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Contents

Introduction

Implementing clinical decision support in seven European countries in the context of an international clinical study poses special requirements, most importantly, the need to conceive of a solution that allows for a standardized decision support intervention while simultaneously allowing for enough flexibility to conform to the requirements of the greatly varying existing technical infrastructures and workflows at the different clinical implementation sites. With the "U-PGx Genetic Information Management Suite" (GIMS), such a consistent, yet flexible decision support solution was implemented. Since January 2017, U-PGx GIMS is accessible via https://upgx-gims-cms.biologisgroup.com. U-PGx GIMS is only accessible by authorized users, therefore this report contains an overview of the functionalities of GIMS including several screenshots of the portal.

U-PGx Genetic Information Management Suite

Role of UPGx GIMS in the PREPARE study

The U-PGx Genetic Information Management Suite (GIMS) is the main portal for the management of guideline translations, upload of genotyping sample files and retrieval of PGx reports in various formats (see Figure 1). Since January 2017, authorized users can access U-PGx GIMS via https://upgx-gims-cms.biologisgroup.com.

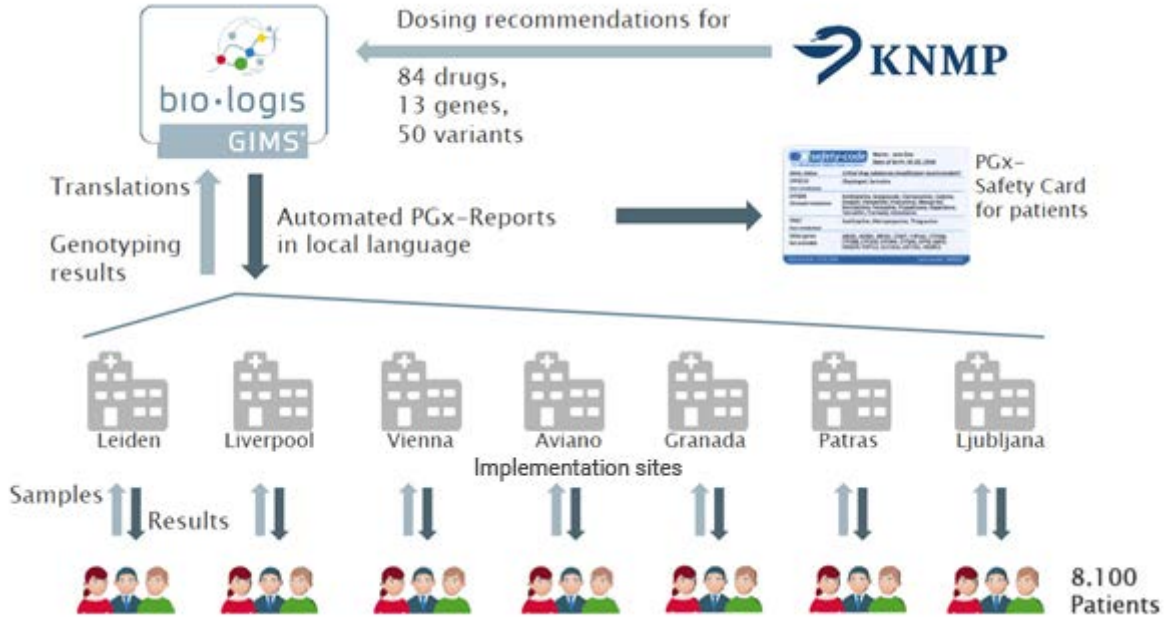


Figure 1. Role of U-PGx GIMS in the delivery of PGx decision support in the PREPARE study. Anonymized genotyping results are transferred to U-PGx GIMS via a secure VPN connection. Based on the content of the Knowledge Management Module, U-PGx GIMS returns a digital PGx report in PDF or ODT format, and a PDF printing template for a safety-code card in the respective local language.

Functionalities

U-PGx GIMS provides several valuable functionalities to authorized users which are described in the following.

Allocation of different roles and writing permissions to users

U-PGx GIMS allows the assignment of roles with different reading and writing permissions to different users:

- Content Publisher
- Content Viewer

- Text Editor
- U-PGx Doctor
- U-PGx LGC Upload
- Text Element Approver
- Text Element Reviewer

Managing guideline texts and translations to local languages

Text elements used for the generation of the PGx report (i.e., guideline texts, report text fragments, active ingredient and trade names) can be viewed and edited in U-PGx GIMS by authorized users. Furthermore, U-PGx GIMS allows the management of translations to the implementation sites' local languages. The assignment of different workflow states to text elements (i.e., outdated, reviewed, approved) ensures that only validated content is displayed to the end users in the automatically generated PGx reports. Figure 2 shows the interface for editing and approving guideline text elements.

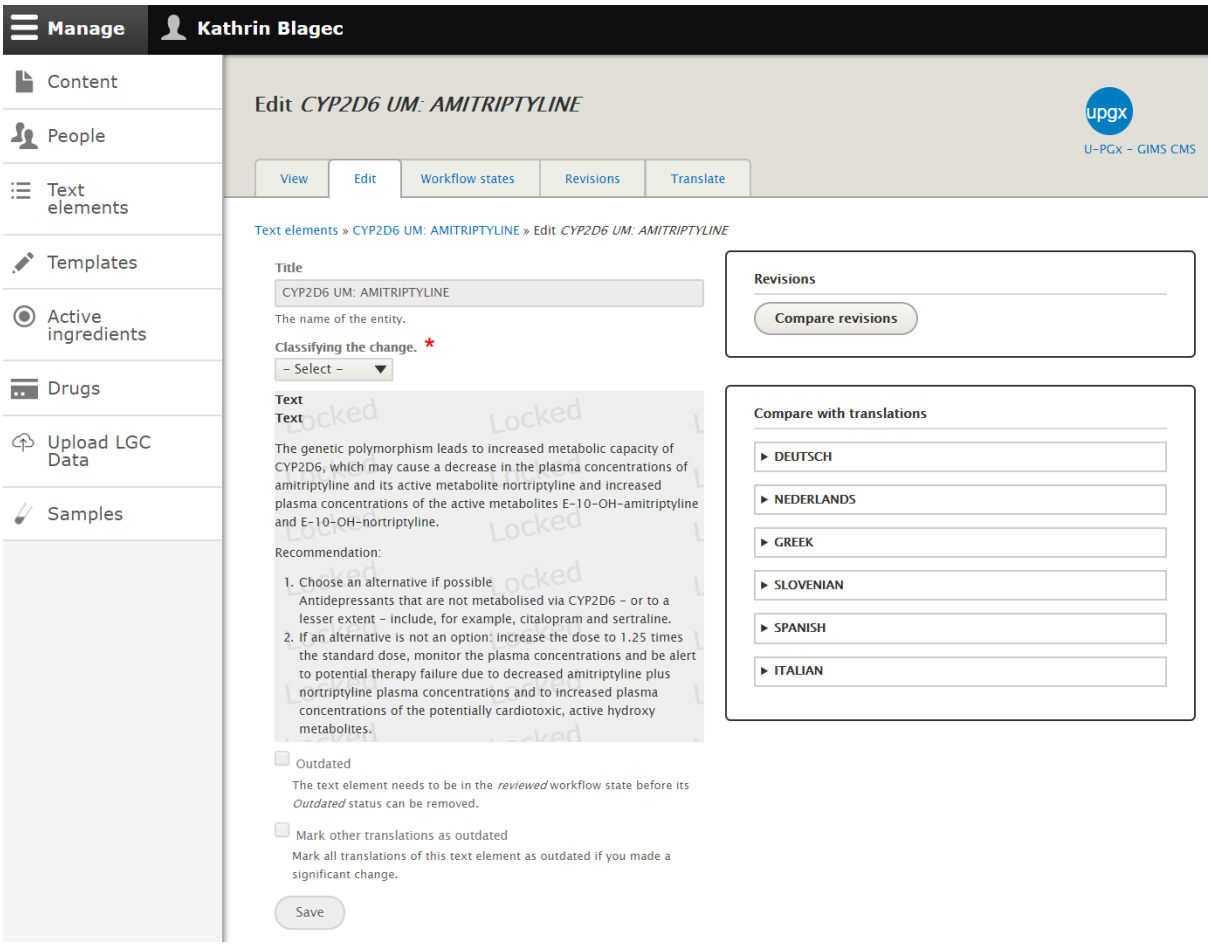


Figure 2. U-PGx GIMS Interface, Editing and approving text elements

Transparent change history

All modifications to text elements, including information on when the changes occurred and who made them, are captured by U-PGx GIMS to ensure maximum transparency and complete traceability.

Uploading and managing files from the U-PGx genotyping platform

CSV files containing the anonymized genotyping results from the LGC platform can be uploaded via the web interface (see Figure 3 and Figure 4).

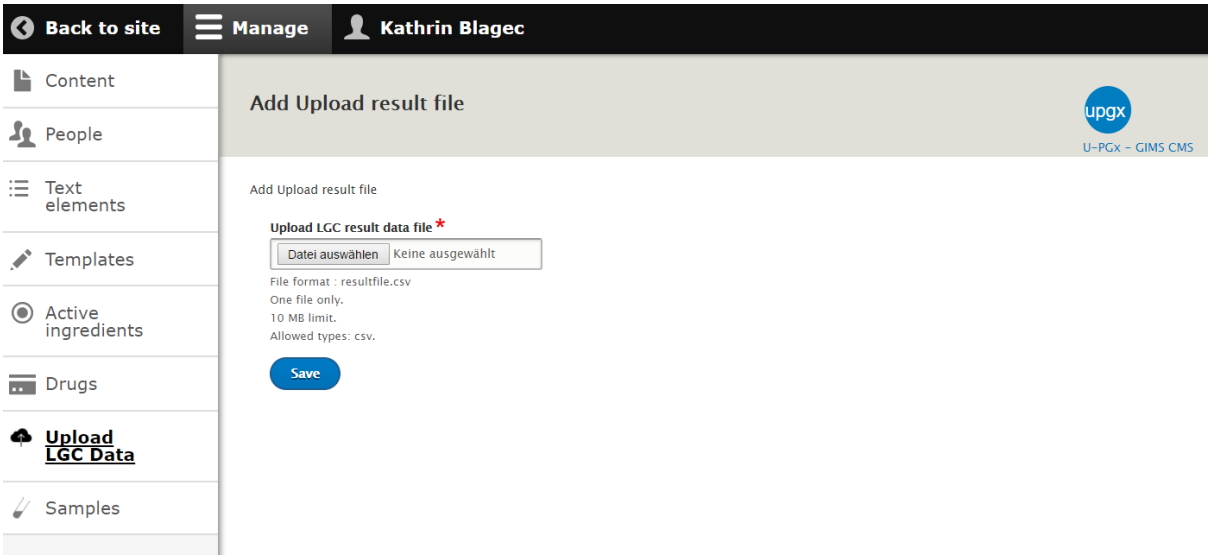


Figure 3. U-PGx GIMS Interface, Upload of genotyping results

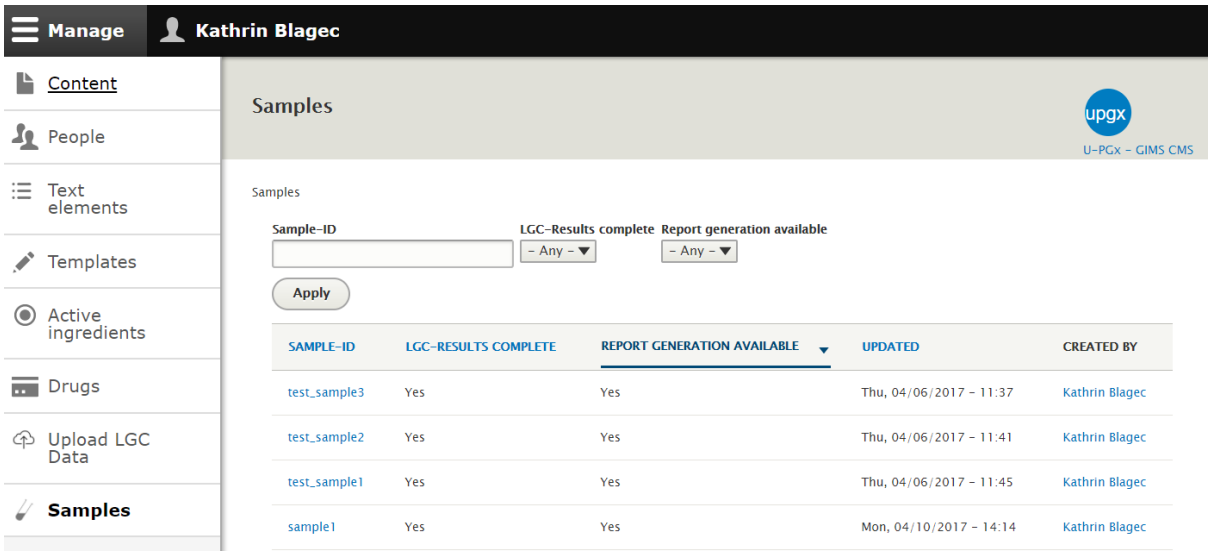


Figure 4. U-PGx GIMS Interface, Overview of uploaded samples

Automatic generation of PGx reports

After a sample file has been uploaded into U-PGx GIMS, a PDF or ODT file containing the PGx report can be generated (see Figure 5). An exemplary PGx report for a fictional patient can be found in Appendix A.

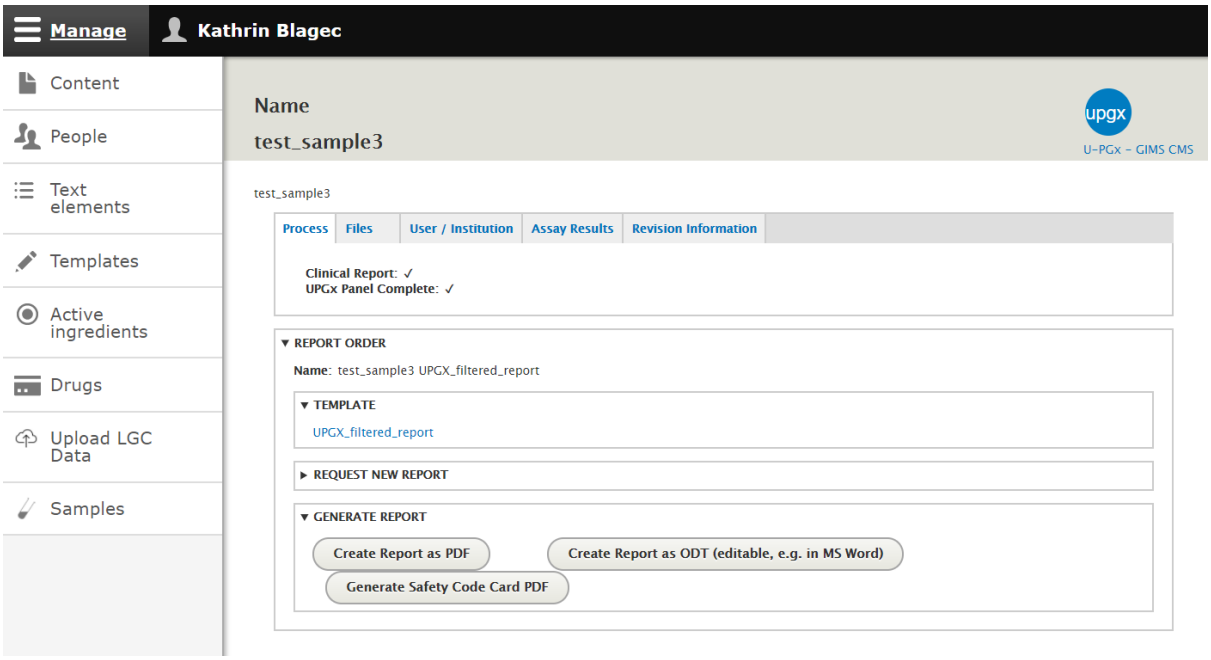


Figure 5. U-PGx GIMS Interface, PGx report and safety-code card retrieval

Automatic generation of safety-code cards

Besides the generation of conventional PGx reports, U-PGx GIMS furthermore enables the generation of PDF printing templates for safety-code cards (see Figure 5). These cards contain an overview of the patient's pharmacogenomics profile and a QR code. Figure 6 and Figure 7 show the front and back side on such an automatically generated safety-code for a Greek test patient. Scanning the QR code leads health care professionals and patients to a website that contains an interactive version of the patient's PGx reports (see Figure 8).

Figure 6. Greek exemplary card, front side

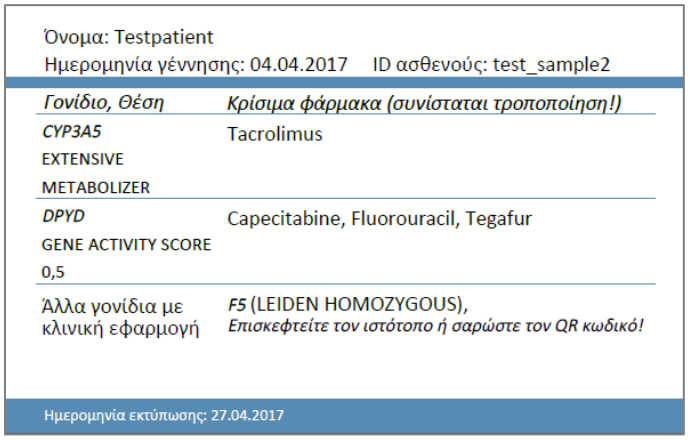
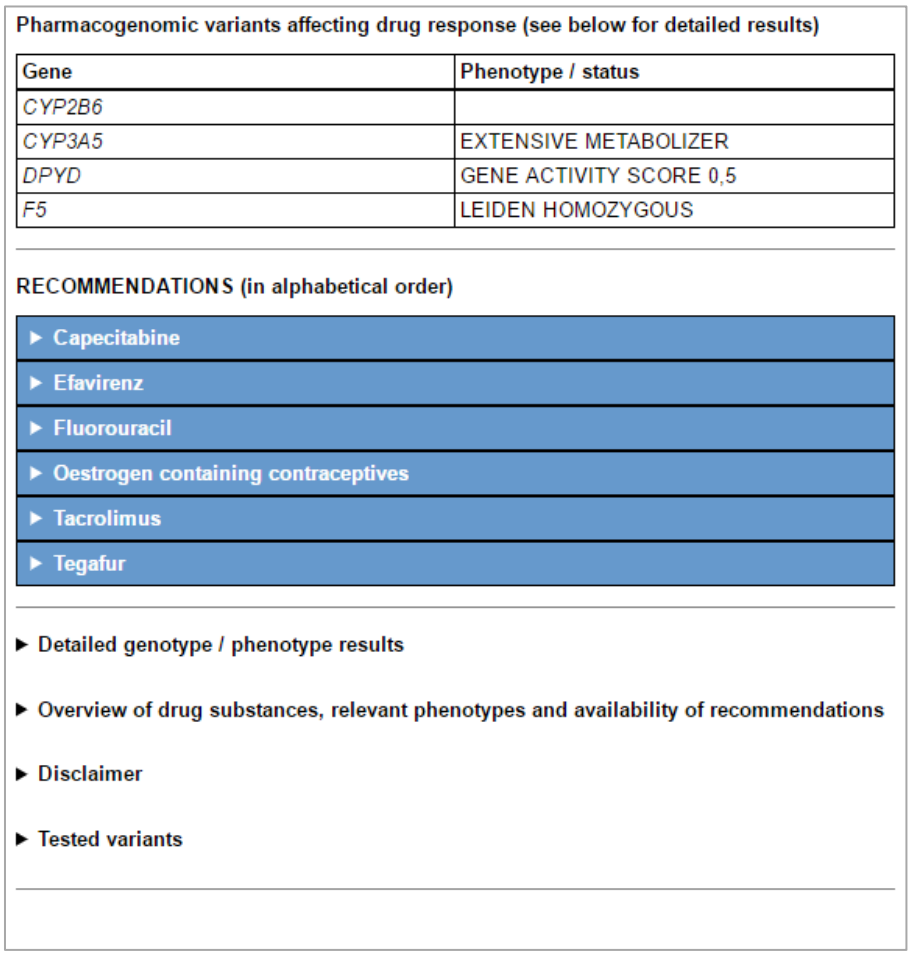


Figure 7. Greek exemplary card, back side



Pharmacogenomic variants affecting drug response (see below for detailed results)

Gene	Phenotype / status
CYP2B6	
CYP3A5	EXTENSIVE METABOLIZER
DPYD	GENE ACTIVITY SCORE 0,5
F5	LEIDEN HOMOZYGOUS

RECOMMENDATIONS (in alphabetical order)

- ▶ Capecitabine
- ▶ Efavirenz
- ▶ Fluorouracil
- ▶ Oestrogen containing contraceptives
- ▶ Tacrolimus
- ▶ Tegafur

- ▶ Detailed genotype / phenotype results
- ▶ Overview of drug substances, relevant phenotypes and availability of recommendations
- ▶ Disclaimer
- ▶ Tested variants

Figure 8. Screenshot of the web-based PGx report accessible via the QR code on the safety-code card. Clicking or tapping on the drug name folds out the recommendations.

Abbreviations

GIMS	Genetic Information Management Suite
MSC	Medication Safety Code
PGx	Pharmacogenomics

List of Figures

Appendix A: Exemplary English PGx report for a fictional patient

Pharmacogenomic test report

Patient information

- Name: John Doe
- Date of birth (DD.MM.YYYY): 15.01.1959
- Patient study ID:

Report information

- Order date (DD.MM.YYYY):
- Ordered by:
- Report date (DD.MM.YYYY):
- Laboratory contact:

Drugs with therapeutic recommendations (in alphabetical order)

- Atorvastatin
- Simvastatin
- Tacrolimus

Pharmacogenomic variants affecting drug response (see below for detailed results)

Gene	Phenotype / status
CYP3A5	EXTENSIVE METABOLIZER
SLCO1B1	DECREASED FUNCTION

RECOMMENDATIONS (in alphabetical order)

Atorvastatin
ATORVASTATINE TABLET 10MG (ALS CA-ZOUT-3-WATER), ATORVASTATINE TABLET 20MG (ALS CA-ZOUT-3-WATER), ATORVASTATINE TABLET 40MG (ALS CA-ZOUT-3-WATER)

Phenotype / Variant: *SLCO1B1* DECREASED FUNCTION

The genetic polymorphism may lead to reduced atorvastatin transport to the liver. This may increase atorvastatin plasma concentrations and therefore the risk of myopathy.

Recommendation:

- Patient has ADDITIONAL SIGNIFICANT RISK FACTORS for statin-induced myopathy:
  - Choose an alternative

    Rosuvastatin and pravastatin are influenced to a similar extent by SLCO1B1 polymorphisms but are not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.

    Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors.
  - If an alternative is not an option: advise the patient to contact their doctor in the event of muscle symptoms.
- Patient has NO additional significant risk factors for statin-induced myopathy:
  - Advise the patient to contact their doctor in the event of muscle symptoms.
- If a GRADUAL REDUCTION in HEART RATE is desired, or in the event of SYMPTOMATIC BRADYCARDIA:
  - increase the dose in smaller steps and/or prescribe no more than 50% of the standard dose
- OTHER CASES:
  - no action required

Simvastatin
SIMVASTATINE TABLET FO 10MG, SIMVASTATINE TABLET FO 20MG, SIMVASTATINE TABLET FO 40MG

Phenotype / Variant: *SLCO1B1* DECREASED FUNCTION

The genetic polymorphism may lead to reduced simvastatin transport to the liver. This may increase simvastatin plasma concentrations and therefore the risk of myopathy.

Recommendation:

1. Choose an alternative

   Consider any additional risk factors for statin-induced myopathy.

   Rosuvastatin and pravastatin are influenced to a lesser extent by SLCO1B1

polymorphisms. They are also not influenced by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem. Fluvastatin is not influenced by SLCO1B1 polymorphisms or CYP3A4 inhibitors.

2. If an alternative is not an option:
    1. Avoid simvastatin doses exceeding 40 mg/day
    2. Advise the patient to contact their doctor in the event of muscle symptoms.

Tacrolimus
TACROLIMUS INFOPL CONC 5MG/ML, TACROLIMUS INFUUS, TACROLIMUS CAPSULE 0,5MG

Phenotype / Variant: *CYP3A5* EXTENSIVE METABOLIZER

Genetic variation results in an increased conversion of tacrolimus to inactive metabolites and as a result a higher dose is required. Adjustment of the initial dose results in an increased chance of reaching a tacrolimus concentration within the target range before the start of therapeutic drug monitoring on day three. However, there is no direct evidence that this results in improved clinical results.

Recommendation:

- Indications OTHER than liver transplantation:
    - Start with 2.5 times the standard initial dose that would yield the desired result in non-expressors Adjustment of the dose should then be based on therapeutic drug monitoring.

      NOTE: The initial dose that yields the desired result in non-expressors can be lower than the standard initial dose. In the example provided below, this dose was 75 % of the standard initial dose. A 2.5 time dose increase corresponds in this case to a 2 time dose increase of the standard initial dose.

      For example: After three days, Thervet et al. found a median trough concentration for tacrolimus of 14.0 ng/mL at an initial dose of 0.15 mg/kg twice daily for four kidney transplant patients, who were homozygous expressors. This was 5.6 ng/mL (n = 6) for an initial dose of 0.1 mg/kg twice daily. Their target value was 10 - 15 ng/mL. This is lower than the target value that is used in the Netherlands in the first two - four weeks after kidney transplantation (15 - 20 ng/mL).

      For the reference group of non-expressors, a median trough concentration of 16.6 ng/mL and

      12.0 ng/mL was achieved at a dosage of 0.1 mg/kg twice daily and 0.075 mg/kg twice daily respectively. In this hospital, the first dose is administered before the CYP3A5 genotype is known. The second dose is reduced according to the genotype.
- LIVER transplantation:

  In addition to the patient's genotype, the metabolism of tacrolimus is also determined by

the genotype of the transplanted liver.

- LIVER is also of the genotype HOMOZYGOUS EXPRESSOR:
  - Start with 2.5 times the standard initial dose Adjustment of the dose should then be based on therapeutic drug monitoring.
- LIVER has a DIFFERENT genotype:

  There is insufficient evidence in the literature to support a dose recommendation.

Detailed genotype / phenotype results

Gene	Genotype	Phenotype / status
CYP2B6	wildtype/wildtype	EXTENSIVE METABOLIZER
CYP2C19	wildtype/wildtype	EXTENSIVE METABOLIZER
CYP2C9	wildtype/wildtype	*1/*1
CYP2D6	wildtype/wildtype	EXTENSIVE METABOLIZER
CYP3A5	wildtype/wildtype	EXTENSIVE METABOLIZER
DPYD	wildtype/wildtype	GENE ACTIVITY SCORE 2 (EXTENSIVE METABOLIZER)
F5	wildtype/wildtype	FACTOR V LEIDEN ABSENT
HLA-A3101	wildtype/wildtype	*3101-NEGATIVE
HLA-B5701	wildtype/wildtype	*5701-NEGATIVE
HLA-B1502	wildtype/wildtype	*1502-NEGATIVE
SLCO1B1	wildtype/*5	DECREASED FUNCTION
TPMT	wildtype/wildtype	EXTENSIVE METABOLIZER
UGT1A1	X	*1/*28 (TA6/TA7)
VKORC1	wildtype/wildtype	1173CC (WILD TYPE)

Overview of drug substances, relevant phenotypes and availability of recommendations

drug substance	Relevant phenotype(s) /	Recommendation shown in this	reason
ABACAVIR			
Acenocoumarol			

AMIODARONE			
Amitriptyline			
Aripiprazole			
ATENOLOL			
Atomoxetine			
Atorvastatin	*SLCO1B1* DECREASED FUNCTION	Yes	Therapy modification recommended according to guideline
Azathioprine			
BISOPROLOL			
Capecitabine			
Carbamazepine			
CARVEDILOL			
Citalopram			
Clomipramine			
CLONIDINE			
Clopidrogrel			
Clozapine			
Codeine			
DEXMETHYLPHENIDATE			
DISOPYRAMIDE			
Doxepin			
DULOXETINE			
Efavirenz			
ELIGLUSTAT			
Escitalopram			
ESOMEPRAZOLE			
Flecainide			
Flucloxacillin			
Fluorouracil			
FLUOXETINE			
FLUPENTIXOL			

FLUPHENAZINE			
FLUVASTATIN	*SLCO1B1* DECREASED FUNCTION	No	No action recommended according to guideline
FLUVOXAMINE			
GEFITINIB			
GLIBENCLAMIDE			
GLICLAZIDE			
GLIMEPIRIDE			
Haloperidol			
Imipramine			
Irinotecan			
KINIDINE			
LANSOPRAZOLE			
Mercaptopurine			
METHYLPHENIDATE			
Metoprolol			
MIRTAZAPINE			
MOCLOBEMIDE			
Nortriptyline			
Oestrogen containing contraceptives			
OLANZAPINE			
OMEPRAZOLE			
Oxycodone			
PANTOPRAZOLE			
Paroxetine			
Phenprocoumon			
Phenytoin			
Pimozide			
PRASUGREL			
Propafenone			

QUETIAPINE			
RABEPRAZOLE			
RISPERIDONE			
Sertraline			
Simvastatin	SLCO1B1 DECREASED FUNCTION	Yes	Therapy modification recommended according to guideline
SOTALOL			
Tacrolimus	CYP3A5 EXTENSIVE METABOLIZER	Yes	Therapy modification recommended according to guideline
Tamoxifen			
Tegafur			
TICAGRELOR			
Tioguanine			
TOLBUTAMIDE			
Tramadol			
Venlafaxine			
Voriconazole			
Warfarin			
Zuclopenthixol			

Disclaimer

General information

This pharmacogenomic test report was issued within the scope of the PREPARE (PREemptive Pharmacogenomic testing for Preventing Adverse drug Reactions) study. PREPARE aims to implement pharmacogenomic testing to guide drug and dose selection in seven European countries, thereby personalizing medicine. PREPARE will provide evidence on the effect of pharmacogenomics-based prescribing on patient outcomes. The PREPARE protocol was initiated by the Ubiquitous Pharmacogenomics Consortium (U-PGx). U-PGx is funded by the European Union's Horizon 2020 grant, and is a project which aims to make effective treatment optimization accessible to every European citizen (www.upgx.eu).

Therapeutic recommendations

The therapeutic recommendations in this report are developed by the Dutch Pharmacogenetics

Working Group of the Royal Dutch Pharmacists Association. The Dutch Pharmacogenetics Working Group formulates the optimal recommendations for each phenotype group based on the available scientific evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

The recommendations in this report are solely based on the phenotypes that were inferred from the variants assayed by the genotyping test deployed in this study. The recommendations do not take into account any other factors that can influence a patient's phenotype and drug response, such as drug-drug interactions, various health conditions or environmental factors. The absence of a recommendation for a specific drug is not to be equated with the general absence of variants that might influence an individual's response to this drug since the patient might have a rarer variant that is currently not covered by the U-PGx genotyping test. In the course of U-PGx, the database that contains the annotations and recommendations to generate this report will continuously be updated as new scientific evidence becomes available. Therefore, the information included in this report is dependent on the report generation date.

Additional information on the recommendation for oral/vaginal contraceptives with estrogens

The recommendation refers to all estrogen containing hormonal contraceptives for systemic use. This includes, but is not limited to, *combination preparations of estrogens* (e.g. ethinylestradiol, estradiol) *with the following progestogens*: Cyproteron, Desogestrel, Dienogest, Drospirenon, Etonogestrel, Gestodeen, Levonorgestrel, Nomegestrol, Norelgestromine, Norethisteron, Norgestimaat.

Genotyping test

Nucleic acid variants were detected by fluorescence-based endpoint genotyping using two allele-specific forward and one common reverse primer. Determined alleles were compared to the corresponding reference sequences. Fluorescence signals were analyzed and classified using computer-based method.

The method applied detects bi- and tri-allelic SNPs (single nucleotide polymorphism), insertions, deletions, and duplications. Assignment of a genotype is based on results at the positions investigated which are listed for each analysis.

As with any PCR-based method, results of genotyping can be influenced by genomic variants in the primer binding region. This can result in findings divergent from those obtained with alternative methods or with PCR products of the region generated with different primers. The method does not preclude point variations, deletions or duplications in regions of the gene other than those investigated.

Results of genotyping reported are frequently checked as part of continuing method development. A correction of the clinical report will be provided in case results turn out to have been influenced

by a genetic polymorphism not known at the time of investigation.

Tested variants

GENE	ALLELE	VARIANT	CORRESPONDING RS ID
CYP2B6	*6/*9	516G>T	rs3745274
CYP2B6	*4/*16	785A>G	rs2279343
CYP2B6	*18	983T>C	rs28399499
CYP2C9	*2	430C>T	rs1799853
CYP2C9	*3	1075A>C	rs1057910
CYP2C9	*5	1080C>G	rs28371686
CYP2C9	*11	1003C>T	rs28371685
CYP2C19	*2	681G>A	rs4244285
CYP2C19	*3	636G>A	rs4986893
CYP2C19	*4A/B	1A>G	rs28399504
CYP2C19	*5	1297C>T	rs56337013
CYP2C19	*6	395G>A	rs72552267
CYP2C19	*8	358T>C	rs41291556
CYP2C19	*9	431G>A	rs17884712
CYP2C19	*10	680C>T	rs6413438
CYP2C19	*17	-806C>T	rs12248560
CYP2D6	*xN	Gene duplication or	X
CYP2D6	*3	2549delA	rs35742686
CYP2D6	*4	1846G>A	rs3892097
CYP2D6	*5	Gene deletion	X
CYP2D6	*6	1707delT	rs5030655
CYP2D6	*8	1758G>T	rs5030865
CYP2D6	*9	2615delAAG	rs5030656
CYP2D6	*10	100C>T	rs1065852
CYP2D6	*14A/B	1758G>A	rs5030865
CYP2D6	*17	1023C>T	rs28371706
CYP2D6	*41	2988G>A	rs28371725
CYP3A5	*3	6986A>G	rs776746
CYP3A5	*6	14690G>A	rs10264272
CYP3A5	*7	27131_27132insT	rs41303343
DPYD	*2A	IVS14 + 1G>A	rs3918290
DPYD	*13	1679T>G	rs55886062

GENE	ALLELE	VARIANT	CORRESPONDING RS ID
DPYD	X	2846A>T	rs67376798
DPYD	X	1236G>A	rs56038477
F5	X	1691G>A	rs6025
HLA-B	*5701	T>G	rs2395029
HLA-B	*1502	G>C	rs3909184
HLA-B	*1502	G>A	rs2844682
HLA-A	*3101	T>C	rs1633021
HLA-A	*3101	A>T	rs1061235
SLCO1B1	*5/*15/*17	521T>C	rs4149056
TPMT	*2	238G>C	rs1800462
TPMT	*3B	460G>A	rs1800460
TPMT	*3C	719A>G	rs1142345
UGT1A1	*6	211(G>A)	rs4148323
UGT1A1	*27	686(C>A)	rs35350960
UGT1A1	*28/*37	A(TA)6TAA>A(TA)7TAA/A	rs8175347
VKORC1	X	1173C>T (C6484T)	rs9934438