Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium

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Implementing Pharmacogenomics

- Evidence for preemptive PGx for **single drug-gene pairs** [1-5]
- DPWG guidelines for 84 gene-drug pairs [7]
- 95% of patients have at least 1 actionable genotype [8]

**Evidence supporting a preemptive panel approach is currently undetermined**

1. NEJM 2008;358:569-79
2. NEJM 2013;369:2304-12
3. NEJM 2013;369:2294# 303
4. Lancet 2015
5. Coenen , Gastroenterology 2015
6. Ehmann, Pharmacogenomics J. 2015
7. Swen, CPT 2011
U-PGx Consortium: Generating Evidence to Support PGx

Objective: to quantify the collective clinical utility of a panel of PGx-markers

1. Systematic implementation of preemptive PGx strategy across multiple drugs/genes/ethnicities/healthcare systems

2. Robust assessment of how this intervention impacts:
   • Patient care (individual + population level)
   • Healthcare service processes
   • Cost-effectiveness
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Ubiquitous Pharmacogenomics

- Funded by EU Horizon 2020 (€15 million)
- Start 1-1-2016
- 5 year project
- Implement preemptive PGx testing in a real world setting across 7 European sites
  - Using the DPWG guidelines to guide drug and dose selection
Objective:
To quantify the collective clinical utility of a panel of PGx-markers covering 13 important pharmacogenes as a new model of personalized medicine.

Hypothesis:
Implementation will result in a 30% reduction of clinically relevant adverse drug reactions (4 → 2.8%).

Design:
Open randomized cross-over study in 7 countries including 8,100 patients.

Outcomes:
Primary: Clinical outcome
Secondary: Process indicators for implementation
Cost-effectiveness
PGx Guided Prescribing Arm

1\textsuperscript{st} Rx
PGx drug

DNA sample

Record in EMR

PGx informed prescribing

Safety code card provided

 Drugs of inclusion (n=42)

<table>
<thead>
<tr>
<th>Antidysrhythmic</th>
<th>Antiepileptic</th>
<th>Anesthetic</th>
<th>Anti-infective</th>
<th>Anti-inflammatory</th>
<th>Antineoplastic</th>
<th>Antineoplastic (TCA)</th>
<th>Antipsychotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic</td>
<td>Anxiolytic</td>
<td>Antihistaminergic</td>
<td>Anti-infective</td>
<td>Anti-inflammatory</td>
<td>Antineoplastic</td>
<td>Antineoplastic</td>
<td>Antipsychotic</td>
</tr>
</tbody>
</table>

1. PPIs excluded because they are only associated with a difference in efficacy among aberrant genotypes.
2. Estrogen containing drugs will only be included in the study as a subsequent prescription.

T=2, 4, 8, 12 weeks

DPWG guidelines
Component 3: A next step into the Future

Leader: Prof. Dr. Matthias Schwab

- **Follow-up study among extreme phenotypes:**
  - Next Generation Sequencing
  - To identify rare variants
  - Blood sample within 24 hours of serious ADR
  - Blood plasma levels of drugs

- **Pharmacokinetic sub-study:**
  - Integrate Gene-Drug and Drug-Drug interactions
  - Apply a systems pharmacology approach
  - Dried blood spot at various time points combined with clinical endpoint data; metoprolol, CAP / 5-FU, atorvastatin, simvastatin, voriconazole

Rare variants among CYPs

[Graph showing fraction of functional variability for different CYPs]

Ingelman-Sundberg, Genetics in Medicine 2016

Wist Genome Medicine 2009;1:11
Update April 2017

• ICT tool developed → Med Safety Code Card
• PGx genotyping platform selected → LGC SNPLine
• PGx panel selected → 13 pharmacogenes; 50 variants; incl. genotype-phenotype translation
• Guidelines translated → English and local languages; validated
• Training and education materials developed
  – Promotional video (www.upgx.eu)
  – eLearnings for participants (nurses, pharmacists, clinicians)
• First U-PGx Pharmacogenomics Day Granada; 2nd in Vienna 12 May
• eCRF: ProMISe
• Study protocol: IRB approval all sites, recruitment started; n=69
Take home message

• U-PGx will quantify collective clinical utility of a panel of PGx-markers

• U-PGx is unique in its multi-center, multi-gene, multi-drug, multi-ethnic, and multi-healthcare system approach

• U-PGx will deliver a large dataset combining detailed phenotypes of adverse drug reactions and individuals’ genetic makeup

• U-PGx is open for collaboration to expand understanding of PGx
Thank you for your attention!

U-PGx Kick-off Leiden Jan 19th, 2016

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