Genomics in Precision Medicine / Personalized Medicine

Urs Albert Meyer
Biozentrum, University of Basel, Switzerland
Homepage: www.ursmeyer.biozentrum.unibas.ch

3rd ESPT Summer School, Belgrade, August 20, 2016

Health Issues

Subtitles

• Basic concepts
  Medical needs and definition of terms
• Progress
  The increasing knowledge base and new technologies
• Issues
  Clinical implementation
• Opportunities
  The future

Health Issues

Lifespan versus Healthspan

Healthy life expectancy, a measure of the number of years of good health that a newborn can expect, stands at 63.1 years globally (64.6 ♀, 61.5 ♂).

Behavioural risk factors

- Tobacco use
- Unhealthy diet
- Being overweight
- Physical inactivity
- Alcohol use

NCD: noncommunicable diseases (68% of all deaths)

Goal: Increase Healthspan

Strategy: Precision Medicine
Unmet Medical Needs

For many common diseases (cancer, dementia, multiple sclerosis, rheumatoid arthritis, emphysema, etc.) there are no effective or curing therapies

Even with well established drug therapies, there are many patients that do not respond

All drug therapies lead to unwanted or adverse effects in some patients

Why do we have no effective prevention or treatments for these diseases?

Why is disease risk and drug response so variable?

How can we improve?

Unmet Medical Needs

Genomics in Precision Medicine

Agenda

Health Issues - Medical Needs
Nature and Nurture (Genotype and Phenotype)
Precision Medicine / Personalized Medicine
Genomics and other Omics
Pharmacogenomics
Opportunities and Challenges

Interindividual variability in drug response

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
How do genotype and phenotype relate to each other?

Take home message 1

Clinical (patient) factors + Omics + Environmental factors determine the phenotype

How much is contribution of genome to phenotype?
How much is contribution by environmental and other factors?
How much is measurable and predictable?

Sydney Brenner: “Science is about making predictions”

Gregor Mendel’s curse

How much is genetic, how much environmental?

Genotype & Phenotype or Nature & Nurture

Genomics in Precision Medicine

Agenda

Health issues - Medical Needs
Nature and Nurture (Genotype and Phenotype)
Precision Medicine / Personalized Medicine
Genomics and other Omics
Pharmacogenomics
Opportunities and Challenges
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)
- Omics Medicine

Tools: Biomarkers – Molecular Diagnostics

Biomarkers
Biomarkers are functional variants or quantitative indices of a biological process that predict or reflect the evolution of or predisposition to a disease or a response to therapy (e.g., HbA1c in diabetes).

Biomarkers serve to integrate preclinical, translational and clinical science.

Personalized / Individualized Medicine
A strategy to predict and improve clinical outcomes

China Daily 6 April 2016
«China has launched a strategic initiative to boost the use of precision medicine - treatments specifically designed for individual patients - that will receive government funding starting 2016 with 60 billion yuan (USD 9.2 billion) spread over 15 years to 2030.»

The China Precision Medicine Initiative (PMI)

From Personalized Medicine to Precision Medicine

U.S. National Research Council 2011

$ 215 million


From Personalized Medicine to Precision Medicine

National Academic Press 2016

The China Precision Medicine Initiative (PMI)

China Daily 6 April 2016
«China has launched a strategic initiative to boost the use of precision medicine - treatments specifically designed for individual patients - that will receive government funding starting 2016 with 60 billion yuan (USD 9.2 billion) spread over 15 years to 2030.»
What is Precision Medicine?

**Concept**
- Develop disease prevention and treatment strategies based on individual variability

**Approach**
- Large cohorts (millions) of individuals willing to share their genomic, medical, lifestyle and environmental exposure data. Link these data to health outcomes. Initially strongly based on genome sequences

**Goals**
- Better diagnosis of rare diseases and conditions
- More targeted treatments for cancer
- Integration of sequence data into routine health care
- Development of a scalable, secure and powerful data infrastructures

**Precision Medicine / Personalized Medicine**

The Promise of the Initiatives

- Better early prediction of individual disease risk with possibilities for prevention
- Precise diagnosis subclassification of disease, biomarkers for stage and prognosis based on genomic and other data
- Individualized therapy pharmacogenomics, biomarkers for efficacy and safety, prediction of individual dose
- Evaluation of individual clinical outcome «N-of-1 trials»

What's in Name?

Personalized Medicine, Individualized Medicine, Precision Medicine:

Conflation of the terms «personalized» and «precision»?

NAS report: Use of «precision» was intended to avoid the implication that drugs or medical devices would be created for a single patient.

Barack Obama: «...and to give us all access to the personalized information we need to keep ourselves and our families healthier».

«one size fits all» average patient model is out

The Big Questions

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?

Sydney Brenner: "Science is about making predictions"

Agenda

Health issues - Medical Needs
Nature and Nurture (Genotype and Phenotype)
Precision Medicine / Personalized Medicine
Genomics and other Omics
Pharmacogenomics
Opportunities and Challenges

Take home message 2

To take interindividual variability into account is the common strategy of

Personalized Medicine
Individualized Medicine
Precision Medicine
**INTERINDIVIDUAL VARIABILITY OF THE HUMAN GENOME SEQUENCE**

A typical individual genome differs from the haploid reference human genome assembly:
- at ~ 4.1 - 5.0 million sites
- by ~ 3.5 to 4.3 million single nucleotide polymorphisms (SNPs, frequency >1%)
- by ~ 546,000 - 625,000 small insertions, deletions (Indels)
- by ~ 1000 large deletions, ~ 10 inversions
- by ~ 160 copy number variants (CNVs)
- by ~ 24-30 variants implicated in rare disease (ClinVar)

Total sequence variation ~ 1 - 2 % (~ 30 million basepairs)

---

**Progress in Genomics**

2001 2004 2010

**Progress in other Omics**

2013 2014 2015 2016

- Microbiome
- Epigenome
- Genome editing
- Exome

---

**Genomes by the Millions**

88 million variants
- 84.7 million SNPs
- 3.6 million Indels
- 60,000 structural variants

---

**Human Genome Sequence Potential Benefits to Medicine**

- Understanding monogenic disorders
- Understanding polygenic complex disorders
- Understanding different cancers
- Provide more precise diagnosis
- Estimate predispositions to disorders
- Opportunities for novel treatments
- Opportunities for precision/personalized medicine

---

**There is no «wild-type» human genome**

We are all «mutants»!

1-2 % difference in WGS

---

Eric Topol, 2014

www.1000genomes.org
Recent developments to explain diversity in disease risk and drug response

- NGS, sequencing faster, cheaper, deeper, more
- HapMap, structural maps
- Genome-wide association studies with SNPs (GWAS)
- Encode (how cells interpret the genome information)
- Parallel development of other ‘omics’ technologies

NGS: next generation sequencing; SNPs, single nucleotide polymorphisms; GWAS: genome-wide association studies

Genomics in Precision Medicine

Agenda

Health issues - Medical Needs
Nature and Nurture (Genotype and Phenotype)
Precision Medicine / Personalized Medicine
Genomics and other Omics
Pharmacogenomics
Opportunities and Challenges

Pharmacogenetics

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

The terms are used interchangeably

Pharmacogenetics

Essential Component of Personalized Medicine / Precision Medicine

Glucose-6-Phosphate Dehydrogenase Deficiency

Drugs and chemicals associated with hemolysis

Most common enzyme deficiency (~ 400 million)
More than 400 variants of the enzyme
Incidence Italy 0.1 to 23.1%
Patients may present with acute hemolysis

McDonagh EM et al. Pharmacogenetics and Genomics 2012
**Actionable Gene-Drug Interactions**

**Definitions**

Gene-drug Interaction (DGI); gene/drug pair: Gene variant or DNA sequence variation associated with altered response to one or several drugs.

**Actionable:** Evidence meets threshold of clinical implementation, i.e. the genotype triggers a change in standard therapy.

---

**PGx TUMOR BIOMARKERS**

*Clinical utility established – Approved tests*

**Examples**

- Anastratol, Exemestan, Fulvestrant, Letrozol, Toremifien, Tamoxifen - Hormone receptors (ER, PR) Breast
- Trastuzumab, Lapatinib, Pertuzumab - HER2 (ERBB2) Breast
- Imatinib, Dasatinib, Nilotinib - BCR-ABL CML
- Imatinib - KIT (C-KIT) GI stromal tumor
- Panitumumab, Cetuximab - KRASwt CRC, Head and Neck
- Erlotinib, Gefitinib, Alatinib, Cetuximab - EGFR CRC, NSCLC
- Crizotinib - EML4-ALK fusion NSCLC
- Vemurafenib, Dabrafenib, Trametinib - BRAFV600E, V600K Melanoma

~15 acquired somatic variants, ~ 30 drugs

---

**Actionable germline genetic variation and associated drugs**

16 genes / 30 drugs

<table>
<thead>
<tr>
<th>Gene</th>
<th>Drug response affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT</td>
<td>Mercaptopurine, thioguanine, allopurinol</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Cisplatin, irinotecan, methotrexate, vinblastine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Thiopterins, antithrombin, Coumadins, warfarin</td>
</tr>
<tr>
<td>HMO1D1</td>
<td>Warfarin, photosensitivity</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Allopurinol, cotia, isoniazide, thioacetamide</td>
</tr>
<tr>
<td>CYP1B1</td>
<td>Isoflavone</td>
</tr>
<tr>
<td>HLA-DQB1</td>
<td>Racemic sulindac, capsaicin, trastuzumib</td>
</tr>
<tr>
<td>IDH2</td>
<td>Rasburicase, fenretroate, temozolomide</td>
</tr>
<tr>
<td>TPMT</td>
<td>Methylprednisolone, atosavir</td>
</tr>
<tr>
<td>SERPIN6</td>
<td>Sorafenib</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Interferon</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Therapeutic</td>
</tr>
</tbody>
</table>

**Genomic changes important for cancer therapy**

**Cancer genome**

- targeted therapies
- immunotherapies
- early detection
- prognostic tests

**Host genome**

- mercaptopurine, thioguanine (TPMT)
- irinotecan, nilotinib (UGT1A1)
- tamoxifen (CYP2D6)

---

**Genomics in Precision Medicine**

**Agenda**

- Health issues - Medical Needs
- Nature and Nurture (Genotype and Phenotype)
- Precision Medicine / Personalized Medicine
- Genomics and other Omics
- Pharmacogenomics

**Opportunities and Challenges**
Implications of whole genome / exome sequencing for pharmacogenomics

Digital drug response profiles
Assessment of rare variants
Copy number variations (CNVs)
Analysis of complex gene loci (CYP2D6)

The personal genome sequence allows to assess the totality of known pharmacogenomic associations:

Stephen Quake genome
650 annotations for potential drug-response phenotypes and 63 pharmacogenetic variants with known potential for clinical relevance evaluated
Lancet 375:1525-35, 2010

The Personal Drug Response Profile
The personal genome sequence allows to assess the totality of known pharmacogenomic associations:

231 ADME related genes sequenced in 482 individuals
17,733 variants / individual
2521 novel variants in 5 selected pharmacogenes (CYP2D6, CYP2C9, VKORC1, UGT1A1, TPMT)
Of these 202 in exons and proximal regulatory regions

WGS captures multiple novel and potentially important rare variants in individual patients

Targeted Sequencing Studies of 82 Pharmacogenes
True Pharmacogenomic Variability by Deep Sequencing

PGRNseq: a targeted capture sequencing panel for pharmacogenetic research and implementation
Adam S. Gordon*, Robert S. Fulton*, Xiang Qin*, Elaine R. Mardis*, Deborah A. Nickerson* and Steve Scherer*

Genetic Variation Among 82 Pharmacogenes:
The PGRNseq Data From the eMERGE Network
Clinical Pharmacol Ther (online June 1, 2016), 51 authors

Utility as an affordable clinical test
Ultra deep coverage data identifies many novel, rare variants
96.2 % (N~5000) had one or more actionable gene variant

Precision / Personalized Medicine
Opportunities

Risk analysis – preventive measures
Precise diagnosis (new taxonomy)
Subphenotypes of disease
Individualized choice of treatment
Increased efficacy of treatment
Prevention of adverse drug reactions
Large databanks for decision tool


Genomics in Precision Medicine
Agenda

Health issues - Medical Needs
Nature and Nurture (Genotype and Phenotype)
Precision Medicine / Personalized Medicine
Genomics and other Omics
Pharmacogenomics
Opportunities and Challenges
Clinical implementation of pharmacogenetic testing has not been widely adopted to improve patient care.

Examples: Abacavir, Allopurinol, Carbamazepine / HLA; Thiopurines / TPMT; Clopidogrel / CYP2C19; Irinotecan / UGT1A; Somatic mutations/Rx in oncology.

Lack of studies demonstrating analytical validity, clinical validity and clinical utility of pharmacogenetic testing
Lack of peer-reviewed guidelines and clinical decision support (CDS) for physicians on how to use genetic data in clinical practice
Limited availability of pharmacogenetic test results at point of care (PoC)

Attempts to solve the translational gap
CPIC: The Clinical Pharmacogenetics Implementation Consortium (open, international non-profit group) creates standardized guidelines on how to use genomic data to inform prescribing
DPWG: The Dutch Pharmacogenetic Working Group. Dose recommendations for gene-drug interactions

From consensus to clinical decision support From ORs/HRs to decision trees, scoring systems

Preemptive genotyping
Whole Genome or Exome Sequence
PCR, Microarrays, etc.
Pharmacogenomic patient cards

Electronic Patient Record
Mobile Patient Records
Clinical Decision Tools

Precision Medicine
Challenges
How will we integrate this data intensive biology or better understanding of disease into tangible benefits for patients?

- Introduction of eHealth
- Electronic Medical Records
- Big data and data mining
- Complexity of common diseases
- Dealing with probabilities
- Internet and social media
- Participation of individuals and patients
- Consumer genomics, wearable devices
In every prescribing decision, the patient's genomic (and other omics) variation is considered as an inherent individual characteristic, in addition to the other individual variables like age, weight, organ function, allergies, etc.