U-PGx | Ubiquitous Pharmacogenomics

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

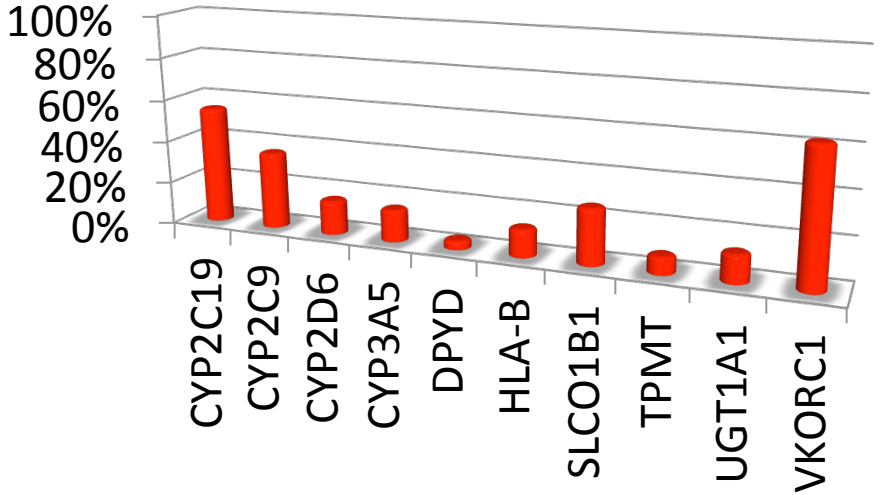
LUMC
Leiden University Medical Center

LNPT
Leiden Netwerk for Personalised Therapeutics

Jesse J. Swen, PharmD PhD
Associate Professor of Pharmacogenetics
Section Chair Laboratory
Dept. of Clinical Pharmacy & Toxicology

Implementing Pharmacogenomics

- Evidence for preemptive PGx for **single drug-gene pairs** [1-5]
- ~15% of EMA labels (1995-2014) actionable PGx [6]
- 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
8. Dunnenberger, Annu Rev Pharmacol Toxicol 2015

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

U-PGx Consortium

LUMC
Leiden University Medical Center
H.J. Guchelaar (Coordinator),
J.J. Swen, M. Kriek

University of Liverpool
M. Pirmohamed, R. Turner

BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte
J. Stingl

Karolinska Institutet
M. Ingelman-Sundberg

The GoldenHelix Foundation
C. Mitropoulou

KNMP
M. van Rhenen, K.C. Cheung

bio-logis
genetic information management
D. Steinberger

Ziekenhuis St Antonius
V.H.M. Deneer

Medical University of Vienna
M. Samwald
G. Sunder-Plassmann

Université Toulouse III Paul Sabatier
A. Cambon-Thomsen

Uppsala Universitet
M. Karlsson
S. Jönsson

CRO Aviano
G. Toffoli
E. Cecchin

Servicio Andaluz de Salud
Junta de Andalucía
Consejería de Salud
C.L. Davila Fajardo

Πανεπιστήμιο Πατρών
University of Patras
G. Patrinos

University of Ljubljana
V. Dolžan

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M. Schwab
E. Schaeffeler

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St Jude Children's Research hospital, Memphis, TN, USA

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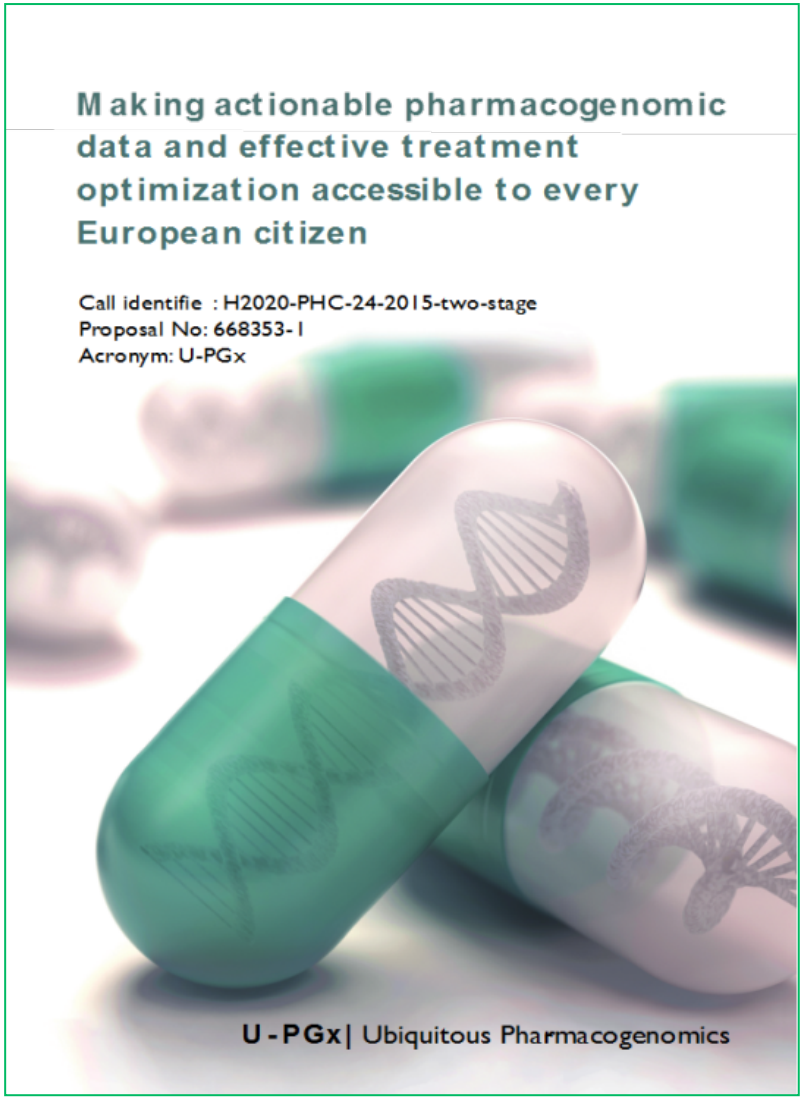
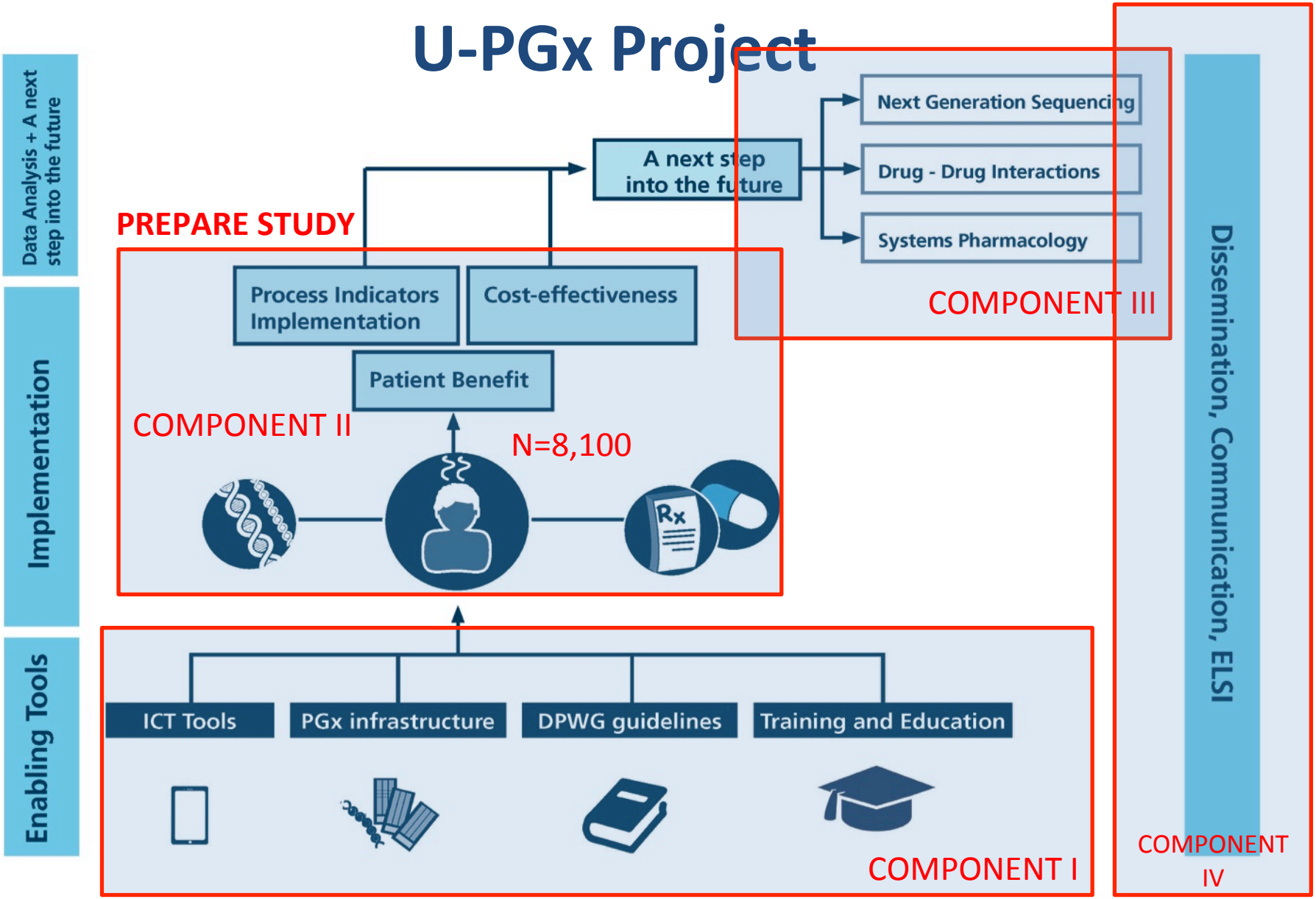
Patient and Consumer Working Party of the European Medicines Agency (EMA), Bern, Switzerland

Ubiquitous Pharmacogenomics



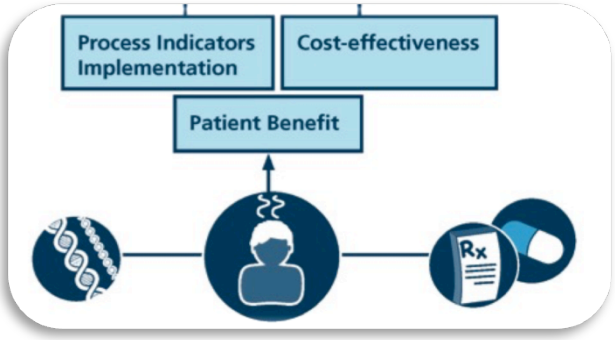
- **Funded by EU Horizon 2020 (€15 million)**
- **Start 1-1-2016**
- **5 year project**
- **Implement preemptive PGx testing in a real world setting across 7 European sites**
  - Using the DPWG guidelines to guide drug and dose selection

U-PGx Project



Component 2: PREPARE

*PRE*emptive *P*harmacogenomic testing for preventing *A*dverse drug *RE*actions



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%)

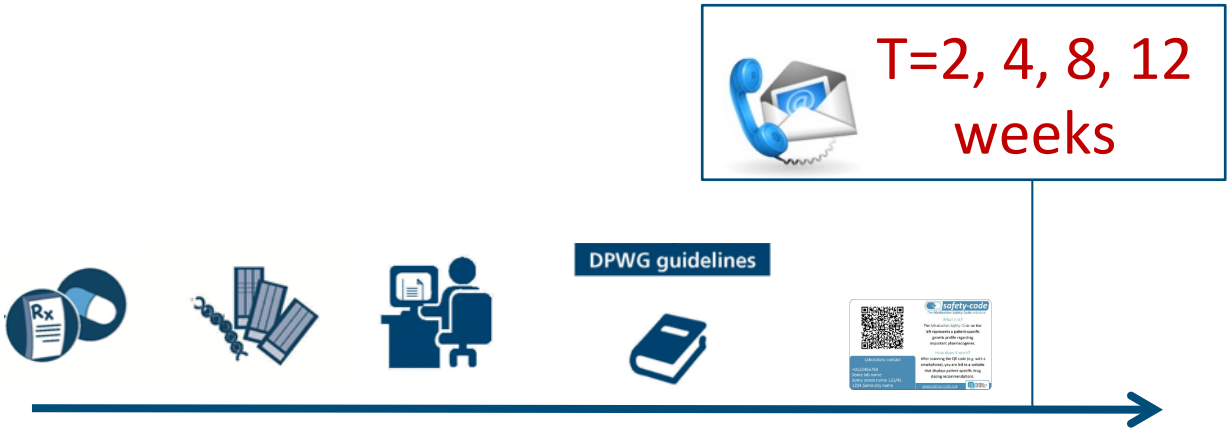
Design:

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



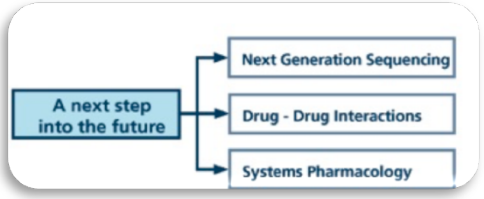
Drugs of inclusion (n=42)

Antiarrhythmic	Flecainide
	Propafenon
Analgesic	Codeine
	Oxycodone
	Tramadol
Anticancer	Capecitabine
	Fluorouracil
	Irinotecan
	Tamoxifen
	Tegafur
Anticoagulant	Acenocoumarol
	Clopidrogel
	Phenprocoumon
	Warfarin
Antidepressant	Citalopram
	Escitalopram
	Paroxetine
	Sertraline
	Venlafaxine
Antidepressant (TCA)	Amitriptyline
	Clomipramine
	Doxepine
	Imipramine
	Nortryptiline

Antiepileptic	Carbamazepine
	Phenytoin
Antihypertensive	Metoprolol
Anti-infective	Efavirenz
	Flucloxacillin
	Voriconazole
Antipsychotic	Aripiprazole
	Clozapine
	Haloperidol
	Pimozide
	Zuclopenthixol
Cholesterol-lowering	Atorvastatin
	Simvastatin
Immunosuppressant	Azathioprine
	Mercaptopurine
	Tacrolimus
	Thioguanine
Psychostimulant	Atomoxetine

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

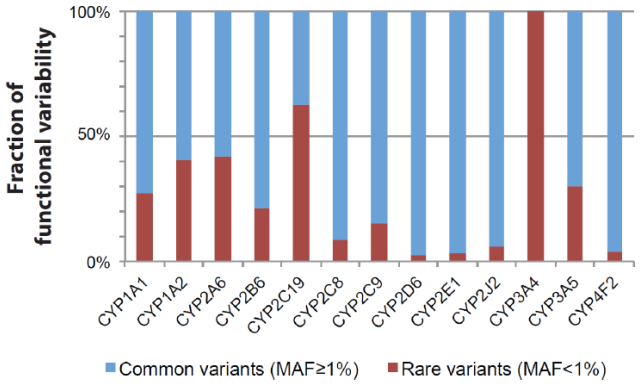
Component 3:
A next step into the Future



Leader: Prof. Dr. Matthias Schwab

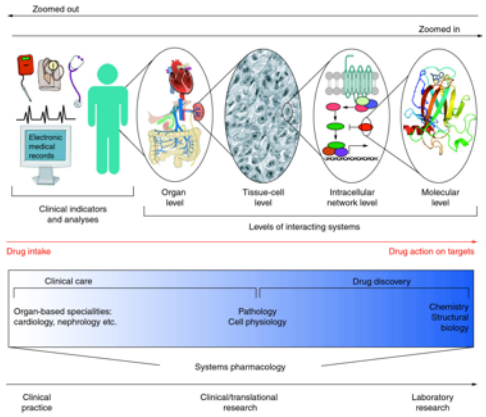
- **Follow-up study among extreme phenotypes:**
  - Next Generation Sequencing
    - To identify rare variants
  - Blood sample within 24 hours of serious ADR
    - Blood plasma levels of drugs

Rare variants among CYPs



Ingelman-Sundberg, Genetics in Medicine 2016

- **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



Wist Genome Medicine2009;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

Clin Pharmacol Ther.
2017 101(3):341-358.

www.upgx.eu

Email: j.j.swen@lumc.nl

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