Personalized Genomics in molecular Diagnostics

Prof. Dr. med. Daniela Steinberger
bio.logis Genetic Information Management GmbH
bio.logis Center for Human Genetics
One title – many questions

Personalized Genomics in molecular Diagnostics

• What means:
  • "personalized" in
    • ... real life?
    • ... a genomics context?
• Why should we:
  • apply genomic information?
  • "personalize" genomics?
• How could we do this?
What is the meaning of personalization?
The meaning of personalization

Adaption of industrially produced mass products to more "individual" needs of customers

Allegory of actual tool culture
The meaning of "personal" in genomics?

Every genome is personal

What could "personal genomics" be?
What is the meaning of personalization in medicine?

Adaption of industrially produced mass products to more "individual" needs of customers

Adoption of medicine (DX and therapy) to personal needs of patients
Personalized Medicine: a very old concept

Symptoms of one person treated under consideration of

• Age
• Sex
• Body weight
• Disease history
• Genetic data...

= more information for „stratification“ to enable better outcomes

„Refinement“ of diagnostics/therapy: nearer to individual need of customer/patient

"You are a poor metabolizer for CYPXXX. You should not take even one single pill of Aspirin, otherwise you will never be able to call me again. You better take 1 ton of Plavix."
The human genome: Dynamics costs and turn around time (TAT) for analysis

Human Genome Project
- TAT: 13 years
- costs: 3'000 mio.$

Project Jim
- TAT: 2 months
- costs: 1 mio.$

Genome as a service
- TAT: 6 weeks
- costs: 0.35 mio.$

- ABI SOLiD 4
  - costs: 6 T$

- Illumina
  - costs: 3.8 T$

- Complete Genomics
  - costs: 1.5 T$

- Ion Torrent
  - costs: 1 T$
1 individual Genome: Numbers

- 2 x 3,000,000,000 genetic bits (nucleotides)
- effects for life/health state by:
  - variations in sequence of genetic bits (many information)
  - combinations of:
    - genetic bits (a great many information)
    - genetic bits + environmental factors (>great many information)
The Problem:
How can large amounts of genetic Data / Individual be used for a "personalised" Medicine?
Big Data

management

genetic information
Genetic Information: Structure of quality

**Ordinary lab report:**
- Delivery data of many parameters
- Interpretation by MD @POC

**Genetic DX report:**
- Delivery data of only one gene
Genetic information @POC

Interpretation by MD???
Use of genetic information by MD @POC

Usable only, if interpretations are delivered by geneticist

Interpretations =
• complex structured texts
• actionable recommendations
Production of non-genetic DX reports: Nearly industrial workflow

Sample → Analysis → measured data → Report → Delivery

LIMS

highly automatical processes to ordinary lab report

Interpretation by MD @POC
Data Analysis for Next Generation genetic diagnostics: what does it mean, many data/individual?

**PGS Panel**

(60 genes/ >200 variants)

<table>
<thead>
<tr>
<th>Bezeichnung Sen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCD1</td>
<td></td>
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<tr>
<td>ADRR1</td>
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<tr>
<td>ADRB2</td>
<td></td>
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<td>AGT</td>
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<td>COL1M</td>
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<td>CYP1A2</td>
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<td>CYP2A6</td>
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<td>CYP2B6</td>
<td></td>
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<tr>
<td>CYP2C19</td>
<td></td>
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<tr>
<td>CYP3A4</td>
<td></td>
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<tr>
<td>CYP3A6</td>
<td></td>
</tr>
<tr>
<td>NAT2</td>
<td></td>
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<tr>
<td>SLC18A1</td>
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<td>ADH03</td>
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<td>AGTR1</td>
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<td>ALDH2</td>
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<td>ALDO9</td>
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<tr>
<td>APDR</td>
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<td>AS3A</td>
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<tr>
<td>ATF7B</td>
<td></td>
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<tr>
<td>PIM</td>
<td></td>
</tr>
</tbody>
</table>

**many print outs**

1000 pages

1,2x BU
Data Analysis for Next Generation genetic diagnostics: what does it mean, many data/individual?

**PGS Panel**  
(60 genes/ >200 variants)

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<tr>
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<td>AOT</td>
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<td>COMT</td>
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<td>CYP1A2</td>
<td></td>
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<tr>
<td>CYP2A6</td>
<td></td>
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<tr>
<td>CYP2B6</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>CYP3A6</td>
<td></td>
</tr>
<tr>
<td>NAT2</td>
<td></td>
</tr>
<tr>
<td>SLC16A1</td>
<td></td>
</tr>
<tr>
<td>VKORC1</td>
<td></td>
</tr>
<tr>
<td>AAT</td>
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<tr>
<td>ADH1B</td>
<td></td>
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<tr>
<td>ADRD3</td>
<td></td>
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<tr>
<td>AGTRI</td>
<td></td>
</tr>
<tr>
<td>ALDH2</td>
<td></td>
</tr>
<tr>
<td>ALD03</td>
<td></td>
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<tr>
<td>APDR</td>
<td></td>
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<tr>
<td>AS3PA</td>
<td></td>
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<tr>
<td>AIF7B</td>
<td></td>
</tr>
<tr>
<td>DIM</td>
<td></td>
</tr>
</tbody>
</table>

many print outs

1000 pages

not usable

- time consuming
- ->expensive
- complex
  - data handling
  - interpretation
Data Analysis for Next Generation genetic diagnostics: what does it mean, many data/individual?

Example: Information in "Brockhaus Units"

<table>
<thead>
<tr>
<th>Information Type</th>
<th>Variants</th>
<th>Pages</th>
<th>Bands</th>
<th>Shelf meters</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brockhaus Encyclopedia 21st edition (2006)</td>
<td>300,000 keywords</td>
<td>817</td>
<td>30</td>
<td>1,7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>40,000 pictures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test-Set PGS</td>
<td>200</td>
<td>1000</td>
<td>1,2</td>
<td>0,1</td>
<td>0,3</td>
</tr>
<tr>
<td>Exome</td>
<td>50,000</td>
<td>250,000</td>
<td>306</td>
<td>17</td>
<td>71</td>
</tr>
<tr>
<td>Genome</td>
<td>6,000,000</td>
<td>30,000,000</td>
<td>36,720</td>
<td>2081</td>
<td>8,568</td>
</tr>
</tbody>
</table>
NG-PGX = how can many genetic data/individual be used?

many *content* for many genes:

basic problem concerning

- Production
- Delivery
- Perception

of clinically usable genetic information
Genetic reports: the problem of Production, Delivery, Perception

1°: proprietary system A
2°: proprietary system B
3°: proprietary system C

4°: central nervous system geneticist/molecular biologist

- review DBs
- compilation information + clin. info
- producing
  - interpretation
  - expression
- production reports
- print

LIMS

gDX clin. reports: laborious

! Production

! Delivery

! Perception
Targeting the production problem

Targeting the production problem with bio·logis

replaces

laborious production gDX reports

by

efficient automat. production gDX reports
bio.logis GIMS: reporting module

Rule Engines

- Import / Conversion Genetic Data
- Import Clinical Information

Clinical Report Compiler

Content Management Systems

- iterative changes content / rules
- validation

Medical Review Modules

Output report

learning
Targeting the Production, Delivery, Perception problem

- **Production**
  - LIMS
  - Bioinformatics
  - Clinical actionable information
  - Review DB
  - Clinical actionable interpretation
  - Review gDX reports
  - Portal

- **Delivery**
  - Access for all stakeholders
  - Patients
  - Healthy clients
  - Portal

- **Perception**
  - HIS
  - Patient
  - MD @ POC II
  - Portal

**Standard Interfaces** (e.g. HL7)

- **Sample & clin. info**
- **Genotyping multiple genes**
- **Raw data**
- **Bioinformatic processing**
- **Bioinformatic analyses**
- **Review DB**
- **Compilation information + clin. info**
- **Finding + formulating interpretation**
- **manually writing multiple reports**
- **Portal**
- **automat. production gDX reports**
Improved access and perception to clinically actionable genetic expert knowledge

GIMS

Portal Perception + Access
- filtering multiple results for diff. perspectives:
  - clin. situation
  - drugs
  - symptoms
  - diseases
  - genes
- scientific background
- interactive tools
- personal accounts
  - personal genomics
- optional order entry
The meaning of "personal" in genomics?

Every genome is personal

What could "personal genomics" be?
The meaning of "personal" in genomics?

Medical data: A question of ownership

Patient is paying for data, but:
had traditionally no access to it
The meaning of "personal" in genomics?

Medical data: A question of ownership

Patient is paying for data, but: had traditionally no access to it
Access codes for Physicians and Clients/Patients

**ARZT**

- **Benutzername:** HgryxC12
- **Passwort:** sasdTZU87
- **DOCID:** 2786

**Klient/Patient**

- **Benutzername:** HgryxC12
- **Passwort:** JKHgj68/8

---

**Access codes for Physicians and Clients/Patients**

**Gene stehen wir Ihnen zur Beantwortung weiterer Fragen zur Verfügung:**

T: 089-530 04 37-0 - Montag – Freitag von 08:00 – 18:00 Uhr

**Bio-logis Zentrum für Humangeneik**

Prof. Dr. med. Daniel Czauderna, Bio-logis Zentrum für Humangeneik, – Albertinenstraße 5 – 80337 München – Deutschland

Tel: 089-530 04 37-0

www.biologis.de
• Without aggregation of results and IT tools for connecting them with evaluated interpretations, physicians can not provide the amounts of knowledge

• Access to personal genomic information must be able:
  • to filter for special clinical context
  • to prioritise for acuteness and relevance

Having **the right information available in the right situation**
Having the right information available in the right situation

### Vorsorge & Ernährung:
Genetische Varianten mit Bedeutung für Vorsorge von Stoffwechselstörungen und Dispositionen sowie der für Verträglichkeit und Verstoffwechselung von Lebensmitteln. Es wurden 82 Varianten in 30 Genen untersucht. Bei Ihnen wurden in folgenden Genen Varianten in dieser Kategorie nachgewiesen:

<table>
<thead>
<tr>
<th>Genname</th>
<th>Ergebnis</th>
<th>Beschreibung</th>
<th>Bedeutung</th>
<th>Maßnahme</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS</td>
<td>c.1601G&gt;A .homo</td>
<td>Thromboserisiko</td>
<td>erhöhtes Risiko Fehlgeburten</td>
<td>Disposition Eisen-</td>
</tr>
<tr>
<td>HFE</td>
<td>c.187C&gt;G .homo</td>
<td>Hämochromatose</td>
<td>Disposition Eisen-</td>
<td></td>
</tr>
<tr>
<td>LCT</td>
<td>c.1521_1523del.het</td>
<td>Mukoviszidose</td>
<td>Anlageträger Mukoviszidose</td>
<td></td>
</tr>
<tr>
<td>5 Gene</td>
<td>22 Gene</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Medikamentenwirkung & Therapie:
Genetische Varianten mit Bedeutung für Verstoffwechselung, Wirksamkeit und Sicherheit von Medikamenten. Es wurden 65 Varianten in 29 Genen untersucht. Bei Ihnen wurden in folgenden Genen Varianten in dieser Kategorie nachgewiesen:

<table>
<thead>
<tr>
<th>Genname</th>
<th>Ergebnis</th>
<th>Beschreibung</th>
<th>Bedeutung</th>
<th>Maßnahme</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>CYP2C19*2/*2</td>
<td>Medikamenten-</td>
<td>langsamer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>stoffwechsel</td>
<td>Metabolisierer</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>CYP2D6*1/*1xN</td>
<td>Medikamenten-</td>
<td>ultraschneller</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>stoffwechsel</td>
<td>Metabolisierer</td>
<td></td>
</tr>
<tr>
<td>VKORC1</td>
<td>VKORC1*3/*3</td>
<td>Medikamenten-</td>
<td>erhöhte</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>stoffwechsel</td>
<td>Enzymmenge</td>
<td></td>
</tr>
</tbody>
</table>
With GIMS, personal genomic information is available for all stakeholders in the right time.

Efficacy and Tolerance of Drugs

The enzyme CYP2D6 determines the rate of metabolism of a number of drugs and other exogenous substances, in addition to substances naturally produced in the body. Table 1 gives drugs metabolized by CYP2D6.

Table 1. Drugs metabolized by CYP2D6 (excerpt)

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Drug group</th>
<th>Treatment of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline, domperidone,</td>
<td>Antidepressant</td>
<td>Depression, neuropathic pain</td>
</tr>
<tr>
<td>desipramine, doxepin,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluoxetine, imipramine,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>minipramine, mirtazapine,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>paroxetine, timolol,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>venlafaxine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics, chlorpromazine,</td>
<td>Neuroleptic</td>
<td>Schizophrenia, psychosis, nausea</td>
</tr>
<tr>
<td>haloperidol, olanzapine,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>paroxetine, pimozide,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>risperidone, thioridazine</td>
<td></td>
<td>Attention deficit/hyperactivity syndrome</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
With Personal Genomics portal well known PGX knowledge is translated for clinical practice with easy access to content.

### Results for simvastatin

<table>
<thead>
<tr>
<th>designation of gene</th>
<th>description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLC01B1</td>
<td>SLC01B1 gene variants are associated with different capacities for hepatic uptake of medications for treatment of enhanced cholesterol, hypertension and diabetes. Typical substances influenced by SLC01B1 variants are statins, simvastatin and repaglinide. Delayed transport into liver cells can lead to enhanced drug plasma levels and unwanted side effects.</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>The validation of the translation of this gene card is still in progress. You will be informed when the translation has been published.</td>
</tr>
</tbody>
</table>
PERSONAL RESULT

Two positions were investigated in the SLCO1B1 gene (Chromosome 12, 12p12.2–12.1).

Genetic investigation revealed variants referred to as genotype SLCO1B1*1B/*15.

<table>
<thead>
<tr>
<th>DNA position</th>
<th>Gene copy 1</th>
<th>Gene copy 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.388</td>
<td>A to G</td>
<td>A to G</td>
</tr>
<tr>
<td>c.521</td>
<td>T</td>
<td>T to C</td>
</tr>
</tbody>
</table>

There was a guanine at position 388 in both copies of the SLCO1B1 gene. In one copy of the gene, thymine was replaced by cytosine at position 521 (c.388A>G, homozygous; c.521T>C, heterozygous). This results in replacement of amino acid asparagine by aspartic acid at position 130 (p.Asn130Asp) and in replacement of valine by alanine at position 174 of the protein (p.Val174Ala).
Information is translated into concrete actionable therapeutic recommendation for MDs

Human genetic report on clinical question: simvastatin intolerance
Analysis of SLCO1B1 gene

Genotype:
SLCO1B1*1B/*15

Phenotype:
Reduced transport capacity

Interpretation:
Increased simvastatin plasma level possible owing to reduced hepatic uptake. Elevated risk for myopathy based on SLCO1B1 genotype (see table 2).

Relevance for medication:
- Maximum daily simvastatin dose of 40 mg* (see table 1).
- Monitoring of creatine kinase activity indicated.
- Use alternative medications (e.g., fluvastatin, pravastatin, rosuvastatin) in case of unwanted side effects (see table 1).
- Variants of CYP2C9 gene are associated with enhanced fluvastatin plasma levels. In case of ADE under fluvastatin therapy genotyping of CYP2C9 can be considered.

General information:
Avoid as possible if you are taking:
- Statins: Co-medication with substances inhibiting SLCO1B1
- Simvastatin: CYP3A4 inhibitors
- Fluvarstatin, rosuvastatin: CYP2C9 inhibitors (see table 3)
Production of genetic reports: The progression trap

**Genome**

![Graph showing genome progression from 2003 to 2012 with percentage values:]

**Interpretome?**

![Graph showing interpretome progression with percentage values:]

**Production geneDX reports**

- Sample Handling: 2-5%
- Lab Processing: 60-70%
- Logistics: 20-40%
- Production: 2-5%

**Source:** Berufsverband Deutscher Humangenetiker (BVDH)
## Production genetic reports: Increased efficacy with GIMS

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Time</th>
<th>GIMS Time</th>
<th>Time Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thrombophilia</td>
<td>0.5 - 1 h/report</td>
<td>&lt;1 min./report</td>
<td>&gt;91%</td>
</tr>
<tr>
<td>2. Nutrition Panel</td>
<td>1 - 2 h/report</td>
<td>&lt;1 min./report</td>
<td>&gt;96%</td>
</tr>
</tbody>
</table>
WE WANT TO MAKE EFFECTIVE TREATMENT OPTIMIZATION ACCESSIBLE TO EVERY EUROPEAN CITIZEN

OUR FOCUS

We want to improve the safety and efficacy of pharmacotherapy for every European patient by making clinical pharmacogenomics

SHARED EUROPEAN GUIDELINES

Maintenance and dissemination of pharmacogenomics guidelines within the European Union

IMPLEMENTATION AND EVALUATION

Clinical implementation and outcome evaluation of pharmacogenomics in real-world settings

ENABLING TECHNOLOGIES

Development of powerful and user-friendly clinical decision support systems and non-invasive genotyping methods

COMMUNICATION AND EDUCATION

Development of programs to reach out to healthcare professionals, researchers, and the general public

EUROPEAN COMMISSION DIRECTORATE-GENERAL FOR RESEARCH & INNOVATION Health HORIZON 2020
Aims to ensure that clinical implementation of genome technologies is relevant and responsive to the needs of all. It offers a stepping stone approach towards the genetics clinic of the future, engaging all stakeholders involved in a process of mutual learning and information exchange. Implements key Science with and for Society issues, ensuring that ethical reflection and stakeholder involvement do not occur in parallel,...
• the amount of useful genetic information is BIG and still increasing
  • to implement it @POC, special infrastructure for
    genetic information management (GIM)
    has to be applied for
      • faster Production of reports with interpretations and
        concrete clinical recommendations
      • Delivery of the whole relevant information biotope
      • Perception of large amounts of information:
        filtering and transportation of detailed
        medical and biological background information
      • Personal Genomics Access to all relevant stakeholders
        incl. patients and healthy clients as the
        data owners will become more relevant
      • Integration into existing infrastructures such as LIMS, PHIS, HIS
        is an important basis for enabling the implementation
dna. information. better decisions.

bio.logis Genetic Information Management GmbH
Altenhöferallee 3
60438 Frankfurt
+49 69-530 84 37-0

dns@bio.logis.de
https://gim.biologisgroup.com/