U-PGx | Ubiquitous Pharmacogenomics

The Ubiquitous Pharmacogenomics Project

Making actionable pharmacogenomic data and effective treatment optimization accessible to every European citizen

LUMC
Leiden University Medical Center

LNPT
Leiden Netwerk for Personalised Therapeutics

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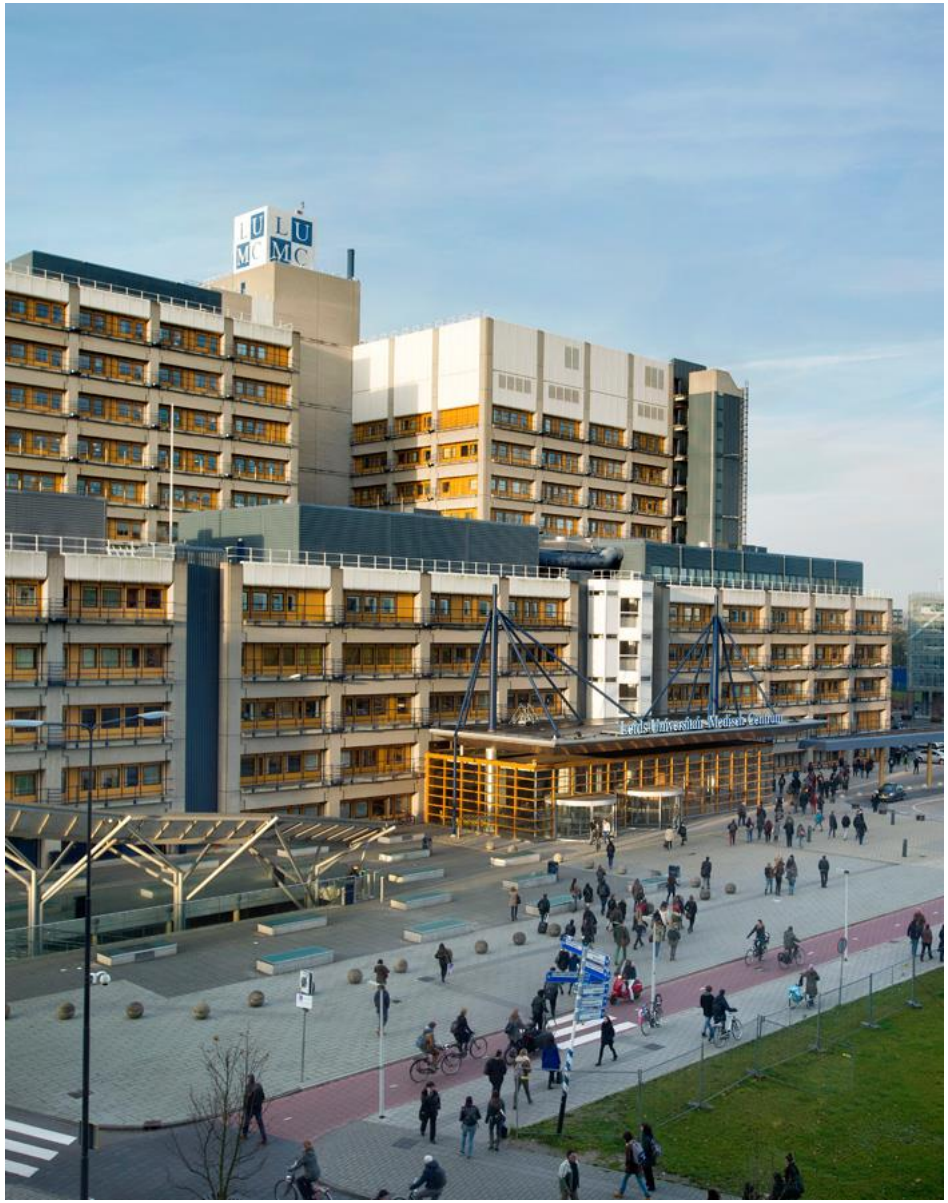
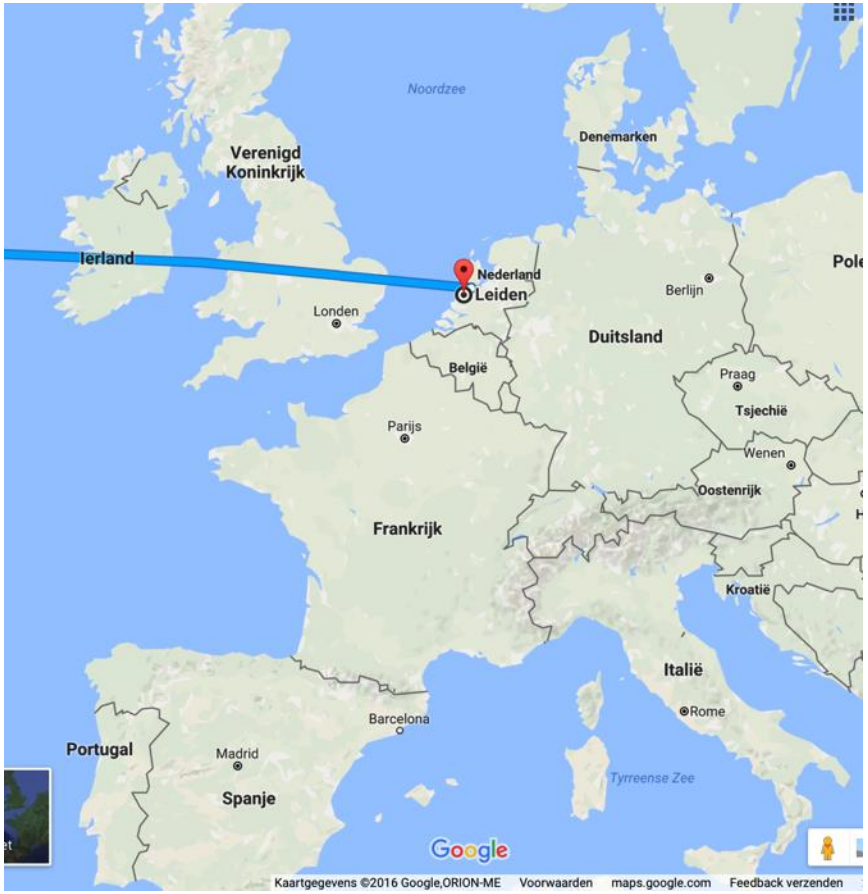


Leiden University
Medical Center



Background

- Results of 5 available RCTs for a variety of drug-gene combinations strongly indicate that PGx testing prior to prescribing (and thus personalizing medicine) leads to improved patient outcome [1-5]

- ~15% of medicinal products evaluated according to EMA centralized procedure between 1995 - 2014 contain PGx information in their label that directly impacts patient treatment [6]

- Availability of Dutch Pharmacogenetics Working Group and CPIC guidelines for >80 gene-drug pairs

1. NEJM 2008;358:569#79
2. NEJM 2013;369:2304#12
3. NEJM 2013;369:2294# 303
4. Lancet 2015
5. Coenen et al Gastroenterology 2015
6. Ehmann et al. Pharmacogenomics J. 2015

Survey physicians and pharmacists

- 97.6% of physicians agreed that genetic variations may influence drug response [1]
- 99.7% of pharmacists agreed that a patients' genetic profile may influence drug response [2]

- *Did you order or recommend a pharmacogenetic test in the preceding 6 months?* [2]

Yes

4%

15%

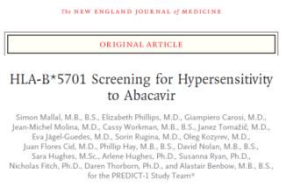
~400 GP's

~667 pharmacists

Current Evidence Supporting Pre-emptive Pharmacogenomics

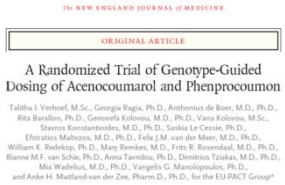
- Gold standard evidence for a variety of **single drug-gene pairs**:

Drug	Clinical Endpoint	Variant
Abacavir	hypersensitivity	HLA-B*5701
Acenocoumarol / Fenprocoumon	% time between therapeutic INR	VKORC1/CYP2C9
Warfarin	% time between therapeutic INR	VKORC1/CYP2C9
Warfarin	% time between therapeutic INR	VKORC1/CYP2C9
Mercaptopurine	leucopenia	TPMT


The NEW ENGLAND JOURNAL of MEDICINE

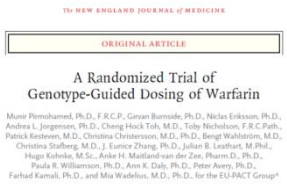
ORIGINAL ARTICLE

HLA-B*5701 Screening for Hypersensitivity to Abacavir


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Genotype-Guided Dosing of Warfarin


The NEW ENGLAND JOURNAL of MEDICINE

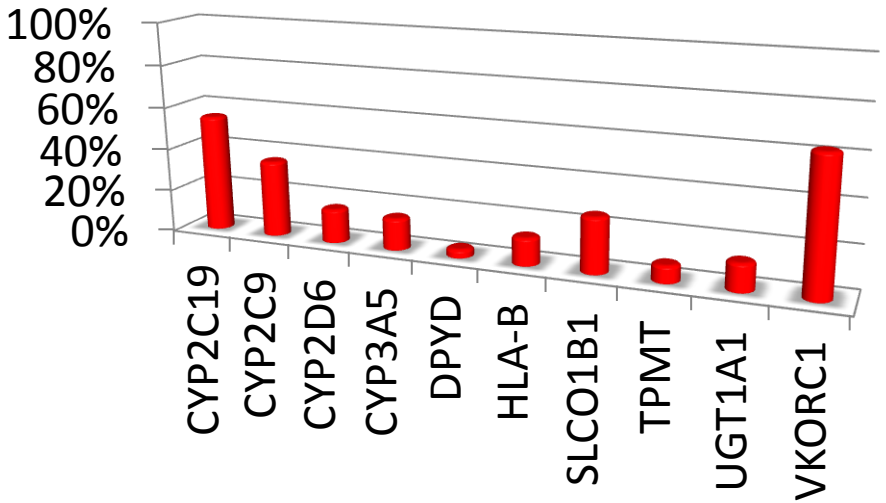
A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

- Sufficient evidence supporting that pre-emptive PGx can lead to improved patient outcome

Evidence base is limited to single drug-gene pairs

PGx Testing for a Panel of Pharmacogenes may be more Relevant

- PGx results are lifelong
- Patients may initiate a number of drugs during their life time which can be more optimally prescribed using PGx
- Actionable PGx variants are common in the population



Limited evidence supporting a panel approach

- 95% of patients have at least 1 actionable genotype

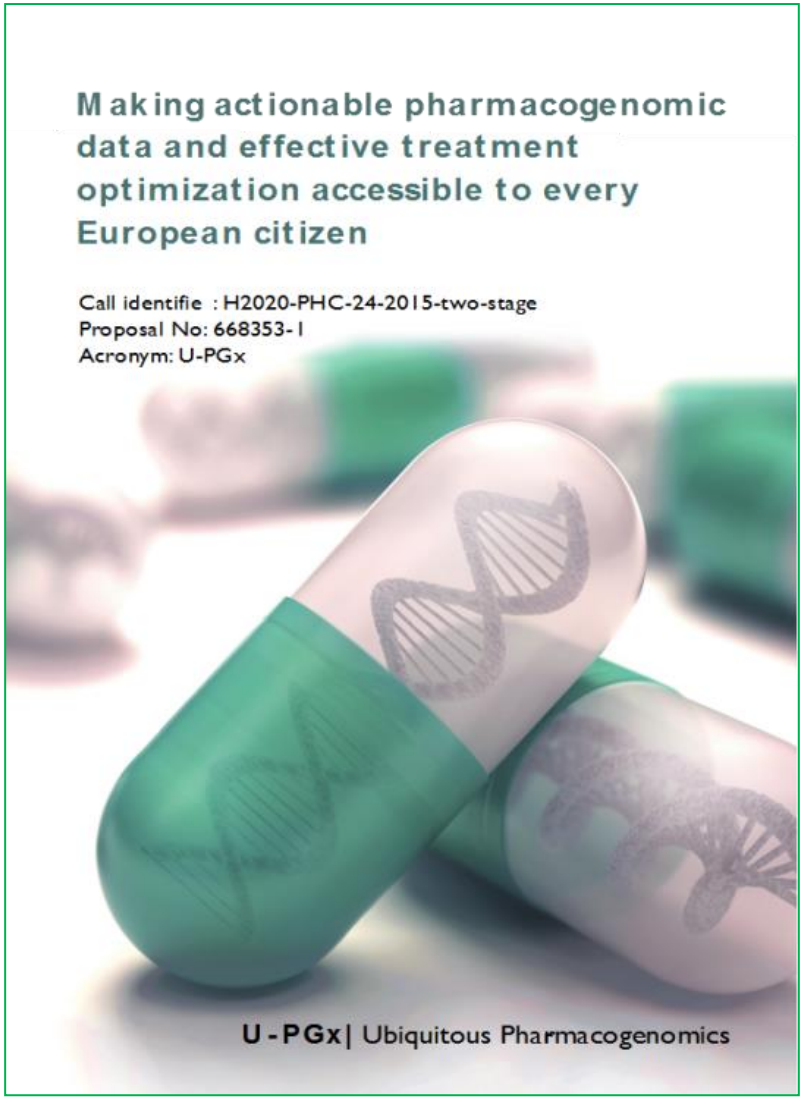
Dunnenberger, Annu Rev Pharmacol Toxicol 2015

U-PGx Consortium: Generating Evidence to Support Pharmacogenomics

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

1. **Systematic implementation of pre-emptive PGx strategy across multiple:**
   - drugs/genes/ethnicities/healthcare systems
2. **Robust assessment of how this intervention impacts:**
   - Patient care (individual and on a population level)
   - Healthcare service processes
   - Cost-effectiveness

Ubiquitous Pharmacogenomics



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

U-PGx consortium

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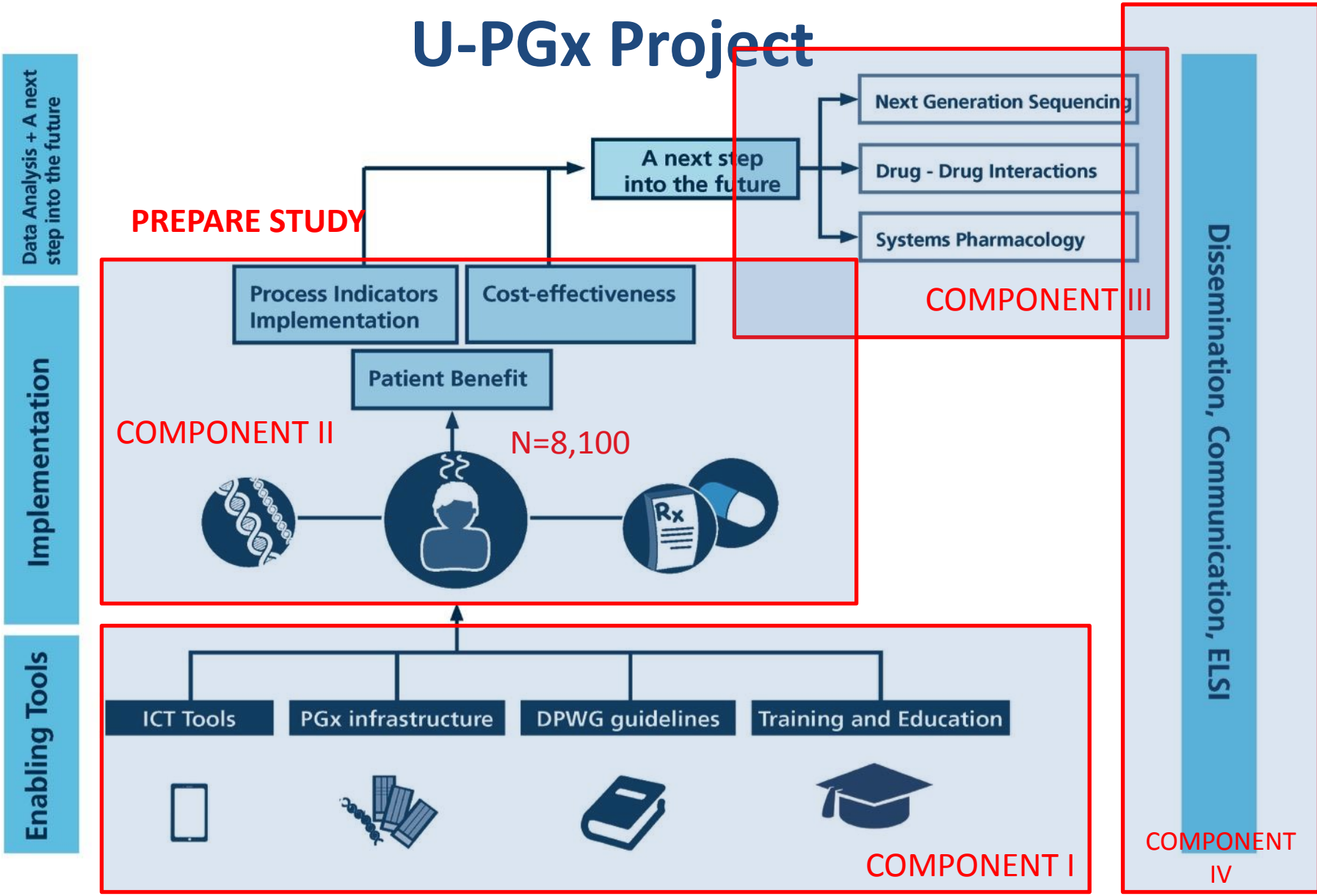
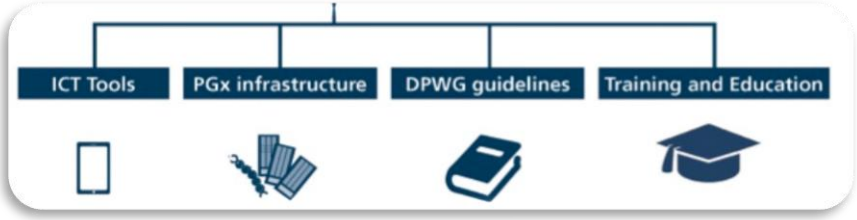
U-PGx Project



I: Enabling Pre-emptive Testing

Leader: Matthias Samwald



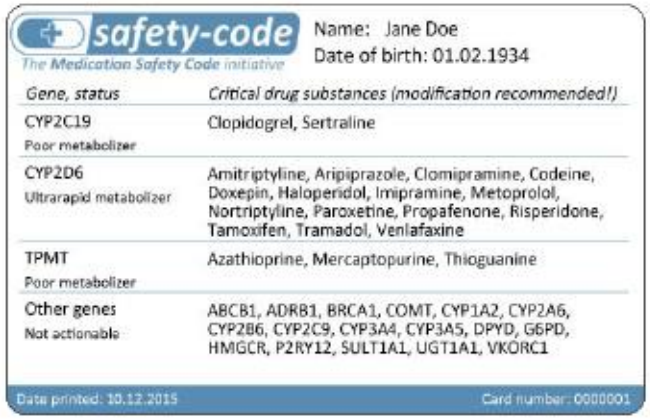
- Development of powerful and barrier-free CDSS
- Provide suitable genotyping technology for the selected panel of variants
- Development, maintenance, sharing of EU PGx guidelines
- Provide training and education to involved healthcare providers

Development of powerful and barrier-free CDSS

Development of powerful and barrier-free CDSS

Scan QR code

Dr. Matthias Samwald

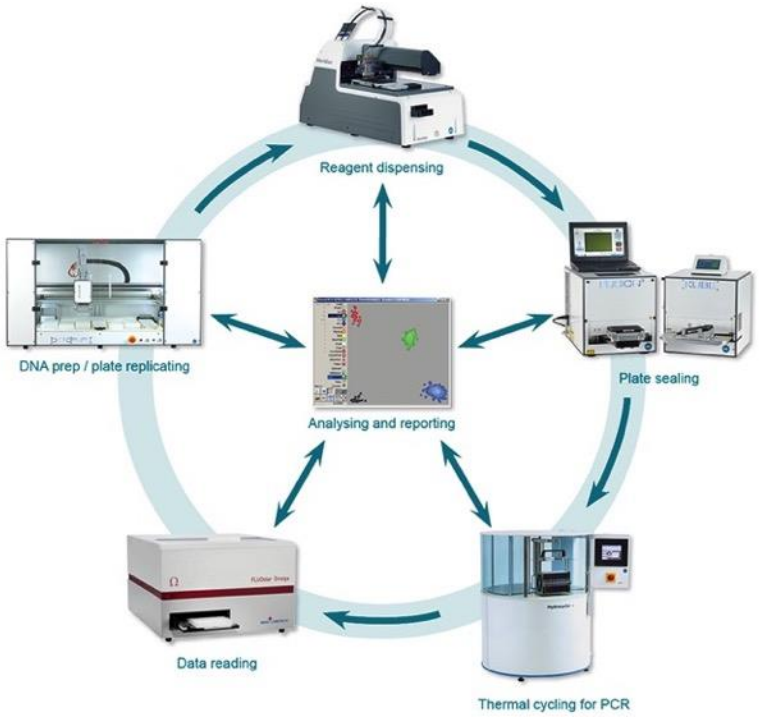


http://safety-code.org/

Provide suitable genotyping technology for the selected panel of variants

Genes	Allele	dbSNP RS ID
CYP1A2	*1C	rs2069514
CYP1A2	*1F	rs762551
CYP2B6	*6	rs3745274
CYP2B6	*16	rs2279343
CYP2B6	*18	rs28399499
CYP2C9	*2	rs1799853
CYP2C9	*3	rs1057910
CYP2C9	*5	rs28371686
CYP2C9	*8	rs7900194
CYP2C9	*11	rs28371685
CYP2C19	*2	rs4244285
CYP2C19	*3	rs4986893
CYP2C19	*4A/B	rs28399504
CYP2C19	*5	rs56337013
CYP2C19	*6	rs72552267
CYP2C19	*7	rs72558186
CYP2C19	*8	rs41291556
CYP2C19	*9	rs17884712
CYP2C19	*10	rs6413438
CYP2C19	*17	rs12248560
CYP2D6	*xN	X
CYP2D6	*3	rs35742686
CYP2D6	*4	rs3892097
CYP2D6	*5	X
CYP2D6	*6	rs5030655
CYP2D6	*8	rs5030865
CYP2D6	*9	rs5030656
CYP2D6	*10	rs1065852
CYP2D6	*14A/B	rs5030865
CYP2D6	*17	rs28371706
CYP2D6	*29	rs61736512
CYP2D6	*29	rs59421388
CYP2D6	*41	rs28371725

Genes	Allele	dbSNP RS ID
CYP3A5	*3	rs776746
CYP3A5	*6	rs10264272
CYP3A5	*7	rs41303343
DPYD	*2A	rs3918290
DPYD	*13	rs55886062
DPYD	X	rs67376798
DPYD	X	rs56038477
fVl	X	rs6025
*HLA-B*5701*	X	
SLCO1B1	*5/*15/*17	rs4149056
TPMT	*2	rs1800462
TPMT	*3B	rs1800460
TPMT	*3C	rs1142345
UGT1A1	*6	rs4148323
UGT1A1	*27	rs35350960
UGT1A1	*28/*37	rs8175347
VKORC1	X	rs9934438



SNPline, LGC group

Development, maintenance, sharing of EU PGx guidelines


Pharmacogenetics: From Bench to Byte

Swen et al, CPT 2008;83(5):781


REPORTS

Pharmacogenetics: From Bench to Byte—An Update of Guidelines

Swen et al, CPT 2011;89(5):662-73

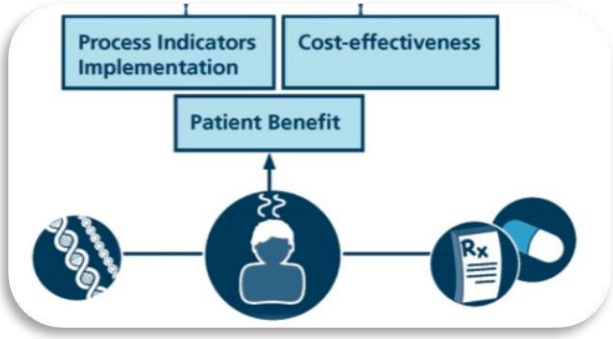
Available DPWG guidelines (N=84)

Solicit Endorsement by Organizations

Translate into local languages

Personalized Medicine
Personalisierte Medizin
Medicina Personalizzata
Gepersonaliseerde Geneeskunde
Prilagojene Medicine
Medicina Personalizada
εξατομικευμένη ιατρική

Component 2: PREPARE Study



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.

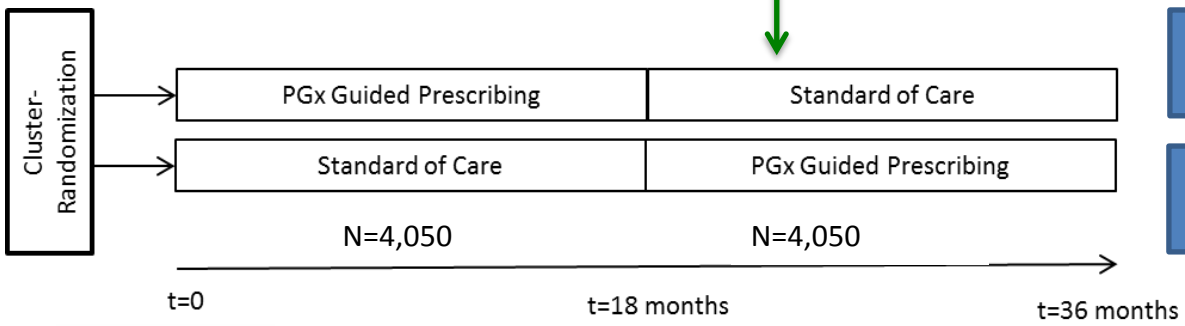
Outcomes:

Primary	Clinical outcome
Secondary	Process indicators for implementation
	Cost-effectiveness

PREPARE

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

New set of patients



Spain, Greece, Slovenia

Netherlands, UK, Austria, Italy

Each site has its own therapeutic focus

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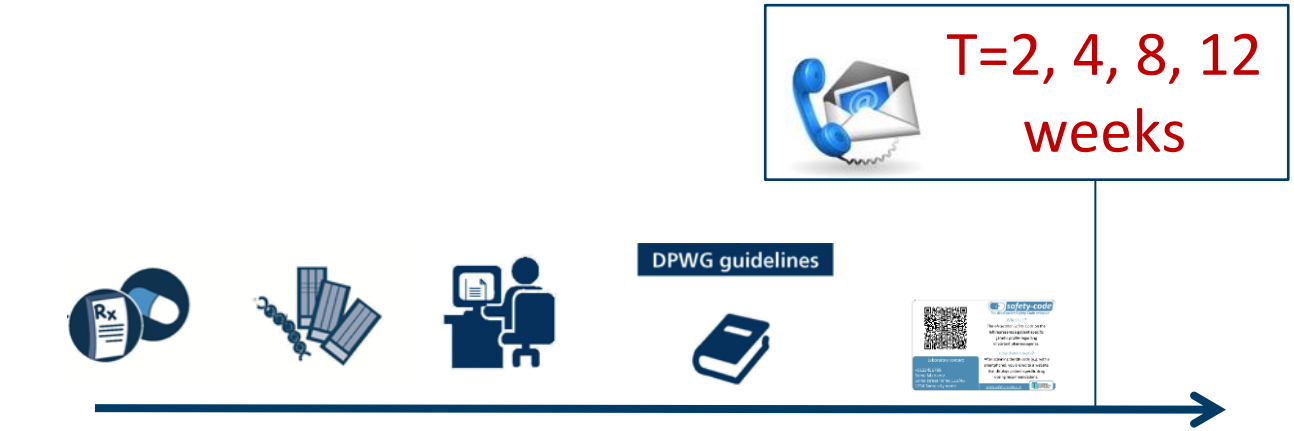
PGx Guided Prescribing Arm



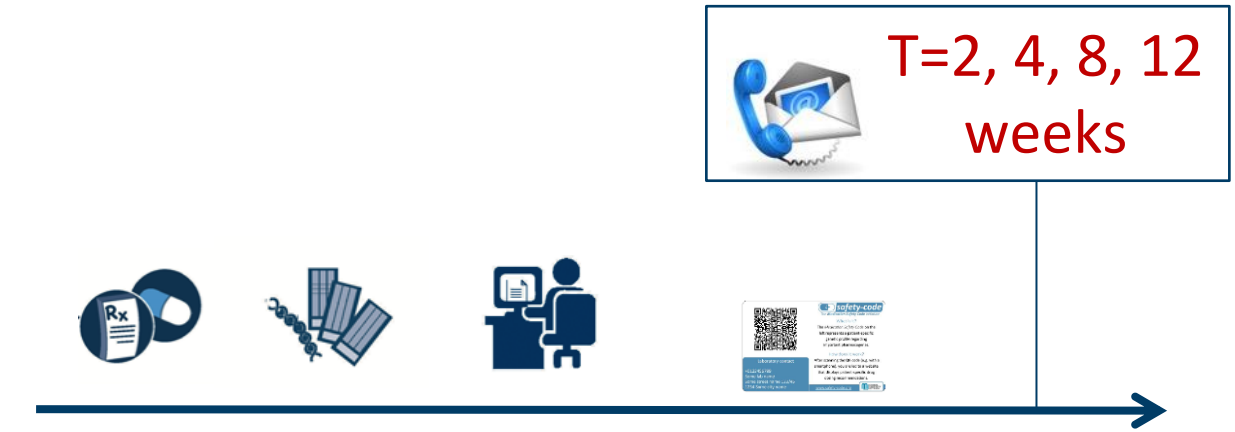
Drugs of inclusion (n=42)

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

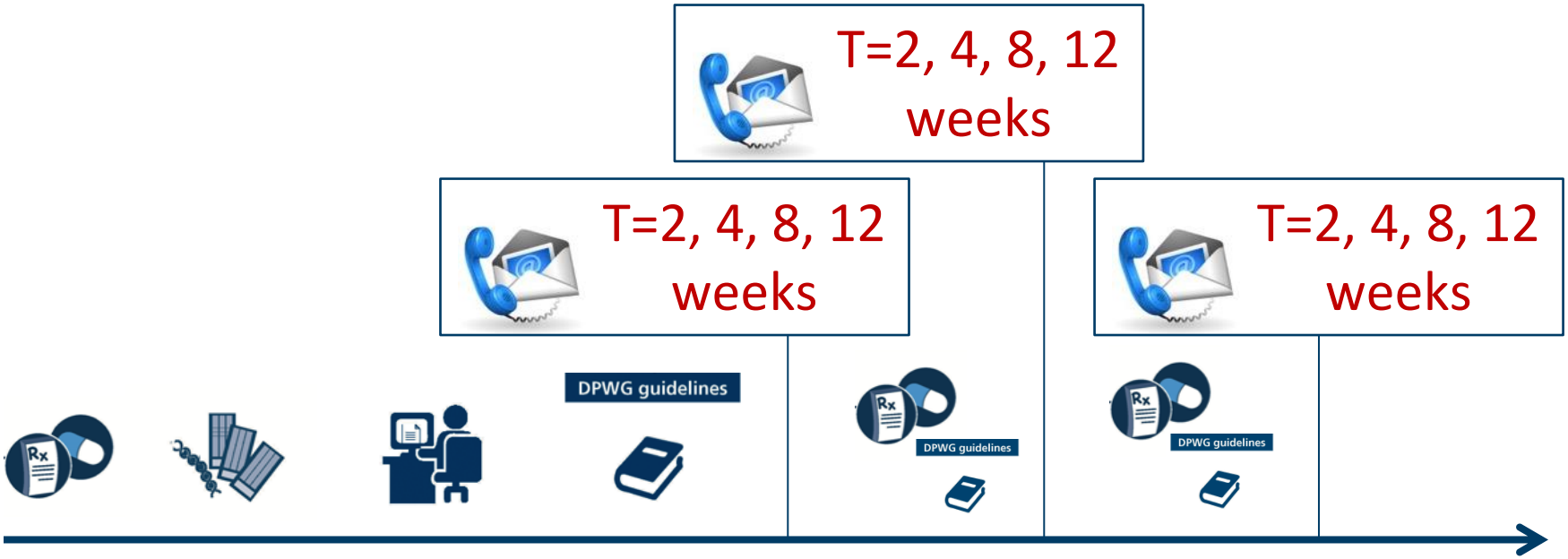
Antiepileptic	Carbamazepine
	Phenytoin
Antihypertensive	Metoprolol
Anti-infective	Efavirenz
	Flucloxacillin
	Voriconazole
Antipsychotic	Aripiprazole
	Clozapine
	Haloperidol
	Pimozide
	Zuclopenthixol
Cholesterol-lowering	Atorvastatin
	Simvastatin
Immunosuppressant	Azathioprine
	Mercaptopurine
	Tacrolimus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

Standard of Care Arm



Subsequent Prescriptions of Interest



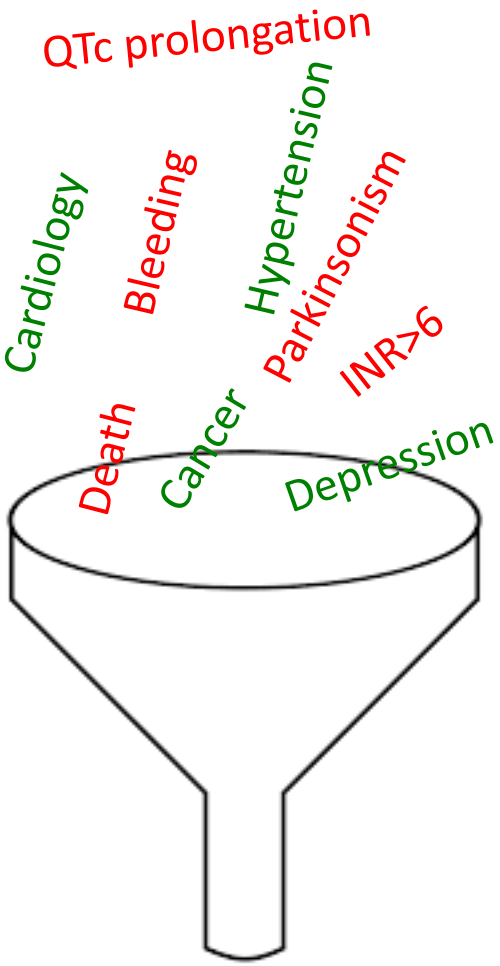
1st Rx PGx drug	DNA Sample	Record in EMR	PGx informed prescribing	2nd Rx PGx drug	3rd Rx PGx drug

~50% 2nd prescription
~30% 3rd prescription

Endpoint

- DPWG guidelines for 84 gene-drug pairs
- Variety of drugs and diseases

- → Composite endpoint



Endpoint based on the DPWG

- Systematic review literature

1. **Score 'level of evidence'**
   - 1-4
2. **Score 'clinical relevance'**
   - A-F, derived from CTC-AE
   - CDEF=2345

Swen, Clin Pharmacol Ther 2008;83(5):781-8

Classification of clinical relevance

Classification of clinical relevance	
AA	Clinical effect (NS) Kinetic effect (NS)
A	Minor clinical effect (S): QTc prolongation (<450 ms ♀, <470 ms ♂), INR increase <4.5 Kinetic effect (S)
B	Clinical effect (S): short-lived discomfort (<48 h) without permanent injury, for example, reduced decrease in resting heart rate, reduction in exercise tachycardia, diminished pain relief from [illegible] resulting from increased [illegible] of codeine (decreased [illegible] disturbance, etc.)
C	Clinical effect (S): long-standing discomfort (48–168 h) without permanent injury, for example, increase risk of failure of therapy with tricyclic antidepressants or atypical antipsychotic drugs: extrapyramidal side effects, parkinsonism: ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects, e.g., dizziness).
D	Clinical effect (S): long-standing effect (>168 h), permanent symptom or invalidating injury, for example, failure of prophylaxis of atrial fibrillation; deep vein thrombosis
E	Clinical effect (S): Increased risk of failure of lifesaving therapy; expected bone marrow depression
F	Clinical effect (S): death; arrhythmia; unexpected bone marrow depression

ADE, adverse drug event; INR, international normalized ratio; NS, not statistically significant difference; S, statistically significant difference.

CTC-AE

Most gene-drug pairs related to ADRs

3

4

5

Swen, Clin Pharmacol Ther 2008;83(5):781-8

Endpoint - 7-point clinical relevance ADR scale

Class	EMA ADE frequency	Clinical Effect
AA#		Positive clinical effect (NS)
AA		Clinical effect (NS): no change or a non-significant change of clinical parameters Kinetic effect (NS): no change or a non-significant change of kinetic parameters.
A	Common ≥ 1/100 to < 1/10	Minor clinical effect (S): QTc prolongation (<450 ms ♀, <470 ms ♂); QTc time increase < 60ms; INR increase < 4.5 Kinetic effect (S): significant change of kinetic parameters
B	Common ≥ 1/100 to < 1/10	Clinical effect (S): short-lived discomfort (< 48 hr) without permanent injury: e.g. reduced decrease in resting heart rate; reduction in exercise tachycardia; decreased pain relief from oxycodone; ADE resulting from increased bioavailability of atomoxetine (decreased appetite, insomnia, sleep disturbance, depressive mood, etc); neutropenia > $1.5x10^9$/l; leucopenia > $3.0x10^9$/l; thrombocytopenia > $75x10^9$/l; moderate diarrhea not affecting daily activities; reduced glucose increase following oral glucose tolerance test; muscle complaints creatine kinase <3 times normal upper limit
C	Common ≥ 1/100 to < 1/10	Clinical effect (S): long-standing discomfort (48-168 hr) without permanent injury e.g. failure of therapy with tricyclic antidepressants, atypical antipsychotic drugs; extrapyramidal side effects; parkinsonism; ADE resulting from increased bioavailability of tricyclic antidepressants, metoprolol, propafenone (central effects e.g. dizziness); increased INR 4.5-6.0; neutropenia 1.0-$1.5x10^9$/l; leucopenia 2.0-$3.0x10^9$/l; thrombocytopenia 50-$75x10^9$/l; muscle complaints creatine kinase 3-10 times normal upper limit
D	Uncommon ≥ 1/1,000 to< 1/100	Clinical effect (S): long-standing discomfort (> 168 hr), permanent symptom or invalidating injury e.g. failure of prophylaxis of atrial fibrillation; venous thromboembolism; decreased effect of clopidogrel on inhibition of platelet aggregation; ADE resulting from increased bioavailability of phenytoin; INR > 6.0; neutropenia 0.5-$1.0x10^9$/l; leucopenia 1.0-$2.0x10^9$/l; thrombocytopenia 25-$50x10^9$/l; severe diarrhea; myopathy (muscle complaints creatine kinase ≥10 times normal upper limit)
E	Uncommon ≥ 1/1,000 to< 1/100	Clinical effect (S): Failure of lifesaving therapy e.g. anticipated myelosuppression; prevention of breast cancer relapse; arrhythmia; neutropenia < $0.5x10^9$/l; leucopenia < $1.0x10^9$/l; thrombocytopenia < $25x10^9$/l; life-threatening complications from diarrhea; rhabdomyolysis
F	Rare ≥ 1/10,000	Clinical effect (S): death; arrhythmia; unanticipated myelosuppression

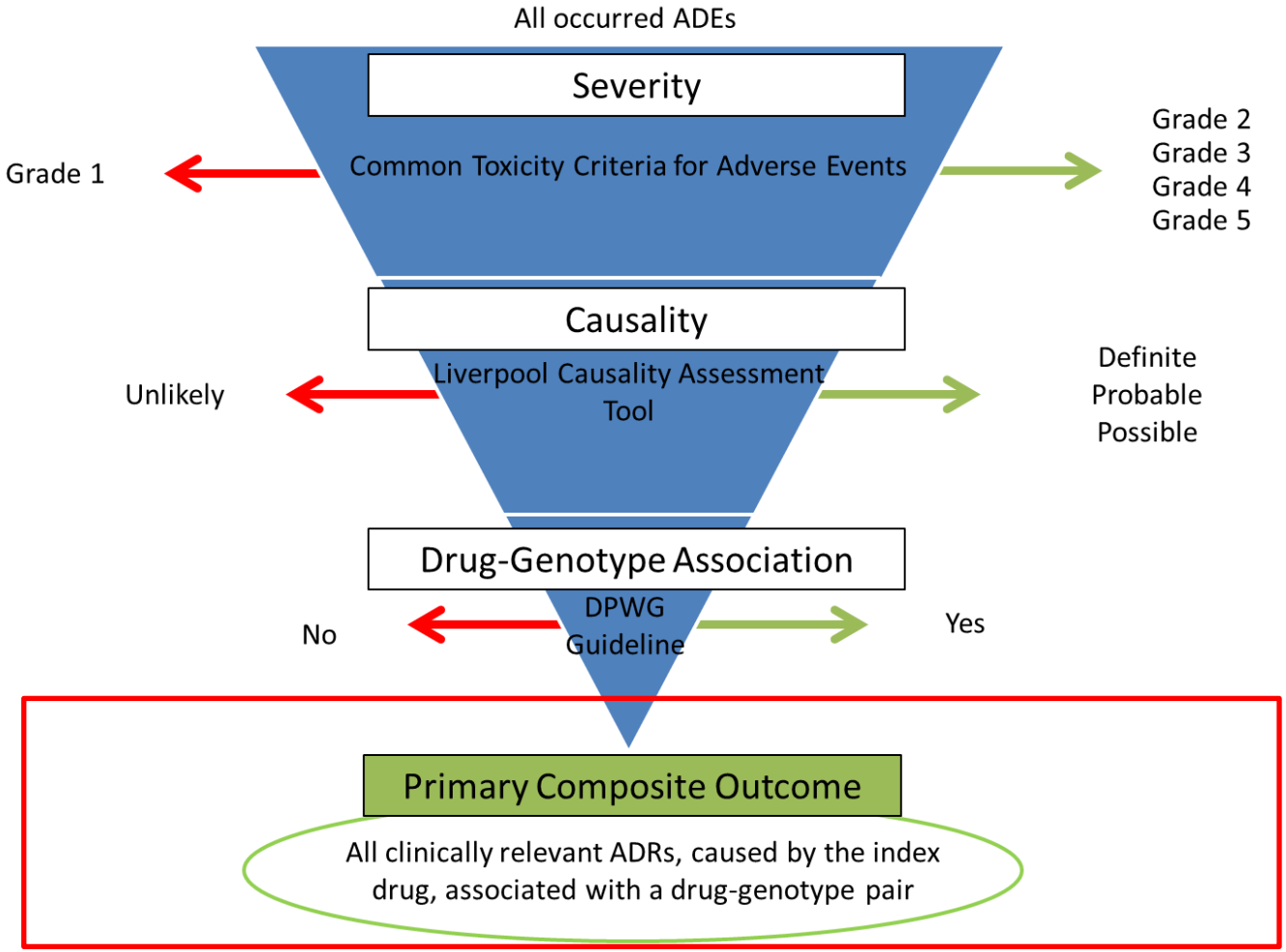
Endpoint - Drugs, Genes and Clinical Effect

		Clinical Effect Class						
Gene	Variant	AA	A	B	C	D	E	F
CYP2D6	PM		Amitryptiline Flecainide Zuclopenthixol Imipramine Pimozide	Atomoxetine Carvedilol Codeïne Oxycodone Tramadol	Aripiprazol Clomipramine Haloperidol Metoprolol Nortryptiline Propafenon Venlafaxine	Risperidone		Doxepine Tamoxifen
	IM		Codeïne Doxepine Flecainide Imipramine Propafenon Zuclopenthixol Oxycodone Pimozide	Metoprolol Tramadol	Amitryptiline Clomipramine Nortryptiline Risperidone Venlafaxine		Tamoxifen	
	UM		Doxepine Flecainide Imipramine Tamoxifen Venlafaxine Zuclopenthixol	Atomoxetine Oxycodone	Amitryptiline Clomipramine Haloperidol Nortryptiline Paroxetine Risperidone Tramadol	Metoprolol Propafenon		**Codeïne**

Primary endpoint:

- 30% reduction of **clinically relevant** adverse drug reactions (4 →2.8%)
- Composite endpoint C,D,E,F

Primary Composite Endpoint



Example: Composite Endpoint

Patient in standard of care arm

- **Drug of inclusion:**
  - Codeine, normal dose
- **Adverse drug reaction:**
  - Respiratory depression
  - Severity: CTCAE Grade 5
  - Causality: LCAT Possible
- **Genotype:**
  - CYP2D6 Ultra Rapid Metabolizer

➢ **Drug genotype association:**

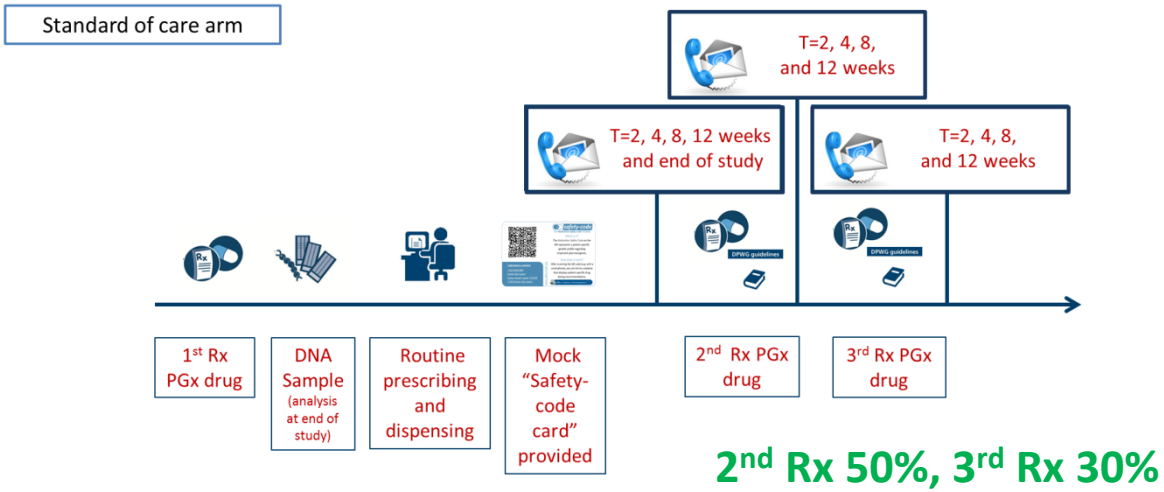
➢ Described in the underlying literature of the codeine DPWG guideline to be associated with CYP2D6 UM

Secondary Endpoints

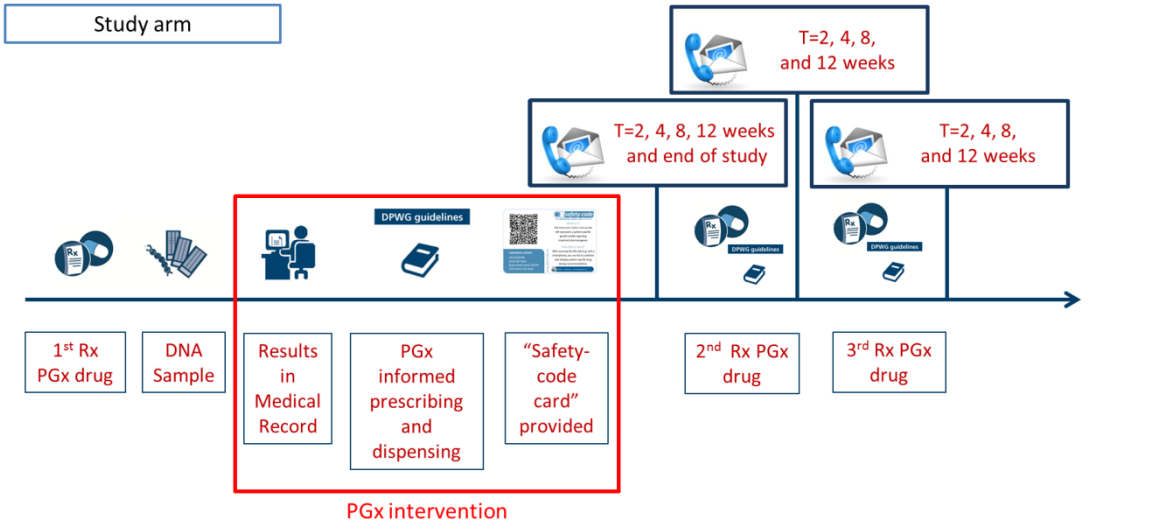
Secondary analyses of the U-PGx project are aimed at evaluating **quantitative and qualitative indicators** for successful implementation strategies.

- **Composite endpoint <u>for all prescriptions</u>**
- **Cost-effectiveness (incl QOL using the EQ5D questionnaire)**
- **Secondary clinical outcome measures**
  - Drug cessation (due to lack of efficacy, due to an ADR)
  - Dose alteration
  - Additional drugs prescribed
- **Survey of patients and physicians regarding:**
  - multi-domains (e.g. beliefs, knowledge, usability)
  - process indicators for implementation (e.g. guideline compliance, extent of adoption, number of tests) among patients and physicians
- **Patient reported outcomes (PROs)**
- **Routine drug levels**
- **Health-care consumption**

PREPARE: Data Collection



2nd Rx 50%, 3rd Rx 30%



1. eCRF: ProMISe

Research Nurse Follow-up

Baseline (± 1 week)*
4 weeks (± 1 week) *
12 weeks (± 1 week)*
End of Study (± 4 weeks)

*For every newly prescribed drug of interest

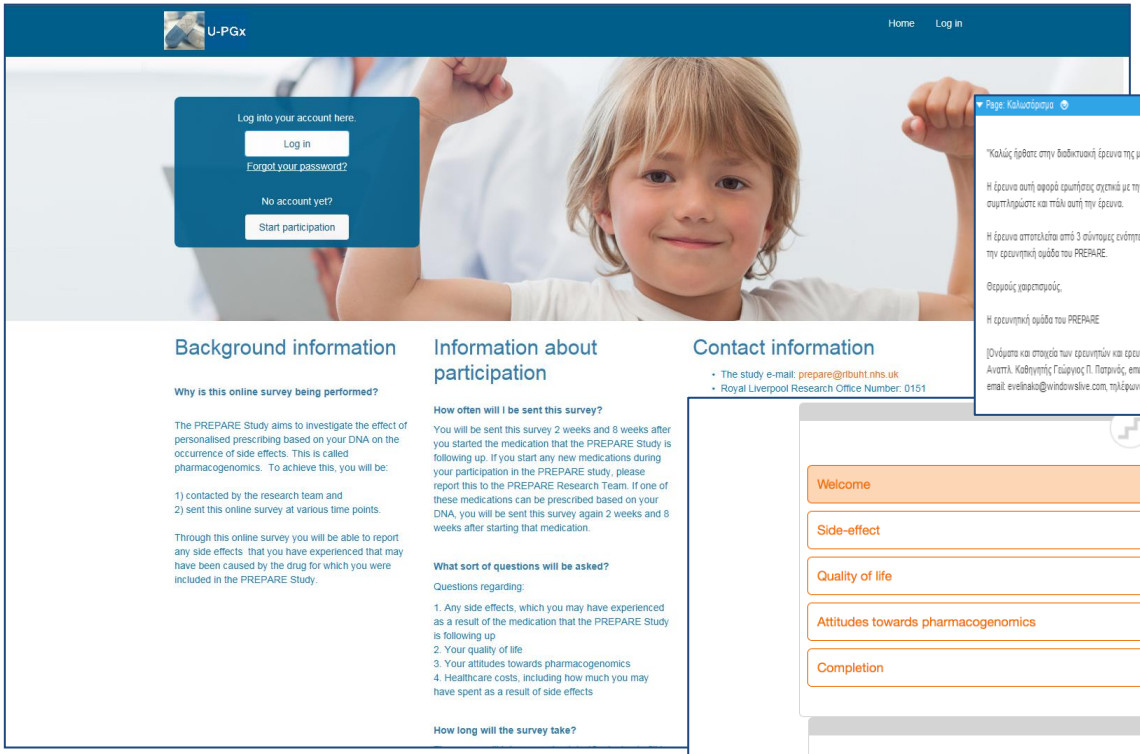
2. LIM

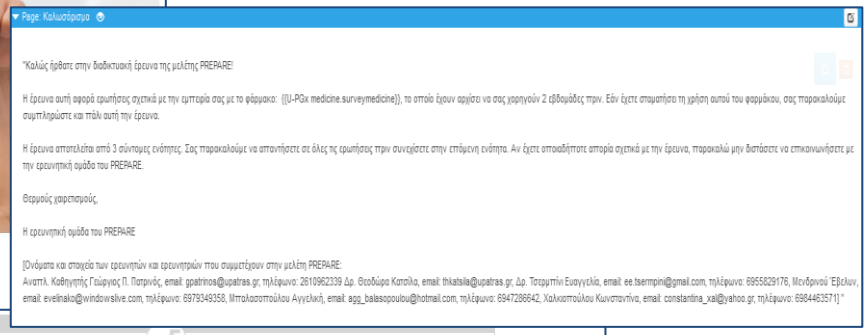
Online Survey Follow-up

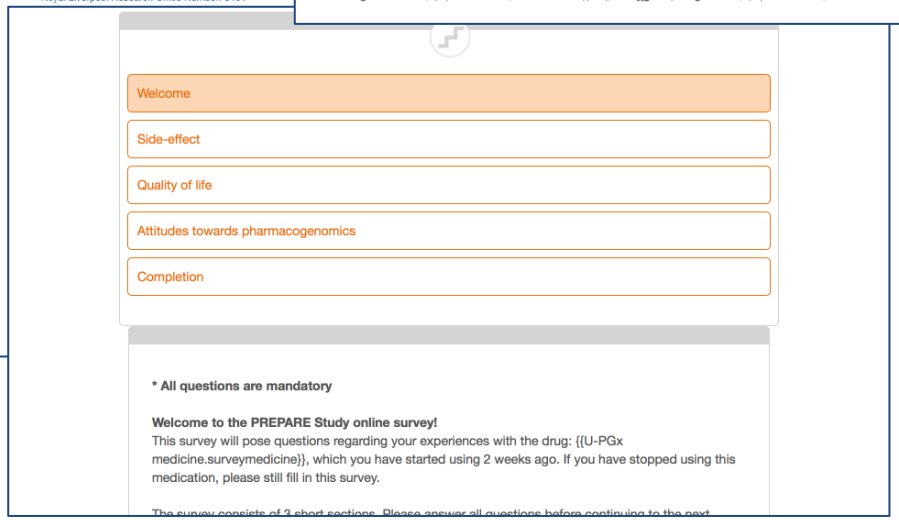
2 weeks*
8 weeks*

*For every newly prescribed drug of interest

Data collection:
Lareb Intensive Monitoring (LIM) Survey

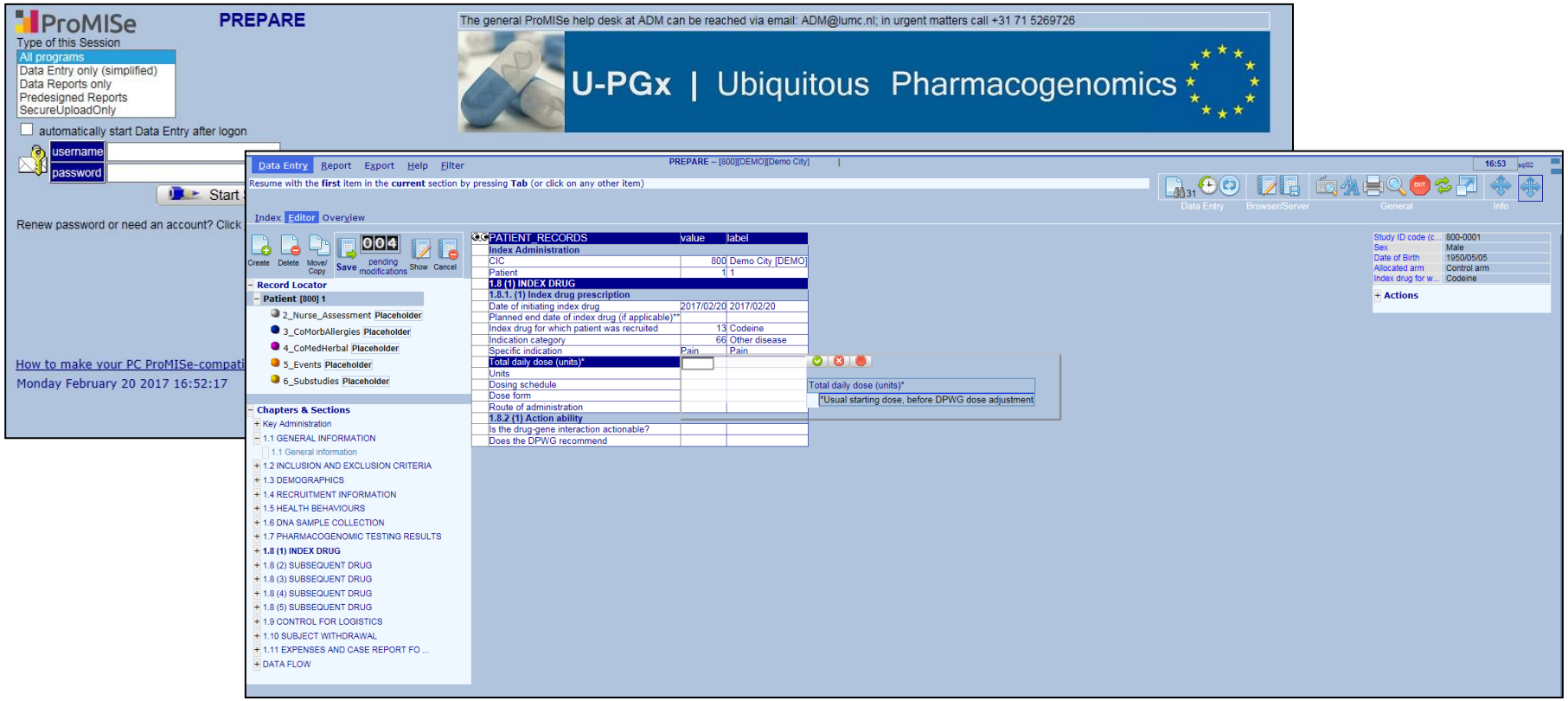






- Patient are able to report adverse events directly, without the intervention of a HCP
- Surveys are translated into local languages

Data collection:
Electronic Case Report Form



- ProMISe facilitates us to store, exchange and retrieve data according to the security conditions demanded by GCP
- Each user has a personal log-in, facilitating an audit trail
- Scripted sections of eCRF are translated into local languages

Primary Statistical Analysis

Logistic regression analysis:

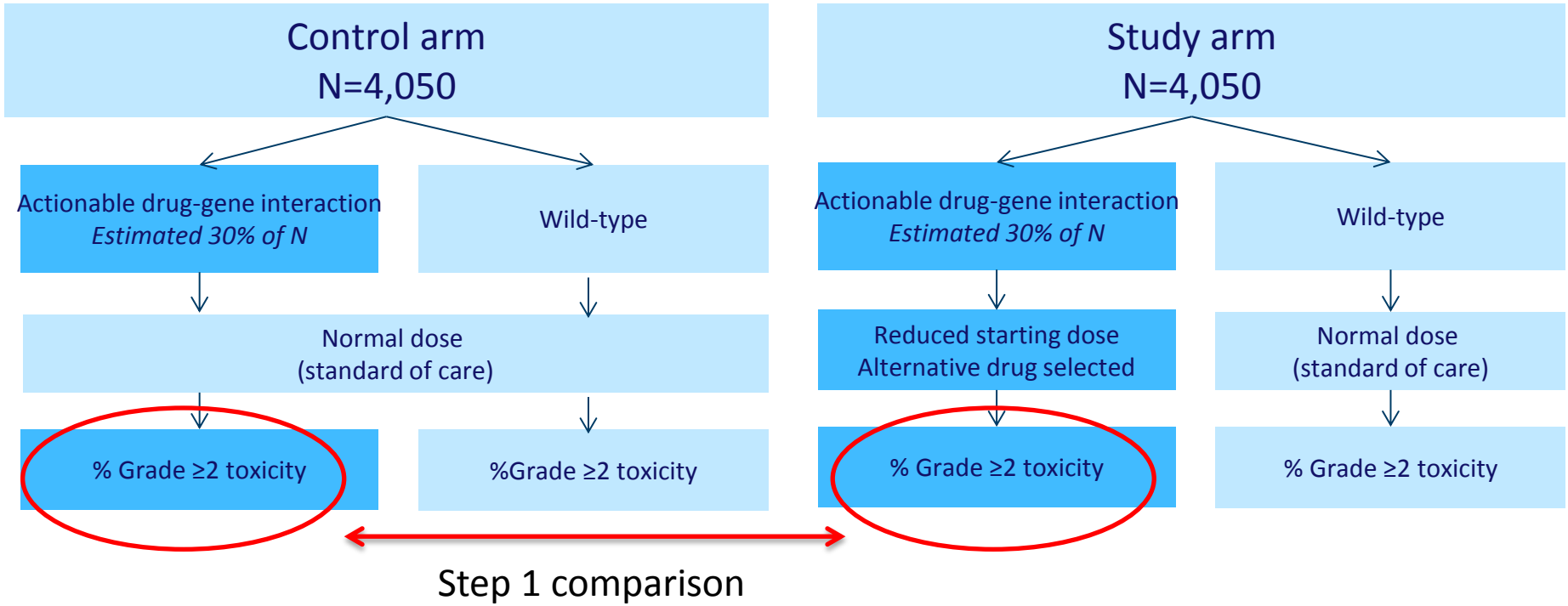
Number of patients who experience at least one ADR contributing to the primary composite endpoint in the study arm vs control arm

Gatekeeping analysis:

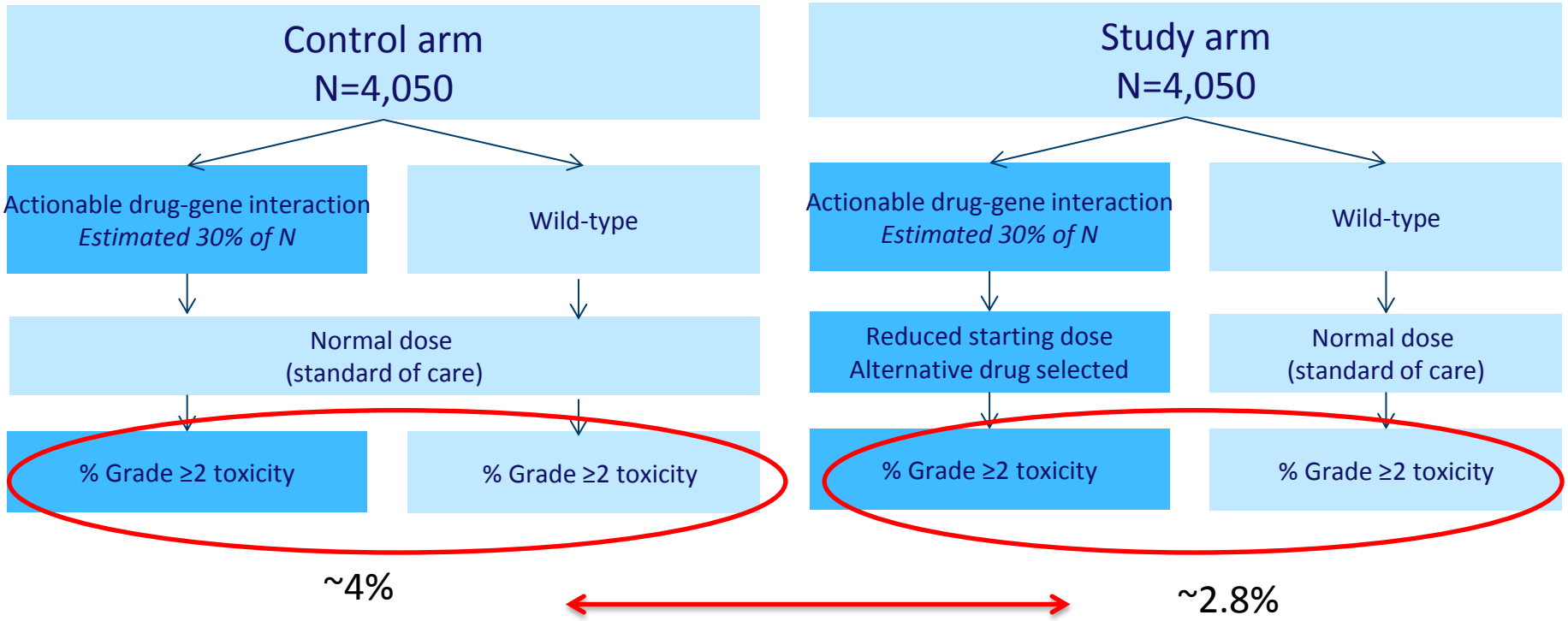
1. Among patients with an actionable drug-genotype interaction

2. Among all patients included in the study

1.
Received Recommendation
vs
Did Not Receive Recommendation

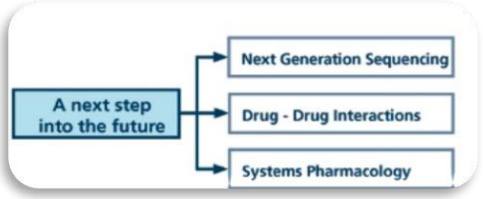


2.
All Patients Included



Step 2 comparison

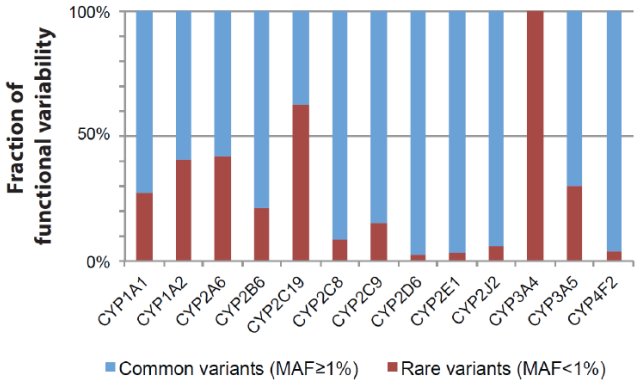
Component 3:
A next step into the Future



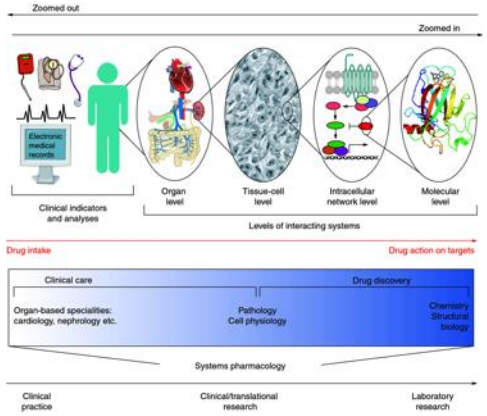
Leader: Prof. Dr. Matthias Schwab

- **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



- **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



Wist Genome Medicine2009;1:11

1. Ingelman-Sundberg, Genetics in Medicine 2016

A Next Step into the Future -- in more detail

- Extreme phenotype follow-up study

Objective: to identify rare variants associated with drug response.

  - Collection of blood sample within 24 hours of ADR for blood plasma concentration of index drug
  - NGS of 200 ADME genes

- Drug-Drug-Gene interaction sub-study

Among patients included in the PREPARE Study for a first prescription of metoprolol, capecitabine, 5-FU, atorvastatin, simvastatin or voriconazole

  - Collection of dried blood spot at various time points
  - Collection of clinical endpoint data

IV: ELSI, Dissemination and Communication

Leader: Christina Mitropoulou

- **Monitoring of all ethical and legal aspects** issued throughout the project and raising ELSI awareness within the U-PGx consortium
- **Increasing PGx awareness to professional stakeholders**, such as healthcare professionals, regulators, policy makers, representatives from ministries, pharmaceutical and biotechnology companies and patients' organizations; 8 U-PGx Personalized Medicine Days in 8 EU countries
- **Increasing PGx awareness to patients and the general public**; 2 major events will be organized in close cooperation with patients' organizations in London and Rome
- A **public-domain web-based PGx information portal** providing up-to date information for specialized scientists and healthcare professionals as well as for the general public and patients (www.upgx.eu)
- The majority of the data and results generated by U-PGx will be published in **open-access scientific journals**.

Current status

- ICT tools developed → msc card
- PGx genotyping platform selected → LGC SNPLine
- PGx panel selected → 13 pharmacogenes; 48 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 Dec 2016; 2nd in Vienna May 12
- Study protocol finished
  - IRB approval for all sites
- SOPs completed e.g. logistics, causality assessment, genotyping
- **Recruitment started, first 40 patients recruited**

Future perspective and collaboration

- Routine PGx guided prescribing will become a reality in the EU in the near future
- PREPARE Study will quantify collective clinical utility of a panel of PGx-markers
- PREPARE is unique in its multi-center, multi-gene, multi-drug, multi-ethnic, and multi-healthcare system approach
- PREPARE 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**

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

van der Wouden CH, Cambon-Thomsen A, Cecchin E, Cheung KC, Lucía Dávila-Fajardo C, Deneer VH, Dolžan V, Ingelman-Sundberg M, Jönsson S, Karlsson MO, Kriek M, Mitropoulou C, Patrinos GP, Pirmohamed M, Samwald M, Schaeffeler E, Schwab M, Steinberger D, Stingl J, Sunder-Plassmann G, Toffoli G, Turner RM, van Rhenen MH, Swen JJ, Guchelaar HJ.

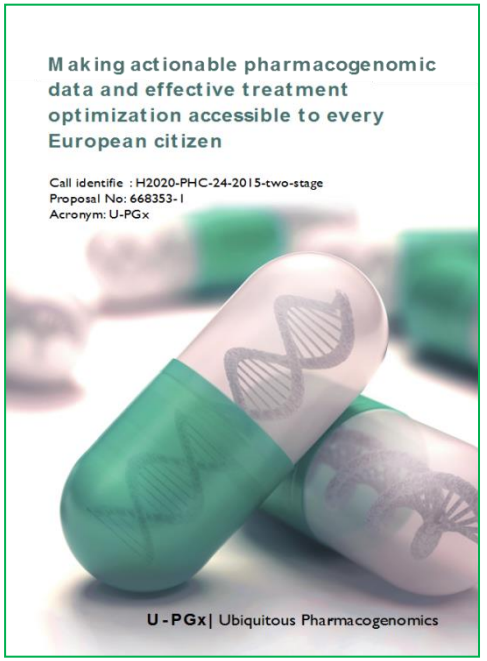
The Ubiquitous Pharmacogenomics Consortium.

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

U-PGx | Ubiquitous Pharmacogenomics

Thank you for your attention!

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



WWW.UPGX.EUx

Email: j.j.swen@lumc.nl

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