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Contents

Introduction

Implementing pharmacogenomics (PGx) clinical decision support in seven different European countries in the context of a multi-centered clinical study entails the need for a consistent model encompassing all entities relevant for translating PGx assay results into actionable therapeutic recommendations. This includes:

1. Translation from assay results to PGx variants
2. Translation from variants to genotypes and haplotypes
3. Translation from genotypes and haplotypes to predicted phenotypes
4. Mapping from phenotypes to actionable therapeutic recommendations

While a shared model is indispensable for a consistent decision support intervention, the international setting of the study, however, also necessitates several adaptations of the underlying data to local requirements, such as:

1. Translations of actionable therapeutic recommendations to local languages.
2. Translations of active ingredients to local languages.

3. Mapping of active ingredients to country-specific trade names.

In the context of this project, a knowledge base containing all of these mappings and data was developed, and a sizable part of these data was released as part of Deliverable 7.3 (see *'Deliverable 7.3 – Release of open-source software artefacts describing semantic model*'). The present deliverable complements the aforementioned data collection by providing an overview and description of the data, mappings and their relationships.

U-PGx Knowledge Base

Overview

The U-PGx Knowledge base is built around a subset of the G-Standaard, a comprehensive Dutch drug database operated by Z-Index. [1] Besides general information about all registered medicines and medical products, the G-Standaard covers regularly updated pharmacogenomics-based therapeutic recommendations authored by the Royal Dutch Pharmacists Association (KNMP) for a variety of drug substances. This subset of the G-Standaard including the data structure that links genotype-predicted phenotypes with active ingredients and therapeutic recommendations was adopted unchanged for the U-PGx knowledge base to ensure high quality and up-to-date recommendations by enabling a smooth update of all data within the G-Standaard's periodic production cycles.

The U-PGx knowledge base was furthermore extended as follows:

(1) A consistent mapping between the variants covered by the U-PGx genotyping panel and the genotypes and the phenotypes covered by the G-Standaard was conceptualized, reviewed by experts in the field and added to the U-PGx knowledge base.

(2) Translations to the local languages (Spanish, German, Italian, Greek, Slovenian) of all active ingredient names and recommendations relevant to the study were added to the U-PGx knowledge base.

(3) Manually curated country-specific trade names and a mapping between these trade names and the respective active ingredients were added to the U-PGx knowledge base.

Figure 1 illustrates which contents of the U-PGx knowledge base were adopted unmodified from the G-Standaard and which content was manually curated and added by the U-PGx consortium.

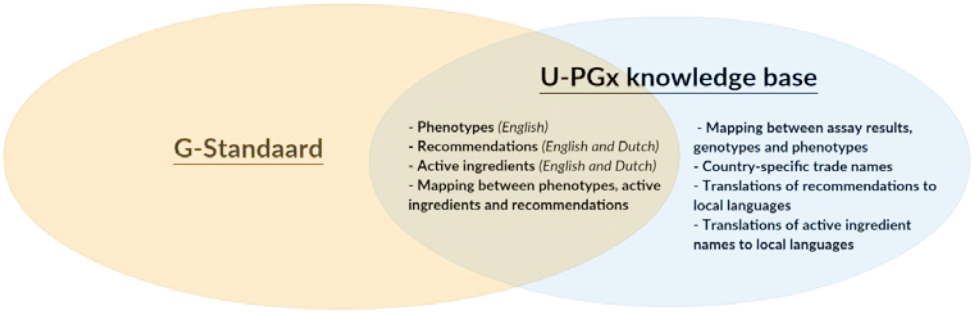

Figure 1. Contents of the U-PGx knowledge base that were adopted unmodified from the G-Standaard (orange and blue circle, overlapping area) and contents that were manually curated and added by the U-PGx consortium (blue circle, non-overlapping area).

Figure 2 gives an overview of the entities that form the basis of the U-PGx knowledge base and their relationships. Description of all data fields are provided in Table 1 and Table 7.

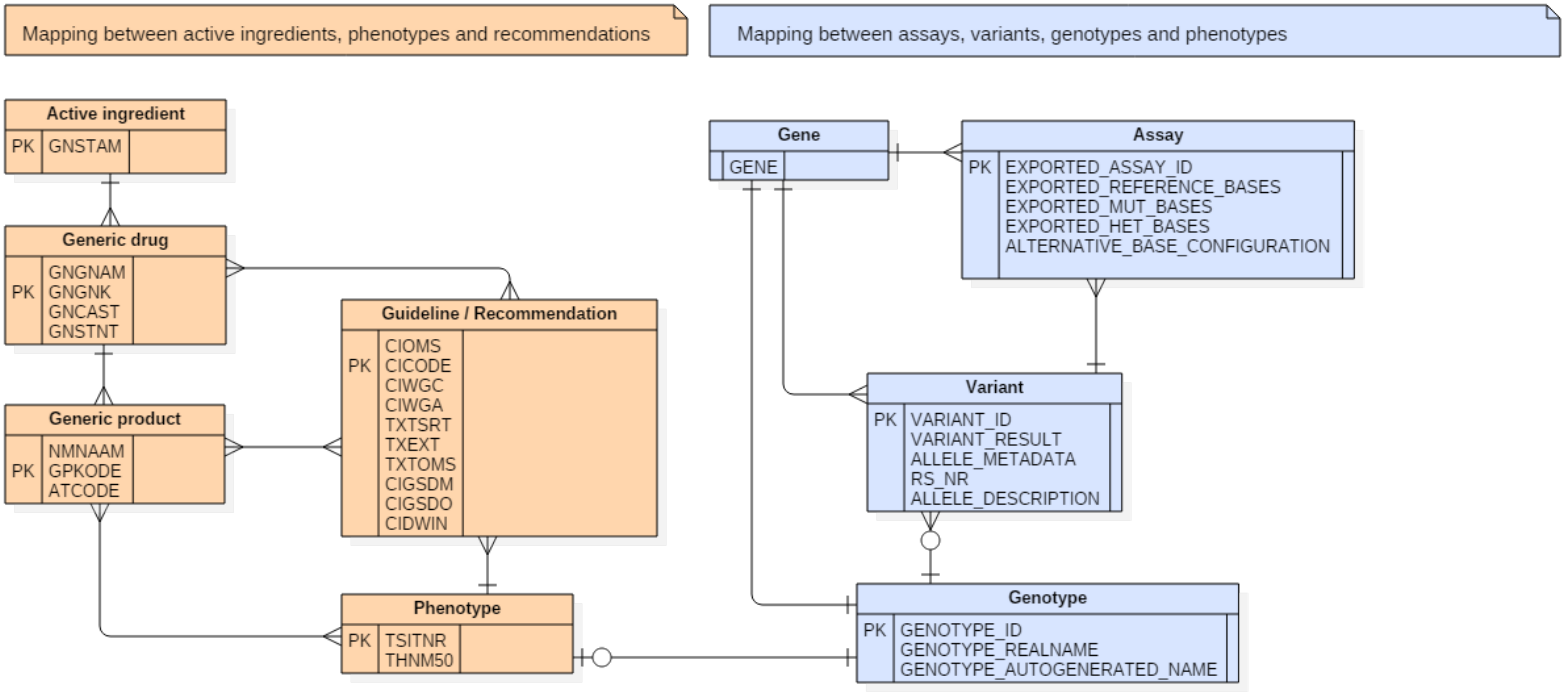

Figure 2. Entity-relationship diagram of the data model; entities adopted from the G-Standaard highlighted in orange.

Table 1. Description of fields adopted from the G-Standaard, sorted alphabetically by field name.

Field	Description	Example
ATCODE	ATC code	J05AF06
CICODE	Guideline identifier	2356
CIDWIN	Date of decision of the Dutch Pharmacogenetics Working Group	20150527
CIGSDM	Date of last guideline update	20150801
CIGSDO	Date of first guideline	20080201
CIOMS	Description / Title of guideline	HLA-B*5701: ABACAVIR
CIWGA	Indicates whether or not a therapeutic recommendation is available. Possible values: Y(es) or N(o)	Y
CIWGC	Indicates whether or not there is a gene/drug interaction. Possible values: Y(es) or N(o)	N
GNCAST	CAS number	136470785
GNGNAM	Generic drug name	ABACAVIR
GNGNK	Generic drug identifier	76783
GNSTAM	Root drug identifier	76783
GNSTNT	Indicates whether a generic drug is also a root ingredient (= active ingredient). Root ingredients are marked by an 'S'.	S
GPKODE	Generic product identifier	165565
NMNAAM	Generic product description: Describes what substance in whatever form it is, its strength and the mode of administration.	ABACAVIR TABLET 300MG

Field	Description	Example
THNM50	Phenotype designation or, if not available, genotype	CYP2C19 POOR METABOLIZER, HLA-B*5701-POSITIEF
TSITNR	Phenotype identifier	536
TXTEXT	Guideline content	Recommendation: Abacavir is contra-indicated for HLA-B*5701-positive patients. (…)
TXTOMS	Text type (i.e., Achtergrondinformatie, Achtergrondinformatie (Engels), Apothekerstekst, Apothekerstekst (Engels), Literatuur)	Achtergrondinformatie
TXTSRT	Text type identifier	210

Pharmacogenes and variants targeted by the U-PGx genotyping panel

Table 2 lists the genetic variants selected for the U-PGx genotyping panel (as per April 2017). For more information on the selection of these variants, please refer to '*Deliverable 2.1 -List of relevant genetic variants for pre-emptive PGx testing – Version 3'*.

Table 2. Pharmacogenes and variants targeted by the U-PGx genotyping panel (as per April 2017)

Genes	Allele	Major Nucleotide Variation	dbSNP RS ID	Effect on protein	Functional Status
CYP2B6	*6/*9	NM_000767.4:c.516G>T~~516G>T~~	rs3745274	Q172H	Decreased or Inactive
CYP2B6	*4/*16	NM_000767.4:c.785A>G~~785A>G~~	rs2279343	K262R	Decreased or Inactive
CYP2B6	*18	NM_000767.4:c.983T>C~~983T>C~~	rs28399499	I328T	Decreased or Inactive

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Genes	Allele	Major Nucleotide Variation	dbSNP RS ID	Effect on protein	Functional Status
CYP2C9	*2	NM_000771.3:c.430C>T~~430C>T~~	rs1799853	R144C	Decreased
CYP2C9	*3	NM_000771.3:c.1075A>C~~1075A>C~~	rs1057910	I359L	Decreased
CYP2C9	*5	NM_000771.3:c.1080C>G~~1080C>G~~	rs28371686	D360E	Decreased
CYP2C9	*11	NM_000771.3:c.1003C>T~~1003C>T~~	rs28371685	R335W	Decreased
CYP2C19	*2	NM_000769.1:c.681G>A~~681G>A~~	rs4244285	Splicing defect	Inactive
CYP2C19	*3	NM_000769.2:c.636G>A~~636G>A~~	rs4986893	W212X	Inactive
CYP2C19	*4A/B	NM_000769.1:c.1A>G~~1A>G~~	rs28399504	M1V	Inactive
CYP2C19	*5	NM_000769.1:c.1297C>T~~1297C>T~~	rs56337013	R433W	Inactive
CYP2C19	*6	NM_000769.1:c.395G>A~~395G>A~~	rs72552267	R132Q	Inactive
CYP2C19	*8	NM_000769.1:c.358T>C~~358T>C~~	rs41291556	W120R	Inactive or Decreased
CYP2C19	*9	NM_000769.1:c.431G>A~~431G>A~~	rs17884712	R144H	Decreased
CYP2C19	*10	NM_000769.1:c.680C>T~~680C>T~~	rs6413438	P227L	Decreased
CYP2C19	*17	NM_000769.2:c.-806C>A~~-806C>T~~[3]	rs12248560	X	Increased
CYP2D6	*xN	Gene duplication or multiplication~~Gene duplication or multiplication~~	X	X	Increased
CYP2D6	*3	2549delA~~2549delA~~	rs35742686	259Framesh ift	Inactive

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Genes	Allele	Major Nucleotide Variation	dbSNP RS ID	Effect on protein	Functional Status
CYP2D6	*4	1846G>A~~1846G>A~~	rs3892097	Splicing defect	Inactive
CYP2D6	*5	Gene deletion~~Gene deletion~~	X	Gene deletion	Inactive
CYP2D6	*6	1707delT~~1707delT~~	rs5030655	118Frameshift	Inactive
CYP2D6	*8	1758G>T~~1758G>T~~	rs5030865	G169X	Inactive
CYP2D6	*9	2615delAAG~~2615delAAG~~	rs5030656	K281 deletion	Decreased
CYP2D6	*10	NM_000106.5:c.100C>T~~100C>T~~	rs1065852	P34S	Decreased
CYP2D6	*14A/B	1758G>A~~1758G>A~~	rs5030865	G169R	Decreased
CYP2D6	*17	1023C>T~~1023C>T~~	rs28371706	T107I	Decreased
CYP2D6	*41	2988G>A~~2988G>A~~	rs28371725	Splicing	Decreased
CYP3A5	*3	6986A>G~~6986A>G~~	rs776746	Splicing defect	Inactive
CYP3A5	*6	14690G>A~~14690G>A~~	rs10264272	Splicing defect	Inactive
CYP3A5	*7	27131_27132insT~~27131_27132insT~~	rs41303343	346Frameshift	Inactive
DPYD	*2A	IVS14 + 1G>A (NM_000110.3:c.1905+1G>A) ~~IVS14 + 1G>A (1905+1G>A)~~	rs3918290	X	Inactive
DPYD	*13	NM_000110.3:c.1679T>G~~1679T>G~~	rs55886062	I560S	Inactive
DPYD	X	NM_000110.3:c.2846A>T~~2846A>T~~	rs67376798	D949V	Decreased
DPYD	X	NM_000110.3:c.1236G>A~~1236G>A~~	rs56038477	E412E	Decreased
F5	X	1691G>A~~1691G>A~~	rs6025	R506Q	Decreased

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Genes	Allele	Major Nucleotide Variation	dbSNP RS ID	Effect on protein	Functional Status
HLA-B	*5701	T>G~~T>G~~	rs2395029		Tagging SNP
HLA-B	*1502	G>C~~G>C~~	rs3909184		Tagging SNP
HLA-B	*1502	G>A~~G>A~~	rs2844682		Tagging SNP
HLA-A	*3101	T>C~~T>C~~	rs1633021		Tagging SNP Asian
HLA-A	*3101	A>T~~A>T~~	rs1061235		Tagging SNP Caucasian
SLCO1B1	*5/*15/*17	NM_006446.4:c.521T>C~~521T>C~~	rs4149056	V174A	Decreased
TPMT	*2	NM_000367.3:c.238G>C~~238G>C~~	rs1800462	A80P	Inactive
TPMT	*3B	NM_001346817.1:c.460G>A~~460G>A~~	rs1800460	A154T	Inactive
TPMT	*3C	NM_001346817.1:c.719A>G~~719A>G~~	rs1142345	Y240C	Inactive
UGT1A1	*6	NM_000463.2:c.211G>A~~211(G>A)~~	rs4148323	G71R	Decreased
UGT1A1	*27	NM_000463.2:c.686C>A~~686(C>A)~~	rs35350960	P229Q	Decreased
UGT1A1	*28/*37	A(TA)6TAA>A(TA)7TAA/A(TA)8TAA~~A(TA)6TAA>A(TA)7TAA/A(TA)8TAA~~	rs8175347	X	Decreased
VKORC1	X	1173C>T (C6484T)~~1173C>T (C6484T)~~	rs9934438		Increased sensitivity

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Mapping from assays to variants

All assays covered by the U-PGx genotyping panel are listed in '*Deliverable 7.3 – upgx_assays.csv*'; a description of the fields used to describe each assay can be found in Table 3.

Table 3. Fields used to characterize each assay covered by the U-PGy genotyping panel (see 'Deliverable 7.3 – upgx_assays.csv')

Field	Description	Example
EXPORTED_ASSAY_ID	Unique assay identifier	CYP2B6_rs3745274
GENE	Gene name	CYP2B6
RS_NR	Corresponding rs identifier	rs3745274
EXPORTED_REFERENCE_BASES	Reference bases	G:G
EXPORTED_MUT_BASES	Mutated bases	T:T
EXPORTED_HET_BASES	Heterozygous mutation	G:T

'Deliverable 7.3 – upgx_variants.csv' contains the characterization of all variants covered by the panel (compare Table 2). A description of all fields of this file is provided in Table 4.

Table 4. Fields used to characterize each variant covered by the U-PGx genotyping panel (see 'Deliverable 7.3 – upgx_variants.csv')

Field	Description	Example
VARIANT_ID	Unique variant identifier. In cases where a variant is defined by only one assay, this ID matches the EXPORTED_ASSAY_ID (compare Table 3)	CYP2B6_rs3745274
GENE	Gene name	CYP2B6
RS_NR	Corresponding rs identifier of the variant	rs3745274
EXPORTED_REFERENCE_BASES	Reference bases	G:G
EXPORTED_MUT_BASES	Mutated bases	T:T
EXPORTED_HET_BASES	Heterozygous mutation	G:T
ALTERNATIVE_BASE_CONFIGURATION	Alternative potential base configuration, if applicable	T:T
ALLELE_DESCRIPTION	Corresponding designation according to star allele nomenclature, HGVS nomenclature or other alternative designation	*6

For variants that are defined by more than one assay (e.g., CYP2D6 duplications or deletions), the mappings between assay results and resulting variants are available in '*Deliverable 7.3 – assayresult_combination_to_variantresult.csv*'. A description of the fields used in this mapping is provided in Table 5.

Table 5. Fields in the mapping between assay results and variants that are defined by more than one assay (see 'Deliverable 7.3 – assayresult_combination_to_variantresult.csv')

Field	Description	Example
TARGET_VARIANT_ID	Identifier of the affected variant	CYP2D6_*5
ASSAY_ID1	Identifier of the first assay affecting the variant result	CYP2D6_*5_1
ASSAY_ID2	Identifier of the second assay affecting the variant result	CYP2D6_*5_2
ASSAY_ID1_EXPORTED_RESULT	Possible result of the first assay	A:A
ASSAY_ID2_EXPORTED_RESULT	Possible result of the second assay	A:C
TARGET_VARIANT_RESULT	Variant result based on the combined results of the first and second assay	no deletion

Phenotypes

As of April 2017, 50 distinct phenotypes across 13 genes are captured by the U-PGx knowledge base. The English designations of these phenotypes were adopted unmodified from the G-Standaard and incorporated into the knowledge base. To preserve a standardized nomenclature, phenotype designations were not translated to the local languages. A detailed list of all captured phenotypes together with their G-Standaard identifier (TSITNR, compare Figure 2 and Table 1) can be found in Table 6 and in '*Deliverable 7.3 List of drugs and phenotypes update 20170419.xls*'. If no phenotype designation is available for a specific genotype, the genotype is reported instead (e.g., CYP2C9 *1/*1).

Table 6. Phenotypes captured in the U-PGx knowledge base. If no phenotype designation is available for a specific genotype, the genotype is reported instead.

Identifier (TSITNR)	Phenotype

Identifier (TSITNR)	Phenotype
500	CYP2D6 POOR METABOLIZER
501	CYP2D6 INTERMEDIATE METABOLIZER
502	CYP2D6 ULTRARAPID METABOLIZER
503	FACTOR V LEIDEN HOMOZYGOUS
504	FACTOR V LEIDEN HETEROZYGOUS
505	CYP2D6 EXTENSIVE METABOLIZER
506	CYP2C9 *1/*1
507	CYP2C9 *1/*2
508	CYP2C9 *1/*3
509	CYP2C9 *2/*2
510	CYP2C9 *2/*3
511	CYP2C9 *3/*3
512	CYP2C9 INTERMEDIATE METABOLIZER
513	CYP2C9 POOR METABOLIZER
514	CYP2C19 EXTENSIVE METABOLIZER
520	CYP2C19 INTERMEDIATE METABOLIZER
521	CYP2C19 POOR METABOLIZER
522	UGT1A1 EXTENSIVE METABOLIZER
523	UGT1A1 *1/*28 (TA6/TA7)
524	UGT1A1 *28/*28 (TA7/TA7)
525	UGT1A1 INTERMEDIATE METABOLIZER
526	UGT1A1 POOR METABOLIZER
527	TPMT INTERMEDIATE METABOLIZER
528	TPMT POOR METABOLIZER
529	VKORC1 1173CT
530	VKORC1 1173TT
533	FACTOR V LEIDEN ABSENT
534	TPMT EXTENSIVE METABOLIZER
535	VKORC1 1173CC (WILD TYPE)
536	HLA-B*5701-POSITIVE
537	HLA-B*5701-NEGATIVE

Identifier (TSITNR)	Phenotype
538	CYP3A5 POOR METABOLIZER (MOST PREVALENT)
539	CYP3A5 INTERMEDIATE METABOLIZER
540	CYP3A5 EXTENSIVE METABOLIZER
541	CYP2C19 ULTRARAPID METABOLIZER
542	DPD GENE ACTIVITY SCORE 0
543	DPD GENE ACTIVITY SCORE 1
544	DPD GENE ACTIVITY SCORE 2 (EXTENSIVE METABOLIZER)
545	SLCO1B1 NORMAL FUNCTION
546	SLCO1B1 DECREASED FUNCTION
547	SLCO1B1 POOR FUNCTION
1342	CYP2B6 EXTENSIVE METABOLIZER
1343	CYP2B6 INTERMEDIATE METABOLIZER
1344	CYP2B6 POOR METABOLIZER
1345	DPD GENE ACTIVITY SCORE 1,5
1346	DPD GENE ACTIVITY SCORE 0,5
1360	HLA-B*1502-POSITIVE
1361	HLA-A*3101-POSITIVE
1363	HLA-B*1502-NEGATIVE

Mapping from variants to genotypes and phenotypes

A crucial part of the U-PGx knowledgebase is the mapping between variants, genotypes and predicted phenotypes. Based on the variants selected for U-PGx, a dedicated translation table that covers relevant combinations was conceptualized and manually reviewed by experts in the field to ensure the validity and soundness of the mapping. Table 7 describes the structure of this table by listing its column labels together with short description. For the complete translation table, please refer to "*Deliverable 7.3 – variant_result_genotype_translation*20170425.*csv*".

Table 7. Description of fields in the genotype-phenotype translation table

Column label	Description

Column label	Description
GENOTYPE_ID	A unique ID assigned to each possible combination of variants which is later used to map the genotypes to the respective phenotypes/recommendations. A separator row containing dashes (----) delimits rows pertaining to unique genotypes.
GENE	This column lists the gene to which the variant described in the respective row belongs to. For a better readability, gene names are only listed once per unique genotype.
GENOTYPE_REALNAME	The manually curated genotype designations assigned to each variant combination. Combinations which could not be assigned to a genotype are marked by an X. Again, for better readability, genotype names are only listed once per unique genotype. The content of this field is displayed in the PGx report.
GENOTYPE_AUTOGENERATED_NAME	An internal identifier for all variant combinations that differ from the reference / wildtype haplotype.
VARIANT_ID	Lists the unique ID of each analysed variant.
VARIANT_RESULT	Lists possible results for each analysed variant (e.g., nucleotide exchanges).
ALLELE_METADATA (SHOWN IF VARIANT_RESULT IS DIFFERENT FROM REFERENCE ALLELE)	If available, lists the corresponding star allele designator for variants that are different from the reference / wildtype haplotype.
G-STANDAARD TSITNR	This column lists the unique IDs that match the respective genotypes to the corresponding phenotypes from the G-Standaard.
GSTANDARD PHENOTYPE NAME	This column lists the phenotype designations as defined in the G-Standaard.
REMARK	This column contains any additional comments on the mapping.

Guidelines and recommendations

Each pharmacogenomic guideline captured by the G-Standaard is segmented into three different parts:

(1) **Recommendation** („Apothekerstekst“): Contains a short statement about the impact of the genetic variant and the actual recommendation.

(2) **Background information** (“Achtergrondinformatie“): Contains more detailed information on the gene-drug mechanism.

(3) **Literature** („Literatuur“): Contains relevant literature references.

Text elements are contained in the field ‘TXTEXT’, while their type is indicated in the field ‘TXTOMS’ (compare Table 1). The relevance of each active ingredient/phenotype combination and associated guideline is classified according to whether or not (1) a gene-drug interaction is present (field ‘CIWGC’), and (2) an actionable therapeutic recommendation is available (field ‘CIWGA’). The interpretation scheme for this classification is presented in Table 8.

For all active ingredients associated with at least one of the variants covered by the U-PGx genotyping panel, the Dutch and English guideline versions captured by the G-Standaard were incorporated into the knowledgebase. Furthermore, the U-PGx knowledge base was extended with translations to the local languages (i.e. Spanish, Slovenian, Greek, German, Italian) of all other implementation sites.

Table 8. Levels of relevance used by the G-Standaard to describe the necessity of modifications to the standard treatment due to drug-gene interactions.

Gene/drug interaction? (Field: CIWGC)	**Therapeutic recommendation? (Field: CIWGA)**	**Interpretation**
Yes	Yes	Yes, there is an interaction and yes, action is needed.
No	Yes	No interaction, but action is necessary nevertheless.
Yes	No	Yes, there is an interaction, no, action is not necessary or not possible.
No	No	No interaction, no action is needed.

Active ingredients

As of April 2017, the U-PGx knowledge base encompasses 77 different active ingredients (referred to as “root ingredients” and indicated by an ‘S’ in the field ‘GNSTNT’ of the data model). The English translations of all active ingredients included in the U-PGx knowledge base are listed below. Active ingredients associated with at least one phenotype that would trigger an actionable therapeutic

recommendation are marked by an asterisk. For all other languages (i.e., German, Spanish, Slovenian, Dutch, Greek and Italian) please refer to *'Deliverable 7.3 – Drug substance translations and common trade names.xls'*. Please note that translations are only available for active ingredients associated with at least one phenotype that would result in triggering a therapeutic recommendation; such combinations are marked by a 'Y' in both the 'CIWGC' and 'CIGWGA' field (compare Table 8). As of April 2017, this criterion applied to 48 out of the 77 active ingredients.

- Abacavir*
- Acenocoumarol*
- Amiodaron
- Amitriptyline*
- Aripiprazole*
- Atenolol
- Atomoxetine*
- Atorvastatin*
- Azathioprine*
- Bisoprolol
- Capecitabine*
- Carbamazepine*
- Carvedilol
- Citalopram*
- Clomipramine*
- Clonidine
- Clopidogrel*
- Clozapine*
- Codeine*
- Disopyramide
- Doxepin*
- Duloxetine
- Efavirenz*
- Eliglustat*
- Escitalopram*
- Esomeprazole*
- Flecainide*
- Flucloxacilline*
- Fluorouracil*
- Fluoxetine
- Flupentixol
- Fluphenazine
- Fluvastatine
- Fluvoxamine
- Gefitinib
- Glibenclamide
- Gliclazide
- Glimepiride
- Haloperidol*
- Imipramine*
- Irinotecan*
- Quinidine
- Lansoprazole*
- Mercaptopurine*
- Methylphenidate
- Metoprolol*
- Mirtazapine
- Moclobemide
- Nortriptyline*
- Olanzapine
- Omeprazole*
- Oral Contraceptives with Estrogens*
- Oxycodone*
- Pantoprazole*
- Paroxetine*
- Phenprocoumon*
- Phenytoin*
- Pimozide*
- Prasugrel
- Propafenone*
- Quetiapine
- Rabeprazole
- Risperidone
- Sertraline*
- Simvastatin*
- Sotalol
- Tacrolimus*
- Tamoxifen*
- Tegafur*
- Ticagrelor
- Tioguanine*
- Tolbutamide
- Tramadol*
- Venlafaxine*

- Voriconazole*
- Warfarine*
- Zuclopenthixol*

Country-specific trade names

For all active ingredients associated with at least one recommendation that would result in triggering a recommendation in the presence of a specific phenotype (compare Table 8), the most common local trade names were manually curated by each implementation site. An exemplary extract of this mapping is shown in Table 9. For the complete mapping between active ingredients and country-specific trade names (state as of December 2016), please refer to *'Deliverable 7.3 – Drug substance translations and common trade names.xls'*.

Table 9. Common trade names of Amitriptyline, Clopidogrel and Venlafaxine in two exemplary countries (i.e. Spain and Slovenia).

Active ingredient	Common Spanish trade names	Common Slovenian trade names
Amitriptyline	Deprelio, Tryptizol	Amyzol
Clopidogrel	Plavix, Iscover, Grepid, Maboclop, Vatoud, Zyllt	Clopez, DuoPlavin (acetilsalicilna kislina & klopidogrel), Klopidogrel, Plavix, Pontius, Zyllt
Venlafaxine	Arafaxina, Dislaven, Dobupal, Flaxen, Levest, Vandral, Venlabrain	Alventa, Efectin ER, Faxiprol, Nefexyl, Venlafaksin

Abbreviations

KNMP	Royal Dutch Pharmacists Association
PGx	Pharmacogenomics

References

1. G-Standaard — Z-Index [Internet]. [cited 19 Apr 2017]. Available: https://www.z-index.nl/english

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