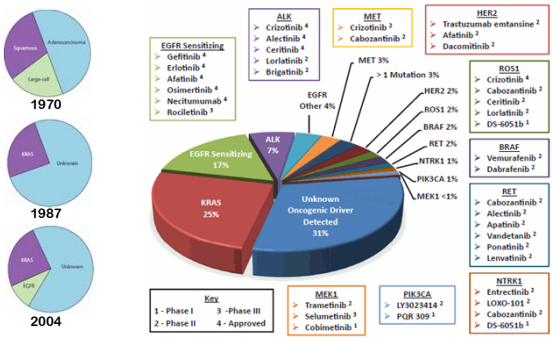
Avoiding serious adverse events by pharmacogenomics

HLA variants and Abacavir, Carbamazepine, etc

Pharmacogenomics (germline) in general

7% of approved drugs,18 % of prescribed drugs have "actionable pharmacogenomic consequences; Variants of 20 genes affect efficacy and safety of ~ 90 drugs

Frequency of Molecular Aberrations in Driver Oncogenes in Lung Adenocarcinoma



J of Thoracic Oncology 11: 613-638 (2016)

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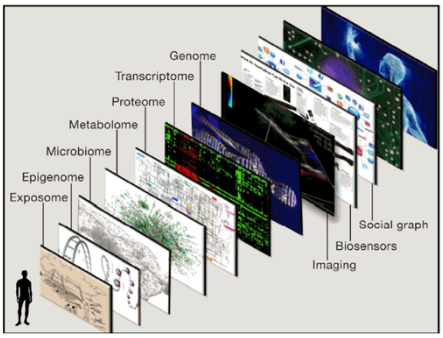
The digital transformation of medicine, BIG DATA, AI

Translational challenges

Defining the Medical Essence of a Human Beeing



Eric Topol: Individualized Medicine from Prewomb to Tomb
Cell 157: 241-253, 2014

There is no wild-type «Human Genome»
There are only «Individual Genomes»
We are all Mutants

Genomes by the Thousends

www.1000genomes.org

A global reference for human genetic variation

An integrated map of structural variation in 2,504 human genomes

October 1, 2015

Nature 526: 68 - 74, 2015
Nature 526: 75 - 81, 2015

A typical individual genome differs from the haploid reference human genome assembly at **~ 4 to 5 million sites**

SNPs, SNVs, structural variants, protein changing variants, new mutations

Total sequene variation ~ 1 % (~ 30 million basepairs)

From DNA to function

Genome	What could happen
Epigenome	What might be happening
Transcriptome	What might be happening
Proteome	What is probably happening
Metabolome	What is happening
Clinical outcome	What is really happening

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Pharmacogenetics – Pharmacogenomics

Essential component of:

- ***Personalized Medicine / Individualized Medicine***
- ***Genomic Medicine***
- ***Stratified Medicine***
- ***Precision Medicine***

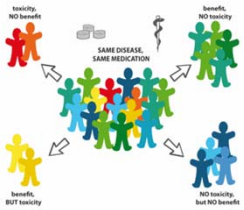
Pharmacogenetics - Pharmacogenomics

Study of how genome diversity (or genetic variation) is related to inter-individual variation in the clinical response to drug therapy

Pharmacogenetics:
Variability in drug response due to heredity. Vogel,1959
Pharmacogenomics:
Role of the genome in human drug response. After 2001

Drug efficacy and drug safety

90 % of treatments are effective in only 30 to 60 % of patients
5 -15 % of patients have adverse drug reactions (ADRs)



Goals of Pharmacogenomics

Identify the conditions in which **heritable factors** allow pharmacogenomic testing to:

Predict the «precise» individual dose

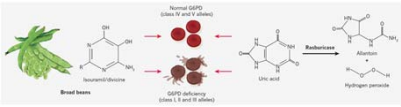
Predict nonresponders & responders to therapy

Predict which individuals are at risk of drug toxicity

History of Pharmacogenetics

G6PD deficiency and«Favism»
Hemolysis after ingestion of Fava beans
A first example of pharmacogenetics ?

Pythagoras
570-495 BC

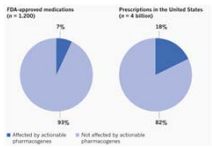


***G6PD*, glucose-6-phosphate dehydrogenase**

510 BC **Pythagoras recognized danger of ingesting broad beans (Vicia fava)**

1954 **Primaquine hemolysis - *G6PD* (Dern et al.)**

Pharmacogenetics – Pharmacogenomics

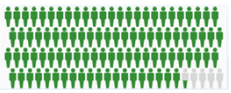


Relling & Evans
Nature 526: 343-350 (2015)

In the USA ~7% of approved drugs, 18 % of prescribed drugs are affected by "actionable" pharmacogenes

Variants of ~20 genes, so-called pharmacogenes, affect efficacy and safety of ~ 90 drugs

95-96 % of individuals have one or more genetic variants in important PGx genes



(lecture Ron van Schaik, many other examples next 3 days, session at FEAM conference)

Consortia, Programs, Data resources

eMERGE PGx
EMRs • Genomics • Pharmacogenomics

SPHINX
A resource of the eMERGE Network

Pharmacogenetics & Stratified Medicine Network

PG4KDS: Clinical Implementation of Pharmacogenetics

U-PGx | Ubiquitous Pharmacogenomics

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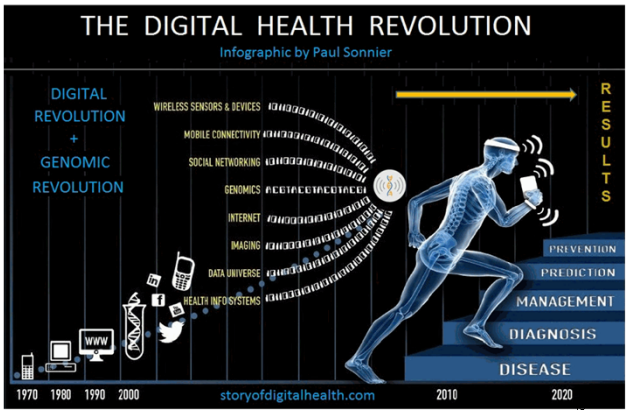
Digital Health & Digital Medicine

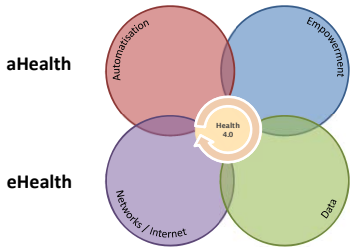
(My personal) overlapping definitions

Digital Health Application of digital technologies to improve health, healthcare, living, and positively affect society

Digital Medicine Application of digital technologies to improve the practice of medicine and help to make it more individualized



The broad scope of digital health

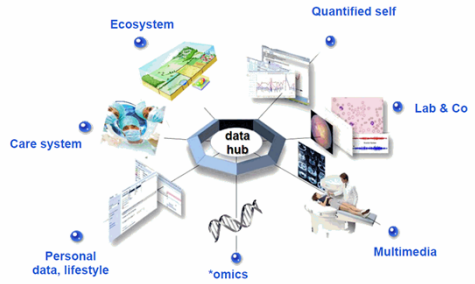


Adapted from Jürgen Holm (2018)

Berner Fachhochschule | Medizininformatik

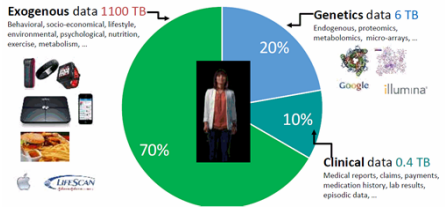
pHealth and eHealth

(Personal Health) (Electronic Health)



(Source: Christian Lovis, Université de Genève)

Health related data during a lifetime



TB, terabyte: 10^{12} bytes

Source: N.S.Hekster, IBM, Innovation for Health 2016

The enormous amount of health-related data cannot be used without **new methods of data processing & interpretation**

Big Clinical Data

The Influence of Big (Clinical) Data and Genomics on Precision Medicine and Drug Development

Joshua C. Denny[1,2], Sara L. Van Driest[2,3], Wei-Qi Wei[1] and Dan M. Roden[1,2,4]

Volume 103, Issue 3

Breaking Down Barriers to Effective Patient Care

Pages: 351-529
March 2018

Denny et al Clin Pharmacol Ther 103:409-418 (2018)

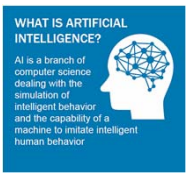
Table 2 Large cohorts leveraging clinical data for genomics research

Biobank	Region	Start Year	Size	Website
eMERGE	US	2007	105,325	gwas.net
BioVU	US	2007	>247,000	victr.vanderbilt.edu/pub/biovu
UK Biobank	UK	2006	512,000	ukbiobank.ac.uk
Million Veteran Program	US	2011	>580,000 Goal: 1 million	www.research.va.gov/MVP/default.cfm
Kaiser Permanente Biobank	US	2009	240,000	www.rpgeh.kaiser.org
China Kadoorie Biobank	China	2004	510,000	ckbiobank.org
All of Us Research Program	US	2017	Goal: 1 million or more	joinallofus.org
Taiwan Biobank	Taiwan	2005	86,695 Goal: 200,000	www.twbiobank.org.tw
Geisinger MyCode	US	2007	>150,000	

Limited to cohorts exceeding 100,000 individuals with biosamples. Sizes reported are as of 9/2017. eMERGE, Electronic Medical Records and Genomics Network.

(see Lecture Vincent Mooser, Christine Currat)

Big Data meets Artificial Intelligence (AI)

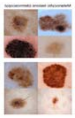


Key applications include data mining, pattern recognition and natural language processing

Source: www.gnshealthcare.com

Promising AI studies in medicine

Diagnoses more precise than doctors can make ?



Skin cancer: Deep learning algorithm does as well as dermatologists, or outperformed the average dermatologist.
*Esteva et al Nature 542:115-118 (2017). Based on **129'450** clinical images.*

Diabetes-related eye problems: Deep learning algorithm for detection of diabetic retinopathy in fundus photographs.
*Gulshan et al. JAMA 316: 2402-2410 (2016). Based on **~10'000** images in ~5000 patients. FDA permitted marketing of IDx-DR device by company IDx (www.eyediagnosis.net)*

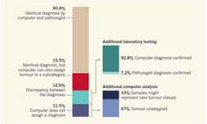
Medication adherence: Using AI to reduce the risk of non-adherence in patients on anticoagulation therapy. ~ 50 % improvement.
Labovitz et al. Stroke 48: 1416-1419 (2017)

AI in oncology

Machine learning classifies cancer

Brain tumours are often classified by visual assessment of tumour cells, yet such diagnoses can vary depending on the observer. Machine-learning methods to spot molecular patterns could improve cancer diagnosis. See Article p469

Capper et al Nature 555: 469-474 (2018)



What AI can and can't do right now

AI can equal or outperform humans at simple, repetitive tasks.

By using deep learning algorithms AI can diagnose disease in many cases as well as physicians.

AI can understand natural language and human speech.

The Achilles'Heel of AI: It requires a large amount of good data.

Because AI can provide predictions based on deep learning algorithms and self-developed functions, one **cannot** tell which features the machine uses to make predictions !!

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eHealth

(Electronic Health)

Multiple definitions. Providing healthcare supported by electronic processes, informatics and communication

Range of services and systems for increased efficiency, quality of care, patient safety

eHealth networks for storage and exchange of data:

Electronic Medical Records / Electronic Health Record (**EMR / EHR**))
Clinical Decision Support (**CDS**)
ePrescribing
Telemedicine devices (CVD,Asthma,COPD, T2D, etc)
Cloud data management
Data from Biobanks
Safety issues / Cybersecurity
etc

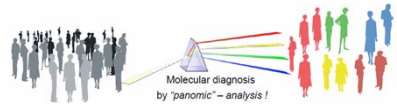
SPHN Swiss Personalized Health Network

SPHN – Planned Activities and Work Packages
(as suggested by the Data Expert Group, 27.01.17)

1) Clinical Research Data Warehouses (CDW)
2) Semantic Interoperability and Data Quality
3) Infrastructure and Security
4) Bioinformatics and Data Analytics (BioDAx)
5) Interoperability with Biobanking (SBP)
6) Training and internal communication
7) Data Coordination Center
8) Development activities and „driver" projects

www.sphn.ch

The digital future of health and medicine



Medicine Today
Reactive, population-based, one-size-fits-all model of care

Personalized Medicine
Predictive, preventive, **digital** patient- centric model of care

- An enormous and rapidly growing amount of health-related data is generated daily
- Digital technologies are used to make healthcare more efficient, increase the quality of clinical decisions and involve the patient as an active «manager» of his personal health
- The health-related data also have the power to be used for research and innovation including drug development

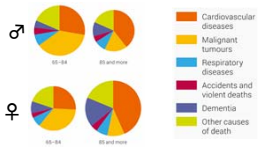
Precision Medicine and Personalized Health
Concepts, Opportunities and Challenges

THANK YOU FOR YOUR ATTENTION

4th ESPT Summer School & SPHN, Geneva, Switzerland
September 24-27, 2018

Lifespan versus Healthspan

Data for **Switzerland** (at birth)
Lifespan: **83.3 years** av both sexes, 81.2 ♂, 85.2 ♀
Healthspan: **73.5 years** av both sexes, 72,4 ♂, 74.5 ♀



Switzerland Leading causes of death 2015 by age group
(FSO 2017)

Difference lifespan – healthspan almost 10 years

An ever increasing digital database

PharmGKB
Pharmacogenomics Knowledge Base
http://www.pharmgkb.org

Clinically-Relevant PGx

- Well-known PGx associations
- Clinically relevant PGx summaries
- PGx drug dosing guidelines
- Drug labels with PGx info
- Genetic tests for PGx
- Star (*) allele translations

PGx Research

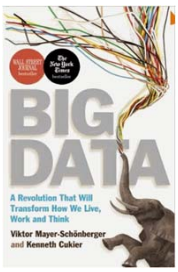
- VIP: Very Important PGx gene summaries
- View PharmGKB pathways
  - Alphabetically
  - By therapeutic category
- Annotated SNPs by gene
- Drugs with genetic information

Drugs	**645**
Drug labels	**509**
Dosing guidelines	**100**
Clinical annotations	**3901**

Pathways	**132**
VIPs *(Very important pharmacogenes)*	**65**
Variant annotations	**20'867**

Accessed September 23, 2018

Scope of Big Data in the Health Sector



Vayena et al Bull World Health Organ 96: 66-68 (2018)