Precision medicine using pharmacogenomic panel testing

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Chapter 7:

Pharmacist-Initiated Pre-Emptive Pharmacogenetic Panel Testing with Clinical Decision Support in Primary Care: Record of PGx Results and Real-World Impact

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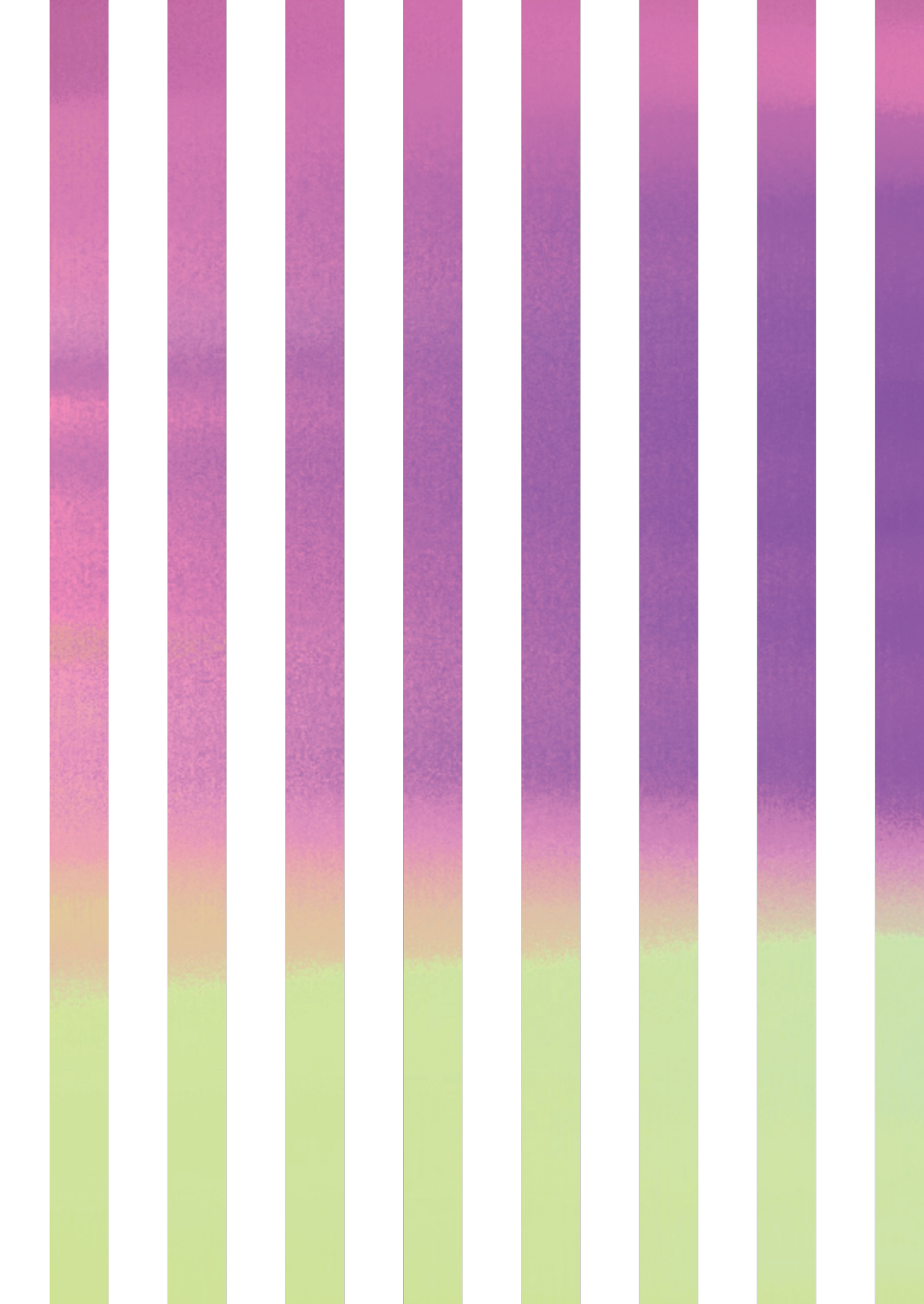


ABSTRACT

Logistics and (cost-)effectiveness of pharmacogenetic (PGx)-testing may be optimized when delivered through a pre-emptive panel-based approach, within a clinical decision support system (CDSS). Here, clinical recommendations are automatically deployed by the CDSS when a drug-gene interaction (DGI) is encountered. However, this requires record of PGx-panel results in the electronic medical record (EMR). Several studies indicate promising clinical utility of panel-based PGx-testing in polypharmacy and psychiatry but is undetermined in primary care. Therefore, we aim to quantify both the feasibility and the real-world impact of this approach in primary care. Within a prospective pilot study, community pharmacists were provided the opportunity to request a panel of eight pharmacogenes to guide drug dispensing within a CDSS for 200 primary care patients. In this side-study, this cohort was cross-sectionally followed-up after a mean of 2.5-years. PGx-panel results were successfully recorded in 96% and 68% of pharmacist and general practitioner (GP) EMRs, respectively. This enabled 97% of patients to (re)use PGx-panel results for at least one, and 33% for up to four newly initiated prescriptions with possible DGIs. A total of 24.2% of these prescriptions had actionable DGIs, requiring pharmacotherapy adjustment. Healthcare utilization seemed not to vary among those who did and did not encounter a DGI. Pre-emptive panel-based PGx-testing is feasible and real-world impact is substantial in primary care.

INTRODUCTION

An individual's response to a drug can be predicted by their pharmacogenetic (PGx) profile (1, 2). Incorporation of an individual's PGx profile into drug prescribing promises a safer, more effective and thereby more cost-effective drug treatment (3, 4). Several randomized controlled trials (RCTs) demonstrate the clinical utility of pre-emptive single gene tests to guide dosing (5-7), and drug selection (8), for individual drug-gene interactions. These studies are perceived as a proof-of-concept supporting the clinical utility of pre-emptive PGx testing, and may therefore also be applied to other drug-gene interactions, for which evidence of the same rigour may lack (9, 10). The Dutch Pharmacogenetics Working Group (DPWG) was established in 2005 to devise clinical guidelines for individual drug-gene interactions based on a systematic review of literature (11, 12). These guidelines provide clinicians with recommendations on how to manage drug-gene interactions. To date, the DPWG has developed guidelines for 97 drug-gene interactions, of which 54 are actionable drug-gene interactions, many of which are encountered principally in primary care. In parallel, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has also devised guidelines for more than 40 drugs (13). The DPWG and CPIC guidelines have ongoing efforts to harmonize the two (14). In the Netherlands, the DPWG guidelines are incorporated into a nationwide clinical decision support system, called the "G-standaard", providing pharmacists and general practitioners (GPs) with relevant clinical recommendations at the point of care when an actionable drug-gene interaction is encountered.

Significant debate persists regarding the optimal approach for implementing PGx testing in clinical care; where some support using a pre-therapeutic single gene approach and others a pre-emptive panel-based approach (15). The pre-therapeutic single gene approach has several drawbacks. In this one-at-a-time strategy, an individual gene is tested in response to a first prescription of an interacting target drug. If, however, patients receive prescriptions for multiple interacting target drugs over time, they may require testing for multiple single genes. Here, pharmacotherapy may be delayed in awaiting the PGx results. Furthermore, the costs of single gene testing may be allocated a multitude of times, while the marginal cost of testing and interpreting additional pharmacogenes simultaneously is near-zero (16, 17). These logistical and cost-effectiveness issues may be overcome and optimized when delivering PGx in a panel-based approach (18). Here, a panel of variants within multiple genes, which are associated with drug response, are tested and saved for later use in preparation of future prescriptions (15). In this way, the panel-results can be reused over time, as multiple drugs which interact with multiple variants are prescribed (19). When an interacting target drug is prescribed, the corresponding PGx guideline can be deployed by the clinical decision support system at the point of care, thereby providing clinicians with the necessary information to guide prescribing by PGx, without any delay. Alternatively, a combination of the two strategies may be the optimal approach for delivering PGx. Here, a panel test is ordered reactively in response to an incident prescription and is saved in the

electronic medical record (EMR) for pre-emptive use in future prescriptions. However, in order for the clinical decision support system to be enabled, it is crucial that the PGx results are recorded and preserved in the EMR. If this fails, a potential drug-gene interaction may go unnoticed. As a result, the added value of testing multiple genes is lost. A recent study showed that PGx results for *CYP2D6* were sparsely recorded; only 3.1% and 5.9% of reported PGx results were recorded in EMRs by general practitioners (GPs) and pharmacists, respectively, within a mean follow-up of 862 days (20). This indicates that correct record of PGx results in the EMR may be a remaining barrier preventing the realization of panel-based testing. However, this is yet undetermined when reporting the results for multiple genes simultaneously. Therefore, we sought to investigate whether pharmacists and GPs are able to record PGx panel testing results within their EMR, in order to enable life-long use of PGx results through a clinical decision support system.

Another barrier preventing implementation of panel-based PGx testing is the lack of evidence demonstrating its clinical utility. Although there is a firm evidence base supporting the clinical utility of pre-emptive single gene PGx testing, evidence of similar quality supporting a panel-based approach is lacking (21). Even so, several smaller studies report promising results indicating that pre-emptive panel-based PGx guided prescribing is indeed (cost-)effective in preventing adverse drug reactions among polypharmacy and psychiatry patients. However, this is yet to be determined within primary care (22-27). Alternatively, the clinical impact of population-wide panel-based testing has previously been modelled by using Medicare prescription data; indicating half of patients above 65 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 (28). Another study showed that more than 60% of the population would benefit from PGx guided prescribing within a 5-year period (19). However, the clinical impact is yet undetermined in a real-world setting. This may differ from modelled estimations since the patients selected by pharmacists to receive panel testing may differ from those included in prescription datasets. Therefore, we aim to quantify the potential real-world impact of implementation of PGx panel in a clinical decision support system within a side-study of the Implementation of Pharmacogenetics into Primary care Project (IP3 study). In this side-study, the primary outcome is the frequency at which patients receive newly initiated prescriptions, with possible drug-gene interactions, for which PGx results are available in the EMR. To explore which target groups may benefit most from panel testing, we aim to investigate which patient sub-groups may more frequently initiate newly prescribed drugs within follow-up. Secondary outcomes include their downstream impact on healthcare utilization. Firstly, we hypothesize that patients who encounter an actionable drug-gene interaction and adhered to the DPWG guidelines will have a similar healthcare utilization compared to those who did not encounter an actionable drug-gene interaction. Secondly, we hypothesize that patients who encounter an actionable drug-gene interaction, but did not

adhere to the DPWG guidelines, have a higher healthcare utilization compared to those who did not encounter an actionable drug-gene interaction.

MATERIALS AND METHODS

Study Design and Participants

We performed a cross-sectional follow-up of The Implementation of Pharmacogenetics into Primary care Project (IP3 study) cohort, as a side-study. The IP3 study is a prospective multi-center observational pilot study with the objective to test the feasibility of pharmacist-initiated pharmacogenetics testing within a clinical decision support system in primary care. The study design, rationale and main study findings have previously been described elsewhere (29). In brief, community pharmacies in the vicinity of Leiden, The Netherlands, were invited to participate in the study. Pharmacists who agreed on participation were provided with the opportunity to request free PGx tests for a panel of 40 variants in eight pharmacogenes (see **Supplementary Table S1**), to guide drug dispensing based on the DPWG guidelines, for a maximum of 200 patients. The genes selected to be tested were based on genes for which DPWG guidelines are available and which are either included in the Affymetrix Drug Metabolizing and Transporters (DMET) array (*CYP2C9, CYP2C19, CYP2D6, CYP3A5, SLCO1B1, TPMT* and *VKORC1*) or determined in clinical care (*DPYD*). This panel can be used in combination with the DPWG guidelines to guide drug prescribing for 41 drugs. Here, a combination of reactive and pre-emptive panel testing is implemented. A PGx panel is ordered reactively in response to an incident prescription and is saved in the EMR for pre-emptive use in future prescriptions. Adult patients receiving a first prescription (defined as no prescription for the first drug within the preceding 12 months) for at least 28 days for one of 10 drugs (amitriptyline, atomoxetine, atorvastatin, (es)citalopram, clomipramine, doxepin, nortriptyline, simvastatin or venlafaxine) in routine care were eligible. Additional in- and exclusion criteria are reported elsewhere (29). After identification of the patients through automated queries, the participating pharmacists manually checked whether patients fulfilled the in- and exclusion criteria. Finally, patients not recruited within 14 days after dispensing the first prescription were excluded. When patients were eligible, pharmacists were able to select these patients for ordering a PGx panel. The panel test result could be used reactively for the drug of enrolment and pre-emptively for future prescriptions of 41 drugs with potential drug-gene interactions.

Healthcare Setting

In the Dutch healthcare system, patients are typically listed with one GP and one pharmacy. The GP plays a gatekeeping role in the provision of healthcare. The GP is consulted for all initial healthcare problems and may refer to specialized care when appropriate. Typically, GPs maintain EMRs for their patients and contain prescription history, lab results, correspondence with specialized physicians and reports regarding ER (emergency

room) visits and hospitalizations. In parallel, pharmacists maintain a separate EMR containing dispensing history, relevant contra-indications and drug allergies and are used for medication surveillance at drug dispensing.

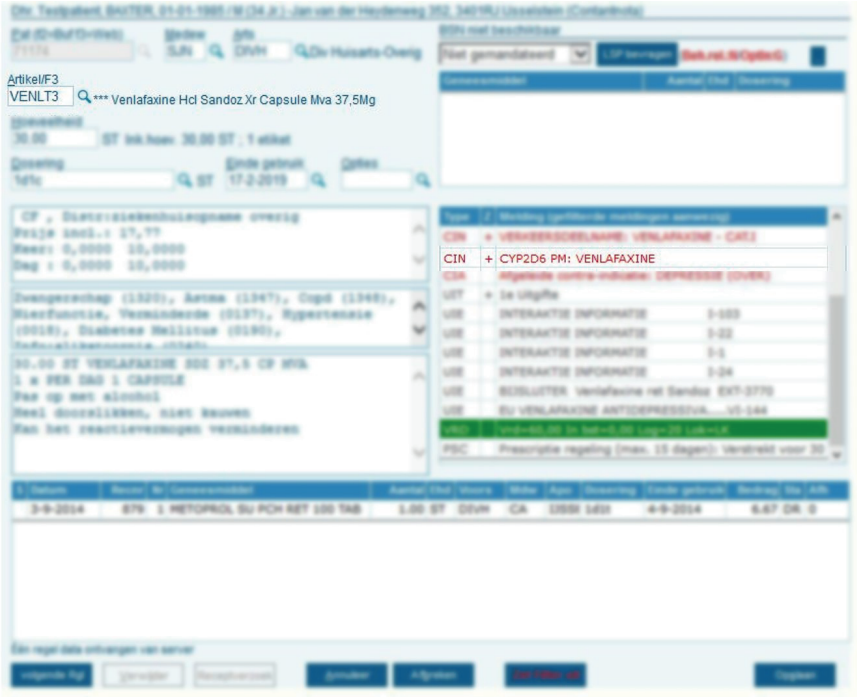
In routine care, PGx testing is predominantly performed within hospital pharmacy or clinical chemistry laboratories. Hospitals additionally maintain a separate EMR for registered patients. Generated PGx results are typically recorded in the hospital's EMR and are communicated with requesting pharmacists of physicians in primary care by paper or electronic reports.

Ethics Approval

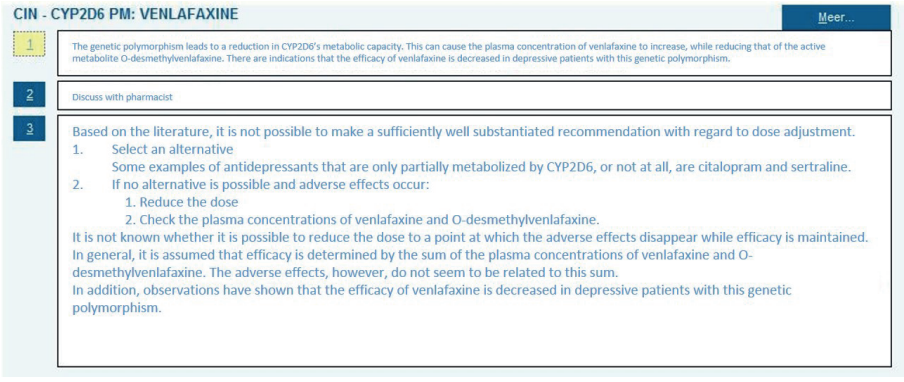
All subjects gave their written informed consent for enrolment before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Leiden University Medical Center (LUMC) (P14.081). Patients provided informed consent for data collection regarding their medication and related outcomes from both pharmacy and GP EMRs within 3 years of enrolment.

DNA Collection, Isolation, Extraction and Genotyping

After providing signed informed consent, pharmacists collected a 2mL saliva sample from participating patients using the Oragene DNA OG-250 (DNA Genotek Inc). The samples were transported to the PGx laboratory in Leiden University Medical Center by research staff or mail. DNA was extracted in accordance to Oragene DNA OG-250 isolation procedure, where a solution volume of 100µL, instead of 200 µL, was used. The DNA concentration was quantified in each sample with NanoDropPhotometer (Thermo Fisher Scientific), and DNA quality was assessed with the use of the 260 nm/280 nm absorbance ratio. Genotypes of *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *SLCO1B1*, *TPMT* and *VKORC1* were determined using the Drug Metabolizing and Transporters (DMET) Plus Array (Affymetrix, Santa Clara, CA). *CYP2D6* copy number variants were detected with qPCR (Thermo Fisher Scientific, Massachusetts, USA). The DMET array was supplemented with the *DPYD* 1236G>A and 2846A>T variants which were routinely tested in clinic at the LUMC. Validation of the assays is described elsewhere (29).



(a)



(b)

Figure 1 Clinical decision support during drug dispensing. A patient who is *CYP2D6* PM (as noted in the electronic medical record (EMR) as contra-indication, as indicated by "CIN" (contra-indication)) receives a prescription for venlafaxine (a) which triggers a pop-up with the relevant Dutch Pharmacogenetics Working Group (DPWG) recommendation directing selection of alternative drug (b).

Translation of Genotype to Phenotype and Return of Results

Genotypes for the eight pharmacogenes were translated into predicted phenotypes using the DPWG guidelines. A paper report holding the genotypes, predicted phenotypes and the DPWG therapeutic recommendation for the drug of enrolment was devised and sent

to the patients' general practitioner (GP) and pharmacist by mail and/or fax (see **Supplementary Figure S1** for an example report). The report held the request to record the entire PGx profile in the EMR to enable the clinical decision support system when drug-gene interaction is encountered during drug prescribing or dispensing (see **Figure 1**). Predicted phenotypes must be recorded in the EMR in a contra-indication format to enable deployment of the relevant guideline through the clinical decision support system. Even if patients are predicted to be extensive metabolizers (EM), we recommend that they still be recorded as contra-indications to record the performance of this test. However, pharmacy EMRs can hold a maximum of 10 contra-indications. It is important to note that the pilot study is initiated through the pharmacists and therefore the GPs who receive the paper report may have had no prior knowledge about the existence of the IP3 pilot study.

Healthcare Provider Incorporation of PGx Results in Drug Prescribing and Dispensing

When an actionable drug-gene interaction is encountered, the DPWG guideline directs adjustment of drug, dose or vigilance of pharmacotherapy to avoid potential adverse drug reactions or lack of efficacy. However, pharmacists are free to choose whether to adhere to the DPWG guidelines. In The Netherlands, and within the IP3 study, pharmacists must discuss pharmacotherapy alteration, resulting from medication surveillance, with the prescribing physicians before the prescription can be altered.

Groups for Analysis

Patients have been stratified into three groups for comparison (see **Table 1**): 1) those who did not encounter an actionable drug-gene interaction for the drug of enrolment, 2) those who encountered an actionable drug-gene interaction for the drug of enrolment and whose health care providers chose to adhere to the DPWG guideline, and 3) those who encountered an actionable drug-gene interaction for the drug of enrolment and whose health care providers chose not to adhere to the DPWG guideline.

Outcomes and Analyses

In this side-study, the primary outcome for quantifying the feasibility of the panel-based approach is whether the PGx panel results were recorded as a contra-indication in both the GP and pharmacist EMRs at the time of follow-up.

In this side-study, the primary outcome for quantifying the real-world impact of the panel-based approach is the number of newly initiated drugs for which potential drug-gene interactions are encountered, since enrolment, and whether these interactions are actionable. A potential drug-gene interaction is encountered when a patient, regardless of their phenotype (e.g., *CYP2D6* PM, IM or EM), receives a new prescription for a drug for which an actionable DPWG guideline is available and the interacting gene was included in the IP3 panel (e.g., metoprolol-*CYP2D6* guideline). A potential drug-gene interaction becomes an

actionable when the patient's predicted phenotype directs adjustment of pharmacotherapy, based on the relevant DPWG guideline (e.g., patient is *CYP2D6* PM and initiates metoprolol). See **Supplementary Table S2** for a list of drugs for which actionable DPWG guidelines are available and IP3 panel results can be used to identify potential and actionable drug-gene interactions. To explore which target group may benefit most from panel testing, we investigate whether baseline demographic variables (gender, age, BMI, number of comorbidities and number of comedications) are associated with an increasing number of prescribed drugs with potential drug-gene interactions within follow-up by using univariate negative binomial regression. The secondary outcome is healthcare utilization as a result of pre-specified drug-gene interaction associated adverse drug reactions within 12 weeks of enrolment. This is a composite endpoint of GP consults (in person, by phone or by e-mail), emergency department (ED) visits, and hospitalizations. These drug-gene interactions associated adverse drug reactions were defined before data collection was initiated and are based on the literature underlying the DPWG guidelines. For example, if a patient enrolled on simvastatin with a *SLCO1B1* TC genotype consults their GP regarding muscle pain symptoms within 12 weeks of initiation, this is considered a drug-gene interaction associated adverse drug reactions since *SLCO1B1* TC and CC carriers are at higher risk for statin-induced myopathy (30). See **Supplementary Table S3** for an overview of pre-specified drug-gene interaction associated adverse drug reactions and underlying literature. We compare the frequency of the composite endpoint among patients who encounter an actionable drug-gene interaction and adhered to the DPWG guidelines (group 2) to those who did not encounter an actionable drug-gene interactions associated adverse drug reactions(group 1), using binomial logistic regression in a non-inferiority analysis. We have set a non-inferiority at a margin of 1.2. Secondly, we compare the frequency of the composite endpoint among patients who encounter an actionable drug-gene interaction but did not adhere to the DPWG guidelines (group 3), to those who did not encounter an actionable drug-gene interaction (group 1), using binomial logistic regression.

RESULTS

IP3 Cohort and Follow-Up

Overall 200 patients were enrolled in the IP3 study between November 2014 and July 2016. Patient characteristics are presented in **Table 1**. The database containing the genotypes and predicted phenotypes is available at https://databases.lovd.nl/shared/individuals (patient IDs 184080-184279). 62 (31.0%) patients encountered an actionable drug-gene interaction for the drug of enrolment, as previously reported by Bank et al. (29). Of these, health care providers chose to adhere to the DPWG guideline in 49 (79.0%) cases. Data collection was performed retrospectively between April 2018 and September 2018 in both pharmacy and GP EMRs; from pharmacy EMRs between May 4th 2018 and May 29th 2018; and from GP EMRs between April 3rd 2018 and September 28th 2018. Data could be retrospectively collected cross-sectionally from 200 (100%) and 177 (88.5%) pharmacy and GP EMRs, respectively (see **Figure 2**). The mean follow-up from pharmacy EMRs was 933 days (range 649–1279), approximately 2.5 years. The mean follow-up from GP EMRs was 917 days (range 622–1238).

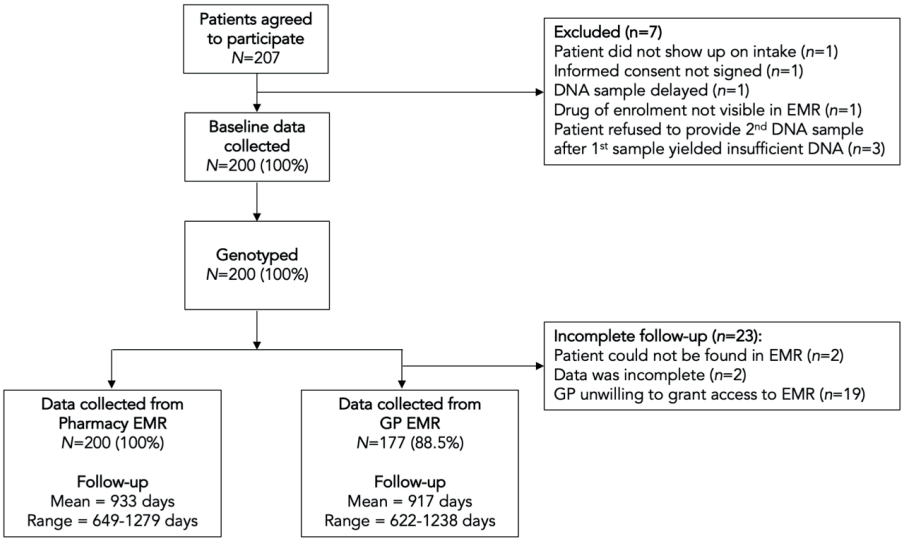


Figure 2 Flow chart or IP3 participant enrolment and follow-up.

Feasibility: Record of PGx Panel Results in the Pharmacy and GP EMRs

Record of PGx panel results by both pharmacists and GPs are shown in **Figure 3**. Pharmacists were able to record predicted phenotypes (including EMs) in 96.0% (*n* = 192) of pharmacy EMRs. In all cases they were recorded as contra-indications (100%, *n* = 192). Pharmacists failed to document the PGx results in 4.0% of cases (*n* = 8). The most common reason for failure of documentation (2.0%, *n* = 4) was merely due to PGx paper reports being lost in the pharmacy. The second most common reason was that the individual did not carry any aberrant variant and was therefore predicted wildtype for all genes; this was the case for three patients (1.5%, *n* = 3). Pharmacists, therefore, felt it was not necessary to record EM phenotypes. Only one set of PGx results was failed to be documented in the EMR since the pharmacist did not know how to (0.5%). A discrepancy between the reported results and documented results was found in the records of two patients (1.0%). This was due to a manual error on account of the pharmacist.

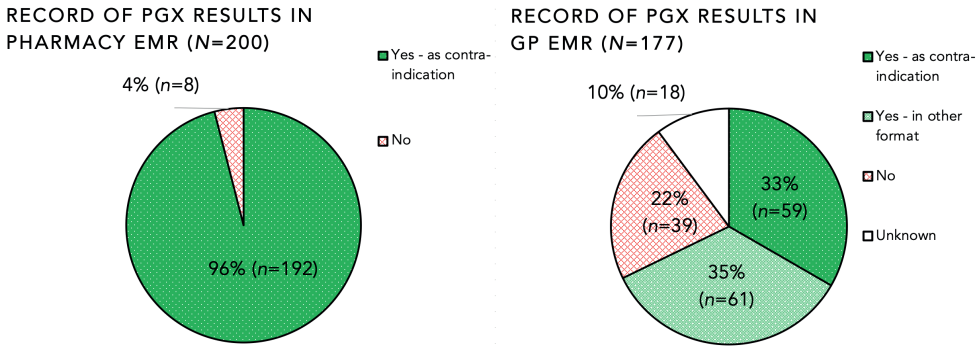


Figure 3 Record of pharmacogenetic panel results in the pharmacy and general practitioner (GP) electronic medical records (EMRs)

General practitioners were able to record the PGx results in 67.8% (*n* = 120) of patient records. Of these, 34% (*n* = 59) were recorded as contra-indications and 35% (*n* = 61) in another format such as a PDF file.

Table 1 Summary of patient characteristics in Implementation of Pharmacogenetics into Primary care Project (IP3) cohort stratified by groups for analysis

		Groups for analysis		
			Actionable drug-gene interaction for the drug of enrolment (*n* = 62, 31.0%)	
	Overall IP3 Study Cohort (*n* = 200)	1) No drug-gene interaction for the drug of enrolment (*n* = 138, 69.0%)	2) Adhered to DPWG guideline (*n* = 49, 24.5%)*	3) Did not adhere to DPWG guideline (*n* = 9, 4.5%)*
Gender				
Female, *n* (%)	103 (51.5)	74 (53.6)	25 (51.0)	3 (33.3)
Male, *n* (%)	97 (48.5)	64 (46.4)	24 (49.0)	6 (66.8)
Age in years, Mean (SD)	61.6 (11.2)	62.3 (11.0)	60.9 (11.5)	56.8 (13.3)
BMI (kg/m^2), Mean (SD)	28.3 (14.9)	28.9 (17.7)	27.1 (4.5)	27.4 (2.4)
Self-reported ethnicity father, *n* (%)				
Caucasian	187 (93.5)	128 (92.8)	47 (95.9)	9 (100.0)
Other	13 (6.5)	10 (7.2)	2 (4.1)	0 (0.0)
Self-reported ethnicity mother, *n* (%)				
Caucasian	188 (94.0)	129 (93.5)	47 (95.9)	9 (100.0)
Other	12 (6.0)	9 (6.5)	2 (4.1)	0 (0.0)
Drug of enrolment, *n* (%)				
Amitriptyline	15 (7.5)	9 (6.5)	5 (10.2)	0 (0.0)
Atorvastatin	115 (57.5)	80 (58.0)	28 (57.1)	5 (55.6)
Citalopram	7 (3.5)	5 (3.6)	1 (2.0)	0 (0.0)
Escitalopram	3 (1.5)	2 (1.4)	1 (2.0)	0 (0.0)
Nortriptyline	17 (8.5)	10 (7.2)	5 (10.2)	2 (22.2)
Simvastatin	29 (14.5)	26 (18.8)	2 (4.1)	1 (11.1)
Venlafaxine	14 (7.0)	6 (4.3)	7 (14.3)	1 (11.1)
Number of comorbidities at baseline, Mean (SD)**	4.6 (2.5)	4.4 (2.4)	4.9 (2.6)	4.4 (2.3)
Number of comedications at baseline, Mean (SD)**	4.0 (3.3)	3.93 (3.4)	4.0 (2.9)	4.4 (3.0)

IP3: Implementation of Pharmacogenetics into Primary care Project; SD: standard deviation; BMI: body mass index; *Excluding others (n = 4): Recommendation given after drug was discontinued (n = 1); same dose (n = 1); dose increased and ECG unknown (n = 1); no drug-gene interaction and no action (n = 1). **Based on n = 177 for whom data collection from GP records was completed.

Real-World Impact: Frequency of Newly Prescribed Drugs for Which PGx Results were Available in the EMR

Table 2 shows the frequency of newly initiated drugs for which there were potential drug-gene interactions and PGx results were available in the EMR. 97.0% (*n* = 194) of patients received at least one subsequent drug for which PGx results were in the EMR. Within the follow-up time, a mean of 2.71 drugs for which the PGx results were available were prescribed, of these 0.66 (24.2%) were actionable drug-gene interactions, requiring pharmacotherapy adjustment. The most commonly prescribed drugs for which PGx results were available were atorvastatin (14.4%), simvastatin (9.4%) and pantoprazole (9.4%). The most common drugs which were actionable drug-gene interactions, however, were atorvastatin (28.2%), metoprolol (13.0%) and amitriptyline (8.4%). To explore who may benefit most from PGx-panel testing, **Table 3** presents baseline demographics stratified by an increasing number of newly initiated drugs for which there were potential drug-gene interaction. It seems that the number of newly initiated prescriptions increases with age, number of comorbidities and number of comedications, but this could not be statistically concluded.

Table 2 Frequency of newly initiated drugs for which there were potential drug-gene interactions in subsequent prescriptions after pharmacogenetics panel in 200 primary care patients with a mean follow-up of 933 days (=2.56 years)

	Number of patients (%)	Three most commonly prescribed with potential drug-gene interaction, N (%)	Actionable drug-gene interaction (%)	Three most commonly prescribed with actionable drug-gene interactions, N (%)
Subsequent drug 1	194 (97%)	1. atorvastatin, 69 (35.6%) 2. omeprazole, 26 (13.4%) 3. pantoprazole, 20 (10.3%)	47 (24.2%)	1. atorvastatin, 19 (40.4%) 2. amitriptyline, 11 (23.4%) 3. citalopram, 6 (12.8%)
Subsequent drug 2	166 (83%)	1. atorvastatin, 32 (19,3%) 2. metoprolol, 29 (17.5%) 3. simvastatin, 21 (12.7%)	46 (27.7%)	1. atorvastatin, 14 (30.4%) 2. metoprolol, 10 (21.7%) 3. codeine, 6 (13.0%)
Subsequent drug 3	115 (57.5%)	1. pantoprazole, 20 (17.4%) 2. omeprazole, 19 (16.5%) 3. simvastatin, 15 (13.0%)	23 (20.0%)	1. metoprolol, 7 (30.4%) 2. simvastatin, 4 (17.4%) 3. codeine/venlafaxine, 3 (13.0%)
Subsequent drug 4	66 (33%)	1. simvastatin, 15 (22.7%) 2. pantoprazole, 11 (16.7%) 3. atorvastatin, 9 (13.6%)	15 (22.7%)	1. atorvastatin, 4 (26.7%) 2. venlafaxine/simvastatin/ clopidogrel, 2 (13.3%) 3. citalopram/omeprazole/ codeine/flecainide/ metoprolol, 1 (6.7%)
Overall	**541**	**1. atorvastatin, 78 (14.4%) 2. simvastatin, 51 (9.4%) 3. pantoprazole, 51 (9.4%)**	**131 (24.2%)**	**1. atorvastatin, 37 (28.2%) 2. metoprolol, 17 (13.0%) 3. amitriptyline, 11 (8.4%)**
Mean per patient (SD)	**2.71 (1.1)**	-	**0.66 (0.8)**	-

SD: standard deviation

Table 3 IP3 cohort stratified by number of newly initiated drugs with a potential drug-gene interaction within follow-up

	Overall IP3 Study Cohort (*n* = 200)	0 (*n* = 6, 3%)	1 (*n* = 27, 13.5%)	2 (*n* = 52, 26%)	3 (*n* = 50, 25%)	≥4 (*n* = 65, 32.5%	*p*-value*
Gender							
Female, n (%)	103 (51.5)	4 (66.7)	12 (44.4)	24 (46.2)	27 (54.0)	36 (55.4)	0.775
Male, n (%)	97 (48.5)	2 (33.3)	15 (55.6)	28 (53.8)	23 (46.0)	29 (44.6)	
Age in years, Mean (SD)	61.6 (11.2)	53.3 (16.3)	59.4 (10.6)	61.0 (11.5)	63.0 (10.5)	62.8 (11.1)	0.442
BMI (kg/m²), Mean (SD)	28.3 (14.9)	25.6 (2.6)	29.1 (5.8)	27.4 (4.5)	27.6 (4.8)	29.6 (25.2)	0.854
Number of comorbidities at baseline, Mean (SD)**	4.6 (2.5)	3.4 (1.1)	4.0 (2.2)	4.0 (2.5)	4.6 (2.3)	5.4 (2.6)	0.232
Number of comedications at baseline, Mean (SD)**	4.0 (3.3)	3.0 (2.1)	3.4 (3.4)	3.3 (3.4)	3.8 (2.7)	5.1 (3.4)	0.279

SD: standard deviation; BMI: body mass index; *Univariate negative binomial regression; **Based on n = 177 for whom data collection from GP records was completed.

Real-World Impact: Downstream Effects of Actionable Drug-Gene Interactions on Healthcare Utilization

Table 4 shows that patients who encountered an actionable drug-gene interaction and whose health care providers adhered to the DPWG guidelines had a similar healthcare utilization as a result of a drug-gene interactions associated adverse drug reaction (40.0%) to those who did not carry an actionable drug-gene interaction (30.0%). This in line with our initial hypothesis. The 95%-CIs of the incidence of composite endpoint drug-gene interactions associated adverse drug reaction of groups 1 and 2 overlap. We therefore observe that there is no difference between the two groups. However, we cannot demonstrate non-inferiority since the upper limit of the 95%-CI of the OR of group 1 is not lower than the non-inferiority margin of 1.2.

We observed a much lower healthcare utilization as a result of a drug-gene interactions associated adverse drug reactions among patients carrying an actionable drug-gene interaction but whose health care providers did not adhere to the DPWG guidelines (0.0%) to those who did not carry an actionable drug-gene interaction (30.0%). This is in contrast to our initial hypothesis.

Table 4 Healthcare utilization as a result of drug-gene interaction associated adverse drug reactions within 12 weeks of enrolment

			Actionable drug-gene interaction for the drug of enrolment	
	Overall IP3 Study Cohort	1) No drug-gene interaction for the drug of enrolment	2) Adhered to DPWG guideline	3) Did not adhere to DPWG guideline
	n = 200	*n* = 138 (69.0%)	*n* = 49 (24.5%)	*n* = 9 (4.5%)
GP EMR follow-up completed (%)	177 (88.5%)	120 (87.0%)	45 (91.8%)	8 (88.9%)
Number of patients experiencing drug-gene interactions associated adverse drug reactions	56 (31.6%)	37 (30.8%)	19 (43.2%)	0 (0.0%)
Composite endpoint drug-gene interactions associated adverse drug reactions				
Number of patients, n (%)	54 (30.5%)	36 (30.0%)	18 (40.0%)	0 (0.0%)
95% CI		66.0% - 80.6%	47.1% – 73.7%	
GP consults as a result of drug-gene interactions associated adverse drug reactions				
Number of patients, n (%)	52 (29.4%)	35 (29.2%)	17 (37.8%)	0 (0.0%)
Number of GP consults, Mean (SD)	53, 2.19 (2.11)	35, 2.06 (1.99)	18, 2.44 (2.36)	0, 0 (0)
ER visit as a result of drug-gene interactions associated adverse drug reactions				
Number of patients, n (%)	3 (1.7%)	1 (0.8%)	2 (4.4%)	0 (0%)
Number of ER visits, Mean (SD)	3, 1 (1)	1, 1 (1)	2, 1 (1)	0, 0 (0)
Hospitalization as a result of drug-gene interactions associated adverse drug reactions				
Number of patients, n (%)	1 (0.6%)	1 (0.6%)	0 (0.0%)	0 (0.0%)
Number of hosp., Mean (SD)	1, 1 (1)	1, 1 (1)	0, 0 (0)	0, 0 (0)
Binomial Logistic Regression (group 1 and 2) OR [95%CI]*		**1.81 [0.89, 3.67]**		

GP: general practitioner; OR: odd ratio; CI: confidence interval; *Including gender, age, and BMI as covariates

DISCUSSION

We report what is, to our knowledge, the first assessment of the real-world impact of pharmacist-initiated pre-emptive panel-based testing in primary care. This side-study demonstrates that recording of PGx panel results in the EMR is feasible and enables health care providers to (re)use these results to inform pharmacotherapy of newly initiated prescriptions. 96% of PGx panel results were successfully recorded in the pharmacy EMR, enabling 97% of patients to (re)use these results for at least one, and 33% of patients for up to four newly initiated prescriptions, within a relatively short 2.5-year follow-up. Of all newly initiated prescriptions with a potential drug-gene interaction (n = 541), 24.2% (n = 131) were actionable drug-gene interactions, requiring pharmacotherapy adjustment. We expect the potential impact of pre-emptive panel-based testing to further increase with time as the likelihood of additional subsequent prescriptions increases.

With their dedication to medication surveillance, pharmacists are leading candidates to manage requesting of PGx testing, recording of PGx results and application of the PGx guidelines. This is confirmed by other pilot studies performed in pharmacy settings (31-35). However, we found that both pharmacists and GPs are very able to record PGx results in their EMRs as contra-indications (96% and 33% of pharmacists and GPs, respectively); enabling deployment of relevant guidelines by the clinical decision support system when a drug-gene interaction is encountered both at prescribing and dispensing. An advantage of applying this double-verification is the minimization of the risk of missing a drug-gene interaction. As a result, it is not disastrous that GPs also recorded them in other formats, thereby not enabling the clinical decision support system at prescribing, in 35% of cases. In contrast, a recent study showed that genotyping results were sparsely communicated and recorded correctly; only 3.1% and 5.9% of reported genotyping results were recorded by GPs and pharmacists, respectively, within a similar follow-up time (20). The discrepancy between these could be due to the pilot study setting or differences in PGx reporting methods. IP3 study researchers have visited the participating IP3 pharmacies multiple times within the follow-up period; possibly unintentionally reminding or motivating pharmacists to record PGx results, which they may otherwise have not performed. However, it is important to note that GPs were outside the scope of the pilot study setting, as they were not the enrolling health care providers, and therefore provide a less biased perspective on recording frequency.

Still, it is much higher than that reported by Simoons et al. (20). Surprisingly, 1.5% of PGx results were not recorded by pharmacists because they did not include actionable genotypes. However, it is still of importance to document these results to avoid unnecessary re-testing of the patient. Finally, the fact that discrepancies between reported results and the recorded result were only observed in 1% of pharmacy EMR cases, indicates that the current manual system of recording is error prone. Regardless of the low error rate, PGx results are static and therefore life-long. It is therefore imperative that errors in the recording of PGx

results are avoided. Future initiatives should focus on the development of automated sharing of PGx results across EMRs. In the Netherlands, such an initiative has been the launched but requires patient consent before it can be utilized. The National Exchange Point ("Landelijk Schakel Punt" (LSP)) is a nationwide secured EMR infrastructure to which nearly health care providers access (36). Only when a patient has provided written consent for the LSP, can a professional summary of the local pharmacy or GP EMR, including PGx results, be downloaded by another treating health care provider in the same region; unless the patient chose to shield this information. Alternatively, providing the PGx results directly to patients may resolve the issue in terms of communicating and recording PGx results; for example, utilizing the Medication Safety-Code card (37, 38).

In the face of a time in which health care providers are confronted with an increasing number of variables to optimize clinical decision making, it is of utmost importance that this information is presented in a structured fashion; this is achieved by a clinical decision support system (39, 40). PGx testing results differ from other laboratory testing results because they remain applicable over a patient's lifetime. We have demonstrated that, even within a relatively short follow-up, the real-world impact of a panel-based approach combined with a clinical decision support system is immense; almost all (97%) of patients used PGx results for at least one, and 33% of patients for up to four prescriptions within a relatively short 2.5-year follow-up. Of these, 24.2% (n = 131) were actionable drug-gene interactions. Similar proportions of actionable drug-gene interactions in primary care were found by Bank et al. (unpublished) (41). Here, investigators overlaid the frequencies of phenotypes as observed within the IP3 cohort with nationwide prescription data spanning one year and found that 3.6 million incident prescriptions encountered a potential drug-gene interactions and of these, 856,002 (23.6%) encountered an actionable drug-gene interaction (41). We observed drugs for which results were useful; these were primarily statins and proton pump inhibitors. This finding is in accordance with Samwald et al. (28). The observed frequencies of potential drug-gene interactions, however, are much higher than reported by others previously (19, 28). Samwald et al. indicated half of the patients above 65 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 (28). Schildcrout et al. reported that 60% of the population would benefit from PGx guided prescribing within a 5-year period (19). The higher frequency we observed could be a result of different target populations and drugs. Our sample consisted of patients selected by pharmacist and who initiated one of ten drugs, and therefore at higher risk for initiating subsequent drugs. Several promising studies indicate the effectiveness and effect of PGx panel-based testing on healthcare utilization in psychiatry and polypharmacy (22-27). For example, Brixner et al. studied the effect of panel-based PGx testing with 6 genes on the healthcare utilization within polypharmacy patients. Results showed that the PGx screened cohort had a lower rate of ER visits (RR = 0.29, 95% confidence interval (CI) = 0.15–0.55, p = 0.0002) and a lower rate of hospitalizations (relative risk (RR) of

0.61, 95% CI = 0.39–0.95, p = 0.027). With this decrease in ER visits and hospitalizations, the authors concluded that PGx panel-based testing could potentially lead to cost-savings (23). These cost savings may be potentially higher than that observed in primary care since polypharmacy patients have a higher a priori risk of hospitalization, as it increases with the number of comedications (42). In this study we aimed to assess the downstream effects of an actionable drug-gene interaction on healthcare utilization. Although we did not observe a statistically significant difference between groups 1 (40%) and 2 (30%), we were not able to conclude non-inferiority, since this is a side-study by design and therefore was underpowered for a non-inferiority analysis. In contrast to our initial hypothesis we observed a much lower healthcare utilization among group 3 (0%) patients when compared to group 2 (30%). However, this cannot be concluded, since the adherence rate of HCPs was high, thereby resulting in a relatively low number of patients carrying an actionable DGI but whose HCPs did not adhere to the DPWG guidelines. Another limitation to this analysis is the retrospectively collected data from GP EMRs, which is prone to reporting bias. Nonetheless, gold-standard evidence demonstrating (cost-)effectiveness of this approach is required to convince stakeholders of population-wide implementation. An RCT aiming to generate such evidence is underway (21).

However, questions regarding who should be tested, and when it is most cost effective to perform pre-emptive panel testing, remain unanswered. In this side-study, we have chosen to perform pre-emptive panel testing among those who received a first prescription for one of ten drugs. Here, there is an initial delay of PGx testing results for the first prescription, but PGx results can be used uninterrupted, if recorded in the EMR, when future drug-gene interactions are encountered. On the one hand, it may be more cost-effective to perform population-wide testing at birth, to ensure maximization of instances in which a PGx result is available when a drug-gene interaction is encountered. In contrast to our approach, not one prescription will be delayed as a result of PGx testing. On the other hand, some may never encounter drug-gene interactions, thereby unintentionally wasting resources on PGx testing. To shed light on this issue, some have predicted which patients may benefit from PGx testing in the near future algorithmically and using prescription data (43, 44). Others have modelled the cost-effectiveness of testing a 40-year old for life-long prevention of adverse drug reactions using a Markov model (45). Overall, a consensus has not been reached regarding whom and when to test (16). Within this side-study we observe the number of newly initiated prescriptions, and thus potential benefit of panel testing, increases with age, number of comorbidities and number of comedications, although this was not statistically significant. However, since 97% of this cohort made re-use of their panel results, we may conclude that the in- and exclusion criteria of this study may be successful criteria in selecting patients who will further benefit from panel testing. The most cost-effective target groups applicable for panel testing must be further investigated.

In addition to unanswered timing and application of testing, the variants selected to be included in a PGx panel also require additional curation. Recently, the DPWG has provided a suggested panel (van der Wouden et al., unpublished) (46). Here, variants included in the panel reflect the entire set of existing DPWG guidelines and are continuously updated as the field of PGx expands. It will be of utmost importance to record the version number of the tested panel, so that it can be retrieved which variants were tested within a specific gene. Moreover, the most cost-effective technique used to determine the PGx profile is also undetermined. As the cost of next-generation sequencing decreases, we envision a future in which we may be able to extract relevant PGx variant alleles from sequencing data (47), possibly making genotype based testing redundant. If this is to come into fruition, the determining the cost-effectiveness of implementing PGx testing will become redundant, as the information on PGx variants become secondary findings, free of additional costs. In this case, only effectiveness will be of interest. Overall, the cost-effectiveness of a panel-approach is a dependant on many variables including the target population, timing, tested variants and testing technique.

CONCLUSIONS

Both pharmacists and GPs are very able to record PGx results into their respective EMRs, thereby maximizing the potential benefits of PGx results when deployed by the clinical decision support system in future prescriptions. Within this cohort, almost all patients were able to benefit from the availability of the PGx-panel results in their EMR, indicating that the real-world impact of a panel approach is immense. The downstream impact on healthcare utilization was unable to be concluded due to the small sample size. Ongoing research will quantify the effects of pre-emptive panel-based testing on patient outcomes (21). Future research should focus on assessing the most cost-effective approach regarding timing, target population, variants and techniques for PGx testing. Regardless, we argue that in terms of logistics, delivery through a clinical decision support system is most feasible.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1 The tested PGx Panel in the IP3 pilot study

Gene	Allele	Reference Sequence + Variant	RS-number
CYP2C9	*2	NG_008385.1:g.3608C>T	rs1799853
CYP2C9	*3	NG_008385.1:g.42614A>C	rs1057910
CYP2C19	*2	NG_008384.3:g.19154G>A	rs4244285
CYP2C19	*3	NG_008384.3:g.17948G>A	rs4986893
CYP2C19	*17	NG_008384.3:g.-806C>T	rs12248560
CYP2D6	*2A	M33388:g.-1584C>G	rs1080985
CYP2D6	*10	M33388:g.100C>T	rs1065852
CYP2D6	*12	M33388:g.124G>A	rs5030862
CYP2D6	*11	M33388:g.883G>C	rs201377835
CYP2D6	*17	M33388:g.1023C>T	rs28371706
CYP2D6		M33388:g.1661G>C	rs1058164
CYP2D6	*6	M33388:g.1707delT	rs5030655
CYP2D6	*4	M33388:g.1846G>A	rs3892097
CYP2D6	*40	M33388:g.1863_1864insTTTCGCCCCTTTCGCCCC	rs72549356
CYP2D6	*20	M33388:g.1973_1974insG	rs72549354
CYP2D6	*19	M33388:g.2539delAACT	rs72549353
CYP2D6	*3	M33388:g.2549delA	rs35742686
CYP2D6	*38	M33388:g.2587delGACT	rs72549351
CYP2D6	*9	M33388:g.2615delAAG	rs5030656
CYP2D6		M33388:g.2850C>T	rs16947
CYP2D6	*7	M33388:g.2935A>C	rs5030867
CYP2D6	*44	M33388:g.2950G>C	rs72549349
CYP2D6	*41	M33388:g.2988G>A	rs28371725
CYP2D6	*29	M33388:g.3183G>A	rs59421388
CYP2D6	*42	M33388:g.3259_3260insGT	rs72549346
CYP2D6	*18	M33388:g.4132_4133insGTGCCCACT	rs1135836
CYP2D6		M33388:g.4180G>C	rs1135840
CYP2D6	*5	NC_000022.10:g.[0]	
CYP2D6	xN	duplication	
CYP3A5	*3	NG_007938.1:g.12083G>A	rs776746
CYP3A5	*6	NG_007938.1:g.19787G>A	rs10264272
DPYD	*2A	NM_000110.3:c.1905+1G>A	rs3918290
DPYD	*13	NM_000110.3:c.1679T>G	rs55886062
DPYD		NM_000110.3:c.1236G>A	rs56038477
DPYD		NM_000110.3:c.2846A>T	rs67376798
SLCO1B1		NM_006446.4:c.521T>C	rs4149056
TPMT	*2	NM_000367.4:c.238G>C	rs1800462
TPMT	*3B	NM_000367.4:c.460G>A	rs1800460
TPMT	*3C	NM_000367.4:c.719A>G	rs1142345
VKORC1		NM_206824.2:c.173+1000C>T	rs9934438

Supplementary Table 2 Actionable drug-gene interactions relevant to the panel used (n=41)

Gene	Interacting drugs for which actionable DPWG guidelines are available	Actionable phenotypes
CYP2C9	phenytoin	PM, IM, *1/*2, *1/*3, *2/*2, *2/*3, *3/*3
CYP2C19	**citalopram**	PM, IM
	clopidogrel	PM, IM
	escitalopram	PM, IM, UM
	imipramine	PM
	lansoprazole	UM
	omeprazole	UM
	pantoprazole	UM
	sertraline	PM
	voriconazole	PM, IM, UM
CYP2D6	**amitriptyline**	PM, IM, UM
	aripiprazole	PM
	atomoxetine	PM, IM, UM
	clomipramine	PM, IM, UM
	codeine	PM, IM, UM
	doxepin	PM, IM, UM
	eliglustat	PM, IM, UM
	flecainide	PM, IM, UM
	haloperidol	PM, UM
	imipramine	PM, IM, UM
	metoprolol	PM, IM, UM
	nortriptyline	PM, IM, UM
	oxycodone	PM, UM
	paroxetine	UM
	pimozide	PM, IM
	propafenone	PM, IM, UM
	tamoxifen	PM, IM
	tramadol	PM, IM, UM
	venlafaxine	PM, IM, UM
	zuclopenthixol	PM, IM, UM
CYP3A5	tacrolimus	Homozygote expressor, heterozygote expressor
DPYD	capecitabine/fluorouracil	Systemic: GAS 0, 0.5, 1, 1.5; Topical: GAS 0
	tegafur	Systemic: GAS 0, 0.5, 1, 1.5
SLCO1B1	**atorvastatin**	TC, TT
	simvastatin	TC, TT
TPMT	azathioprine/mercaptopurine	PM, IM
	thioguanine	PM, IM
VKORC1	**acenocoumarol**	AA
	fenprocoumon	AA

Drugs primarily prescribed in primary care are bolded

Supplementary Figure 1 Example report sent to physicians and pharmacists

Department Clinical Pharmacology and Toxicology
postzone L-00-P

sender
visiting address
Phone fax
e-mail

Date 26 november 2014
subject Genotype results for patiënt XXXX

to [PHARMACIST NAME]

cc [GENERAL PRACTITIONER NAME]

Dear Colleague,

Through this letter I would like to inform you that patient [PATIENT NAME], born [DATE OF BIRTH], participates in the IP3 study and has been genotyped for 8 genes that are related to the effectiveness and toxicity of drugs. This letter contains the results of the genotyping and the interpretation of the genotypes.

.

Patient: [PATIENT NAME]
Date of Birth: XX-XX-XXXX
General Practitioner: [GENERAL PRACTITIONER NAME]
Pharmacy: [PHARMACY NAME]
Studynumber: IP3-XXX

Method
The DNA was isolated from saliva using the Oragene kit and then analyzed with the Affymetrix DMET array according to the manufacturer's protocol. In addition, the number of CYP2D6 copies has been determined with a Taqman genotyping test. The translation from genotype to phenotype was carried out in accordance with the guidelines drawn up by the pharmacogenetics working group of the KNMP.

Results

Gene	Tested variant alleles	Patient genotype	Predicted Phenotype
CYP2C9	*2, *3	*1/*2	**Intermediate metabolizer**
CYP2C19	*2, *17	*1/*1	Extensive metabolizer
CYP2D6	22 allelen*	*4/*5	**Poor metabolizer**
CYP3A5	*3, *6	*3/*3	Non-expressor
DYPD	*2A, *13	*1/*1	Extensive metabolizer
SLCO1B1	521T>C	521 TC	**Decreased function**
TPMT	*2, *3C, *3B	*1/*1	Extensive metabolizer
VKORC1	1173C>T	1173 CC	Normal sensitivity

Interpretation of abberant genotypes

The CYP2C9 * 1 / * 2 genotype leads to the intermediate metabolizer phenotype. Persons with this phenotype have a reduced metabolic capacity of the enzyme CYP2C9 and an increased risk of side effects and efficacy in drugs metabolised by CYP2C9

The CYP2D6 * 4 / * 5 genotype leads to the poor metaboliser phenotype. Individuals with this phenotype have a greatly reduced or absent metabolic capacity of the enzyme CYP2D6 and a greatly increased risk of side effects and efficacy in drugs metabolised by CYP2D6.

The SLCO1B1 521 TC genotype leads to a reduced transport activity of statins from the portal vein to the liver cells. As a result, the plasma concentration of statins and thereby the risk of myopathy can increase.

Recommendation for drug of enrolment

The recommendation the KNMP pharmacogenetics working group for the use of atorvastatin in patients with the SLCO1B1 521 TC genotype is:

1. If this patient has additional risk factors for statin-induced myopathy *:
    1.1. to choose an alternative to atorvastatin.
    Rosuvastatin and pravastatin are similarly affected by SLCO1B1 polymorphisms, but are not affected by CYP3A4 inhibitors such as amiodarone, verapamil and diltiazem.
    Fluvastatin is not affected by SLCO1B1 polymorphisms and CYP3A4 inhibitors.
    1.2. or if an alternative is not possible: advise the patient to contact muscle complaints.
    * Use of CYP3A4 inhibitors, colchicine, fusidic acid and gemfibrozil as co-medication.
2. If this patient has no significant additional risk factors for statin-induced myopathy:
Advise the patient to contact him if you have a muscle complaint.

I request you to record the patient's genotypes found as a contraindication in your electronic prescribing system. A notification will automatically follow if there is a relevant gene-drug interaction.

I hope to have informed you sufficiently. If you have any questions, you can always contact us by email or telephone.

Kind regards,

[NAME CLINICAL PHARMACIST]

Supplementary Table 3 Pre-defined drug-gene associated adverse drug reactions based on literature underlying the DPWG

Drug	Gene	Phenotype	Increased risk of adverse event	Effect measure*
Amitriptyline	*CYP2D6*	PM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6, causing an increase in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and a decrease in the plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH-nortriptyline.[1] The side effects are correlated to the plasma concentration of nortriptyline. The hydroxy-metabolites may be cardiotoxic.[1] Theoretically, the risk of side effects such as dry mouth, constipation, dizziness, sedation, reduction of sexual functions and perspiration is increased with high plasma concentration of nortriptyline.[1]	Studies found an increase of 30-69% of the plasma concentration amitriptyline plus nortriptyline.[1] PMs did not have excessive side effects.[2]
Amitriptyline	*CYP2D6*	IM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6, causing an increase in the plasma concentrations of amitriptyline and its active metabolite nortriptyline and a decrease in the plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH-nortriptyline.[1] The side effects are correlated to the plasma concentration of nortriptyline. The hydroxy-metabolites may be cardiotoxic.[1] Theoretically, the risk of side effects such as dry mouth, constipation, dizziness, sedation, reduction of sexual functions and perspiration is increased with high plasma concentration of nortriptyline.[1]	In a study an increase of the percentage of patients with substantial side effects was found by a factor of 6. For the subgroup of patients without co-medication affecting CYP2D6, the percentage increased by a factor of 16. This study found for patients with phenotypes IM versus EM + UM an increase in the percentage of patients with substantial side effects from 12.1% to 76.5% (S by 523%) The same for patients without CYP2D6-relevant comedication: from 4.2% to 69.2% (S by 1548%).[3]
Amitriptyline	*CYP2D6*	UM	The genetic polymorphism leads to an increased metabolic capacity of CYP2D6, which may decrease the plasma concentrations of amitriptyline and its active metabolite nortriptyline and increase the plasma concentrations of the active metabolites E-10-OH-amitriptyline and E-10-OH-nortriptyline.[1]	A study found a decrease of the plasma concentration of amitriptyline plus nortriptyline with 20% (non-significant).[4]

			Result: Possible failure of therapy due to decreased plasma concentrations of amitriptyline and nortriptyline and an increase in the plasma concentration of the potentially cardiotoxic, active hydroxy-metabolites.[1]	
Atomoxetine	*CYP2D6*	PM	The genetic variation increases the plasma concentration of atomoxetine and thus the risk of side effects (such as loss of appetite, vomiting, abdominal pain, constipation, insomnia, early awakening, drowsiness, irritability, pupil dilation, itching, dry mouth, urinary retention, erectile dysfunction, excessive sweating, increase of heart rate, increase in diastolic blood pressure palpitations, dizziness, increased systolic blood pressure, tremor and sedation).[5-8]	Results vary from no reduced appetite to an increase in the incidence of reduced appetite with 42% or OR = 2.0. The incidence of tremor increased by 364% and the incidence of insomnia by 54% or OR = 2.1.[4][9] In a study with 117 adult PM, PMs had a higher risk of urinary retention (OR = 9.1), an erectile dysfunction (OR = 3.1), a dry mouth (OR = 2.2), an increase in diastolic blood pressure (OR = 2.2), excessive sweating (OR = 2.0) and an increase in heart rate (OR = 1.7). Sedation, depression, early awakening, pruritus and mydriasis are also more common in PMs.[5] In 131 healthy male PMs, a dose of 60 mg 2x daily resulted in a statistically significant but not clinically significant increase in the QT interval. For the increase relative to placebo, the upper limit of the confidence interval was less than 10 msec. There were no subjects at any time with a corrected QT interval greater than 500 msec or an increase in the corrected QT interval by more than 60 msec with respect to pre-treatment.[7] The results for the incidence of discontinuation of therapy due to side effects vary from no difference, an increase by 3-50% or a decrease after 6 months by 100%.[5]
Atomoxetine	*CYP2D6*	IM	The genetic variation increases the plasma concentration of atomoxetine and can therefore reduce the dose requirement.[5] Side effects related to high atomoxetine levels: dry mouth, sleep disturbances, dizziness, nausea and abdominal pain.[6,10]	The plasma concentration of atomoxetine is a factor 2-3 times higher for IM than for EM at the same dose. Results range from no difference in frequency, severity and nature of the side effects to an increase in the risk of a sleep disorder (OR = 1.7) or dry mouth (OR = 1.6). IM were not overrepresented in patients who did not finish treatment and the mean dose was similar for IM and EM/UM.[6] One study found that of 10 patients who had side effects and/or a late response at normal dosing, 6 were IM. In the two IMs where the dose was reduced (up to 1.14 mg/kg per day and 0.42 mg/kg per day), this led to maintenance of efficacy and decrease in side effects.[8]
Atomoxetine	*CYP2D6*	UM	The genetic variation leads to an increased conversion of atomoxetine into the active metabolite 4-hydroxyatomoxetine, which has a much lower plasma concentration. Because the plasma concentration of the	-

			active substances decreases as a result, the gene variation can lead to a reduced effectiveness.	
Atorvastatin	*SLCO1B1*	521TC	The genetic polymorphism can lead to a reduced transport of atorvastatin to the liver. This may increase the plasma concentration of atorvastatin and thus the risk of myopathy.[11]	Myopathy Results range from no significant effect of the genetic polymorphism on the risk of myopathy or muscle complaints (two studies with 143-146 atorvastatin users and two case-control study with 10-13 cases) to an association of the 521C allele with intolerance or muscle complaints with OR = 2.7 (case-control study with 46 case).[12] In one case involving two related patients with atorvastatin-induced muscle pain, one patient had genotype 521CC and the other genotype 521TC.[11] Cholesterol reduction In two studies, there was no difference in the decrease of LDL cholesterol.[11]
Atorvastatin	*SLCO1B1*	521CC	The genetic polymorphism can lead to a reduced transport of atorvastatin to the liver. This may increase the plasma concentration of atorvastatin and thus the risk of myopathy.[11]	Myopathy Results range from no significant effect of the genetic polymorphism on the risk of myopathy or muscle complaints (two studies with 143-146 atorvastatin users and two case-control study with 10-13 cases) to an association of the 521C allele with intolerance or muscle complaints with OR = 2.7 (case-control study with 46 case).[12-16] In one case involving two related patients with atorvastatin-induced muscle pain, one patient had genotype 521CC and the other genotype 521TC.[11] Cholesterol reduction In two studies, there was no difference in the decrease of LDL cholesterol.[17,18]
Citalopram	*CYP2C19*	PM	This gene variation leads to an increase in plasma concentrations of citalopram. This causes a hogher risk of QT-prolongation and torsade de pointes.[19]	A study found a 3.0% greater QTc interval for a group of 16 IM and 1 PM. The study found no difference for this group in the median dose and the percentage of patients with a dose higher than 40 mg/day.[20] Two studies found no difference in the occurrence of side effects. A study with new-borns found no difference in severity of serotonergic symptoms after mother's citalopram use for a group of 4 IM and 1 PM.[21] For the probability of remission, the effect varies from no difference to an increase of 48%.[22]
Citalopram	*CYP2C19*	IM	This gene variation leads to an increase in plasma concentrations of citalopram. This causes a higher risk of QT prolongation and torsade de pointes.[19] The relationship between plasma concentration and efficacy and side effects has not been established. The risk of induction of QT prolongation and torsade de pointes by	A study with 16 IM found a trend for a 2.4% larger QTc interval. The study found a significant increase in the QTc interval for a group of 16 IM and 1 PM and no difference in the median dose and the percentage of patients with a dosage higher than 40 mg/day.[20] A study with 25 IM found no difference in the occurrence of side effects.[23] A study with new-borns found no difference in severity of serotonergic symptoms after mother's citalopram use for a group of 4 IM

			citalopram is dose-dependent and therefore plasma concentration-dependent.[19]	and 1 PM. For IM + PM, the results for the probability of tolerance vary from no difference in the validation study to a decrease.[21] A study with 298 IM found no difference in the chance of remission. The same study found no association between set dose and genotype.[22]
Citalopram	*CYP2C19*	UM	The gene variation increases the conversion of escitalopram to a low active substance. However, no significant effect on plasma concentration of citalopram, tolerance and response has been demonstrated.[19]	A study with 60 UM found no difference in the likelihood of tolerance and remission.[22] Two studies found no difference in set dosage. A study with 18 UM found no significant increase in the percentage of patients with plasma concentrations below the therapeutic range.[4]
Escitalopram	*CYP2C19*	PM	The gene variation leads to an increase in the plasma concentration of escitalopram. This increases the risk of QT prolongation and torsade de pointes.[24] Side effects related to higher escitalopram levels are dry mouth, dizziness and diarrhoea.[25]	A study found no increase in the QTc interval for a group of 1 PM and 21 IMs. However, the IM + PM group and the EM group were not comparable. The percentage of women was significantly lower for IM + PM. Women had a 3.7% higher QTc interval than men. In addition, the percentage of patients with a CYP2C19 substrate, inhibitor or inducer was significantly higher for IM + PM. There was a trend for a 2.8% higher QTc interval when using this co-medication.[20] A study with 6 PM found no difference between the genotypes in adverse events and in the percentage of patients who discontinued in the study.[25] Another study found no difference in neurological, psychological and 'other' side effects for a group of 23 IM + PM after 1 week. The score for autonomic side effects, such as sweating and gastrointestinal complaints, was reduced after 1 week, but this is probably not clinically relevant.[26] There was no difference in the dose adjusted according to side effects and effect. Three studies found no difference in response to depression (one with 16 PM, one with 9 PM and one with 23 IM + PM).[25-27] A study with 1 PM found no difference in response to peripheral neuropathy.[28] For a group with 22 IMs and 1 PM, a study found no difference in response to autism spectrum disorder.[29] There was no association of escitalopram plasma concentration found with the number of side effects or the occurrence of side effects. The adverse events dry mouth was increased with high escitalopram plasma concentration (OR = 1.48). The side effect diarrhoea occurred less frequently with higher ratios of desmethylescitalopram/escitalopram (OR = 0.60; S).[25]

Escitalopram	*CYP2C19*	IM	The gene variation leads to an increase in the plasma concentration of escitalopram. This increases the risk of QT prolongation and torsade de pointes.[24] Side effects related to higher escitalopram levels: dry mouth, dizziness and diarrhoea.[25]	A study found no increase in the QTc interval for a group of 1 PM and 21 IMs. However, the IM + PM group and the EM group were not comparable. The percentage of women was significantly lower for IM + PM. Women had a 3.7% higher QTc interval than men. In addition, the percentage of patients with a CYP2C19 substrate, inhibitor or inducer was significantly higher for IM + PM. There was a trend for a 2.8% higher QTc interval when using this co-medication.[20] A 94 IM study found no difference between the genotypes in adverse reactions and in the percentage of patients who discontinued the study. Another study found no difference in neurological, psychological and 'other' side effects for a group of 23 IM + PM after 1 week. The score for autonomic side effects, such as sweating and gastrointestinal complaints, was reduced after 1 week, but this is probably not clinically relevant. There was no difference in the dose adjusted according to side effects and effect. A study with 116 IM found no difference in response to depression. Another study found no difference for a group of 23 IM + PM.[26] A study with 7 IM found no difference in response to peripheral neuropathy.[28] For a group with 22 IMs and 1 PM, a study found no difference in response to autism spectrum disorder.[29] There was no association of escitalopram plasma concentration found with the number of side effects or the occurrence of side effects. The adverse events dry mouth was increased with high escitalopram plasma concentration (OR = 1.48). The side effect diarrhoea occurred less frequently with higher ratios of desmethylescitalopram/escitalopram (OR = 0.60; S).[25]
Escitalopram	*CYP2C19*	UM	NO action is required with this gene-drug interaction. The gene variation increases the conversion of escitalopram to a low active substance. However, this does not lead to a reduced effect, a need for a higher dose or an increase in side effects.[24] High desmethylescitalopram plasma concentration increased the occurrence of vertigo (OR = 1.56; S).[25]	A study with 28 UM found no difference in response to depression.[25] A study with 2 UM found no difference in response to peripheral neuropathy.[28] For a group with 9 UMs and 17 times *1/*17, a study found no difference in response to autism spectrum disorder.[29] The first and last study also found no effect of the genotype on the final dose. The latter study found no difference in the rate of dose increase during the whole 6 week treatment period, but found a lower rate of dose increase in the fourth, fifth and sixth week after the start of treatment.[29] Two studies with a total of 27 UM found no difference in side effects.[24,25]
Clomipramine	*CYP2D6*	IM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6. As a result,	In a study, an increase in the percentage of patients with adverse events was found with a factor of 1.9.[31]

			the plasma concentrations of clomipramine and the active metabolite may increase and those of the potentially cardiotoxic hydroxy-metabolites may decrease. Side effects include dry mouth, constipation, dizziness, sedation, reduction of sexual functions and transpiration.[30]	
Clomipramine	*CYP2D6*	PM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6. As a result, the plasma concentrations of clomipramine and the active metabolite may increase and those of the potentially cardiotoxic hydroxy-metabolites may decrease. Side effects include dry mouth, constipation, dizziness, sedation, reduction of sexual functions and perspiration.[30]	In two cases, side effects were observed.[32] The side effects disappeared in a case after lowering the clomipramine dose.[33] As a result, plasma concentrations of clomipramine and N-desmethylclomipramine reached the therapeutic range. There was an increase in plasma concentration of clomipramine + desmethylclomipramine by 88-199%.[4,34] For the plasma concentration of clomipramine, the results vary of a decrease by 34% to an increase of 185%.[34,35] After single administration, clomipramine clearance decreased by 43% and half-life increased by 21%.[34]
Clomipramine	*CYP2D6*	UM	The genetic polymorphism leads to an increased metabolic capacity of CYP2D6. As a result, the plasma concentrations of clomipramine and the active metabolite may decrease and those of the potentially cardiotoxic hydroxyl-metabolites may increase. The inactive hydroxy-metabolites may be cardiotoxic. These are formed to an increased extent at UM and at dose increases. The hydroxy-metabolites accumulate in severe renal dysfunction. The active metabolite desmethylclomipramine does not have serotonin reuptake activity. The metabolite therefore does not appear to contribute to the treatment of obsessive-compulsive disorder and other anxiety disorders. The metabolite does contribute to toxicity and treatment of depression.[30]	In two cases with non-response, increased plasma concentrations due to dose escalation or CYP2D6 inhibition led to recovery of the problem.[36,37] The dose increase involved an increase of 150-300 mg/day. Other reports of dose increase at UM are not known. On theoretical grounds, the risk of adverse reactions due to the possible cardiotoxic hydroxy-metabolites increases with higher plasma concentrations.[30]
Nortriptyline	*CYP2D6*	PM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6 which may increase the plasma concentration of nortriptyline.[38] Side effects include dry mouth, constipation, dizziness, nervousness and tinnitus (tinnitus), instability of the	In a study no significant change in the percentage of patients with side effects was found after 6 weeks use of nortriptyline.[40] In a case, side effects were observed, which disappeared after normalization of the plasma concentration of nortriptyline and E-10-hydroxynortriptyline by dose reduction.[41] The plasma concentration and AUC of nortriptyline increase by 146% and 232%,

			knees, drowsiness, inertia, anxiety, agitation, hypotension and fatigue.[39]	respectively. Oral clearance decreases with 62%.[42-44]
Nortriptyline	*CYP2D6*	IM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6, which may increase the plasma concentration of nortriptyline.[38] Anticholinergic adverse reactions (dry mouth, constipation, dizziness) reported in 1 case, disappeared with dose reduction. In another case, nervousness and tinnitus (ringing in the ears), instability of the knees, drowsiness, slowness, anxiety, agitation and side effects have been reported.[39]	The plasma concentration and AUC of nortriptyline increase by 35-123% and 86-179%, respectively.[42-43,45-46] Clearance decreases by 31% -57%.[44,46] The dose decreases to 70% of the dose at EM.[38]
Nortriptyline	*CYP2D6*	UM	The genetic polymorphism leads to an increased metabolic capacity of CYP2D6, which may decrease the plasma concentration of nortriptyline and increase the plasma concentration of the active metabolite E-10-OH-nortriptyline. E-10-hydroxynortriptyline is about half as potent as the parent compound in inhibiting norepinephrine uptake. It has a much lower anticholinergic activity than nortriptyline and is associated with cardiotoxicity.[38]	On theoretical grounds, the risk of cardiotoxic adverse reactions is increased with an increased plasma concentration of E-10-hydroxynortriptyline and the risk of reduced effectiveness of therapy is increased with a reduced plasma concentration of nortriptyline.[15] In studies, the AUC of nortriptyline was reduced by 23-41% and the oral clearance increased by 85%.[44,47] At 13 functional alleles: for nortriptyline increase clearance by 62% -315% and decrease half-life by 12%.[43,44]
Simvastatin	*SLCO1B1*	521TC	The genetic polymorphism can lead to a reduced transport of simvastatin to the liver. This may increase the plasma concentration of simvastatin and thus the risk of myopathy.[48]	Myopathy The risk of myopathy was increased. The increase of myopathy seems to increase with the simvastatin dose. In a study with simvastatin 80 mg/day, the OR for myopathy with creatine kinase was higher than 3 or 10 times the upper limit of normal 4.5 (95% CI [2.6-7.7]) per 521C allele. The calculated cumulative myopathy risk was 3% for 521CT versus 0.6% for 521TT. The OR for myopathy per 521C allele was 2.6 (95% CI [1.3-5.0]) for simvastatin 40 mg/day.[49] In a study with simvastatin 30 mg/day on average there was no significant increase in the risk of myopathy with creatine kinase higher than 10 times the upper limit of normal for (521TC + 521CC).[15] In a study with simvastatin 20 mg/day followed by 80 mg/day, the percentage of patients who either discontinued the study prematurely due to an adverse reaction or developed myalgia or muscle cramps or increased creatine kinase to more than 3 times the upper limit of normal had increased by a factor of 2.2 for (521TC + 521CC).[14]

				Cholesterol reduction In three studies there was no difference in the decrease of LDL cholesterol.[50-52] In one study, the decrease in LDL-cholesterol decreased by 3.2% per 521C allele.[48]
Simvastatin	*SLCO1B1*	521CC	The genetic polymorphism leads to a reduced transport of simvastatin to the liver. This increases the plasma concentration of simvastatin and thus the risk of myopathy.[48]	The risk of myopathy was increased. The increase of myopathy seems to increase with the simvastatin dose. In a study with simvastatin 80 mg/day, the OR for myopathy with creatine kinase was higher than 3 or 10 times the upper limit of normal 4.5 (95% CI [2.6-7.7]) per 521C allele. The calculated cumulative myopathy risk was 3% for 521CT versus 0.6% for 521TT. The OR for myopathy per 521C allele was 2.6 (95% CI [1.3-5.0]) for simvastatin 40 mg/day.[49] In a study with simvastatin 30 mg/day on average there was no significant increase in the risk of myopathy with creatine kinase higher than 10 times the upper limit of normal for (521TC + 521CC).[15] In a study with simvastatin 20 mg/day followed by 80 mg/day, the percentage of patients who either discontinued the study prematurely due to an adverse reaction or developed myalgia or muscle cramps or increased creatine kinase to more than 3 times the upper limit of normal had increased by a factor of 2.2 for (521TC + 521CC).[14] Cholesterol reduction In three studies there was no difference in the decrease of LDL cholesterol.[50-52] In one study, the decrease in LDL-cholesterol decreased by 3.2% per 521C allele.[48]
Venlafaxine	*CYP2D6*	PM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6. As a result, the plasma concentration of venlafaxine may increase and that of the active metabolite O-desmethylvenlafaxine may decrease. There are indications that the effectiveness of venlafaxine is reduced in patients with this genetic polymorphism.[53] Side effects related to elevated venlafaxine levels: elevation of alkaline phosphatase levels, sweating, insomnia, dry mouth, increased appetite, drowsiness, diminished effect, nausea, anxiety, palpitations, vomiting and diarrhoea.[53-55] Cardiac events (syncope, palpitations, dizziness) have been reported. Venlafaxine is possibly cardiotoxic. In one study, reduced efficacy in depression was found in	The results of a decrease in effectiveness vary to no difference in efficacy with respect to EM + IM in patients with depression. In a study with 3 PM there was 100% non-response.[53] In obsessive compulsive disorder, there was no difference in effectiveness.[56] For side effects, the results vary from no difference to an increase in the number of side effects by 369% (increase in the number of side effects per patient from 0.49 to 2.3 (S by 369%).[54,57] There is virtually no effect on the sodium concentration (decrease by 3%).[54] Cardiac adverse reactions (syncope, palpitations, dizziness) have been reported.[58] A study found an statistically significant increase in the number of patients with high alkaline phosphatase levels by a factor of 20.5 (from 0.2% to 4.1%) when comparing PM versus EM+IM+UM. The number of patients which has sweating as side-effect was statistically significant increased by a factor of 1.9 (from 13.3% to 24.5%) and the number of patients with insomnia increased

			patients with an elevated ratio of venlafaxine/active metabolite (PM).[53]	statistically significant by a factor of 1.7 (from 22.4% to 38.8%).[57]
Venlafaxine	*CYP2D6*	IM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6. As a result, the plasma concentration of venlafaxine may increase and that of the active metabolite O-desmethylvenlafaxine may decrease.[53] Venlafaxine is possibly cardiotoxic. In one study, reduced efficacy in depression was found in patients with an elevated ratio of venlafaxine/active metabolite (PM). Cardiac events (syncope, palpitations, dizziness) have been reported. Side effects related to elevated venlafaxine levels: elevation of alkaline phosphatase levels, sweating, insomnia, dry mouth, increased appetite, drowsiness, diminished effect, nausea, anxiety, palpitations, vomiting and diarrhoea.[53-55]	For venlafaxine + O-desmethyl venlafaxine, AUC increases by 14-17% and plasma concentration by 1-22%.[54,59-60] The ratio of plasma concentrations of O-desmethylvenlafaxine/venlafaxine decreases by 52-66%.[54,60] The decrease in the ratio is mainly caused by an increase in the plasma concentration of venlafaxine.[53]
Venlafaxine	*CYP2D6*	UM	The genetic polymorphism leads to an increased metabolic capacity of CYP2D6. As a result, the plasma concentration of venlafaxine may decrease and that of the active metabolite O-desmethylvenlafaxine may increase.[53]	In one study, the number of adverse events did not significantly decrease by 39% (0.49 to 0.3) and there was no difference in therapeutic efficacy (both 1.7 points).[54] In another study there was no effect on the sodium concentration.[53]
Doxepin	*CYP2D6*	IM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6, which may increase plasma concentrations of doxepin and nordoxepin.[61] On theoretical grounds, the risk of side effects increases when plasma concentrations of doxepin and nordoxepin increase.[61]	In single-dose administration of 75 mg doxepin, the AUC of doxepin + nordoxepin increased by 19% and the oral clearance of doxepin decreased by 42%.[62]
Doxepin	*CYP2D6*	UM	Genetic polymorphism leads to increased metabolic capacity of CYP2D6, which may decrease plasma concentrations of doxepin and nordoxepin and increase plasma concentrations of the hydroxy-metabolites.[61] On theoretical grounds, the risk of reduced effectiveness of therapy increases when plasma concentrations of doxepin and nordoxepin decrease.[61]	The AUC of doxepin + nordoxepin was reduced by 55% (from 1061 to 479 nmol.h/L).[62]

Doxepin	*CYP2D6*	PM	The genetic polymorphism leads to a reduced metabolic capacity of CYP2D6, which may increase plasma concentrations of doxepin and nordoxepin.[61]	The AUC of doxepin + nordoxepin increases by 116-190% with a single administration.[62,63] For multiple-dose administration, results vary from a decrease of 12% in plasma concentration of doxepin (a case) to an increase in the frequency of PMs from 0-50% in patients with high plasma concentrations versus patients with low to normal plasma concentrations.

PM, poor metabolizer; IM, intermediate metabolizer; UM, ultrarapid metabolizer; EM, extensive metabolizer.

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