Precision medicine using pharmacogenomic panel testing

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Chapter 5:

Development of the PGx-Passport: a Panel of Actionable Germline Genetic Variants for Pre-Emptive Pharmacogenetic Testing

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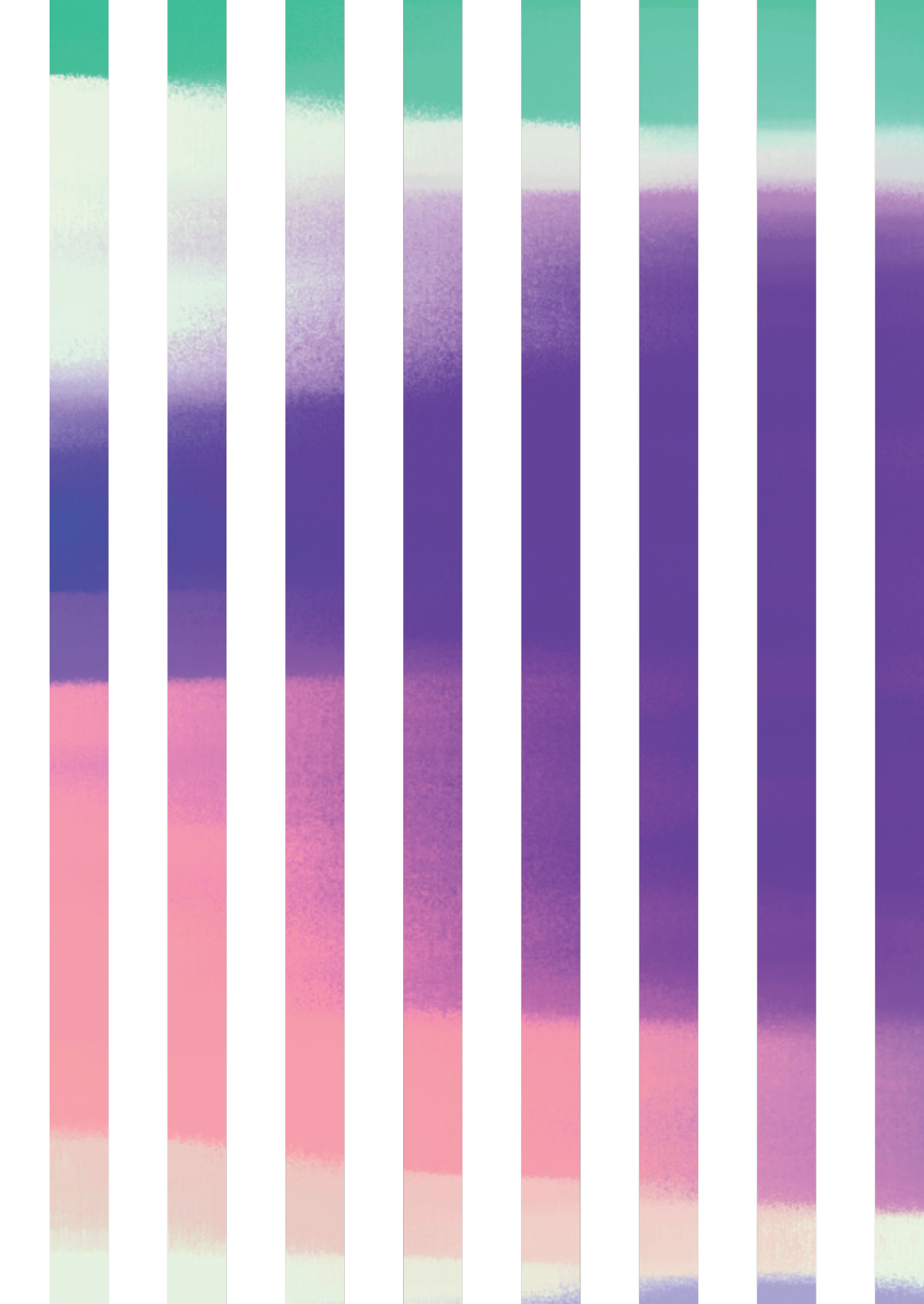


ABSTRACT

Pre-emptive pharmacogenetic (PGx) testing of a panel of germline genetic variants represents a new model for personalised medicine. Clinical impact of PGx testing is maximized when all variant alleles for which actionable clinical guidelines are available, are included in the test panel. However, no such standardized method has been presented to date, impeding adoption, exchange and continuity of PGx testing. We, therefore, developed such a panel, hereafter called the PGx-Passport, based on the actionable Dutch Pharmacogenetics Working Group (DPWG) guidelines. Germline variant alleles were systematically selected using pre-defined criteria regarding allele population frequencies, effect on protein functionality and association with drug response. A PGx-Passport of 58 germline variant alleles, located within 14 genes (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1* and *VKORC1*) was composed. This PGx-Passport can be used in combination with the DPWG guidelines to optimize drug prescribing for 49 commonly prescribed drugs.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

- Absence of a widely accepted pharmacogenetics panel is impeding adoption, exchange and continuity of panel-based pre-emptive PGx testing. Clinical impact of PGx a panel is optimized when it includes all variant alleles for which actionable clinical guidelines are available.

What question did this study address?

- Here we present the methods used and resulting selected variant alleles included in a proposed standardized panel, based on the actionable Dutch Pharmacogenetics Working Group (DPWG) guidelines; hereafter called the PGx-Passport.

What does this study add to our knowledge?

- The resulting PGx-Passport is a concise panel encompassing 58 germline clinically actionable variant alleles, located within 14 pharmacogenes (*CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, DPYD, F5, HLA-A, HLA-B, NUDT15, SLCO1B1, TPMT, UGT1A1* and *VKORC1)* which can be determined at lost costs.

How might this change clinical pharmacology or translational science?

- This PGx-Passport can be used in combination with the DPWG guidelines to optimize drug prescribing for 49 commonly prescribed drugs and improve acceptance of PGx testing.

INTRODUCTION

Pharmacogenetics (PGx) guided prescribing promises to personalize drug therapy by using an individual's germline genetic makeup (1, 2). This ameliorates the conventional 'trial and error' approach of drug prescribing, thereby promising safer, more effective and cost-effective drug treatment (3). Several randomized controlled trials support the clinical utility of individual gene-drug pairs to either optimize dosing (4-7) or drug selection (8). While there is extensive evidence supporting the utility of pre-emptive PGx testing for individual gene-drug pairs, significant implementation barriers remain (9-11). One of the previously surmounted barriers is the development of clinical guidelines directing clinical application of PGx test results. In 2005, the Dutch Pharmacogenetics Working Group (DPWG) was established to devise pharmacotherapeutic recommendations based on systematic review of literature (12, 13). From 2005 onwards, the DPWG has systematically reviewed 97 potential gene-drug interactions. Of these, 54 are actionable gene-drug interactions, providing a therapeutic recommendation for at least one interacting phenotype (12, 13). In parallel, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has devised guidelines for over 40 drugs (14). The DPWG and CPIC guidelines have been formally compared and efforts are ongoing to harmonize the two (15).

Significant debate persists regarding the optimal timing and methodology of testing for delivering PGx testing in clinical care (16). Some support a pre-therapeutic single gene-drug approach, in which a PGx test of a single relevant gene is ordered once a target drug is prescribed; while others advocate for a pre-emptive panel-based strategy in which multiple genes are tested simultaneously and saved for later use, in preparation of future prescriptions throughout a patient's lifetime (17). When combined with a clinical decision support system (CDSS), the corresponding PGx guideline can be deployed by the CDSS at the point of care, thereby providing clinicians with the necessary information to optimize drug prescribing, when a target drug is prescribed. Patients will receive multiple drug prescriptions with potential gene-drug interactions within their lifetime (16, 18). It has been estimated that half of patients above 65 years will use at least one of the drugs for which PGx guidelines are available during a four year period, and one fourth to one third, will use two or more of these drugs (19). Logistics and cost-effectiveness are therefore optimized when delivered in a pre-emptive panel-based approach; pharmacotherapy does not have to be delayed, in awaiting single gene testing results and costs for genotyping are minimized, as marginal acquisition costs of testing and interpreting additional pharmacogenes is near-zero (20). While a sufficiently powered and well-designed study assessing the (cost-)effectiveness of pre-emptive PGx testing is yet te be concluded (21), a number of small randomized observational studies indicate promising clinical utility of PGx panel testing (22-26). Another important challenge hampering adoption of pre-emptive panel testing is the lack of standardization regarding variants included in such panels. Additionally, recommendations on which variants to test differ strikingly across the FDA and EMA labels and also CPIC and DPWG

recommendations (27). Standardization, however, would enable clinicians to understand PGx test results without extensive scrutiny of the alleles included in the panel. Despite the identification of standardization as a potential accelerator for PGx adoption, exchange and continuity (28), there are currently no standards defining which variants must be tested (29, 30).

Although some initiatives have developed standardized panels of relevant variants within individual genes (31), and other initiatives across multiple genes (32), a panel covering widely-accepted genetic variants reflecting an entire set of guidelines is not yet available. Thus, in order to facilitate the clinical implementation of PGx testing, we here present such a panel based on actionable Dutch Pharmacogenetics Working Group (DPWG) guidelines, hereafter called the PGx-Passport. Clinical impact of such a PGx panel is maximized when all variant alleles for which actionable clinical guidelines are available are included. When implemented, it will maximize the incidence at which both an individual's predicted phenotype and the associated clinical guideline is available at the point of care, when a potential gene-drug interaction is encountered. In contrast, including variant alleles for which no clinical guidelines are available would not provide added clinical value, since results are not clinically actionable. This is an initiative of the Ubiquitous Pharmacogenomics Consortium (U-PGx) (21).

RESULTS

The PGx-Passport represents the complete set of clinically actionable variant alleles for which the DPWG provides actionable recommendations. The selected genes and respective variant alleles are listed in **Table 1**. Overall 58 variant alleles in 14 pharmacogenes complied to the selection criteria. Of these, 6 variant alleles are found in *CYP2B6*, 4 in *CYP2C9*, 9 in *CYP2C19*, 12 in *CYP2D6*, 3 in *CYP3A5*, 4 in *DPYD*, 1 in *F5*, 1 in *HLA-A*, 4 in *HLA-B*, 4 in *NUDT15*, 1 in *SLCO1B1*, 4 in *TPMT*, 4 in *UGT1A1*, and 1 in *VKORC1*. The panel can be used to optimize pharmacotherapy for 49 commonly prescribed drugs ranging multiple therapeutic classes, including antidepressants (n=10), immunosuppressants (n=5), anticancer drugs (n=5), anti-infectives (n=4), anticoagulants (n=4), antiepileptics (n=4), antipsychotics (n=4), proton pump inhibitors (n=3), antiarrhythmics (n=2), analgesics (n=2), antilipidemic (n=2), an antihypertensive (n=1), a psychostimulant (n=1), treatment of Gaucher disease (n=1) and anti-contraceptives (n=1).

Table 1 Systematically selected clinically relevant variant alleles which reflect the complete set of actionable DPWG guidelines (58 variant alleles located in 14 pharmacogenes)

Genes	Variant allele	Allele Functional Status	Drug for which actionable DPWG guideline is available
CYP2B6	*6	Decreased function or No function	Efavirenz
	*9	Decreased function or No function	
	*4	Decreased function or No function	
	*16	Decreased function or No function	
	*18	Decreased function or No function	
	*5	Decreased function or Full function	
CYP2C9	*2	Decreased function	Phenytoin Warfarin
	*3	Decreased function	
	*5	Decreased function	
	*11	Decreased function	
CYP2C19	*2	No function	Clopidogrel Citalopram Escitalopram Sertraline Imipramine Lansoprazole Omeprazole Pantoprazole Voriconazole
	*3	No function	
	*4A/B	No function	
	*5	No function	
	*6	No function	
	*8	Decreased function or No function	
	*9	Decreased function	
	*10	Decreased function	
	*17	Increased function	
CYP2D6	*xN	Increased function	Amitriptyline Aripiprazole Atomoxetine Clomipramine Codeine Doxepin Eliglustat Flecainide Haloperidol Imipramine Metoprolol Nortriptyline Paroxetine Pimozide Propafenone Tamoxifen Tramadol Venlafaxine Zuclopenthixol
	*3	No function	
	*4	No function	
	*5	No function	
	*6	No function	
	*8	No function	
	*9	Decreased function	
	*10	Decreased function	
	*14A	Decreased function	
	*14B	Decreased function	
	*17	Decreased function	
	*41	Decreased function	
CYP3A5	*3	No function	Tacrolimus
	*6	No function	
	*7	No function	
DPYD	*2A	No function	5-Fluorouracil Capecitabine Tegafur
	*13	No function	
	2846A>T	Decreased function	
	1236G>A	Decreased function	

F5	1691G>A	Decreased function	Estrogen contraceptive agents
HLA-A	*3101	High-risk allele	Carbamazepine
HLA-B	*1502	High-risk allele	Carbamazepine Oxcarbazepine Phenytoin Lamotrigine
	*1511	High-risk allele	Carbamazepine
	*5701	High-risk allele	Abacavir Flucloxacillin
	*5801	High-risk allele	Allopurinol
NUDT15	*2	Decreased function	6-Mercaptopurine Azathioprine Thioguanine
	*3	Decreased function	
	*6	Decreased function	
	*9	Decreased function	
SLCO1B1	*5/*15/*17	Decreased function	Atorvastatin Simvastatin
TPMT	*2	No function	6-Mercaptopurine Azathioprine Thioguanine
	*3A	No function	
	*3B	No function	
	*3C	No function	
UGT1A1	*6	Decreased function	Irinotecan
	*27	Decreased function	
	*28	Decreased function	
	*37	Decreased function	
VKORC1	-1639G>A; 1173 C>T	Decreased expression	Acenocoumarol Phenprocoumon Warfarin

CYP: Cytochrome P450; *DPYD*: Dihydropyrimidine Dehydrogenase; *F5*: Factor V Leiden; *HLA*: Human Leucocyte Antigen; *NUDT*: Nudix Hydrolase; *SLCO*: Solute Carrier Organic Anion Transporter; *UGT*: UDP-glucuronosyltransferase; *TPMT*: Thiopurine S-methyltransferase; *VKORC*: Vitamin K Epoxide Reductase Complex.

DISCUSSION

The presented PGx-Passport encompasses 58 variant alleles within 14 pharmacogenes (*CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *F5*, *HLA-B*, *NUDT15*, *SLCO1B1*, *TPMT*, *UGT1A1* and *VKORC1)* and can be used to optimize pharmacotherapy for 49 commonly prescribed drugs throughout a patient's lifetime. Essentially, the PGx-Passport represents the first curated summary of alleles across multiple genes for which, based on the consensus of the DPWG, adequate evidence is available to be applied in the clinic. A clear advantage of such curated summary is that all results translate into predicted phenotypes and clear clinical guidelines; avoiding report of clinically ambiguous results for which clinical guidelines are absent. Therefore, it can easily be implemented into the workflow of laboratories and clinicians worldwide. However, as with any curation process, deliberations and assumptions are made to justify simplification. Here, we present these deliberations order to recognize the strengths and limitations of the PGx-Passport.

A significant limitation, which is applicable not only to this variant selection but to PGx testing and interpretation as it is performed today, is that guidelines provide pharmacotherapeutic recommendations based on individual predicted phenotype categories rather than continuous scores. For example, for *CYP2D6*, patients are categorized into normal metabolizers (NM), intermediate metabolizers (IM), poor metabolizers (PM) or ultrarapid metabolizers (UM) based upon their diplotype. However, the actual *CYP2D6* phenotype is likely normally distributed. Imposing categorization, as opposed to the interpretation of the actual diplotype, therefore sacrifices information in order to simplify clinical interpretation. In addition, we interpret the functionality of each allele individually and assume that the sum of these activity scores equals the total activity of the diplotype, thereby abstracting from potential compensatory effects. Furthermore, these categorizations are currently substrate invariant, even though the effects on metabolic capacity may differ between substrates (33). However, categorization is currently justified due to the lack of evidence to devise pharmacotherapeutic recommendations per diplotype or per substrate. For example, the *CYP2D6* activity score is now set at 0.5 for *CYP2D6**10 for all substrates. However, in reality, the effect on activity score may be different across substrates. As the field of PGx evolves we foresee that phenotypes will be predicted substrate specifically on a continuous scale, and pharmacotherapeutic recommendations are provided for each value.

Even though multiple variants have been discovered within the selected actionable genes, we chose to restrict testing to a subset of these variants, based on their effect on protein functionality, MAF and association with drug response. Restricting testing to individual variants disregards untested or undiscovered variants that may also influence the functionality of the gene product. However, despite progress in the computational interpretation of functional consequences of such uncharacterized variations (34), these variants are currently not clinically actionable. Significant debate persists regarding both the nature and strength of evidence required for clinical application of variant alleles. Fundamentally, the potential of a variant to accurately predict the genetic component of drug response is a function of both the predictability of a variant's effect on protein functionality and the extent to which the protein functionality is associated with clinical outcome. Since the strength of these functions differs across genes and gene-drug interactions, we do not foresee a one-size-fits-all consensus regarding an evidence threshold across all gene-drug interactions, but rather a different evidence threshold per individual gene-drug interaction based on the genetics and pharmacology of the interaction. For example, in the case of the *TPMT*-thiopurine interaction, the effect of *TPMT* variation on protein functionality has been firmly established since it exhibits behaviour similar to monogenetic co-dominant traits (35). Therefore, identified variants in *TPMT* (*3A/*3B/*3D) are considered to have sufficient evidence to be applied in the clinic, even in the absence of studies specifically investigating clinical effects in patients carrying these particular variants. On the other hand, clinically relevant variant alleles in *CYP2D6* are based on the pharmacology of the interaction. For

example, the flecainide-*CYP2D6* interaction is based on the associations between decreasing *CYP2D6* activity leading to increasing flecainide plasma levels which in turn leads to increased risk for flecainide intoxication. Therefore, all identified variants in *CYP2D6*, have shown to have a significant effect on CYP2D6 enzyme activity are defined to have sufficient evidence to be applied in the clinic.

Here, we chose to limit variant selection to relatively common variant alleles. Therefore, we consider the PGx-passport a minimal list of clinically relevant variant alleles. An advantage of this approach is that the number of patients carrying actionable variants within their PGx-Passport is maximized, while costs remain reasonable. On the other hand, a disadvantage is that the tested variants are unable to fully predict phenotype in patients carrying untested rare variants, which may indeed have an effect on protein functionality. In other words, including these very rare variants may strengthen the potential of the panel to predict drug response. However, since these are very rare variants, the absolute number of patients in which this is the case will be low. Still, a recent study has shown that indeed 30-40% of functional variability in pharmacogenes can be attributed to rare variants (36). On the contrary, the functional effect of many rare variants is yet unknown and may differ across substrates. Including these variants of unknown effect in the reported results would again provide clinically ambiguous results, and therefore we argue to exclude these until methods have been developed which enable accurate prediction of functional effects (37). Thus, until the effects of these variations on functional effect and subsequent drug response are validated, in silico (38), in vitro or in vivo, we are unable to apply the results of testing for these variant alleles in clinical care. However, for some alleles for which the association with drug response is already well-established, it may be useful to determine these alleles even though the frequency may be low. For example, the DPYD variant alleles *DPYD**2A (MAF<1%), *DPYD**13 (MAF<1%), *DPYD* c.2846A>T (MAF<1%) were selected regardless of their MAF since their association with fluoropyrimidine-induced toxicity has been well-established and adopted clinically. Other examples include *CYP2C19* *5, *6, *8 and *10.

In addition, many pharmacogenetic variant alleles have frequencies which vary across ethnicities (39). As self-reported ethnicity is not always in agreement with genetic ethnicity (40), it is of clinical importance that the PGx-Passport contains all variant alleles, which are considered common in at least one defined ethnicity. For example, *CYP2D6**6 has a global MAF<1% but a MAF of 2% in Europeans and was therefore selected to be included in the panel. Determining this variant allele may be less relevant (but not irrelevant) in non-European populations.

Importantly, we have selected variant alleles, representing haplotype blocks, as opposed to defining variants within the PGx-Passport. Clinical evidence on associated drug response is commonly presented using variant alleles as opposed to defining variants. Therefore, the resulting pharmacotherapeutic recommendations and allele selection are also

based on the *alleles. Nonetheless, in order to operationalize the PGx-Passport one must select defining variants representing variant alleles. Where sequencing platforms enable testing of the entire allele haplotype block without additional costs, it is much more economical to test a set of SNPs unique to haplotype blocks when using a genotyping platform. An example of an operationalized panel fit for genotyping platforms, for a subset of genes in the PGx-Passport, can be found in **Supplementary Table 1**. One must take special consideration when selecting and interpreting tagging SNPs for *HLA* genotyping since frequencies as linkage disequilibrium (LD) patterns vary across ethnicities. For example, *HLA-B*57:01* may be tested by using tagging SNP rs2395029(T>G). However, while rs2395029(T>G) is in complete LD with *HLA-B*57:01* in Han Chinese, LD is lower in Southeast Asians (41-43). Therefore, this result should be interpreted with caution in certain populations. Further examples are tagging SNPs for *HLA-A*31:01* and *HLA-B*15:02* in Asian populations, which cannot be interpreted in Caucasians due to lower LD (44, 45).

To support wide-spread adoption of the PGx-Passport we recognize that evidence regarding clinical acceptance, clinical utility and (cost-)effectiveness is required by stakeholders. Clinical acceptance of a panel similar to the PGx-passport has been demonstrated among community pharmacists (46). Here, pharmacists requested a PGx panel test for 18% of eligible patients, indicating a relatively high level of acceptance. Additionally, clinical acceptance of PGx panel testing has also been shown by other initiatives (47). To appeal to the request for evidence demonstrating clinical utility, the collective clinical utility for a subset of genes in the PGx-Passport (**Supplementary Table 1**) is being assessed in a cluster randomized controlled trial including 8,100 patients across healthcare institutions in seven European countries (21). Several promising studies indicate the (cost-)effectiveness of PGx panel-based testing on healthcare utilization in psychiatry and polypharmacy (22-24, 26), where observed cost savings ranged from $218 (23) to $2,778 (48) per patient. Others have modelled the cost-effectiveness of one-time genetic testing to minimize a lifetime of adverse drug reactions and concluded an incremental cost-effectiveness ratio (ICER) of $43,165 per additional life year and $53,680 per additional quality-adjusted life year, and therefore cost-effective (49). However, cost-effectiveness may vary across ethnic populations, as a result of varying in allele frequencies; the target population, as a result of varying prescription patterns; and the healthcare setting, as a result of varying healthcare costs and ICER cost-effectiveness thresholds.

The PGx-Passport is a recommendation of alleles to be included in clinical laboratory assays but it does not include information on genotype-to-phenotype translation or clinical interpretation of the PGx results. However, the correlation of genotypes to predicted phenotypes and recommendations for clinical actions based on these phenotypes are included in the clinical practice guidelines published by DPWG, CPIC and other professional societies and regulatory bodies.

We recognize that as the field of pharmacogenetics continues to advance and novel associations between variant alleles and clinically relevant drug response are validated, new variant alleles will be added, and the PGx-Passport panel will be updated. The DPWG continuously reviews literature and updates each guideline every two years. Additionally, the selected panel of variants also depends on the timepoint of selection; as available information on MAFs and allele functional status may change over time. An important example of this dynamic nature of the panel is the omission of *CYP2C9*6* and *8 from the presented PGx-Passport. At the time of variant selection, these variants did not comply to the selection criteria based on available information. At this timepoint *CYP2C9*6* was found to have a MAF <1% in both global and selected populations (50) and the allele functional status of *CYP2C9*8* was defined to be increased function. Therefore, CYP2C9*6 did not comply to criterion 4 and CYP2C9*8 did not comply to criterion 1, since there was no DPWG guideline corresponding to the associated phenotype. However, based on current literature, these variants would be included in the panel. Therefore, the presented panel should not be perceived as a static entity, but rather a dynamic curated summary of clinically relevant variant alleles underlying the continuously updated guidelines. The updated PGx-Passport will be published on the U-PGx website (www.upgx.eu).

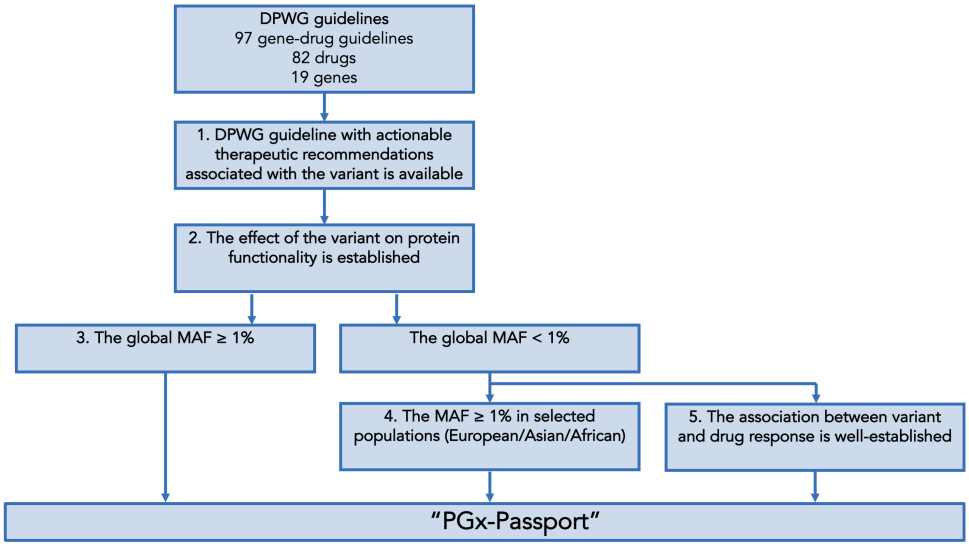
In summary, the selected variant alleles included in this panel fully cover the available, clinically actionable DPWG guidelines. This, now publicly available, panel can be used in combination with the DPWG guidelines to guide drug prescribing and dispensing of 49 commonly used drugs. The proposed PGx-passport is currently limited to the DPWG guidelines and common variants. As such, it can be considered a minimal list of clinically relevant variant alleles. We recommend commercial and hospital laboratories to incorporate these variant alleles in their clinical repertoire thereby adopting a new model for personalised medicine, in which dose and drug selection are personalized based upon an individual's PGx-passport.

MATERIALS AND METHODS

Variant alleles included in the PGx-Passport were systematically selected based on the five selection criteria shown in **Figure 1**. The DPWG guidelines were the starting point of the variant allele selection. At the time of initial selection (February 2017) these consisted of 90 gene-drug guidelines covering 81 drugs and 16 genes (see **Supplementary Table 2**). After this initial selection, the panel was updated, since the DPWG released novel and updated guidelines. The update of the panel is a continuous process and is performed once an update is deemed necessary. The update was performed in January 2019 and based on 97 gene-drug guidelines covering 82 drugs and 19 genes (see **Supplementary Table 3**). For the updated selection, actionable DPWG guidelines were compiled, consisting of 54 gene-drug guidelines covering 49 drugs and 14 genes (see **Supplementary Table 4**). For the initial selection variant alleles, within 13 actionable genes, reported within the DPWG, CPIC,

PharmGKB and CYPAlleles and other monographs were compiled (see **Supplementary Table 5**). Secondly, a list of variant alleles of which the effect on protein functionality is established was compiled. Of these, all variant alleles with a global minor allele frequency (MAF) ≥ 1 % were included in the panel, as defined using 1,000 Genomes project phase 3 allele frequencies. The global MAF is defined as the mean frequency across all populations. In addition, variant alleles which had a global MAF < 1% but a MAF ≥ 1 % among selected populations (European/Asian/African) were also included in the panel; again based on the 1,000 Genomes project phase 3 allele frequencies for subpopulations. When variant alleles had both a global and selected population MAF of < 1%, then they were excluded from the panel unless the association between a variant allele and drug response is well-established. This included variants that were already tested for in routine clinical practice in one of the U-PGx sites.

Figure 1 Decision tree to select relevant variant alleles to be included in the PGx-Passport



MAF: Minor Allele Frequency, U-PGx: Ubiquitous Pharmacogenomics Consortium, DPWG: Dutch Pharmacogenetics Working Group

REFERENCES

1. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526(7573):343-50.
2. Weinshilboum R, Wang L. Pharmacogenomics: bench to bedside. Nature reviews Drug discovery. 2004;3(9):739-48.
3. Pirmohamed M. Personalized pharmacogenomics: predicting efficacy and adverse drug reactions. Annual review of genomics and human genetics. 2014;15:349-70.
4. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, et al. A randomized trial of genotype-guided dosing of warfarin. The New England journal of medicine. 2013;369(24):2294-303.
5. Wu AH. Pharmacogenomic testing and response to warfarin. Lancet (London, England). 2015;385(9984).
6. Verhoef TI, Ragia G, de Boer A, Barallon R, Kolovou G, Kolovou V, et al. A randomized trial of genotype-guided dosing of acenocoumarol and phenprocoumon. The New England journal of medicine. 2013;369(24):2304-12.
7. Coenen MJ, de Jong DJ, van Marrewijk CJ, Derijks LJ, Vermeulen SH, Wong DR, et al. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. Gastroenterology. 2015;149(4):907-17.e7.
8. Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. The New England journal of medicine. 2008;358(6).
9. Abbasi J. Getting Pharmacogenomics Into the Clinic. Jama. 2016.
10. Haga SB, Burke W. Pharmacogenetic testing: not as simple as it seems. Genetics in medicine : official journal of the American College of Medical Genetics. 2008;10(6).
11. Swen JJ, Huizinga TW, Gelderblom H, de Vries EG, Assendelft WJ, Kirchheiner J, et al. Translating pharmacogenomics: challenges on the road to the clinic. PLoS medicine. 2007;4(8):e209.
12. Swen JJ, Nijenhuis M, de Boer A, Grandia L, Maitland-van der Zee AH, Mulder H, et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662-73.
13. Swen JJ, Wilting I, de Goede AL, Grandia L, Mulder H, Touw DJ, et al. Pharmacogenetics: from bench to byte. Clinical pharmacology and therapeutics. 2008;83(5):781-7.
14. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clinical pharmacology and therapeutics. 2011;89(3).
15. Bank P, Caudle KE, Swen JJ, Gammal RS, Whirl-Carrillo M, Klein TE, et al. Comparison of the Guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. Clinical pharmacology and therapeutics. 2018;103(4):599-618.
16. Dunnenberger HM, Crews KR, Hoffman JM, Caudle KE, Broeckel U, Howard SC, et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. Annual review of pharmacology and toxicology. 2015;55:89-106.

17. Weitzel KW, Cavallari LH, Lesko LJ. Preemptive Panel-Based Pharmacogenetic Testing: The Time is Now. Pharmaceutical Research. 2017;34(8):1551-5.
18. Driest VSL, Shi Y, Bowton EA, Schildcrout JS, Peterson JF, Pulley J, et al. Clinically actionable genotypes among 10,000 patients with preemptive pharmacogenomic testing. Clinical pharmacology and therapeutics.95(4).
19. Samwald M, Xu H, Blagec K, Empey PE, Malone DC, Ahmed SM, et al. Incidence of Exposure of Patients in the United States to Multiple Drugs for Which Pharmacogenomic Guidelines Are Available. PloS one. 2016;11(10).
20. Roden DM, Van Driest SL, Mosley JD, Wells QS, Robinson JR, Denny JC, et al. Benefit of Preemptive Pharmacogenetic Information on Clinical Outcome. Clinical pharmacology and therapeutics. 2018;103(5):787-94.
21. van der Wouden CH, Cambon-Thomsen A, Cecchin E, Cheung KC, Dávila-Fajardo CL, Deneer VH, et al. Implementing Pharmacogenomics in Europe: Design and Implementation Strategy of the Ubiquitous Pharmacogenomics Consortium. Clinical pharmacology and therapeutics. 2017;101(3):341-58.
22. Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLOS ONE. 2017;12(2).
23. Brixner D, Biltaji E, Bress A, Unni S, Ye X, Mamiya T, et al. The effect of pharmacogenetic profiling with a clinical decision support tool on healthcare resource utilization and estimated costs in the elderly exposed to polypharmacy. Journal of medical economics. 2016;19(3):213-28.
24. Pérez V, Salavert A, Espadaler J, Tuson M, Saiz-Ruiz J, Sáez-Navarro C, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC psychiatry. 2017;17(1):250.
25. Walden LM, Brandl EJ, Tiwari AK, Cheema S, Freeman N, Braganza N, et al. Genetic testing for CYP2D6 and CYP2C19 suggests improved outcome for antidepressant and antipsychotic medication. Psychiatry research. 2018.
26. Espadaler J, Tuson M, Lopez-Ibor JM, Lopez-Ibor F, Lopez-Ibor MI. Pharmacogenetic testing for the guidance of psychiatric treatment: a multicenter retrospective analysis. CNS spectrums. 2017;22(4):315-24.
27. Lauschke VM, Zhou Y, Ingelman-Sundberg M. Novel genetic an epigenetic factors of importance for inter-individual differences in drug disposition, response and toxicity. Pharmacology & therapeutics. 2019.
28. Caudle KE, Keeling NJ, Klein TE, Whirl-Carrillo M, Pratt VM, Hoffman JM. Standardization can accelerate the adoption of pharmacogenomics: current status and the path forward. Pharmacogenomics. 2018;19(10):847-60.
29. Pratt VM, Everts RE, Aggarwal P, Beyer BN, Broeckel U, Epstein-Baak R, et al. Characterization of 137 Genomic DNA Reference Materials for 28 Pharmacogenetic Genes: A GeT-RM Collaborative Project. The Journal of molecular diagnostics : JMD. 2016;18(1):109-23.
30. Pratt VM, Zehnbauer B, Wilson J, Baak R, Babic N, Bettinotti M, et al. Characterization of 107 Genomic DNA Reference Materials for CYP2D6, CYP2C19, CYP2C9, VKORC1, and

UGT1A1 A GeT-RM and Association for Molecular Pathology Collaborative Project. The Journal of Molecular Diagnostics. 2010;12(6):835-46.
31. Pratt VM, Del Tredici AL, Hachad H, Ji Y, Kalman LV, Scott SA, et al. Recommendations for Clinical CYP2C19 Genotyping Allele Selection: A Report of the Association for Molecular Pathology. The Journal of molecular diagnostics : JMD. 2018;20(3):269-76.
32. Bush WS, Crosslin DR, Owusu-Obeng A, Wallace J, Almoguera B, Basford MA, et al. Genetic variation among 82 pharmacogenes: The PGRNseq data from the eMERGE network. Clinical pharmacology and therapeutics. 2016;100(2):160-9.
33. Hicks JK, Swen JJ, Gaedigk A. Challenges in CYP2D6 phenotype assignment from genotype data: a critical assessment and call for standardization. Current drug metabolism. 2014;15(2):218-32.
34. Zhou Y, Mkrtchian S, Kumondai M, Hiratsuka M, Lauschke VM. An optimized prediction framework to assess the functional impact of pharmacogenetic variants. The pharmacogenomics journal. 2018.
35. Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. American journal of human genetics. 1980;32(5):651-62.
36. Kozyra M, Ingelman-Sundberg M, Lauschke VM. Rare genetic variants in cellular transporters, metabolic enzymes, and nuclear receptors can be important determinants of interindividual differences in drug response. Genetics in medicine : official journal of the American College of Medical Genetics. 2016.
37. Drogemoller BI, Wright GE, Warnich L. Considerations for rare variants in drug metabolism genes and the clinical implications. Expert opinion on drug metabolism & toxicology. 2014;10(6):873-84.
38. Li B, Seligman C, Thusberg J, Miller JL, Auer J, Whirl-Carrillo M, et al. In silico comparative characterization of pharmacogenomic missense variants. BMC genomics. 2014;15 Suppl 4:S4.
39. Zhou Y, Ingelman–Sundberg M, Lauschke VM. Worldwide Distribution of Cytochrome P450 Alleles: A Meta-analysis of Population-scale Sequencing Projects. Clinical Pharmacology & Therapeutics. 2017.
40. Shraga R, Yarnall S, Elango S, Manoharan A, Rodriguez SA, Bristow SL, et al. Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. BMC genetics. 2017;18(1):99.
41. Melis R, Lewis T, Millson A, Lyon E, McMillin GA, Slev PR, et al. Copy number variation and incomplete linkage disequilibrium interfere with the HCP5 genotyping assay for abacavir hypersensitivity. Genetic testing and molecular biomarkers. 2012;16(9):1111-4.
42. Rodriguez-Novoa S, Cuenca L, Morello J, Cordoba M, Blanco F, Jimenez-Nacher I, et al. Use of the HCP5 single nucleotide polymorphism to predict hypersensitivity reactions to abacavir: correlation with HLA-B*5701. The Journal of antimicrobial chemotherapy. 2010;65(8):1567-9.
43. Badulli C, Sestini R, Sbarsi I, Baroncelli M, Pizzochero C, Martinetti M, et al. Tag SNPs of the ancestral haplotype 57.1 do not substitute HLA-B*57:01 typing for eligibility to abacavir treatment in the Italian population. Pharmacogenomics. 2012;13(3):247-9.

44. de Bakker PI, McVean G, Sabeti PC, Miretti MM, Green T, Marchini J, et al. A high-resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. Nature genetics. 2006;38(10):1166-72.
45. Amstutz U, Ross CJ, Castro-Pastrana LI, Rieder MJ, Shear NH, Hayden MR, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. Clinical pharmacology and therapeutics. 2013;94(1):142-9.
46. Bank PC, Swen JJ, Schaap RD, Klootwijk DB, Baak-Pablo RF, Guchelaar HJ. RESULTS OF THE IMPLEMENTATION OF PHARMACOGENOMICS INTO PRIMARY CARE PROJECT. Clinical Pharmacology & Therapeutics. 2017;101(S1):S6-S.
47. Peterson JF, Field JR, Shi Y, Schildcrout JS, Denny JC, McGregor TL, et al. Attitudes of clinicians following large-scale pharmacogenomics implementation. The pharmacogenomics journal. 2016;16(4):393-8.
48. Winner JG, Carhart JM, Altar CA, Goldfarb S, Allen JD, Lavezzari G, et al. Combinatorial pharmacogenomic guidance for psychiatric medications reduces overall pharmacy costs in a 1 year prospective evaluation. Current medical research and opinion. 2015;31(9):1633-43.
49. Alagoz O, Durham D, Kasirajan K. Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions. The pharmacogenomics journal. 2015;16(2):129-36.
50. Kirchheiner J, Tsahuridu M, Jabrane W, Roots I, Brockmoller J. The CYP2C9 polymorphism: from enzyme kinetics to clinical dose recommendations. Personalized medicine. 2004;1(1):63-84.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 An example of an operationalized panel fit for genotyping platforms, for a subset of genes in the PGx-Passport

Genes	Defining variant dbSNP RS ID	Genomic position	Allele	Effect on protein	Allele Functional Status	Drug for which actionable DPWG guideline is available
CYP2B6	rs2279343; rs3745274	NC_000019.9:g.41515263A>G; NC_000019.9:g.41512841G>T	*6		Decreased function or No function	Efavirenz
CYP2B6	rs3745274	NC_000019.9:g.41512841G>T	*9	Q172H	Decreased function or No function	
CYP2B6	rs2279343	NC_000019.9:g.41515263A>G	*4	K262R	Decreased function or No function	
CYP2B6	rs2279343; rs28399499	NC_000019.9:g.41515263A>G; NC_000019.9:g.41518221T>C	*16		Decreased function or No function	
CYP2B6	rs28399499	NC_000019.9:g.41518221T>C	*18	I328T	Decreased function or No function	
CYP2B6	rs3211371	NC_000019.9:g.41522715C>T	*5		Decreased function or Full function	
CYP2C9	rs1799853	NC_000010.10:g.96702047C>T	*2	R144C	Decreased function	Phenytoin Warfarin
CYP2C9	rs1057910	NC_000010.10:g.96741053A>C	*3	I359L	Decreased function	
CYP2C9	rs28371686	NC_000010.10:g.96741058C>G	*5	D360E	Decreased function	
CYP2C9	rs28371685	NC_000010.10:g.96740981C>T	*11	R335W	Decreased function	
CYP2C19	rs4244285	NC_000010.10:g.96541616G>A	*2	Splicing defect	No function	Clopidogrel Citalopram Escitalopram Sertraline Imipramine Lansoprazole Omeprazole Pantoprazole Voriconazole
CYP2C19	rs4986893	NC_000010.10:g.96540410G>A	*3	W212X	No function	
CYP2C19	rs28399504	NC_000010.10:g.96522463A>G	*4A/B	M1V	No function	
CYP2C19	rs56337013	NC_000010.10:g.96612495C>T	*5	R433W	No function	
CYP2C19	rs72552267	NC_000010.10:g.96535210G>A	*6	R132Q	No function	
CYP2C19	rs41291556	NC_000010.10:g.96535173T>C	*8	W120R	Decreased function or No function	
CYP2C19	rs17884712	NC_000010.10:g.96535246G>A	*9	R144H	Decreased function	
CYP2C19	rs6413438	NC_000010.10:g.96541615C>T	*10	P227L	Decreased function	
CYP2C19	rs12248560	NC_000010.10:g.96521657C>T	*17	X	Increased function	
CYP2D6	X		*xN	X	Increased function	Amitriptyline

CYP2D6	rs35742686	NC_000022.10:g.42524244delT	*3	259Frameshift	No function	Aripiprazole Atomoxetine Clomipramine Codeine Doxepin Flecainide Haloperidol Imipramine Metoprolol Nortriptyline Paroxetine Pimozide Propafenone Tamoxifen Tramadol Venlafaxine Zuclopenthixol
CYP2D6	rs3892097; (rs1065852)	NC_000022.10:g.42524947C>T; (NC_000022.10:g.42526694G>A)	*4	Splicing defect	No function	
CYP2D6	X	X	*5	Gene deletion	No function	
CYP2D6	rs5030655	NC_000022.10:g.42525086delA	*6	118Frameshift	No function	
CYP2D6	rs5030865	NC_000022.10:g.42525035C>A	*8	G169X	No function	
CYP2D6	rs5030656	NC_000022.10:g.42524176delCTT	*9	K281 deletion	Decreased function	
CYP2D6	rs1065852	NC_000022.10:g.42526694G>A	*10	P34S	Decreased function	
CYP2D6	rs5030865; rs1065852	NC_000022.10:g.42525035C>T; NC_000022.10:g.42526694G>A	*14A	G169R	Decreased function	
CYP2D6	rs5030865	NC_000022.10:g.42525035C>T	*14B		Decreased function	
CYP2D6	rs28371706	NC_000022.10:g.42525772G>A	*17	T107I	Decreased function	
CYP2D6	rs28371725	NC_000022.10:g.42523805C>T	*41	Splicing	Decreased function	
CYP3A5	rs776746	NC_000007.13:g.99270539C>T	*3	Splicing defect	No function	Tacrolimus
CYP3A5	rs10264272	NC_000007.13:g.99262835C>T	*6	Splicing defect	No function	
CYP3A5	rs41303343	NC_000007.13:g.99250393_99250394insA	*7	346Frameshift	No function	
DPYD	rs3918290	NC_000001.10:g.97915614C>T	*2A	X	No function	5-Fluorouracil Capecitabine Tegafur
DPYD	rs55886062	NC_000001.10:g.97981343A>C	*13	I560S	No function	
DPYD	rs67376798	NC_000001.10:g.97547947T>A	X	D949V	Decreased function	
DPYD	rs56038477	NC_000001.10:g.98039419C>T	X	E412E	Decreased function	
F5	rs6025	NC_000001.10:g.169519049T>C	X	R506Q	Decreased function	Estrogen contraceptive agents
HLA-B	rs2395029	NC_000006.11:g.31431780T>G	*57:01	Tagging SNP	High-risk allele	Abacavir Flucloxacillin
SLCO1B1	rs4149056	NC_000012.11:g.21331549T>C	*5/*15/*17	V174A	Decreased function	Atorvastatin Simvastatin
TPMT	rs1800462	NC_000006.11:g.18143955C>G	*2	A80P	No function	6-Mercaptopurine

TPMT	rs1142345; rs1800460	NC_000006.11:g.18130918T>C; NC_000006.11:g.18139228C>T	*3A	Y240C A154T	No function	Azathioprine Thioguanine
TPMT	rs1800460	NC_000006.11:g.18139228C>T	*3B	A154T	No function	
TPMT	rs1142345	NC_000006.11:g.18130918T>C	*3C	Y240C	No function	
UGT1A1	rs4148323	NC_000002.11:g.234669144G>A	*6	G71R	Decreased function	Irinotecan
UGT1A1	rs35350960	NC_000002.11:g.234669619C>A	*27	P229Q	Decreased function	
UGT1A1	rs8175347	NC_000002.11:g.234668881_234668882TA[7]	*28	X	Decreased function	
UGT1A1	rs8175347	NC_000002.11:g.234668881_234668882TA[8]	*37	X	Decreased function	
VKORC1	rs9934438	NC_000016.9:g.31104878G>A	X		Decreased expression	Acenocoumarol Phenprocoumon Warfarin

Supplementary Table 2 DPWG guidelines (n=90): covering 81 drugs and 16 genes at the time of initial selection (13/02/2017)

1	Abacavir - *HLA-B*57:01*	42	Phenprocoumon - *VKORC1*	83	Clonidine - *CYP2D6*
2	Contraceptive with ethinylestadiol – *F5*	43	Paroxetine - *CYP2D6*	84	Disopyramide - *CYP2D6*
3	Zuclopenthixol - *CYP2D6*	44	Sertraline - *CYP2C19*	85	Quinidine - *CYP2D6*
4	Amitriptyline - *CYP2D6*	45	Clopidogrel - *CYP2C19*	86	Methylphenidate - CYP2D6
5	Clomipramine - *CYP2D6*	46	Warfarin - *CYP2C9*	87	Sotalol - *CYP2D6*
6	Imipramine - *CYP2D6*	47	Warfarin - *VKORC1*	88	Clozapine - *CYP1A2*
7	Nortriptyline - *CYP2D6*	48	Atomoxetine - *CYP2D6*	89	Olanzapine - *CYP1A2*
8	Venlafaxine - *CYP2D6*	49	Imipramine - *CYP2C19*	90	Esomeprazole - *CYP2C19*
9	Doxepin - *CYP2D6*	50	Ribavirin -*HLA-B*44*		
10	Atorvastatin - *SLCO1B1*	51	Olanzapine - *CYP2D6*		
11	Oxycodone - *CYP2D6*	52	Atenolol - *CYP2D6*		
12	Tramadol - *CYP2D6*	53	Bisoprolol - *CYP2D6*		
13	Codeine - *CYP2D6*	54	Fluphenazine - *CYP2D6*		
14	Efavirenz - *CYP2B6*	55	Quetiapine - *CYP2D6*		
15	Flucloxacillin - *HLA-B*57:01*	56	Flupentixol - *CYP2D6*		
16	Fluorouracil/capecitabine - *DPYD*	57	Duloxetine - *CYP2D6*		
17	Azathioprine/mercaptopurine - *TPMT*	58	Prasugrel - *CYP2C19*		
18	Tioguanine - *TPMT*	59	Rabeprazole - *CYP2C19*		
19	Tacrolimus - *CYP3A5*	60	Glibenclamide - *CYP2C9*		
20	Tegafur - *DPYD*	61	Gliclazide - *CYP2C9*		
21	Metoprolol - *CYP2D6*	62	Glimepiride - *CYP2C9*		
22	Citalopram - *CYP2C19*	63	Tolbutamide - *CYP2C9*		
23	Escitalopram - *CYP2C19*	64	Fluvoxamine - *CYP2C19*		
24	Simvastatin - *SLCO1B1*	65	Mirtazapine - *CYP2C19*		
25	Flecainide - *CYP2D6*	66	Sertraline - *CYP2D6*		
26	Propafenone - *CYP2D6*	67	Ticagrelor - *CYP2C19*		
27	Phenytoin - *CYP2C9*	68	Moclobemide - *CYP2C19*		
28	Carbamazepine – *HLA-B*15:11*	69	Citalopram/escitalopram - *CYP2D6*		
29	Carbamazepine – *HLA-A*31:01*	70	Mirtazapine - *CYP2D6*		
30	Carbamazepine – *HLA-B*15:11*	71	Fluvastatin - *SLCO1B1*		
31	Eliglustat - *CYP2D6*	72	Acenocoumarol - *CYP2C9*		
32	Voriconazole - *CYP2C19*	73	Phenprocoumon - *CYP2C9*		
33	Aripiprazole - *CYP2D6*	74	Gefitinib - *CYP2D6*		
34	Haloperidol - *CYP2D6*	75	Risperidone - *CYP2D6*		
35	Lansoprazole - *CYP2C19*	76	Methotrexate - *MTHFR*		
36	Omeprazole - *CYP2C19*	77	Clozapine - *CYP2D6*		
37	Pantoprazole - *CYP2C19*	78	Quetiapine - *CYP3A4*		
38	Irinotecan - *UGT1A1*	79	Fluvoxamine - *CYP2D6*		
39	Pimozide - *CYP2D6*	80	Fluoxetine - *CYP2D6*		
40	Tamoxifen - *CYP2D6*	81	Carvedilol - *CYP2D6*		
41	Acenocoumarol - *VKORC1*	82	Amiodaron - *CYP2D6*		

Supplementary Table 3 DPWG guidelines (n=97): covering 82 drugs and 19 genes, at the time of updated selection (25/01/2019)

1	Abacavir - *HLA-B*57:01*	41	Tamoxifen - *CYP2D6*	81	Fluoxetine - *CYP2D6*
2	Contraceptive with ethinylestadiol – *F5*	42	Acenocoumarol - *VKORC1*	82	Carvedilol - *CYP2D6*
3	Zuclopenthixol - *CYP2D6*	43	Phenprocoumon - *VKORC1*	83	Amiodaron - *CYP2D6*
4	Amitriptyline - *CYP2D6*	44	Paroxetine - *CYP2D6*	84	Clonidine - *CYP2D6*
5	Clomipramine - *CYP2D6*	45	Sertraline - *CYP2C19*	85	Disopyramide - *CYP2D6*
6	Imipramine - *CYP2D6*	46	Clopidogrel - *CYP2C19*	86	Quinidine - *CYP2D6*
7	Nortriptyline - *CYP2D6*	47	Warfarin - *CYP2C9*	87	Methylphenidate - *CYP2D6*
8	Venlafaxine - *CYP2D6*	48	Warfarin - *VKORC1*	88	Sotalol - *CYP2D6*
9	Doxepin - *CYP2D6*	49	Atomoxetine - *CYP2D6*	89	Clozapine - *CYP1A2*
10	Atorvastatin - *SLCO1B1*	50	Imipramine - *CYP2C19*	90	Olanzapine - *CYP1A2*
11	Oxycodone - *CYP2D6*	51	Ribavirin -*HLA-B*44*	91	Methylfenidaat - *COMT*
12	Tramadol - *CYP2D6*	52	Olanzapine - *CYP2D6*	92	Esomeprazole - *CYP2C19*
13	Codeine - *CYP2D6*	53	Atenolol - *CYP2D6*	93	Azathiopurine/mercaptopurine - *NUDT15*
14	Efavirenz - *CYP2B6*	54	Bisoprolol - *CYP2D6*	94	Tioguanine - *NUDT15*
15	Flucloxacillin - *HLA-B*57:01*	55	Fluphenazine - *CYP2D6*	95	Lamotrigine – *HLA-B*15:02*
16	Fluorouracil/capecitabine - *DPYD*	56	Quetiapine - *CYP2D6*	96	Phenytoin – *HLA-B*15:02*
17	Azathioprine/mercaptopurine - *TPMT*	57	Flupentixol - *CYP2D6*	97	Oxcarbazepine – *HLA-B*15:02*
18	Tioguanine - *TPMT*	58	Duloxetine - *CYP2D6*		
19	Tacrolimus - *CYP3A5*	59	Prasugrel - *CYP2C19*		
20	Tegafur - *DPYD*	60	Rabeprazole - *CYP2C19*		
21	Metoprolol - *CYP2D6*	61	Glibenclamide - *CYP2C9*		
22	Citalopram - *CYP2C19*	62	Gliclazide - *CYP2C9*		
23	Escitalopram - *CYP2C19*	63	Glimepiride - *CYP2C9*		
24	Simvastatin - *SLCO1B1*	64	Tolbutamide - *CYP2C9*		
25	Flecainide - *CYP2D6*	65	Fluvoxamine - *CYP2C19*		
26	Propafenone - *CYP2D6*	66	Mirtazapine - *CYP2C19*		
27	Phenytoin - *CYP2C9*	67	Sertraline - *CYP2D6*		
28	Carbamazepine – *HLA-B*15:02*	68	Ticagrelor - *CYP2C19*		
29	Carbamazepine – *HLA-A*31:01*	69	Moclobemide - *CYP2C19*		
30	Carbamazepine – *HLA-B*15:11*	70	Citalopram/escitalopram - *CYP2D6*		
31	Eliglustat - *CYP2D6*	71	Mirtazapine - *CYP2D6*		
32	Allopurinol – *HLA-B*58:01*	72	Fluvastatin - *SLCO1B1*		
33	Voriconazole - *CYP2C19*	73	Acenocoumarol - *CYP2C9*		
34	Aripiprazole - *CYP2D6*	74	Phenprocoumon - *CYP2C9*		
35	Haloperidol - *CYP2D6*	75	Gefitinib - *CYP2D6*		
36	Lansoprazole - *CYP2C19*	76	Risperidone - *CYP2D6*		
37	Omeprazole - *CYP2C19*	77	Methotrexate - *MTHFR*		
38	Pantoprazole - *CYP2C19*	78	Clozapine - *CYP2D6*		
39	Irinotecan - *UGT1A1*	79	Quetiapine - *CYP3A4*		
40	Pimozide - *CYP2D6*	80	Fluvoxamine - *CYP2D6*		

Supplementary Table 4 DPWG guidelines which had an actionable therapeutic recommendation for at least one of the predicted phenotypes (n=54): covering 49 drugs and 14 genes, at the time of updated selection (25/01/2019)

1	Abacavir – *HLA-B*57:01*	42	Acenocoumarol - *VKORC1*
2	Contraceptive with ethinylestadiol – *F5*	42	Phenprocoumon - *VKORC1*
3	Zuclopenthixol - *CYP2D6*	43	Paroxetine - *CYP2D6*
4	Amitriptyline - *CYP2D6*	44	Sertraline - *CYP2C19*
5	Clomipramine - *CYP2D6*	45	Clopidogrel - *CYP2C19*
6	Imipramine - *CYP2D6*	46	Warfarin - *CYP2C9*
7	Nortriptyline - *CYP2D6*	47	Warfarin - *VKORC1*
8	Venlafaxine - *CYP2D6*	48	Atomoxetine - *CYP2D6*
9	Doxepin - *CYP2D6*	49	Imipramine - *CYP2C19*
10	Atorvastatin - *SLCO1B1*	50	Azathioprine/mercaptopurine - *NUDT15*
11	Tramadol - *CYP2D6*	51	Tioguanine - *NUDT15*
12	Codeine - *CYP2D6*	52	Lamotrigine – *HLA-B*15:02*
13	Efavirenz - *CYP2B6*	53	Phenytoin – *HLA-B*15:02*
14	Flucloxacillin - *HLA-B*57:01*	54	Oxcarbazepine – *HLA-B*15:02*
15	Fluorouracil/capecitabine - *DPYD*		
16	Azathioprine/mercaptopurine - *TPMT*		
17	Tioguanine - *TPMT*		
18	Tacrolimus - *CYP3A5*		
19	Tegafur - *DPYD*		
20	Metoprolol - *CYP2D6*		
21	Citalopram - *CYP2C19*		
22	Escitalopram - *CYP2C19*		
23	Simvastatin - *SLCO1B1*		
24	Flecainide - *CYP2D6*		
25	Propafenone - *CYP2D6*		
26	Phenytoin - *CYP2C9*		
27	Carbamazepine – *HLA-B*15:02*		
28	Carbamazepine – *HLA-A*31:01*		
29	Carbamazepine – *HLA-B*15:11*		
30	Eliglustat - *CYP2D6*		
31	Allopurinol – *HLA-B*58:01*		
32	Voriconazole - *CYP2C19*		
33	Aripiprazole - *CYP2D6*		
34	Haloperidol - *CYP2D6*		
35	Lansoprazole - *CYP2C19*		
36	Omeprazole - *CYP2C19*		
37	Pantoprazole - *CYP2C19*		
38	Irinotecan - *UGT1A1*		
39	Pimozide - *CYP2D6*		
40	Tamoxifen - *CYP2D6*		

Supplementary Table 5 References used to compile variants in actionable pharmacogenes (n=13). Accessed in March 2016.

	References Assessed						
Gene	**DPWG guidelines monograph**	**PharmGKB.org and CPIC**	**CYPalleles.ki.se**	**HLA.alleles.org**	**IMH.liu.se**	**Pharmaco-genomics. phaulaval.ca**	**Variant alleles reported**
CYP2B6	X	X	X				*6, *5, *16, *18
CYP2C9	X	X	X				*2,*3,*4, *5, *6, *7,*8, *11
CYP2C19	X	X	X				*1, *2, *3, *4A, *4B, *5, *6, *7, *8, *9, *10, *16, *17, *19, *22, *24, *25, *26
CYP2D6	X	X	X				*1xN (2-13), *2xN (2-13), *3, *4, *4xN, *5, *6, *6xN, *7, *8, *9, *9xN, *10, *10xN, *11, *12, *13, *14A, *14B, *15, *16, *17, *17xN, *18, *19, *20, *21, *29, *29xN, *31, *33xN, *36, *38, *40, *41, *41xN, *42, *44, *45xN, *47, *50, *51, *53, *54, *55, *56A, *56B, *57, *59, *62, *66, *67, *68A, *68B, *69, *72, *76, *77, *78, *79, *80, *92, *100, *101
CYP3A5	X	X	X				*1, *2, *3, *4, *5, *6, *7
DPYD	X	X					*1, *2A, *3, *4, *5, *6,*7, *8, *9A,*9B, *10, *11,*12, *13, *16, *17, *18, *19. *20, *21, 2846A>T, 1236G>A,
F5	X	X					1691G>A
HLA-A and HLA-B	X	X		X			HLA-B*57:01, HLA-B*15:02, HLA-A*31:01, HLA-B*15:11
SLCO1B1	X	X					*1, *1B, *4, *16, *5/*15/*17
TPMT	X	X			X		*1, *1A, *1S, *2, *3A/*3B/*3D, *3D, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18
UGT1A1	X	X				X	*1, *2, *3, *4, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14, *15, *16, *17, *18, *19, *20, *21, *22, *23, *24, *25, *26, *27, *28, *29, *30, *31, *32, *33, *34, *35, *36, *37
VKORC1	X	X					-1639G>A, 1173C>T