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# Title: Report on models identified to be developed

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**Comment:**

## Introduction

The main goal of the U-PGx consortium is to investigate, in a clinical study, a pre-emptive genotyping approach of a panel of important pharmacogenomic (PGx) variants as a new model of personalised medicine. The PGx variants and drugs to be studied are based on the Dutch Pharmacogenetics Working Group (DPWG) PGx-based therapeutic treatment recommendations.

The aim of WP9A is a next step into the future to improve the existing DPWG PGx guidelines by integrating knowledge of non-genetic factors based on a systems pharmacology approach.

The two first objectives pf WP9 are:

- 9A.1: To develop pharmacometric models integrating PGx information with other sources of variability to predict expected effect for genetic variant groups on various outcomes.

- 9A.2: To identify clinically relevant drug-drug interactions (DDI) as potential major confounder in the interventional pre-emptive U-PGx-trial.

In meeting these two objectives, one focus is the utilization of pharmacometric and systems pharmacology models for interpretation of the influence of PGx and non-genetic (e.g. demographics, interacting drugs, food intake etc.) factors on drug plasma concentrations as well as on biomarkers/clinical endpoints for safety and efficacy.

The work will strive toward assessing the relative contribution of PGx to the variability in drug response by utilizing mathematical models that integrate PGx with other sources of variability. Pharmacometric (mainly developed in NONMEM) and/or physiologically-based pharmacokinetic (PBPK) models (developed in PKSim or NONMEM) with the purpose to describe the events from dose to drug response, including effects of PGx on pharmacokinetics (PK) and/or pharmacodynamics (PD), will be derived based on published models or developed based on available data.

The models will aim to predict the impact of genetic variability on PK and/or PD variables and to demonstrate the impact of clinically relevant drug-drug, and drug-drug-gene interactions. The results of these model predictions have the potential to be helpful in treatment of patients.

**The purpose of this deliverable** is to report the models that have been identified for further development. The identification has been guided by the drugs of interest and clinical endpoints to be collected in the U-PGx clinical study.

The research groups collaborating in WP9 are: i) Pharmacometrics Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden; ii) Clinical Pharmacy,

Saarland University, Saarbrücken, Germany; iii) Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany/Department of Clinical Pharmacology, Institute of Experimental and Clinical Pharmacology and Toxicology, University Hospital, Tuebingen, Germany.

# Results

## Models identified based on literature search (published models)

A literature search (PubMed) was performed to find population PK, PD, (adverse event endpoints particularly) and/or exposure-response (PKPD) models including PGx info.

The search was performed for a selection of the drugs included in the DPWG PGx-based therapeutic treatment recommendations as follows:

- Drugs with the highest clinical relevance, i.e. categories D, E, F according to clinical relevance based on the seven-point scale derived from the National Cancer Institute's Common Toxicity Criteria (see Appendix 1), were first chosen, and a list of these 23 drugs sorted by gene in Appendix 2.

- Out of these drugs, literature search was performed for 5-fluorouracil, capecitabine, metoprolol, codeine, clopidogrel, efavirenz, flucloxacillin, simvastatin, azathioprine, mercaptopurine, thioguanine, irinotecan and warfarin thus covering DPYD (GAS 0-1.5), CYP2D6, CYP2C19, CYP2B6, HLA-B (*5701 pos), SLCO1B1 (521CC), TMTP, UGT1A1, CYP2C9 and VKORC1.

The following (mainly NONMEM models) drug/models were identified as candidates for development:

- **5-fluorouracil (DPYD):** Population PK, population PK-PGx and population PK-myelosuppression (5-fluorouracil, epidoxorubicin and cyclophosphamide[FEC] regimen) models were found. The plan is to combine these into one joint model with PK including PGx and then predicting the myelosuppression (following FEC regimen or if possible only after 5-flurouracil) (1-4). If possible, capecitabine will be considered as part of the model as well (5-7).
- **Mercaptopurin (TPMT):** Population PK-PGx and PBPK-PGx models were found(8, 9). Logistic regression for leukopenia has been published but no model was described. However, the plan is to build a model for PK including PGx and predict myelosuppression for a variety of different drug potencies for myelosuppression. Further consideration to find information to derive a model with respect to NUDT15 will be made, since it has been shown to be related to the development of myelosuppression (10).

- **Irinotecan (UGT1A1):** Population PK, population PK-PGx (possibly also further sources to contact), PK-diarrhoea and PK-myelosuppression models were found. The

plan is to combine these models being able to predict PK including PGx and the outcome on myelosuppression and occuence of diarrhoea, respectively (1, 11-13).

- ***Clopidogrel (CYP2C19):*** Population PK-PGx, PK-antiplatelet activity models were found (14-16). However, predictions have already been described fairly thoroughly in the literature with respect to PK-PGx and the relation to inhibition of platelet aggregation. A potential plan is to build a model for risk for myocardial infarction (MI) and/or bleeding by the use of information from other drugs with similar drug effects, which include some further literature search.

- ***Warfarin (CYP2C9; VKORC1):*** Several models are available in the literature describing population PK-PGx-INR outcome. However, also in this case the influence of PGx has been fairly well described in the literature already, but it is still an option to use one of these models for illustration purposes (17, 18).

## Models available or under development in research groups

In the U-PGx clinical study protocol a number of clinical relevant drugs were identified to be specifically monitored (plasma concentrations) as follows: "In a sub-study, patients included in the study for a first prescription of *voriconazole, metoprolol, simvastatin, atorvastatin, fluorouracil or capecitabine* will be asked to provide additional blood spot samples at multiple time points and at the time of an ADR.". Thus, for development of new models the focus was on these drugs.

The models developed or under development are categorized below based on whether they are developed as pharmacometric (developed in NONMEM) or PBPK models (developed in PKSim or SimCYP).

### PBPK models

A PBPK model for tamoxifen exists but needs update (19).

Currently, PBPK models are under development for simvastatin and voriconazole. Potentially, PBPK models may be developed for metoprolol and 5-FU/capecitabine.

A PBPK model is finalized for dabigatran and currently under publication (drug not included in clinical study, but still of interest).

### NONMEM models

A population PK model including PGx for **tamoxifen** has been established and currently an exposure-response (survival model) is under development.

A population PK model including PGx for **voriconazole** has been developed and is published (20).

For dabigatran (drug not included in clinical study, but still of interest) population PK-PGx, PK-PD (biomarker) and PK/biomarker-clinical endpoint models have been developed (21,

22). These models are also included in a Shiny app to easily illustrate the effects of various PGx variants on outcomes (PK, PD, clinical endpoint).

## Summary/Conclusions

The literature search and the survey over models available and under development in the involved research groups have been successful. The following lists the models, which have been identified as potential candidates to make simulations and predictions of PK and clinical endpoints from. This list may involve more models than what will be developed and simulated from eventually.

1. Although dabigatran is not included in the DPWG recommendations, this example serves as a very good, already available, example of how we can use simulations to scrutinize the effect of PGx variants. Thus, this model will be used to show how models can illustrate consequences of various PGx variant and DDI on PK and clinical endpoints.

2. The NONMEM models will be used for model simulations to study PK and, most importantly, PD outcome for various PGx variants. The following are candidates for this activity
5-fluorouracil/capecitabine (DPYD): PK (incl PGx) → myelosuppression (FEC regimen)
Mercaptopurin (TPMT): PK (incl. PGx) → myelosuppression
Irinotecan (UGT1A1): PK (incl. PGx) → myelosuppression; PK (incl PGx) → diarrhoea
Tamoxifen (CYP2D6): PK (incl. PGx) → Clinical endpoint (survival)
Warfarin (CYP2C9; VKORC1): PK (incl. PGx) → INR

3. The PBPK models will be used mainly for simulations to study PK for various PGx variants and the influence of interacting drugs (DDI). The following are candidates for this activity:
Simvastatin (SLCO1B1, ABCG2 (23))
Tamoxifen (CYP2D6)
Voriconazole (CYP2C19)
Metoprolol (CYP2D6)
5-FU/capecitabine (DPYD)

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# Appendix 1: Clinical relevance

Clinical relevance of the potential adverse drug event, decreased therapeutic response, or other clinical effect resulting from the gene-drug interaction.

The clinical relevance was scored on a seven-point scale derived from the National Cancer Institute's Common Toxicity Criteria. A clinical or pharmacokinetic effect that was not statistically significant was classified as AA (lowest impact), whereas death, for example, was classified as F (highest impact). At every level of this point scale, new events are added after assessment by the DPWG.

| Clinical Relevance | Definition (Classification of Clinical Relevance) |
|---|---|
| AA | Clinical effect (NS); Kinetic effect (NS) |
| A | Minor clinical effect (S): QTc prolongation (<450 ms female, <470 ms male); INR increase < 4.5; Kinetic effect (S) |
| B | 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 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. |
| C | 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); INR 4.5-6.0; neutropenia 1.0-$1.5x10^9$/l; leucopenia 2.0-$3.0x10^9$/l; thrombocytopenia 50-$75x10^9$/l. |
| D | 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. |
| E | 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. |
| F | Clinical effect (S): death; arrhythmia; unanticipated myelosuppression. |

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

# Appendix 2

| Drug | Gene (variant) | Therapeutic area | Clinical relevance category (DPWG guidelines) |
|---|---|---|---|
| Efavirenz | CYP2B6 (IM) | Anti-infective | D |
| Efavirenz | **CYP2B6 (PM)** | Anti-infective | E |
| Clopidrogel | **CYP2C19 (IM)** | Anticoagulation | F |
| Clopidrogel | CYP2C19 (PM) | Anticoagulation | F |
| Acenocoumarol | CYP2C9 (*1/*2) | Anticoagulation | F |
| Phenprocoumon | CYP2C9 (*1/*2) | Anticoagulation | F |
| Warfarin | CYP2C9 (*1/*2) | Anticoagulation | F |
| Acenocoumarol | CYP2C9 (*1/*3) | Anticoagulation | F |
| Phenprocoumon | CYP2C9 (*1/*3) | Anticoagulation | F |
| Warfarin | **CYP2C9** (*1/*3) | Anticoagulation | D |
| Phenytoin | CYP2C9 (*1/*3) | Antiepileptic | D |
| Acenocoumarol | CYP2C9 (*2/*2) | Anticoagulation | F |
| Phenprocoumon | CYP2C9 (*2/*2) | Anticoagulation | F |
| Acenocoumarol | CYP2C9 (*2/*3) | Anticoagulation | F |
| Phenprocoumon | CYP2C9 (*2/*3) | Anticoagulation | F |
| Phenprocoumon | CYP2C9 (*3/*3) | Anticoagulation | E |
| Acenocoumarol | CYP2C9 (*3/*3) | Anticoagulation | F |
| Phenytoin | CYP2C9 (*3/*3) | Antiepileptic | D |
| Tamoxifen | CYP2D6 (IM) | Anticancer | E |
| Flecainide | CYP2D6 (PM) | Antiarrhythmic | F |
| Tamoxifen | CYP2D6 (PM) | Anticancer | F |
| Doxepine | CYP2D6 (PM) | Antidepressant (TCA) | F |
| Risperidone | CYP2D6 (PM) | Antipsychotic | D |
| Codeine | CYP2D6 (UM) | Analgesic | F |
| Propafenon | CYP2D6 (UM) | Antiarrhythmic | D |
| Metoprolol | CYP2D6 (UM) | Antihypertensive | D |
| Tacrolimus | CYP3A4 (*1/*22) | Immunosuppressive | D |
| Tacrolimus | CYP3A4 (*22/*22) | Immunosuppressive | D |
| Tacrolimus | CYP3A5 (*1/*1) | Immunosuppressive | E |
| Tacrolimus | CYP3A5 (*1/*3) | Immunosuppressive | E |
| Tegafur | DPYD (GAS 0-1.5) | Anticancer | E |
| Capecitabine | DPYD (GAS 0-1.5) | Anticancer | F |
| Fluorouracil | DPYD (GAS 0-1.5) | Anticancer | F |
| Flucloxacillin | HLA-B (*5701 pos) | Anti-infective | D |
| Simvastatin | SLCO1B1 (521CC) | Cholesterol-lowering | D |
| Simvastatin | SLCO1B1 (521TC) | Cholesterol-lowering | D |
| Azathioprine | TPMT (IM) | Immunosuppressive | E |
| Mercaptopurine | TPMT (IM) | Immunosuppressive | E |
| Thioguanine | TPMT (IM) | Immunosuppressive | E |
| Azathioprine | TPMT (PM) | Immunosuppressive | F |
| Mercaptopurine | TPMT (PM) | Immunosuppressive | F |
| Thioguanine | TPMT (PM) | Immunosuppressive | F |
| Irinotecan | UGT1A1 (*1/*28) | Anticancer | F |
| Irinotecan | UGT1A1 (*28/*28) | Anticancer | E |
| Phenprocoumon | VKORC1 (CT) | Anticoagulation | D |
| Phenprocoumon | VKORC1 (TT) | Anticoagulation | D |
| Acenocoumarol | VKORC1 (TT) | Anticoagulation | F |