Precision, Personalized and Stratified Medicine

Central role of Lab Medicine in its development and clinical utilization

Where do we stand, where can we go?
Pharmacogenetics

DNA analysis to explain/to predict the response of to drug therapy

Personalized Medicine
Tonight (Jan 2015)
I am launching the
Precision Medicine
Initiative: $215,000,000
(State of the Union)
Pharmacogenetics

Can **YOU** still do without…..?

Off course,
Because I have been working without pharmacogenetics for years!
Prof van Schaik,
I have a problem....
Metabolism of drugs

- CYP2C9
- CYP2C19
- CYP2D6
- CYP3A4
- TPMT
- ...

Liver

Blood
ADVERSE DRUG REACTIONS

5-7% of hospitalizations are due to Adverse Drug Reactions: 5th cause of death (Lazarou 1998).

Only 25-60% of all drugs prove to be effective in treatment.

SUBTHERAPEUTIC
Pharmacogenomics: Can we make it happen?

Scientific evidence for 1 gene and 3 SNPs

Pharmacologists (TDM)

Health Insurers

Politicians

Ethics

General Public

Test Accepted!

Scientific evidence for 1 gene and 3 SNPs
EU quality control program
Ensuring high quality genotyping

Development of new genotyping/multiplex platforms for cheaper and faster analyses

Creating Pharmacogenetic testing facilities in 18 EU countries: integration of pre-emptive genotyping for Cardiology, Internal Medicine, Psychiatry and Oncology

EU Network for exchanging information

Reimbursement and Regulatory Aspects Working Group

Dissemination of knowledge through IFCC, ESPT and national PgX networks

Scientific Trials for identification of scientific gaps and design of new projects

Development of a Decision Support Tool and a safe IT environment for reliable and rapid translation of PGx results into the clinic

Evidence-based dosing recommendations, EU-wide, and up-to-date

Health Technology Assessment and Economical Evaluation For evaluation of cost/benefit

www.eu-pic.net
18 countries
37 institutes
106 participants
PGx request at Erasmus MC
Pakketten:
- DNA Paspoort - Basis: (CYP2C9, CYP2C19, CYP2D6, CYP3A4, VKORC1)
- DNA Paspoort - Uitgebreid: (CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, VKORC1, SLCO1B1)
- Psychiatrie Panel: (CYP2C9, CYP2C19, CYP2D6, CYP3A4)
- Cardiac Panel: (CYP2C9, CYP2C19, CYP2D6, VKORC1, SLCO1B1, ABCB1)
- Pijn Panel: (CYP2C9, CYP2D6, OPRM1, COMT)
- Oncologie Panel: (CYP2D6, DPYD)

Individuele bepalingen:

**Cytochromen:**
- CYP1A2
- CYP2B6
- CYP2C8
- CYP2C9
- CYP2C19
- CYP2D6

**Overige enzymen:**
- BChE, pseudocholinesterase
- DPD
- TPMT
- UGT1A1
- UGT1A9

**Transporters:**
- ABCB1
- ABCG2
- SLCO1B1

**HLA-markers:**
- HLA-A*3101
- HLA-B*1502
- HLA-B*5701

Overig:
- VKORC1
PGx test distribution at Erasmus MC

2015:
55% CYP450
45% other

Antidepressants (Psychiatry)

CYP3A5 3%
CYP2C9 5%
CYP1A2 6%
CYP3A4 9%
CYP2C19 12%
TPMT 10%
HLA-B*5701 16%

Abacavir (HIV)

Antidepressants (Psychiatry)

6MP/aza
ALL, dermatol

Capecitabine (5-FU) (Oncology)

DPYD 19%

Antidepressants (Psychiatry)
CYP2D6 activity distribution

(Slide (adapted) courtesy of M. Schwab)
CYP2D6 and psychoactive drugs

(Stingl 2013 Mol Psychiatry)
Imipramine metabolism

Paul Schenk et al 2008 Mol Psychiatry
Effect of PGx guided therapy

Responders by depression rating at 8 weeks

<table>
<thead>
<tr>
<th>Measure</th>
<th>Unguided</th>
<th>Guided</th>
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<tbody>
<tr>
<td>QIDS-C16</td>
<td>23.7</td>
<td>44.4</td>
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<tr>
<td>HAMD-17</td>
<td>26.9</td>
<td>43.1</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>31.2</td>
<td>50.7</td>
</tr>
</tbody>
</table>

Response defined as ≥50% reduction in score. P-values are derived from $\chi^2$ test.

(Hall Flavin 2013 Pharmacogenomics)
Breast cancer and Tamoxifen

TAM → CYP2D6 → Trans-4-OH-TAM

CYP3A4/5
(CYP1A1)
(CYP1A2)
(CYP1B1)
(CYP2C9)
(CYP2C19)

N-desmethyl-TAM → CYP2D6 → Endoxifen

Effective metabolite
CYP2D6 and tamoxifen

(Schroth et al 2009 JAMA)
**Published Articles: contradictory results**

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Genotyping</th>
<th>Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goetz et al. JCO 2005</td>
<td>190</td>
<td>*4</td>
<td></td>
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<tr>
<td>Lim et al. JCO 2007</td>
<td>21</td>
<td>*10</td>
<td></td>
<td></td>
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<tr>
<td>Bijl et al. Breast Cancer Res Treat 2009</td>
<td>85</td>
<td>*4</td>
<td></td>
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<tr>
<td>Xu et al. Ann Oncol 2008</td>
<td>152</td>
<td>*10</td>
<td></td>
<td></td>
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<tr>
<td>Stingl et al. Curr Med Res Opin 2010</td>
<td>496</td>
<td>*4</td>
<td></td>
<td></td>
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<tr>
<td>Leyland-Jones et al. San Antonio 2010 (abstract)</td>
<td>1243</td>
<td>*4</td>
<td>DFS</td>
<td>-</td>
</tr>
<tr>
<td>Dezentje et al. JCO 2010</td>
<td>747</td>
<td></td>
<td>DFS</td>
<td>-</td>
</tr>
<tr>
<td>Wegman et al. Breast Cancer Res 2005</td>
<td>76</td>
<td>*4</td>
<td>RR</td>
<td></td>
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</table>

### Hardy Weinberg equilibrium

**Minor allele frequency:** 10%

<table>
<thead>
<tr>
<th></th>
<th>Expected</th>
<th>Observed</th>
<th>p &gt; 0.05</th>
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</thead>
<tbody>
<tr>
<td>Wild type</td>
<td>90%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Heterozygote</td>
<td>9%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Homozygote mut</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

**Rae et al:** not in Hardy Weinberg Equilibrium \( p < 10^{-91} \)
CPT Aug 2013

CYP2D6 Genotype Should Not Be Used to Determine Endocrine Therapy in Postmenopausal Breast Cancer Patients
JM Rae1,2

Big study, no effect for CYP2D6

CYP2D6 Genotype and Tamoxifen Activity: Understanding Interstudy Variability in Methodological Quality
MJ Ratain1,3, Y Nakamura1-4 and NJ Cox1-3,5

Plausability, many positive studies, fits with PK endoxifen, study Rae not in HW
Abstract

The International Tamoxifen Pharmacogenomics Consortium (ITPC) was established to address the controversy over CYP2D6 status and clinical outcomes in tamoxifen therapy. We performed a meta-analysis on data from 4,973 tamoxifen treated patients (twelve globally-distributed sites).

Using strict eligibility requirements (postmenopausal women with estrogen receptor (ER) positive breast cancer receiving 20 mg/day tamoxifen for 5 years, Criterion 1), CYP2D6 poor metabolizer status was associated with poorer Invasive Disease-Free Survival (IDFS: HR=1.25; 95% CI 1.06, 1.47; P=0.009).
Clopidogrel needs activation by CYP2C19

Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

Tabassome Simon, M.D., Ph.D., Céline Verstuyft, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrière, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators

CONCLUSIONS

Among patients with an acute myocardial infarction who received clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of cardiovascular events than those who were not. This effect was observed among the patients undergoing percutaneous coronary intervention ( gov number, NCT00673036.)
**Meta-analysis** (Geisler et al 2011 CPT)

CY2C19*2 carriers are at risk

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Subjects/Subgroups</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined Cardiovascular Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, MI, stroke, stent thrombosis + coronary revasc</td>
<td>PCI-patients Overall (n=227)</td>
<td>Shuldiner A, JAMA 2009</td>
</tr>
<tr>
<td></td>
<td>Patients on clopidogrel at event (n=95)</td>
<td></td>
</tr>
<tr>
<td>Composite death, MI, stroke</td>
<td>Overall, ACS (n=2203)</td>
<td>Simon T, NEJM 2009</td>
</tr>
<tr>
<td></td>
<td>PCI-patients (n=1535)</td>
<td></td>
</tr>
<tr>
<td>Composite CV-death, MI, stroke</td>
<td>ACS, planned PCI (n=1466)</td>
<td>Collet JP, Lancet 2009</td>
</tr>
<tr>
<td></td>
<td>Young survivors of MI (n=259)</td>
<td></td>
</tr>
</tbody>
</table>

**Test for CYP2C19 variants:**

Negative → clopidogrel (€)

Positive → prasugrel (€€€)

Effects on outcome

Hazard Ratio + 95% confidence interval
The EMA drug label contains the following wording:

Section 4.4: Cytochrome P450 2C19 (CYP2C19)

"Pharmacogenetics: In patients who are poor CYP2C19 metabolizers, clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function. Tests are available to identify a patient's CYP2C19 genotype."
DNA passport for Drug Therapy

**Farmacogenetica Profiel**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Gen:</td>
<td>Uitslag:</td>
<td>Metabolisme</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>*1/*1</td>
<td>Normaal</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>*4/*6</td>
<td>Intermediair</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>*1/*2</td>
<td>Intermediair</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>*1/*1</td>
<td>Normaal</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>*1/*2xN</td>
<td>Ultrasnel</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>*1/*1</td>
<td>Normaal</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>*3/*3</td>
<td>Nonexpressor</td>
</tr>
<tr>
<td>BChE</td>
<td>U/S</td>
<td>Normaal</td>
</tr>
<tr>
<td>DYPD</td>
<td>*1/*2A</td>
<td>Intermediair</td>
</tr>
<tr>
<td>HLA-B*5701</td>
<td>NEG</td>
<td>Normaal</td>
</tr>
<tr>
<td>TPMT</td>
<td>*1/*1</td>
<td>Normaal</td>
</tr>
<tr>
<td>VKORC1</td>
<td>AA</td>
<td>Gevoelig</td>
</tr>
</tbody>
</table>

1. In blanke bevolking. Kan afwijken bij andere etniciteiten
CYP2D6 PM

Apothekertekst

Het genetisch polymorfisme leidt tot een verlaagde metabole capaciteit van CYP2D6 waardoor de plasmaconcentraties van Imipramine en de actieve metaboliet kunnen stijgen.

Advies:

1. verlaag de dosering tot 30% van de normale dosering en monitor de plasmaconcentraties van Imipramine en desipramine voor het instellen van de onderhoudsdosering

Baletekst:

De omzetting van Imipramine door het enzyn CYP2D6 is verlaagd als gevolg van een genetische variatie.

Overleg met de apotheker.

1. verlaag de dosering tot 30% van de normale dosering en monitor de plasmaconcentraties van Imipramine en desipramine voor het instellen van de onderhoudsdosering