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Outcomes and Clinical Relevance of a 16-Gene Pharmacogenetic Panel Test for Medication Management - A Cohort Study in 135 Patients

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Abstract

Background and Purpose: There is an increasing number of evidence-based indications for pharmacogenetic (PGx) tests and a growing demand for PGx screening. We aimed to evaluate clinical relevance of a 16-gene panel test for PGx-guided pharmacotherapy. Experimental Approach: Observational cohort study of subjects tested with a PGx panel for variants of ABCB1, COMT, CYP1A2, CYP2B6, CYP3A4, CYP3A5, CYP2C9, CYP2C19, CYP2D6, CYP4F2, DPYD, OPRM1, POR, SLCO1B1, TPMT and VKORC1. Specialized clinical pharmacology consultations with PGx-guided pharmacotherapy management were supported by the PGx expert system SONOGEN XP. Study outcomes were PGx-based changes and recommendations regarding current and potential future medication. Key Results: PGx-testing was triggered by specific drug-gene pairs in 102 subjects, whereas screening was performed in 33. Based on PHARMGKB expert guidelines the 16-gene panel identified at least one "actionable" variant relevant for current or potential future medication in all 135 (100%) tested patients. Drugs that triggered PGx-testing were clopidogrel in 60, tamoxifen in 15, polypsychopharmacotherapy in 9, opioids in 7, and other in 11 patients. Among those, PGx variants resulted in clinical recommendations to change PGx-triggering drugs in 33 (32.4 %), and other current pharmacotherapy in 23 (22.5%). Conclusion and Implications: The 16-gene PGx panel detected clinically relevant variants in a high proportion of tested patients, and SONOGEN XP supported their interpretation based on latest evidence. Additional costs of panel vs. single gene tests are moderate, and the efficiency of PGx panel testing challenges traditional cost-benefit calculations for single drug-gene pairs. However, PGx-guided pharmacotherapy requires specialized consultations with interdisciplinary collaborations.

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ABSTRACT

Background and Purpose There is an increasing number of evidence-based indications for pharmacogenetic (PGx) tests and a growing demand for PGx screening. We aimed to evaluate clinical relevance of a 16-gene panel test for PGx-guided pharmacotherapy.

Experimental Approach Observational cohort study of subjects tested with a PGx panel for variants of ABCB1, COMT, CYP1A2, CYP2B6, CYP3A4, CYP3A5, CYP2C9, CYP2C19, CYP2D6, CYP4F2, DPYD, OPRM1, POR, SLCO1B1, TPMT and VKORC1. Specialized clinical pharmacology consultations with PGx-guided pharmacotherapy management were supported by the PGx expert system SONOGEN XP. Study outcomes were PGx-based changes and recommendations regarding current and potential future medication.

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Conclusion and Implications The 16-gene PGx panel detected clinically relevant variants in a high proportion of tested patients, and SONOGEN XP supported their interpretation based on latest evidence. Additional costs of panel vs. single gene tests are moderate, and the efficiency of PGx panel testing challenges traditional cost-benefit calculations for single drug-gene pairs. However, PGx-guided pharmacotherapy requires specialized consultations with interdisciplinary collaborations.

Bullet Point Summary

1 | INTRODUCTION

Pharmacogenetics is the study of variability in drug responses associated with genetic differences amongst individuals. Drugs for which such variability in their effects has been linked to genetic polymorphisms are also referred to as pharmacogenetic (PGx) drugs [1].

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Today, there is a growing list of PGx drugs, but the question of clinical relevance and implications of PGx test results in individual patients poses the next challenge. A widely accepted classification of the relevance of PGx testing for specific drug-gene pairs has been established by the Pharmacogenomics Knowledgebase (PHARMGKB). The three PHARMGKB categories with the highest level of evidence and clinical relevance for PGx-testing are termed "required", "recommended" and "actionable". Information from PHARMGKB is publicly available, continuously updated and based on expert opinions, published research studies, and PGx information from official Summary of Product Characteristics (SmPCs).

Until today, only few PGx drug-gene pairs fall into PHARMGKB's "required" category based on the establishment of a very high attributable risk for (formerly) idiosyncratic, life-threatening adverse drug reactions (ADR) or lack of therapeutic efficacy and therefore a high predictive value of a detected PGx variant. For example, the association of severe skin reactions under abacavir and carbamazepine with genetic variations that code for human leucocyte antigens (HLA) fall into that category. After the establishment of sufficient evidence this information is now included in the labels of corresponding drugs, and PGx testing is mandatory before their first administration [2]. For drugs like e.g. the immunosuppressant azathioprine, PGx testing is not mandatory but classified as "recommended" to determine an effective and yet safe starting dose [3]. Other drug-gene pairs are currently only classified as "actionable", in spite of a growing body of evidence on the strength of a clinically relevant association. Other factors such as lower costs and widespread availability of PGx-testing may further challenge their classification and promote a general recommendation of preemptive PGx testing for more drug-gene pairs in the future. Examples include prodrugs such as the platelet inhibitor clopidogrel, or tamoxifen for the secondary prevention of breast cancer [4-6].

PGx testing does not only promise to improve efficacy and safety outcomes for patients, it could also lead to overall savings in health care costs due to more efficient patient management strategies. Particularly preemptive PGx testing with multi-gene panels may have a high chance to identify clinically relevant variants. If they are used in a high number of subjects, costs of PGx testing may decrease considerably and therefore have a major impact on calculations that weigh costs vs. benefits.

Despite many potential benefits, the implementation of PGx testing in clinical practice remains a slow process, particularly outside academic hospitals. Challenges include limited and sometimes controversial evidence with regard to improved clinical outcomes for many drug-gene pairs [7], discrepancies between guidelines from PGx expert groups vs. different medical specialty associations [6, 8, 9], reaction time of regulatory authorities regarding the implementation of new PGx evidence, and limited reimbursement of the costs for PGx tests [10, 11]. Furthermore, even if a valid PGx test is performed, it may be challenging to find an expert who can interpret its findings and manage pharmacotherapy within a patient's individual clinical context [12]. Clinical PGx experts must not only consider interactions for one or several drug-gene pairs, but also many other relevant cofactors such as age, comorbidities, comedication and patients' personal perceptions of risks and benefits.

Therefore, the utility of PGx as a guiding tool for pharmacotherapy in clinical practice is subject to ongoing studies and controversial debates. There is still limited data on the implementation of PGx services in routine clinical practice and subsequent PGx-based changes in medication management. Therefore, the present study describes our experience from the implementation and interpretation of a PGx panel test, and its relevance for the management of current and future pharmacotherapy in individual patients.

2 | METHODS

2.1 Study design

We conducted an observational cohort study that evaluated the results of a 16-gene PGx panel test and their implementation for personalized pharmacotherapy. The primary outcome of the study was the proportion of patients where PGx panel testing had clinically relevant management implications for current or potential future medication.

The study protocol was reviewed and approved by the local ethics board (EKNZ project ID 2020-00565),

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and all included patients had signed informed consents for PGx testing and scientific use of their health data.

2.2 Study population and procedures

An overview of the study procedures is presented in **Figure 1** . We included all subjects who underwent PGx testing with a 16-gene PGx panel between June 2018 and June 2020 through clinical pharmacology services at two Swiss tertiary care hospitals and associated outpatient clinics. The reason for PGx testing was either a specific drug-gene pair relating to current or planned pharmacotherapy, or a request for preemptive PGx screening. For all subjects the indication for PGx testing was first evaluated by a senior clinical pharmacologist (SR), including a consultation and review of all medical diagnoses and pharmacotherapy. If the indication for PGx testing was confirmed, venous blood samples were obtained using EDTA containing Vacutainers. After receipt of PGx test results and automated reports from the SONOGEN XP expert system, the clinical pharmacologist and a senior clinical pharmacist (DN) evaluated all available information and wrote a comprehensive report for each tested subject. The report included personalized PGx-based management recommendations for the attention of patients and treating physicians. If the clinical pharmacologist was in charge of the patient's therapy, he would also be able to directly change the medication. Patients also received a summary of the PGx profile in a credit card format (**supplementary Figure S1**). If necessary, there was another follow-up consultation with a personal discussion of all results and adjustments of pharmacotherapy.

2.3 Genetic analysis

DNA extraction and PGx analyses were performed by Labor Risch molecular genetics laboratory, Bern-Liebefeld, Switzerland. DNA was extracted using the QIAsymphony DSP DNA Mini Kit according to manufacturer's instructions. The isolated DNA was subsequently amplified by means of the iPLEX assay which consists of multiplex-PCR, SAP reaction and iPLEX primer extension. The modified products were then separated using the MassARRAY MALDI-TOF System by Agena Bioscience. The analysis included SNPs of the following genes: ABCB1, COMT, CYP1A2, CYP2B6, CYP3A4, CYP3A5, CYP2C9, CYP2C19, CYP2D6, CYP4F2, DPYD, OPRM1, POR, SLCO1B1, TPMT and VKORC1. A list of the tested SNPs for each gene is provided in**supplementary Table S1** .

2.4 SONOGEN XP

Results of molecular genetics analyses were forwarded to SONOGEN and further processed by its XP expert system. The SONOGEN XP expert system (www.sonogen.eu) provides an interpretation of identified SNPs of the 16 tested genes. Patients are categorized into metabolizer phenotypes by means of established star allele nomenclature [13], and the SONOGEN XP system generates automated recommendations for current and potential future pharmacotherapy based on pharmacogenetic phenotypes and the classification of their clinical relevance according to PHARMGKB (https://www.pharmgkb.org), as well as other available guidelines from CPIC (https://cpicpgx.org) and DPWG (https://upgx.eu/guidelines).

2.5 Retrospective documentation and validation

For the retrospective data analysis and validation as part of this study, the clinical pharmacologist (SR), the clinical pharmacist (DN) and a pharmacist in training (AR) reviewed all available original medical records, referral letters, pharmacotherapy prescriptions and laboratory results. Patient characteristics and clinical factors including current pharmacotherapy, laboratory results and medical history were extracted and compiled in a study database. Comedications were also categorized according to their potential for moderate or strong inhibition of cytochrome P450 enzymes 2C19 and 2D6 according to the mediQ-database (www.mediq.ch).

All clinical recommendations from the reports were validated and categorized as appropriate.

First, in patients where a specific drug-gene pair was the indication of PGx testing, we documented if the test result of the related gene led to a recommendation to change therapy with the drug that triggered PGx testing.

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Second, current comedication and results for all 16 genes of the PGx panel were analysed for any additional clinically relevant drug-gene interactions.

Third, for all subjects including those with a screening indication, we documented if any PGx variants were detected that related to a drug-gene pair with "actionable", "recommended" or "required" classification according to PHARMGKB. Such variants were presented in our PGx reports as potentially relevant for future medication and further discussed in the individual clinical context of tested subjects.

Drug-gene pairs, their classification of clinical relevance according to PHARMGKB, and the assignment of genotypes to according phenotypes are presented in **supplementary Table S2** .

2.6 Data analysis

Data analysis was descriptive with stratification and presentation of results in tables as appropriate. Data management, analyses and creation of figures were performed with STATA MP Version 15.1 (STATA Corporation, College Station, TX, USA).

3 | RESULTS

3.1 Characteristics of the study population

During the observation period from June 2018 to June 2020 135 patients underwent testing with the 16-gene PGx panel (**Figure 1**). Patient characteristics are presented in **Table 1** , including a stratification over drug-specific indication vs. screening. Compared to 33 subjects with a screening indication, the 102 patients with a drug-specific indication for PGx testing were older (median 70 vs. 58 years) and took a higher number of drugs (median 6 vs. 3). The three most frequent drug-specific indications for PGx-testing were therapy with clopidogrel (n = 60), tamoxifen (n = 15) and polypsychopharmacotherapy (n = 9). Medications in the tested population were predominantly related to cardiovascular diseases, but we also observed frequent use of analgesics, antidepressants, antidiabetics and benzodiazepines.

Furthermore, drug-gene interactions may be particularly relevant in the presence of additional drug-drug interactions that affect the same metabolic pathway or in case of impaired renal function. It is therefore of interest that 19.3% of the study population took inhibitors of CYP2D6 and 8.2% of CYP2C19, and that 14.1% had an eGFR below 60 ml/min.

3.2 Pharmacogenetic variants and their clinical relevance for current medication

Phenotypes of the 16 tested genes were derived from the identified PGx variants, and their frequencies in the study population are presented in**Figure 2** . **Table 2** presents an overview of the tested genes, drugs that are affected by these variants along with their corresponding PHARMGKB classification, as well as the frequency of these variants in our study population. A detailed listing of drug-gene pairs and their classification of clinical relevance according to PHARMGKB is presented in **Table S2** .

The 16-gene PGx panel detected genetic variants, i.e. non wildtype genes, in 3.7 % (for DPYD) to 78.5 % (for ABCB1) of all patients. CYP2D6, CYP2C19, CYP2C9 and TPMT variants are of particular interest because they relate to drugs where PGx testing is classified as required or recommended. Phenotype variants were detected for CYP2D6 in 50%, CYP2C19 in 52%, CYP2C9 in 34% and TPMT in 5.9% of the study population. Of note, Table 2 provides the numbers and proportions of all patients with non-wildtype variants, but not all variants necessarily have the same classification for all listed drugs. E.g. the number of subjects with CYP2C19 variants in Table 2 refers to IM, PM as well as to EM phenotypes, but for clopidogrel only the IM and PM phenotypes are "actionable".

Therefore, **Table 3** presents a detailed analysis for each drug that triggered PGx-testing including the number of patients with related genetic variants. The additional columns present an analysis of the clinical relevance of those variants. First, we present the number of patients where SONOGEN XP recommends to consider a change of the drug that triggered PGx testing. Second, we present the number of patients where the subsequent clinical pharmacology expert evaluation recommended a change of that trigger drug. Third,

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we present the number of patients where the 16-gene PGx panel identified additional drug-gene variant interactions in their current comedication.

Overall, among 102 patients with a drug-specific indication for PGx testing, actionable variants for the triggering drugs were identified in 36 patients (35.3%) according to SONOGEN XP, and after clinical expert evaluation including further patient-specific factors recommendations to change PGx-triggering drugs were actually issued in 33 patients (32.4 %). The majority of these recommendations (19 patients) referred to current therapy with clopidogrel.

Furthermore, the 16-gene PGx panel identified genetic variants that related to the current comedication and led to "coincident" additional clinical recommendations to adjust comedication in 23 out of 102 patients (22.5%) with a drug-specific indication for PGx testing, and in 3 out of 33 patients (9.1%) with a screening indication.

3.3 Pharmacogenetic variants and their clinical relevance for potential future medication

The frequencies of patients with a given number of identified PGx variants of different PHARMGKB classifications and according recommendations to adjust potential future pharmacotherapy are presented in **Figure 3** and **Table 4** . The 16-gene panel identified at least one "actionable", "recommended" or "required" variant in 100% of the tested patients, and in 74.1% we found 2 or more concomitant "actionable" variants. The prevalence of the highly relevant "recommended" and "required" variants was lower. Still, 73.3% had one, and another 6.7% even two "recommended" variants, 38.5% one "required" variant, and 86.7% of all patients had at least one "recommended" *or* "required" variant.

As shown in **Table 4** , the median number of alerts regarding clinically relevant PGx variants for potential future medication was 5 according to SONOGEN XP. Our reports provided a listing of those recommendations as an attachment, but the actual personalized expert assessments highlighted only those with the highest clinical relevance, hence the median number of recommendations in our personalized clinical reports was only 3 and therefore lower.

4 | DISCUSSION

This study describes our experience from the implementation of a 16-gene PGx panel in routine clinical practice with a focus on clinical relevance. The 16-gene PGx panel test was able to detect variants that are clinically relevant according to the PHARMGKB classification in 100% of tested patients. More important, results of PGx testing led to an actual change of medication or specific recommendations to do so in a high proportion of tested patients. These adjustments of current medication and specific recommendations regarding potential future medication were supported by a PGx expert system and implemented through personalized clinical pharmacology consultations.

Overall, frequencies of PGx variants shown in Figure 2 are in agreement with previous studies in Caucasian populations [14-16]. The detection rate of 100% for at least actionable variants is also not an unexpected finding for a 16-gene PGx panel if one considers that in a previous study even a panel with only 5 genes had a reported detection rate of 99% [15]. Detection rates are typically based on the PHARMGKB classification of clinical relevance, which may be considered as the single best currently available PGx knowledgebase. SONOGEN XP further enhances PGx clinical decision support through additional reviews of other knowledgebases, thorough review of the original literature, collaborations with external experts, and an array of separate reports for different purposes. These range from concise reports written for patients, over specific therapeutic recommendations for prescribing physicians, to extensive summaries for experts of ten and more pages including references to original research publications. The very high detection rate of PGx panel tests for variants that are classified as "required", "recommended" or "actionable" support the use of such multi-gene PGx panels with the automated interpretation from expert systems for preemptive testing with the ultimate goal to improve efficacy of pharmacotherapy, and to reduce adverse reactions and costs [15, 17].

Furthermore, the experience reported in our study looks beyond PGx panel tests with automated clinical decision support for PGx-based pharmacotherapy and their merely theoretical impact on pharmacotherapy.

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Whereas Table 2 lists a large number of PGx drugs for the identified PGx variants including some that are hardly ever used (e.g. pimozide or atazanavir), Table 3 provides a real-life insight into the prevalence of specific drugs plus relevant PGx variants that required a change of therapy in our patients. In our subpopulation of patients with a specific indication for PGx testing and a median number of 6 concomitant drugs we provided personalized clinical pharmacology consultations and issued personalized expert recommendations to adjust therapy with the PGx-triggering drug, current concomitant medication and potential future medication. We recommended or, if the clinical pharmacologist was directly involved in patient care, directly changed the PGx-triggering drug in 32.4%, and any other concomitant medication as a "bycatch" in 22.5% of patients based on PGx panel results. This high value supports the clinical relevance of PGx panels for actual clinical decision making and, to our knowledge, has not been investigated in this way before. Because additional costs of panel vs. single gene tests are moderate and likely to further decrease with advancing technology and widespread use, these findings further support the cost-efficiency of PGx panel testing and provide an alternative view at traditional cost-benefit calculations based on single drug-gene pairs.

However, a closer look also reveals that PGx-based management of pharmacotherapy in real-life clinical practice is a complex process, and that the standardized PHARMGKB classification can be highly heterogeneous within the same class. For example, PGx testing for clopidogrel and tamoxifen is merely classified as "actionable" according to PHARMGKB. But the lack of efficacy associated with the tested PGx variants is potentially lethal, and based on a review of the latest evidence, PGx expert guidelines, as well as our own clinical experience, we conclude that PGx testing indeed makes an important contribution to clinical decisions related to those frequently prescribed drugs and can even improve patient compliance [4-6, 18-20]. Furthermore, one must realize that most PGx variants do not have a high predictive value for efficacy or adverse reactions of a drug in individual patients. Rather, they act as one of several factors with complex and often poorly understood interactions, and their effect may be best described by a causative pie model [21]. Accordingly, our clinical experience from PGx-supported clinical decision making also taught us that PGx decision support algorithms are helpful, but that they do not comprehensively capture the complexity of (shared) clinical decision making. As shown in Table 1, we identified a considerable number of patients with comedication inhibiting CYP2C19 or CYP2D6, or renal impairment, and our therapeutic decisions considered all those factors and their interactions with PGx variants, as well as alternative therapeutic options. Indeed, the number of new drugs where the SmPC includes information on PGx variants is steadily increasing. For example, prescription of siponimod (Mayzent®) requires preemptive CYP2C9 PGx testing, and the prescribing information of bexpiprazole (Rexulti®) provides dosing recommendations that consider both, PGx variants as well as concomitant therapy with inhibitors of CYP2D6 or CYP3A4. And even for drugs that have been marketed for a long time, postmarketing studies may identify previously unknown relevant PGx variants [22]. Therefore, we expect a growing demand for PGx testing with integrated expert consulting in clinical pharmacology in the near future, also outside academic centres.

Some limitations of our study should also be addressed. Our study population was selected, partially through physicians that referred patients for specific drug-gene indications, and partially through "mere" screening indications. Characteristics of our patients are therefore transparently presented in Table 1, and one may consider that those may be different in other institutions that offer PGx services. Although our recommendations are a critical appraisal of clinical relevance, we were not able to conduct a larger study with longitudinal follow-up in order to evaluate outcomes of our PGx-based recommendations. These must be addressed in prospective large controlled studies for specific PGx-guided therapy [4, 20]. Nevertheless, we were able to perform a separate analysis for our PGx consultations in patients with clopidogrel therapy, and our results appear to be in line with those studies [18]. Another limitation concerns the 16-gene panel itself that we were able to use. Due to technical reasons this panel did not include relevant HLA variants associated with severe adverse reactions towards carbamazepine or abacavir [23, 24], but from a medical point of view this would certainly be desirable.

In conclusion, our study demonstrates the value of PGx panel testing in routine clinical practice and the valuable contribution of a PGx clinical decision support system. Additional costs of panel vs. single gene tests are moderate, and the efficiency of PGx panel testing challenges traditional cost-benefit calculations

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based on single drug-gene pairs. However, a closer look also reveals that truly personalized pharmacogenetic medication management will not achieve its full potential without individual patient consultations where additional factors and individual weighing of risks vs. benefits and pharmacotherapeutic as well non-pharmacotherapeutic care are considered. Limited availability of experts and specialized clinics may become a bottle neck for the implementation of PGx-guided pharmacotherapy, which is a challenge but also an opportunity and responsibility for clinical pharmacology and clinical pharmacy services to seek direct patient contact and involvement in PGx-guided medication management.

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The work presented in this manuscript was investigator-initiated and performed without external funding. All authors declare that no conflicts of interest influenced content of the presented manuscript. KH is co-founder and Chairman of the Board of Directors of INTLAB AG, provider of the SONOGEN XP expert system. KDH is Chief Medical Officer and member of the board of directors of INTLAB AG.

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

TABLES AND FIGURES

TABLE 1: Patient characteristics

	All patients with PGx panel testing n (%)	**Patients with specific drug-gen**
n (%)	135 (100)	102 (75.5)
Age: median (range)	68 (25 - 92)	70 (25 - 92)
<60	48 (35.6)	30 (29.4)
61 - 70	25 (18.5)	22 (21.6)
71 - 80	41 (30.4)	33 (32.4)
>80	21 (15.6)	17 (16.7)
Sex		
male	81 (60)	56 (54.9)
female	54 (40)	46 (45.1)
eGFR < 60 ml/min[1]	19 (14.1)	16 (15.7)
Indication PGx panel test		
Clopidogrel	60 (44.4)	60 (58.8)
Tamoxifen	15 (11.1)	15 (14.7)
Polypsychopharmacotherapy	9 (6.7)	9 (8.8)
Opioids	7 (5.2)	7 (6.9)
Statins	6 (4.4)	6 (5.9)
Phenprocoumon	2 (1.5)	2 (1.9)
Chemotherapy	2 (1.5)	2 (1.9)
PPI	1 (0.7)	1 (0.9)
Pharmacotherapy		
Number of drugs: median (range)[2]	6 (0 - 19)	6 (0 - 19)
Aspirin	43 (31.9)	38 (37.3)
Clopidogrel	48 (35.6)	48 (47.1)
Prasugrel or Ticagrelor	1 (0.7)	1 (0.9)
Coumarines or NOAC	25 (18.5)	22 (21.6)
Beta blockers	44 (32.6)	35 (34.3)
ACE or ARB	60 (44.4)	48 (47.1)
CCB	20 (14.8)	16 (15.7)
Diuretics	34 (25.2)	28 (27.5)
PPI	45 (33.3)	40 (39.2)

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	All patients with PGx panel testing n (%)	**Patients with specific drug-gene**
Cholesterol lowering drugs	55 (40.7)	48 (47.1)
NSAR	12 (8.9)	11 (10.8)
Opioids	17 (12.6)	14 (13.7)
Uric acid lowering drugs	5 (3.7)	3 (2.9)
Benzodiazepines	18 (13.3)	14 (13.7)
Antidepressants	28 (20.7)	24 (23.5)
Antipsychotics	10 (7.4)	9 (8.8)
Antiepileptics	9 (6.7)	8 (7.8)
Antidiabetics	22 (16.3)	17 (16.7)
Tamoxifen	12 (8.9)	12 (11.8)
CYP2C19 Inhibitor[3]	11 (8.2)	10 (9.8)
CYP2D6 Inhibitor[3]	26 (19.3)	20 (19.6)

[1] No data on eGFR was available for x patients, calculated by using CKD-EPI creatinine formula[2] One patient with indication of tamoxifen did not take any drugs at the time of PGx testing[3] Patients with at least one inhibitor, List of considered CYP2C19 inhibitors according to mediQ provided in Table S4

TABLE 2: Genes tested with SONOGEN panel, PGx levels and detected genetic variants

Gene

Drugs with

required PGx-testing[1]

Drugs with

recommended PGx-testing[1]

Drugs with

actionable PGx-testing[1]

n (%) Patients with phenotype variants[2]

ABCB1

-

-

-

106 (78.5)[4]

CYP2C9

siponimod

-

celecoxib, phenytoin, warfarin

46 (34)

CYP2C19

-

atazanavir

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amitriptyline, carisoprodol, citalopram, clobazam, clomipramine, clopidogrel, desipramine, doxepin, imipramine, nortriptyline, pantoprazole, trimipramine, voriconazole

71 (52)

CYP2D6

pimozide, tetrabenazine

-

amitriptyline, aripiprazole, atomoxetine, brexpiprazole, carvedilol, cevimeline, citalopram, clomipramine, clozapine, codeine, darifenacin, desipramine, doxepin, fesoterodine, iloperodine, nortriptyline, perphenazine, propafenone, tamoxifen, thioridazine, tramadol, trimipramine, vortioxetine

67 (50)

SLCO1B1[3]

-

-

-

30 (22)

VKORC1

-

-

warfarin

86 (63.7)

COMT

-

-

-

73 (54.1)

CYP1A2

-

-

-

65 (48.6)

CYP2B6

-

-

efavirenz

67 (49.6)

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CYP3A4

-

-

codeine, tamoxifen

6 (4.4)

CYP3A5

-

-

-

17 (12.6)

CYP4F2

-

-

warfarin

66 (48,9)[4]

DPYD

-

-

capecitabin, fluorouracil

5 (3.7)

OPRM1

-

-

codeine

34 (25.2)

POR

-

-

-

72 (53.3)[4]

TPMT

-

azathioprine, mercaptopurine

tioguanine

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8 (5.9)

[1] PGx level of drug-gene pairs accodring to PharmGKB,**genes in bold** feature at least one corresponding drug with a PGx level of required / recommended, informative not listed[2] Variant Phenotype = "non-normal" phenotype according to PharmGKB, not all variants are clinically relevant[3] PGx level has been changed to actionable by FDA for rosuvastatin and to recommended by Swissmedic for simvastatin during the course of the study[4] Re-Check with SONOGEN how to phrase this > 50 % prevalence of non-wildtype...

TABLE 3: Drugs triggering PGx-testing, detected phenotype variants and recommendations to change patients' current medication

n	Drugs that triggered PGx-testing	Relevant gene(s)	Detected phenotype vari
102	**All patients with specific indication**	n.a.	n.a.
60	Clopidogrel	2C19	**1 PM / 19 IM** / 19 UM
15	Tamoxifen	2D6	**3 IM** / 1 UM
9	Polypsycho-pharmacotherapy	1A2 2D6 2C19	1A2: **6 UM** 2D6: **7 IM** /
7	Opioids	OPRM 2D6	OPRM1 **3 decreased func**
6	Statins	SLCO1B1	4 decreased function
2	Phenprocoumon	VKORC1 CYP4F2 CYP2C9	**1 VKORC: G/G / 1 VK**
2 CYP2C9: *1/*1			
2 CYP4F2: C/C	1 (50.0 %)	2 (100 %)	0
2	Chemotherapy	DPYD	0
1	PPI	2C19	**1 UM**
33	**Screening**	n.a.	n.a.

n.a. = not applicable (no triggering drugs in screening patients)[1] Variant = "non-normal" phenotype according to PharmGKB, **phenotypes in bold** = clinically relevant for triggering drug(s)[2] Based on PGx results, concerned drug-gene pairs reported in Table S2

TABLE 4: Detected phenotype variants and related alerts relevant for potential future medication

Trigger for PGx-testing	**n patients**	**n patients with [?]1 "required" or "recommended" PGx variant[1]**	**n SONOGEN XP recommendations[2] per patient** median (range)	**n highlighted clinical expert recommendations[3] per patient** median (range)
Specific PGx drug	**102**	88 (86.3%)	2 (2-11)	2 (0-6)
Screening	**33**	29 (87.9%)	5 (3 - 9)	3 (1 - 5)
All Patients	**135**	**117 (86.7 %)**	**5 (2 - 11)**	**3 (0 - 6)**

[1] Patients with at least one relevant phenotype variant for a gene featuring a PGx level of required or recommended on PharmGKB, i.e. IM or PM for TPMT, 2C19 or 2D6[2] Automatically generated, based on clinical annotations on PHARMGKB[3] Assessed as clinically relevant considering expert evaluation and individual patient history

FIGURES

FIGURE 1

Study population and flowchart

see separate graphic file

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Legend for Figure 1:

[1] formally classified as "actionable" according to SONOGEN XP based on PHARMGKB guidelines

FIGURE 2

Frequency distribution of pharmacogenetic phenotypes in the study population

see separate graphic file

FIGURE 3

Distribution of number of variants per patient for "actionable", "recommended" and "required"-level pharmacogenetic variants

see separate graphic file

Supplementary Tables and Figures

Table S1: SNPs analysed by the 16-gene panel test

Gene	Allele	rs number
ABCB1	Haplotypes 1236-2677-3435	rs1045642
ABCB1		rs1128503
ABCB1		rs2032582
COMT	Haplotypes 6269-4633-4818-4680	rs4633
COMT		rs4680
COMT		rs4818
COMT		rs6269
CYP1A2	*1C	rs2069514
CYP1A2	*1F	rs762551
CYP1A2	*1K	rs12720461
CYP1A2	*7	rs56107638
CYP1A2	*11	rs72547513
CYP2B6	*6	rs3745274
CYP2B6	*18	rs28399499
CYP2C19	*2	rs4244285
CYP2C19	*3	rs4986893
CYP2C19	*4	rs28399504
CYP2C19	*5	rs56337013
CYP2C19	*6	rs72552267
CYP2C19	*7	rs72558186
CYP2C19	*8	rs41291556
CYP2C19	*17	rs12248560
CYP2C9	*2	rs1799853
CYP2C9	*3	rs1057910
CYP2C9	*4	rs56165452
CYP2C9	*5	rs28371686
CYP2C9	*6	rs9332131
CYP2C9	*8/*27	rs7900194
CYP2C9	*11	rs28371685
CYP2C9	*12	rs9332239
CYP2C9	*13	rs72558187
CYP2C9	*15	rs72558190
CYP2C9	*25	rs869277704

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Gene	Allele	rs number
CYP2D6	*2	rs1135840
CYP2D6	*2/*17/...	rs16947
CYP2D6	*2/*41	rs28371725
CYP2D6	*3	rs35742686
CYP2D6	*4	rs3892097
CYP2D6	*4/*10/...	rs1065852
CYP2D6	*5	CYP2D6del
CYP2D6	*6	rs5030655
CYP2D6	*7	rs5030867
CYP2D6	*8/*14	rs5030865
CYP2D6	*9	rs5030656
CYP2D6	*11	rs201377835
CYP2D6	*12	rs5030862
CYP2D6	*15	rs774671100
CYP2D6	*17	rs28371706
CYP2D6	*18	Dup4125_4133
CYP2D6	*19	rs72549353
CYP2D6	*20	rs72549354
CYP2D6	*29	rs59421388
CYP2D6	*36	rs28371735
CYP3A4	*2	rs55785340
CYP3A4	*17	rs4987161
CYP3A4	*22	rs35599367
CYP3A5	*2	rs28365083
CYP3A5	*3	rs776746
CYP3A5	*7	rs41303343
CYP4F2	*3	rs2108622
DPYD	*2	rs3918290
DPYD	*13	rs55886062
DPYD	rs67376798 A	rs67376798
OPRM1	A118G	rs1799971
POR	*28	rs1057868
SLCO1B1	*5	rs4149056
TPMT	*2	rs1800462
TPMT	*3A/*3C	rs1142345
TPMT	*3A/*3B	rs1800460
TPMT	*4	rs1800584
VKORC1	-1639 A	rs9923231

Table S2: Drug-gene pairs and relevance class according to PHARMGKB

Drug	Therapeutic area	Gene	Relevance class
pimozid	psychiatry	CYP2D6	required
tetrabenazin	neurology	CYP2D6	required
siponimod	neurology	CYP2C9	required
atazanavir	infectiology	UGT1A1, (CYP2C19)	recommended
azathioprin	rheumatology	TPMT1, NUDT15	recommended
mercaptopurin	oncology	TPMT1, NUDT15	recommended
amitriptylin	psychiatry	CYP2D6, CYP2C19	actionable

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Drug	Therapeutic area	Gene	Relevance class
aripiprazol	psychiatry	CYP2D6	actionable
atomoxetin	psychiatry	CYP2D6	actionable
atorvastatin	cardiology	SLCO1B1	actionable
brexpiprazol	psychiatry	CYP2D6	actionable
capecitabin	oncology	DPYD	actionable
carisoprodol	rheumatology	CYP2C19	actionable
carvedilol	cardiology	CYP2D6	actionable
celecoxib	rheumatology	CYP2C9	actionable
cevimelin	autoimmune disease	CYP2D6	actionable
citalopram	psychiatry	CYP2C19, (CYP2D6)	actionable
clobazam	neurology	CYP2C19	actionable
clomipramin	psychiatry	CYP2D6, CYP2C19	actionable
clopidogrel	cardiology	CYP2C19	actionable
clozapin	psychiatry	CYP2D6	actionable
codein	pain therapy	CYP2D6, OPRM1, CYP3A4	actionable
darifenacin	urology	CYP2D6	actionable
desipramin	psychiatry	CYP2D6, CYP2C19	actionable
doxepin	psychiatry	CYP2D6, (CYP2C19)	actionable
efavirenz	infectiology	CYP2B6	actionable
fesoterodin	urology	CYP2D6	actionable
fluorouracil	oncology	DPYD	actionable
iloperidon	psychiatry	CYP2D6	actionable
imipramin	psychiatry	CYP2C6, CYP2C19	actionable
nortriptylin	psychiatry	CYP2D6, CYP2C19	actionable
pantoprazol	gastroenterology	CYP2C19	actionable
perphenazin	psychiatry	CYP2D6	actionable
phenytoin	neurology	CYP2C9	actionable
propafenon	cardiology	CYP2D6	actionable
simvastatin	cardiology	SLCO1B1	actionable
tamoxifen	oncology	CYP2D6, CYP3A4	actionable
thioridazin	psychiatry	CYP2D6	actionable
tioguanin	oncology	TPMT1, NUDT15	actionable
tramadol	pain therapy	CYP2D6	actionable
trimipramin	psychiatry	CYP2D6, CYP2C19	actionable
voriconazol	infectiology	CYP2C19	actionable
vortioxetin	psychiatry	CYP2D6	actionable
warfarin	cardiology	CYP2C9, VKORC1, CYP4F2	actionable
acenoumarol	cardiology	CYP2C9, VKORC1,CYP4F2	informative
diclofenac	rheumatology	CYP2C9	informative
escitalopram	psychiatry	CYP2C19	informative
flecainid	cardiology	CYP2D6	informative
fluribiprofen	rheumatology	CYP2C9	informative
fluvoxamin	psychiatry	CYP2D6	informative
haloperidol	psychiatry	CYP2D6	informative
ibuprofen	rheumatology	CYP2C9	informative
lansoprazol	gastroenterology	CYP2C19	informative
methoxyfluran	anaesthesiology	CACNA1S, RYR1	informative
metoprolol	cardiology	CYP2D6	informative
mirtazapin	psychiatry	CYP2D6 (CYP1A2, CYP3A4)	informative
morphin	pain therapy	OPRM1	informative

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Drug	Therapeutic area	Gene	Relevance class
olanzapin	psychiatry	CYP1A2, (CYP2D6)	informative
omeprazol	gastroenterology	CYP2C19	informative
ondansetron	oncology	CYP2D6	informative
oxycodon	pain therapy	CYP2D6 (CYP2C19)	informative
paroxetin	psychiatry	CYP2D6	informative
phenprocoumon	cardiology	CYP2C9, VKORC1,CYP4F2	informative
piroxicam	rheumatology	CYP2C9	informative
propofol	anaesthesiology	CYP2B6	informative
risperidon	psychiatry	CYP2D6	informative
rosuvastatin	cardiology	SLCO1B1	informative
sertralin	psychiatry	CYP2C19	informative
tacrolismus	transplantation	CYP3A5, POR (CYP3A4)	informative
tropisetron	oncology	CYP2D6	informative
venlafaxin	psychiatry	CYP2D6	informative
zuclopenthixol	psychiatry	CYP2D6	informative

Table S3: Additional Clinical Recommended Changes to Current Drug(s)

Drug	Phenotype variant	n patients	Drugs triggering PGx test
metoprolol	CYP2D6 IM	4	clopidogrel
metoprolol	CYP2D6 IM	1	opioids
metoprolol	CYP2D6 UM	1	clopidogrel
atorvastatin	SLCO1B1 decreased function	1	opioids
atorvastatin	SLCO1B1 decreased function	3	clopidogrel
rosuvastatin	SLCO1B1 decreased function	1	clopidogrel
simvastatin	SLCO1B1 decreased function	1	clopidogrel
phenprocoumon	CYP2C9 NM, CYP4F2 PM, VCORC1 decreased function	1	clopidogrel
phenprocoumon	CYP2C9 NM, CYP4F2 PM, VCORC1 normal function	1	clopidogrel
phenprocoumon	CYP2C9 PM, CYP4F2 NM, VKORC1 decreased function	1	clopidogrel
phenprocoumon	CYP2C9 IM, CYP4F2 IM, VKORC1 decreased function	2	clopidogrel
phenprocoumon	CYP2C9 NM, CYP4F2 NM, VKORC1 decreased function	1	clopidogrel
Oxycodon	CYP2D6 IM	2	clopidogrel
Oxycodon	CYP2D6 IM	1	opioids
Oxycodon	CYP2D6 IM	1	polypsychopharmacotherapy
Tramadol	CYP2D6 IM	1	polypsychopharmacotherapy
pantoprazol	CYP2C19 UM	1	opioids
pantoprazol	CYP2C19 UM	2	clopidogrel
tacrolimus	CYP3A5 expresser	1	opioids
flupenthixol	CYP2D6 IM	1	polypsychopharmacotherapy
Sertralin	CYP2C19 UM	1	polypsychopharmacotherapy
Bisoprolol	CYP2D6 IM	1	screening
atorvastatin	CYP2D6 IM	1	screening
amitriptylin	CYP2D6 PM	1	screening

TABLE S4 – CYP2C19 inhibitors according to mediQ.ch

Active Substance	Inhibition

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	2=moderately strong, 3=strong
armodafinil	2
cannabidiol	2
chloramphenicol	2
clinafloxacin	2
dasabuvir	2
desmethoxyyangonin	2
eslicarbazepin	2
eslicarbazepinacetat	2
esomeprazol	2
ethinylestradiol	2
felbamat	2
fischöl	2
fluconazol	3
fluoxetin	3
fluvoxamin	3
isoniazid	2
kava	2
maribavir	2
meropenem	2
mestranol	2
moclobemid	2
modafinil	2
omeprazol	2
oxcarbazepin	2
piperaquin	2
stiripentol	2
sultiam	2
topiramat	2

TABLE S5 - CYP2D6 inhibitors according to mediQ

Active Substance	**Inhibition**
	2=moderately strong, 3=strong
abirateron	3
asunaprevir	2
budipin	2
cannabidiol	2
chlorphenamin	2
clobazam	2
dapoxetin	2
darunavir-ritonavir	2
dimenhydrinat	2
lorcaserin	2
amodiaquin	2
maribavir	2
mirabegron	2
peginterferon alf a-2b	2
resveratrol	2
ajmalin	2
amiodaron	2

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bupranolol	2
bupropion	3
celecoxib	2
chinidin	3
chloroquin	2
chlorpromazin	2
cimetidin	2
cinacalcet	2
citalopram	2
clomipramin	2
cocain	2
darifenacin	2
deramciclan	2
diphenhydramin	2
duloxetin	2
escitalopram	2
flecainid	2
fluoxetin	3
gefitinib	2
halofantrin	2
haloperidol	2
hydroxychloroquin	2
kava	2
levomepromazin	2
ecstasy	2
melperon	2
metoclopramid	2
midodrin	2
moclobemid	2
norfluoxetin	2
orphenadrin	3
paroxetin	3
perazin	2
promethazin	2
propafenon	2
propoxyphen	2
ritonavir	2
terbinafin systemisch	2
thiodirazin	3
timolol systemisch	2
trifluperidol	2
saquinavir-ritonavir	2
tizanidin	3
cinnamon	2

Figure S1: Example of credit-card sized pharmacogenomic profile issued to patients

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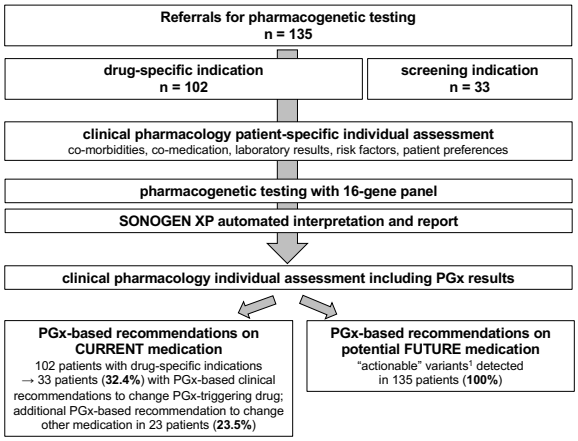
PHARMACOGENETIC ID CARD

Felix Muster	1976-09-16	male
name	date of birth (y/m/d)	gender

GENE	GENOTYPE	EFFECT	EXAMPLES OF AFFFECTED DRUGS
ABCB1	CGC/TTT	drug-dep. alt. efficacy	
COMT	low/im	slow metabolism	
CYP1A2	*1F/*1F	very fast metabolism	clozapine, coffeine, zolmitriptane, ropinirol
CYP2B6	*1/*6	slow metabolism	efavirenz, bupropion, methadone, pethidine
CYP2C9	*1/*1	normal metabolism	
CYP2C19	*1/*1	normal metabolism	
CYP2D6	*1/*2	normal metabolism	
CYP3A4	*1/*1	normal metabolism	
CYP3A5	*3/*3	normal metabolism	
CYP4F2	C/T	slow metabolism	
DPYD	*1/*1	normal metabolism	
OPRM1	A/G	drug-dep. alt. efficacy	morphine
POR	*28/*28	fast metabolism	
SLCO1B1	*1a/*1a	normal drug efficacy	
TPMT	*1/*1	normal metabolism	
VKORC1	G/A	increased drug efficacy	acenocoumarol, phenprocoumon, warfarin

Genetic analyses may not detect all known mutations of a gene. List of affected drugs is not comprehensive.
Consequences of pharmacogenetics on medication should be discussed with consulting physician.



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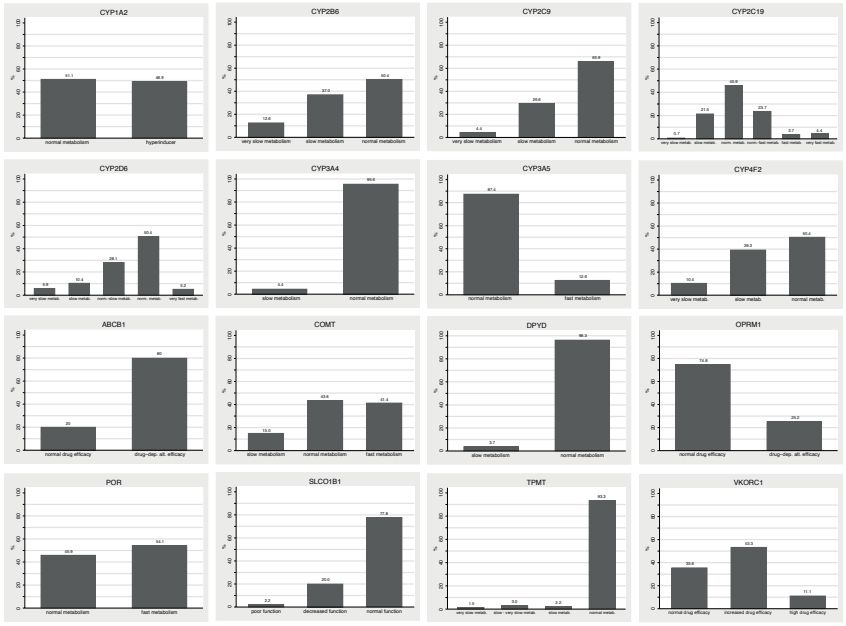
Frequency distribution of pharmacogenetic phenotypes in the study population (N=135)



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Frequency of pharmacogenetic variants by clinical relevance level (N=135)