Implementation of Pharmacogenotyping in Pharmaceutical Care

Inauguraldissertation

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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2023

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät

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Basel, den 21. Juni 2022

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Everything will be alright in the end and if it's not alright it's not the end.

Oscar Wilde

Acknowledgement

My journey as a PhD candidate was an enriching experience thanks to the support of the people surrounding me. I would like to express my sincerest thanks to everyone that, in one or the other way, contributed to this work and encouraged me during this pleasant endeavor.

First and foremost, my gratitude goes to my first supervisor Prof. Dr. Kurt Hersberger. I am very thankful for the opportunity to be part of the Pharmaceutical Care Research Group. Kurt was my role model from the first day I started to work with him. His endless commitment to pharmacy and his enthusiasm for many little and big things in life guided me along my scientific journey and were a source of constant inspiration. Along the way, he was not only a great supervisor and coach to me, but also became a valuable friend. Thanks for paving the way for pharmacogenotyping in pharmaceutical care.

I am indebted to my second supervisor Prof. Dr. Henriette Meyer zu Schwabedissen. Henriette guided me through difficult questions in the field of pharmacogenetics and provided helpful inputs during our project meetings. Although I was often overwhelmed by upcoming tasks, I managed them in the end because she believed in me and showed me that the task was not as hard as I thought. Thanks for the support all the way across from the Biopharmacy research group. And it was great having conversations from woman to woman every now and then.

A special thanks also to Prof. Dr. Samuel Allemann who accompanied me during the last year of my doctoral studies. I am grateful for his guidance and his motivation to strive for the implementation of pharmacogenetics.

Thank you Prof. Dr. Martina Teichert for carefully reading my thesis and joining the doctoral committee for the examination of my thesis.

I express my deepest thanks to Dr. Katja Suter who supported me during the first two years of my PhD. Whenever I told her about my struggles, she smiled and told me not to worry as all these struggles were simply part of the (PhD) process. She always had a spark in her eyes whenever she came up with a new idea and she was always proud when I had managed to get a step further.

An important person or rather coach for me was Diana Abegglen. With her, I worked on my motto “Es [die Doktorarbeit] ist die Kür und nicht die Pflicht.” She took my concerns seriously, and was mostly able to get a grip of my current emotion and its influence on my PhD. I am very grateful for all the sessions we had.

I also want to thank Céline Stäuble, my PhD fellow in pharmacogenetics. Together, we managed to accomplish several milestones. It was a great opportunity as well as a great pleasure to work towards an overarching goal while, pushing each other, and supporting one another.

Moreover, it was also a great pleasure to be part of the Pharmaceutical Care Research Group with warm-hearted people always respecting one another. A particular thanks goes to my fellow PhDs and Fabienne Abt. It was good to have social events to enjoy time and have fun together.

Thank you, PD Dr. Markus Lampert for giving me the opportunity to be part of a competent expert team offering further educations for pharmacogenetics in the pharmacy. I really hope to continue on that!

It was a pleasure to work with Ralf Weiner from humatrix AG. Although his sarcastic and dramatically paraphrased explanations sometime made us look more puzzled than before, it was always a good entertainment. Thanks for your investments in a good clinical decision support system in pharmacogenetics.

Thanks to the people from PharmGKB for enabling a collaboration from all across the ocean.

Special thanks go to my PhD buddies Dr. Carole Marxer and Dr. Alexandra Probst. We always had good exchanges about life as a PhD and we kept encouraging each other for the next task we had to tackle.

I do not want to miss out my master students Ursina Wernli, Anna-Lena Sandstedt, and Stefanie Mutter whom I worked with during a small part of the way and which was also fruitful for me.

Not to forget the numerous patients I recruited and the physicians that referred them; without them, my research would not have been possible. Further thanks go to Lukas Meister and Semira Bichsel-Thomi for offering their pharmacies as study pharmacies. Many thanks also to the Biopharmacy team that welcomed me whenever I showed up in their laboratory.

Although I did not often see him often during my PhD, I want to thank Markus Messerli for engaging in lively exchanges. It was a huge motivation to know that there are young pharmacists in the primary care section that continuously engage in clinical pharmacy.

I also thank my pharma friends Patricia, Emanuela, Jacqueline, and Lara. They always wanted to know how my PhD was going and were very proud to hear that it was going well.

Moreover, I want to thank my tandem partner Guillermo. It made the day shorter whenever we could spend lunch time talking in Spanish, especially in home-office times and no matter what weather there was. Muchas gracias.

I acknowledge my proofreader Laura Wiles for checking my English.

Last but not least, I express my immense gratitude to my family. First and foremost, a great thanks goes to my parents Daniel and Claudine Jeiziner. They definitely did their best to support me and always believed in me. Although they were often afraid they wouldn't understand the answer, they asked specific questions on my PhD. I appreciated that very much. Thank you. Further, I want to thank

my sister Annik and her partner Patrick. I want to thank Annik for her valuable recommendations from career woman to career woman: they were very straightforward, but they helped! And then I want to thank my partner Janique Nils Arnold. I was halfway through my PhD when I met you and I told you, that if you wanted me, you would have to take both: me and my PhD. Thanks for hanging on.

Abbreviations

ADME	*Absorption, distribution, metabolism, and excretion*
ADRs	*Adverse drug reactions*
aka	*also known as*
CDSS	*Clinical decision support system*
CTU	*Clinical trial unit*
CYP	*Cytochrome*
DDGI	*Drug-drug-gene interaction*
DDI	*Drug-drug interaction*
DGI	*Drug-gene interaction*
DL	*Drug label*
DPYD	*Dihydropyrimidine dehydrogenase*
EHR	*Electronic health record*
EM	*Extensive Metabolizer*
EMA	*European Medicines Agency*
FDA	*Food and Drug Administration*
G6PD	*Glucose-6-phosphate dehydrogenase*
GWAS	*Genome-wide association study*
HCP	*Health care professional*
HCSC	*Health Canada/Sonté Canada*
HLA	*Human leucocyte antigen*
IM	*Intermediate Metabolizer*
MTX	*Methotrexate*
NCCN	*National Comprehensive Cancer Network*
NM	*Normal Metabolizer*
PD	*Pharmacodynamics*

P-gp	*P-glycoprotein*
PGx	*Pharmacogenetics / pharmacogenetic*
PharmGKB	*Pharmacogenomic Knowledge Base*
PK	*Pharmacokinetics*
PM	*Poor Metabolizer*
PMDA	*Pharmaceutical and Medical Devices Agency*
RA	*Rheumatoid Arthritis*
RCT	*Randomized controlled trial*
SNP	*Single nucleotide polymorphism*
SOP	*Standard operating procedure*
SSRIs	*Selective serotonin reuptake inhibitors*
TF	*Therapy failure*
TMX	*Tamoxifen*
TPMT	*Thiopurine S-methyltransferase*
UGT1A1	*Uridine diphosphate glucuronosyltransferase 1A1*
UM	*Ultrarapid Metabolizer*
U-PGx	*Ubiquitous Pharmacogenomics*

Summary

"One size fits all" is the common strategy of dose-finding studies and, consequently, in most drug therapies a standard dosage is applied. However, drugs may cause therapy failure (TF), and/or may induce considerable adverse drug reactions (ADRs). Variations in the genes of proteins involved in absorption, distribution, metabolism, and excretion (ADME) can influence their activity and thus lead to phenotypic, i.e. measurable, inter-individual differences in the efficacy and tolerability of a drug. Pharmacogenetics (PGx) is defined as "the study of variations of DNA characteristics as related to drug response". The influence of patients' genetic predispositions on drug response has been studied over decades [1] and now, pharmacogenetics is gaining importance in patient-centered research and personalized medicine.

PGx testing (aka pharmacogenotyping) consists of a test where certain genetic variations are associated with drug response to prevent TF or ADRs. In these days, it is uncontested that PGx findings contribute significantly to our current understanding of drug response. Therefore, PGx panel tests comprising several genes involved in the ADME process, have been developed. By covering several genes, PGx panel tests enable to detect reasons for ADRs and TF pre-emptively, i.e. before taking a therapeutic decision.

To date, PGx testing is not standard in primary care in Switzerland. Yet, several attempts of pre-emptive PGx testing have been conducted in other European countries showing the feasibility and a potential real-world impact in primary care [2-5]. Furthermore, it has been shown that pharmacists in the primary care setting can contribute to the optimization of pharmacotherapy when considering the patient's genetic background [6]. Besides, pharmacists have expressed their willingness to learn more about PGx already ten years ago [7]. As pharmaceutical care [8, 9] designates a field where drug-related problems are identified, resolved, and prevented, it seems to be the right field for the initiation of PGx. Therefore, the Pharmaceutical Care Research Group decided to implement pharmacogenotyping in pharmaceutical care to show the potential of the pharmacist as facilitator of PGx in primary care.

Project A

Project A aimed to identify pharmacogenetic information for clinical practice.

The drug label (DL) is one of the first sources for health care professionals (HCPs) to check for information on a drug. The Pharmacogenomics Knowledge Base (PharmGKB) [10] is an expert curated knowledge base which collects and disseminates information on drug-gene interactions, including information provided in DLs. The Swiss DL is organized in different sections with defined headings; however, no section is dedicated to PGx. At the time, no overview or comparison of PGx information in Swiss DLs existed. Therefore, in this project, we analyzed the Swiss DLs to get an overview of the current state of PGx-relevant information on metabolizing enzymes and transporters as well as HLA

risk alleles, to classify the recommendations provided to HCPs by the PGx levels as suggested by PharmGKB [11], and finally, to compare the respective PGx level with those provided in DLs authorized by agencies of other countries. The analysis of PGx information in Swiss DLs revealed a large heterogeneity. PGx information varies not only in wording used to describe the information but also in the section, where the information appears. In addition, the instructions for clinical practice are rather vague. In summary, this makes the identification and the interpretation of PGx information difficult for HCPs.

One of the identified DLs was that for abacavir (commercial name: Ziagen®), where pre-emptive testing for *HLA-B*57:01* is required to prevent administration to patients with a higher risk of hypersensitivity reaction [12]. This suggested practice is supported by the findings of a randomized controlled trial [13, 14] where carriers of the *HLA-B*57:01* allele showed a higher risk to develop the abacavir hypersensitivity syndrome compared to non-carriers. Especially in the case of HLA alleles, it has been suggested that so-called HLA-typing (pre-emptive testing for a specific HLA allele) may prevent the associated ADRs if exposure of carriers of certain HLA alleles is avoided. Besides abacavir, there are other examples of clinically applied drugs where ADRs are assumed to be associated with HLA alleles. Nevertheless, translation into clinical practice is still limited. Presumably, this is due to the opinion of various HCPs saying that there is insufficient evidence for HLA-typing in association with a drug intervention. Therefore, in this project, we summarized studies investigating HLA alleles in relation to ADRs to give an overview of the evidence on the described ADRs and the investigated genetic factors. In conclusion, the literature search identified a considerable number of studies that investigated various substances, HLA alleles, and associated ADRs. It became clear that pre-emptive testing of HLA alleles (HLA-typing) may have a potential; however, it is not possible to derive the actual clinical relevance from these studies. The overview of HLA-associated ADRs ranged from poor to strong available evidence, thereby revealing a prevailing complexity and uncertainty.

Project B

Project B aimed to develop a standard operating procedure for pharmacist-led PGx testing and counseling in primary care.

With the developing knowledge on genetic variants influencing pharmacokinetics and/or pharmacodynamics of frequently applied drugs, multiple providers are now offering PGx testing using DNA isolated from buccal swaps. One of the commercial products offering a PGx test is Stratipharm (humatrix AG, Pfungstadt, Germany, https://www.stratipharm.de). Stratipharm offers genotyping in combination with evidence-based interpretation of the genotype. We established a case series of patients with ADRs or TF where the PGx panel test Stratipharm was applied to determine the hereditable component of the patient's susceptibility of experiencing the observed ADRs or TF. The aim of the case series was to compile case reports to gather experience and later, develop a standard operating procedure for "PGx testing and counseling" in primary care. In addition to the results of PGx testing, the individual

patient cases were always supplemented with information on health-related factors such as medication history, diagnoses, drug-drug interactions, adherence, renal function, etc. This information was collected in two visits of the patient to the study pharmacy and then integrated into a comprehensive medication review led by the pharmacist. In the end, the patient as well as the treating physician received the list of concerned substances and the written recommendation with the individual recommendations. In the following, the patients' and physicians' current understanding, appraisal, and implementation of the results from the pharmacist-led service "PGx testing and counseling" were inquired to evaluate the PGx service.

In total, 100 patients were collected for PGx testing and counseling in the community pharmacy. In this thesis, two cases are reported in detail. The case of a patient with tamoxifen suffering from ADRs on the one hand, revealed the added value of a large PGx panel, and on the other hand, showed the complexity of integrating a PGx profile into a recommendation. The case of a patient with methotrexate suffering from ADRs indicated that PGx panel testing is still limited to experts due to the complex pathway and the many genetic variants. A survey of 42 patients indicated that more than two thirds of the patients had changed at least one drug as suggested by the PGx recommendations.

In conclusion, the pharmacist-led service comprising PGx panel testing and counseling in the community pharmacy is appreciated by patients and physicians. The application of a PGx panel test offers the possibility to counsel on several drugs and the results should be integrated into a pharmacist-led medication review. Finally, the PGx service gives opportunity to initiate an interdisciplinary collaboration with physicians and other HCPs.

A detailed overview on the projects is provided in the chapter "Project Overview".

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General Introduction

1. Introduction to thesis and scope

"One size fits all" is the common strategy of dose-finding studies and, consequently, in most drug therapies a standard dosage is applied. However, drugs may cause therapy failure (TF), and/or may induce considerable adverse drug reactions (ADRs). The influence of patients' genetic predispositions on drug response has been studied over decades [1] and now, pharmacogenetics (PGx) is gaining importance in patient-centered research and personalized medicine. Not only is PGx used to study drug response, but the use of PGx testing (aka pharmacogenotyping), where a genetic test is associated with a certain drug treatment to prevent TF or ADR, is extensively discussed these days. Although it is uncontested that PGx findings contribute significantly to our current understanding of drug metabolism, drug response, and drug safety, PGx testing has still not been widely introduced into practice. Moreover, it has been shown that pharmacists in the primary care setting can contribute to the optimization of pharmacotherapy when considering the patient's genetic background [6]. Particularly in the field of psychiatry, there is evidence that PGx can enhance the application of PGx testing before the start of pharmacotherapy [2, 15, 16].

Early on during my studies in pharmacy, I was gripped by the potential of PGx. Patients have a right to receive a drug that is tailored to them instead of being confronted with several trial-and-error regimens. Besides factors such as drug-drug interactions, allergies, renal or liver function, adherence, smoking status, etc., it is indispensable to also take a patient's PGx profile into account. The time has come to introduce health care services that offer PGx testing and counseling to ensure safe and efficient pharmacotherapy. By applying PGx, the pharmacist could play a significant role in the movement toward personalized medicine.

In 2018, a survey conducted among the Swiss community (n = 238) and hospital (n = 134) pharmacists showed that about 75% of the pharmacists considered it their duty to counsel patients in the matter of PGx, although the same number of pharmacists also admitted that their perceived knowledge of PGx was insufficient and expressed willingness to participate in an advanced training course [17]. Thus, there is much implementation work to be done. This thesis shows the potential of putting the pharmacist in the role of providing PGx, thereby focusing on the primary care setting. Pharmaceutical care [8, 9] designates a field where drug-related problems are identified, resolved, and prevented, and therefore serves as the ideal framework for the facilitation of PGx. For the implementation of PGx in pharmaceutical care, two decisive preparation steps are necessary.

First, fundamental matters need to be clarified. Where can information on PGx be found? What is the evidence for PGx? How does evidence differ from one drug to another? How does evidence differ from one gene to another?

Second, the pharmacy as a potential setting for PGx testing and counseling needs to be explored and defined. What does PGx testing show for patients with ADRs or TF? How can a service comprising PGx testing and counseling be set up? What do patients and physicians think of a pharmacist-led PGx service?

It was the aim of my projects to answer all these questions. A detailed overview of the different projects of the thesis "Implementing pharmacogenotyping in pharmaceutical care" is provided in the chapter "Project Overview".

Now, I would like to introduce the field of PGx by starting with basic principles from biopharmacy, then moving on to available evidence on PGx, information on PGx, and PGx testing and finally, indicating a possible approach for pharmacist-led PGx testing and counseling in primary care.

2. Pharmacokinetics and pharmacodynamics

On the one hand, the processing of a drug by the human organism is summarized as pharmacokinetics (PK) and involves absorption, distribution, metabolism, and excretion (ADME) of the drug taken. The mechanisms of ADME involve a variety of proteins (enzymes and transporters), where changes in activity affect systemic exposure and therefore drug response. Variations in the genes of proteins involved in ADME can influence their activity and thus lead to phenotypic, i.e. measurable, inter-individual differences in the efficacy and tolerability of a drug. The drug-metabolizing enzyme system cytochrome (CYP) P450 represents an illustrative example where genetic variants on the level of PK frequently occur. On the other hand, the process manipulations by the drug to the human organism are summarized as pharmacodynamics (PD). If target structures of drugs are structurally altered by genetic variation, the binding of the drug to the drug target is strengthened, weakened, or even inhibited. Two examples are provided in Figure 1. PGx focuses on alterations in genes leading to an altered activity of proteins involved in PK and PD. Examples of genetic variants in enzymes, transporters, drug targets, human leucocyte antigens (HLAs), and cells with somatic mutations are presented in the following.

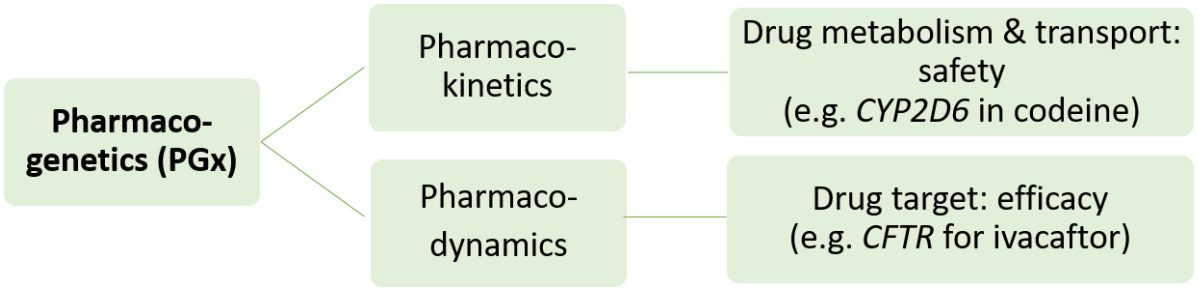

Figure 1 Pharmcocokinetics and pharmacodynamics

Enzymes

Enzymes enable the inactivation, degradation, and finally, elimination of the drugs from the body or, in the case of prodrugs, they are important for the activation of substances to achieve a desired effect in the organism. The enzymes of the CYP P450 superfamily are estimated to be involved in up to 75% of all metabolic reactions. Most drugs are metabolized by *CYP3A4* (about 50% of all drugs biotransformed by CYP) followed by *CYP2D6* (about 25%) [18]. *CYP2D6* shows high variability in its activity and is particularly well studied with regard to the influence of genetic variants leading to different metabolizer states (see Table 1). The Extensive Metabolizer (EM) (aka Normal Metabolizer, NM) carries two normally functioning gene variants. The Ultrarapid Metabolizer (UM) carries one or more *CYP2D6* gene duplications whereas an Intermediate Metabolizer (IM) or a Poor Metabolizer (PM) carry genetic variants with functional limitations (absent or reduced enzyme function) on one or both *CYP2D6* gene loci, respectively. In the case of the combination of normal function and increased function alleles, experts also differentiate Rapid Metabolizers from UMs possessing two increased function alleles, or more than two normal function alleles [19].

The influence of *CYP2D6* on metabolism by the organism has been documented for some substrates, e.g. metoprolol. After its operation at the adrenoreceptor B1, metoprolol undergoes oxidative degradation in the liver where *CYP2D6* hydroxylates it to alpha-hydroxymetoprolol, O-desmethylmetoprolol, or N-desisopropyl metoprolol, three metabolites without any further pharmacological effect. In contrast, codeine, used as an analgesic, is a prodrug and is degraded to morphine before acting as a painkiller. In this process, the O-demethylation of codeine to morphine is mainly catalyzed by *CYP2D6*. Intoxication may occur in people who have excessive *CYP2D6* activity. In nursing mothers with *CYP2D6* UM state, life-threatening respiratory depression in the child can occur [20].

Table 1 Different metabolizer states of CYP2D6 with definitiosn and examples of an active substance and a prodrug, adapted from Zanger et al. [18]

Phenotype	***Poor Metabolizer [PM]***	***Intermediate Metabolizer [IM]***	***Extensive Metabolizer [EM]***	***Ultrarapid Metabolizer [UM]***
Alleles	Two inactive alleles	Two alleles coding for an enzyme with reduced activity or one intact allele and one mutated allele	Two intact alleles	Amplification of the activating alleles
Definition	No function of the enzyme	Reduced function of the enzyme	Normal function of the enzyme	Overexpression of the enzyme
Active substance, e.g. metoprolol	The active substance is not broken down and accumulates; possible ADRs	The active substance is not or incompletely broken down and accumulates; possible ADRs	Expected effect and tolerance	Too fast metabolism; no effect
Prodrug, e.g. codeine	The prodrug is not activated; no effect	The prodrug is not or incompletely activated; incomplete/missing effect	Expected effect and tolerance	Accumulation of the metabolites in the plasma; possible ADRs

Legend: ADRs = Adverse drug reactions

Transporters

Transporters of drugs transport the active substance into (uptake transporters) or out of (efflux transporters) a cell. This can be done actively with energy investment (adenosine triphosphate, ATP) or by passive diffusion along a concentration gradient. They are found in almost all cells, predominantly in cells of the liver, kidney, intestine, and brain. Examples for both an uptake and an efflux transporter shall be illustrated in the following.

The gene *SLCO1B1* encodes the organic anion transporter OATP1B1 and mediates the sodium-independent uptake of its substrates into hepatocytes. *SLCO1B1* has genetic variants that result in a reduction of transport activity and thus increase the maximum concentration of substrates, such as statins where the OATP1B1 transporter is responsible for the selective accumulation of active substances in the liver. If the *SLCO1B1* gene for the OATP1B1 transporter is present only in one copy or not at all, a high risk of myopathies and in rare cases potentially life-threatening rhabdomyolysis may occur because of increased statin concentrations in plasma.

ABCB1, ABCG2, and ABCC1 are the genes of the three most abundant proteins in the superfamily of human ATP-binding cassette (ABC) transporters. Together with breast cancer resistance protein and multi-resistance protein 1, P-glycoproteine (P-gp) belongs to the best-studied efflux transporters each covering a broad profile of substrates that partially overlap with each other. They can be found in different cell membranes where they have excretory and protective functions. P-gp (gene: *ABCB1*) was initially described as one of the underlying factors for the development of so-called multidrug resistance of tumor cells. Besides its role in the biliary and renal elimination of substances, P-gp is expressed in the apical membrane of enterocytes of the intestine and actively pumps substrates back into the lumen of the gastrointestinal tract thereby limiting the uptake (bioavailability) of substrates of the transport protein. P-gp is also responsible for the maintenance of the blood-brain barrier by selectively extruding its substrates, in particular certain substances with central nervous effects. For P-gp substrates, genetic variants in *ABCB1* can decisively contribute to the chance of remission for patients with major depressive disorder [21, 22].

Drug targets

For every substance taken, there is a drug target at which the substance ultimately takes effect. This target structure can be altered and thus have an influence on the drug sensitivity, e.g. in the case of *VKORC1*. The *VKORC1* gene encodes vitamin K epoxide reductase catalyzing the conversion of vitamin K epoxide to vitamin K, an important step in the vitamin K cycle and pharmacological target of warfarin, phenprocoumon, and acenocoumarol. In the case of a genetic variant in the noncoding region of the *VKORC1* gene, its transcription is decreased and in consequence, the protein is expressed less often. Due to the decreased levels of the VKORC1 enzyme, patients with this genetic variant have increased drug sensitivity and require lower doses. In addition to this common variant, there are also rare variants of VKORC1 that are associated with warfarin resistance (i.e. higher required doses).

Another example is ivacaftor, a substance prolonging the open state of the chloride channel defective in patients with cystic fibrosis. Ivacaftor is only effective in the presence of a gating mutation of class III or an *R117H* mutation; for all other mutations responsible for cystic fibrosis, ivacaftor is not effective. In consequence, a validated genotyping method must be conducted before prescribing ivacaftor.

Human leucocyte antigen

Human leucocyte antigen (HLA) is part of the adaptive immune system and contributes to the functionality of the immune system [23, 24]. To bind and present a variety of peptides to the immune system, HLA genes are highly polygenic and polymorphic by allelic variation. The HLA genes consist of different variant alleles, thereby leading to different binding specificities of the HLA proteins. It has been shown that drugs and endogenous proteins can interact with certain HLA molecules and form an immunogenic self-peptide complex. These complexes are recognized by the immune system, thereby inducing an autoimmune-like reaction. Therefore, they are assumed to be determinants of hepatic and cutaneous ADRs known as drug-induced liver injury and drug-induced skin injury, respectively. For example, in abacavir, the presence of a specific HLA-B allele is associated with an increased risk of hypersensitivity reaction. It is therefore recommended that a HLA screening (aka HLA-typing) should be performed before initiation of treatment to exclude the presence of the gene marker *HLA-B*57:01*.

Somatic mutations

In contrast to all the above-mentioned inherited germline mutations, which are anchored in the human genome from birth on, there are also acquired somatic mutations, which a cell develops in the course of its lifetime. These play an important role in the rapidly changing tumor cells. In oncology, it is very common nowadays to examine the patient for the presence or absence of a receptor, a surface protein on the tumor cell, or a genetic defect of signal transduction factors. Only if the result of this examination is positive, will the highly specific (and usually expensive) drug be used. This is also called target-oriented stratification (drug-targeted therapy). Imatinib, for instance, is specifically designed to bind the BCR-ABL kinase overexpressed in Philadelphia chromosome-positive chronic myeloid leukemia, thereby inhibiting increased cell proliferation.

To sum up, PGx is not limited to the integration of information on inherited genetic variability of genes involved in PK and PD, but also includes the detection of genetic variations in cancer cells; however, the latter aspect is not covered in this thesis.

3. Pharmacogenetics (PGx)

Seventy years ago [25, 26], the structure of the DNA was revealed and thereby an entirely new field of discovery to science was opened. It was only in 1990 that the Human Genome Project [27], the first project on large-scale biology, was launched with the aim of completely decoding the human genome. Finally, after 13 years, 98% of the human genome had been sequenced with 99.99% accuracy. Alongside the project, new technologies to obtain and analyze this genetic information were developed. Twenty years earlier, Arno Motulsky [28], an American geneticist, was one of the first to promote the concept of PGx by suggesting that genetics could influence a person's drug response. At that time, general assumptions were made that genetic inheritance might influence drug response.

> *"Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency has become a model system for understanding the interaction between hereditary enzyme deficiencies and drugs. Although the frequency of severe drug-induced hemolysis among G-6-PD-deficient subjects is low, the vast number of individuals at risk provides this enzymatic defect with a principal pharmacogenetic importance."*
>
> Arno Motulsky, 1971 [28]

In 2002, the preliminary work for a large randomized controlled trial (RCT) — "PREDICT-1" [13] — was started and in the following years, research within the field of PGx on HLA alleles associated with ADRs made a great leap forward.

Definitions

The European Medicines Agency (EMA) [29] defines the concept of pharmacogenomics as

> *"The study of variations of DNA and RNA characteristics as related to drug response."*

and pharmacogenetics (PGx) as

> *"[…] a subset of pharmacogenomics and […] the study of variations in DNA sequence as related to drug response."*

The terms pharmacogenomics and pharmacogenetics are often used synonymously because they both investigate genetic influences on a drug's metabolism and drug response. A gene involved in drug metabolism is often referred to as a pharmacogene.

It is important to differentiate between genetic diagnostics and PGx testing. Genetic diagnostics is a discipline within the field of genetics that investigates whether a person is a carrier of a particular mutation that causes a hereditary disease (e.g. the predisposition to a certain cancer type) and therefore

aims at preventive measures. In contrast, PGx testing investigates the variability of expression in genes relevant for drug response [30].

DNA and Single nucleotide polymorphisms

If changes occur in the base sequence of a coding region of a gene (exon), this can lead to an amino acid exchange, i.e. a different amino acid is incorporated into the protein than was intended in the reference sequence. This can affect the function of the affected protein. Changes in the base sequence can also occur in non-coding regions of a gene (intron). This can then affect, for example, how often or whether a gene sequence is translated into a protein at all.

An allele refers to a DNA sequence that occurs in two or more variants at a specific location in the genome. The reference sequence is the *wild type* whereas the others sequences are genetic variations mostly based on mutations within an allele on the same gene. If the prevalence of a genetic alteration involving a single base position is less than 1% within a given population, it is called a point mutation. If genetic alterations occur more than 1% within a given population, they are called single nucleotide polymorphisms (SNPs) [30]. SNPs are pivotal for the manifestation of a phenotype and they vary considerably between individuals.

Ethnicity

SNPs occur in different frequencies depending on the population [31]. Motulsky et al. [28] discovered variants of the enzyme Glucose-6-phosphate dehydrogenase (G6PD) in different ethnic groups. G6PD is involved in the redox reactions of hemoglobin. A deficiency in the activity of the enzyme can result in hemolytic anemia (aka favism), especially when fava beans and certain drugs are consumed. Rasburicase, for instance, is contraindicated in G6PD deficient patients with or without chronic non-spherocytic hemolytic anemia [32]. Overall, the average G6PD deficiency is estimated at 5%. However, in malaria-endemic countries such as those in Asia and Africa, the average frequency can be as high as 30% or more in certain populations [33] as G6PD deficiency is associated with protective functions.

Actionability

Genetic variation is natural and therefore almost every patient is affected. In contrast to a drug-drug interaction (DDI), health care professionals (HCPs) should also consider a drug-gene interaction (DGI). Similar to a DDI, not all DGIs need an action. This depends both on the genetic code of the protein and the substance to be metabolized and finally, results in different levels of actionability. An actionable genetic variation refers to the genetic variation which calls for “action” depending on the drug taken. In contrast, a non-actionable genetic variation is one that is present and does not correspond to the *wild type*, but it does not require an action. By screening big populations, it was demonstrated that the vast majority of patients carry a so-called actionable pharmacogenes [34-36].

Example: clopidogrel

While thinking of DDIs and DGIs as two separately running processes, one has to be cautious. It is very possible that drug-drug-gene interactions (DDGI) occur. An illustrative example is clopidogrel, which has been the target of many PGx studies [37-39]. In the case of clopidogrel intake by a patient who is a *CYP2C19* IM, the activation of the prodrug clopidogrel into the active metabolite is constrained. In case of an acute coronary syndrome or a percutaneous coronary intervention, the Clinical Pharmacogenomics Implementation Consortium (CPIC) [40] recommends avoiding the standard dose of clopidogrel and instead of using prasugrel or ticagrelor in patients with *CYP2C19* IM. In addition to clopidogrel, these patients might also be taking omeprazole, a proton pump inhibitor. Omeprazole is a potent *CYP2C19* inhibitor thereby causing the already constrained enzyme to work even less, i.e. turning it into a PM. This phenomenon of a DDGI is called phenoconversion [41, 42]. To date, electronic systems have rarely been able to integrate DDGIs sufficiently, thereby illustrating an important gap that needs to be bridged by an HCP.

4. Pharmacogenetic information

The Pharmacogenomics Knowledge Base (PharmGKB) [43] is an expert-curated knowledge base that collects and disseminates information on drug-gene interactions (DGIs). The website (https://www.pharmgkb.org/) is publicly available and supports researchers and clinicians in the interpretation of human genetic variation concerning drug response. The information available includes prescribing information from clinical guidelines, curated pathways, pharmacogene summaries, annotations on associations between genetic variants and drug responses as reported in the literature, and drug labels containing PGx information [10].

Guidelines

Guidelines on PGx are generated by research consortia and refer to drugs in relation to different possible genetic variations. The recommendations on PGx variants are very specific, providing recommendations on drug switches and dosage adaptations. PharmGKB provides clinical guideline annotations by using the levels of evidence "high" (level 1A and 1B), "moderate" (level 2A and 2B), "low" (level 3), and "unsupported" (level 4). The two major consortia at present are the Clinical Pharmacogenetics Implementation Consortium, CPIC (https://cpicpgx.org/), and the Dutch Pharmacogenetics Working Group, DPWG (https://www.knmp.nl/media/1058).

The DPWG was founded by the Royal Dutch Pharmacists Association in 2005 and provides about 50 therapeutic recommendations on DGIs. The consortium is composed of a multidisciplinary team of 14 members. Besides the development of PGx-based therapeutic recommendations, the DPWG aims to assist drug prescribers and pharmacists in the integration of PGx recommendations into practice. The CPIC was set up as a joint project between PharmGKB and the Pharmacogenomics Research Network (https://www.pgrn.org/) and it is funded by the National Institute of Health. It aims to facilitate the use of PGx testing for patient care by addressing the barriers to clinical implementation. The CPIC creates, maintains, and publishes freely available, peer-reviewed, evidence-based, updatable, and detailed gene and drug guidelines for clinical practice. The 26 guidelines (as of 31.03.2022) on more than 40 drug-gene or drug group-gene combinations are always structured the same way and each guideline is published in the *Journal of Clinical Pharmacology and Therapeutics*. In 2017, Bank et al. [44] compared both guidelines and discovered slight discrepancies in methodology and therapeutic recommendations, such as the translation of *CYP2D6* with an activity score of 1.0, which is translated to a phenotype of NM by CPIC and IM by DPWG. Although the aim of both consortia is very similar, it is important to be aware of different recommendations when working with both guidelines.

Further existing guidelines on PGx from other countries comprise the French National Network of Pharmacogenetics (RNPGx) guideline, the Spanish Pharmacogenetics and Pharmacogenomics Society (SEFF), the Spanish Society of Medical Oncology (SEOM), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS).

In April 2022, the PharmGKB counted 73 recommendations by CPIC, 63 recommendations by DPWG, and 26 recommendations by other consortia.

Drug labels

The drug label (DL) (aka summary of product characteristics) is one of the sources for an HCP to check for PGx information. The DL includes general guidance without giving any concrete recommendations on dosage adaptations or drug changes, neither do they refer to concrete genetic variants but only gene-drug combinations. In Switzerland, every drug product must pass a rigorous examination performed by Swissmedic. Swissmedic takes most decisions in analogy to the directories of the European Medicines Agency (EMA), but not always. Being able to decide on certain laws autonomously gives Switzerland a special status within Europe. All Swiss DLs are publicly accessible and are available on www.swissmedicinfo.ch.

The PharmGKB has defined the four PGx levels "Testing required", "Testing recommended", "Actionable PGx", and "Informative PGx" to classify PGx information mentioned in DLs according to the need for action [11]. PharmGKB evaluated DLs from the regulatory authorities Food and Drug Administration (FDA), EMA, Pharmaceutical and Medical Devices Agency (PMDA), and the Health Canada/Santé Canada (HCSC). Since 2019, DLs approved by Swissmedic have also been integrated into PharmGKB, thereby allowing a comparison of DLs across different regulatory authorities.

MediQ

MediQ (https://www.mediq.ch/) is an interaction database where active ingredients or drug names are checked for DDIs. In addition (and in contrast to many other databases on DDIs), phytopharmaceuticals, genetic polymorphisms, and foods and stimulants are also included in the database. Thereby, genetic polymorphisms are listed as phenotypes (e.g. *CYP2C19* UM). Because MediQ checks interactions only by comparing two components at a time, an overall interpretation of a drug-drug-gene interaction in a patient with polypharmacy is not possible and has to be interpreted by an HCP.

5. Pharmacogenetic testing

There are different approaches to accessing the PGx profile of a patient. Based on the various test options, a PGx profile can be obtained by testing reactively or pre-emptively, conducting a single gene or a panel test, or applying advanced technologies such as whole genome sequencing. Table 2 gives an overview of different PGx tests. In the following, the background for single gene testing and PGx panel testing shall be further developed.

Table 2 Different PGx tests adapted from the joint working party "Personalized Prescribing", UK [45]

	PGx gene panel	***Gene targeted***	***Gene targeted at point of care***	***Large gene panels with secondary PGx targets***	***Whole genome sequencing***
Turnaround time	3-7 days	24-72 hours	<24 hours (can be 30 minutes)	7-14 days	4-6 weeks
Definition	Panel of several genes involved in the ADME process of a drug	Test of one single gene	Test of a single gene in secondary care/clinics	Panel of several genes, of which pharmacogenes only represent a fraction	A comprehensive method of analyzing the entire genomic DNA of a cell at a single time by using sequencing techniques such as Sanger sequencing, shotgun approach or high-throughput next-generation sequencing
Example	*Variant-targeted SNP panel (e.g. Stratipharm, humatrix AG)*	*Loop-mediated isothermal amplification testing for DPYD*	*Algorithm for warfarin guiding*	*DPYD testing added to large cancer panels*	*Short-read sequencing for CYP2D6*
Advantages	Simultaneous testing of multiple PGx targets to inform future prescribing; cost-effective in long term	Rapid; targeted; inexpensive	Rapid; targeted; technology advances may lower costs	Cost-effective; easily incorporated into existing clinical procedures	Optimizes use of existing data
Disadvantages	High cost; implementation across all health care sectors; requires linked electronic health care records; treatment algorithms may change as PGx evidence develops	Multiplexing is more challenging	Different procedure (requires training of clinical staff)	Limited applications (may only be relevant for a subset of patients)	Requires bioinformatics pipeline and interpretation; implementation issues for PGx panel testing apply

Legend: ADME = absorption, distribution, metabolism, and excretion; DPYD = dihydropyrimidine dehydrogenase; SNP = single nucleotide polymorphism

5.1. Single gene testing

For a few drug-gene interactions (DGIs), strong actionable genetic variants are available, e.g. for abacavir and the gene *HLA-B*57:01*. This DGI leads to a high risk of severe hypersensitivity reactions and should therefore be avoided. Most drug labels require a genetic test before the intake of abacavir [12]. This procedure is called pre-emptive PGx testing and it has been suggested, especially in the case of HLA alleles, that HLA-typing (pre-emptive testing for a specific HLA allele) may reduce the associated ADRs by avoiding exposure of carriers to certain HLA alleles [14.] In the case of abacavir, this practice is supported by the findings of "PREDICT-1" [13, 14]. Besides abacavir, there are other examples of clinically applied drugs (e.g. carbamazepine [46], allopurinol [47], or oxcarbazepine [48]) where ADRs are assumed to be associated with HLA alleles.

5.2. Pharmacogenetic panel testing

Besides patients suffering from ADRs, some patients experience no therapeutic effect, i.e. a therapy failure (TF). According to Roden et al. [49], pre-emptive PGx panel testing comprises an approach where PGx testing is applied for multiple genetic variants influencing either the efficacy or safety of drug response. The results are saved in an electronic system and can later be incorporated into a therapeutic decision for a new pharmacotherapy. Often ADRs, as well as TF, occur not only in one drug but in several. In both cases, it can be worthwhile to conduct a PGx test that covers several genes involved in pharmacokinetics (PK) and pharmacodynamics (PD), a so-called PGx panel test. In the context of a PGx panel test, there is often talk of "pre-emptive" PGx panel testing, i.e. before taking a therapeutic decision. Especially in psychiatry, many patients experience an insufficient therapeutic effect and therefore undergo numerous trial-and-error sessions. Because there are many pharmacogenes relevant for psychiatric drugs, the hitherto existing adoptions of PGx-guided treatment can be mostly found in psychiatry [15, 16].

To date, several advantages of pre-emptive PGx testing have been demonstrated [4, 5, 50] with the need of further implementation efforts. Notably, in the UK, physicians have joined to write a report on personalized prescribing by the application PGx to improve patient outcomes [45].

The clinical benefit of pre-emptive PGx testing is still controversial. Although considered one part of personalized medicine [51, 52], there are also voices saying that it is too early for implementation of PGx testing in the medical routine [53]. Despite many barriers to overcome and many resources lacking, a change in the health care landscape can be observed. We need pragmatic resources to overcome gaps and challenges in the changing landscape of pre-emptive PGx testing in primary and specialty care now to show the cost-effectiveness in the long-term [50]. Besides evidence on actionability [34-36] for selected drugs, studies have been set up to show the feasibility of the implementation of PGx testing in a primary care setting by pharmacists [3, 54-57].

5.3. Clinical decision support systems

The field of PGx is vast, extremely complex, and above all, constantly evolving. For the promotion of PGx knowledge, the maintenance of an electronic health record (EHR) is crucial [58]. However, as an EHR substitutes the paper-based reports this is by far not sufficient to enable HCPs in applying PGx in clinical practice. HCPs must be aided with a clinical decision support system (CDSS) which ideally can be linked to the EHR. In addition to assistance provided by a CDSS to HCPs, the EHR is essential for sustainable storage of PGx data. To make a real-world impact and to ensure widespread implementation of PGx panel testing, there is no way around a sophisticated CDSS. As PGx expert team, we searched the market for a company providing genotyping as well as a corresponding CDSS to be used by the pharmacist.

The commercial tool: Stratipharm

With the developing knowledge on genetic variants influencing the pharmacokinetics and/or pharmacodynamics of frequently applied drugs, multiple providers are now offering PGx assessment using DNA isolated from buccal swabs. One of the commercial products is Stratipharm (humatrix AG, Pfungstadt, Germany, https://www.stratipharm.de). Stratipharm offers genotyping (based on the DNA obtained from a buccal swab) in combination with an advanced evidence-based interpretation of the genotype. The service is available for accredited physicians and pharmacists in German-speaking countries (Germany, Austria, Switzerland). The commercial tool covers almost 100 genetic variants corresponding to 30 genes of pharmacogenetic relevance that encode the most relevant drug transporters and metabolizing enzymes, but also a selection of drug targets, see Figure 2 (details on genes, SNPs, and positions are specified in the appendix). The interpretation of the genotype is based on current and systematically updated evidence reviewed by experts. The resulting recommendations for a single drug in view of the individual genotype are categorized as "Hinweis" (*Engl.*: note, problems could arise and careful monitoring is needed), "Verdacht" (*Engl.*: suspicion, high probability for problems, change of dose or drug needed) or "Gefahr" (*Engl.*: danger, risk for an acute problem, drug to be avoided or used with utmost precaution and/or dose adaption). To ease patients' understanding, a traffic light system is used to visualize medications with "note" in yellow, "suspicion" in orange, and "danger" in red. Moreover, the service comprises a complete profile of the tested genes and their variants as well as an individualized list of concerned substances.

☑ ABCB1	☑ ABCG2	☑ ADRB1	☑ ADRB2	☑ COMT	☑ COQ2
☑ CYP1A2	☑ CYP2B6	☑ CYP2C8	☑ CYP2C9	☑ CYP2C19	☑ CYP2D6
☑ CYP3A4	☑ CYP3A5	☑ DPYD	☑ GNB3	☑ GSTP1	☑ HLA-A
☑ HLA-B	☑ HMGCR	☑ HTR2A	☑ IFNL3	☑ ITPA	☑ MTRNR1
☑ NAT2	☑ OPRM1	☑ SLC19A1	☑ SLCO1B1	☑ TPMT	☑ VKORC1

Figure 2 Genes tested for by humatrix AG (Stratipharm)

5.4. Challenges of pharmacogenetic testing

Despite the opportunities offered by PGx, prevailing challenges still need to be addressed. From a global point of view, Chenoweth et al. [59] formulate ten different challenges for the application of PGx in terms of personalized medicine. Table 3 provides an overview.

Table 3: Challenges of global pharmacogenomics, adapted from Chenoweth et al. [59]

1	There is no global network of experts to help drive basic PGx research and clinical implementation.
2	Mechanistic understanding of PGx phenotypes is hindered by the lack of large data sets and available biosamples.
3	Compared with common genetic variation, few is known regarding the impact and clinical actionability of rare genetic variation.
4	Models (e.g. genome-wide association studies, GWAS) are underutilized to understand PGx variation.
5	Validated biomarkers are an untapped resource to improve PGx discovery and implementation
6	Special and diverse populations are understudied.
7	Many PGx tests are not standardized, reimbursed, or regulated, limiting their clinical utility.
8	Successful widespread PGx implementation is limited by a lack of evidence of clinical utility and cost-effectiveness studies.
9	Education and advocacy initiatives are needed to increase the adoption of PGx
10	Additional challenge: The threshold for clinical actionability based on cell-free DNA testing is unknown.

As the scope of this thesis covers merely a part of the prevailing challenges, only a selection thereof (namely challenge 7, 8, and 9) is developed in the following.

Limited evidence for the clinical utility of PGx testing

A major obstacle to the translation of knowledge about PGx variability into practice is the lack of studies on clinical utility for PGx testing. Although numerous associations of genetic variations with altered drug response have been demonstrated and guidelines on drug management in case of gene variations are available, the practice of PGx (testing) is still discussed due to missing prospective randomized controlled trials (RCTs). Up to date, prospective RCTs have been compulsory to show the effectiveness of new tests. However, if one compares a PGx test with a non-genetic diagnostic test where no RCT was needed, this approach appears unjustified as the inclusion of renal and hepatic insufficiencies into therapeutic decision-making did not need evidence from RCT. One could argue that non-genetic diagnostic tests are much cheaper; however, they have to be repeated several times in contrast to genetic tests [60].

In consequence, the question remains, whether one needs RCTs to show the benefit of PGx testing. In fact, there is sufficient evidence to go for PGx testing in a selected set of patients. Whereas clinical trials generate evidence for the efficacy of interventions in a controlled setting, case reports yield evidence

for effectiveness in a real-world setting. Even if case reports provide low to no evidence for hereditable factors contributing to the susceptibility, they can help to discover underlying mechanisms, especially if the ADR is rare (rare genetic variant) and/or if the drug is given to a small number of patients (rare disease). In addition, case reports are also crucial for the improvement of the education of HCPs [61].

Awareness and knowledge of PGx and PGx testing

To date, most HCPs and patients are not aware of the high prevalence of actionable PGx variations for common drugs [50].

For HCPs, being aware of the significance of a PGx test means being able to appraise [50]

- the appropriateness of the specific genes and variants detected (e.g. *SLCO1B1* is tested for statins whereas *PROM2* is a disease-related gene),
- the robustness of testing (e.g. whether the copy number variation is tested for in *CYP2D6*),
- how test results are documented (e.g. with a PGx profile or with a substance query directly deviating from the available phenotypes),
- how test results are available (e.g. only to the patient because of data protection),
- what kind of clinical guidance is provided (e.g. current updates),
- cost and reimbursement possibilities (e.g. whether the patients have to pay all by themselves),
- the turnaround time for test results (e.g. one day or 14 days) [50].

One important reason for the missing awareness in HCPs is that they do not know about resources on evidence-based guidance for the interpretation of a PGx test (e.g. PharmGKB). The goal is not for every clinician to become a geneticist, but clinicians need to be ready for the use, interpretation, and application of PGx data in practice [50].

Moreover, the current state of education on PGx for either pharmacists or physicians is not as thorough as needed for the implementation and practice of PGx. In Switzerland, PGx is taught as part of the pharmacology curriculum. However so far, PGx mainly features in advanced education [62-64]. Kuzelicki et al. [65] showed that the majority of the study programs in global schools of medicine, pharmacy, nursing, and other HCPs include education on PGx; however, not as a separate subject.

In the end, the patients will decide whether they like PGx. Just as awareness strategies must be sought for HCPs, the same must be done for patients. Patients' perspectives on commercial PGx panel testing have been evaluated [66, 67], with the call for further research.

Lack of standard operating procedure for PGx testing

When looking into clinical practice, besides reimbursement and regulations for PGx testing, also standard operating procedures (SOPs) for PGx testing are still lacking to a large extent. Possible reasons are the great complexity of PGx and the lack of collaborations between medical and technological

organizations not allowing the necessary information transfer from literature into clinics [68]. Nonetheless, the development of an SOP for PGx testing was regarded as important initial step in this thesis.

5.5. Pharmacist-led pharmacogenetic testing – a chance

Recently, numerous attempts have been taking place to overcome the barriers. Belief in the clinical utility of PGx, the setup of EHRs, the implementation of interdisciplinary education structures as well as the building of interdisciplinary networks for exchange on PGx have been stated as enablers of PGx testing [69]. Additionally, the pharmacist as a potential provider of PGx testing and counseling is increasingly being discussed. The American Society for Health-System Pharmacists (ASHP) made a statement on the pharmacist's role in clinical pharmacogenomics [70], where they appraised the pharmacist as uniquely positioned to lead interprofessional structures for the translation of PGx testing in patient care. Not only do they see a role in the pharmacist, but they also see the rational, ethical use, and clinical application of PGx in the responsibility of the pharmacist. In the UK [50] and the Netherlands [45, 69], studies have revealed the emerging role of the pharmacist in the implementation of PGx testing. Trained clinical pharmacists are especially well-positioned to implement PGx testing, considering their expertise in pharmacokinetics, pharmacodynamics, and patient care [71]. With their dedication to medication surveillance, pharmacists are leading candidates to manage requesting PGx testing, recording PGx results, and applying the PGx guidelines [3]. Application of PGx testing demands a comprehension of the influence of genetic variations on drug response (i.e. PK and PD) in combination with multiple further factors (adherence, comorbidities, renal function, etc.). It seems that the pharmacist is well suited to take this responsibility. In the following chapter, an example of a large European study on PGx testing including the competencies of pharmacists shall be shown.

6. The PREPARE study

U-PGx consortium

"Making actionable PGx information and effective treatment optimization accessible to every European citizen."

The U-PGx consortium

The Ubiquitous Pharmacogenomics (U-PGx) consortium (https://upgx.eu/) comprises 17 universities from different European countries working on the implementation of PGx testing in patient care. The consortium is coordinated by Leiden University Medical Care (LUMC) in the Netherlands and aims to focus on the challenges of PGx testing by addressing the topic ubiquitously (all over Europe), setting up a large study (the PREPARE study), providing educational material, and curating guidelines on PGx (DPWG Guidelines).

Because this large European study was repeatedly referred to for further decisions during the thesis, a brief overview shall be provided hereafter.

Pilot study

Before the start of the PREPARE study, a two-year pilot study in 200 patients was conducted in the Netherlands [55]. Community pharmacists could dispense a free PGx test for patients with a prescription for a selection of drugs. The majority of the patients received an incident prescription on atorvastatin (n = 115), simvastatin (n = 29), amitriptyline (n = 15), citalopram (n = 7), escitalopram (n = 3), nortriptyline (n = 17) or venlafaxine (n = 14) and the PGx test covered eight genes, including 40 variants (*CYP2C9, CYP2C19, CYP2D6CYP2D6, CYP3A5, DPYD, SLCO1B1, TPMT* and *VKORC1*). The results were transmitted to the pharmacist as well as to the physician. The PGx test results revealed an actionable test result for 90% of the patients, of which 31% needed therapeutic intervention. Up to 90% of the suggested recommendations were adopted. The pilot study was able to show the feasibility of pre-emptive PGx testing in the community pharmacy [55].

Study Design

The large European study PREPARE (PREemptive Pharmacogenomic testing for prevention of Adverse Drug Reactions) was launched in October 2016. The program was unique in its multicenter, multigene, multidrug, multi-ethnic, and multi-health-care system approach. The PREPARE study aimed for a 30% regression of ADRs with PGx testing. Seven European countries were included and 8100 patients were recruited over six years. Patients were randomized either into the cohort of standard care or into the cohort of additional PGx testing. Pharmacists and physicians received online training on PGx. As tools, they used a safety code system for the patients and a diagnostic report tool for HCPs. In contrast to many previous studies based on the CPIC guidelines, the PREPARE study applied the guidelines from the DPWG. Patients were asked to provide a blood or saliva sample which was analyzed for up to 50 variants

across 13 important pharmacogenes and genotyping was performed with an array specifically designed for the PREPARE study using the LGC SNPline platform. Patients were recruited at their first prescription of a drug for which a DPWG dosing recommendation was present. Therapeutic areas comprised primary care, general medicine, cardiology, oncology, psychiatry, neurology, and transplantation. To assess the primary composite outcome of ADRs, a follow-up was added at 4 weeks, 12 weeks, and the end of the study. The recommendations from the PGx results that were relevant to the individual patient were included in the written PGx report to support the HCPs [64].

Education

In the education part of the PREPARE study [64], an e-learning based knowledge platform was developed. Lectures covered the main topics (basics of PGx, drug metabolism, drug dosing, targeted therapies, regulations and guidelines for PGx diagnostics in drug development and pharmacovigilance, companion diagnostics, obligatory genetic tests, good genomic practice, and PGx information in drug labels) necessary for the implementation and practice of PGx in the patient setting. It was offered to physicians, pharmacists, and post-academics.

CDSS

One of the great challenges of the U-PGx project consisted in the development of a flexible clinical decision support system (CDSS) [72]. The CDSS had to meet the requirements of different workflows, different languages, and PGx results presented on digital, paper-, or mobile-based tools. The goal of the CDSS was that all the HCPs could access the PGx recommendations by scanning the QR code of the personal safety-code card that each patient received. The QR-code seemed a simple but powerful solution. Nevertheless, a lot of time had to be invested, first for the setup and then for the maintenance of the CDSS, especially the mapping of raw data on genetic variants with the interpretation of the corresponding phenotype. Furthermore, a lot of time had to be invested at the user level for the HCPs to be sufficiently trained to apply the CDSS in clinical practice. Though, it has been shown that HCPs – indeed, pharmacists (96%) more so than general practitioners (68%) – were able to record PGx information into the EHR, and therefore, almost all patients had access to their PGx results for therapeutic decision making [3].

7. Rationale, goal and approach of thesis

Rationale: Pharmacist-led PGx testing and counseling

To date, PGx is not standard in primary care in Switzerland. The Federal Act on Human Genetic Testing (Gesetz für genetische Untersuchungen am Menschen, GUMG) [73] currently only allows physicians to initiate PGx testing as part of their therapeutic decision. PGx testing in Switzerland can be applied with reimbursement by health insurance for only five substances defined by the Swiss Society for Clinical Pharmacology and Toxicology (Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie, SGKPT) [74]. In detail, the five substances comprise abacavir (to exclude *HLA-B*5701*), carbamazepine (to exclude *HLA-A*3101* and *HLA-B*1502*), 6-mercaptopurin/azathioprine (to exclude *TPMT* IM or PM Status), for 5-fluoruracil/capecitabin (to exclude *DPYD* IM or PM Status), and irinotecan (to exclude *UGT1A1* with low expression levels). The Federal Law on Human Genetic Testing (GUMG) has been revised in 2018. A new differentiation is made between genetic testing in medical and non-medical fields. In general, investigations in the medical field are reserved to physicians whereas pharmacists and other HCPs are able to start investigations in the non-medical field (e.g. ancestry). However, the Federal Council has the option of attributing certain investigations in the medical field to non-medical specialists (e.g. pharmacogenetic examinations to pharmacists) [75]. Currently, the legal ordinance on human genetic testing (Verordnung über genetische Untersuchungen am Menschen, GUMV) as of 14 February 2007 [76] is being revised and final agreements for law enforcement are expected.

Although knowledge of PGx has already been available for a long time [1], awareness of PGx among HCPs has only emerged in the last few years, as shown by the efforts to implement PGx services in other European countries, such as the Netherlands [77] and the UK [5]. Experts agree that the time for pre-emptive PGx panel testing is now, thereby stressing that the remaining gaps must be closed, and missing resources must be made accessible [50]. Even ten years ago, pharmacists expressed their willingness to learn more about PGx [7].

All these facts urged the Pharmaceutical Care Research Group to also strive for implementation of PGx in Switzerland.

Goal: Implementation of PGx in pharmaceutical care

To prepare for the implementation of PGx in pharmaceutical care, the goals of this thesis were to identify PGx information for clinical practice and to develop a SOP for pharmacist-led PGx testing and counseling in primary care. The thesis approaches this goal in two projects.

Approach: Pharmacist-led PGx testing and counseling in Switzerland

The first project focused on pharmacogenetic information for clinical practice. Swiss DLs were analyzed to get an overview of the current state of PGx-relevant information on metabolizing enzymes and

transporters as well as HLA risk alleles, to classify the recommendations provided to HCPs by the PGx levels as suggested by PharmGKB [11], and finally, to compare the respective PGx level with those provided in DLs authorized by agencies of other countries. Furthermore, studies investigating HLA alleles in relation to ADRs were summarized to give an overview of the evidence on the described ADRs and the investigated genetic factors, as an illustrative example.

In the second project, a case series with patients with adverse drug reactions (ADRs) or therapy failure (TF) was established. PGx panel testing was applied to determine the hereditable component of the patient's susceptibility of experiencing the observed ADRs or TF when taking substances known to be affected by PGx. The aim was the compilation of case reports to gather experience and later, develop a SOP for "PGx testing and counseling" in primary care. By presenting and discussing individual cases, where pharmacist-led PGx testing and counseling had been applied in primary care, the potential benefit of PGx to improve the efficacy or safety of a patient's pharmacotherapy was demonstrated. Finally, the PGx service was evaluated from the perspective of patients and their treating physicians.

A detailed overview on the projects is provided in the following chapter.

Project Overview

Project Overview Project A –Pharmacogenetic information for clinical practice

Project A aimed to identify pharmacogenetic information for clinical practice.

Project A1	**Pharmacogenetic information in Swiss drug labels - a systematic analysis** **Publication in *Pharmacogenomics J. 2021;21(4):423-34.*** [78] Health care professionals (HCPs) use drug labels (DLs) as reliable information about drugs. Swiss DLs were analyzed to give an overview on the currently available PGx instructions. **Aims**: ➢ to provide an overview of the current state of PGx-relevant information on metabolizing enzymes and transporters as well as HLA risk alleles in Swiss DLs, ➢ to classify PGx recommendations provided to HCPs in Swiss DL by the PGx levels as suggested by PharmGKB [11], ➢ to compare the respective PGx level in Swiss DL with those provided in DLs authorized by agencies of other countries.

Abstract

Implementation of pharmacogenetics (PGx) and individualization of drug therapy is supposed to obviate adverse drug reactions or therapy failure. Health care professionals (HCPs) use drug labels (DLs) as reliable information about drugs. We analyzed the Swiss DLs to give an overview on the currently available PGx instructions. We screened 4306 DLs applying natural language processing focusing on drug metabolism (pharmacokinetics) and we assigned PGx levels following the classification system of PharmGKB. From 5979 hits, 2564 were classified as PGx-relevant affecting 167 substances. 55% (n = 93) were classified as "actionable PGx". Frequently, PGx information appeared in the pharmacokinetics section and in DLs of the anatomic group "nervous system". Unstandardized wording, appearance of PGx information in different sections and unclear instructions challenge HCPs to identify and interpret PGx information and translate it into practice. HCPs need harmonization and standardization of PGx information in DLs to personalize drug therapies and tailor pharmaceutical care.

Project A2	**HLA-associated adverse drug reactions - scoping review** ***Publication in Clin Transl Sci. 2021;14(5):1648-58.*** [79] Alleles of the human leukocyte antigen (HLA) system have been associated with the occurrence of idiosyncratic adverse drug reactions (ADRs). Accordingly, it is assumed that pre-emptive testing for the presence of certain HLA alleles (HLA-typing) could prevent these ADRs in carriers. **Aim:** ➢ to perceive the current evidence for HLA-associated ADRs as an illustrative example.

Abstract

Alleles of the human leukocyte antigen (HLA) system have been associated with the occurrence of idiosyncratic adverse drug reactions (ADRs). Accordingly, it is assumed that pre-emptive testing for the presence of certain HLA alleles (HLA-typing) could prevent these ADRs in carriers. In order to perceive the current evidence for HLA-associated ADRs, we conducted a scoping review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The literature searches on PubMed and on Embase was carried out on the July 8 and 9, 2020, respectively. To be included in the scoping review, the studies had to investigate an association of any HLA-associated ADR with any small molecule approved and available on the Swiss market. We considered English and German primary literature published since 2002. A total of 149 studies were included, whereof most were retrospective, whereas one was a prospective randomized controlled trial. The majority of the studies (n = 33) described the association of *HLA-B*15:02* with carbamazepine. It was not possible to directly compare the studies, as they were too heterogeneous in terms of the ADR definition, the HLA alleles, the number of participants, and the study types. Therefore, we summarized the results in a descriptive manner. Even if an interpretation of the outcomes remains open, the descriptive overview revealed the prevailing complexity and uncertainty in the field. For the future, consistent definitions on the different phenotypes need to be established and applied and the reporting of association studies should follow a harmonized structure.

Project B – Pharmacogenetic testing of patients with adverse drug reactions or therapy failure - development of a standard operating procedure in primary care

Project B aimed to develop a standard operating procedure (SOP) for pharmacist-led PGx testing and counseling in primary care.

Project B1	**Case series - Pharmacogenetic testing of patients with unwanted adverse drug reactions or therapy failure – study protocol** (Clinicaltrials.gov: NCT04154553) With the developing knowledge on genetic variants influencing pharmacokinetics and/or pharmacodynamics of frequently applied drugs, multiple providers are now offering PGx testing using DNA isolated from buccal swaps. Stratipharm offers genotyping in combination with evidence-based interpretation of the genotype. For the development of a reliable SOP for PGx testing and counseling in primary care, a case series where PGx panel testing was applied to determine the hereditable component of the patient's susceptibility of experiencing the observed ADRs or TF was set up. **Aims**: ➢ to establish a case series of patients with adverse drug reactions (ADRs) or therapy failure (TF) where PGx panel testing is applied to determine the hereditable component of the patient's susceptibility of experiencing the observed ADRs or TF, ➢ to compile and discuss individual cases, where pharmacist-led PGx testing and counseling is applied in primary care, including: o cases, where PGx panel testing was applied reactively to patients with TF or ADR with substances known to be affected by PGx, o cases, where PGx panel testing was applied pre-emptively to patients with prescribed substances known to affected by PGx, o cases, where PGx panel testing was applied pre-emptively to patients with relatives with ADRs or TF with substances known to be affected by PGx, ➢ to develop a SOP for the pharmacist-led service "PGx testing and counseling".

Study description

Genetic makeup of a patient influences the efficacy and safety profile of a drug. This study is to summarize individual cases, where PGx has been applied during pharmaceutical care. Health-related data of patients experiencing TF or ADRs is collected and will then be supplemented with pharmacogenetic testing during pharmaceutical care in a study pharmacy. The patient data (diagnoses, medications and results of pharmacogenetic testing) is harmonized in order to generate a compilation of case reports. The primary objective is the compilation of case reports, where pharmacogenetic testing is applied to determine the hereditable component of the patient's susceptibility to experience therapy failure and/or adverse drug reactions. The experience with the compiled cases will be basis for the development of a reliable standard of procedure for pharmacogenetic testing in the community pharmacy. The cases will be supplemented with information on additional parameters reported in the literature to affect efficacy or safety of the respective drug.

The project was approved by the local ethics committee northwestern and central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, Hebelstrasse 53, 4056 Basel, eknz@bs.ch) (EKNZ-2019-01452) on 31.10.2019.

Project B2	**Enriching medication review with a pharmacogenetic profile - a case of tamoxifen adverse drug reactions** **Publication in *Pharmgenomics Pers Med*. 2021;14:279-86.** [80] One drug that has been extensively studied for the relevance of the patient's genetic predisposition is tamoxifen (TMX). Nonetheless, only little is known about the influence of the variability of other CYPs involved in the metabolism of TMX. **Aims:** ➢ to present the case of a patient, where ADRs with TMX had prompted the patient to do PGx testing, ➢ to reveal the added value of a medications review enriched with a large PGx panel, ➢ to show the complexity of integrating a PGx profile into a recommendation.

Abstract

Pharmacogenotyping is applied to determine the hereditable component of a patient's susceptibility to experience therapy failure and/or adverse drug reactions (ADRs). We present the case of a female patient diagnosed with breast cancer and treated with tamoxifen as recurrence therapy who experienced various ADRs. Pharmacogenotyping revealed variants in the cytochrome P450 (CYP) enzymes *CYP2D6*, *CYP2C9*, and *CYP2C19*. The observed genotype was associated with a risk for lower tamoxifen efficacy. Aside from the tamoxifen therapy, the co-medication was reviewed for the influence of the patient's pharmacogenetic profile. As a result of this pharmacist-led medication review with pharmacogenetic analyses, concrete genotype-driven recommendations for the treating gynecologist were compiled. This case revealed the added value of a large pharmacogenetic panel and the complexity of integrating a pharmacogenetic profile into a recommendation.

Project B3	**Is pharmacogenetic panel testing applicable to low-dose methotrexate in rheumatoid arthritis? - a case report** **Publication in *Pharmgenomics Pers Med. 2022.*** [81] Methotrexate (MTX) is another drug where explanations for the interindividual differences in drug response may be due to its complex metabolism. Various enzymes and transporters that are part of the MTX metabolism are described and those, where genetic variants have been linked to changes in MTX efficacy or safety are highlighted. **Aims**: ➢ to recap the pathway of MTX and, simultaneously, highlight genetic variations influencing transport and metabolism of MTX, ➢ to discuss the case of a patient who was treated with MTX, suffered from ADRs, and obtained a reactive PGx panel testing.

Abstract

Pharmacogenetic (PGx) panel testing could help to determine the heritable component of a rheumatoid arthritis (RA) patient's susceptibility for therapy failure and/or adverse drug reactions (ADRs) from methotrexate (MTX). Considering the literature mentioning the potential applicability of PGx panel testing within MTX regimens, we discuss the case of a patient who was treated with MTX, suffered from ADRs, and obtained a reactive PGx panel testing. We used a commercial PGx panel test involving the ABC-transporters P-glycoprotein (P-gp; gene: *ABCB1*), and breast cancer resistance protein (BCRP; gene: *ABCG2*), the solute carriers reduced folate carrier 1 (RFC1; gene: *SLC19A1*), and organic anion transporting polypeptide 1B1 (OATP1B1; gene: *SLCO1B1*), and the enzymes inosine triphosphatase (*ITPA*), and glutathione transferase P1 (*GSTP1*). In addition, we genotyped the patient for the enzymes 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR)/inosine monophosphate (IMP) cyclohydrolase (gene name: ATIC), gamma-glutamyl hydrolase (gene name: GGH) and methylenetetrahydrofolate reductase (gene name: *MTHFR*). The PGx profile of the patient revealed genetic variants in *SLC19A1*, *ABCB1*, and *MTHFR*, which may explain the ADRs experienced during the treatment with MTX and a potentially lower efficacy of MTX. Based on our interpretation of the PGx profile, we recommended the patient to avoid MTX in the future. The MTX pathway is complex, which makes the interpretation of genetic variants affecting metabolism challenging. A reactive PGx panel test was applicable to explain ADRs experienced during MTX treatment for a patient with RA. However, the clinical utility of PGx-guided MTX treatment in a primary care setting is still limited. In order to base a recommendation for MTX on PGx data, we need genome-wide association studies, large prospective multicenter studies and PGx studies, which analyze different multi-gene haplotypes and gene-drug-drug interactions for MTX.

Project B4	**Pharmacogenetic testing and counselling in the community pharmacy: mixed-methods study of a new pharmacist-led service** **Publication in *International Journal of Clinical Pharmacy. 2023.*[141]** Pharmacogenetic (PGx) testing and counseling in the community pharmacy is not routinely practiced. A comprehensive pharmacist-led service where PGx information is integrated into medication reviews is proposed. **Aim**: ➢ to evaluate the pharmacist-led service comprising PGx testing and counseling from the perspective of patients and their treating physicians.

Abstract

Background Pharmacogenetic (PGx) testing and counselling (short: PGx service) in the community pharmacy is not routinely practiced. We propose a comprehensive pharmacist-led service where PGx information is integrated into medication reviews.

Aim To evaluate the pharmacist-led service comprising PGx testing and counselling (PGx service) from the perspective of patients.

Method For this mixed-methods study, we conducted two follow-up interviews F1 and F2 with patients recruited for the PGx service in a community pharmacy after 1st of January 2020. The semi-structured interviews were held by phone call and covered understanding of PGx, the implementation of recommendations, handling of PGx documents (list of concerned substances and PGx recommendation), gain in medication knowledge, and willingness to pay for the PGx service.

Results We interviewed 25 patients in F1 and 42 patients in F2. Patients were generally able to understand and use results of the PGx service. At least one PGx recommendation was implemented for 69% of the patients. Handling of PGx documents ranged from patients having forgotten about the PGx results to patients consulting the list for every medication-related decision; the latter often expecting negative effects. Finally, 62% of the patients were willing to pay for the PGx service.

Conclusion For future PGx testing and counselling, HCPs should consider the patients' health literacy in a standardized way and use adequate communication skills to enhance the patient's understanding in PGx and to attenuate potential negative expectations.

Project A – Pharmacogenetic information for clinical practice

Project A1

The Pharmacogenomics Journal
https://doi.org/10.1038/s41397-020-00195-4

ARTICLE

Pharmacogenetic information in Swiss drug labels – a systematic analysis

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Received: 24 March 2020 / Revised: 18 August 2020 / Accepted: 5 October 2020

Abstract

Implementation of pharmacogenetics (PGx) and individualization of drug therapy is supposed to obviate adverse drug reactions or therapy failure. Health care professionals (HCPs) use drug labels (DLs) as reliable information about drugs. We analyzed the Swiss DLs to give an overview on the currently available PGx instructions. We screened 4306 DLs applying natural language processing focusing on drug metabolism (pharmacokinetics) and we assigned PGx levels following the classification system of PharmGKB. From 5979 hits, 2564 were classified as PGx-relevant affecting 167 substances. 55% ($n = 93$) were classified as "actionable PGx". Frequently, PGx information appeared in the pharmacokinetics section and in DLs of the anatomic group "nervous system". Unstandardized wording, appearance of PGx information in different sections and unclear instructions challenge HCPs to identify and interpret PGx information and translate it into practice. HCPs need harmonization and standardization of PGx information in DLs to personalize drug therapies and tailor pharmaceutical care.

Introduction

"One size fits all" is the common strategy of dose-finding studies and consequently, the standard of drug therapy. However, drug therapies may fail, and/or may induce considerable adverse drug reactions (ADRs). The influence of patients' genetic predispositions on drug response has been studied over decades and therefore, pharmacogenetics (PGx) is gaining attendance in patient-centered research and personalized medicine [1–3].

For the translation of PGx information into clinical decisions, health care professionals (HCPs) have to consider drug-gene interactions (DGIs) in addition to drug-drug interactions (DDIs). Similar to DDIs, not all DGIs require an intervention. The level of actionability depends on both the genetic variant of an enzyme and the metabolized substrate. Almost 100% of the population carry at least one actionable genetic variant [4, 5]. Consequently, it is expected that implementation of PGx into clinical decisions might be a strategy to reduce the substantial burden of ADRs [6], still representing a major concern in health care [7]. Considering the high number of drug-relevant genes and the multitude of available substances on the market, genetic variability potentially affects a large number of patients.

In this study, we focused on the drug label (DL), one of the first sources for HCPs to check for information on a drug. The Pharmacogenomics Knowledgebase (PharmGKB) [8] is an expert curated knowledgebase which collects and disseminates information on DGIs. The website (https://www.pharmgkb.org) is publicly available and supports researchers

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Supplementary information The online version of this article (https://doi.org/10.1038/s41397-020-00195-4) contains supplementary material, which is available to authorized users.

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Published online: 17 October 2020

Table 1 Definition of PGx levels of PharmGKB [10].

Nr.	PGx level	Definition
1	Testing required	The label states or implies that some sort of gene, protein, or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients. PharmGKB considers labels that state the variant is an indication for the drug, as implying a test requirement. If the label states a test "should be" performed, this is also interpreted as a requirement.
2	Testing recommended	The label states or implies that some sort of gene, protein or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended before using this drug. This recommendation may only be for a particular subset of patients. PharmGKB considers labels that say testing "should be considered" to be recommending testing.
3	Actionable PGx	The label may contain information about changes in efficacy, dosage, metabolism or toxicity due to gene/protein/chromosomal variants or phenotypes (e.g., "poor metabolizers"). Or, the label may mention contraindication of the drug in a particular subset of patients with particular variants/genotypes/phenotypes. However, the label does not require or recommend gene, protein or chromosomal testing.
4	Informative PGx	1. The label contains information stating that particular gene/protein/chromosomal variants or metabolizer phenotypes do not affect a drug's efficacy, dosage, metabolism, or toxicity. Or, the label states that particular variants or phenotypes affect a drug's efficacy, dosage, metabolism or toxicity, but this effect is not "clinically" significant. OR 2. The label appears or appeared on the FDA Biomarker List but does not currently meet the requirements to be assigned as "Testing required", "Testing recommended" or "Actionable PGx." PharmGKB annotates every label that appears on the FDA Biomarker list, regardless of whether we would otherwise annotate the label.

and clinicians in the interpretation of human genetic variation in relation to drug response. Information available includes prescribing information from clinical guidelines, curated pathways, pharmacogene summaries, annotations on associations between genetic variants and drug responses as reported in the literature, and DLs containing PGx information [9]. The PharmGKB has defined four PGx levels (see Table 1) to classify PGx information mentioned in DLs according to the potential for action [10].

Several groups have compared the information on PGx in DLs authorized by different agencies [11–14]. In the United States, the Food and Drug Administration (FDA) approves the DLs, and provides a table of pharmacogenomic biomarkers in DLs [15]. In Switzerland, Swissmedic approves all Swiss DLs before they become publicly available (www.swissmedicinfo.ch). The Swiss DL is organized in different sections with defined headings; however, no section is dedicated to PGx. For the DLs of Switzerland, no overview or comparison of PGx information in the DLs exists at this time. By analyzing the DLs, we will get an overview of the current state of PGx information helping us to identify inconsistencies and to suggest potential improvement for the future.

Accordingly, it was the aim of this project to provide a systematic analysis of the Swiss DL sections reporting PGx-relevant information on metabolizing enzymes and transporters as well as HLA risk alleles, to evaluate the instructions provided to HCPs on PGx information and finally, to compare the respective PGx level with those provided in DLs authorized by agencies of other countries.

Methods

Natural language processing (NLP)

We applied natural language processing (NLP). Terms used to search for PGx information within the DLs were gathered based on preliminary analysis of DLs (in German language), literature [16–18], and the AmiKoWeb website (https://amiko.oddb.org). The selected search terms to identify specific genes were related to genetic polymorphisms (defined as genetic variants with a prevalence of more than 1% in a population [3]) known to be involved in drug metabolism. An expert group (CJ, KS, KH, HMzS) selected 25 eligible word stems corresponding to 245 different search terms for the NLP (for details, see Supplementary Fig. 1). We used AmiKoWeb for the full-text search on 4th February 2019. All 4306 Swiss DLs available in German describing the 15,367 products on the Swiss market (including different dosages and package sizes) were screened for PGx information by NLP. The search identified 5979 hit sentences (corresponding to 606 chemical substances and 1399 different brand drugs) (Fig. 1). Supplementary Fig. 2 gives an overview of the primary NLP search.

Evaluation of the identified sentences for PGx-relevance

We examined all hit sentences for PGx-relevance. Any information related to a genetic polymorphism of an enzyme known to be involved in drug metabolism or drug

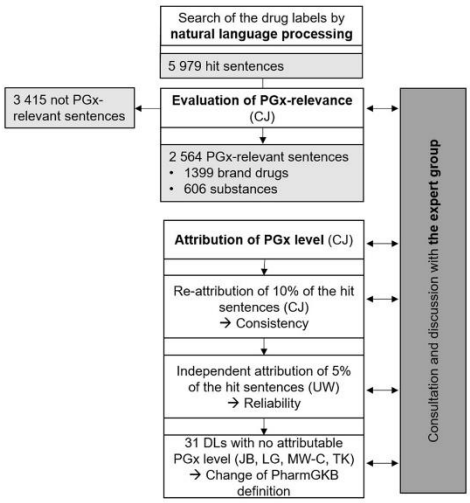

Fig. 1 Flow chart depicting the process of analysis. The natural language processing was followed by evaluation of the PGx-relevance as well as the attribution of the PGx level, which was both conducted under consultation of the expert group.

transport (pharmacokinetics) and any information on HLA risk types was considered PGx-relevant. We consequently excluded genetic mutations (prevalence <1%), disease-related gene defects (e.g., genetic hypercholesterolemia), disease-related chromosomal abnormalities (e.g., Philadelphia chromosome), nonhuman genetic factors (e.g., genotype of viruses), genes encoding proteins used for treatment selection (e.g., in oncology), and biomarkers related to a drug other than the referenced drug (e.g., in the case of an interaction).

Classification of the PGx-relevant sentences

The classification of the sentences in the identified DLs was based on the PGx levels proposed by PharmGKB [10] (Table 1). If one sentence in one DL resulted in a higher PGx level compared to other sentences in the same DL, the highest annotated PGx level was considered in the analysis. After the first annotation of PGx levels, 10% of the sentences were reannotated to evaluate consistency and 5% were independently annotated by a second person to test reliability. After each step, the expert group was consulted. We translated the PGx-relevant sentences into English and submitted them to PharmGKB. Final discrepancies were solved in collaboration with experts of the PharmGKB group (Fig. 1).

We checked the PGx-relevant sentences of the same chemical substances (indicated by the ATC code level 1) and in case of multiple brand products with the same text in the DL, we defined one reference DL (refDL); either we selected the original product (brand name) or we arbitrarily choose the first generic drug in the list. We refer to Supplementary Table 1 for details on the refDLs. We analyzed the PGx-relevant sentences and the refDLs by the section where the PGx information was located, the anatomic groups (indicated by the ATC code level 1 of the corresponding substance), and the biomarker mentioned in the concerned PGx-relevant sentence, respectively.

Annotations entered into the PharmGKB knowledgebase

PharmGKB applied their process of quality control to the translated DLs, annotated and entered them into the PharmGKB knowledgebase (for details see Supplementary Fig. 3).

Comparison of PGx levels with those of other regulatory authorities

We conducted a comparative analysis of the annotated PGx levels available on PharmGKB of selected DLs with US Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada/Santé Canada (HCSC), and Pharmaceuticals and Medical Devices Agency (PMDA), Japan. For the quantitative analysis, the PGx level was coded with points, with an increasing number of points for the severity of the PGx level, resulting in 1 point for "informative PGx" and 4 points for "testing required."

Results

PGx-relevant information in Swiss Drug Labels searched by NLP

From the 5979 identified hit sentences identified by the NLP search, 2564 sentences were classified as PGx-relevant. In total, 3415 sentences were excluded due to the lack of PGx-relevance. Most of the PGx-relevant sentences were part of the section on pharmacokinetics ($n = 1110$), followed by the precautionary measures section ($n = 839$). The other PGx-relevant sentences were distributed homogenously in the other sections (dosage/application, contraindications, interactions, adverse effects, or properties/effects). A small number of PGx-relevant sentences appeared in the sections on indication ($n = 3$), pregnancy ($n = 7$), or overdose ($n = 10$) (Fig. 2A). No PGx-relevant information appeared in any of the ten remaining sections, such as ability to drive or operate machines, preclinical data, or other hints.

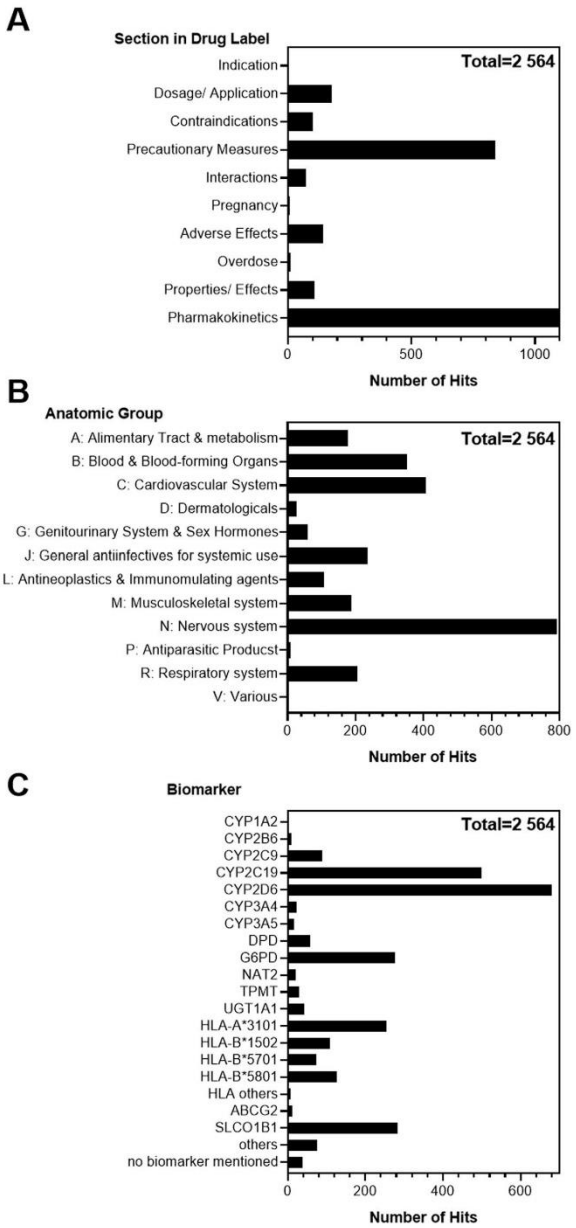

Fig. 2 Analysis of the 2564 PGx-relevant sentences. Appearance in the different drug label sections (**A**), in the anatomic groups (indicated by the ATC code) of the drug described by the drug label (**B**) and of the biomarker mentioned in the sentences (**C**). Data shown are total number of PGx-relevant sentences per category.

Most of the PGx-relevant sentences were found in the ATC group "N: Nervous system" ($n = 793$), followed by "C: Cardiovascular system" ($n = 408$), and "B: Blood and blood building systems" ($n = 352$). The lowest number of PGx-relevant sentences appeared in the ATC group "V: Various" ($n = 3$). No PGx-relevant sentences were

ATC-Code	Substance	Brand name	Biomarker	PGx-level	Indication	Dosage/ Application	Contrai-ndications	Precaution measures	Interactions	Pregnancy	Adverse Effects	Overdose	Properties/ Effects	Pharmaco-kinetics	SUM
A02BC01	Omeprazol	**Antramups®**	CYP2C19	3										■	1
B01AC04	Clopidogrel	**Plavix®**	CYP2C19	2		■		■					■	■	4
B01AC30	Clopidogrel, ASS	**DuoPlavin® 75/100 mg**	CYP2C19	3		■	■	■			■		■		5
C10AA07	Rosuvastatin	**Crestor®**	SLCO1B1	3		■	■	■						■	4
D11AX	Fluorouracil, Salicylsäure	**Actikerall®**	DPD	1				■	■					■	3
J01CF05	Flucloxacillin	**Floxapen®**	HLA-B*5701	3				■			■				2
J01EE01	SMX/ TMP	**Bactrim® forte**	G6PD	3				■		■					2
J05AF06	Abacavir	**Ziagen®**	HLA-B*5701	1	■		■	■					■		4
N06AB04	Citalopram	**Seropram®**	CYP2D6 & CYP2C19	3										■	1
R05DA20	DPH, Codeine	**Benylin® mit Codein N**	CYP2D6	3			■	■					■	■	4

CYP=Cytochrome; DPD=Dihydropyrimidinedehydrogenase; DPH=Diphenhydramin; G6PD=Glucose-6-Phoshate-Dehydrogenase; HLA=Human Leucocyte Antigene; SLCO1B1=Organic Anion Transporter 1B1; SMX/TMP=Sulfamethoxazol & Trimethoprim

Fig. 3 Drug label (DL) sections with PGx information. Ten examples of DLs indicating the different DL sections in which the information on PGx is given. The corresponding section is marked with black color. The last column shows the sum of sections that specify PGx information.

discovered in the ATC group "H: Systemic hormonal preparations" (Fig. 2B).

The PGx biomarker most frequently mentioned was the drug metabolizing enzyme CYP2D6 ($n = 679$), followed by CYP2C19 ($n = 499$). The drug transporter SLCO1B1 (OATP1B1), the enzyme glucose 6-phosphate dehydrogenase (G6PD), and the HLA-allele HLA-A*3101 were named in $n = 254$, $n = 277$, and $n = 284$ sentences, respectively. Overall, 76 PGx-relevant sentences referred to other biomarkers, e.g., IL28B. However, in 39 cases, PGx information was provided without mentioning any specific biomarker (Fig. 2C).

Analysis of the reference drug labels (refDLs)

Based on the PGx-relevant sentences, we defined 167 refDLs. Almost in all cases (166 of 167) the DL of the generics contained the same text as the original product. For the ATC code L01BC02 (fluorouracil), we defined two refDLs, because the texts of the DLs of Efudix® and Fluorouracil Labatec® differed in information. Of the defined refDLs, there were 17 combination products where PGx information was the same as for the mono products of each component. Therefore, these refDLs were not annotated separately. Moreover, there were four products (carbamazepine, escitalopram, fluorouracil, and codeine/acetaminophen) addressing more than one biomarker in the PGx-relevant sentences with different PGx levels.

The PGx information of the refDLs was identified in 10 out of 20 different sections in the DL. One example, where PGx-relevant information is given in multiple sections namely "indication," "precautionary measures," "contraindications," and "properties/effects" is abacavir (Ziagen®); for further examples see Fig. 3 (for details on all substances see Supplementary Table 1).

Most of the refDLs ($n = 92$ substances, 55%) were assigned to PGx level 3 "actionable PGx" and PGx level 4 "informative PGx" ($n = 26$, 16%). Only 9 (5%) or 4 (2%) DLs were assigned to PGx level 1 "testing required," or PGx level 2 "testing recommended," respectively. In total, 19 DLs (11%) could not be classified using the original definition of the PGx levels, as the information given did not meet the criteria proposed by PharmGKB, and 17 (10%) refDLs on combination products reported the same information as the mono product (Fig. 4A). Summarizing the PGx level annotated refDLs in anatomic groups (ATC code of level 1), revealed that PGx level 3 appeared most frequently (Fig. 4B). The anatomic group "J: general anti-infectives for systemic use" represented an exception as it contained abacavir (including three combination products), all labeled with PGx level 1. The same PGx level was attributed to carbamazepine, oxcarbazepine, codeine, and tetrabenazine as well as fluorouracil in the anatomic groups "N: Nervous system" and "L: antineoplastic and immunomodulating agents", respectively (Fig. 4C).

Looking at the specific biomarkers in the refDLs (Fig. 4D), CYP2D6 was most frequently mentioned ($n = 52$), followed by G6PD ($n = 35$). In total, 12 refDLs informed on PGx without mentioning a specific biomarker. Many refDLs stated two biomarkers, e.g., G6PD and CYP2D6 in Co-Dafalgan®, one accounting for acetaminophen and the other for codeine. Overall, biomarkers in drug-metabolizing enzymes predominated (Fig. 4E).

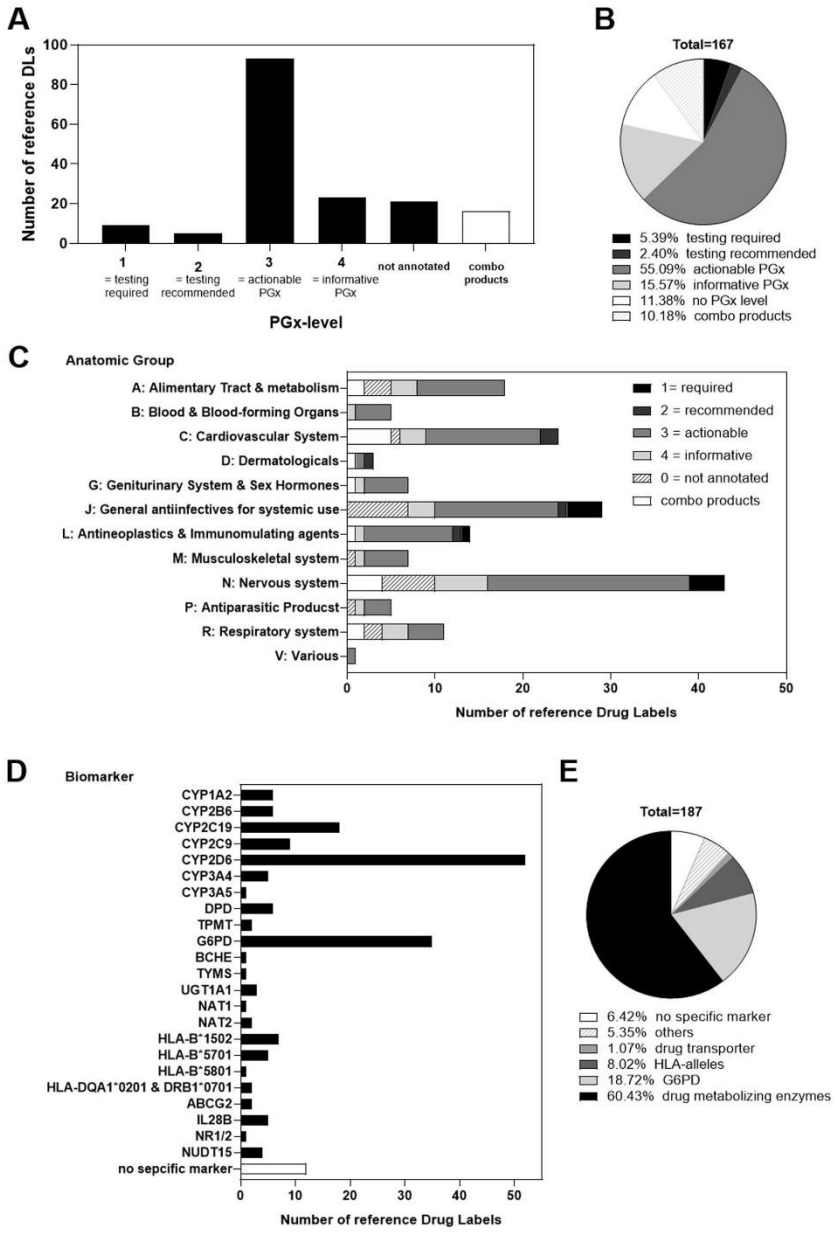

Fig. 4 Analysis of the reference drug labels (refDLs). Number of reference drug labels per PGx level (**A**, **B**), per anatomic group and the assigned PGx levels (**C**), and per biomarker (**D**, **E**).

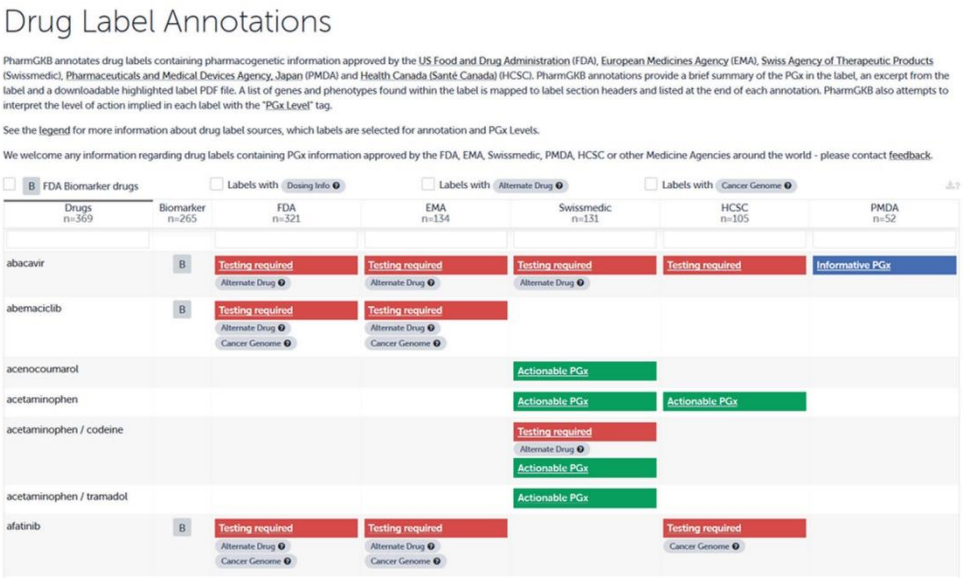

Fig. 5 Excerpt of the Drug Label Annotations on the PharmGKB website. Since 08/07/2019 the Drug Label Annotations include excerpts of the drug labels of the Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Swissmedic, the Health Care Service Cooperation (HSCS), and the Pharmaceutical and Medical Devices Agency (PMDA).

Annotations entered into the PharmGKB knowledgebase

The extracts of the Swiss DLs were translated and entered into the PharmGKB knowledgebase on 22.10.2019 (https://www.pharmgkb.org/labelAnnotations) and resulted in 131 annotations (Fig. 5). In addition, the collaboration with PharmGKB led to a new definition for PGx level 4 "informative PGx." The original definition of this category was "label mentioning a gene or protein involved in the metabolism or pharmacodynamics of the drug, with no information to suggest that variation in these genes/proteins leads to changes in drug response." Due to difficulties in our primary analysis, we started a discourse with PharmGKB, which finally resulted in an adaptation of the definition of PGx level 4 (published on 08/07/2019).

Comparison of PGx levels with those of other regulatory authorities

We compared the assigned PGx levels of the 126 uploaded DLs of Swissmedic with those authorized by other regulatory authorities, and observed that the majority was rated as "actionable PGx". This is also indicated, when determining a mean after translating the different categories into points. Here, the mean ± SD was 1.984 ± 0.693 ($n = 126$), 2.053 ± 0.831 ($n = 76$), 2.100 ± 0.8847 ($n = 30$), 2.178 ± 0.777 ($n = 45$), and 2.077 ± 0.688 ($n = 26$) points for Swissmedic, FDA, EMA, HCSC, and PMDA, respectively. However, the comparison also revealed that the PGx levels assigned (Fig. 6A, C, E, G) and the number of DLs reporting PGx-relevant information (Fig. 6B, D, F, H) were different. According to PharmGKB, "test required" was assigned to eight Swissmedic DLs, one EMA DL, and three FDA DLs. No PGx levels for these compounds were assigned to the DLs of HCSC or PMDA. From the FDA, eight DLs are rated as "test required"; while four of these DLs (gefitinib, rasburicase, tamoxifen, and ibrutinib) were rated differently in the Swissmedic DLs. Looking at the 126 DLs under consideration, all five regulatory authorities had a majority of DLs rated as "actionable PGx." However, only the FDA have about the same number of DLs with "actionable PGx" as Swissmedic.

Discussion

To our knowledge, this is the first NLP-based extraction of information related to PGx from the Swiss DLs. We focused genes involved in drug metabolism and transport (pharmacokinetics) and information on HLA risk alleles. We extracted 2564 PGx-relevant sentences, which corresponded to 167

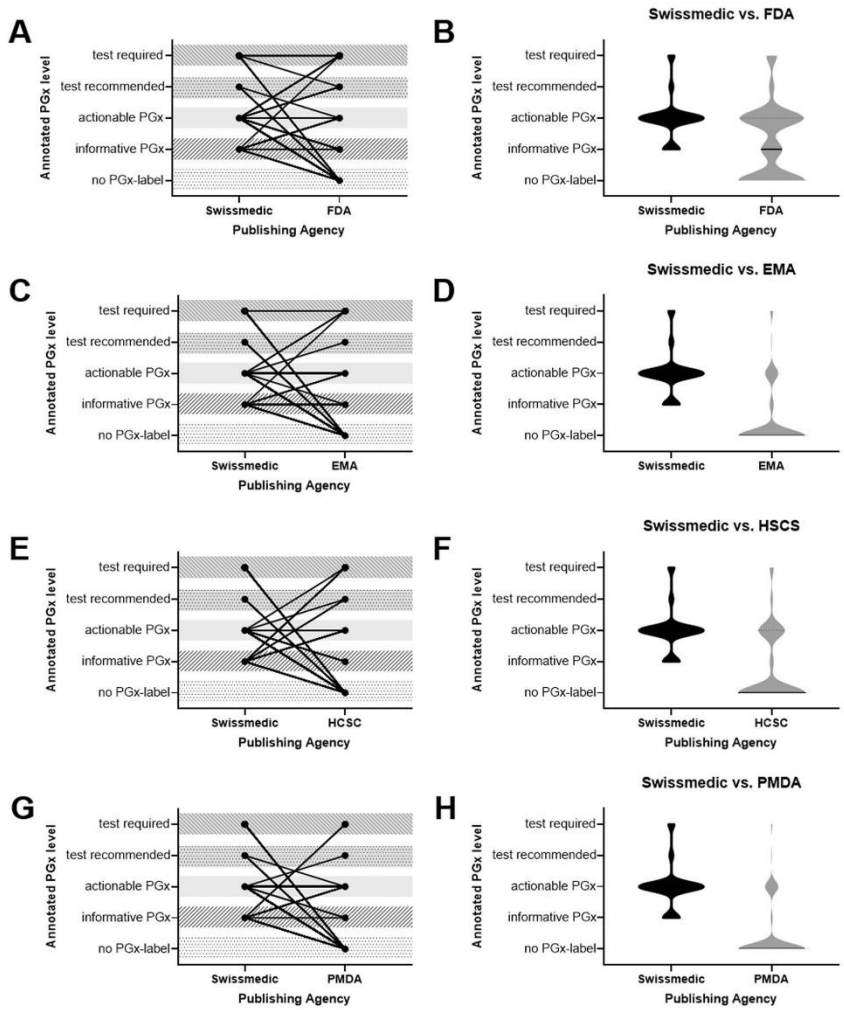

Fig. 6 Comparative analysis of the attributed PGx levels of the Swiss DLs with those of other regulatory authorities, namely the Food and Drug Administration (FDA), the European Medicines Agency (EMA), the Health Care Service Cooperation (HSCS), and the Pharmaceutical and Medical Devices Agency (PMDA). Each drug was included in the schematic of **A**, **C**, **E**, and **G** linking its PGx level indicated by the respective DL of the publishing agency to visualize heterogeneity. In **B**, **D**, **F** and **H** the number of drugs in each category is indicated by the width of the violin.

chemical substances. Our analysis showed that 9.47% of all Swiss DLs (167 out of 1763 different ATC codes by 31st January 2019 [19]) mentioned PGx-relevant information. Most of this PGx information (55%) was classified as "actionable PGx".

We identified the pharmacokinetics section as the prevailing section reporting on PGx. However, this particular section is – not only in the Swiss DLs, but also in those approved by other agencies – one of the last sections in a DL [20]. Therefore, it may be speculated that there is a risk that PGx information could be overseen by the HCPs. For some drugs coded with PGx level 1, the PGx-relevant information was located within the section on precautionary measures, which reports on genetic polymorphisms known

to be associated with ADRs (especially in the case of HLA-associated ADRs, e.g., carbamazepine). Our findings are in line with those by Ehmann et al. [11] reporting that the pharmacokinetic and the precautionary measures section are most likely to state PGx information in DLs approved by the EMA. Other sections such as indications, dosage/use and contraindications rarely provide PGx information. In contrast to the study of Shimazawa et al. [21], we did not prioritize one section per DL, but we analyzed all sections mentioning PGx information.

In accordance with findings from other countries [14, 16, 17, 22], CYP2D6 was the most frequently mentioned biomarker in the Swiss DLs. This cytochrome P450 enzyme is known for its genetic variability with about 100 different alleles [23] resulting in the phenotypes of poor, intermediate, normal, and ultra-rapid metabolizer (UM) with a prevalence of 0.4–5.4%, 0.4–11%, 67–90%, and 1–21%, respectively [24]. Moreover, CYP2D6 is known to be involved in the metabolism of a wide range of commonly used drugs [25] including SSRIs [26], opioids [27–29], and tamoxifen [30]. The second most cited biomarker in the Swiss DLs was CYP2C19. This enzyme also affects a large number of drugs [25] including SSRIs [26, 29], opioids [29], and in particular the bioactivation of clopidogrel [31]. However, none of the Swiss DL contained the biomarker ABCB1, although the Swiss guideline on the treatment of unipolar depressive episodes recommends to test for selected genetic variants of ABCB1 (P-Glycoprotein) in patients taking antidepressants [32–34].

Although ABCB1 was not mentioned in the Swiss DLs, the anatomic group N (nervous system) dominated when analyzing PGx levels per anatomic group. This group contains antiepileptics (carbamazepine [35–37], oxacarbazepine [38], phenytoin [39, 40]), antidepressants such as SSRIs [29], or analgesics such as opioids [29]. The anatomic group N relates to various drugs where treatment is associated with more difficulties (e.g., therapy failure) compared to therapies of other anatomic groups. Indeed, Bschor et al. [41] and Muller et al. [42] assume that psychiatric patients would likely benefit from a PGx test prior to the therapy in order to avoid ADRs or therapy failure. The PGx-relevant information in anatomic group C mostly referred to statins [41] (e.g. fluvastatine [42]) and beta-blockers (e.g., metoprolol [43]). Almost all hits in the anatomic group B were related to clopidogrel, which is well-studied for the influence of genetic variability [31, 44, 45].

We identified nine (5%) refDLs with statements categorized as PGx level 1 and four (2%) refDLs as PGx level 2. For these drugs there is convincing evidence for the clinical benefit of PGx testing prior to treatment initiation. This may be explained by the severity of the potential ADRs [46]. For HCPs, the instruction in these DLs is clear. Accordingly, DLs containing information with PGx level 1 or 2 are most evident to handle, as clear recommendations on therapeutic consequences are given. The majority (55%) of the refDLs were classified as PGx level 3. They mention the influence of a genetic variant on drug efficacy or safety without recommending genetic testing. Here, the question is, how are HCPs supposed to handle this information. Should HCPs inform the patient, or simply take note of the information in case of ADRs or nonresponse? The predominance of PGx level 3 illustrates the insecurity which still dominates in the field of PGx. PGx level 4 was the second most applied PGx level (16%) for the Swiss DLs. The original definition of this category was adapted in a discourse with PharmGKB.

Overall, the presentation of PGx information is very heterogeneous; not only in terms of localization in the DL but also leading to different PGx levels and various associated recommendations. The information on PGx is often not precise and the presentation lacks a predefined structure. Similar findings have also been reported by Ehmann et al. (EMA) [11] and Shimazawa & Ikeda (US and Japan) [21]. By entering the extracts of 126 Swiss DLs on the PharmGKB website, we were able not only to make this information publically accessible but also comparable to the information approved by regulatory agencies of four other countries. The individual comparisons of the Swiss DLs with the DLs of the four different regulatory authorities listed in PharmGKB revealed a large heterogeneity not only in number of compounds with PGx information, but also in terms of assigned PGx levels for the available PGx information. Accordingly, there is a clear need for a standardized presentation with a well-defined structure.

Based on our analysis, there is a tendency toward more PGx testing (PGx level 1 and 2) in the Swiss DLs, compared to FDA or EMA. However, it has to be taken into account that the DLs of the EMA represent rather a general guidance, still enabling differences in the recommendations in national DLs. It has been recommended during the revision process of this manuscript that it should be considered to compare the Swiss DLs to the DLs published by the regulatory agencies of selected European countries. One country that would be suitable for such a comparison are the Netherlands, where guidelines on PGx are available and which appears to have an initiative for PGx implementation with the Dutch pharmacogenetic working group [47]. However, their DLs are only available in Dutch [48]. For Germany, we found a list of drugs published by VFA (Verein der Pharma-Forschenden) [49] with all substances which require or recommend PGx testing (analog to PGx level 1 and 2). In the context of pharmacogenotyping of genes relevant for pharmacokinetics, we are able to compare seven substances (see Supplementary Table 2).

Shekhani et al. [50] analyzed the concordance of the DLs of regulatory agencies with guidelines provided by

CPIC/DPWG and revealed that out of 54 drugs with an actionable gene–drug interaction in the CPIC and DPWG guidelines, only 50% of the agencies described actionable PGx information in the DLs and they were in agreement in only 18% of the cases. We agree with Tan-Koi et al. [51] who suggested after a cross-sectional study of PGx associations in six different countries that there should be an international consensus for PGx presentation in DLs. Also Ehmann et al. [11] stated that the number of DLs mentioning PGx is steadily increasing and that a new legislation is necessary to support HCPs in the application of PGx information. In contrast to the FDA using subheadings on PGx, the current structure of the Swiss DLs does not support the incorporation of standardized PGx information.

Limitations

We have to mention, that we searched for PGx-relevance with word stems concerning pharmacokinetics, thereby excluding information on pharmacodynamics. Our major concern was the inter-individual variability in drug metabolism, which is known to affect a great large number of patients in daily care. However, focusing on pharmacokinetics, we missed information on most oncological drugs, where genotyping is part of compound selection.

In contrast to most previous studies analyzing the DLs for PGx information by reviewers reading the DLs [11, 14], we applied an automated search by NLP. Of the total hit sentences identified by NLP, 43% contained PGx-relevant information. We consider NLP as a strength, even though we are aware of the effort which was necessary for the semantic standardization. As no predefined standardization for the presentation of PGx information in the Swiss DLs exists, the definition of word stems was challenging. In order to facilitate accessibility of DLs for NLP, standardization would be necessary.

During the attribution of PGx levels, we found DLs reporting on the same chemical substance, but stating different information. One reason for these discrepancies might be the different date of market admission. Moreover, a few DLs involved two or more biomarkers resulting in two PGx levels. Finally, some reference DLs inform on the influence of PGx on the drug's efficacy or safety without mentioning a specific biomarker. These particular DLs were excluded from publishing on the website by PharmGKB, as they do not provide usable information for the HCP.

Conclusion

The analysis of PGx information provided in Swiss DLs revealed large heterogeneity. PGx information varies not only in wording used to describe the information but also in the section, where the information appears. In addition, the instructions for clinical practice are rather vague. In summary, this makes the identification and the interpretation of PGx information difficult for HCPs. However, the predominance of PGx level 3 "actionable PGx" demonstrates that numerous actionable DGIs are existing, which could be considered in an optimized drug therapy. For their decision-making and patient counseling, HCPs depend on a supportive DL. Therefore, a specific section dedicated to PGx for the efficient identification of PGx information is favorable. Here, standardized language and well-structured, consistent presentation of PGx information within the DL would be required to facilitate accessibility (e.g., to NLP and then in a further step to clinical decision support systems). Finally, instructions on PGx testing should become more implicit, to support HCPs in personalizing drug therapies and tailoring pharmacotherapy.

Acknowledgements We are grateful to Zeno Davatz and Isabelle Arnet for their support to the search of the Swiss DLs by natural language processing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Project A2

Received: 24 February 2021 | Revised: 14 April 2021 | Accepted: 16 April 2021

DOI: 10.1111/cts.13062

REVIEW

HLA-associated adverse drug reactions - scoping review

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Funding information
No funding was received for this work.

Abstract

Alleles of the human leukocyte antigen (HLA) system have been associated with the occurrence of idiosyncratic adverse drug reactions (ADRs). Accordingly, it is assumed that pre-emptive testing for the presence of certain HLA alleles (HLA-typing) could prevent these ADRs in carriers. In order to perceive the current evidence for HLA-associated ADRs, we conducted a scoping review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The literature search on PubMed and on Embase was carried out on the July 8 and 9, 2020, respectively. To be included in the scoping review, the studies had to investigate an association of any HLA-associated ADR with any small molecule approved and available on the Swiss market. We considered English and German primary literature published since 2002. A total of 149 studies were included, whereof most were retrospective, whereas one was a prospective randomized controlled trial. The majority of the studies ($n = 33$) described the association of HLA-B*15:02 with carbamazepine. It was not possible to directly compare the studies, as they were too heterogeneous in terms of the ADR definition, the HLA alleles, the number of participants, and the study types. Therefore, we summarized the results in a descriptive manner. Even if an interpretation of the outcomes remains open, the descriptive overview revealed the prevailing complexity and uncertainty in the field. For the future, consistent definitions on the different phenotypes need to be established and applied and the reporting of association studies should follow a harmonized structure.

INTRODUCTION

Adverse drug reactions (ADRs) are a major concern in health care. Besides the substantial economic burden, they can lead to hospitalization[1] or even death of patients. Stevens-Johnson syndrome (SJS) and the toxic epidermal necrolysis (TEN) are both examples of life-threatening ADRs presenting as delayed hypersensitivities, which are often associated with different variants of the human leukocyte antigen (HLA). HLA is part of the adaptive immune system. Presenting peptides to T-cells, the highly polymorphic HLA receptors are responsible for immune recognition as part of the immune response.[2,3] The HLA genes consist of different variant alleles, thereby leading to different binding specificities of the HLA proteins.[3] It has been shown that drugs and endogenous proteins can

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interact with certain HLA molecules, thereby leading to the formation of an immunogenic self-peptide complex. These complexes are recognized by the immune system inducing an autoimmune-like reaction[4] and are assumed to be determinants of hepatic and cutaneous ADRs known as drug-induced liver injury (DILI) and drug-induced skin injury (DISI), respectively. Liver failure due to DILI is often life-threatening,[5] and assumed to be responsible for approximately 15% of the cases of acute liver failure in Europe and the United States.[6] The incidence of DISI is approximately 5–15% of all ADRs.[7] SJS and TEN are the most severe phenotypes associated with long-term morbidity and high mortality.[8]

The use of pharmacogenetic (PGx) testing, where a genetic test is associated with a certain drug treatment, to prevent ADR is extensively discussed these days.[9–11] However, the clinical benefit of pre-emptive (prior to therapy start) PGx testing is still controversial. Although being considered one part of individualized medicine,[12,13] there are also voices saying that it is too early for implementation of PGx testing in medical routine.[14] However, it is uncontested that PGx findings contributed significantly to our current understanding of drug metabolism, drug response, and drug safety.

In a previous project,[15] we elaborated an overview on how PGx information is presented in Swiss drug labels (DLs). We identified all PGx-relevant sections, extracted the mentioned biomarkers, and anatomic groups, and classified the available PGx information according to the four PGx levels proposed by Pharmacogenomics Knowledgebase (PharmGKB).[16] Moreover, we reported on how precise the instructions on PGx testing and its consequences for drug therapy are. Within our analysis, we identified DLs where pre-emptive testing is required. One of the identified DLs was that for abacavir, where pre-emptive testing for HLA-B*57:01 is required to prevent administration to patients with a higher risk of hypersensitivity reaction.[17] This suggested practice is supported by the findings of "PREDICT-1" (a randomized controlled trial [RCT] including 1650 patients), published in 2002,[18,19] where carriers of the HLA-B*57:01 allele showed a higher risk to develop the abacavir hypersensitivity syndrome compared to non-carriers (odds ratio [OR] 117 [29–481]).[19] Especially in the case of HLA alleles (e.g., abacavir[18]), it has been suggested that so-called HLA-typing (pre-emptive testing for a specific HLA allele) may prevent the associated ADRs if exposure of carriers of certain HLA alleles is avoided.[18] Besides abacavir, there are other examples of clinically applied drugs (e.g., carbamazepine,[20] allopurinol,[21] or oxcarbazepine[22]) where ADRs are assumed to be associated with HLA alleles. Nevertheless, translation into clinical practice is still limited. Presumably, due to the opinion of various health care professionals (HCPs) saying that there is insufficient evidence for HLA-typing in association with a drug intervention. It was the aim of the herein reported project to identify and summarize studies investigating HLA alleles in relation to ADRs and to give an overview of the evidence on the described ADRs and the investigated genetic factors.

METHODS

Analysis of the Swiss drug labels

We have screened all 4306 Swiss DLs (also known as Summary of Product Characteristics [SmPC]) describing the 15,367 products on the Swiss market in German for PGx information by natural language processing (NLP). Here, we report the substances identified by NLP mentioning HLA alleles as biomarker and the respective phenotypes of the adverse event. For details on the systematic analysis of the Swiss DLs, please refer to ref. 15

Literature search

For our literature search, we defined three determinants, namely HLA for the different human leucocyte antigen (HLA) alleles, ADR (phenotype) for the different adverse drug reactions (ADRs), and DRUG for the different active substances involved. The strings applied in the literature search on Pubmed and Embase are available as Supplementary File S1, and S2. The literature search was carried out on PubMed and on Embase on July 8, 2020, and on July 9, 2020, respectively. The publications were extracted into an Endnote library. We performed the scoping review according to the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[23]

Definition of phenotype

For the definition of the phenotypes, we referred to the Phenotype Standardization Project,[24] where the ADRs (drug-induced torsade de pointes, DILI, and DISI) involving HLA alleles are defined.[24] Notably, due to the various existing terminologies for cutaneous ADRs, we have to specify that DISI is a collective term including severe cutaneous manifesting phenotypes such as SJS/TEN, acute generalized exanthematous pustulosis (AGEP), and the hypersensitivity syndrome (HSS), also called drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS).[24] However, the definition of DISI by the Phenotype Standardization Project does not include the maculopapular exanthema (MPE).[24]

Nomenclature of HLA alleles

For the nomenclature of HLA alleles, we refer to the naming rules of Marsh et al. (http://hla.alleles.org/nomenclature/naming.html).[25]

Eligibility criteria

We included studies that investigated an association between the frequency of a certain HLA allele and the occurrence of any ADRs during the intake of a certain active substance. Inclusion was irrespective of ethnicity. However, we restricted our literature search to small molecules approved and available on the Swiss market. We considered English and German primary literature published since 2002 as in this year, the preliminary work for the first RCT with PGx testing (PREDICT-1) was conducted.[19] We included (non)-randomized controlled trials (n-RCT), case-control studies, cohort studies, and case reports. Furthermore, genomewide association studies (GWAS) examining frequencies of single nucleotide polymorphisms (SNPs) to identify alleles contributing to a specific phenotype were included.

Book chapters, conference abstracts, workshop proceedings, poster presentations, oral presentations, dissertations, and letters to the editor were excluded. In addition, we excluded articles with no access to the abstract, or if no author could be identified. During full text screening, authors of articles with no access to the full text were contacted. Finally, articles where we could not establish access to full text were excluded. See Table 1 for details on the inclusion and exclusion criteria.

TABLE 1 Eligibility criteria for articles identified by literature search

Inclusion
• Investigation of an association (positive, negative, or protective) between the frequency of an HLA allele and the occurrence of adverse drug reactions (ADRs)
• Human (all ethnies)
• Drug (small molecules) available on the Swiss market
• Primary literature in English or German language
• Publication from year 2002 onward
○ Intervention studies (randomized controlled trials [RCTs])
○ Analytical studies (case-control studies [CCSs]), PGx analysis (PGxA), cohort studies (CSs), genomewide association studies (GWASs), and case reports (CRs)→Retrospective and prospective settings
Exclusion
• HLA disease related
• Vaccines, blood products
• Stem cell donation, transplantation
• Allergens (venom, solvents)
• Assay development, laboratory genotyping method
• Structural elucidation of HLA regions and discovery of new loci (unless association with ADRs and small molecule drug)
• In silico docking
• Secondary literature
• HLA in immunology (e.g., T cell-binding assay)
• Altered efficacy due to HLA alleles described
• Cost-effectiveness studies
• No author and/or no abstract available
• Study types such as conference reports, posters, letter to the editors
• Drug not approved for the Swiss market

Selection of publications

Duplicates of citations retrieved from PubMed and Embase were removed and then a title/abstract screening followed by a full text screening was carried out. Eligibility was assessed by two investigators (authors U.W. and C.J.). Any disparity was resolved by consensus. We applied the same procedure for full text screening. The screening process was documented in Endnote (Clarivate Analytics, version X9).

Data charting process and quality assessment

The results of each study included were summarized in a descriptive manner without assessment of the quality of the respective study. Data extraction was performed by one investigator (U.W. or C.J.), whereas a second investigator (C.J. or U.W.) checked the workflow for completeness and accuracy. Disagreements were resolved by consensus. Table 2 summarizes the extracted data items. For the control populations, we differentiated between drug-tolerant controls (tolerant for the investigated drug) and other control groups (e.g., general population). If the control population was not a drug-tolerant control group, we specified it in the comment column of Table S1 Raw Data.

Synthesis of results

For an overview, we gathered all studies in Table S2 PRISMA Scoping Review. In terms of study types, we differentiated between double-blind randomized studies, case-control studies, PGx analysis (defined as studies where selected genotypes were used to define the study groups), GWAS, cohort studies, and exploratory studies. In the table, we sorted the substances and substance groups according the Anatomic Therapeutic Chemical (ATC) code in the fifth level, which refers to the anatomic groups. From each report, we provide the biomarker identified in multiple studies, which confirmed positive associations. In addition, we reported the corresponding phenotype of the ADR, the total number, and type of studies for the substance. For analysis and discussion, we extracted the remaining identified biomarkers, where we differentiated among positive

TABLE 2 Extracted data items

Details on reference	Author, year, study type, drug, biomarker (HLA allele), phenotype, ethnicity
Participants	Cases (patients with ADR) with number of carriers per cases controls (patients without ADR) with number of carriers per controls
Further relevant data items for the search	Odds ratio (OR), positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and a final rating (by the authors of the study)

Abbreviation: ADR, adverse drug reaction.

(confirmed association), negative (no association), and protective (HLA allele demonstrated possible protective effects). Importantly, if there was no HLA allele specifically investigated in multiple studies, we listed them in the HLA alleles (or the respective single nucleotide polymorphism), or allele combinations investigated. The raw data with all the essential information collected from the studies (see data charting process) are listed in the Table S1 Raw Data.

RESULTS

Analysis of Swiss drug labels

At first, we conducted an analysis of the Swiss DLs in order to identify those mentioning HLA as a biomarker in the context of a therapeutic intervention. This analysis conducted by NLP revealed eight drugs mentioned in association with HLA-alleles and adverse drug events. The identified substances are summarized in Table 3.

Selection of publications

The subsequently conducted literature search yielded 2193 articles. After removal of duplicates ($n = 334$), the titles and abstracts of 1859 articles were screened for eligibility. Based on this first screening, a total of 1571 articles were excluded because they did not describe HLA-mediated ADRs, were non-human related, discussed development of new assays for PGx or genetic testing, were not primary literature, or were not meeting the inclusion criteria in terms of publication type. Furthermore, we had to exclude articles where we had no access to the abstract and/or the list of authors. Full text screening was performed for 288 articles, whereof 149 articles were included in the qualitative synthesis. Of the 149 articles, 27 were GWAS, whereas the other 122 were of other study types. Figure 1 depicts the flow chart describing the selection process from identification to inclusion.

TABLE 3 Swiss drug labels mentioning HLA biomarkers

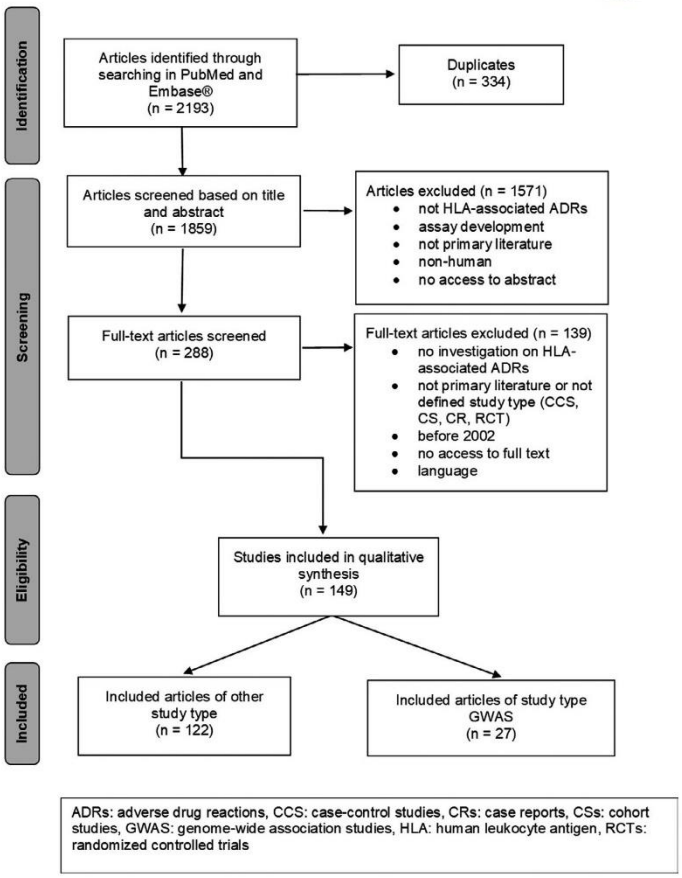
Substance	Biomarker	Associated phenotype
Abacavir	HLA-B*57:01	Abacavir hypersensitivity reaction
Allopurinol	HLA-B*58:01	DRESS, SJS/TEN
Carbamazepine	HLA-A*31:01	SJS/TEN, DRESS, AGEP, maculopapular rash
	HLA-B*15:02	SJS/TEN
Flucloxacillin	HLA-B*57:01	Increased alanine transaminase values
Lapatinib	HLA-DQA1*02:01	Hepatotoxicity
	HLA-DRB1*07:01	Hepatotoxicity
Oxcarbazepine	HLA-B*15:02	SJS/TEN
	HLA-A*31:01	SJS/TEN, DRESS, AGEP, maculopapular rash
Pazopanib	HLA-B*57:01	Hepatotoxicity
Phenytoin	HLA-B*15:02	SJS/TEN

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Characteristics of the publications included in literature search

Of the 149 articles included in the scoping review, 76 were case-control studies, 19 were PGx analyses, 16 were case reports, and 6 were cohort studies; one study was randomized and double-blinded and two were exploratory studies. Another two articles were a combination of PGx analysis and case-control study. In total, 27 GWASs were included in the qualitative synthesis. Of these studies, 11 confirmed the results of their GWAS by an additional study (8 conducted a case-control study, 1 a cohort study, and 2 a PGx analysis).

FIGURE 1 Flow chart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scoping review



Results of publications

Table S2 PRISMA Scoping Review gives details on the identified studies. In detail, the literature search provided results on HLA-associations for 26 substances and 7 substance groups (HMG-CoA reductase inhibitors, thyreostatics, beta-lactam antibiotics, agents for the treatment of tuberculosis, pyrimidine analogues, anti-epileptic drugs, and cold medicines). The raw data of all extracted studies are summarized in Table S1 Raw Data.

Synthesis of results

Overall, the association of carbamazepine-induced cutaneous drug reactions with HLA-B*15:02 was most frequently reported ($n = 33$), followed by allopurinol and HLA-B*58:01 allele-mediated cutaneous ADRs ($n = 17$), and by abacavir and HLA-B*57:01 allele-mediated hypersensitivity reactions ($n = 16$). Studies that confirmed the association of HLA-A*31:01 in carbamazepine-induced ADRs ($n = 10$) as well as oxcarbazepine-induced ADRs were also frequent, but the latter drug was investigated in only two studies. The associations of HLA-B*15:02 and phenytoin-($n = 10$) as well as oxcarbazepine-induced ($n = 4$) cutaneous ADRs were also found. See Table S2 PRISMA Scoping Review for references.

The involvement of HLA-DRB1*0701 and HLA-DQA1*0201 in lapatinib-induced hepatotoxicity was investigated and confirmed in three studies.[26 28] Only one study[29] investigated the involvement of HLA-B*57:01 in pazopanib-induced ADRs. One GWAS investigated the involvement of HLA alleles in patients treated with flucloxacillin,[30] where the associations of HLA-B*57:01 and HLA-B*57:03 were found and confirmed. Consequently, the majority of the found literature represents knowledge on HLA-associated ADRs that has already been found its way into the DLs (see Table 3). Based on this literature search, the anatomic groups, J Antiinfectives for systemic use (6 substances and 2 substance groups), L

Antineoplastic and immunomodulating agents (6 substances and 2 substance groups), and N nervous system (7 substances and 1 substance group) contain most of the substances currently investigated for the association of HLA alleles with ADRs (see Table S2 PRISMA Scoping Review).

The literature search included many further HLA allele associations with ADRs, which are not yet addressed in the DLs. Starting from 5-amino-salicylic-acid associated with nephrotoxicity in HLA-DRB1*03:01,[31] ending with cold medicine associated to ADRs, such as SJS and TEN, combined with severe ocular complications.[32–36] HLA alleles were also associated with nevirapine-induced rash or terbinafine-induced hepatotoxicity. In detail, HLA-B*35:05[37–39] and HLA-C*04:01[40,41] showed an association with rash in nevirapine-treated patients. Moreover, in one study, HLA-DRB1*01[41] was associated with nevirapine-induced hepatotoxicity, whereas in another study the HLA-DRB1*0101 allele was not involved in "global toxicity" of nevirapine.[42] In terbinafine-treated patients with DILI, the alleles HLA-A*33:01[43,44] and HLA-A*33:03[39] as well as the haplotypes HLA-A*33:01-B*14:02-C*0802[43] and HLA-A*33:01-B*14:02-C*08:02[39] were shown to be associated with hepatotoxicity.

The clozapine-induced agranulocytosis was focus of three GWASs reporting an association with the region of HLA-B,[45,46] or HLA-DQB1.[47] Besides, the association of two different HLA-B alleles (HLA-B*57[48] and HLA-B*59:01[49]) and HLA-DRB5*02:01[48] with clozapine-induced agranulocytosis was shown in two studies. Testing the association of seven selected HLA alleles to clozapine-induced myocarditis, Lacaze et al.[50] found that six of the investigated alleles were rather protective.

Finally, antibiotics have been investigated for an association of HLA alleles with ADRs, namely beta-lactam antibiotics,[51,52] metronidazole,[53] and cotrimoxazole. The latter was investigated in three studies[54–56] testing several HLA-alleles for an association with cotrimoxazole-induced skin injuries (DISI) or SJS/TEN. Furthermore, metronidazole was found to be significantly associated with cutaneous ADRs (cADRs) in carriers of HLA-A*24:01.[53]

HLA-alleles show differences in terms of frequency in different populations.[57] Overall, the most studied population for HLA-associated ADRs were Asians (n = 84, 56%), followed by Whites (29, 19%), Africans (4, 3%), American Indians (2, 1%), and Pacific Islands (2, 1%). Moreover, there were mixed populations (14, 9%), or studies where ethnicity was not specified (13, 9%).

DISCUSSION

The methodologic approach of a scoping review was applied to generate an overview of studies reporting on HLA-associated ADRs. In our summary, we included all 149 studies that met the search criteria and were not excluded (compare Table 1). Importantly, we did not actively modify the resulting study selection even if we were made aware during our peer review, that some of the studies considered important in the field are not included in the data extraction. Notably, we restricted our literature search to small molecules, because knowledge on the PGx of biologics and other protein-derived substances is still limited. However, the limitation to drugs currently approved at the Swiss market resulted in the active exclusion of studies on dapsone, ximelagatran, ticlopidine, stavidine, lomefloxacin, and flupirtine.

The 149 studies included in the scoping review reported on 26 substances or 7 substance groups (HMG-CoA reductase inhibitors, thyreostatics, betalactam antibiotics, agents for the treatment of tuberculosis, pyrimidine analogues, antiepileptic drugs, and cold medicine) as indicated by the ATC code. The descriptive summary of the 149 studies revealed a large heterogeneity in terms of used definitions for the ADRs, examined HLA alleles, number and origin of study participants, and study types. HLA alleles were associated with an increased risk for ADRs, no association with the ADR, or were reported to be protective (reducing the risk for the ADR). Given the prevailing complexity and uncertainty, a few reflections should be made.

All of the substances identified in our analysis of the Swiss DLs mentioning HLA risk alleles (see Table 3), also appeared in the studies gathered within the literature search. However, the literature search also revealed HLA allele associations of substances that were not expected based on the analysis of the Swiss DLs. One example is terbinafine; this antimycotic was reported to be associated with hepatotoxicity in carriers of HLA-A*33:01, HLA-A*33:03, and HLA-A*33:01-B*14:02-C*080.[43,44] In contrast, for flucloxacillin, the HLA risk allele HLA-B*57:01 is mentioned in the Swiss DL,[58] yet explicitly recommending not to test prior to use. However, only one study (a GWAS with confirmatory case control study [CCS]) in our literature search reported on its association with DILI.[30] Surprisingly, also over-the-counter drugs, such as acetaminophen, appeared in the literature search.[36]

It seems important to mention that there are multiple factors influencing the recommendation for HLA-typing prior to drug use. One factor is certainly the frequency of the ADR. Flucloxacillin-induced liver injury is very rare and according to Alfirevic et al.,[59] the number needed to genotype is 13,500 to prevent one case. Nevertheless, reactive PGx testing could be affected to exclude random DILI; this is possible due to the high negative predictive value of the respective HLA-test. Considering that flucloxacillin is an antibiotic with a currently increasing use in primary care, this could be of advantage.[59,60]

HLA-B*15:02 was the most frequently investigated HLA allele. The association with ADRs induced by carbamazepine

has been confirmed in many Asian populations.[61–69] However, for other drugs (e.g., phenytoin), the ADRs could not be directly connected to a specific HLA allele but rather multiple influencing HLA alleles.[20,61,70–74]

Suggesting HLA alleles as biomarkers for an ADR, one has to consider that there may be multiple HLA alleles with influence on the therapeutic outcome. One example is allopurinol, where not only the confirmed risk allele HLA-B*58:01, but also the HLA-Cw*0302 allele is considered an HLA risk allele for severe cutaneous adverse reactions (SCAR).[75] The notion of multiple HLA alleles influencing the risk for certain ADRs, has already been put forward by Alfirevic et al. who are suggesting an "HLA panel."[59] Su et al. even went a step further and were able to show that a so-called multiplex genetic test combining HLA risk alleles and CYP2C9 substantially increases the outcome (combined sensitivity 64.7%; combined specificity 71.9%) in the prevention of phenytoin hypersensitivity reactions in Asian populations.[70] In terms of combined genotypes, Ueta et al. described the additive effect of HLA-A*02:06 and PTGER3 (prostaglandin E receptor 3) polymorphism for SJS/TEN with severe ocular complications.[32]

Importantly, the presence of a certain HLA allele cannot only increase the risk of an ADR but can also be protective. One example would be carbamazepine where in addition to the risk alleles (HLA-B*15:02, HLA-A*31:01) several HLA alleles (e.g., HLA-B*40:01, HLA-Cw*01:02, and HLA-DRB1*04:05 for SJS/TEN,[76] HLA-B*15:01 for SJS/TEN, HLA-B*40:01 for SJS/TEN and DRESS,[77] HLA-B*46:01 for SCARs[68]) were reported to reduce the risk for the ADR. These alleles are considered protective. Protective alleles have also been reported for beta-lactam antibiotics,[51] cotrimoxazole,[56] cold medicines,[35] acetaminophen,[36] and clozapine.[50] Taken together, a panel of several HLA alleles would have to be applied in order to predict the risk of ADRs for most substances. However, considering that there are risk alleles and protective alleles, which may be present at the same time in the same patient, will certainly challenge the translation in concise recommendations for HCPs.

The studies included in our scoping review investigated many various HLA-associated ADRs. HLA-associated ADRs are versatile and present in different phenotypes. Especially for cADRs, it is extremely difficult to decide whether the investigators are reporting on the same manifestation or a different one, as in many cases there is no clear definition of the phenotype. For allopurinol, an association of the HLA-B*58:01 was investigated for the following cutaneous manifestations: SJS/TEN, SCARs, DIHS, cADRs, MPE, and DRESS. Moreover, for lamotrigine different alleles were tested for association with SJS/TEN, hypersensitivity reaction, cADRs, MPE, SCARs, and DRESS. Looking at these examples, it may be hypothesized that the high amount of different cutaneous manifestations results from different definitions. The Phenotype Standardization Project[24] supports streamlining definitions in order to have more coherent phenotypes and thereby an international harmonization. In addition to harmonized phenotype definitions, the independent clinical confirmation of an ADR phenotype appears very important.

Looking at the included study types, the PREDICT-1 study[18] investigating HLAassociated ADRs for abacavir was the only RCT. This was also the first study revealing that HLA-typing could help to reduce ADRs. Except from the PREDICT-1 study, all the other HLA-associated ADRs were investigated in retrospective studies (CCSs, cohort studies, PGx analysis, etc.) where the testing was performed after manifestation of ADR. A CCS is a reasonable study design to confirm associations of HLA alleles with certain ADRs. However, in retrospective studies, one has to consider the bias of potentially including incorrectly diagnosed cases as it is extremely difficult to validate the ADR retrospectively. Accordingly, a confirmation of the clinical diagnosis can rarely be performed. In the end, this poses the danger of overestimating the prevalence of an ADR. Furthermore, our literature search also included a substantial number of GWAS, which shows the importance of this study type in PGx. We think that GWAS with focus on the HLA region are a good approach to obtain unbiased evidence on potential associations in patients with ADRs. In total, 15 case reports (thereof 6 for carbamazepine) were included in our literature search, most of them describing the case of a single patient. Even if case reports provide low to no evidence for hereditable factors contributing to the susceptibility, they can help to discover underlying mechanisms, especially if the ADR is rare (rare genetic variant) and/or if the drug is given to a small number of patients (rare disease). The genotype reported in a single case can be basis for further analyses in CCSs.

We should discuss the wide range of the number of study participants. For abacavir, carbamazepine, and allopurinol, the number of study participants ranged from 3 to 842, from 2 to 949, and from 1 to 3000, respectively. Furthermore, most studies were investigating defined subpopulations. Asians were most frequently the population, where HLA-associated ADRs were reported. Accordingly, HLA-typing and corresponding prescribing changes is warranted in Asian populations.[78] Other populations were Whites and Africans, and some studies investigated mixed populations. Interestingly, for more than 9% of the studies, ethnicity was not defined. The frequency of a certain risk allele depends on the population. Accordingly, the findings of the studies cannot be generalized, but should be interpreted respecting the specific population. Therefore, specific knowledge on the study population should be taken into account; even if this increases the complexity.

Speaking of study types, we should not forget publication bias. As it might be the case for flucloxacillin, many

associations with a low allele prevalence and/or a non-severe ADR, are likely not to be reported in the literature. Furthermore, the general bias in empirical studies has previously been discussed by Joensen et al.[79] In their work, the authors associated specific genes to adverse events of methylphenidate. In contrast to our work, they conducted a systematic review of nine studies, and also addressed the different applied definitions of ADRs together with other limitations on the ADRs (prevalence, seriousness, type, causality, and evaluation). This once more shows the advantages of a scoping review, as a systematic review seems premature at the current state of evidence. In our work, the objective was not to find out the clinical relevance of the HLA-associated ADRs, but to see which associations have been described in literature until the moment conducting the search.

However, we were not able to directly compare values, such as the positive and the negative predictive value (PPV and NPV), sensitivity, specificity, and OR. This is as some of the NPVs and PPVs have been calculated in the original studies directly from case-control data without correction for the real population prevalence of the drug hypersensitivity leading to a substantial risk of overestimation of the PPV and underestimation of the NPV. Nevertheless, we would like to discuss the clinical validity of PGx testing and take up the discussion of Tonk et al.[80]

We will base the following on the example of lapatinib, where the presence of HLA-DRB1*0701 has a high NPV, but only a moderate PPV.[26] Essentially, the majority of the individuals who experience serious lapatinib-induced liver injuries carry the allele, but the majority of HLA-DRB1*0701 allele carriers will not experience liver injuries.[27] Looking at the illustrative example of lapatinib, makes us come to an important reasoning: The clinical validity of HLA-typing does not only depend on the association of the HLA risk allele and the ADR, but also on the frequency of the HLA risk allele and the frequency of the ADR. Furthermore, for evaluation of the clinical relevance, the severity of the ADR should also be considered. In addition, one should consider that if HLA-typing is included in therapeutic decision on a drug, where the frequency of the HLA risk allele is higher than the frequency of the ADR there may be patients excluded from a therapy even if they would not experience the ADR. For the application in clinical practice, this means that even if a test seems of clinical utility, this is not necessarily the case. Therefore, we need to balance the frequency of the HLA risk allele against the frequency of use in practice, and measure clinical validity to know how to interpret PGx testing.[80] Manson et al. effected a systematic review on diagnostic criteria for HLA-typing to prevent ADRs. The tests were almost all highly specific and had a high NPV; however, the sensitivity of HLA-typing showed wide ranges from 0% to 100%. Moreover, with exception of HLA-typing for abacavir hypersensitivity, the positive predictive value was low.[81] More studies are needed to evaluate diagnostic test criteria.

To assemble the necessary evidence for an association of HLA alleles and ADRs, studies with sufficient participants in mixed populations designed as large prospective studies are needed. This is not limited to HLA but also affects the implementation of pharmacogenotyping in patient care. Although RCTs are the gold standard for the comparison of two interventions, it can be questioned whether RCTs are the only way to establish the value of PGx. However, even if there is a mechanistic link supporting PGx findings influencing patient outcome, and even if there are guidelines translating these findings in clinical recommendations, the implementation of PGx testing in clinical practice is often questioned due to the lack of data from RCTs.

CONCLUSION

The scoping review identified a considerable number of studies that investigated various substances, HLA alleles, and associated ADRs. It became clear that pre-emptive testing of HLA alleles (HLA-typing) may have a potential; however, it is not possible to derive the actual clinical relevance from these studies. The overview of HLA-associated ADRs ranged from poor to strong available evidence, whereby revealing a prevailing complexity and uncertainty. Screening the different factors influencing the HLA-associated ADRs helped to identify the basic points for further investigations in the field of HLA-associated ADRs. That is to say, previously confirmed associations, where more evidence needs to be generated, potential protective alleles to further explore, or also negative associations that can be excluded in a future systematic analysis in order to receive comprehensible data of good quality and validity. Thus, for the future consistent definitions on the different phenotypes need to be established and applied and the reporting of association studies should follow a harmonized structure.

CONFLICT OF INTERESTS

All authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Jeiziner C, Wernli U, Suter K, Hersberger KE, Meyer zu Schwabedissen HE. HLA-associated adverse drug reactions - scoping review. *Clin Transl Sci.* 2021;00:1–11. https://doi.org/10.1111/cts.13062

Project B – Pharmacogenetic testing of patients with adverse drug reactions or therapy failure - development of a standard operating procedure in primary care

Project B1

Pharmacogenetic Testing of Patients with unwanted Adverse Drug Reactions or Therapy Failure

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Observational study: research project in which biological material is sampled from humans
Risk Categorization:	Risk category A
Project Leader:	Prof. Dr. Kurt Hersberger Pharmaceutical Care Research Group Department of Pharmaceutical Sciences University Basel Klingelbergstrasse 50 CH-4056 Basel Phone: +41 61 207 19 71 Mail: kurt.hersberger@unibas.ch

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PROTOCOL SIGNATURE FORM

Pharmacogenetic Testing of Patients with unwanted Adverse Drug Reactions or Therapy Failure

The project leader has approved the protocol version 3.0 dated 31.10.2019 and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements (1, 2), current version of the World Medical Association Declaration of Helsinki (3) and the principles of Good Clinical Practice.

Project leader/Sponsor Investigator: Prof. Dr. Kurt Hersberger

Site: *University of Basel, Klingelbergstrasse 50, 4056 Basel*

Name: Prof. Dr. Kurt Hersberger

Date: 31.10.19 Signature: _____

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Local Principal Investigators at study sites:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the Swiss legal requirements (1, 2), current version of the World Medical Association Declaration of Helsinki (3) and the principles of Good Clinical Practice.

Site: *Institut für Spitalpharmazie Solothurner Spitäler AG, Baslerstrasse 150, 4600 Olten*

Name: *Dr. Markus Leopold Lampert Waldner*

Date: 31. Oct. 2019 Signature:

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GLOSSARY OF ABBREVATIONS

ADME	*absorption, distribution, metabolism and excretion*
ADR	*adverse drug reaction*
ASC	*ambulatory study center*
BASEC	*Business Administration System for Ethical Committees*
CRF	*case report form*
CYP	*Cytochrome P450 Enzyme*
FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
PCRG	*Pharmaceutical Care Research Group*
PGx	*Pharmacogenetics*
SmPC	*Summary of Product Characteristics*
SNP	*Single nucleotide polymorphism*
TF	*therapy failure*

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1 BACKGROUND AND PROJECT RATIONALE

Interindividual differences in drug effects, which range from therapy failure (TF) to adverse drug reactions (ADRs), find their basis in multiple factors. One of the factors contributing to the variability in drug response is the functionality of the mechanisms influencing the manipulation of the drug by the organism. These mechanisms are summarized in the term pharmacokinetics and actually involve the absorption, distribution, metabolism and excretion (ADME) of the molecule taken. The mechanisms of ADME involve a variety of proteins (enzymes and transporters), where changes in activity affect systemic exposure (area under the curve) and therefore drug response. The activity of enzymes and transporters is modulated by multiple factors including disease factors, drug-drug interactions, drug-food interactions and especially genetics. Indeed, several of the ADME genes are polymorph, with some of the polymorphisms translating into changes of enzyme/transporter activity.

In the last three decades, there has been an extensive evolution of our knowledge on the genetic factors influencing drug metabolism and transport. Some of these findings on drug-gene associations are translated into the recommendation for indication, posology, contraindication, safety information, or pharmacokinetics in the respective drug label, called summary of product characteristics (SmPC) in Europe. Furthermore, the information is collected at the expert curated PharmGKB website (https://www.pharmgkb.org/).

In particular for drugs which are depending on the polymorphic thiopurine S-methyl transferase (TPMT), uridine glucuronosyl transferase 1A1 (UGT1A1), the cytochrome P450 enzymes CYP2D6, CYP2C19, or CYP2C9, the drug transporters Organic anion transporting polypeptide 1B1 (OATP1B1, aka SLCO1B1), or the ATP-binding cassette transporter B1 (ABCB1, aka P-glycoprotein), this information is included in the SmPC of the drugs. Examples for drugs where polymorphisms of the above mentioned genes are basis for interindividual differences in response or the occurrence of ADRs are: 6-mercaptopurine (TMPT(1)), irinotecan (UGT1A1(2)), codeine (CYP2D6(3)), clopidogrel (CYP2C19(4)), celecoxib (CYP2C9(5)), simvastatin (SLCO1B1(6)), and antidepressants (ABCB1, (7)). In Switzerland, pharmacogenetic testing can currently be applied with reimbursement by the health insurance for: abacavir (to exclude HLA-B*5701), for carbamazepin (to exclude HLA-A*3101 and HLA-B*1502), for 6-mercaptopurin/azathioprine (TPMT), for 5-fluoruracil/ capecitabin (DPYD), and irinotecan (UGT1A1). Here, genetic testing has to be initiated by physicians as part of their therapeutic decision. Taken together, pharmacogenetics (PGx) is currently reaching drug therapy in the framework of pharmaceutical care in community and hospital pharmacies.

With the developing knowledge on genetic variants influencing pharmacokinetics and/or pharmacodynamics of frequently applied drugs, multiple providers are now offering PGx assessment using DNA isolated from buccal swaps. One of the commercial products is Stratipharm (Humatrix AG, Pfungstadt, Germany, https://www.stratipharm.de). Stratipharm offers genotyping (based on the DNA obtained from a buccal swap) in combination with sophisticated evidence-based interpretation of the genotype. The service is limited to accredited physicians and pharmacists in German speaking countries (Germany, Austria, Switzerland). Their test system covers almost 100 genetic variants corresponding to 30 genes of pharmacogenetic relevance. The interpretation is based on current and systematically updated evidence reviewed by experts. The resulting recommendations for a single drug in view of the individual genotype are categorized as “Hinweis” (problems could arise and careful monitoring is needed), “Verdacht” (high probability for problems, change of dose or drug needed) or “Gefahr” (risk for an acute problem, drug to be avoided or used with ultimate precaution and/or dose adaption). Moreover, the service comprises a complete profile of the tested genes and their variants, an individualized

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list of affected substances and recommendations for health care professionals for selected substances (see also detailed explanations on Stratipharm in 3.3. study procedures).

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Genetic makeup of a patient influences the efficacy and safety profile of a drug. In the herein proposed study, it is intended to summarize individual cases, where PGx has been applied during pharmaceutical care.
The primary objective is the compilation of case reports, where pharmacogenetic testing is applied to determine the hereditable component of the patient's susceptibility to experience therapy failure and/or adverse drug reactions. The experience with the compiled cases will be basis for the development of a reliable standard of procedure for pharmacogenetic testing in the community and hospital pharmacy. The cases will be supplemented with information on additional parameters reported in the literature to affect efficacy or safety of the respective drug.

2.2 Primary endpoints / outcomes

The primary endpoint is that the patient is pharmacogenotyped and receives the report of its personal risk in the context of the genotyping by Stratipharm.
In the framework of the study, the pharmacogenetic panel of Stratipharm will be supplemented by testing additional genetic variants reported to influence the pharmacokinetics of the respective drug (EDTA blood sample analysis conducted in the Biopharmacy Laboratory). These are variants known to be associated with drug efficacy and safety and are involved in the metabolism of the drugs analyzed in a specific case, but which are not included in the commercial panel offered by Stratipharm (e.g. UGT1A1 or rare variants of the gene included). If the patients are still taking the underlying drug, the data will be in addition supplemented with a monitoring of the drug level (serum sample).

2.3 Project design

This is an observational study over 3 years.

Health-related data of patients experiencing TF or ADR is collected and will then be supplemented with pharmacogenetic testing during pharmaceutical care in a study pharmacy. Afterwards, the patient data (diagnoses, medications and results of pharmacogenetic testing) is harmonized in order to generate a compilation of case reports.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

The patient population are patients experiencing TF and/or ADRs with substances known to be affected by genetic variants that influence their drug metabolism (pharmacokinetics) and/or the activity of the drug target (pharmacodynamics). All patients included have to be able to give informed consent.

Eligibility

Inclusion criteria:

- At least 18 years old
- One of the following criteria:
  - New medication with known PGx association (preemptive)
  - Current medication with observation of adverse drug reactions probably linked to drugs with known PGx association (reactive)
  - Current medication with observation of therapy failure probably linked to drugs with known PGx association (reactive)
  - Current and/or new medication and a family history of adverse drug reactions/therapy failure probably linked to drugs with known PGx association
- Signed informed consent

Exclusion criteria:

- Insufficient German knowledge
- Not able to personally visit to the study pharmacy

3.2 Recruitment

Physicians will be informed (e.g. in a quality circle) about the study and encouraged to hand out flyers to the patients eligible for the study with unwanted drug effects (TF or ADR). For patients who are interested in participating in the study, the physician can either encourage the patient to directly contact the study pharmacy, or on agreement of the patient can transfer the contact information of the patient directly to the study pharmacy.
The informed consent process is coordinated upon agreement with the patient at the study pharmacy. The informed consent process is performed by a pharmacist certified by Stratipharm (see also 3.3 step 1 first visit). The patient has to sign two informed consents, namely the patient information for the study and the patient information by Stratipharm. (PGX-Studieninformation and PGX-Laborauftrag-blanko-Klinik). According to the current law in Germany, Stratipharm needs to receive a written informed consent signed by the patient prior to the pharmacogenetic panel testing. A total of 150 patients shall be recruited.

3.3 Study procedures (including screening and informed consent procedure)

The study procedure is depicted in Figure 1 and described in Figure 2.

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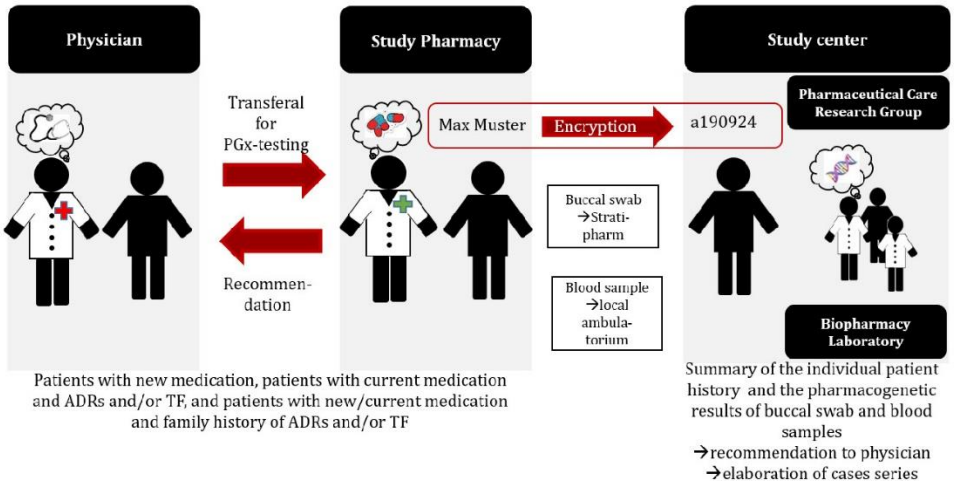

Figure 1: Study procedure with patient recruitment, transfer of patient and management of patient data

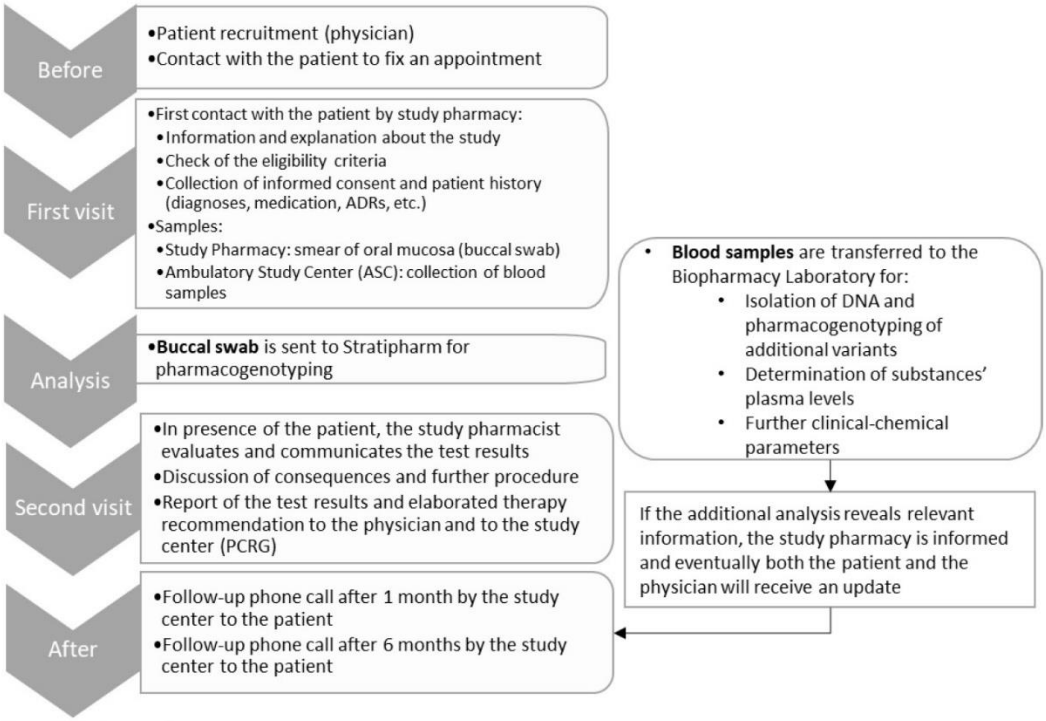

Figure 2: Study procedure

Before the first visit, the study pharmacy contacts the patient to schedule an appointment.

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Step 1: First visit

At the first visit, the patient is informed about the procedure and receives structured information on pharmacogenotyping and the outcome that can be expected. Hereby, the pharmacist emphasizes the difference between pharmacogenotyping and genetic testing, explains the data protection, and affirms confidentiality. The main task will be, to evaluate whether a pharmacogenetic profile assessment is appropriate for the patient according to the inclusion / exclusion criteria. If suitable, the patient is asked to sign an informed consent after an introductory talk. Each patient has the possibility to postpone the pharmacogenetic analysis in order to have more time for consideration. Then, a first interview with an evaluation of the case will take place (patient medication history including self-medication, diagnoses, eventual TF, ADRs or other negative experiences with pharmacotherapy). Still in the study pharmacy, a swab of the oral mucosa (buccal swap) is taken and the patient is referred to the ambulatory study center (ASC) at the University Hospital of Basel, Schanzenstrasse 55, 4031 Basel where two blood samples are taken. Alternatively, at the study site of Solothurner Spitäler AG the two blood samples are taken at the associated Solothurner Spitäler clinical laboratory.

Step 2: Analysis

The laboratory analysis of the samples is performed to determine the pharmacogenetic data.

a. **Buccal swab**: Pharmacogenetic panel testing is conducted by Stratipharm with the DNA of the buccal swab. In the lab, a TaqMan® polymerase chain reaction is proceeded to express the genetic information. The study pharmacy is informed by email when the result is available and in parallel, the patient receives his personal code by post.

In addition, the two blood samples will be processed by the Biopharmacy Laboratory at the Pharmacenter of the University of Basel, led by Prof. Dr. Henriette Meyer zu Schwabedissen, Klingelbergstrasse 50, 4056 Basel. The latter executes genetic testing of additional potentially relevant genetic variants using the DNA extracted from the EDTA blood sample. The substances' serum levels will be determined applying analytical methods. In the following, the blood samples are described more in detail.

b. **EDTA-blood sample (4.9mL):** The sample will be drawn, aliquoted into two 2mL-cryovials (0.5mL/cryovial), labelled with the patient's identifier, and will then be immediately stored at -20°C in the Biopharmacy Biobank. In the Biopharmacy Laboratory, genetic testing takes place. Here, DNA will be extracted using one aliquot and the QiaCube®. The DNA will be collected in an 1.5 mL tube labeled with the patient's identifier. DNA samples will be stored at -20°C until further use. The freezer is under continuous monitoring and the laboratory is only accessible to authorized personal. Genetic testing will be performed either using pre-developed TaqMan® genotyping assays commercially available from Applied Biosystems, or by direct sequencing applying primer directed Sanger sequencing gathering only information of short DNA-segments containing the respective polymorphism.

   The genetic variants assessed in addition will be selected after analyzing the patient's genetic Stratipharm profile, in association with the observed phenotype. In cases where genetic variants of additional genes have been reported in the literature to be associated with the handling of the respective drug, and that are not included in the Stratipharm profile (e.g. UGT1A1), these will be determined and included in the evaluation of the patient's risk.

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c. **Serum samples (7.5mL)**: Patients still on medication assumed to be associated to the observed ADR (phenotype), will be asked to provide a blood sample to determine the actual levels of the compound. The blood will be drawn at the ASC at the University Hospital of Basel or at according clinical laboratory of the Solothurner Spitäler AG. After drawing, the blood sample will be centrifuged under standard conditions, and the supernatant will be transferred into three 2mL cryovials, each containing 0.5mL of the serum sample labeled with the patient's identifier. The sample will immediately be stored at -80°C. For transfer to the Biopharmacy Laboratory (Biopharmacy Biobank), a freezer box will be used. Quantification of drug levels will be performed applying analytical methods (LC-MS/MS or HPLC). The samples will be stored at -80°C until further use. The freezer is under continuous monitoring and the laboratory is only accessible to authorized personal.

If the additional analysis reveals relevant information (the decision is made by Prof. H. Meyer zu Schwabedissen in collaboration with the study team), the study pharmacy is informed and eventually both the patient and the physician will receive an update of the recommendations .

Step 3: Second visit

The patient comes to the study pharmacy for a second visit. For the second visit, a certified pharmacist assesses, evaluates, and interprets the test results. In case of doubts, the expert panel consisting of members of the study center (PCRG and Biopharmacy Laboratory) and members of Stratipharm can be consulted.

At the second visit, the pharmacist communicates all clinically relevant results to the patient. The consequences for the drug therapy will be explained to and discussed with the patient. In addition, the test results and the elaborated therapy recommendations are reported to the responsible physician. The patient and the corresponding physician have the right to request further in-depth queries for any drugs of interest.

Follow up: One and six months after the second visit, the study center will make a phone call to the patient for an unstructured interview in order to gather information about potential outcomes for a future intervention study.

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Stratipharm

What is Stratipharm?

Stratipharm is a product offered by Humatrix AG. It consists of a laboratory analysis of approximately 100 pharmacological relevant genetic variations (polymorphisms) in over 30 different genes, which code for transport proteins, metabolizing enzymes, or drug targets as represented in Figure 3 (see supplementary excel document PGx CRF Stratipharm SNPs& annotations for details). The pharmacogenetic profile resulting from the laboratory analysis is stored securely in the STRATIPHARM data bank and can be retrieved at any time with the consigned texts, recommendations and warnings coming from international pharmacogenetic studies and guidelines of pharmacogenetic consortia. These contents are continuously updated.

☑ ABCB1	☑ ABCG2	☑ ADRB1	☑ ADRB2	☑ COMT	☑ COQ2
☑ CYP1A2	☑ CYP2B6	☑ CYP2C8	☑ CYP2C9	☑ CYP2C19	☑ CYP2D6
☑ CYP3A4	☑ CYP3A5	☑ DPYD	☑ GNB3	☑ GSTP1	☑ HLA-A
☑ HLA-B	☑ HMGCR	☑ HTR2A	☑ IFNL3	☑ ITPA	☑ MTRNR1
☑ NAT2	☑ OPRM1	☑ SLC19A1	☑ SLCO1B1	☑ TPMT	☑ VKORC1

Figure 3: Genes included in the pharmacogenetic panel offered by Stratipharm*How does Stratipharm work?*

Patients need to give their authorization to the pharmacist, who is then able to access the results of the laboratory analysis. Hence, the patient alone decides whether the pharmacist is allowed to have access to his or her pharmacogenetic profile by giving authorization. Patients are only able to access their pharmacogenetic profile with the help of their pharmacist certified by Stratipharm. This is a protection measure, so that patients receive professional interpretation and do not try to interpret the highly complex pharmacogenetic profile on their own.

How are the laboratory results presented ?

On the Stratipharm online portal, the laboratory results are presented in three different ways: 1. Concerned substances, 2. Pharmacoenetic profile, and 3. Query of active substance. Stratipharm uses a color code system, which is based on the current evidence of different international guidelines (Clinical Pharmacogenetics Implementation Consortium, CPIC and Dutch Pharmacogenetics Working Group, DPWG). Every active substance and every gene registered in Stratipharm is coded with one of the four colors. Figure 4 shows what each color stands for (The Stratipharm information is only available in German).

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Die vier Warnstufen

Normal

Keine Warnung vorhanden. Wirkstoff kann nach Verordnung verabreicht werden.

Hinweis

Ein Problem könnte auftreten. Wirkstoff zunächst normal verabreichen, Problem beobachten.

Verdacht

Das Problem wird sehr wahrscheinlich auftreten. Dosisanpassung oder Alternativmedikation empfohlen.

Gefahr

Es besteht ein akutes Problem. Alternativmedikation oder starke Dosisanpassung dringend empfohlen.

Figure 4: The four warning levels of Stratipharm

The following paragraph explains the qualities of each section with the help of an example of a example patient.

1. **Concerned substances:** Figure 5 presents a list of all substances, which are included in the data bank coded with yellow, orange or red colors according to the individual's pharmacogenetic profile.

Warnstufe: Hinweis

Ein Problem könnte auftreten. Folgende Wirkstoffe zunächst normal verabreichen, Probleme beachten:

Acebutolol, Acetylsalicylsäure, Agomelatin, Amisulprid, Aripiprazol, Atenolol, Atorvastatin, Betaxolol, Bisoprolol, Bupranolol, Bupropion, Busulfan, Capecitabin, Carbamazepin, Carboplatin, Carvedilol, Celecoxib, Celiprolol, Chlorprothixen, Ciclosporin, Cisplatin, Citalopram, Clonazepam, Clonidin, Clopidogrel, Clozapin, Cyclophosphamid, Daunorubicin, Deferasirox, Dexamethason, Diclofenac, Digoxin, Docetaxel, Doxorubicin, Droperidol, Duloxetin, Efavirenz, Epirubicin, Escitalopram, Eslicarbazepin, Esmolol, Ethosuximid, Felbamat, Fexofenadin, Fluorouracil, Fluoxetin, Fluphenazin, Flurbiprofen, Fluspirilen, Fluvastatin, Fluvoxamin, Folinsäure, Gabapentin, Haloperidol, Ibuprofen, Idarubicin, Irinotecan, Isoniazid, Ketorolac, Lamotrigin, Ledipasvir, Levetiracetam, Levomepromazin, Lithium, Lornoxicam, Losartan, Lovastatin, Loxapin, Maprotilin, Methotrexat, Mianserin, Mirtazapin, Mitoxantron, Moclobemid, Morphin, Mycophenolsäure, Naproxen, Nebivolol, Nelfinavir, Nepafenac, Nevirapin, Nicotin, Opipramol, Oxaliplatin, Oxcarbazepin, Paclitaxel, Paliperidon, Paroxetin, Penbutolol, Perazin, Perphenazin, Phenobarbital, Pimozid, Pioglitazon, Piroxicam, Pitavastatin, Pravastatin, Pregabalin, Primidon, Propofol, Propranolol, Quetiapin, Reboxetin, Repaglinid, Rifampicin, Rosiglitazon, Rosuvastatin, Sertindol, Sertralin, Sildenafil, Simvastatin, Sofosbuvir, Sulfasalazin, Sulpirid, Sumatriptan, Tacrolimus, Talinolol, Thalidomid, Tiotropium bromid, Tolterodin, Topiramat, Tranylcypromin, Trazodon, Tryptophan, Valproinsäure, Verapamil, Vigabatrin, Voriconazol, Ziprasidon, Zonisamid

Warnstufe: Verdacht

Das Problem wird sehr wahrscheinlich auftreten. Dosisanpassung oder Alternativmedikation empfohlen für:

Acenocoumarol, Amitriptylin, Boceprevir, Clomipramin, Codein, Desipramin, Doxepin, Flecainid, Imipramin, Metoprolol, Nortriptylin, Olanzapin, Oxycodon, Peginterferon alfa-2a, Peginterferon alfa-2b, Phenprocoumon, Phenytoin, Propafenon, Ribavirin, Risperidon, Tamoxifen, Telaprevir, Tramadol, Trimipramin, Venlafaxin, Warfarin, Zuclopenthixol

Warnstufe: Gefahr

Es besteht ein akutes Problem. Alternativmedikation oder starke Dosisanpassung dringend empfohlen für:

Thioridazin

Figure 5: Example of list of concerned substances

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2. **Pharmacogenetic profile**: Figure 6 shows a selection of genes which are coded for their functionality according the obtained pharmacogenetic profile of the individual. For each gene a detailed description of the underlying genetic variation can be viewed (compare Figure 7). Here, the individual annotations of the single nucleotide polymorphisms (SNP) are listed. Moreover, a text explains the setting of the gene and then interprets the current state of the gene in view of an eventual therapy.

Figure 6: Example of a pharmacogenetic profile

3. **Query of active substance:** This is the most useful tool for pharmacists, as it enables a direct query on one specific substance. In first step, an overview on the corresponding substance appears (see Figure 7) and in a second step, the genes involved are shown with an overall recommendation (see Figure 8Figure 7).

Figure 7: Example of a query of an active substance

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ABCB1-Gen Chromosom 7q21.12

Ergebnis der untersuchten Variationen

ANNOTATION	AS-AUSTAUSCH	POS.-INFO	IN HAPLOTYP	GENOTYP			
rs1045642	I1145I	NM_000927.4:o.3435T>C	*2	C/C	C/T	T/T	
rs1128503	G412G	NM_000927.4:o.1236T>C	-	C/C	C/T	T/T	
rs2032582	A893T	NM_000927.4:o.2677G>A	-	G/G	G/A	A/A	neg.
rs2032582	A893S	NM_000927.4:o.2677G>T	-	G/G	G/T	T/T	neg.
rs2032583	-	NM_000927.4:o.2685+49T>C	-	C/C	C/T	T/T	

ABCB1-Gen Chromosom 7q21.12

Ergebnis der untersuchten Variationen

ANNOTATION	AS-AUSTAUSCH	POS.-INFO	IN HAPLOTYP	GENOTYP			
rs1045642	I1145I	NM_000927.4:o.3435T>C	*2	C/C	C/T	T/T	
rs1128503	G412G	NM_000927.4:o.1236T>C	-	C/C	C/T	T/T	
rs2032582	A893T	NM_000927.4:o.2677G>A	-	G/G	G/A	A/A	neg.
rs2032582	A893S	NM_000927.4:o.2677G>T	-	G/G	G/T	T/T	neg.
rs2032583	-	NM_000927.4:o.2685+49T>C	-	C/C	C/T	T/T	

CYP2C19-Gen Chromosom 10q24

Ergebnis der untersuchten Variationen

ANNOTATION	AS-AUSTAUSCH	POS.-INFO	IN HAPLOTYP	GENOTYP		
rs4244285	-	NM_000769.1:o.681G>A	*2	G/G	G/A	A/A
rs4986893	W212X	NM_000769.1:o.636G>A	*3	G/G	G/A	A/A
rs12248560	-	NG_008384.1:g.4195C>T	*17	C/C	C/T	T/T
rs28399504	M1V	NM_000769.1:o.1A>G	*4	A/A	A/G	G/G

Auswertung und Interpretation

Verschiedene Variationen im CYP2C19-Gen führen zu stark verminderter Enzymaktivität. Ist nur eine der beiden Genkopien, die man normalerweise trägt, betroffen, wird die Person als Intermediate Metabolizer (IM) bezeichnet. Sind beide Kopien betroffen, spricht man von einem Poor Metabolizer (PM). Nicht betroffene Personen sind Extensive Metabolizer (EM). Eine bestimmte Variation verstärkt jedoch auch die CYP2C19-Aktivität, was zum sog. Ultrarapid Metabolizer (UM)-Status führt.

CYP2C19 spielt eine wichtige Rolle beim Metabolismus verschiedener Antidepressiva, Benzodiazepine und Protonenpumpen-Inhibitoren, ist aber z.B. auch an der Aktivierung des Prodrugs Clopidogrel beteiligt. Der individuelle Metabolisierungsstatus kann bei der Einnahme dieser Medikamente berücksichtigt werden, um Unwirksamkeiten und Nebenwirkungen zu vermeiden.

Aus dem vorliegenden Genotyp resultiert der UM-Status mit erhöhter Enzymaktivität. Citalopram wird daher in verstärktem Maße abgebaut. Aufgrund der möglichen Unwirksamkeit wird empfohlen, auf einen alternativen, nicht durch CYP2C19 metabolisierten Wirkstoff (z.B. Fluoxetin, Paroxetin) auszuweichen oder die Dosis unter engmaschigem Monitoring (z.B. durch therapeutisches Drug-Monitoring, TDM) in Abhängigkeit von erwünschten und unerwünschten Arzneimittelwirkungen auf maximal 150% der Standardanfangsdosis zu steigern.

Figure 8: Example of detailed description of genes with overall recommendation

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3.4 Withdrawal and discontinuation

Patients have the right to discontinue their participation in the trial for any reason and at any time without prejudice to further treatment.
For withdrawal, the patient must contact Stratipharm under info@stratipharm.de about consent withdrawal, (this can only be done by the pharmacogenotyped individual). Consequently, the sample will not be analyzed, analysis will be interrupted, or the gene interpretation on Stratipharm will be deleted. In addition, the project leader needs to be informed. Upon withdrawal, all samples in the Biopharmacy Biobank will be destroyed. No further analysis (data collection) will be performed.
Patients who withdraw their consent (e.g. refuse further data collection) will be informed that all data collected until the time point of their withdrawal will be kept coded and used for case description so that the study does not lose its value.The patient himself has still the option to ask the study pharmacy to receive ongoing pharmaceutical care with respect to pharmacogenotyping, but on his own costs and fully independently of the research project.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

The case reports at the end of the study will not need any special statistical analysis.

4.2. Handling of missing data

In case of relevant missing patient data, we can ask the patient again and then also the physician.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki (10), the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) (8), as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both, the Project Leader and the Sponsor Investigator.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

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5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project termination, the Ethics Committee is notified within 90 days.

5.7 Insurance

All activities executed in the study pharmacy are part of standard of care and are therefore covered by the mandatory liability insurance. In the event of project-related damage or injuries, the liability of the University of Basel provides compensation, except for claims that arise from misconduct or gross negligence. However, we cannot think of project-related damage or injuries at this point.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

This study is of social and scientific value as pharmacogenetic testing is one of the approaches in the concept of personalized medicine. Within this approach the personal pharmacogenetic profile of a patient is considered to render it possible to individualize the therapy. The herein investigated genetic testing approach by Stratipharm is commercially available and it will be of great impact to evaluate its applicability in the community setting. As long as the pharmacogenetic and personal health data protection are assured, no ethical considerations have to be addressed. Furthermore, we will obtain results from the general population, and generalizability will be given. The results of the submitted project will fill a gap in current practice by showing what benefits and challenges are associated with pharmacogenetic testing in a community and hospital pharmacy. The overall burden and time effort is moderate for the pharmacists involved, minor for the physicians, and low for the patients. Participation is voluntary. In addition, patients will have the opportunity to discuss issues with the pharmacist who will, in case of current problems, counsel on a treatment or refer the patient to the physician.

6.2 Risk-Benefit Assessment

The risk is consistent with routine clinical procedures. Blood sampling may result in bruising, inflammation, blood vessel or nerve injury. Aside from minor risks, we cannot think of any risk

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

linked to the pharmacogenetic testing. On the contrary, patients benefit from the knowledge of their complete pharmacogenetic panel, enabling them to improve their drug therapy. Moreover, these results of the pharmacogenetic testing are valid a life-long as a person's genetics will not change. In case the pharmacist or the physician disposes of the Stratipharm software, insight into the pharmacogenetic profile is possible at any time by the patient's code. However, such further services are outside this project and the costs will be charged to the patient.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

To validate the results of Stratipharm, every pharmacogenetic profile will be submitted to a plausibility test, which includes substances known to be linked to a specific gene with high evidence according to PharmGKB (https://www.pharmgkb.org/). The selected drug-gene combinations are summarized in Table 1.

Table 1: Substances and linked genes of the plausibility test

Substance	Gene locus
Tamoxifen	CYP2D6
Carbamazepin	HLA-B 1502
Simvastatin	SLCO1B1
Isoniazid	NAT-2
Clopidogrel	CYP2C19
Warfarin	CYP2C9 and VKORC1

7.2 Data recording and source data

Access to the pharmacogenetic profile in the Stratipharm Database is only possible with the patient code, which the patient and the study pharmacy certified by Stratipharm will receive. Recommendations to the physician are conveyed via a secure HIN address of the study pharmacy or of the study center.

Buccal swab: Stratipharm requires patient data (full name, address, and birth date) for informed consent, delivery of patient card, and verification of the patient's majority, respectively. The patient's sample is destroyed two to three weeks after completion of the analysis and only the genetic data remains. Details about the data process at Stratipharm are described in an annex document "STRATIPHARM system concept."

All information about the patient including the patient history (diagnoses, medication, ADRs, etc.) are stored in the study pharmacy in a locked paper folder or a password-protected electronic folder. The key list for the patients' identifiers consists in a MS Word® file named "Identifkationslogbuch" and always stays in the study pharmacy. All persons who have access to

the data as part of the project are subject to secrecy. The requirements of data protection are held and the patient has the right to access into his/her data at any time.

Blood samples: The blood samples provided will be used to collect additional parameters related to the observation. These are genotyping of genes of pharmacological relevance and/or the plasma concentration of the substance investigated in the case. As mentioned before, the samples (EDTA-blood and serum) drawn at the ACS or according clinical laboratory will be transferred to the Biopharmacy Laboratory, University of Basel, labeled with the patients identifier. In the laboratory the samples will be processed, stored and analyzed. Collected data will be reported to the Pharmaceutical Care Research Group (PCRG) using the patient's identifier. The collected or processed samples will be destroyed either on demand by the study center (in case of consent withdrawal) or at the end of the study.

7.3 Confidentiality and coding

Buccal swab: In the laboratory, the sample is prepared, analyzed and used to determine the pharmacogenetic profile. The patient's sample is destroyed two to three weeks after completion of the analysis and only the genetic data remain. These are encrypted with the sample number for evaluation and thus assigned to a database (server without Internet access). Only Stratipharm employees have access to the data and must comply with strict data protection regulations. The genetic data will be kept until withdrawal (this allows to query the active substance at any time in the future). The laboratory in Germany has standards equivalent to those in Switzerland. The project leader is responsible for compliance with national and international data protection guidelines and guarantees equivalent data protection abroad. Finally, when the results are ready the study pharmacy is informed. From that point in time, the results of the pharmacogenetic testing by Stratipharm are saved on the web portal, which is only accessible by the password (study pharmacy certified by Stratipharm) and the patient code (patient card). Within the scope of the study, we require the patient's consent, which allows the research team to use the patient code in the patient's absence, and thus to view the genetic data in unencrypted form.

All information about the patient is stored in the study pharmacy. Before data transfer to the study center (PCRG), all data are encrypted with the corresponding patient identifier. Any further data extracted from the pharmacogenetic profile are also encrypted by the patient's identifier. The blood samples collected at the ASC or according clinical laboratory will be labelled with the patient's identifier that the patient brings in an envelope before they are transferred to the biobank of the Biopharmacy Laboratory or before they are analyzed at the Biopharmacy Laboratory.

EDTA-blood sample (4.9mL): The sample will be drawn, aliquoted into two 2mL-cryovials (0.5mL/cryovial), labelled with the patient's identifier. The coded EDTA-blood samples will then be immediately stored at -20°C and transferred frozen to the Biopharmacy Biobank. In the Biopharmacy Laboratory, DNA will be extracted using 0.2mL/isolation and the QiaCube. The DNA will be collected in an 1.5mL tube labeled with the patient's identifier. The coded DNA samples will be stored at -20°C in the Biopharmacy Biobank until further use. The freezer is under continuous monitoring and the laboratory is only accessible to authorized personal. Genetic testing of the coded samples will be performed either using pre-developed TaqMan® genotyping assays commercially available from Applied Biosystems, or by direct sequencing applying primer directed Sanger sequencing. The results associated to the patient's identifier will be reported to

the study pharmacy. At no time of the laboratory work process, the laboratory personal has access to any other information of the individual.

Serum samples (7.5mL): Patients still on medication assumed to be associated to the observed ADR, will be asked to provide a blood sample to determine the actual levels of the compound at the ASC at the University Hospital of Basel. After drawing, the blood sample will be centrifuged under standard conditions, and the supernatant will be transferred into three 2mL cryovials, each containing 0.5mL of the serum sample labeled with the patient's identifier (coded). The coded sample will immediately stored at -80°C. For transfer of the coded to the Biopharmacy Biobank, a freezer box will be used. Quantification of drug levels will be performed applying analytical methods (LC-MS/MS or HPLC). The coded samples will be stored at -80°C until further use. The freezer is under continuous monitoring and the laboratory is only accessible to authorized personal. The results associated to the patient's identifier will be reported to the study pharmacy. At no time of the laboratory work process, the laboratory personal has access to any other information of the individual.

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique patient identifier.

7.4 Retention and destruction of study data and biological material

Data collected from the study patients can be divided in the genetic data in the Stratipharm portal, and the health-related data collected at the study pharmacy and in the Biopharmacy Laboratory for eventual further investigations by the PCRG.
At Stratipharm, the buccal swab and the extracted DNA are destroyed after two to three weeks after the accomplished labor analysis. The individual patient data with the gene interpretation is kept until withdrawal.
The patient data stored at the study pharmacy and the study center (PCRG), which are summarized in the project file, will be stored for at least 10 years after the end of the study. Blood samples will be stored at -80°C in the Biobank of Biopharmacy Laboratory.

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8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

The Pharmaceutical Care Research Group and the Biopharmacy Group will provide the main funding for this study. Details about funding can be found in the MS Excel® file "Funding Study PGx Case Series".
The patient receives all analyses and according counselling for free.
As mentioned above, further pharmacogenetic services are outside this project and the costs will be charged to the patient.

Collaborations with the community and hospital pharmacies (e.g.at this point in time namely "Toppharm Apotheke Hersberger", Spalenberg 41, CH-4051 Basel; Institut für Spitalpharmazie Solothurner Spitäler AG, Baslerstrasse 150, 4600 Olten) will be set up for the patients to be received and counseled. Further study pharmacies that will be involved for recruitment will be communicated to the ethics committee. By the end, study results will be published in the form of different case reports. The case reports will be elaborated for education and publication in peer reviews.

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Project B2

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CASE REPORT

Enriching Medication Review with a Pharmacogenetic Profile – A Case of Tamoxifen Adverse Drug Reactions

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine

Chiara Jeiziner[1]
Céline K Stäuble[1,2]
Markus L Lampert[1]
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Abstract: Pharmacogenotyping is applied to determine the hereditable component of a patient's susceptibility to experience therapy failure and/or adverse drug reactions (ADRs). We present the case of a female patient diagnosed with breast cancer and treated with tamoxifen as recurrence therapy who experienced various ADRs. Pharmacogenotyping revealed variants in the cytochrome P450 (CYP) enzymes CYP2D6, CYP2C9, and CYP2C19. The observed genotype was associated with a risk for lower tamoxifen efficacy. Aside from the tamoxifen therapy, the comedication was reviewed for the influence of the patient's pharmacogenetic profile. As a result of this pharmacist-led medication review with pharmacogenetic analyses, concrete genotype-driven recommendations for the treating gynecologist were compiled. This case revealed the added value of a large pharmacogenetic panel and the complexity of integrating a pharmacogenetic profile into a recommendation.

Keywords: pharmacogenetics, PGx, CYP2D6, CYP2C9, CYP2C19, medication review, tamoxifen

Background

The first thing a pharmacist does, when a patient reports adverse drug reactions (ADRs), is to go through the patient's medication in order to check for overdosing, contraindications, potential drug–drug or drug–disease interactions, and/or adherence problems. At the point, where there is no plausible explanation for the reported ADRs, pharmacogenetics (PGx) might help. PGx is the study of genetic variations related to drug response.[1] Indeed, PGx testing can be applied to determine the hereditable component of a patient's susceptibility to experience therapy failure and/or ADRs. PGx testing aims to identify patients who benefit from a particular drug (responders) or to identify those patients, who carry a predictable risk of non-response or ADRs due to their genetic make-up. The result of pharmacogenotyping has to be evaluated in the context of the active substances taken, therefore also referred to as "stratified pharmacotherapy".[2] It has been shown that pharmacists in the primary care setting are able to contribute to the optimization of the pharmacotherapy by considering the patient's genetic background.[3–5] One drug that has been extensively studied for the relevance of the patient's genetic predisposition is tamoxifen (TAM). This selective estrogen receptor modulator is used in the prevention and treatment of pre- and postmenopausal breast cancer patients. The endocrine therapy is administered to women

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http://doi.org/10.2147/PGPM.S285807

with estrogen and/or progesterone receptor-positive breast cancer after chemotherapy, radiotherapy, or surgery for 5 years in a dose of 20 mg per day.[6] By intake of TAM, the annual cancer recurrence rate is halved and the mortality rate is reduced by one-third.[7]

TAM is a prodrug and known for its bioactivation involving multiple cytochrome P450 (CYP) enzymes. In order to form the most active metabolite endoxifen (END), TAM is metabolized either to the intermediate metabolite N-desmethyl-tamoxifen (DM-TAM) or to 4-hydroxy-tamoxifen (4-OH-TAM). The major metabolite DM-TAM is formed by demethylation catalyzed by CYP3A4 among other CYPs.[8] DM-TMA is then oxidized by CYP2D6 to END (up to 100 fold more active than TAM) and several other metabolites. Of the remaining TAM, 7% are oxidized to 4-OH-TAM by CYP2D6 among other CYPs (CYP2C9, CYP2C19 and CYP2B6).[8,9] In a second step, 4-OH-TAM will be demethylated to END by CYP3A4.

Together with TAM, the three metabolites DM-TAM, 4-OH-TAM, and END can enter the target cancer cells to exert the modulatory effect on estrogen receptors.[9] Finally, glucuronidation mainly inactivates TAM and its metabolites, so that 75% of the initial dose will be biliarly excreted as glucuronides.[10]

Regardless of the pathway by which TAM is metabolized, the highly polymorphic CYP2D6 is always involved. Therefore, it is not surprising that changes in CYP2D6 activity associated with inhibition or genetic variants are influencing the bioactivation of TAM.[11] However, only little is known about the influence of the variability of other CYPs involved in the metabolism of TAM.

Case Presentation

A premenopausal 49-year-old woman was diagnosed with recurrent breast cancer 12 years after the first diagnosis, where she was initially treated with tumorectomy and sentinel lymphadenectomy, adjuvant radiotherapy, and subsequent endocrine therapy with GnRH-analogs and TAM 20 mg for 24 months. The adjuvant therapy with the GnRH-analogs and TAM was suspended after 2 years, due to various ADRs such as hot flashes, enormous perspirations, psychological distress and the inability to work. Some of these ADRs are known to be linked to TAM therapy.[12] After the second breast cancer recurrence, a skin-sparing mastectomy with breast reconstruction was performed. Since the initial diagnosis of breast cancer, the treating physician had changed and the new physician was not aware of the previously reported ADRs and therefore, the adjuvant therapy with TAM 20 mg was started again. Due to pronounced climacteric (perspirations and hot flashes) as well as psychological symptoms (irritability, weariness, and depressiveness), the patient asked for a decrease of the TAM dose. Twenty-four months after the re-start of TAM, the dose was decreased to 10 mg per day. Three months later, the patient contacted her gynecologist because ADRs remained and she wanted to learn more about her own TAM response. The gynecologist decided to refer the patient to pharmacists with specific expertise in PGx. The pharmacist performed a medication review supplemented with a pharmacogenetic panel testing. Besides TAM, the patient was taking additional medication (see Table 1 for details). Therefore, the pharmacist also screened comedication for potentially relevant polymorphisms and evaluated potential alternative medication.

Genetic Analyses of Single-Nucleotide Polymorphisms

After initial consultation and informed consent by the patient following the protocol as approved by the local ethics committee (EKNZ-2019-01452), pharmacogenetic panel testing was conducted applying the commercial test Stratipharm® by humatrix AG (Pfungstadt, Germany), which provides not only the results of genetic testing but also drug-specific interpretation of the corresponding phenotype (pharmacogenetic profile). Table 2 presents the interpretation of a selection of the patient's genotyping results relevant to the herein reported case. The patient held the star alleles *6 (no function) and *41 (decreased function) of the CYP2D6 enzyme resulting in

Table 1 Patient's Medication at the Time of the Medication Review

Substance	Dosage	Indication
Tamoxifen 10 mg	0-0-1	Adjuvant endocrine therapy of breast cancer after mastectomy
Mistletoe preparation	As needed	Supportive herbal cancer therapy
Ibuprofen 600 mg	As needed: 0.5–0.5–0.5	Pain
Metamizole 500 mg	As needed	Pain
Pantoprazole 20 mg	1–0–0	As long as therapy with ibuprofen
Lorazepam 1 mg	As needed	Difficulties falling asleep

Table 2 Genetic Profile of the Patient

Gene	CYP2D6	CYP2C19	CYP2C9
Annotation, genotype	rs5030655, T/-; rs28371725 G/A	rs12248560 C/T	rs1799853 C/T
Haplotypes	*6/*41	*1/*17	*1/*2
Predicted phenotype	IM	UM	IM

Abbreviations: IM, intermediate metabolizer; UM, ultrarapid metabolizer.

the phenotype of intermediate metabolizer (IM). At the same time, the patient had a CYP2C19 ultrarapid metabolizer (UM) status with the star alleles *1 (wildtype) and *17 (increased function) and a CYP2C9 IM status with the star alleles *1 (wildtype) and *2 (decreased function).

For TAM, Stratipharm® reported the CYP2D6 IM status, which is linked to reduced enzyme activity, and consequently, an insufficient activation of the prodrug TAM to the major active metabolite END. Stratipharm® did not report results related to any other genes relevant to the TAM metabolism. For pantoprazole, the increased enzyme activity of CYP2C19 may lead to increased degradation of the metabolized substance. Therefore, ineffectiveness of pantoprazole was predicted for standard dosage in our patient. For ibuprofen, the decreased enzyme activity of CYP2C9 may lead to an accumulation of the metabolites. Consequently, the patient has a higher risk of ADRs, eg gastrointestinal bleedings.

Discussion and Decision-Making

Both genetic predisposition and the patient's medication were considered when evaluating the reported ADRs observed during TAM treatment. We will start with the description of our considerations for TAM, as we assumed the ADRs to be linked to the treatment with the selective estrogen receptor modulator, even though we are aware that the pathophysiology of hot flushes especially in breast cancer survivors is not fully understood.[13] Based on our knowledge on TAM metabolism and its function as selective estrogen receptor modulator, we expected a CYP2D6 UM status leading to an excess of END, thereby resulting in the reported ADRs. However, the pharmacogenetic profile showed that the patient had the star alleles *6 (no function) and *41 (decreased function) of the CYP2D6 enzyme resulting in the phenotype of an IM. Moreover, the testing revealed the patient's CYP2C19 UM status with the star alleles *1 (wildtype) and *17 (increased function), and a CYP2C9 IM status with the star alleles *1 (wildtype) and *2 (decreased function).

If PGx data for a patient are available, one should be able to consult the official drug label or the guidelines by the respective medical expert panel for information on the handling of a drug. For TAM, Swiss drug labels (www.swissmedicinfo.ch) does not recommend CYP2D6 testing, but simply states, that in published studies, the simultaneous use of CYP2D6 inhibitors reduced plasma concentrations of the active metabolite endoxifen, which may be associated with a loss of efficacy (see 'Interactions'). According to a published study, the loss of efficacy of TAM in combination with treatment with SSRI paroxetine increased mortality. TAM should therefore not be administered together with CYP2D6 inhibitors (eg SSRI antidepressants such as paroxetine or fluoxetine, cinacalcet, quinidine). Reduced endoxifen concentrations and thus reduced efficacy can also be expected in so-called poor metabolizers for CYP2D6 (see 'Pharmacokinetics' and 'Properties/Effects').[14] This information is similar to the drug label issued by the FDA and Health Canada.[15] Finally, the National Comprehensive Cancer Network (NCCN) Breast Cancer Panel does not recommend CYP2D6 genotyping.[16] Accordingly, these sources did not provide the information we were looking for.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) or the Dutch Pharmacogenetics Working Group (DWPG) provide recommendations on the implementation of PGx information in medical decisions for a selection of drugs including TAM. In their expert summary on TAM, both report a clear association of the herein observed genotype of CYP2D6 *6/*41 (IM), with lower END levels and with a higher risk of breast cancer recurrence in premenopausal women. In the case of a CYP2D6 IM status, they recommend considering alternative substances for the endocrine therapy such as aromatase inhibitors (AIs).[17–19] In their update of guidelines, Swen et al[19] confirmed an increased recurrence rate of breast cancer and strongly recommended to avoid the use of potent CYP2D6 inhibitors for CYP2D6 IMs. For postmenopausal women, they suggested considering the use of AIs, even though two large randomized double-blind trials[20,21] concluded that the CYP2D6 genotype does not predict the clinical outcome with TAM. However, there are studies confirming[22–24] and studies contradicting[20,21] the predictive value of the CYP2D6 genotype for the clinical outcome, which certainly contributes to the lack of agreement on the pharmacogenotyping prior to TAM treatment.

There are data suggesting that despite the enhanced activation of TAM to END in patients with UM status, this status is linked to a higher intake of symptom-relieving drugs (antinausea, anxiolytics, medications for relief from hot flushes), a higher frequency of early treatment discontinuation, and a worse prognosis for breast cancer compared to extensive metabolizers.[25]

Another option to overcome the decreased END levels in patients with CYP2D6 IM status might be a dose-escalation, but this was not recommended in the guidelines of the CPIC/DWPG and no option for our patient, suffering from various ADRs from TAM. Nevertheless, we would like to mention that there are experts[26] reporting that there is no impact on quality of life when applying monitoring of END plasma concentrations and according to TAM dose escalation in CYP2D6 poor metabolizers (PMs). Besides, we were unable to collect blood samples in the community pharmacy.

Toremifene is another selective estrogen receptor modulator indicated for the treatment of metastatic breast cancer in postmenopausal women.[27] Even if CYP2D6 is involved in the toremifene metabolism as shown in vitro,[28] this enzyme seems to play a minor role in vivo.[29] Within the herein reported case, toremifene was no therapeutic option as the drug has been discontinued in the Swiss market.

As it remained unclear whether the observed ADRs are linked to the patient's genotype, we focused on the bioactivation of TAM. The first step, namely the demethylation of TAM to DM-TAM, which is considered as the main pathway of TAM degradation,[10] is mainly catalyzed by CYP3A4.[9,30] However, for CYP3A4 no function predicting polymorphisms exist.[31] Furthermore, it is well known that CYP2D6 is a major contributor to the hydroxylation both of TAM to the intermediate metabolite 4-OH-TAM and of the intermediate metabolite DM-TAM to END. If less CYP2D6 is available, we must assume both steps to be slower. Consequently, smaller amounts of END might be formed. In 2009, Schroth et al[22] retrospectively genotyped a cohort of 1325 patients with breast cancer at an early stage and demonstrated that the existence of a non-functional (PM) or reduced-function allele (IM) instead of two functional alleles of CYP2D6 lead to worse clinical outcomes. Even though there is a link between the bioactivation of TAM and CYP2C19, the DPWG and CPIC guidelines do not consider this relationship. Indeed, CYP2C19 is known to be capable of catalyzing the 4-hydroxylation to 4-OH-TAM and the demethylation to END.[11] In addition, there are data linking CYP2C19 to both estrogen and progesterone metabolism.[32] In detail, the authors demonstrated in a cohort study with 306 pre- and post-menopausal women, that patients with a decreased activity of the CYP2D6 enzyme, thus poor activation of TAM, in combination with an increased activity in CYP2C19 UM, thus lower levels of sexual hormones, have worse clinical outcome. Looking only at CYP2C19, it has been shown that the CYP2C19*17 allele (UM) is associated with a better response to the TAM therapy, fewer ADRs, and disease-free survival.[10,33] Furthermore, Schroth et al report an analysis considering both the CYP2D6 and the CYP2C19*17 genotype revealing a more accurate stratification of the patients with poor and moderate outcomes when also considering CYP2C19*17.[33] In addition, the CYP2C9 is assumed to be involved in the formation of the intermediate metabolites DM-TAM and 4-OH-TAM.[11] Therefore, the CYP2C9 IM status of our patient might have led to a decreased level of the intermediate metabolites DM-TAM and 4-OH-TAM. Finally, CYP3A4 is involved in the demethylation of TAM to DM-TAM, and of 4-OH-TAM to END.[9,10,30] However, based on the current understanding genetic variants in CYP3A4 are not predictive for its metabolic activity, but CYP3A4 is often involved in drug–drug interactions either increasing or decreasing its activity. Taken together, the genetic findings suggest that the herein reported patient is carrying a risk for lower TAM efficacy (CYP2D6 IM, CYP2C9 IM), which is slightly reduced by the enhanced activity of CYP2C19.

Even though an initial screening of drug–drug interactions using the interaction tool MediQ (www.mediq.ch) did not show any significant drug–drug interactions, we performed an in-depth analysis of the potential drug–drug interactions. On one hand, there is the possibility of induction of enzymes involved in TAM metabolism. This is especially known for CYP3A4, but also for other enzymes involved in TAM metabolism such as CYP2C9 and CYP2C19.[31] However, there are no drugs present in the patient's comedication currently known to induce CYP3A4, CYP2C9, and CYP2C19 function. On the other hand, processes of inhibition are possible. In the context of TAM comedication, it seems noteworthy that pantoprazole is considered to be a CYP2C19 substrate, and therefore might have had a weak inhibitory effect on the increased activity of CYP2C19 in the patient.[34] Another compound, that may influence drug metabolism is the herbal medication *Viscum album* taken by the patient

as a complementary therapy. Weissenstein et al[35] treated the human breast cancer cell line MCF-7 with END, either with or without the presence of estradiol. Viscum album extracts were added to all samples and proliferation, apoptosis and cell cycle were analyzed. In addition, possible inhibition of CYP3A4/5 and CYP2D6 was examined in human liver microsomes. *Viscum album* did neither influence the anti-estrogenic effect of endoxifen; nor interact with the bioactivation of TAM.

After consulting drug labels, guidelines, and literature, it still remained unclear whether the observed ADRs are linked to the patient's genotype. In this context, we want to cite the results from Regan et al[21] investigating the development of hot flashes in 1706 patients treated with TAM in the first 2 years of treatment. Contrary to the hypothesis of worse disease control in patients with CYP2D6 PM and IM phenotypes, they found an increased risk for development of hot flashes in patients with CYP2D6 PM and IM phenotypes. No such association was observed by Sestak et al[36] assessing the same outcome in a smaller patient population (n=54). According to Vries et al[11], PGx alone cannot answer the question of the reactions on treatment with TAM, as this depends on multiple factors, eg the menopausal status of the woman. For the herein presented case, we are unable to explain the ADRs, but the CYP2D6 IM status of the patient let us to decide that TAM is not a good treatment option. Testing the patient for the END plasma levels in a therapeutic drug monitoring would have certainly helped to provide further insights into the case.[37] However, this is not applicable in the herein presented setting of patient care in a community pharmacy.

Finally, we want to refer to the single drug analysis of the patient's comedication (see Table 1), which was possible due to the pharmacogenetic profile, and which influenced the pharmacist's recommendations for this particular patient. The first active substance we want to mention is pantoprazole. A few studies have demonstrated that CYP2C19 is an important determinant in its metabolism[38–40] linking changes in plasma levels to the phenotype of CYP2C19 metabolism.[38] The recommendations on PGx implementation suggest a four-fold (400%) elevation in the dose of pantoprazole in the therapy of the *H. pylori* infection and other indications to ensure the intended pharmacological activity.[19] The majority of drugs in the class of proton pump inhibitors are mainly metabolized via CYP2C19. However, rabeprazole is metabolized via a non-enzymatic pathway; therefore, it is less susceptible to the influence of genetic polymorphisms of CYP2C19.[41]

The second active substance in this context is ibuprofen, which is metabolized by CYP2C9, CYP2C8, CYP2C19 and multiple UDP-glucuronosyltransferases, where CYP2C9 is assumed to be of major relevance.[42] In 2020, the CPIC published a guideline for non-steroidal anti-inflammatory drugs (NSAIDs) in the context of genetic variants of CYP2C8 and CYP2C9[43], where IMs might have a higher risk for adverse events such as gastrointestinal bleeding than others. They recommend starting the therapy with the lowest effective dose for the shortest duration and in agreement with patients' preferences.

Decision

We recommended to discontinue TAM due to the CYP2D6 IM phenotype and the fact that dose escalation would not be an option for this patient due to ADRs, which might be linked to the genetic-associated changes in TAM metabolism. In the recommendation, we suggested a switch to letrozole, a non-steroidal AI for post-breast cancer recurrence therapy after breast cancer. AIs represent a good alternative to TAM also supported by a meta-analysis of the Early Breast Cancer Trials Collaborative Group. Here, the comparison of TAM and AIs revealed that the recurrence rates of AIs are reduced by 30% compared to TAM and that 10-year mortality is reduced by 15% by AIs compared to TAM.[44] Jeong et al[45] also support the switch to AIs as they have shown to be superior to TAM.[16] Furthermore, letrozole is primarily catalyzed by CYP2A6 and CYP3A4 and it is assumed to be independent of metabolism by CYP2D6, CYP2C9 and CYP2C19.

In addition, we recommended ibuprofen for short-term intake only and advised the additional intake of a proton pump inhibitor, as the CYP2C9 IM status may increase the risk of gastrointestinal bleedings during the ibuprofen therapy. For the proton pump inhibition, we recommended discontinuing pantoprazole, due to the CYP2C19 UM status which might lead to subtherapeutic pantoprazole plasma levels and suggest to switch to rabeprazole, which is mainly metabolized by a non-enzymatic pathway.

Follow-Up

The recommendations were forwarded to the treating gynecologist, who decided – together with the patient – to start letrozole in combination with the GnRH-agonist leuprorelin (also known as leuprolide). Despite the patient's fear of further ADRs caused by the new treatment, the pharmacogenetic profile provided sufficient argumentation for the patient to adapt her post-breast

cancer recurrence therapy. Accordingly, TAM was stopped and switched to a monthly injection of leuprorelin 2.75 mg (due to the premenopausal status of the patient) and supplemented by letrozole 2.5 mg once daily initiated 2 weeks after the initiation of leuprorelin. Six months after the initiation of letrozole and leuprorelin, the patient reported a minimal local reaction at the injection site of the leuprorelin, but she does not suffer from any other ADRs. Moreover, the patient was also able to go back to work part-time. Furthermore, the patient stopped the ibuprofen treatment, and therefore the proton pump inhibitor was not indicated anymore to prevent gastrointestinal bleeding, but the patient wanted to have rabeprazole on-hold in case of an ibuprofen intake in the future.

Conclusion

This case presents a patient showing ADRs in the adjuvant therapy with TAM. We analyzed the patient's medication and used a pharmacogenetic profile provided by a commercially available panel comprising 30 genes with up to 100 variants and drug-specific interpretation. Relevant variants in the CYP enzymes CYP2D6, CYP2C9, and CYP2C19 were detected. As a result of this pharmacist-led medication review with pharmacogenetic analyses, concrete genotype-driven recommendations for the treating physician were compiled.

At first, considering only the described ADRs would have tempted us to reduce the TAM dosage, assuming that the patient's END blood concentrations might be elevated. Surprisingly, the assessed CYP2D6 genotype (CYP2D6 IM) did not support this hypothesis. On the contrary, respecting the PGx guidelines[16,18,19] according to the revealed CYP2D6 genotype, the patient might suffer from limited TAM effectiveness due to decreased bioactivation to END via CYP2D6 and therefore will not benefit from a dose reduction. Consequently, we recommended to stop TAM and switch to letrozole in combination with leuprorelin. Furthermore, we were able to deliver recommendations to the comedication of the patient.

This case showed the added value of a large pharmacogenetic panel and the complexity of integrating a pharmacogenetic profile into a recommendation. Consequently, the decision-making process needs an interdisciplinary approach for the clinical implementation of PGx.

Acknowledgments

We would like to thank Tamara Imfeld-Isenegger for proofreading the manuscript.

Author Contributions

Chiara Jeiziner led the execution of the report and was part of conception, study design, acquisition of data, analysis and interpretation of the case. She drafted the article. Céline Stäuble was part of analysis and interpretation of the case. She reviewed the article critically. Markus Lampert was part of conception and interpretation of the case. He reviewed the article critically. Kurt Hersberger was part of conception, study design, execution, and interpretation of the case. He reviewed the article critically. Henriette Meyer zu Schwabedissen was part of conception and study design of the case and she led data analysis and interpretation. She revised the article. All the authors have agreed on the submission of the article to the journal Pharmacogenomics and Personalized Medicine. All the authors reviewed and agreed on all versions of the article before submission, and during revision, accepted the final version for publication, and any significant changes introduced at the proofing stage. All the authors agree to take responsibility and be accountable for the contents of the article.

Ethics Disclosure

The patient has provided informed consent for the use of her data as well as for the publishing of the case details for research purposes. The case was collected in the framework of the observational study "Pharmacogenetic Testing of Patients with unwanted Adverse Drug Reactions or Therapy Failure" approved by the local ethics committee (PGx-exHerberger-01452) on 31.10.2019.

Disclosure

There are no conflicts of interest.

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CASE REPORT

Is Pharmacogenetic Panel Testing Applicable to Low-Dose Methotrexate in Rheumatoid Arthritis? – A Case Report

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Purpose: Pharmacogenetic (PGx) panel testing could help to determine the heritable component of a rheumatoid arthritis (RA) patient's susceptibility for therapy failure and/or adverse drug reactions (ADRs) from methotrexate (MTX). Considering the literature mentioning the potential applicability of PGx panel testing within MTX regimens, we discuss the case of a patient who was treated with MTX, suffered from ADRs, and obtained a reactive PGx panel testing.

Genotyping: We used a commercial PGx panel test involving the ABC-transporters P-glycoprotein (P-gp; gene: *ABCB1*), and breast cancer resistance protein (BCRP; gene: *ABCG2*), the solute carriers reduced folate carrier 1 (RFC1; gene: *SLC19A1*), and organic anion transporting polypeptide 1B1 (OATP1B1; gene: *SLCO1B1*), and the enzymes inosine triphosphatase (ITPA), and glutathione transferase P1 (GSTP1). In addition, we genotyped the patient for the enzymes 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR)/inosine monophosphate (IMP) cyclohydrolase (gene name: *ATIC*), gamma-glutamyl hydrolase (gene name: *GGH*) and methylenetetrahydrofolate reductase (gene name: *MTHFR*).

Results: The PGx profile of the patient revealed genetic variants in SLC19A1, ABCB1, and MTHFR, which may explain the ADRs experienced during the treatment with MTX and a potentially lower efficacy of MTX. Based on our interpretation of the PGx profile, we recommended the patient to avoid MTX in the future.

Conclusion: The MTX pathway is complex, which makes the interpretation of genetic variants affecting metabolism challenging. A reactive PGx panel test was applicable to explain ADRs experienced during MTX treatment for a patient with RA. However, the clinical utility of PGx-guided MTX treatment in a primary care setting is still limited. In order to base a recommendation for MTX on PGx data, we need genome-wide association studies, large prospective multicenter studies and PGx studies, which analyze different multi-gene haplotypes and gene-drug-drug interactions for MTX.

Keywords: pharmacogenetics, PGx, ABCB1, SLC19A1, MTHFR, rheumatoid arthritis, methotrexate, MTX

Introduction and Background

Rheumatoid arthritis (RA) is a common chronic disease with a prevalence of 0.5% to 1.1%,[1] where a suitable pharmacotherapy can prevent irreversible joint deformation, and thereby increase the quality of life. Here, it is assumed that an early diagnosis with adequate treatment is crucial as early treatments have been linked to better response rates,[2] thereby leading to less joint damage in the long term.

Methotrexate (MTX) is a folic acid antagonist with anti-inflammatory and immune-modulating effects. Low-dose MTX regimens are indicated in the treatment of arthritis.[3] In this context, MTX is considered as a "disease-modifying anti-rheumatic drug" (DMARD) and is considered first choice,[4] where it can be combined with other DMARDs including small molecules (eg, JAK-inhibitors) or biologicals (eg, TNF-alpha-inhibitors) in patients exhibiting insufficient MTX-response.[3] However, nearly 30% of the patients treated with MTX experience inefficacy or adverse drug reactions (ADRs).[4,5]

Received: 20 December 2021
Accepted: 3 April 2022
Published: 9 May 2022

Interindividual differences in MTX response may find its explanation in its complex metabolism.[6–8] In the following, we will describe various enzymes and transporters, which are part of the MTX metabolism (see Figure 1), and we will highlight those, where genetic variants have been linked to changes in MTX efficacy or safety (see "evidence for polymorphism" in Tables 1 and 2). We are also reporting on genes, which are not mentioned in the Swiss drug label (summarized at https://www.pharmgkb.org/labelAnnotations and[9]), and which are not assessed for genetic variability in our patient.

In the context of oral application, MTX has to pass enterocytes. Here, entry is assumed to be primarily governed by the reduced folate carrier (RFC1, gene name: *SLC19A1*), and the proton-coupled folate transporter (PCFT, gene name: *SLC46A1*).[10] Early findings linked the G80A (rs1051266) variant in RFC1 to changes in folate status,[11] which is the physiologic substrate of this particular transporter. There are multiple reports linking the G allele to an increased risk of drug-induced toxicity, especially gastrointestinal toxicity,[10,12] hepatotoxicity,[12,13] and alopecia.[13] However, other reports associated the A allele with an enhanced efficacy of MTX and also with higher intracellular levels of methotrexate polyglutamate (MTX-PG), an active metabolite of MTX.[14]

While *SLC19A1* and *SLC46A1* are facilitating cellular entry, there are members of the ATP-binding cassette transporter family, namely *ABCB1*,[15] *ABCC2* and *ABCG2*, that are assumed to limit methotrexate bioavailability by active efflux of the molecule.[16] MTX response depends on the expression of *ABCG2* (breast cancer resistance protein, BCRP)[17] and it has been shown that genetic variants influenced MTX plasma levels in pediatric patients.[18] Moreover, ABCG2 was associated with MTX discontinuation in a clinical PGx model.[19] For ABCB1 (P-glycoprotein, P-gp), there are reports testing the association of genetic variants with efficacy or safety of MTX. The T allele in the C3435T (rs1045642) polymorphism was associated with a higher risk for ADRs,[20] non-response,[21] and low disease activity.[22] However, the C allele has been associated with increased toxicity[12,23] Therefore, we only know that there might be a certain effect; however, it is impossible to precisely define the impact of ABCB1 on the MTX pathway.

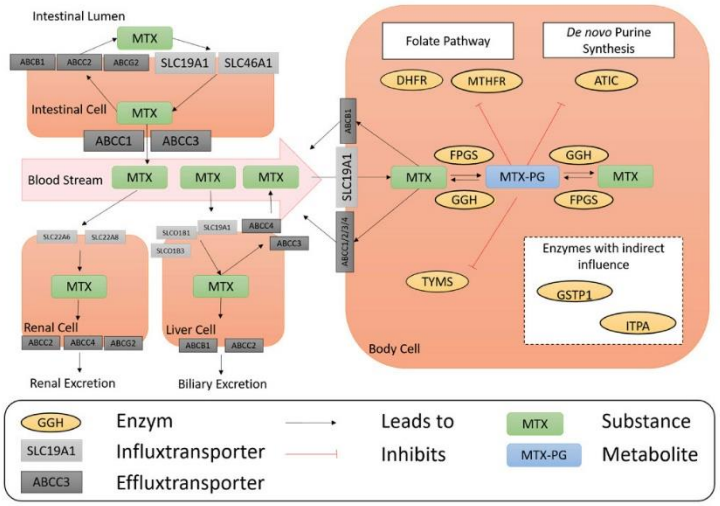

Figure 1 Overview of the current understanding on enzymes and transporters involved in the pharmacokinetics and pharmacodynamics of methotrexate (MTX).
Abbreviations: ABCB1, ATP-binding cassette transporter B1 (aka P-glycoprotein); ABCC1–4, ATP-binding cassette transporter C1-C4 (aka multidrug resistance protein) (MRP1 to MRP4); ABCG2, ATP-binding cassette transporter G2 (aka breast cancer resistance protein BCRP); ATIC, 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR)/inosine monophosphate (IMP) cyclohydrolase; DHFR, dihydrofolate reductase; FPGS, folylpolyglutamyl synthase; GGH, gamma-glutamyl hydrolase; GSTP1, glutathione transferase P1; ITPA, inosine triphosphate pyrophosphatase; MTHFR, methylenetetrahydrofolate reductase; MTX-PG, methotrexate polyglutamate; SLC19A1, solute carrier 19A1 (aka reduced folate carrier 1, RFC1); SLCO1B1/1B3, organic anion transporting polypeptide (OATP) 1B1 and OATP1B3; SLC22A6/A8, organic anion transporter (OAT)1 and OAT3; SLC46A1, proton-coupled folate transporter (PCFT); TYMS, thymidylate synthase.

Table 1 Summary of the Genetic Variants of the Patient Determined with a Commercial PGx Panel Test for MTX

Gene, NE (Nucleotide Exchange); AE (Amino Acid Exchange)	Genotype of the Patient	Function in Pathway	Evidence for Polymorphism
ATP-binding cassette transporter B1 (ABCB1) aka P-glycoprotein, Efflux transporter →altered transport			
ABCB1, g.2685+49T>C	rs2032583 CT	Active cellular efflux[16]	No studies in relation to low-dose MTX
ABCB1 c.3435T>C; p.I1145I	rs1045642 CC		T allele: a higher risk for ADRs,[20] non-response,[21] low disease activity;[22] C allele: increased toxicity[12,23]
ABCB1 c.1236T>C; p.G412G	rs1128503 CC		Conflicting evidence[19,24]
ABCB1 c.2677G>A; p.A893T	rs2032582 GG		No studies in relation to low-dose MTX
ABCB1 c.2677G>T; p. A893S	rs2032582 GG		No studies in relation to low-dose MTX
ATP-binding cassette transporter G2 (ABCG2) aka Breast cancer resistance protein (BCRP), Efflux transporter →no alternation in transport			
ABCG2 c.421C>A; p.Q141K	rs2231142 CC	Active cellular efflux[16]	A allele: adverse events[47]
ABCG2 g.1194+928A>G,	rs13120400 GG		G allele: reduced improvement or reduced severity[48]
ABCG2 g.89055379G>A,	rs17731538 GG		A allele: reduced improvement or reduced severity[48]
Glutathione transferase P1 (GSTP1), Detoxification of organic substances and protection of the organism from oxidative stress →no risk			
GSTP1 c.313A>G; p.I105V	rs1695 AG	Detoxification of drugs	Conflicting evidence[38,39]
Inosine triphosphate pyrophosphatase (ITPA), Adenosine pathway →no risk			
ITPA c.94C>A; p. P32T	rs1127354 CC	Conversion of inosine triphosphate (ITP) to inosine monophosphate (IMP)	C allele: decreased risk of gastrointestinal toxicities and increased response to MTX[32,37]
Organic anion transporting polypeptide 1B1 (SLCO1B1), Uptake transporter →no alteration in transport			
SLCO1B1 c.521T>C; p.V174A	rs4149056 TT	Hepatic MTX excretion[26]	No studies in relation to low-dose MTX
SLCO1B1 c.463C>A; p.P155T	rs11045819 CC		No studies in relation to low-dose MTX
SLCO1B1 c.388A>G; p.N130D	rs2306283 AA		No studies in relation to low-dose MTX
SLCO1B1 c.-910G>A or g.4195G>A	rs4149015 GG		No studies in relation to low-dose MTX
Solute carrier 19A1 (SLC19A1), Uptake transporter → higher risk for toxic side effects; lower chance for remission			
SLC19A1 (RFC1) c. 80G>A; p. H27R	rs1051266 GG	Entry in enterocytes[10]	G allele: gastrointestinal toxicity,[10,12] hepatotoxicity,[12,13] and alopecia;[13] A allele: enhanced efficacy of MTX[14]

Notes: The subtitle consists of the gene name, the abbreviation, the pathway and the evaluation of the commercial PGx panel test for MTX.

MTX is primarily excreted through renal glomerular filtration, however in the tubular system there are multiple transporters expressed that are known to interact with MTX including the aforementioned *SLC19A1, ABCG2, ABCB1, ABCC2*. However, *ABCG2, ABCB1, and ABCC2* are also expressed in the canalicular membrane of hepatocytes, thereby influencing biliary excretion of MTX involving the efflux transporters *ABCC2, ABCB1* and *ABCG2*, while the sinusoidal

Table 2 Summary of the Observed Genotypes Detected in Additional Genes Involved in the MTX Pathway

Gene, NE (Nucleotide Exchange); AE (Amino Acid Exchange)	Genotype of the Patient	Function in Pathway	Evidence for Polymorphism
5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR)/ inosine monophosphate (IMP) cyclohydrolase (ATIC), De novo purine synthesis pathway →no risk			
ATIC c.347C>G; p. Thr116Ser	rs2372536 CC	Conversion of AICAR into formyl aminoimidazole carboxamide ribonucleotide (FAICAR).[36]	G allele: increased risk of toxicity and better response.[21,36,37]
Gamma-glutamyl hydrolase (GGH), Polyglutamation →no risk			
GGH−401 C>T	rs3758149 CC	Conversion of MTX-PG to MTX depends on the gamma-glutamyl hydrolase.[49]	T allele: decreased conversion of MTX to active metabolite and decreased MTX response[28,49]
Methylenetetrahydrofolate reductase (MTHFR), Folate pathway → risk of higher toxicity and lower MTX response			
MTHFR c.1298 A>C; p. Glu429Ala	rs1801131 AC	Conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate	C allele: central nervous system toxicity,[32] hepatotoxicity,[33] gastrointestinal ADRs[34] or overall toxicity;[25] A allele: better MTX response[25,35]
MTHFR c.67765 C>T; p. p. Ala222Val	rs1801133 CT		T allele: increased risk for gastrointestinal ADRs,[29,30] hepatotoxicity,[13,30] and neurotoxicity[31]

Notes: The subtitle consists of the gene name, the abbreviation, the pathway and the evaluation for MTX.

transporters *ABCC3* and *ABCC4* extrude MTX back into the circulation.[6,10] Finally, the hepatocellular entry of MTX is assumed to involve the sinusoidal organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, which are encoded by *SLCO1B1* and *SLCO1B3*, respectively. Even if only a small part of the MTX dose is excreted via the bile, there are data obtained in a transgenic mouse model supporting OATP1B1 as a determinant of hepatic MTX excretion.[26] In particular, for OATP1B1 we know that there are genetic variants influencing its transport function.[27]

In addition to transmembrane transport, MTX also undergoes conversion catalyzed by multiple enzymes. One of these conversions is the polyglutamation process catalyzed by the folylpolyglutamate synthetase (*FPGS*) resulting in the biologically more active methotrexate polyglutamate (MTX-PG). Both MTX and MTX-PG interact with enzymes in the folate pathway, thereby exerting the pharmacological function. The conversion of MTX-PG to MTX depends on the gamma-glutamyl hydrolase (*GGH*),[6] where the C401T (rs3758149) polymorphism has been tested for its influence on MTX-PG levels, drug response and the risk for ADRs.[13,28] The homozygous genotype TT was associated with higher MTX-PG-levels and altered MTX-response, whereas the wild-type genotype CC was associated with a higher risk of overall ADRs.[13,28]

Intracellular MTX and its polyglutamated metabolite (MTX-PG) inhibit the dihydrofolate reductase (DHFR), which catalyzes the reduction of dihydrofolate (DHF) to tetrahydrofolate (THF), thereby leading to less THF, which is important for the *de novo* purine synthesis and the production of biologically active folate cofactors.[6] Indeed, the reduction in THF is assumed to impact enzymes of the folate pathway, eg, the methylenetetrahydrofolate reductase (*MTHFR*). For *MTHFR*, the two polymorphisms A1298C (rs1801131) and C677T (rs1801133) have been extensively investigated. The T allele within the C677T polymorphism was associated with an increased risk for toxicity, especially gastrointestinal ADRs,[29,30] hepatotoxicity,[13,30] and neurotoxicity.[31] The C allele within the A1298C polymorphism of *MTFHR* was linked to a higher risk for ADRs, such as central nervous system toxicity,[32] hepatotoxicity,[33] gastrointestinal ADRs[34] or overall toxicity,[25] whereas the A allele was linked to a higher probability of response measured as a percentage of improvement in the JADAS-71 score[35] at 3 and 6 months after treatment start and at the last follow-up visit.[25]

In addition to the folate pathway, MTX-PG inhibits the bifunctional purine biosynthesis protein (PURH), also known as inosine monophosphate (IMP) cyclohydrolase (gene name: *ATIC*), which converts aminoimidazole carboxamide

ribonucleotide (AICAR) into formyl aminoimidazole carboxamide ribonucleotide (FAICAR). The C347G (rs2372536) variant in *ATIC* has been associated with decreased *ATIC* activity leading to an accumulation of AICAR and adenosine. The increased concentration of adenosine in the extracellular space is thought to be part of the mechanism of MTX action as adenosine exerts anti-inflammatory functions and antiproliferative effects.[36] The G allele in the C347G polymorphism is extensively discussed as a factor impacting the risk for toxicity and improved response to MTX at the same time.[21,37] Also involved in the purine homeostasis is the inosine triphosphate pyrophosphatase (*ITPA*) converting inosine triphosphate (ITP) to inosine monophosphate (IMP). In *ITPA*, the C allele in the C94A (rs1127354) variant has been linked to a decreased risk of gastrointestinal toxicities as well as an increased response to MTX.[32,37] The last enzyme of the MTX pathway we want to mention is the glutathione transferase P1 (*GSTP1*). Glutathione transferases are involved in the detoxification of drugs, and their variants have been associated with increased drug toxicity. The G allele in the A313G (rs1695) variant in *GSTP1* has been associated with central nervous system toxicity;[38] however, in another study, no association with hepatotoxicity[39] was found.

Taken together, the MTX pathway has to be rated as rather complex, where various genetic variants have been associated with changes in pharmacokinetics and/or drug response and safety. Already in 2006, Ranganathan et al[36] suggested that Pharmacogenetics (PGx), the study of genetic variations related to drug response,[40] could help individualize the treatment with MTX. Consequently, pharmacogenetic (PGx) testing could be applied to determine and/or predict the heritable component of a RA patient's susceptibility to experience therapy failure and/or ADRs from MTX treatment in a reactive and/or pre-emptive PGx test setting.[7,8,41]

Considering the literature mentioning the potential applicability of PGx panel testing within MTX regimens, we would like to discuss the case of a patient with RA, who was treated with MTX, suffered from ADRs, and obtained a reactive PGx panel testing within the setting of a case series called "Pharmacogenetic Testing of Patients with Adverse Drug Reactions or Therapy Failure" (Clinicaltrials.gov: NCT04154553).

Case Presentation

A male patient of 87 kg, born 1980, presented his case in a community pharmacy offering a commercial PGx panel test. The patient was diagnosed with rheumatic arthritis in 2014 by the physician (CCP 911 kU/L (<7), Rheuma factors 304 kU/L (<14), CRP 1.5 mg/l (<10)). One year later, a therapy with MTX was started, increasing from 12.5 mg subcutaneously weekly, by 2.5 mg at a time up to the target dose of 20 mg. This dosage is in agreement with the S2 guidelines published by the German Society of Rheumatology[42] and the guidelines of the American College of Rheumatology.[4] To bridge the gap until the effectiveness of MTX could be expected (about six to eight weeks), the patient received prednisone 20 mg for one week, then 10 mg and 7.5 mg for 2 weeks each until a provisional maintenance dose of 5 mg was reached. In addition, an intake of 5 mg folic acid was recommended 12 to 24 hours after MTX application to reduce ADRs. After four months of treatment, the MTX therapy was discontinued due to various ADRs, such as nausea, headache, and sore muscles. According to information from the treating rheumatologist, the monthly measured lab values (CRP, transaminases, blood count) did not show any abnormalities. The patient's symptoms stopped as soon as he discontinued drug intake. He then started taking low-dose steroids for about six months. Later on, he switched to biological DMARDs, namely baricitinib and tofacitinib. The latter was used for the longest period of time with a dose regimen of 5 mg twice a day. The reason for switching from baricitinib to tofacitinib was symptoms of influenza which he suffered from every now and then. At the time of counselling, the patient was taking tofacitinib and prednisone as anti-rheumatics, supplemented with NSAIDs and the proton pump inhibitor dexlansoprazole (summarized in Table 3). Even if the patient is currently on a treatment with biologics, which are hitherto not known to be linked in efficacy or safety to genetic variants in the pharmacokinetically relevant genes typically screened for genetic variability in PGx testings, a PGx panel test was issued on a reactive basis in order to determine whether his PGx profile would be applicable to explain the ADRs he experienced during intake of MTX.

Table 3 Medication of the Patient at the Time of Pharmacogenetic Panel Testing

Substance	Dosage	Indication
Tofacitinib 5 mg	1-0-1	Rheumatoid arthritis
Prednisone 5 mg	1-0-0	Rheumatoid arthritis
Diclofenac 150 mg	0-1-0	Influenza symptoms
Ibuprofen 200 mg	1-0-1 as necessary	Influenza symptoms
Dexlansoprazole 30 mg	0-1-0	as long as Ibuprofen
Vitamin D3 4500 IE/ml, 10ml	2 bottles per month	Vitamin D3 deficiency

Analyses of Single Nucleotide Polymorphisms in the MTX Pathway

Following the protocol as approved by the ethics committee northwestern and central Switzerland (EKNZ-2019-01452), the patient signed an informed consent. We used the commercial PGx panel test called Stratipharm issued by humatrix AG (Pfungstadt, Germany). It consists of a laboratory analysis of approximately 100 pharmacologically relevant polymorphisms in over 30 different genes, which code for transport proteins, metabolizing enzymes, or drug targets. Polymorphisms are detected applying real-time PCR using the automated Life Technologies QuantStudio 12 k flex (Thermo Fisher, Waltham, MA, USA) with the respective chemistry. Humatrix AG provides not only the results of genetic testing but also the prediction of a drug-specific phenotype (PGx profile). In addition to the commercial PGx panel test we genotyped two variants of the methylenetetrahydrofolate reductase (*MTHFR*), one variant of the gamma-glutamyl hydrolase (*GGH*) and one variant of the 5-aminoimidazole-4-carboxamide ribonucleotide formyl-transferase (AICAR)/inosine monophosphate (IMP) cyclohydrolase (gene name: *ATIC*). These variants were selected as important determinants in the MTX pathway based on previous reports on MTX efficacy and safety. The additional genotyping was performed after DNA extraction from blood samples using the QIAcube and respective chemistry (qiagen, Hilden, Germany) and followed by real-time PCR based genotyping using commercially available TaqMan probe/primer mixes and genotyping chemistry (Applied Biosystems, Thermo Fisher, Waltham, MA, USA).

For MTX, the commercial PGx panel test considers genetic variants in the ATP-binding cassette (ABC)-transporter P-glycoprotein (P-gp, gene: *ABCB1*) and breast cancer resistance protein (BCRP; gene: *ABCG2*), and the solute carriers reduced folate carrier 1 (RFC1; gene: *SLC19A1*), and organic anion transporting polypeptide 1B1 (OATP1B1; gene: *SLCO1B1*). Furthermore, the commercial PGx panel test evaluates genetic variants of the enzymes inosine triphosphatase (*ITPA*), and the glutathione transferase P1 (*GSTP1*). The genetic profile of the patient for these genes and the predicted MTX phenotype are summarized in Table 1. In detail, based on the heterozygosity in ABCB1 phenotypically associated with "altered transport activity", the heterozygosity in GSTP1 associated with "no elevated risk", and the homozygosity in SLC19A1 associated with an "increased risk for toxic ADRs and lower chance for remission", the overall interpretation by the commercial PGx panel test was as follows:

> The genetic profile of the patient may result in a reduced response and an increased risk of adverse drug effects. The therapy with MTX can be continued, but should be monitored for that.

Moreover, we have determined the genetic make-up of the patient for the enzymes 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR)/inosine monophosphate (IMP) cyclohydrolase (gene name: *ATIC*), gamma-glutamyl hydrolase (gene name: *GGH*) and methylenetetrahydrofolate reductase (gene name: *MTHFR*). The results of the genotyping of selected variants and the respective function within the MTX pathway is summarized in Table 2. Here, our patient is heterozygous carrier of both variants assessed within the MTHFR gene locus.

Finally, we also had a look at the genetic constellation of our patient evaluating his co-medication consisting of diclofenac, ibuprofen, prednisone, dexlansoprazole and vitamin D3 (see Table 3). For the non-steroidal anti-inflammatory

drugs (NSAR), the CYP2C9 intermediate metabolizer status was detected. No further PGx warnings appeared for other co-medications. For vitamin D3, no PGx information was available.

Interpretation and Recommendation

Interpretation

As illustrated in the introduction and shown in Figure 1 the MTX pathway is complex, which makes the interpretation of genetic variants affecting metabolism challenging. The PGx profile of the patient revealed genetic variants in SLC19A1, ABCB1, and MTHFR, which may explain the ADRs experienced during the treatment with MTX and a potentially lower efficacy of MTX.

SLC19A1 codes for the reduced folate carrier and facilitates cellular entry, making it a crucial step in the MTX pathway. Our patient is homozygous carrier of the risk allele (G) in SLC19A1 G80A (rs1051266). There are multiple reports linking the G allele with ADRs, such as gastrointestinal toxicity,[10,12] hepatotoxicity,[12,13] and alopecia,[13] supporting our conclusion that the genetic constellation of the *SLC19A1* of the patient leads to a high probability of ADRs. Moreover, as the 80G allele has been linked to a lower chance for remission,[43] a treatment with MTX of a patient with this genotype appears unfavorable.

The patient is heterozygous in ABCB1 T49C (rs2032583), and homozygous to the C allele in ABCB1 C3435T (rs1045642). Both variants are located within the gene locus *ABCB1*, which encodes for the efflux transporter P-glycoprotein: The observed genotype led to the indication of "altered transport" in the results of the commercial PGx panel test. We are not aware of studies investigating the influence of T49C polymorphism on MTX efficacy and safety. Studies on C3435T polymorphism had diverging results. The 3435C allele was associated with increased toxicity,[17] while the 3435T allele has been associated with high disease activity and increased ADRs,[20] non-response,[21] and with a low disease activity score[22] and PharmGKB[44] cites that carriers of the 3435T allele might have an increased risk of toxicity. With these inconclusive findings reported in the literature, it is difficult to decide on the impact the variants in *ABCB1* would have on MTX transport, thereby making a predictive decision impossible.

In addition to the variants identified with the commercial PGx panel test, we observed the patient's heterozygosity for the variants A1298C (rs1801131) and C677T (rs1801133) in the *MTHFR* coding for methyltransferase folate reductase. There are many studies in patients with low-dose MTX linking these two variants to ADRs or even toxicities. In summary, the findings of these studies suggest that the 677T allele is a risk factor for gastrointestinal ADRs,[29,30] hepatotoxicity,[13,30] and neurotoxicity[31] and that the 1298C allele is linked to an increased risk for central nervous system toxicity,[32] hepatotoxicity,[33] gastrointestinal ADRs[34] or overall toxicity.[25] Here, a part of the patients' ADRs (nausea) might be explained. However, a study[34] also described a better response in patients carrying 1298AA or 677CC, supporting the assumption that our patient might have had insufficient response to MTX.

In addition to transport and polyglutamation, the pharmacology of MTX also involves pathways such as the adenosine pathway, folate pathway, methionine pathway, and *de novo* purine synthesis. So far, 120 variants in more than 30 genes implicated in the MTX pathway have been investigated.[45] For example, a systematic review of genetic biomarkers for the efficacy of MTX described *SLC19A1* rs1051266, *ATIC* rs7563206, dihydrofolate reductase (*DHFR*) rs836788, thymidylate synthase (*TYMS*) rs2244500, rs2847153, and rs3786362 as relevant genes.[7] With respect to the amount of the literature and the level of evidence, the 19 variants in nine genes assessed within our patient can only be considered candidate genes. Overall 15 variants in 6 genes (mostly transporters) were tested through commercial PGx panel test to which in-house genotyping of 4 variants in 3 genes was added. As the patient was heterozygous to some of the variants, they could have explained the ADRs seen during the treatment.

Recommendation

Based on our interpretation, we concluded that the ADRs previously experienced by the patient were possibly linked to his PGx profile. We therefore recommended the patient to avoid MTX in the future and to stay on his current treatment (tofacitinib, 5 mg, 2 times daily). There were no alerts for this tofacitinib in the PGx profile. The small molecule is metabolized by CYP3A4. Even though this enzyme exhibits high interindividual variability, it is currently assumed that the CYP3A-phenotype is not well predicted by genetic variants.[46] Moreover, the patient also wanted to know if

biological DMARDs, such as abatacept or rituximab would be an option for his future treatment of RA. However, for biologics (as well as for janus kinase inhibitors), there is still little to no evidence for the impact of genetic variants involved in pharmacokinetics as summarized in the herein applied PGx panel. As the recommendations provided by the commercial PGx panel test are based on published evidence, both biologics and janus kinase inhibitors appear as uncritical ("no warning") in the PGx profile by the commercial panel test.

By effecting a PGx panel test, we had the opportunity to analyze the impact of the patient's genetic make-up on his comedication. Accordingly, we were able to provide additional recommendations related to PGx. In detail, due to his CYP2C9 intermediate metabolizer status, treatment with non-steroidal anti-inflammatory drugs (NSAR) should only be applied at the lowest possible dose over the shortest possible period. Moreover, the interaction of the NSAR with prednisone increases the risk of gastrointestinal bleeding. Therefore, we recommended to continue the intake of a proton pump inhibitor, which was already prescribed (dexlansoprazole). All other substances on his current prescription could be continued as described.

Discussion

We presented a case of PGx panel testing for a patient experiencing ADR during MTX treatment. As MTX is still the first-choice drug[4,42] in RA and counts as one of the most effective treatments, the patient was curious about the ADRs, which he experienced under MTX and wanted to know if they had a genetic basis. Our patient learned that his genetic constellation is unfavorable to a treatment with MTX and as he had made the experience of these various described ADRs, he then regained confidence in his current treatment.

Although we were able to link the ADRs to genetic variability in this reactive setting, the question remains whether pre-emptive PGx panel testing in the primary care setting can be used to guide low-dose MTX treatment. Our recommendation to avoid use of MTX in the present case should be nuanced as firstly, PGx results are probabilistic and patients can behave differently from what is expected based on the PGx test and secondly, many individuals may carry these variations and if a general avoidance is adopted, many of them will be deprived of a useful and cost-effective drug. At this point, we argue that due to the complexity of the MTX pathway involving various polymorphic genes, the current evidence for pre-emptive PGx panel testing is insufficient, and it is difficult to translate the prevailing evidence as a whole into clinical recommendations.

When considering all relevant genes, a PGx panel testing for MTX will almost always identify one or more variants potentially affecting efficacy or toxicity. Under the current circumstance, this would lead us to the recommendation to avoid MTX in most cases as evidence-based dosing recommendations are missing. We would argue that the clinical applicability for preemptive PGx panel testing for MTX is currently lacking.

Conclusion

A reactive PGx panel test was applicable to explain ADRs experienced during MTX treatment for a patient with RA. At the moment, the clinical utility of PGx-guided MTX treatment in a primary care setting is limited. In order to base a recommendation for MTX on PGx data, we need genome-wide association studies, large prospective multicenter studies and PGx studies, which analyze different multi-gene haplotypes and gene-drug-drug interactions for MTX. For now, PGx panel testing for MTX appears to be limited to experts which have the possibility of in-depth pharmacological investigations, including therapeutic drug monitoring. In the future, we need a PGx panel text for MTX with clear weight given to each genetic variant. For this, the established and clinically evaluated algorithms augmented by artificial intelligence that are considering the relevance of all tested variants together with other relevant data at the same time in one patient, as well as the inclusion of PGx data into an electronic medical health record, will enable PGx-guided MTX therapy in a primary care setting.

Ethics

The patient has provided informed consent for the use of her data as well as for the publishing of the case details for research purposes. The case was collected in the framework of the observational study "Pharmacogenetic Testing of Patients with unwanted Adverse Drug Reactions or Therapy Failure" (Clinicaltrials.gov: NCT04154553) approved by the

ethics committee northwestern and central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, Hebelstrasse 53, 4056 Basel, eknz@bs.ch) (EKNZ-2019-01452) on 31.10.2019.

Acknowledgment

We would like to thank Dr. med. Pascale Exer for transferring the interesting patient case.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal *Pharmacogenomics and Personalized Medicine*; and agree to be accountable for all aspects of work.

Disclosure

The authors report no conflicts of interest in this work.

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Project B4

International Journal of Clinical Pharmacy
https://doi.org/10.1007/s11096-023-01596-8

RESEARCH ARTICLE

Pharmacogenetic testing and counselling in the community pharmacy: mixed-methods study of a new pharmacist-led service

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Received: 2 January 2023 / Accepted: 23 April 2023

Abstract

Background Pharmacogenetic (PGx) testing and counselling (short: PGx service) in the community pharmacy is not routinely practiced. We propose a comprehensive pharmacist-led service where PGx information is integrated into medication reviews.

Aim To evaluate the pharmacist-led service comprising PGx testing and counselling (PGx service) from the perspective of patients.

Method For this mixed-methods study, we conducted two follow-up interviews *F*1 and *F*2 with patients recruited for the PGx service in a community pharmacy after 1st of January 2020. The semi-structured interviews were held by phone call and covered understanding of PGx, the implementation of recommendations, handling of PGx documents (list of concerned substances and PGx recommendation), gain in medication knowledge, and willingness to pay for the PGx service.

Results We interviewed 25 patients in *F*1 and 42 patients in *F*2. Patients were generally able to understand and use results of the PGx service. At least one PGx recommendation was implemented for 69% of the patients. Handling of PGx documents ranged from patients having forgotten about the PGx results to patients consulting the list for every medication-related decision; the latter often expecting negative effects. Finally, 62% of the patients were willing to pay for the PGx service.

Conclusion For future PGx testing and counselling, HCPs should consider the patients' health literacy in a standardized way and use adequate communication skills to enhance the patient's understanding in PGx and to attenuate potential negative expectations.

Keywords Interprofessional pharmaceutical care · Medication review · Personalized pharmacotherapy · Pharmacy service

Impact statements

- Evaluation of a new pharmacist-led service comprising pharmacogenetic (PGx) panel testing covering up to 30 genes and 100 variations integrated into a comprehensive medication review.
- Our study covers the broad patient population which is encountered in the community pharmacy.
- We used a mixed-methods study to evaluate the new pharmacist-led PGx service from the perspective of patients.
- In more than two-thirds of the patients, at least one PGx recommendation was implemented.
- When communicating PGx results, healthcare professionals need adequate communication skills to attenuate potential negative expectations towards the medication.

Introduction

In clinical practice, interindividual drug response ranges from ineffectiveness to adverse drug reactions (ADRs). Pharmacogenetics (PGx) is the study of genetic variations related to drug response [1], i.e., activity and/or expression of enzymes and transporters involved in drug metabolism. Of 167 substances containing information on PGx influencing drug safety and/or efficacy in Swiss drug labels, 55%

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Published online: 20 June 2023

(93) are classified as "actionable" PGx information [2], thereby referring to changes in efficacy, dosage, metabolism or toxicity due to genetic variations without mentioning the requirement for a genetic test [3]. Furthermore, international recommendations on PGx-guided drug selection and dosing are available today [4, 5]. However, PGx is not yet routinely used in neither primary nor secondary care. There are numerous barriers to the adoption of PGx ranging from lack of education to the reluctance of health insurances to reimburse healthcare professionals (HCPs) for unacknowledged procedures [6–8]. Nevertheless, there are also clear enablers, such as accumulating evidence about clinical utility of PGx and the option of putting the pharmacist in the role of providing a PGx service [6, 9]. Notably, the application of a PGx panel test offers the possibility to counsel on several drugs and not only one.

We performed a case series (Clinicaltrials.gov: NCT04154553) where more than 100 patients experiencing ADRs and/or therapy failure (TF) with substances known to be affected by PGx were recruited for pharmacist-led PGx testing and counselling (short: PGx service) [10, 11]. The comprehensive pharmacist-led PGx service is depicted in Fig. 1. For the PGx service, we worked with a commercial provider offering PGx panel testing covering up to 30 genes and 100 variations together with evidence-based interpretation. The resulting recommendations for a single drug in view of the individual genotype are categorized as "Hinweis" (*Engl.*: indication, problems could arise and careful monitoring is needed), "Verdacht" (*Engl.*: suspicion, high probability for problems, change of dose or drug needed) or "Gefahr" (*Engl.*: danger, risk for an acute problem, drug to be avoided or used with ultimate precaution and/or dose adaption). To ease understanding by the patient, a traffic light system was used to visualize medications with "indication" in yellow, "suspicion" in orange, and "danger" in red. Moreover, the service comprises a complete profile of the 30 tested genes and their variants as well as an individualized list of concerned substances. The patient received the list of concerned substances (list of all substances, which are included in the data bank coded with a traffic light system [yellow, orange, red] according to the individual's pharmacogenetic profile), and an individualized PGx recommendation (written report from the pharmacist).

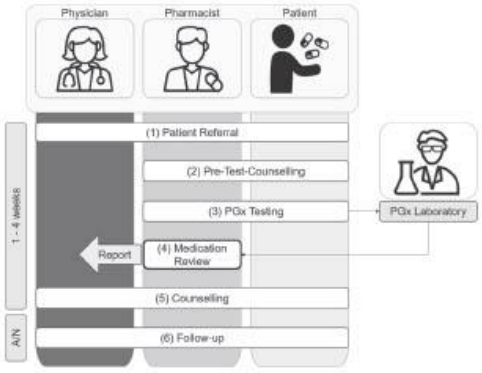

Fig. 1 Overview of pharmacist-led service PGx testing and counselling (short: PGx service) [10]

Patients' perspectives on commercial PGx panel testing have been evaluated with the call for further research [12–14]. If a pharmacist provides a pharmacist-led service involving PGx testing and counselling, the patient needs to be able to understand, and in the following, implement the PGx-based recommendations.

Aim

As part of the case series study, we aimed to evaluate the patients' perspective of the pharmacist-led service comprising PGx testing and counselling. The service included a follow-up. In this study, we conducted semi-structured interviews with counselled patients one month and at least four months after the PGx service. Patients' understanding of PGx, implementation of recommendations, handling of PGx documents (list of concerned substances and PGx recommendation), gain in medication knowledge, and willingness to pay for the PGx service were collected.

Ethics approval

The case series "Pharmacogenetic Testing of Patients with unwanted Adverse Drug Reactions or Therapy Failure" was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local ethics committee in northwestern and central Switzerland (Ethikkommission Nordwest- und Zentralschweiz, Hebelstrasse 53, 4056 Basel, eknz@bs.ch) (EKNZ-2019–01,452) on 31.10.2019.

Method

For the elaboration and reporting of our study, we considered the COREQ (Consolidated criteria for Reporting Qualitative research) checklist [15].

Study design and setting

We used a mixed-methods study design [16, 17] with predefined themes aiming to explore patients' understanding of PGx, implementation of recommendations, handling of PGx documents (list of concerned substances and PGx recommendation), gain in medication knowledge, and willingness

to pay for the PGx service. The PGx service took place in a community pharmacy in Basel. We conducted two semi-structured interviews with patients one month (*F*1) and 4 months or more (*F*2) after the PGx service. The use of both quantitative and qualitative data enabled a broad insight into the perspective of the patient.

Participant recruitment

All patients recruited into the case series after December 1st 2020 were included for *F*1 and *F*2. In addition, and to increase the sample size, all patients recruited to the case series from January 1st 2020 to November 30th 2020 were included for *F*2. To check for data saturation, an interim analysis was conducted on September 30th 2021.

Data collection

For the semi-structured interviews, CJ, PhD, female, a pharmacist by training who had met all participants in the case series previously, developed a separate interview guide for each of the two follow-up interviews, which were reviewed by two members of the PGx expert team (KH and HMzS) and piloted with five patients each. Data were collected by one interviewer (CJ) during bilateral phone calls and documented in a MS word template. During follow-up interview 1 (*F*1), patients answered six closed questions and three assessments via a 10-item Likert-scale in three sections about understanding of PGx, medication knowledge, and general feedback on the PGx service. During follow up-interview 2 (*F*2), patients answered 11 closed questions, three assessments via a 10-item Likert scale, and five open questions in four sections about PGx-related medication changes, handling of PGx-documents, medication knowledge, and willingness to pay for the PGx testing and counselling after having experienced the pharmacist-led service free of cost. For the latter, we explained to the patients the split in costs for the laboratory test (400 EUR) and costs for the counselling (300 EUR) including a first and second visit of 30 min each, sample collection, and preparation of the recommendation letter of at least 40 min. The 10-item Likert-scales were defined as follows:

- Appropriateness/comprehensibility: 0 = "not at all appropriate/comprehensible" to 10 = "fully appropriate/comprehensible"
- Clarity: 0 = "not at all clear" to 10 = "fully clear"
- Usability: 0 = "not at all usable" 10 = "fully usable"

To categorize the medication, we used the first level of the Anatomical Therapeutic Chemical (ATC) classification system.

Interview guides are available on request from the authors.

Data analysis

The qualitative and quantitative elements of the mixed-methods study are presented in a convergent form for each of the interviewed themes. We analysed the data as follows:

- For quantitative data, we calculated proportions for two-point questions and medians for the 10-item Likert scales. For one open question in *F*1 and *F*2, the interviewer had to note if the patient had mentioned the list of concerned substances and/or the PGx recommendation or not.
- For qualitative data, we used the process of quantitizing, i.e. we transformed the quotes into numeric variables for comparison with the quantitative data [18]. Therefore, CJ and KH defined different categories based on answers to questions from follow-up interviews 1 and 2. Subsequently, three PGx experts (CJ, HMzS, AS) independently categorized the text answers according to the defined categories. In case of discrepancies between the three PGx experts, a discussion was held until consensus was found. Illustrative patient quotations were reported with the corresponding patient identifier, birth year, and sex. A description of the categorization is available on request from the authors.
- Finally, we reported qualitative data in narrative form (e.g., quotations) to enrich quantitative data.

Results

We interviewed 25 of 26 approached patients for the first follow-up interview (*F*1) and 42 of 47 approached patients for the second follow-up (*F*2). The characteristics of patients interviewed in *F*1 and *F*2 were comparable in gender and age (Table 1). The broad range of 120 to 429 days since the second visit for *F*2 was due to the inclusion of patients that had been recruited into the case series study before Dec 1st 2020.

Understanding of PGx (F1)

We interviewed two (6%) patients with only compulsory education, 11 (44%) patients with secondary level of education, and 12 (48%) patients with tertiary level of education. Patients valuated the language used by the pharmacist in the first and second visit as appropriate and the explanations of the PGx results as comprehensible on a 10-item Likert scale. In consequence, most patients (80%) felt no need for a further consultation.

Table 1 Patient characteristics and specifications of follow-up interviews 1 (*F1*) and 2 (*F2*)

Characteristics	Follow-up interview 1 ($n=25$)	Follow-up interview 2 ($n=42$)
Female gender	17 (68%)	31 (74%)
Median age (IQR) [years]	56 (41–71); range: 18–79	54 (45–69.75); range 27–89
Mean time since 2nd visit [days]	47; range: 21–85	22;5 range: 120–429
Time period of recruitment to the case series study	Dec 1st 2020 to Sept 30th 2021	Jan 1st 2020 to Sept 30th 2021
Mean interview duration [min]	9; range: 6—22	22; range: 12–36 min

By quantitizing the question "How would you explain the result of the pharmacogenetic test to a friend?", we deduced the understanding of patients. Depending on the explanations provided by the patients, we differentiated four groups as follows:

- very good understanding, e.g.

  "Through genetic information, I can see to which substances I react best, with which substances side effects could occur, and which substances are better suited. […] So I can start [a medication] with pre-knowledge or try again with a specific medication." a210825, female, 2003

- good understanding, e.g.

  "I would explain what it is about and if the person understands it, I would explain my case, namely that my drugs have been classified differently, that there is none that is dangerous, but with two drugs I have to be careful, and there is one drug that I should not take because I have certain genetic predispositions so that I metabolize it quickly." a210907, male, 2001

- partial understanding, e.g.

  "I cannot explain it scientifically. Due to genetic studies, they studied my medications, whereof two were not optimal." a210223, female, 1947

- no understanding, e.g.

  "It is difficult to make an own interpretation." a210409, male, 1955

In comparison with the reported level of education, patients with higher level of education tended to demonstrate a better understanding for PGx information (Fig. 2).

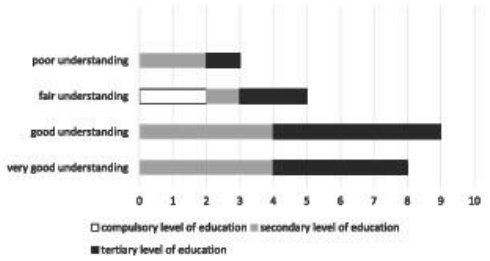

Fig. 2 Level of understanding by the patient of the PGx results versus their level of education by number of individuals ($n=25$)

Implementation of recommendations (F2)

Referring physician Half of the patients ($n=21$) were referred by a general practitioner, whereas the other half were referred by a medical specialist. Thereof, rheumatologists ($n=11$) and psychiatrists ($n=8$) were the most frequent referring specialists. At the time of *F2*, 36 (86%) of the patients had a consultation with their referring physician since the second visit to the community pharmacy. Patients' statements about the reaction of the referring physician differed from positive ($n=16$, 38%), neutral ($n=7$, 17%), negative ($n=4$, 10%), or no statement ($n=15$, 36%) because the physician did not take the time to consult the PGx documents or because consultation with the physician had not yet taken place.

Other physician 29 (69%) patients also visited other (non-referring) physicians and informed them of the PGx testing and provided them with the PGx recommendation. The three most frequent types of other physicians who had received PGx recommendations were general practitioners ($n=11$), psychiatrists ($n=9$), cardiologists ($n=4$) as well as rheumatologists ($n=4$). On average, recommendations were handed over to one (range: zero to five) other physicians.

Comparison of medication plans between current and the first visit revealed that, we identified a total of 75 changes with at least one implemented PGx

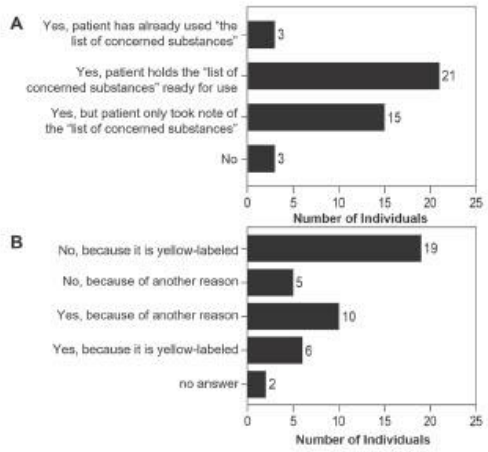

Fig. 3 A: Use of the list of concerned substances; B: Purchase of ibuprofen in case of a yellow indication on the list of concerned substances ($n=42$)

recommendation for 29 (69%) of the patients. Of the 75 implemented PGx recommendations, almost half of them ($n=34$) concerned substances of the anatomic group N "nervous system". Part of these changes 16 (21%) comprised the start of new medication followed by a stop shortly afterwards.

Handling of documents (F2)

The PGx recommendations were read by 35 (83%) of the patients and the clarity was rated with a median of 8 on a 10-item Likert. The list of concerned substances was used by 38 (90%) of the patients and the usability was rated with a median of 9 on a 10-item Likert scale.

We asked patients if they had used the list of concerned substances (Fig. 3A). Depending on the context, in which the list of concerned substances was used, we differentiated four groups as follows:

- patients who have already actively made use of the list, e.g.

"Whenever I get a new medication, I look at the list first. (Either the doctor already looks, or I point it out to him.) I keep the list in my purse." a200205, female, 1962

- patients who hold the list ready for use, e.g.

"I looked at it and studied it, […] I also have it on my smartphone and consult it when a change is due." a200618, female, 1970

- patients who only took note of the list, e.g.

"In the beginning…, I do not know in which drugs all these active ingredients are in. I read the list and saw what kind of drugs there are. I also looked at it together with the doctor. It should be him to give the necessary indication." a201014, male, 1932.

- patients who had not looked at the list of concerned substances.

Furthermore, patients were asked whether they would buy the over-the-counter drug ibuprofen if it were labelled with a yellow indication on their list of concerned substances, (Fig. 3B). Depending on the reason given for or against the purchase of ibuprofen, we differentiated four groups as follows:

- patients who would not buy it, because it is yellow-labelled, e.g.

"After all, I have this clue that something else would probably work, which is why if there's something else, I'd rather buy something else." a210601, male, 1989

- patients who would not buy it, because of another reason, e.g.

"Since I took Lamotrigine and Fycompa [i.e., perampanel], I am very careful, because both times I had an allergic reaction and once, I landed at the emergency ward." a210525, female, 1980

- patients who would buy it, because of another reason, e.g.

"If I have made good experience so far [….] or no alternative is available. Otherwise, I would notice the side effects." a200408, female, 1982:

- patients who would buy it, because it is yellow-labelled, e.g.

"Yellow is an indication, so I can take it if I need it. It is not orange, so it is no suspicion. I would be a little uncertain, but I would try it out." a200124, female, 1971

Patients that did not cite the list of concerned substances as a reason for or against the purchase of ibuprofen, provided numerous other reasons. Reasons for a purchase of ibuprofen comprised urgency in case of strong pain, willingness to try the substance and to give it a chance, good experiences before, the hope for an effect, or the awareness that its use would only be for a short term. Reasons against a purchase of ibuprofen comprised general scepticism towards medication, the wish to consult the physician prior to the intake of a new drug, the fear of interactions with drugs of the current regimen, or bad experiences with this particular drug (e.g., allergies).

Gain in medication knowledge (F2)

If a new medication is suggested by the physician, 24 (57%) of the patients would consult their PGx documents (list of concerned substances/ PGx recommendation). For a further evaluation of the gain in medication knowledge, we asked patients whether they think they know better about their medications since the PGx service in *F2* (Fig. 4). We differentiated four groups as follows:

- patients who were able to actively apply their gained knowledge, e.g.

  "Yes, I now know differently about medication. The discussion with the pharmacist was useful. I have a better knowledge that certain medication groups work worse with me and that they are not so good for my body. That already helps me." a201005, female, 1961.

- patients who find the information, e.g.

  "It's interesting, it is clear to me. I do not understand so much, which is a pity, but I will always look from now on." a210223, female, 1947

- patients who only have marginal gain in knowledge, e.g.

  "Not better, but I no longer feel that I am crazy because I know that many [medication] is not so suitable for me…" 201,112, female, 1976

- patients who had no gain in knowledge, e.g.

  "No, I do not think so." a201110, female, 1979

Fig. 4 Gain in medication knowledge at follow-up interview 2 ($n=42$)

Willingness to pay (F2)

For most of the patients, both the laboratory (72%) and the counselling (76%) costs were adequate. A majority of the patients (62%) said that they would pay the complete cost for the PGx service. Lack of financial capacity was the most frequent reason for an inability to pay.

Discussion

In this study, we evaluated a pharmacist-led service comprising PGx testing and counselling by conducting semi-structured interviews with counselled patients.

Similarly to our study, Martin et al. [14] assessed the perspective of 16 patients towards a pharmacist-provided PGx service in semi-structured interviews and identified four major themes, namely heterogeneity of patient PGx preferences and experiences, pharmacists as appropriate providers of a PGx service, considerations regarding the use of PGx results in routine healthcare, and perceived applications of PGx testing. These findings were confirmed in our study comprising 77 follow-up interviews.

In general, patients were able to understand PGx results. However, as most patients are unfamiliar with PGx testing, the language used during the communication of PGx results needs to be chosen very carefully [19]. When asking patients how they would explain the results of the PGx test to a friend, we recognized different levels of understanding. Accordingly, we could see a tendency of patients with high educational backgrounds to have a better understanding of PGx results. This observation corresponds with the literature showing that health literacy is positively associated with education [20]. Therefore, patients with higher education have a higher likelihood of accessing, understanding, appraising, and applying PGx information [21].

In our study, we saw that more than two thirds of the patients had at least one recommendation implemented. Almost half of the recommendations concerned substances

of the nervous system, thereby confirming the need of PGx in the psychiatric setting [22, 23]. It has been shown that psychiatric patients are likely to benefit from a PGx test prior to the therapy to avoid ADRs or treatment failure [24, 25]. However, a part of the newly started medications was stopped shortly afterwards. Considering that 50% of patients with unipolar depression do not experience remission under a first-line antidepressant treatment [26], we claim that the addition of PGx information to therapeutic decision-making is substantial to help reduce the amount of trial and error regimens, even though PGx will not completely eliminate the percentage of unsuccessful regimens as there are other factors such as drug-drug interactions, medication adherence, and others influencing pharmacokinetics and pharmacodynamics of drugs.

The PGx recommendation as well as the list of concerned substances were evaluated as clear and usable for most patients. When asking patients about the list of concerned substances, more than half of them said that they held the list ready, and three patients reckoned they had already used it. As ibuprofen is the most frequently used Swiss drug known to be affected by PGx [27], we wanted to know how patients would proceed when they were confronted with a yellow indication for such a common drug on their list of concerned substances. A majority of the patients would use the list of concerned substances to decide for or against a purchase of ibuprofen. Only a small percentage would buy ibuprofen if it were yellow-labelled whereas a majority of the patients would not buy ibuprofen in the same situation. The latter patients seemed to be afraid of taking ibuprofen because of the indicated potential risk of ADRs or inefficacy. In 2009, Haga et al. [28] already postulated that PGx information could cause adverse effects or lack of adherence due to negative expectations triggered by the assumption that a drug could not work. Especially anxious patients might screen the list too critically and decide to a change their pharmacotherapy, thereby leading to wrong behaviour. On the one hand, a careful dose titration with the possibility of therapeutic drug monitoring is essential and on the other hand, HCPs need adequate communication skills to avoid potential negative expectations about the medication [29].

In our study, more than half of the patients reported that they would consult their PGx documents in case a new medication is suggested by the physician. Besides, more than half of the patients were able to actively apply their knowledge on PGx or were able to find the information on PGx. Both results show that patients experienced a gain in medication knowledge through the PGx service. It has been shown that patients perceive PGx testing as useful; however, the communication of PGx results still needs effort on the part of HCPs so that patients' knowledge about their medication is increased [30].

In a systematic review by Hansen et al. [13], one of the main barriers mentioned is the cost of the PGx service. In our study, more than half of the patients would be willing to pay the estimated cost for the pharmacist-led PGx service comprising the laboratory costs and the counselling costs for a first and second visit of 30 min each, sample collection, and preparation of the recommendation letter of at least 40 min. Similar willingness to pay for a medication review with an average duration of 20 min was observed in an earlier Swiss study with acceptance of the price as appropriate by 87.9% of the patients [31]. The costs of 700 EUR should be set in the context of the Swiss median income of 6665 EUR/month [32].

Strengths and limitations

Our study has several strengths. Firstly, we conducted a total of 77 follow-up interviews, thereby covering an extensive range of patients. Secondly, the mixed-methods design enabled the research team to collect quantitative and qualitative data, thereby allowing for an evaluation of the relative importance of the investigated aspects. In addition to the questions in the interview guide, patients got the opportunity to express their appraisal of the PGx service in open questions.

We acknowledge some limitations for the interpretation of our study. Firstly, the positive appraisal of the service may be influenced by a social desirability bias [33], as the PGx service as well as the follow-up interviews *F*1 and *F*2 were conducted by the same person (CJ). Secondly, we cannot exclude that patients did not remember the details of pharmacy visits 1 and 2 and the subsequent consultation with the physician, especially patients who were interviewed far more than four months after the PGx service. Initially a period of four to six months after the second visit to the pharmacy was estimated as adequate by the PGx expert team, because some patients did not arrange a consultation with the referring physician directly after the second visit and the titration of drugs (especially in psychiatry) takes time. However, with a mean time of 229 days since the 2nd visit this intent could not be met. Thirdly, we did not make any standardized measurements of health literacy, but only categorized the educational background. Fourthly, patients participating in this study were subject to a selection bias for patients receiving PGx testing and do not represent the general population. It would be valuable to also include the view of those not currently targeted for PGx testing.

Looking forward

As cited before [13, 14], we see the pharmacist as provider of the PGx service. To collect the appraisal of referring physicians, we effected a pilot focus group with four physicians. We think that the PGx service does not only seek interprofessional collaborations but also represents a chance to enable shared decision-making. In the future, we intend to extend the interprofessional collaboration with physicians, and we also intend to assess the perspective of the pharmacist to enable a successful implementation of the PGx service.

Conclusion

The evaluation of a new pharmacist-led service comprising PGx panel testing and counselling showed a relevant optimization of the pharmacotherapy in primary care with more than two thirds of the patients having at least one recommendation implemented. Most patients were able to understand the PGx recommendations provided by the PGx service and the usability of the documents they received was rated as very high. Overall, patient experienced a gain in medication knowledge and most of the patients were willing to pay for the PGx service.

For future PGx testing and counselling, HCPs should consider the patients' health literacy in a standardized way and use adequate communication skills to enhance the patient's understanding in PGx and to attenuate potential negative expectations.

Acknowledgements We would like to thank Stefanie Mutter for setting up parts of this work as part of her master thesis. A special thanks to Anima Schäfer (AS) for helping with the categorization of the patient statements.

Funding Open access funding provided by University of Basel. No specific funding was received.

Conflicts of interests The authors have no conflicts of interests to declare.

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General Discussion

To prepare for the implementation of PGx in pharmaceutical care, the goals of this thesis were to identify pharmacogenetic (PGx) information for clinical practice and to develop a standard operating procedure (SOP) for a pharmacist-led service comprising PGx testing and counseling in primary care.

In the following, the projects will be discussed separately. Each section starts with a summary, proceeds with a discussion of results, strengths, and limitations, and finally, follows with a conclusion of the respective project. Wherever appropriate, an overall discussion or conclusion has been included.

1. Project A1 - Pharmacogenetic information in Swiss drug labels

Summary

Currently, no overview of PGx-relevant information in Swiss drug labels (DLs) exists. Project A1 aimed to get an overview of the current state of PGx-relevant information on metabolizing enzymes and transporters as well as HLA risk alleles, to classify recommendations provided to HCPs by the PGx levels as suggested by PharmGKB [11], and finally, to compare the respective PGx level with those provided in DLs authorized by agencies of other countries. The PGx information from Swiss DLs was extracted by natural language processing (NLP). The analysis showed that up to 10% of all Swiss DLs mentioned PGx-relevant information. In total, 167 reference drug labels were defined and the most PGx information (55%) was classified as "actionable PGx" (PGx level 3).

Discussion

General

The pharmacokinetics section represented the most frequent section containing PGx-relevant information. Indeed, this particular section is one of the last specified sections in a DL, not only in Swiss DLs, but also in those approved by other agencies [82]. Therefore, it may be speculated that there is a risk that PGx information could be overlooked by the health care professionals (HCPs). For some drugs coded with PGx level 1 ("testing required"), the PGx-relevant information was located within the section on precautionary measures which reports on genetic polymorphisms known to be associated with adverse drug reactions (ADRs) (especially in the case of HLA-associated ADRs, e.g. carbamazepine). The findings are in line with those by Ehmann et al. [83] reporting that the pharmacokinetic and the precaution measures section are most likely to state PGx information in DLs approved by the EMA.

CYP2D6 was the most frequently mentioned biomarker, which was also in accordance with findings from other countries [84-87]. This cytochrome P450 enzyme is known for its genetic variability with about 100 different alleles [88] resulting in the phenotypes of poor, intermediate, normal, and ultra-rapid metabolizer with a prevalence of 0.4–5.4%, 0.4–11%, 67–90%, and 1–21%, respectively [89]. Moreover,

CYP2D6 is known to be involved in the metabolism of a wide range of commonly used drugs [18], including selective serotonin reuptake inhibitors (SSRIs), opioids, and tamoxifen.

The most frequently retrieved information on PGx concerned drugs from the anatomic group N "nervous system" involving antiepileptics, antidepressants such as SSRIs, or analgesics such as opioids, all of these representing substance groups where treatment is often associated with difficulties (e.g. therapy failure (TF)). Indeed, Bschor et al. [15] and Muller et al. [16] assume that psychiatric patients would likely benefit from a PGx test before the therapy to avoid ADRs or TF.

Although some of the recommendations on drug-gene interactions (DGIs) are translated into the sections "indication", "dosage/application", "contraindication", "precautionary measures", or "pharmacokinetics" in the respective DL, the representation of PGx information shows a remarkable heterogeneity. To give an example: the DL on rosuvastatine holds information in the sections on "dosage/application", "precautionary measures", "contraindication", and "pharmacokinetics" whereas the DL on omeprazole only contains information in the section on "pharmacokinetics"; however, both are classified as "actionable PGx". In addition, the information on PGx is often not precise and the presentation lacks a predefined structure, thereby leading to different PGx levels and various recommendations. Similar findings have also been reported by Ehmann et al. (EMA) [83] and Shimazawa & Ikeda (the USA and Japan) [90].

Entering the extracts of 126 Swiss DLs on the PharmGKB website enabled making the information not only publicly accessible but also comparable to the information approved by regulatory agencies of four other countries. A striking discrepancy can be recognized for some drugs. In the case of carbamazepine and the variant *HLA-B*15:02*, Swissmedic and FDA (USA) require a test whereas HSCS (Canada) recommends a test, PMDA (Japan) provides actionable PGx information, and EMA (Europe) does not provide any information at all.

Limitations

For the extraction of PGx information from Swiss DLs, the search was restricted to stem words associated to pharmacokinetics (drug metabolism and transport) and HLA risk alleles. PGx information related to pharmacodynamics (e.g. information on testing for the *CFTR* gene in the ivacaftor DL) and also PGx information on drug-targeted therapy (e.g. imanitib) was thereby excluded. This decision was taken because a clear delineation from genetics related to disease prognostics as well as drug-targeted therapies mainly used in oncology was pursued.

Moreover, the definition of stem words for NLP was challenging. First of all, in-depth knowledge of PGx as well as of the format of the DL was required. Additionally, it was the first time that the PGx expert team worked with this new technological approach. Therefore, communication between pharmacist and information scientist was not always straightforward.

Indeed, a direct comparison of Swiss DLs with DLs of selected European countries was not possible, with exception of a comparison of seven substances in German DLs.

Finally, some substances posed problems in terms of categorization of the PGx levels.

Strengths

This is the first work where NLP was applied to Swiss DLs to screen for PGx information. NLP represents an attractive technology for further investigations of DLs and other health care-related information. Notably, for the accessibility of DLs for NLP, standardization would be a necessary facilitator.

Additionally, it was a great opportunity to collaborate with the experts of PharmGKB and to benefit from their specific knowledge of PGx. Not only did they help classify Swiss DLs, but they were open to discussions about the current definitions of DLs which thereafter were adopted. The collaboration with PharmGKB, which resulted in the integration of the PGx-related Swiss DLs into the knowledge base, is a good example of scientific collaboration seeking harmonization on a global level.

Implication for practice

Finally, the question is, whether optimization of the DL would change clinical practice. Giacomini et al. [91] declare that there is no reason in associating missing PGx information in the DL with a barrier to PGx testing. Unfortunately, no investigations checking either the frequency of use of DLs by HCPs or how many physicians prescribe single gene testing for the five drugs listed according to the SGKPT [74] were available. Therefore, one should be careful when relying too much on the fact that if something is written in the DL, this will change clinical practice, as this may not be the case.

Conclusion

The analysis of PGx information provided in Swiss DLs revealed a large heterogeneity. PGx information varies not only in the wording used to describe the information but also in the section in which the information appears. The predominance of PGx level 3 “actionable PGx” demonstrates that numerous actionable DGIs exist, which could be considered in optimized drug therapy. Here, the instructions for clinical practice are rather vague. In addition, a large discrepancy was also present when comparing DLs on an international level. In summary, this makes the identification and interpretation of PGx information difficult for HCPs.

2. Project A2 - HLA-associated adverse drug reactions

Summary

One of the identified drug labels (DLs) in project A1 was that for abacavir, where pre-emptive testing for *HLA-B*57:01* is required to prevent administration to patients with a higher risk of hypersensitivity reaction. This PGx testing is supported by the findings of "PREDICT-1" [13, 14] where carriers of the *HLA-B*57:01* allele showed a higher risk of developing the abacavir hypersensitivity syndrome compared to non-carriers. In the case of HLA alleles, it has been suggested that pre-emptive testing for a specific HLA allele (aka HLA-typing) may prevent the associated ADRs if exposure to carriers of certain HLA alleles is avoided. Project A2 aimed to summarize the current evidence for HLA-associated ADRs. The methodologic approach of a scoping review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was applied to generate an overview of studies reporting on HLA-associated ADRs. In the summary, 149 studies reporting on 26 substances or 7 substance groups (HMG-CoA reductase inhibitors, thyreostatics, betalactam antibiotics, agents for the treatment of tuberculosis, pyrimidine analogs, anti-epileptic drugs, and cold medicine) as indicated by the ATC code were included. The *HLA-B*15:02* risk allele in carbamazepine was the most frequently described association (n=33). The descriptive summary of the 149 studies revealed a large heterogeneity in terms of used definitions for the ADRs, examined HLA alleles, number and origin of study participants, and study types. HLA alleles were associated with an increased risk for ADRs, had no association with the ADR, or were reported to be protective (reducing the risk for the ADR).

Discussion

General

The studies investigated many various HLA-associated ADRs. It is extremely difficult, especially for cutaneous ADRs, to decide whether the investigators are reporting on the same manifestation or a different one because in many cases there is no clear definition of the phenotype. For example, for allopurinol, an association of the HLA-B*58:01 was investigated for the cutaneous manifestations with six different definitions, namely Stevens-Johnson syndrome/toxic epidermal necrolysis, severe cutaneous adverse reaction, drug-induced hypersensitivity syndrome, cutaneous ADRs, maculopapular exanthema, and drug reaction with eosinophilia and systemic symptoms.

The association with ADRs induced by carbamazepine has been confirmed in many Asian populations [92-100]. Indeed, Asians are the most studied population for HLA-associated ADRs, followed by Caucasians.

Except for the PREDICT-1 study [13], all the other HLA-associated ADRs were investigated in retrospective studies (case control studies, cohort studies, PGx analysis, e.g. [101]) where the testing was performed after manifestation of ADR. A case control study is a reasonable study design to confirm associations of HLA alleles with certain ADRs. However, in retrospective studies, one has to consider

the bias of potentially including incorrectly diagnosed cases as it is extremely difficult to validate the ADR retrospectively. Accordingly, confirmation of the clinical diagnosis can rarely be performed. In the end, this poses the danger of overestimating the prevalence of an ADR. Furthermore, the literature search also included a substantial number of genome-wide association studies (GWAS), e.g. [102], examining frequencies of single nucleotide polymorphisms (SNPs) to identify alleles contributing to a specific phenotype, which shows the importance of this study type in PGx. GWAS with a focus on the HLA region are a good approach to obtain unbiased evidence on potential associations in patients with ADRs. In total, 15 case reports (thereof 6 for carbamazepine, e.g. [103]) were included in the literature search, most of them describing the case of a single patient. Even if case reports provide low to no evidence for hereditable factors contributing to the susceptibility, they can help to discover underlying mechanisms: the genotype reported in a single case can be the basis for further analyses in case control studies.

The anatomic groups J "antiinfectives for systemic use", L "antineoplastic and immunomodulating agents", and N "nervous system" contain most of the substances currently investigated for the association of HLA alleles with ADRs. According to project A1, the anatomic group J mainly covers substances rated with PGx level 1 ("testing required") whereas substances in the anatomic group N mostly include a PGx level 3 ("actionable PGx").

Besides the association of carbamazepine-induced cutaneous drug reactions with HLA-B*15:02, allopurinol and HLA-B*58:01 allele-mediated cutaneous ADRs, and abacavir and HLA-B*57:01 allele-mediated hypersensitivity reactions were frequently reported. Of all HLA alleles mentioned in Swiss DLs, *HLA-B*15:02* was mentioned third most after *HLA-A*31:01* (with carbamazepine) and *HLA-B*58:01* (with allopurinol). This shows that HLA-associated ADRs with clear evidence have found their way into the DL. There is one GWAS [102] indicating that the *HLA-B*57:01* is associated with a risk of drug-induced liver injury (DILI) at the intake of flucloxacillin. Although there is just this GWAS, the DL indicates a risk of flucloxacillin-induced liver damage for patients carrying the *HLA-B*57:01* allele. In contrast, the scoping review revealed that terbinafine, an antimycotic drug, was associated with hepatotoxicity in carriers of *HLA-A*33:01*, *HLA-A*33:03*, and *HLA-A*33:01-B*14:02-C*080* in two well developed PGx analyses [101, 104]. However, the DL on terbinafine does not mention such an association.

Finally, an important topic that came up during the scoping review was clinical validity. The clinical validity of HLA-associated ADRs depends on a positive association of the HLA risk allele and the ADR, on the frequency of the HLA risk allele, on the frequency of the ADR, and finally, also on the severity of the ADR. *HLA-DRB1*0701* was associated with hepatotoxicity for patients taking lapatinib [105], an oncologic drug. The association had a high NPV, but only a moderate PPV, which means that the majority of individuals who experience serious lapatinib-induced liver injuries carry the allele, but the majority of *HLA-DRB1*0701* allele carriers will not experience liver injuries. In consequence, if HLA-

typing is included in the therapeutic decision of lapatinib, where the frequency of the HLA risk allele is higher than the frequency of the ADR, there might be patients who are deprived of efficient therapy.

Limitations

With the performance of the scoping review, the inclusion of the studies, and later, the extraction and analysis of the data had to be figured out. Notably, the literature search was restricted to small molecules, because knowledge of the PGx of biologics and other protein-derived substances is still limited. However, the limitation to drugs currently approved in the Swiss market resulted in the active exclusion of studies on dapsone, ximelagatran, ticlopidine, stavidine, lomefloxacin, and flupirtine. In the scoping review, different values, (e.g. the odds ratio) were also extracted; however, without being able to compare the values but rather to give a descriptive summary.

Strengths

Screening the different factors influencing the HLA-associated ADRs helped to identify the basic points for further investigations in the field of HLA-associated ADRs. The aim of the scoping review was not to find out the clinical relevance of the HLA-associated ADRs but to see which associations have been described in the literature until the moment of searching. The different possibilities to analyze extracted studies show one of the big advantages of a scoping review, because a systematic review seemed premature at the current state of evidence. For this not so simple task, the help of an information specialist was enlisted.

Conclusion

The scoping review identified a considerable number of studies that investigated various substances, HLA alleles, and associated ADRs. The extracted studies revealed large heterogeneity in terms of definitions for the ADRs, examined HLA alleles, number and origin of study participants, and study types. Despite the prevailing complexity and uncertainty, it became clear that pre-emptive testing of HLA alleles (HLA-typing) may have potential. However, it is not possible to derive the actual clinical relevance from these studies because the overview of HLA-associated ADRs ranged from poor to strong available evidence. Nevertheless, the screening of the different factors influencing the HLA-associated ADRs helped to identify the basic points for further investigations in the field of HLA-associated ADRs.

3. Project B1 - Case series - Pharmacogenetic testing of patients with unwanted adverse drug reactions or therapy failure

Summary

The genetic makeup of a patient influences the efficacy and safety profile of a drug. The aim of the herein proposed study was the compilation of case reports, where PGx testing was applied to determine the hereditable component of the patient's susceptibility to experiencing ADRs and/or TF. Reactive testing was applied to patients who observed TF or ADRs with past substances known to be affected by PGx whereas pre-emptive testing was applied to patients with future substances known to be affected by PGx, and to patients with relatives with ADRs or TF. By summarizing individual cases, where pharmacist-led testing and counseling had been applied in primary care, the potential benefit of PGx to improve the efficacy or safety of a patient's pharmacotherapy was demonstrated. In total, 100 patients were collected for PGx testing and counseling in the primary care setting. The case series enabled to develop a standard operating procedure (SOP) for PGx testing and counseling as a pharmacist-led service.

Discussion

Refinements

The SOP of the pharmacist-led service is divided into the steps of patient referral (1), pre-test counseling (2), PGx testing (3), medication review (4), counseling (5), and follow-up (6). In the following, the refinements for the SOP that were undertaken within the corresponding steps are outlined (no refinements to the two steps pre-test counseling (2) and PGx testing (3) were made) [106].

Patient Referral (1): Initially, patients were referred to PGx testing and counseling by their treating physicians who had been informed about this opportunity in quality circles. However, drug-related problems were frequently addressed by patients during consultations and drug dispensing in the community pharmacy. Therefore, pharmacists started to directly approach eligible patients. In a few cases, patients also approached the pharmacists on their own initiative due to word of mouth. In all cases, treating physicians were informed and asked for their support for the planned pharmacist-led PGx service.

Medication Review (4): Based on the experience collected alongside the case series, pharmacists started to supplement the medication review report with a general overview of the patient's PGx profile and thereof predicted phenotypes. Furthermore, whenever reasonable, the pharmacists provided interpretations for the impact of pharmacogenetically predicted phenotypes in pharmacokinetic considerations for substances without explicit PGx guidelines.

Counseling (5): During the case series, some physicians and patients expressed different preferences regarding the format of counseling, which was originally intended to take place as a visit between the

pharmacist and the patient in the community pharmacy. Therefore, an individual adaption was initiated, so that the medication review provided by the pharmacist was explained to the patient via video conference or phone (instead of a second visit to the pharmacy) and in a few cases the treating physician wished to be part of the video conference for counseling with the patient and the pharmacist.

Follow-up (6): Patients and physicians got the opportunity to clarify open questions and to place further queries. The planned follow-up calls to patients were primarily intended to evaluate the implementation of the pharmacists' recommendations within the case series study analysis. However, the follow-up call was valuable because pharmacists were able to collect continuous feedback on their recommendations, and patients were reminded of the lifelong validity of their PGx profile. Therefore, the follow-up calls were used for the assessment of further data, which is shown in project B4.

Strengths

Even if case reports provide low to no evidence for hereditable factors contributing to susceptibility, they offer the opportunity of gathering experience and generating evidence at the same time. Case reports enabled us to better understand the underlying mechanisms including the genetic variants. Moreover, the establishment of case series enabled the development of a SOP for PGx testing and counseling in primary care.

At the start of the case series, the whole PGx expert team was offered a PGx test to discover and explore their personal PGx profile. This was important with regard to the advocacy of PGx in practice. This strategy has also been applied by Thornley et al. [57], where not only patients but several pharmacists and physicians were offered a PGx test to increase awareness. Lee et al. [107] managed to show that personal PGx testing is one possible awareness strategy to improve HCPs' attitude on PGx is personal PGx testing.

Prior to effecting PGx testing and counseling, each pharmacist had to complete a very basic PGx-training provided by Stratipharm. During the case series, the pharmacists, as well as the treating physicians, were subject to continuous learning when they worked through the report on an individual patient. Cicali et al. [108] and Hayashi et al. [109] have shown the efficacy of discussing case reports in terms of education for physicians and pharmacists, respectively. Subsequently, the PGx expert team decided to start a more developed further education program for pharmacists [63].

As this observational study involving the collection of saliva and blood samples designated for genotyping was the first of its kind, guidance and support were obtained from the clinical trial unit (CTU) from the University of Basel. The CTU revised the study protocol, made further suggestions for adoption (in particular, to collect and store blood samples in case of new evidence in the future), submitted the protocol to the local ethics committee northwestern and central Switzerland, and provided study nurses as well as a location for blood sampling.

4. Project B2 - Enriching medication review with a pharmacogenetic profile - a case of tamoxifen adverse drug reactions

Summary

A drug that has been extensively studied for the relevance of the patient's genetic predisposition is tamoxifen (TMX). Project B2 aimed to present the case of a patient, where ADRs with TMX had prompted the patient to do PGx testing, to reveal the added value of a medications review enriched with a large PGx panel, and to show the complexity of integrating a PGx profile into a recommendation. Both genetic predisposition and the patient's medication were considered when evaluating the reported ADRs observed during TMX treatment. Based on previous knowledge on TMX metabolism and its function as a selective estrogen receptor modulator, a *CYP2D6* Ultrarapid Metabolizer (UM) status leading to an excess of endoxifen, thereby resulting in the reported ADRs, was expected. However, the PGx profile showed that the patient had the star alleles *6 (no function) and *41 (decreased function) of the *CYP2D6* enzyme resulting in the phenotype of an Intermediate Metabolizer (IM). Moreover, the testing revealed the patient's *CYP2C19* UM status with the star alleles *1 (wildtype) and *17 (increased function), and a *CYP2C9* IM status with the star alleles *1 (wildtype) and *2 (decreased function).

Decision: It was recommended to discontinue TMX due to the *CYP2D6* IM phenotype and the fact that dose escalation would not be an option for this patient due to ADRs, which might be linked to the genetic-associated changes in TMX metabolism. In the recommendation, a switch to letrozole, a non-steroidal aromatase inhibitor for post-breast cancer recurrence therapy after breast cancer, was suggested.

Discussion

Considerations for TMX

For the decision, the metabolism of TMX as well as the information found in the drug label of TMX, the guidelines on breast cancer, and the PGx guidelines for TMX and *CYP2D6* were considered.

In addition to the demethylation by *CYP3A4* (no polymorphism known, no DDI present) and the hydroxylation by *CYP2D6* (IM status associated with worse clinical outcomes because of lower endoxifen concentrations), the genetic variations of *CYP2C19* (UM status) in the side pathway were considered. On the one hand, *CYP2C19* is involved in estrogen/progesterone metabolism, and on the other hand, there are studies indicating worse clinical outcomes of *CYP2D6* PM and *CYP2C19* UM [110] or better response of *CYP2C19* UM alone [111]. Therefore, it remains unclear how important it is to take the side pathway into account.

Both the Swissmedic and the FDA drug labels show actionable PGx information on TMX, thereby not explicitly recommending a PGx-guided treatment. Moreover, the S-3 guideline on mamma carcinoma by the *Guideline Program Oncology* [112] and the guideline on breast cancer of the *National*

Comprehensive Cancer Network (NCCN) [113]do not recommend genotyping, mainly because of a lack of agreement between those for [114-116] and those against pre-emptive testing [117, 118]. Notably, the latter studies demonstrating that there is knowledge of the influence of *CYP2D6* PM date from 10 years ago but a consensus is still lacking. Ultimately, the Sanford Health Pharmacogenetics Committee [119] submitted a request to the NCCN Breast Cancer Panel to change TMX guidelines to state recommendation of alternative hormonal therapy such as aromatase inhibitors (plus or minus ovarian suppression) for *CYP2D6* PMs, thereby referring to the CPIC guideline [120] for *CYP2D6* and TMX therapy.

Alternative drugs to TMX

As alternative drugs to TMX, the following options were discussed. Dose escalation as proposed by the guideline [120] was no option for this patient who already suffered from ADRs with a dosage of 10mg TMX. These ADRs might be linked to the genetic-associated changes in TMX metabolism; that is to say, to the accumulation of TMX in the blood plasma. However, this remains unclear, because no plasma samples for therapeutic drug monitoring were available. Toremifene is another selective estrogen receptor modulator indicated for the treatment of metastatic breast cancer in postmenopausal women; however, because is it not available on the Swiss market, it was not an option. Finally, the option of letrozole, a non-steroidal aromatase inhibitor for post-breast cancer recurrence therapy after breast cancer, was chosen. Aromatase inhibitors represent an equally good – if not even better [121, 122] – alternative to TAM, and besides, letrozole is primarily metabolized by *CYP2A6* and *CYP3A4*, where no genetic variants are known so far.

Conclusion

Considering only the described ADRs would have tempted us to reduce the TMX dosage, suspecting that the patient's endoxifen blood concentrations might be elevated due to an UM status. Surprisingly, the assessed *CYP2D6* genotype (*CYP2D6* IM) did not support this hypothesis. On the contrary, according to the PGx guidelines respecting the revealed *CYP2D6* genotype, the patient might suffer from limited TMX effectiveness due to decreased bioactivation to endoxifen via *CYP2D6* and therefore would not benefit from a dose reduction. It was recommended to stop TMX and switch to letrozole in combination with leuprorelin. Furthermore, recommendations on the co-medication of the patient were made. This case revealed the added value of a large PGx panel and showed the complexity of integrating a PGx profile into a recommendation.

5. Project B3 - Is pharmacogenetic panel testing applicable to low-dose methotrexate in rheumatoid arthritis? - a case report

Summary

Nearly 30% of the patients treated with methotrexate (MTX) experience inefficacy or ADRs. Project B3 aimed to recap the pathway of MTX and, simultaneously, highlight genetic variations influencing transport and metabolism of MTX and discuss the case of a patient who was treated with MTX, suffered from ADRs, and obtained a reactive PGx panel testing. The MTX pathway is complex, which makes the interpretation of genetic variants affecting metabolism challenging. A commercial PGx panel test involving P-glycoprotein (P-gp; gene: *ABCB1*), breast cancer resistance protein (BCRP; gene: *ABCG2*), reduced folate carrier 1 (RFC1; gene: *SLC19A1*), organic anion transporting polypeptide 1B1 (OATP1B1; gene: *SLCO1B1*), inosine triphosphatase (*ITPA*), and glutathione transferase P1 (*GSTP1*) was applied. In addition, the patient was genotyped for 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR)/inosine monophosphate (IMP) cyclohydrolase (gene name: *ATIC*), gamma-glutamyl hydrolase (gene name: *GGH*) and methylenetetrahydrofolate reductase (gene name: *MTHFR*). The PGx profile of the patient revealed genetic variants in *SLC19A1*, *ABCB1*, and *MTHFR*.

Decision: Based on the interpretation of the PGx profile, it was recommended that the patient avoid MTX in the future and stay on his current treatment with tofacitinib (5mg, 2 times daily), a small molecule that is metabolized by *CYP3A4* which is not currently well predicted by genetic variants.

Discussion

Complex pathway of MTX

Due to its complexity, compiling the whole metabolism of MTX with the corresponding genetic variants behind proved hard work. As of May 2022, the PharmGKB describes clinical annotations in 30 genes covering up to 60 variants [123] involved in MTX with RA. In the case report, nine genes covering 19 variants for MTX were examined, thereby representing only a part of the genetic landscape. The complex pathway of MTX and the many genetic variants involved makes it difficult for current PGx panel tests to draw a conclusion that is applicable in clinical practice. To date, the available commercial tests (e.g. Stratipharm) are still rather primitive, so the algorithm gives a warning as soon as there is a variant. If a drug such as MTX with several genetic variants is queried, there will always be some kind of warning. In consequence, patients would be deprived of the useful and cost-effective drug too frequently. Moreover, HCPs and patients would be lulled into a false sense of security in the case of an MTX treatment guided by such a PGx panel test. It is the overall interpretation of all variants that remains challenging and needs to be overcome.

Alternatives for MTX

Thus, the question arises as to whether it would be easier to apply alternative drugs for a baseline treatment in RA. From the point of view of cost-effectiveness, surely not (MTX is a very effective and low-cost drug [124]). However, from the point of view of ADRs [125] and inefficacy [126], there are constraining components. According to the guidelines on RA [127, 128], further treatment options would be biological DMARDs such as abatacept or rituximab and Janus kinase inhibitors. There is still little to no evidence for the impact of genetic variants involved in pharmacokinetics on these drugs. The recommendations provided by the commercial PGx panel test Stratipharm describe both biologics and Janus kinase inhibitors as uncritical ("no warning"). In contrast to the above-mentioned so to speak "always" present warning for MTX, there will be no warning for other drugs for treatment of RA.

The application of PGx testing in both cases – MTX, always showing variants and biologicals and Janus kinase inhibitors, never showing a warning – creates a feeling of false security.

Conclusion

The pathway of MTX is complex and the prevailing genetic variants of diverse clinical relevance. A reactive PGx panel test was applicable to explain ADRs experienced during MTX treatment for a patient with RA. The PGx profile of the patient revealed genetic variants in *SLC19A1*, *ABCB1*, and *MTHFR*, which may explain the ADRs experienced during the treatment with MTX and potentially lower efficacy of MTX. For the patient, the genetic variants might or might not have explained the ADRs. There is still insufficient evidence for PGx in MTX (as well as in biologics and complex new small molecules, such as Janus kinase inhibitors) because the translation into clinical recommendations remains challenging. At the moment, the clinical utility of PGx-guided MTX treatment in a primary care setting is limited. For now, PGx panel testing for MTX appears to be limited to experts who have the possibility of in-depth pharmacological investigations, including therapeutic drug monitoring.

6. Project B1, B2, B3 – overall discussion on patient cases

Interestingly, in case reports from project B2 and B3, the described ADRs affecting the patients could not be measured by lab values. In the case of TMX, the patient suffered from menopausal and psychological symptoms leading to an inability to work. The treating gynecologist did not report any deviating lab values. In the case of MTX, the patient suffered from nausea, headache, and sore muscles. According to information from the treating rheumatologist, the monthly measured lab values (CRP, transaminases, blood count) did not show any abnormalities. Still, it can be assumed that other patients might also be confronted with ADRs that are not perceived by lab values. This shows the importance of HCPs taking note of the patients' statements. On the one hand, clinical parameters can be collected by observing and examining the patient, but on the other hand, a lot of parameters must be collected by talking to the patient and asking questions. The latter can be perfectly effected by the pharmacist, especially when it comes to ADRs or inefficacy of a drug. Messerli et al. [129] were able to show the benefits of the Swiss Poly Medication Check (aka medication review) in an RCT, whereby patients appreciated recommendations resulting from the complex pharmacist-led intervention. Similarly, A medication review enriched with a large PGx panel might serve as complex pharmacist-led service for the implementation of pharmacogenotyping in pharmaceutical care.

Notably, the processing of both patient cases urged the investigating pharmacists to go one step back and delve into the metabolism of the corresponding substance to be able to comprehend the impact of the genetic variants on the mechanism of action. Thereby, it became more and more intuitive to interpret drug-gene interaction in combination with a drug-drug interaction. In the course of the case series, much expertise in the interpretation of drug-drug-gene interactions was aggregated. For example, agomelatine and duloxetine, which are both metabolized by *CYP1A2*, generate no warning in the algorithm of Stratipharm because there is no evidence of the inducibility of *CYP1A2* in the context of these specific drugs. However, in the case of smokers, the induced *CYP1A2* metabolism might be responsible for non-response and should therefore be considered. So far, most algorithms lack the integration of several parameters. Consequently, the pharmacist as an expert could play an important role in the facilitation of PGx in clinical practice.

Indeed, the keeping apart of ADRs and disease remains difficult. In the case of MTX, the described ADRs (nausea, headache, and sore muscles) are very unspecific, the latter most possibly being a consequence of rheumatoid arthritis. In addition, the delineation of genetics related to drug response and disease prognostics is no less a challenge. In the case of TMX, possible disease-related symptoms, such as the hot flushes observed in the patient, had to be evaluated carefully because the pathophysiology of hot flushes, especially in breast cancer survivors, is not fully understood [130]. Besides, there are studies linking *CYP2D6* IM and PM to higher risk of hot flushes [118] whereas other studies claim there is no association [131].

Primarily, PGx-guided recommendations were provided on a reactive basis in both cases. Thanks to the added value of the PGx panel test, additional recommendations on co-medication were delivered. Interestingly, both patients were taking a non-steroidal anti-inflammatory drug (ibuprofen) in combination with a proton pump inhibitor. As seen in the course of the case series and another study [132], many patients with chronic pain or gastrointestinal reflux reveal genetic variants relevant to their pharmacotherapy. That is why pre-emptive testing was also applied for patients in the case series coming solely with a reactive quest.

7. Project B4 - Pharmacogenetic testing and counseling in the community pharmacy: evaluation of a new pharmacist-led service

Summary

Patients' perspectives on commercial PGx panel testing are not well known. Project B4 aimed to evaluate the pharmacist-led service comprising PGx testing and counseling from the perspective of patients and their treating physicians. In general, patients were able to understand PGx results and experienced a gain in medication knowledge. Although most patients had yet not used them, the majority of the patients held their PGx documents ready for use. Moreover, PGx documents were available to referring as well as non-involved physicians. As for the list of concerned substances, the physicians expressed their concern about a potential nocebo effect. Despite the comment of the physicians that the PGx results were complex and difficult to transfer into clinical practice, two thirds of the patients had changed at least one drug as suggested by the PGx recommendations. Patients would recommend the pharmacist-led service and were also willing to pay for PGx testing and counseling. Finally, the follow-up interviews helped to remind the patient of the availability and life-long validity of the PGx results and further questions could be clarified.

Discussion

General

As most patients are unfamiliar with PGx testing, the language used during the communication of PGx results needs to be chosen very conscientiously [133]. In our opinion, a subsequent consultation with the treating physician is compulsory for an adequate appraisal of PGx information. It has been shown that patients perceive PGx testing as useful [134]; however, the communication of PGx results still needs effort on the part of HCPs so patients' knowledge about their medication is increased. Therefore, the health literacy of the patient needs to be taken into account during PGx testing and counseling.

According to the physicians, the substances labeled in yellow are prone to trigger an undesirable nocebo effect in patients. In 2009, Haga et al. [135] already postulated that PGx information could cause adverse effects or lack of adherence due to negative expectations triggered by the assumption that a drug would maybe not work. In particular, anxious patients might screen the list too critically and decide to change their pharmacotherapy, thereby leading to wrong behavior.

Although the written recommendation was appraised as clear, it remains difficult for the treating physicians to translate the complex information on PGx into practice.

In our study, two thirds of the patients had at least one recommendation implemented. Almost half of the recommendations consisted of substances of the nervous system, thereby confirming the need for PGx in the psychiatric setting in particular.

Patients and physicians appreciated the pharmacist-led service. This was previously shown by Haga et al. [54, 134], where the majority of patients would recommend a PGx test. Furthermore, more than half of the patients were willing to pay the estimated cost for the pharmacist-led PGx service. A similar willingness to pay for a pharmacist-led service was observed in a study on Swiss medication reviews [129].

The explanation of PGx results, the impact of PGx results on pharmacotherapy, and the life-long validity of PGx results are the three types of information that are necessary for the patient [133]. A positive side effect of our study was that the follow-up interviews conducted by phone one month and more than four months after the PGx service reminded the patients of the availability and long-term validity of PGx results.

Limitations

PGx testing and counseling as well as the follow-up interviews F1 and F2 were conducted by the same pharmacist, therefore a social desirability bias cannot be excluded. Moreover, no standardized measurements of health literacy were made. Besides, the focus group discussion with four physicians was rather small. Finally, no patients and no treating physicians were involved in consensus finding because the evaluation of the results requested PGx expertise which could only be provided by members of the PGx expert team and otherwise would have overburdened patients and treating physicians.

Conclusion

In general, the pharmacist-led service involving PGx panel testing and counseling in the community pharmacy is appreciated by patients and physicians. Patients and physicians are able to understand and use the PGx recommendations. For PGx counseling, it is crucial to take the patient's health literacy into account during PGx testing and counseling. The yellow-labeled substances on the list of concerned substances are prone to trigger an undesirable nocebo effect in the patient, which needs to be respected when communicating PGx results to the patient.

8. Project B – conclusion

The case series was beneficial for several reasons. With case reports the underlying mechanisms of drugs with the respective genetic variants could be thoroughly investigated. In the course of the case series, it was possible to refine the SOP for PGx testing and counseling. Moreover, every single patient case also consisted of a learning opportunity for the application of PGx in the real-life setting. The case of TMX revealed the added value of a large PGx panel integrated into a medication review and showed the complexity of translating PGx results into a recommendation. Currently, PGx panel testing for MTX appears to be limited to experts who have the possibility of in-depth pharmacological investigations including therapeutic drug monitoring.

The compiled case reports contributed to the development of a SOP for the pharmacist-led service "PGx testing and counseling" in primary care. To conclude, the following can be said:

- PGx results must be integrated into a pharmacist-led medication review,
- the application of a PGx panel test offers the possibility to counsel on several drugs,
- a pharmacist-led service gives opportunity to initiate an interdisciplinary collaboration with physicians.

Although the core part of the SOP for the pharmacist-led service PGx testing and counseling is set up in the meantime, slight refinements will continue to be necessary for the future. Examples could be the further optimization of the communication to the patients by considering a patient's health literacy, the improvement of the written recommendation to the physician, or the integration of PGx data into the electronic health record. Finally, potential future decisions on the legal level might also force adoption of the SOP. The pharmacist-led service can therefore be considered as a service constantly evolving by receiving regular feedback.

Outlook

1. Project A - Pharmacogenetic information for clinical practice

A1 - Pharmacogenetic information in Swiss drug labels

If we start from the fact that health care professionals (HCPs) depend on the drug label (DL) as a supportive tool for their therapeutic decision-making and patient counseling in clinical practice, the following considerations for the future can be made.

- Considering DLs in general, they need a more structured presentation as well as a more standardized language. This is particularly important for facilitating the integration and in consequence, the accessibility of corresponding PGx-relevant information. In addition, a more structured and standardized presentation of the DL would pave the way for further natural language processing of other topics.
- Notably, a specific section on PGx within the DL, as is already the case for the predefined format of the FDA DL, could be useful. A specific PGx section would enable efficient identification of PGx information, especially for those HCPs who are aware of PGx and seek specific PGx information. In the long run, a specific PGx section could also help to increase awareness of the topic of PGx.
- Furthermore, the instructions for clinical practice related to PGx must become more explicit. A substantial part of DLs includes "actionable" PGx, i.e. information on the influence of a genetic variant on drug efficacy or safety is mentioned but without a recommendation for genetic testing. In these cases, the consequent handling of HCPs remains difficult and HCPs have good reason to ignore the information because of a lack of concrete instructions.
- There is a need for a better transfer of PGx information from guidelines into DLs. To date, most HCPs are not aware of clinical guidelines on PGx. Shekani et al. [136] have shown that only 50% of actionable PGx information provided in guidelines from DPWG and CPIC are represented in the DLs of the FDA and the EMA and thereof only 18% of the DLs were in agreement with the guideline. Particularly when taking a more detailed look at the anatomic group N referring to the nervous system, there are numerous substances where more information on PGx (e.g. on the *ABCB1* gene [21, 22]) would be helpful for a PGx-guided treatment.
- Also the harmonization of PGx information provided by regulatory agencies needs to improve. Koutsilieri et al. [137, 138] are working on the harmonization of guidance on PGx provided by regulatory authorities and have issued a call for action: consistency of PGx recommendations presented in DLs across the world is crucial for the implementation of PGx testing into clinical practice [137, 138]. Therefore, regular comparisons and harmonization of the different existing guidelines on PGx are important, such as has been effected by Bank et al. [44] for the guidelines

of CPIC and DPWG. In this project, the collaboration with experts from PharmGKB proved as valuable. In the future, further international collaborations should be repeated in the light of harmonization of PGx information on a global level.

- Finally, a fully automatized natural language processing of PGx information in Swiss DLs and the subsequent transmission to PharmGKB should be established in the future. For the near future, at least a manual update of PGx information in Swiss DLs is necessary.

A2 - HLA-associated adverse drug reactions

Because the summary of the current evidence on HLA alleles showed a still prevailing complexity and uncertainty in the field of HLA-associated ADRs, further investigations based on the following considerations in relation to HLA-associated ADRs should be set up.

First, genome-wide association studies (GWAS) can help to assess genetic variants associated with ADRs.

- For newly confirmed HLA-associated ADRs, generation of more evidence is needed. In addition, the clinical confirmation (if possible, by an independent institution of the HLA-associated ADR) is crucial.
- For HLA alleles that have been revealed as protective, further exploration is needed.
- For HLA alleles for which no associations to ADRs were demonstrated, an exclusion from further systematic analyses is important to receive comprehensible data of good quality and validity.

Second, large prospective multicenter studies need to be set up to capture all genetic variants affecting HLA-associated ADRs.

- Studies need to include a large number of participants to get significant values, e.g. positive and negative predictive values.
- Studies should ideally be set up on a global level to collect a preferably heterogeneous population.
- Consistent definitions for ADRs as suggested by the Phenotype Standardization Project [139] should be applied.
- A harmonized structure for the reporting of further HLA-associated ADRs (e.g. GWAS and their inclusion in larger biobanks) should be aimed for.

Third, PGx studies analyzing multi-gene haplotypes as well as drug-drug interactions are essential for a thorough comprehension and interpretation of the impact of genetic variants.

Last but not least, publication bias should be broached. As might be the case for flucloxacillin, many associations with a low allele prevalence and/or a non-severe ADR are likely not to be reported in the literature. To limit publication bias and increase transparency, an evidence-based medicine approach should engage all scientists in publishing results of HLA alleles with no associations as well as those of low prevalence and/or non-severe ADRs.

Indeed, HLA-typing does seem to have potential. In the future, testing of HLA alleles should be integrated into a panel covering HLA risk alleles associated with ADRs as well as HLA alleles with potential protective functions. However**,** it might be of use not only to create a panel on HLA alleles but to integrate it into a large PGx panel with other genes involved in drug metabolism and transport. A

meta-analysis by Su et al. [140] of four combined risk alleles for *HLA-B*15:01* and *CYP2C9* showed significant associations with phenytoin-induced adverse skin reactions. The commercial tool Stratipharm (by humatrix AG, Germany) also includes HLA risk alleles in their panel besides other genes involved in drug response. Both examples show that a combined risk assessment makes sense, thereby potentiating the usefulness of pre-emptive PGx testing. For the further development and optimization of PGx panels, the algorithms behind the panel could be augmented by artificial intelligence.

2. Project B - Pharmacogenetic testing of patients with adverse drug reactions or therapy failure - development of a standard operating procedure in primary care

For the future of PGx testing and counseling, a few implications for practice are mentioned:

Medication review enriched with a PGx panel

The information provided by a PGx panel test should be embedded into a medication review.

- A medication review offers an excellent opportunity for the integration of PGx. By talking to the patient and asking concrete questions on the tolerability and efficacy of medication, several non-measurable aspects can be assessed to integrate PGx-guided recommendations. A medication review enriched with a large PGx panel might soon be implemented in primary care as a complex pharmacist-led service.
- In the future, PGx panels should give clear weight to each of the prevailing genetic variants thereby showing the respective clinical relevance. This implies the use of algorithms augmented by artificial intelligence that consider the relevance of all tested variants in addition to further relevant patient data.
- Furthermore, pre-emptive PGx testing should be practiced to provide PGx-guided recommendations on co-medication as well as potential future medication, thereby using a lifelong valid PGx panel to its full capacity.

As next steps, further experience with single patient cases shall be gathered, the SOP shall be further refined, and at last, a well-chosen implementation strategy for the SOP in primary care shall be set up. Furthermore, a prospective study with the defined SOP in a selected patient group, e.g. polypharmacy in geriatric patients, should be established. In the long run, also cost-effectiveness for an SOP for PGx testing and counseling needs to be investigated.

PGx - an interdisciplinary discipline

The implementation of PGx seeks an interdisciplinary approach. Networks for effective exchange and collaboration need to be set up and continuously strengthened.

- Because it is difficult to establish therapeutic drug monitoring in primary care, collaboration with pharmacologists is essential. The examination of individual patient cases revealed the necessity of in-depth knowledge of pharmacokinetics and pharmacodynamics. Pharmacists can provide this knowledge. In drugs with sufficient evidence on PGx (e.g. tamoxifen), the pharmacist should be able to provide PGx-guided recommendations for therapeutic decision-making. In drugs with insufficient evidence on PGx (e.g. methotrexate), comprehensive

pharmacological knowledge and the ability to establish therapeutic drug monitoring is necessary for the application of PGx-guided recommendations.

- Notably, contact between pharmacists and physicians such as general practitioners, psychiatrists, rheumatologists, and cardiologists that treat patients who are potentially taking substances affected by PGx, should be held regularly (e.g. quality circles). That way, knowledge and awareness of PGx can be further developed and exchange can contribute to further learning.
- Furthermore, a regular exchange between pharmacists as PGx providers and stakeholders from the commercial PGx test is indispensable to understand the needs and procedures of each other and to foster team-based solutions for an efficient application of PGx panel tests in clinical practice.
- Further efforts for HCPs to collaborate with information specialists to find digital solutions to support pharmacotherapy need to be initiated. With the further progress of digitalization, electronic patient dossiers, online tools for PGx education, and electronic health record with integrated PGx results can be expected. This will help to accelerate the implementation of PGx into clinical practice; however, the applicability of information solutions clearly depends on the quality of the teamwork. The natural language processing in project A1 was a promising start of a first collaboration between pharmacist and information specialist. However, further developments in personalized medicine, such as whole genome sequencing, will bring challenges demanding good quality discussions.
- Finally, stakeholders such as regulatory agencies, health insurers, etc. must be addressed to find solutions for the regulation and reimbursement of PGx testing and counseling.

In the end, an interdisciplinary approach also involves the patient. For a successful implementation of PGx, a shared decision-making process should be enabled.

Bringing PGx to the patient

At the level of the patient, awareness and knowledge on PGx and personalized medicine need to be reinforced.

- HCPs need to learn good communication strategies when talking to the patient about a complex information concerning PGx. Notably, it is essential to further evaluate how the nocebo effect can be minimized during PGx counseling.
- When explaining PGx, it is important to take into account a patient's health literacy. In the future, assessments of PGx understanding related to a patient's health literacy should be initiated. At last, health literacy of patients in general must be further promoted so that they can understand and use the advancements in PGx and personalized medicine.

By integrating a patient's PGx profile into therapeutic decision-making, the pharmacist can contribute to the optimization of a patient's pharmacotherapy and thereby facilitate the implementation of pharmacogenotyping in primary care.

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Appendix

Project A1

Project A1 - Supplementary Figure 1

Word stems	Translation
Afrikan	African (population)
Allel	allele
Asiat	Asian (population)
DPD	dihydropyrimidine-dehydrogenase
Ethnie	ethnicity
Genetisch	genetic
Genotyp	genotype
Gentest	gene test
Glucose-6-Phosphat-Dehydrogenase	Glucose-6-phosphate-dehydrogenase
Haplotyp	haplotype
HLA	human leucocyte antigene
Japan	Japanese (population)
Kaukas	Caucasian (population)
Metabolisierer / metabolizer / metaboliser	metabolizer
NAT	N-acetyltransferase
Phänotyp / Phenotyp	phenotype
Pharmakogenetik	pharmacogenetics
Pharmako-genetisch	pharmacogenetic
Pharmakogenomik	pharmacogenomics
Pharmako-genomisch	pharmacogenomics
Polymorph	polymorph
SLCO1B1	organic anion transporter
TPMT	thiopurin-methyltransferase
UGT1A1	UDP-glucoronsyltransferase 1
Variant	variant

Variations of the word stem "genetisch"	Number of hits
GENETISCHE	1
Genetisch	1
Genetische	25
Genetischer	8
genetisch	111
genetische	210
genetischem	2
genetischen	143
genetischen Polymorphismus	74
genetischer	58
genetisches	14

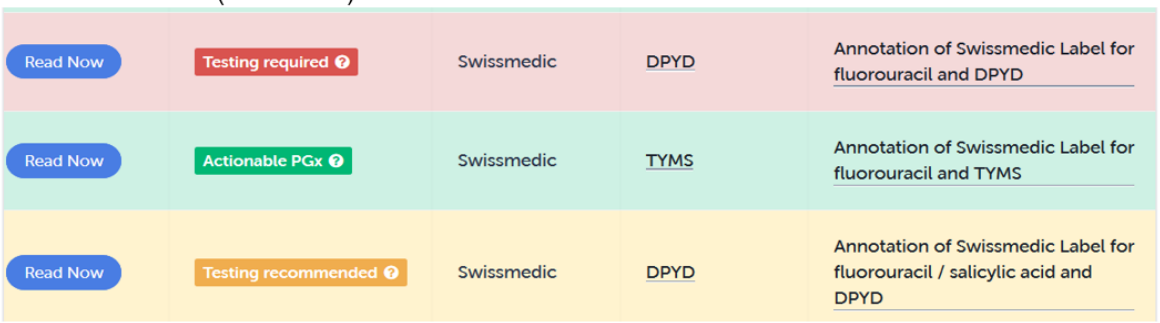
Different spelling possibilities of «G6PD deficiency»
G-6PDH-Mangel
G-6-PDH-Mangel
G6PD-Mangel
G-6-PD-Mangel
Glucose-6-Phosphat
Glucose-6-phosphatase
Glucose-6-Phosphatdehydrogenase
Glucose-6-Phosphat-Dehydrogenase
Glucose-6-phosphat-dehydrogenase
Glucose-6-phosphat-Dehydrogenaseaktivität
Glucose-6-Phosphatdehydrogenase-Mangel
Glucose-6-Phosphat-Dehydrogenasemangel
Glucose-6-phosphat-Dehydrogenasemangel
Glucose-6-Phosphat-Dehydrogenase-Mangel
Glucose-6-phosphat-Dehydrogenase-Mangel
Glucose-6-phosphat-dehydrogenase-Mangel
Glucose-6-phosphate-Dehydrogenase-Mangel
PD-Mangel

Project A1 - Supplementary Figure 2

automatic							manual		
Search term	Substance	Brand	ATC	Section	Sentence	Link	PGx-relevance	Biomarker	PGx level
genetischen Polymor-phismus	Codeine	Maka-tussin®	R05DA04	Pharmaco-kinetics	Die O-Demethylierung von Codein verläuft über das Cytochrom-P450-Isoenzym CYP2D6 und unterliegt somit dem gleichen genetischen Polymorphismus wie die 4-Hydroxylierung von Debrisoquin.	Δ	Yes	CYP2D6	Informa-tive PGx (4)

Project A1 - Supplementary Figure 3

After the consolidation by PharmGKB, we ended up with 131 tags on the PharmGKB website. Of the 167 examined reference DLs, 17 combo products were not mentioned specifically (as they had the same content as the mono product, e.g. Aspirin Cardio 100/300, Aspirin, Aspirin-C [see https://www.pharmgkb.org/chemical/PA448497/labelAnnotation/PA166183782]
In total, 19 reference DLs were not annotated with the PGx levels proposed by PharmGKB. To show why, a few examples are illustrated in the following.
•Fluorouracil: Only the Efudix® DL states an obligatory testing for fluorouracil in contrast to the generic. Moreover, the product for topical application (Verrumal®), only described actionable PGx information. Theses discrepancies are primarily due to the different indications (topic or intravenous), but then for the differences in the two products for intravenous application (Efudix® and generics) also might be due to different literature sources (based on studies with different outcomes). Finally, it ended up with three annotations (PGx levels).



Fluorouracil: Three tags of fluorouracil on PharmGKB website.

•Four reference DLs mentioned more than one biomarker leading to different annotations (PGx levels):
- •Codein / Paracetamol: https://www.pharmgkb.org/chemical/PA166184061/labelAnnotation
- •Carbamazepin: https://www.pharmgkb.org/chemical/PA448785/labelAnnotation
- •Escitalpram: https://www.pharmgkb.org/chemical/PA10074/labelAnnotation
- •Fluorouracil: https://www.pharmgkb.org/chemical/PA128406956/labelAnnotation

Brivex® (Brivudine), Precautionary measures
A time interval of at least 4 weeks must be observed between treatment with Brivex and the start of therapy with 5-fluoropyrimidine-containing drugs. As an additional precaution, in patients who have recently received Brivex, DPD enzyme activity should be determined before starting treatment with a 5-fluoropyrimidine-containing drug (see "Interactions" section).precaution, in patients who have recently received Brivex, DPD enzyme activity should be determined before starting treatment with a 5-fluoropyrimidine-containing drug (see "Interactions" section).

Brivudine: DL excerpt of Brivex® (Brivudine) →Testing is only indicated in case of interactions, which does not fit the criteria by PharmGKB.

Prevymis® (Letermovir), Pharmacokinetics
Pharmacogenomics
The effect of genetic variants in the OATP1B1 gene SLCO1B1 (rs4149056, rs2306283, rs4149032) and UGT1A1 (rs4148323 and promoter TA repeat variants) on the pharmacokinetics of Letermovir was evaluated in 299 study participants. There were no clinically relevant effects of these variants on Letermovir exposure.

Letermovir: DL excerpt of Prevymis® (Letermovir) →The PGx level is not clear, because biomarkers are mentioned, however they are not clinically relevant.

Project A2

Project A2- Supplementary Figure 1: Search string Embase

Exported Print HTML | Embase https://www.embase.com/search/results

Embase®

Embase Session Results

No.	Query	Results
#26	#11 AND #19 AND #25	983
#25	#22 OR #23 OR #24	185,358
#24	'hla antigen'/exp OR 'hla antigen class 1'/exp OR 'hla antigen class 2'/exp	101,582
#23	'hla system' OR 'human leukocyte antigen antigen*' OR 'human leucocyte antigen antigen*' OR 'hl antigen*' OR 'hl-antigen*' OR 'blood group hl a system' OR 'hl a' OR 'hl a antigen system' OR 'hl a leucocyte antigen system' OR 'hl a leukocyte antigen system' OR 'hl a system' OR 'hla complex' OR 'hla phenotype' OR 'human lymphocyte antigen system' OR 'leucocyte antigen hl a system' OR 'leukocyte antigen hl a system' OR 'leucocyte hl a system' OR 'leukocyte hl a system' OR 'leucocyte system hl a' OR 'leukocyte system hl a' OR 'tissue group hl a system' OR 'tissue group hla system' OR 'human leucocyte antigen*' OR 'human leukocyte antigen*' OR 'leucocyte antigen 7d' OR 'leukocyte antigen 7d' OR 'blood group hl a antigen' OR 'hl a antigen*' OR 'hla abc antigen*' OR 'hla antigen*' OR 'leucocyte antigen hl a' OR 'leukocyte antigen hl a' OR 'tissue group hl a antigen' OR 'tissue group hla abc antigen' OR 'tissue group hla antigen' OR 'hla' OR 'class 1 hla antigen*' OR 'histocompatibility antigen* class i' OR 'hla class 1 antigen*' OR 'hla class i antigen*' OR 'hla a antigen*' OR 'hla-a antigen*' OR 'major histocompatibility antigen class 1 a' OR 'major histocompatibility antigen class 1a' OR 'hla a1 antigen' OR 'hla-a1 antigen*' OR 'hla a11 antigen' OR 'hla a 11' OR 'hla a 11 antigen*' OR 'hla a11' OR 'hla-a11' OR 'hla-a11 antigen*' OR 'hla a2 antigen' OR 'leucocyte antigen 2' OR 'leukocyte antigen 2' OR 'tissue group a2 antigen*' OR 'antigen hl a2' OR 'leucoyte antigen mac' OR 'leukocyte antigen mac' OR 'leucocyte antigen pigrly b1' OR 'leukocyte antigen pigrly b1' OR 'leucocyte antigen to 9' OR 'leukocyte antigen to 9' OR 'hl a 2 antigen*' OR 'hl a2 antigen*' OR 'hl-a2 antigen*' OR 'leucocyte antigen 8a' OR 'leukocyte antigen 8a' OR 'leucocyte antigen dau 1' OR 'leukocyte antigen dau 1' OR 'leucocyte antigen dau 11' OR 'leukocyte antigen dau 11' OR 'leucocyte antigen lc 2' OR 'leukocyte antigen hl a2' OR 'leucocyte antigen la2' OR 'leukocyte antigen lc 2' OR 'leucocyte hb a2 antigen*' OR 'leukocyte antigen la2' OR 'leucocyte antigen antigen hl a2' OR 'leukocyte hb a2 antigen*' OR 'thrombocyte hl a2 antigen*' OR 'hla a24 antigen' OR 'antigen* hla a24' OR 'hla a 24' OR 'hla a 24 antigen*' OR 'hla a24' OR 'hla-a24' OR 'hla-a24 antigen*' OR 'hla a3 antigen' OR 'hla-a3 antigen*' OR 'hla b antigen' OR 'hl b antigen*' OR 'hla b pot antigen*' OR 'hla bw15 antigen*' OR 'hla-b antigen*' OR 'major histocompatibility antigen* class 1 b' OR 'major histocompatibility antigen* class 1b' OR 'hla b antigens' OR 'hla b13 antigen*' OR 'hla b13' OR 'hla-b13' OR 'hla-b13 antigen*' OR 'hla b14 antigen*' OR 'hla b14' OR 'hla-b14' OR 'hla-b14 antigen*' OR 'hla b15 antigen*' OR 'hla b15' OR 'hla-b15' OR 'hla-b15 antigen*' OR 'hla b18 antigen*' OR 'hla b18' OR 'hla-b18' OR 'hla-b18 antigen*' OR 'hla b27 antigen*' OR 'antigen b 27' OR 'antigen hla 27b' OR 'hl a 27b antigen' OR 'hl a b27' OR 'hla 27b antigen*' OR 'hla b27' OR 'hla-b27 antigen*' OR 'human lymphocyte antigen 27b' OR 'hla b35 antigen*' OR 'hla-b35 antigen*' OR 'hla b37 antigen*' OR 'hla b37' OR 'hla-b37' OR 'hla-b37 antigen*' OR 'hla b38 antigen*' OR 'hla b38' OR 'hla-b38' OR 'hla-b38 antigen*' OR 'hla b39 antigen*' OR 'hla b39' OR 'hla-b39' OR 'hla-b39 antigen*' OR 'hla b40 antigen*' OR 'hla b40' OR 'hla-b40' OR 'hla-b40 antigen*' OR 'hla b44 antigen*' OR 'hla b44' OR 'hla-b44' OR 'hla-b44 antigen*' OR 'hla b51 antigen*' OR 'antigen hla b51' OR 'hla b51' OR 'hla-b51' OR 'hla-b51 antigen*' OR 'hla b52 antigen*' OR 'hla b52' OR 'hla-b52' OR 'hla-b52 antigen*' OR 'hla b57 antigen*' OR 'antigen hla b57' OR 'hla b57' OR 'hla b60 antigen*' OR 'hla b60' OR 'hla b7 antigen*' OR 'hla-b7 antigen' OR 'hla b8 antigen*' OR 'antigen hla b8' OR 'hla-b8 antigen*' OR 'leucocyte antigen hla b8' OR 'leukocyte antigen hla b8' OR 'hla c antigen*' OR 'hla-c antigen*' OR 'hla d antigen*' OR 'hl a d antigen*' OR 'hla-d antigen*' OR 'hla e antigen*' OR 'hla f antigen*' OR 'hla g antigen*' OR 'hla-g antigen*':ti,ab	181,725
#22	'class 2 hla antigen*' OR 'histocompatibility antigen* class ii' OR 'hla antigen class ii' OR 'hla class 2 antigen' OR 'hla class ii antigen*' OR 'hla dm antigen*' OR 'hla do antigen*' OR 'hla dp antigen*' OR 'hla dp alpha chain*' OR 'hla dp beta chain*' OR 'hla-dp alpha-chain*' OR 'hla-dp antigen*' OR 'hla-dp beta-chain*' OR 'hla dpb1 antigen*' OR 'antigen hla dpb1' OR 'hla dpb1' OR 'hla-dpb1' OR 'hla dq antigen*' OR 'antigen hla dq' OR 'hla dq alpha chain*' OR 'hla dq beta chain*' OR 'hla dqw1 antigen*' OR 'hla dqw3 antigen*' OR 'hla dqw7 antigen*' OR 'hla-dq alpha-chain*' OR 'hla-dq antigen*' OR 'hla-dq beta-chain*' OR 'hla dq1 antigen*' OR 'antigen hla dq1' OR 'hla dq1' OR 'hla-dq1' OR 'hla-dq1 antigen*' OR 'hla dq2 antigen*' OR 'antigen hla dq2' OR 'hla dq2' OR 'hla-dq2' OR 'hla-dq2 antigen*' OR 'hla dq8 antigen*' OR 'hla dq8' OR 'hla-dq8' OR 'hla-dq8 antigen*' OR 'hla dqa1 antigen*' OR 'antigen hla dqa1' OR 'hla dqa1' OR 'hla-dqa1' OR 'hla dqb1 antigen*' OR 'antigen hla dqb1' OR 'hla dqb1' OR 'hla-dqb1' OR 'hla dr antigen*' OR 'dr antigen*' OR 'hla dr alpha chain*' OR 'hla dr beta chain*' OR 'hla dr serological subtypes' OR 'hla dra' OR 'hla-dr alpha-chain*' OR 'hla-dr antigen*' OR 'hla-dr beta-chain*' OR 'hla-dr serological subtypes' OR 'tissue group hla dr antigen*' OR 'hla dr1 antigen*' OR 'hla-dr1 antigen*' OR 'hla dr11 antigen*' OR 'antigen hla dr11' OR 'hla dr11' OR 'hla-dr11' OR 'hla dr15 antigen*' OR 'hla dr2 antigen*' OR 'antigen hla dr2' OR 'hla-dr2 antigen*' OR 'hla dr3 antigen*' OR 'hla dr 3 antigen' OR 'hla-dr3 antigen' OR 'hla dr4 antigen*' OR 'hla dr 4 antigen' OR 'hla-dr4 antigen' OR 'hla dr5 antigen*' OR 'hla dr 5 antigen*' OR 'hla drw5 antigen*' OR 'hla-dr5 antigen' OR 'hla dr6 antigen*' OR 'hla dr 6 antigen*' OR 'hla-dr6 antigen*' OR 'hla dr7 antigen*' OR 'hla-dr7 antigen*' OR 'hla drb1 antigen*' OR 'hla drb1' OR 'hla drb1 chain*' OR 'hla-drb1' OR 'hla-drb1 antigen*' OR 'hla-drb1 chain*' OR 'hla drb3 antigen*' OR 'hla drb3' OR 'hla drb3 chain*' OR 'hla-drb3' OR 'hla-drb3 antigen*' OR 'hla-drb3 chain*' OR 'hla drb4 antigen*' OR 'hla drb4' OR 'hla drb4 chain*' OR 'hla-drb4' OR 'hla-drb4 antigen*' OR 'hla-drb4 chain*' OR 'hla drb5 antigen*' OR 'hla drb5' OR 'hla drb5 chain*' OR 'hla-drb5' OR 'hla-drb5 antigen*' OR 'hla-drb5 chain*' OR 'ia antigen*' OR 'immune response antigen*' OR 'immune response gene product*':ti,ab	53,823
#19	#17 OR #18	130,719
#18	'pharmacogenomic*' OR 'pharmacogenetic*' OR 'pharmacogenetic testing' OR 'genetic testing' OR 'pharmacogenetic analysis' OR 'pharmacogenetic analyses' OR 'pharmacogenomic analysis' OR 'pharmacogenomic analyses' OR 'pharmacogenetic study' OR 'pharmacogenetic studies' OR 'pharmacogenetic screening*' OR 'pharmacogenomic screening*' OR 'pharmacogenomic study' OR 'pharmacogenomic studies' OR 'pharmacogenomic testing':ti,ab	77,299
#17	'pharmacogenetics'/exp OR 'genetic screening'/exp	101,989
#15	'pharmacogenomic analysis'	149
#11	#7 OR #10	1,682,851
#10	'adverse event'/de OR 'adverse drug reaction'/exp OR 'side effect'/exp	728,985
#7	'adverse drug reaction*' OR 'adverse drug event*' OR 'adverse drug effect*' OR 'drug adverse reaction*' OR 'drug adverse effect*' OR 'drug side effect*' OR 'drug-related side effects and adverse reactions' OR 'drug-related side effect and adverse reaction*' OR 'drug-related side effect* and adverse reactions' OR 'long term adverse effect*' OR 'metabolic side effect* of drugs and substances' OR 'drug eruption*' OR 'dermatitis medicamentosa' OR 'exanthema medicamentum' OR 'drug dermatitis' OR 'drug exanthema' OR 'drug rash' OR 'paradoxical drug reaction*' OR 'unspecified side effect*' OR 'drug fatality' OR 'drug mortality' OR 'fatal adverse drug reaction*' OR 'fatal adverse reaction*' OR 'fatal side effect*' OR 'drug hypersensitivity' OR 'drug hypersensitivities' OR 'allergic drug reaction*' OR 'allergic reaction*' OR 'drug induced allergy' OR 'drug induced allergies' OR 'drug allergic reaction*' OR 'drug allergy' OR 'drug allergies' OR 'drug contact hypersensitivity' OR 'drug contact hypersensitivities' OR 'drug intolerance*' OR 'dress syndrome*' OR 'allopurinol hypersensitivity syndrome*' OR 'anticonvulsant hypersensitivity syndrome*' OR 'dapsone hypersensitivity syndrome*' OR 'drug hypersensitivity syndrome*' OR 'drug induced hypersensitivity syndrome*' OR 'drug rash with eosinophilia and systemic symptom*' OR 'drug rash with eosinophilia and systemic symptoms syndrome*' OR 'drug reaction with eosinophilia and systemic symptoms syndrome*' OR 'hypersensitivity syndrome*' OR 'side reaction*' OR 'drug induced disease*' OR 'drug complication*' OR 'drug disease*' OR 'drug injury' OR 'drug injuries' OR 'drug related disease*' OR 'iatrogenic drug*':ti,ab	1,546,559

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Project A2 – Supplementary Figure 2: Search string Pubmed

Pubmed 20.3.2019 Search String komplett

Search ((((((("HLA Antigens"[Mesh] OR "Histocompatibility Antigens"[Mesh] OR "Histocompatibility Antigens Class I"[Mesh] OR "Histocompatibility Antigens Class II"[Mesh] OR "HLA-A Antigens"[Mesh] OR "HLA-B Antigens"[Mesh] OR "HLA-C Antigens"[Mesh] OR "HLA-D Antigens"[Mesh] OR "HLA-G Antigens"[Mesh])))) OR (("HLA A Antigen"[Title/Abstract] OR "HLA A Antigens"[Title/Abstract] OR "HLA-A Antigen"[Title/Abstract] OR "HLA-A Antigens"[Title/Abstract] OR "HLA A1 Antigen"[Title/Abstract] OR "HLA-A1 Antigen"[Title/Abstract] OR "HLA-A*01"[Title/Abstract] OR "HLA-A1"[Title/Abstract] OR "HLA A1"[Title/Abstract] OR "HLA A11 Antigen"[Title/Abstract] OR "HLA-A11 Antigen"[Title/Abstract] OR "HLA-A*11"[Title/Abstract] OR "HLA-A*11"[Title/Abstract] OR "HLA A11"[Title/Abstract] OR "HLA A2 Antigen"[Title/Abstract] OR "HLA A2 Antigens"[Title/Abstract] OR "HLA-A2 Antigen"[Title/Abstract] OR "HLA-A2 Antigens"[Title/Abstract] OR "HLA-A*02"[Title/Abstract] OR "HLA-A2"[Title/Abstract] OR " HLA A2"[Title/Abstract] OR "HLA A24 Antigen"[Title/Abstract] OR "HLA A24 Antigens"[Title/Abstract] OR "HLA-A24 Antigen"[Title/Abstract] OR "HLA-A24 Antigens"[Title/Abstract] OR "HLA-A*24"[Title/Abstract] OR "HLA-A24"[Title/Abstract] OR "HLA A24"[Title/Abstract] OR "HLA A3 Antigen"[Title/Abstract] OR "HLA A3 Antigens"[Title/Abstract] OR "HLA-A3 Antigen"[Title/Abstract] OR "HLA-A3 Antigens"[Title/Abstract] OR "HLA-A*03"[Title/Abstract] OR "HLA-A3"[Title/Abstract] OR "HLA A3"[Title/Abstract] OR "HLA B Antigen"[Title/Abstract] OR "HLA B Antigens"[Title/Abstract] OR "HLA B13 Antigen"[Title/Abstract] OR "HLA B13 Antigens"[Title/Abstract] OR "HLA-B13 Antigen"[Title/Abstract] OR "HLA-B13 Antigens"[Title/Abstract] OR "HLA-B*13"[Title/Abstract] OR "HLA-B13"[Title/Abstract] OR "HLA B13"[Title/Abstract] OR "HLA B14 Antigen"[Title/Abstract] OR "HLA B14 Antigens"[Title/Abstract] OR "HLA-B14 Antigen"[Title/Abstract] OR "HLA-B14 Antigens"[Title/Abstract] OR "HLA-B*14"[Title/Abstract] OR "HLA-B14"[Title/Abstract] OR "HLA B14"[Title/Abstract] OR "HLA B15 Antigen"[Title/Abstract] OR "HLA-B15 Antigen"[Title/Abstract] OR "HLA-B*15"[Title/Abstract] OR "HLA-B15"[Title/Abstract] OR "HLA B15"[Title/Abstract] OR "HLA B18 Antigen"[Title/Abstract] OR "HLA B18 Antigens"[Title/Abstract] OR "HLA-B18 Antigen"[Title/Abstract] OR "HLA-B18 Antigens"[Title/Abstract] OR "HLA-B18"[Title/Abstract] OR "HLA B18"[Title/Abstract] OR "HLA-B*18"[Title/Abstract] OR "HLA B27 Antigen"[Title/Abstract] OR "HLA B27 Antigens"[Title/Abstract] OR "HLA-B27 Antigen"[Title/Abstract] OR "HLA-B27 Antigens"[Title/Abstract] OR "HLA-B*27"[Title/Abstract] OR "HLA-B27"[Title/Abstract] OR "HLA B27"[Title/Abstract] OR "HLA B35 Antigen"[Title/Abstract] OR "HLA B35 Antigens"[Title/Abstract] OR "HLA-B35 Antigen"[Title/Abstract] OR "HLA-B35 Antigens"[Title/Abstract] OR "HLA-B*35"[Title/Abstract] OR "HLA-B35"[Title/Abstract] OR "HLA B35"[Title/Abstract] OR "HLA-B*37"[Title/Abstract] OR "HLA-B37"[Title/Abstract] OR "HLA B37"[Title/Abstract] OR "HLA B38 Antigen"[Title/Abstract] OR "HLA-B38 Antigen"[Title/Abstract] OR "HLA-B38"[Title/Abstract] OR "HLA-B38"[Title/Abstract] OR "HLA B38"[Title/Abstract] OR "HLA B39 Antigen"[Title/Abstract] OR "HLA-B39 Antigen"[Title/Abstract] OR "HLA-B*39"[Title/Abstract] OR "HLA-B39"[Title/Abstract] OR "HLA B39"[Title/Abstract] OR "HLA B40 Antigen"[Title/Abstract] OR "HLA B40 Antigens"[Title/Abstract] OR "HLA-B40 Antigen"[Title/Abstract] OR "HLA-B40 Antigens"[Title/Abstract] OR "HLA-B*40"[Title/Abstract] OR "HLA-B40"[Title/Abstract] OR "HLA B40"[Title/Abstract] OR "HLA B41 Antigen"[Title/Abstract] OR "HLA-B41 Antigen"[Title/Abstract] OR "HLA-B*41"[Title/Abstract] OR "HLA-B41"[Title/Abstract] OR "HLA B41"[Title/Abstract] OR "HLA B51 Antigen"[Title/Abstract] OR "HLA-B51 Antigen"[Title/Abstract] OR "HLA-B*51"[Title/Abstract] OR "HLA-B51"[Title/Abstract] OR "HLA B51"[Title/Abstract] OR "HLA B52 Antigen"[Title/Abstract] OR "HLA B52

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eosinophilia and systemic symptoms syndrome"[Title/Abstract])) OR ("drug rash with eosinophilia and systemic symptoms"[Title/Abstract])) OR ("Drug Related Side Effects and Adverse Reactions"[Title/Abstract])) OR ("Drug Related Side Effect and Adverse Reaction"[Title/Abstract])) OR ("Drug Related Side Effects and Adverse Reaction"[Title/Abstract])) OR ("Drug-Related Side Effects and Adverse Reactions"[Title/Abstract]))

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Project B1

Project B1 – Ethics approval

EKNZ

Ethikkommission
Nordwest- und
Zentralschweiz

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Basel, 03. Oktober 2019 / SK

Verfügung der Ethikkommission Nordwest- und Zentralschweiz (EKNZ)

Project-ID	2019-01452
Projekttitel	Pharmacogenetic Testing of patients with unwanted Adverse Drug Reactions or Therapy Failure
Haupt-Prüfer / Koordinierender Prüfer	Prof Dr. Kurt Hersberger
Sponsor	Universitätsspital Basel, Prof Dr. Kurt Hersberger
Zentren	• Prof Dr. Kurt Hersberger, Universitätsspital, Basel

Entscheid

- ☒ Die Bewilligung wird erteilt → die Bedingungen der EKNZ vom 28. August 2019 wurden erfüllt
- ☐ Die Bewilligung wird mit Auflagen erteilt
- ☐ Die Bewilligung kann noch nicht erteilt werden
- ☐ Die Bewilligung wird nicht erteilt
- ☐ Auf das Gesuch wird nicht eingetreten

Klassifizierung

☒ Forschungsprojekt gemäss HFV — Kategorie: A

- ☒ Forschung mit Personen
- ☐ Weiterverwendung des biologischen Materials oder der gesundheitsbezogenen Personendaten
- ☐ mit Verstorbenen
- ☐ mit Embryonen / Föten
- ☐ mit ionisierender Strahlung

Entscheidverfahren

☐ ordentliches Verfahren ☐ vereinfachtes Verfahren ☒ Präsidialverfahren

Die Ethikkommission bestätigt, dass sie nach ICH-GCP arbeitet.

Geschäftsführerin Irene Oberli | Hebelstrasse 53 | 4056 Basel | Tel 061 268 13 50 | Fax 061 268 13 51 | eknz@bs.ch | www.eknz.ch

Gebühren

Betrag: **CHF** **Tarifcode:**

Gemäss der geltenden Gebührenordnung von swissethics.

Rechtsmittelbelehrung

Gegen diesen Entscheid kann an den Regierungsrat des Kantons Basel-Stadt (Rathaus, Marktplatz 9, 4051 Basel) rekurriert werden. Der Rekurs ist innert 10 Tagen seit Eröffnung des Entscheides bei der Rekursinstanz anzumelden; innert 30 Tagen, vom gleichen Zeitpunkt an gerechnet, ist die Rekursbegründung einzureichen, welche die Anträge und deren Begründung mit Angabe der Beweismittel zu enthalten hat. Bei völliger oder teilweiser Abweisung des Rekurses können die Kosten der Rekurrentin respektive dem Rekurrenten ganz oder teilweise auferlegt werden.

Kopie an

☐ BAG

☒ Sponsor Universitätsspital Basel, kurt.hersberger@unibas.ch

☐ Andere

Unterschrift

i.V. MJoner.

Prof. Dr. med. Christoph Beglinger
Präsident

Anhang:
1. Pflichten des Sponsors/der Prüfperson oder der Projektleitung
2. Mögliche Entscheide und ihre Bedeutung
3. Eingereichte Dokumente (01.10.2019)

Anhang 1

Pflichten des Sponsors/der Prüfperson oder der Projektleitung:

Einreichung Dokumente: revidierte Dokumente und neue Dokumente zur Studie/zum Projekt sollen ausschliesslich über das Web-Portal BASEC eingereicht werden, auf der entsprechenden Formularseite des betreffenden Gesuches. Obsolete Dokumente sind dabei zu entfernen und Datums- und Versionsangaben entsprechend zu ergänzen. Die erfolgten Änderungen müssen im Korrekturmodus abgefasst werden und zusätzlich als ‚clean'-Version eingereicht werden. Die Studieninformationen und -einwilligungen, das Protokoll und die Amendments müssen in durchsuchbaren PDF-Dateien eingereicht werden, insbesondere müssen gescannte Dokumente eine Texterkennung durchlaufen haben (OCR). Das unterschriebene und datierte Begleitschreiben muss die Antworten auf eventuell von der EK gestellte Fragen enthalten. Revidierte Dokumente sind auch den weiteren Zulassungsbehörden zuzustellen, sofern diese involviert sind.

Anmerkung: Die zuständige Ethikkommission überprüft im Rahmen des Bewilligungsverfahrens Aufklärungsbogen und Einwilligungserklärung in einer der Amtssprachen Deutsch, Französisch oder Italienisch. Aufklärungsbogen und Einwilligungserklärung in einer anderen Sprache werden von der Ethikkommission lediglich zur Kenntnis genommen. Für die korrekte Übersetzung ist der Sponsor oder die Projektleitung verantwortlich.

Meldepflichten: Die rechtlich bindenden Melde- resp. Bewilligungspflichten an die Ethikkommission für wesentliche Änderungen, einen vorzeitigen Studienabbruch, unerwünschte Ereignisse u.a. sind einzuhalten (Verordnungen des Bundes). Der Abschlussbericht ist spätesten ein Jahr nach Studienende der Ethikkommission einzureichen.

Registrierungspflicht: Der Sponsor muss – falls es sich um einen klinischen Versuch handelt – diesen in einem WHO-Primärregister oder im Register der Nationalen Medizinbibliothek der USA (clinicaltrials.gov) erfassen und anschliessend diese Nummer im BASEC-Portal eingeben. Die Übertragung der erforderlichen Daten in das Swiss National Clinical Trials Portal (SNCTP) kann nach Bewilligung der Ethikkommission und Zustimmung des Gesuchstellers automatisch erfolgen. Die Informationen über den klinischen Versuch sind in beiden Registern öffentlich zugänglich. Zusätzlich veröffentlicht swissethics wenige Informationen wie Titel, Projekttyp oder Leit-Ethikkommission aller durch die kantonalen Ethikkommissionen bewilligten Gesuche auf swissethics.ch (ausser Phase-I-Studien).

Anhang 2

Mögliche Entscheide und ihre Bedeutung

Die Bewilligung wird erteilt: Das Vorhaben kann gemäss bewilligtem Forschungsplan und im Rahmen der anwendbaren rechtlichen Bestimmungen durchgeführt werden. Weitere Bewilligungspflichten (Swissmedic/BAG) sind zu beachten

Die Bewilligung wird mit Auflagen erteilt: Das Vorhaben kann gemäss bewilligtem Forschungsplan gestartet werden und im Rahmen der anwendbaren rechtlichen Bestimmungen durchgeführt werden. Die Auflagen sind zu erfüllen und die Gesuchsunterlagen innert 30 Tagen entsprechend anzupassen. Die revidierten Dokumente werden nach Einreichung im Präsidialverfahren geprüft. Weitere Bewilligungspflichten (Swissmedic/BAG) sind zu beachten

Die Bewilligung kann noch nicht erteilt werden: Das Vorhaben kann noch nicht gestartet werden. Die nachfolgenden Bedingungen sind zu erfüllen bzw. die Fragen zu beantworten und die revidierten Dokumente erneut bei der Ethikkommission einzureichen. Die Ethikkommission überprüft die revidierten Dokumente und erteilt die Bewilligung, wenn die Bedingungen erfüllt bzw. die Fragen zufriedenstellend beantwortet sind.

Die Bewilligung wird nicht erteilt: Das Vorhaben kann in der vorliegenden Form nicht durchgeführt werden. Eine Neueinreichung ist möglich.

Auf das Gesuch wird nicht eingetreten: Begründung siehe vorne, z.B. nicht zuständig oder nicht bewilligungspflichtig.

Anhang 3

Eingereichte Dokumente für das Hauptzentrum

Prof Dr. Kurt Hersberger, Pharmaceutical Care Research Group, Basel

Dokument	Dok.Datum	Version
pgx-begleitbrief-eknz-bedingungen-20190930.pdf	30.09.2019	
pgx-studieninformation-v2-0-20190930-korrekturmodus.docx	30.09.2019	2.0
pgx-arzteinformation-v2-0-20190916.docx	16.09.2019	2.0
pgx-arzteinformation-v2-0-20190916.pdf	16.09.2019	2.0
pgx-studieninformation-v2-0-20190930-sauber.docx	30.09.2019	2.0
pgx-studieninformation-v2-0-20190930o.pdf	30.09.2019	2.0
pgx-study-protocol-v2-0-20190930.pdf	30.09.2019	2.0
pgx-study-protocol-v2-0-20190930-sauber.docx	30.09.2019	2.0
pgx-study-protocol-v2-0-20190930-korrekturmodus.docx	30.09.2019	2.0
pgx-flyer-fur-patient-v2-0-20190916.pdf	16.09.2019	2.0
pgx-flyer-fur-patient-v2-0-20190916.docx	16.09.2019	2.0
pgx-stratipharm-system-concept-v1-0-20190925.pdf	25.09.2019	

Project B1 – Case report form

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Patientencode: _____
Geschlecht: _____
Jahrgang: _____

CRF für die Apotheke – vor dem Erstgespräch

Patientenüberweisung

- Art der Rekrutierung:
  - ☐ Arzt
    - ☐ schriftlich
    - ☐ telefonisch
    - ☐ andere: _____
  - ☐ andere: _____
- Kontaktaufnahme mit Patient:
  - ☐ Telefon: _____
  - ☐ Mail: _____

Terminvereinbarung	Ja	Nein
• Termin mit Patient vereinbart	☐	☐
• Termin mit dem Ambulanten Studienzentrum der CTU abgemacht: _____		

Allgemeine Angaben	Ja	Nein
• Datum: ___/___/_____ (tt.dd.jjjj)		
• Stammdaten Patient wurden vollständig im *Identifikationslogbuch* (Anhang CRF\PGX_Identifikationslogbuch_V1.0_20190601.docx) aufgenommen	☐	☐
• Diagnoseliste vom Arzt erhalten	☐	☐

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Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

CRF für die Apotheke - Erstgespräch

Einführung zur Studie *Pharmakogenetische Untersuchung von Patienten mit unerwünschten Arzneimittelwirkungen oder Wirkungsausfällen*
0. Wer sind wir? ☐ Ich bin _____ ☐ Wir sind eine Forschungsgruppe des Departements Pharmazeutische Wissenschaften der Universität Basel, welche die „Pharmakogenetische Untersuchung von Patienten mit unerwünschten Arzneimittelwirkungen oder Wirkungsausfällen» in der klinischen Praxis untersuchen möchte.
1. Was ist Pharmakogenetik? ☐ Genetische Variabilität ist normal →Jeder Mensch hat einen andern Stoffwechsel (langsam-normal-schnell). ☐ Nach dem heutigen Stand der Wissenschaft möchte man immer weiter in Richtung einer individualisierten Pharmakotherapie gehen. ☐ Mittlerweile gibt es für viele Substanzen Hinweise dafür, dass ein Zusammenhang zwischen der genetischen Konstellation und der Art, wie das Medikament verstoffwechselt wird besteht. ☐ In der Pharmakogenetik geht es also darum, den Stoffwechsel eines Menschen in Bezug auf die eingenommene Substanz zu untersuchen. ☐ Abgrenzung: Wir untersuchen nur die Gene, welche einen Einfluss auf den Stoffwechsel haben. Es ist nicht möglich, aus diesen Daten Krankheiten vorauszusagen oder Abstammungen zu erforschen.
2. Wie werden die Gene untersucht? ☐ Wir nehmen einen Abstrich ihrer Mundschleimhaut. Aus einer Mundschleimhautzelle wird die DNA extrahiert und dann genotypisiert. ☐ Das geschieht in einem Labor in Deutschland. Der Test heisst Stratipharm® analog zu „stratifizierte Pharmakotherapie“. ☐ Nach der Auswertung erhalten wir die Daten, welche nur mit Ihrem persönlichen Code zugänglich sind. „Sie sind Herr Ihrer Daten.“ Dieser Code wird Ihnen nach Hause geschickt. ☐ Für die Einsicht der Daten braucht es die Stratipharm® Software, welche für Apotheker und Ärzte verfügbar ist. Dies mit der Idee, dass Daten niemals ohne Fachkompetenz benutzt werden.
3. Wie läuft die Studie ab? ☐ Erstgespräch: Aufnahme ihrer aktuellen Therapie und der bisherigen Erfahrungen mit Wirkungen der Medikamente, Einverständniserklärung, und Entnahme der Probe ☐ Blutentnahme im Ambulanten Studienzentrum des USB ☐ Genotypisierung im Labor (t=14d) ☐ Zweitgespräch: Interpretation und Evaluation der Daten ☐ Empfehlungsschreiben an den behandelnden Arzt

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Patientencode: _____
Geschlecht: _____
Jahrgang: _____

Kriterien	Ja	Nein
Einschlusskriterien • ≥ 18 Jahre • Proband hat die Einverständniserklärung verstanden und unterschrieben • Mindestens eines der folgenden Kriterien trifft zu: ☐ Ein neues Medikament mit bekannter pharmakogenetischer Assoziation ☐ Beobachtung von auffallenden Nebenwirkungen, welche wahrscheinlich mit Medikamenten mit bekannter pharmakogenetischer Assoziation verknüpft sind ☐ Beobachtung von Therapieausfällen, welche wahrscheinlich mit Medikamenten mit bekannter pharmakogenetischer Assoziation verknüpft sind ☐ Familienanamnese mit auffallenden Nebenwirkungen/Therapieausfällen, welche wahrscheinlich mit Medikamenten mit bekannter pharmakogenetischer Assoziation verknüpft sind	☐ ☐ ☐	☐ ☐ ☐
Ausschlusskriterien • Ungenügende Deutschkenntnisse • Proband ist nicht in der Lage, in die öffentliche Apotheke zu kommen	☐ ☐	☐ ☐

Anamnese	Ja	Nein
• *PMC* (Anhang CRF\PGX_Formular-PolyMedCheck-Erstgespräch_20190601.pdf) durchgeführt ○ Anzahl Medikamente verordnet: _____ ○ Selbstmedikation (ja / nein): _____	☐	☐
• *Anamnese für die pharmakogenetische Analyse Teil 1* (Anhang CRF\PGX_Anamnese-PGx-Analyse-Erstgespräch_V1.0_20190626.docx) ausgefüllt	☐	☐
• Ist eine Blutspiegelmessung indiziert? ○ Falls ja: *Anamnese für die pharmakogenetische* Analyse Teil 2 ausgefüllt ○ Falls ja: auf *Laborblatt ASC*(Anhang CRF\PGX_Laborblatt_ASC_V1.0_20190704.docx) vermerkt	☐ ☐ ☐	☐ ☐ ☐
• Personalien von Patient in Stratipharm erfasst	☐	☐
• Abstrich der Mundschleimhaut genommen	☐	☐
• *Laborauftrag* (Anhang CRF\PGX_Laborauftrag-blanko-Klinik-personalisiert_V1.0_20190701.pdf) 2 Mal unterschrieben	☐	☐
• Probe an Stratipharm versendet	☐	☐
• Zeitbedarf für das Gespräch in Minuten: _____		

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Weiterleitung an ambulantes Studienzentrum	Ja	Nein
• *Laborblatt ASC* (Anhang CRF\PGX_Laborblatt_ASC_V1.0_20190704.docx) ausgefüllt	☐	☐
• dem Patient ein Kuvert mit Patientencode-Etiketten , Laborblatt und *Lageplan Schanzenstrasse 55* (*Anhang CRF\PGX_LageplanSchanzenstr-für-Patient_20190708.pdf*) mitgegeben	☐	☐

Dokumentation	Ja	Nein
• Anonymisierte Kopie von *PMC* dem Patientendossier beigelegt	☐	☐

„CRF Erstgespräch" abgeschlossen am ___/___/_____ (Datum, tt.dd.jjjj)

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Weiterleitung an ambulantes Studienzentrum	Ja	Nein
• *Laborblatt ASC* (Anhang CRF\PGX_Laborblatt_ASC_V1.0_20190704.docx) ausgefüllt	☐	☐
• dem Patient ein Kuvert mit Patientencode-Etiketten , Laborblatt und *Lageplan Schanzenstrasse 55* (*Anhang CRF\PGX_LageplanSchanzenstr-für-Patient_20190708.pdf*) mitgegeben	☐	☐

Dokumentation	Ja	Nein
• Anonymisierte Kopie von *PMC* dem Patientendossier beigelegt	☐	☐

„CRF Erstgespräch" abgeschlossen am ___/___/_____ (Datum, tt.dd.jjjj)

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Patientencode: _____
Geschlecht: _____
Jahrgang: _____

CRF für die Apotheke – Zweitgespräch

Allgemeine Angaben	Ja	Nein
• Datum: ___/___/_____ (tt.dd.jjjj)		
• Zeitbedarf für das Gespräch in Minuten: _____ • Zeitbedarf für Erstellung Empfehlung an den Arzt in Minuten: _____		
• Genetische Daten abgespeichert und in Masterfile (Anhang CRF\PGX_CRF-Stratipharm-SNPs&annotations_20190601.xlsx) abgelegt • Liste der betroffene Wirkstoffe abgespeichert und gedruckt • Relevante Wirkstoffanalysen als PDF abgespeichert • Formular *Empfehlung nach einer pharmakogenetischen Analyse* (*Anhang CRF\PGX_Vorlage-Empfehlung-Zweitgespräch_V1.0_201901627.docx*) ausgefüllt	☐ ☐ ☐ ☐	☐ ☐ ☐ ☐
• Empfehlung an Arzt geschickt	☐	☐
• Follow-Up: Patient wird in 1 und 6 Monaten nochmals telefonisch kontaktiert. ○ Patient informiert ○ Datum dem Studienzentrum der PCRG mitgeteilt	 ☐ ☐	 ☐ ☐
• Anonymisierte Kopie von *Empfehlung nach einer pharmakogenetischen Analyse* dem Patientendossier beigelegt	☐	☐

„CRF Zweitgespräch" abgeschlossen am ___/___/_____ (Datum, tt.dd.jjjj)

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CRF für die Apotheke – Follow up

- Telefongespräch nach 1. Monat
  - Datum: ___/___/_____ (tt.dd.jjjj)
  - Zeit: _____ Minuten

Notizen

- Telefongespräch nach 6. Monat
  - Datum: ___/___/_____ (tt.dd.jjjj)¨
  - Zeit: _____ Minuten

Notizen

„CRF Follow Up“ abgeschlossen am ___/___/_____ (Datum, tt.dd.jjjj)

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Project B1 – Form for polymedication check

Polymedikations-Check pharmaSuisse

Name	Vorname	Pat.-Nr.
Str.	Ort	Tel.

Der Patient/die Patientin nimmt zurzeit täglich 4 oder mehr Medikamente auf ärztliche Verordnung und über längere Zeit (mind. 3 Monate) ein ☐

Der Patient/die Patientin ist einverstanden, dass der Apotheker/die Apothekerin einen Polymedikations-Check macht ☐

Geburtsdatum _____ / _____ / _____ | Geschlecht ☐ männlich ☐ weiblich

1. Check Zeit Beginn: _____._____ Uhr

	Aktuelle Medikamente auf ärztliche Verordnung) (dieser Check basiert auf Informationen des Patienten und/oder auf Dokumentationen der Apotheke) Fortsetzung auf Blatt 2	Abklärung Bedarf für Beratung zur Anwendung dieses Medikamentes: Wissen, **wie**	Wissen, **weshalb**	**Vergessen** Sie manchmal dieses Medikament einzunehmen?	**Kommentare & weitere Angaben** (bei Bedarf Fortsetzung auf Rückseite)
1	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
2	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
3	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
4	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
5	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
6	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
7	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
8	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	
9	Name/ Stärke / Galenische Form neu ? ☐	Beratung ? ☐	Beratung ? ☐	Ja☐ Nein☐ Beratung ? ☐	

Selbstmedikation Ja☐ Nein☐ Auflistung mit Dosierung

Kommentare / Fortsetzung auf Rückseite

2. Beratung

☐ Beratung zur Handhabung

3. Empfehlungen	Patient/in ist einverstanden	Kommentare:
☐Wochen-Dosiersystem durch den Apotheker	Ja ☐ Nein ☐	
☐Bedarf intensivierte Compliance-Unterstützung	Ja ☐ Nein ☐	
☐Bedarf Wiederholung Check in ..... Monaten	Ja ☐ Nein ☐	
☐Weiterleitung an Arzt/andere Fachperson	Ja ☐ Nein ☐	NAME Tel
☐Bedarf vertiefte Analyse (z.B. Wechselwirkungen, Nebenwirkungen, Duplikationen)		
☐		
☐		
☐		

Datum: ____ / ____ / _____ Zeit Ende: ____.____ Uhr

Unterschrift Patient/in

Stempel Apotheke /Unterschrift Apotheker/in:

Project B1 – Form for PGx anamnesis

toppharm Apotheke Hersberger

Apotheke Hersberger am Spalebärg
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Anamnese für die pharmakogenetische Analyse Teil 1

Patientencode		Geschlecht	☐w ☐m	Jahrgang	

Von wem ging der Wunsch zur pharmakogenetischen Testung aus?

☐ Kunde	☐ Apotheker	☐ Arzt	☐ andere_____

Was war die Grundlage der Entscheidung zur pharmakogenetischen Testung?

☐ die Abgabe eines neuen Medikaments mit bekannter PGx-Assoziation (pre-emptive)

Medikament(e)	
Erstverschreibung	☐ Ja. ☐ Nein. ☐ Nicht bekannt.
Abgabe	☐ Ja. ☐ Nein. ☐ Unter Vorbehalt.

☐ die Beobachtung von auffallenden Nebenwirkungen

Medikament(e)	Beobachtungen

☐ Verdacht auf fehlende Wirkung

Medikament(e)	Beobachtungen

☐ Unverträglichkeiten für Medikamente in der Familienanamnese

Medikament(e)	Beobachtungen

toppharm
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Anamnese für die pharmakogenetische Analyse Teil 2

Falls pharmakogenetisch relevante Medikamente zum Zeitpunkt der Blutentnahme eingenommen wurden, braucht es noch folgende Angaben:

Wirkstoff 1

Wirkstoffname (inkl. Dosierstärke)	
Seit wann wird das Medikament eingenommen?(Datum)	__/__/____
Datum der letzten Einnahme?	__/__/____
Zeitpunkt der letzten Einnahme	__:__ Uhr
Einnahmeschema	__-__-__-__

Wirkstoff 2

Wirkstoffname (inkl. Dosierstärke)	
Seit wann wird das Medikament eingenommen?(Datum)	__/__/____
Datum der letzten Einnahme?	__/__/____
Zeitpunkt der letzten Einnahme	__:__ Uhr
Einnahmeschema	__-__-__-__

Wirkstoff 3

Wirkstoffname (inkl. Dosierstärke)	
Seit wann wird das Medikament eingenommen?(Datum)	__/__/____
Datum der letzten Einnahme?	__/__/____
Zeitpunkt der letzten Einnahme	__:__ Uhr
Einnahmeschema	__-__-__-__

Project B1 – Form for laboratory

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Patientencode: _____

Datum: _____

Visum: _____

Laborblatt Ambulatorium CTU

Auszufüllen durch die Apotheke **(Dieses Blatt ist dem Patienten in einem Kuvert mitzugeben!)**

Allgemeine Angaben	Ja	Nein
• Patient hat Einverständniserklärung unterschrieben	☐	☐
• Folgende Blutentnahmen sollen durchgeführt werden: ○ EDTA 4.9 ml ○ Serum 7.5 ml *(Zusätzlich zu EDTA soll auch eine Serumprobe entnommen werden.)*	☐	☐
• Unterschrift Apotheke: _____		

Auszufüllen durch **das ambulante Studienzentrum**

Allgemeine Angaben	Ja	Nein
• Patient ist mit Kuvert erschienen	☐	☐
• Datum ___/___/_____ (tt.dd.jjjj)		
• Folgende Blutentnahmen wurden gemacht: ○ EDTA 4.9 ml: ○ 2 Cryovials eingefroren (-20°C) ▪ Uhrzeit ___:____Uhr(00:00)	☐	☐
○ Serum 7.5 ml: zentrifugiert 3 Cryovials eingefroren (-80°C) ▪ Uhrzeit ___:____Uhr(00:00)	☐	☐
• Etiketten wurden aufgeklebt und mit Datum versehen	☐	☐

- Blutentnahme abgeschlossen und Übergabe einer Kopie des Laborblattes sowie der Proben an das Studienzentrum der PCRG am ___/___/_____ (tt.dd.jjjj)
- Unterschrift Ambulatorium CTU: _____

Universität Basel
Departement Pharmazeutische Wissenschaften
Petersplatz 14, Postfach 2148
4001 Basel, Switzerland
pharmacare.unibas.ch

Prof. Dr. Kurt E. Hersberger
Pharmaceutical Care Research Group
Tel.+41 61 207 19 71
Kurt.hersberger@unibas.ch

Project B1 – Stratipharm SNPs and annotations

Gen	Annotation	Pos-Info
ABCB1	rs1045642	NM_000927.4:c.3435T>C
ABCB1	rs1128503	NM_000927.4:c.1236T>C
ABCB1	rs2032582	NM_000927.4:c.2677G>A
ABCB1	rs2032582	NM_000927.4:c.2677G>T
ABCB1	rs2032583	NM_000927.4:c.2685+49T>C
ABCG2	rs2231142	NM_004827.2:c.421C>A
ABCG2	rs13120400	NM_004827.2:c.1194+928A>G
ABCG2	rs17731538	NC_000004.11:g.89055379G>A
ADRB1	rs1801252	NM_000684.2:c.145A>G
ADRB1	rs1801253	NM_000684.2:c.1165G>C
ADRB2	rs1042713	NT_029289.11:g.9369367G>A
ADRB2	rs1042714	NC_000005.9:g.148206473G>C
COMT	rs4680	NM_000754.3:c.472G>A
COMT	rs165599	NM_000754.3:c.*522G>A
COMT	rs4646316	NM_000754.3:c.615+310C>T
COMT	rs9332377	NM_000754.3:c.616-367C>T
COQ2	rs4693075	NC_000004.11:g.84192168G>C
COQ2	rs6535454	NM_015697.7:c.894T>C
CYP1A2	rs2069514	NC_000015.9:g.75038220G>A
CYP1A2	rs762551	NC_000015.9:g.75041917C>A
CYP2B6	rs8192709	NM_000767.4:c.64C>T
CYP2B6	rs28399499	NM_000767.4:c.983T>C
CYP2B6	rs3745274	NM_000767.4:c.516G>T
CYP2C8	rs10509681	NM_000770.3:c.1196A>G
CYP2C8	rs11572080	NM_000770.3:c.416G>A
CYP2C8	rs1934951	NG_007972.1:g.35707G>A
CYP2C9	rs1799853	NM_000771.3:c.430C>T
CYP2C9	rs1057910	NM_000771.3:c.1075A>C
CYP2C9	rs9332131	NM_000771.3:c.817delA
CYP2C9	rs7900194	NM_000771.3:c.449G>A
CYP2C9	rs28371685	NM_000771.3:c.1003C>T
CYP2C19	rs4244285	NM_000769.1:c.681G>A
CYP2C19	rs4986893	NM_000769.1:c.636G>A
CYP2C19	rs12248560	NG_008384.1:g.4195C>T
CYP2C19	rs28399504	NM_000769.1:c.1A>G
CYP2D6	-	copy number variation
CYP2D6	rs35742686	NM_000106.4:c.775delA
CYP2D6	rs3892097	NM_000106.4:c.506-1G>A
CYP2D6	rs5030655	NM_000106.4:c.454delT
CYP2D6	rs5030867	NM_000106.4:c.971A>C
CYP2D6	rs5030865	NM_000106.4:c.505G>T
CYP2D6	rs5030865	NM_000106.4:c.505G>A
CYP2D6	rs5030656	NM_000106.5:c.841_843delAAG
CYP2D6	rs1065852	NM_000106.4:c.100C>T
CYP2D6	rs201377835	NM_000106.5:c.181-1G>C
CYP2D6	rs28371706	NM_000106.4:c.320C>T
CYP2D6	rs59421388	NM_000106.4:c.1012G>A
CYP2D6	rs28371725	NM_000106.4:c.985+39G>A
CYP3A4	rs2740574	NG_000004.3:g.135607G>A

CYP3A4	rs2242480	NM_017460.5:c.1026+12G>A
CYP3A5	rs776746	NM_000777.3:c.219-237G>A
DPYD	rs3918290	NM_000110.3:c.1905+1G>A
DPYD	rs72549303	NM_000110.3:c.1898delC
DPYD	rs72549309	NM_000110.3:c.298delTinsTCAT
DPYD	rs55886062	NM_000110.3:c.1679T>G
DPYD	rs67376798	NM_000110.3:c.2846A>T
DPYD	rs2297595	NM_000110.3:c.496A>G
GNB3	rs5443	NM_002075.2:c.825C>T
GSTP1	rs1695	NM_000852.3:c.313A>G
HLA-A	rs1061235	NM_002116.7:c.*66A>T
HLA-A	rs1633021	NC_000006.12:g.29779092T>C
HLA-B	rs3909184	NM_005803.2:c.724-507C>G
HLA-B	rs2395029	NM_006674.3:c.*568T>G
HLA-B	rs2844682	NC_000006.11:g.30946148G>A
HMGCR	rs17238540	NM_000859.2:c.2457+117T>G
HMGCR	rs17244841	NM_000859.2:c.451-174A>T
HTR2A	rs6311	NC_000013.10:g.47471478C>T
HTR2A	rs6313	NM_000621.3:c.102C>T
HTR2A	rs7997012	NM_000621.3:c.614-2211T>C
HTR2A	rs9316233	NC_000013.10:g.47433355C>G
HTR2A	rs6314	NC_000013.10:g.47409034G>A
IFNL3	rs8099917	NC_000019.9:g.39743165T>G
IFNL3	rs12979860	NC_000019.9:g.39738787C>T
ITPA	rs1127354	NM_181493.1:c.43C>A
MT-RNR1	rs267606617	NC_012920.1:m.1555A>G
NAT2	rs1801280	NM_000015.2:c.341T>C
NAT2	rs1799930	NM_000015.2:c.590G>A
NAT2	rs1799931	NM_000015.2:c.857G>A
OPRM1	rs1799971	NM_000914.3:c.118A>G
SLC19A1	rs1051266	NM_194255.1:c.80A>G
SLCO1B1	rs4149056	NM_006446.4:c.521T>C
SLCO1B1	rs11045819	NM_006446.4:c.463C>A
SLCO1B1	rs2306283	NM_006446.4:c.388A>G
SLCO1B1	rs4149015	NG_011745.1:g.4195G>A
TPMT	rs1800462	NM_000367.2:c.238G>C
TPMT	rs1800460	NM_000367.2:c.460G>A
TPMT	rs1142345	NM_000367.2:c.719A>G
TPMT	rs1800584	NM_000367.2:c.626-1G>A
TPMT	rs12201199	NM_000367.2:c.419+94T>A
VKORC1	rs9923231	NC_000016.9:g.31107689C>T
VKORC1	rs7294	NM_024006.4:c.*134G>A
VKORC1	rs17708472	NM_024006.4:c.173+525C>T
VKORC1	rs2359612	NM_024006.4:c.283+837T>C
VKORC1	rs8050894	NM_024006.4:c.283+124G>C
VKORC1	rs9934438	NM_024006.4:c.174-136C>T

Project B1 – Template for written recommendation

toppharm
Apotheke Hersberger

Name		Vorname		Geb.-Dat.	___/___/____
Str.		Ort		Tel.-Nr.	

Patientencode		Geschlecht	☐männlich ☐weiblich	Jahrgang	

Diagnosen (ICD)

-

Medikamente

Wirkstoff	Dosierung	Bemerkung

Reservemedikamente:

History:

Allergien:

Fragestellung

Gibt es pharmakogenetische Erklärungen für das Nicht-Ansprechen auf die bisherige Pharmakotherapie?

Gibt es pharmakogenetische Erklärungen für die unerwünschten Wirkungen auf die bisherige Pharmakotherapie?

Gibt es pharmakogenetische Variabilität, die bei einer neu geplanten Pharmakotherapie berücksichtigt werden muss? (Pre-emptive Testing)

Gibt es auffällige Erfahrungen mit Medikamenten in der Familienanamnese, welche mit pharmakogenetischer Variabilität erklärbar ist?

Empfehlung nach einer pharmakogenetischen Analyse V7.0, 18.02.2022 1

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Apotheke Hersberger

Resultate der pharmakogenetischen Analyse

Legende:	
	Normal: Das pharmakogenetische Profil dieses Patienten zeigt keine Warnung. Wirkstoff kann nach Verordnung verabreicht werden
	Hinweis: Ein Problem könnte auftreten. Wirkstoff zunächst normal verabreichen, Problem beobachten.
	Verdacht: Das Problem wird sehr wahrscheinlich auftreten. Dosisanpassung oder Alternativmedikation empfohlen.
	Gefahr: Es besteht ein akutes Problem. Dosisanpassung oder Alternativmedikation dringend empfohlen.
	Ohne Berechnung: Dieser Wirkstoff ist von keiner pharmakogenetischen Variabilität betroffen; gilt für alle Patienten. Wirkstoff kann nach Verordnung verabreicht werden.
Vgl. genetisches Profil erstellt von www.stratipharm.de	

Genetisches Profil bezogen auf die Fragestellungen:

Gen	Erklärung	Prognose des Phänotyps

Nachstehende Kurz-Kommentare und die Diskussion beziehen sich auf die bisherigen bzw. geplanten Therapien gemäss Überweisungsformular und/oder Angaben des Patienten:

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Indikation 1

Wirkstoff	Gene	Erklärung

Indikation 2

Wirkstoff	Gene	Erklärung

Indikation 3

Wirkstoff	Gene	Erklärung

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Beurteilung von Interaktionen[1]

Betroffener Wirkstoff	Verursachender Wirkstoff	Mechanismus

In der aktuellen Medikation sind keine schwerwiegenden Interaktionen erkennbar.

Empfehlung aufgrund der pharmakogenetischen Analyse

Indikation 1

Indikation 2

Indikation 3

Es gibt keine Hinweise aus der pharmakogenetischen Analyse zu ... .

Zu ... gibt es keine Hinweise aus der pharmakogenetischen Analyse.

***NOTA BENE**: Der Vorschlag für die oben erwähnten Substanzen basiert in erster Linie auf dem pharmakogenetischen Profil und den daraus resultierenden pharmakokinetischen Eigenschaften. Er stellt eine Entscheidungshilfe dar, lässt aber pharmakodynamische Unterschiede (Wirkprofil) weitgehend unberücksichtigt. Für eine optimale Therapie sollen aber sowohl Wirkprofil als auch pharmakokinetische Eigenschaften gleichermassen auf die Gegebenheiten des Patienten abgestimmt werden*

Bei einer zukünftigen Behandlung, ist die Patientin/der Patient aufgerufen, die **Liste der betroffenen Wirkstoffe** zu konsultieren bzw. dem behandelnden Arzt zur Kenntnis zu bringen.

Basel, XX.XX.XXXX

Chiara Jeiziner

Prof. em. Dr. Kurt Hersberger

Pharmaceutical Care Research Group
Klingelbergstrasse 50
CH-4056 Basel
Mail: pcrg.pgx@hin.ch
Tel: 061 207 61 80

Beilagen

- genetisches Profil
- Liste der betroffenen Wirkstoffe (Wir empfehlen den Patienten, eine Kopie / ein Foto dieser Liste bei sich zu tragen)
- einzelne Wirkstoffprüfungen

[1] www.mediq.ch

Project B4

Project B4 – Guide follow-up interview 1

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Interviewguide Follow-Up 1 nach t= 1 Monat

Patientencode:
Datum (TT.MM.JJ:
Visum Interviewer:

Einleitung

Guten Tag Herr/Frau , mein Name ist .

Ich arbeite für die Universität Basel und melde mich bezüglich der pharmakogenetischen Studie.

(Pause zur Begrüssung)

Vielleicht können Sie sich noch erinnern, dass wir Sie im Zweitgespräch darauf hingewiesen haben, dass zur pharmakogenetischen Analyse auch zwei Nachfolgegespräche dazugehören. So ein Nachfolgegespräch möchte ich jetzt mit Ihnen durchführen in Form eines Interviews.

Das Interview dauert in etwa 10 Minuten.

Wir behandeln Ihre Angaben selbstverständlich vertraulich. Sie können das Interview jederzeit unterbrechen, abbrechen oder auch einzelne Antworten verweigern. Falls Unklarheiten bei den gestellten Fragen auftreten, dürfen Sie sich melden. Sonstige Fragen werde ich sehr gerne am Ende des Interviews beantworten.

Können wir gleich beginnen? (...)

Demographie

Bevor ich den Hauptteil des Interviews starte, möchte ich noch zwei allgemeine Fragen zur Ihrer Person stellen.

Was ist Ihr höchster Bildungsabschluss?

- ☐ weniger als 7 Jahre Schule
- ☐ Obligatorische Schule
- ☐ Anlehre
- ☐ Berufslehre/-schule
- ☐ Maturitätsschule, Berufsmaturität, Diplommittelschule
- ☐ Höhere Fach- und Berufsausbildung
- ☐ Universität, Fachhochschule
- ☐ Nicht feststellbar, unbekannt.

Notizen:

Bei wie vielen Ärzten sind Sie in Behandlung?

Welche Funktion haben diese Ärzte?

1

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Startzeitpunkt (HH.MM):

Das Interview hat 3 Bereiche. Nun möchte ich mit dem ersten Bereich anfangen.

Bereich 1 Sprache/Verständnis

Zuerst möchte ich einige Fragen stellen, wie gut Ihnen die Resultate der pharmakogenetischen Analyse erklärt und kommuniziert worden sind.

Wenn sie zurückdenken an die Gespräche mit der Apothekerin...

Wie angemessen war die Sprach- und Wortwahl während den beiden Gesprächen in der Apotheke auf einer Skala von 0 bis 10?

Dabei bedeutet 0 «überhaupt nicht angemessen» und 10 bedeutet «voll und ganz angemessen»

Wie verständlich waren die Erklärungen zu den Ergebnissen des genetischen Tests auf einer Skala von 0 bis 10?

Dabei bedeutet 0 «überhaupt nicht verständlich» und 10 bedeutet «voll und ganz verständlich»

Hatten Sie nach den beiden Gesprächen das Bedürfnis nach einem weiteren Gespräch?

☐ Ja

☐ Nein

Weshalb?

Wie würden Sie das Resultat der pharmakogenetischen Analyse einem Freund erklären?

2

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Bereich 2: Sicherheit

Im zweiten Themengebiet werde Ich Ihnen ein paar Fragen stellen, in dem es um die Sicherheit im Umgang mit Arzneimitteln geht.

Stellen Sie sich vor, Ihr Arzt macht einen Vorschlag für eine neue Therapie. Wie gehen Sie vor?

Denken Sie, dass Sie seit der pharmakogenetischen Analyse besser über Ihre Medikamente Bescheid wissen?

(Zeit lassen für eine generelle Antwort)

Wenn Sie Ihre Antwort auf einer Skala von 0 bis 10 angeben müssen, wie sicher fühlen Sie sich im Umgang mit Ihren Medikamenten seit der Teilnahme an der Studie?

Dabei bedeutet 0 «überhaupt nicht sicher» und 10 bedeutet «voll und ganz sicher»

Fremdeinschätzung der Sicherheit des Patienten aus Sicht des Interviewenden von einer Skala von 0 bis 10?

Dabei bedeutet 0 «überhaupt nicht sicher» und 10 bedeutet «voll und ganz sicher»

3

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Bereich 3: Allgemeine Rückmeldung

Zum Schluss des Interviews geht es im letzten Bereich noch um Ihre Rückmeldung zur Studie.

Würden Sie die Teilnahme an dieser Studie weiterempfehlen?

☐ Ja

☐ Nein

Weshalb?

Gibt es etwas, das wir aus Ihrer Sicht verbessern können?

Schluss

Wir sind nun am Ende des Interviews.

Haben Sie noch Anmerkungen zum Interview, oder sonst noch Fragen?

Endzeitpunkt (TT.MM):

In ungefähr einem halben Jahr werden wir erneut mit Ihnen Kontakt aufnehmen für das 2. Nachfolgegespräch.

Ich möchte mich nochmals ganz herzlich für Ihre Teilnahme an der Studie bedanken und wünsche Ihnen noch einen schönen Tag/Abend.

4

Project B4 – Guide follow-up interview 2

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Interviewguide Follow-Up 2: Retrospektiv ab t=4 Monaten

Patientencode:
Datum (TT.MM.JJ):
Visum Interviewer:

Einleitung

Guten Tag Herr/Frau , mein Name ist .

Ich arbeite für die Universität Basel und melde mich bezüglich der pharmakogenetischen Studie für ein Nachfolgegespräch in Form eines Interviews.
(Pause zur Begrüssung)

Unter Umständen fällt Ihnen die Beantwortung der Fragen leichter, wenn Sie Ihren aktuellen Medikamentenplan, sowie die Liste der betroffenen Wirkstoffe und das Empfehlungsschreiben der pharmakogenetischen Analyse vor sich haben. Ich gebe Ihnen nun kurz Zeit, damit Sie diese Dokumente hervornehmen können. (...)

Das Interview dauert in etwa 20 Minuten.

Wir behandeln Ihre Angaben selbstverständlich vertraulich.

Sie können das Interview jederzeit unterbrechen, abbrechen oder auch einzelne Antworten verweigern. Falls Unklarheiten bei den gestellten Fragen auftreten, dürfen Sie sich melden. Sonstige Fragen werde ich sehr gerne am Ende des Interviews beantworten.

Können wir gleich beginnen? (...)

Startzeitpunkt (HH.MM):

Das Interview hat insgesamt 4 Bereiche. Nun möchte ich mit dem ersten Bereich anfangen.

1

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Interviewguide Follow-Up 2: Retrospektiv ab t=4 Monaten

Patientencode:
Datum (TT.MM.JJ):
Visum Interviewer:

Einleitung

Guten Tag Herr/Frau , mein Name ist .

Ich arbeite für die Universität Basel und melde mich bezüglich der pharmakogenetischen Studie für ein Nachfolgegespräch in Form eines Interviews.
(Pause zur Begrüssung)

Unter Umständen fällt Ihnen die Beantwortung der Fragen leichter, wenn Sie Ihren aktuellen Medikamentenplan, sowie die Liste der betroffenen Wirkstoffe und das Empfehlungsschreiben der pharmakogenetischen Analyse vor sich haben. Ich gebe Ihnen nun kurz Zeit, damit Sie diese Dokumente hervornehmen können. (...)

Das Interview dauert in etwa 20 Minuten.

Wir behandeln Ihre Angaben selbstverständlich vertraulich.

Sie können das Interview jederzeit unterbrechen, abbrechen oder auch einzelne Antworten verweigern. Falls Unklarheiten bei den gestellten Fragen auftreten, dürfen Sie sich melden. Sonstige Fragen werde ich sehr gerne am Ende des Interviews beantworten.

Können wir gleich beginnen? (...)

Startzeitpunkt (HH.MM):

Das Interview hat insgesamt 4 Bereiche. Nun möchte ich mit dem ersten Bereich anfangen.

1

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Bereich 2: Dokumente

Im nächsten Bereich geht es um die Dokumente, welche Sie im Rahmen der Studie erhalten haben.

Haben Sie das Empfehlungsschreiben gelesen?

☐ Ja

☐ Nein

Wie übersichtlich finden Sie die Darstellung des Empfehlungsschreibens auf einer Skala von 0-10?

Dabei bedeutet 0 «überhaupt nicht übersichtlich» und 10 bedeutet «voll und ganz übersichtlich»

Haben Sie sich mit der Liste der betroffenen Wirkstoffe bereits auseinandergesetzt?

☐ Ja

☐ Nein

Wenn ja, in welchem Zusammenhang?

Wie hilfreich finden Sie die Liste der betroffenen Wirkstoffe auf einer Skala von 0 bis 10?

Dabei bedeutet 0 «überhaupt nicht hilfreich» und 10 bedeutet «voll und ganz hilfreich»

Auf dieser Liste befinden sich einige gelbe Wirkstoffe. Stelle Sie sich vor, das freiverkäufliche Schmerz- und Entzündungsmittel Ibuprofen wäre auf Ihrer Liste gelb.

Würden Sie den Wirkstoff in der Apotheke kaufen?

☐ Ja

☐ Nein

Weshalb?

3

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Bereich 3: Sicherheit

Im dritten Bereich geht es um die Sicherheit im Umgang mit Arzneimitteln.

Stellen Sie sich vor, Ihr Arzt macht einen Vorschlag für eine neue Therapie. Wie gehen Sie vor?

Denken Sie, dass Sie seit der pharmakogenetischen Analyse besser über Ihre Medikamente Bescheid wissen?

(Zeit lassen für eine generelle Antwort)

Wenn Sie Ihre Antwort auf einer Skala von 0 bis 10 angeben müssen, wie sicher fühlen Sie sich im Umgang mit Ihren Medikamenten seit der Teilnahme an der Studie?

Dabei bedeutet 0 «überhaupt nicht sicher» und 10 bedeutet «voll und ganz sicher»

Fremdeinschätzung der Sicherheit des Patienten aus Sicht des Interviewenden von einer Skala von 0 bis 10?

Dabei bedeutet 0 «überhaupt nicht sicher» und 10 bedeutet «voll und ganz sicher»

4

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Bereich 4: Kosten

Im vierten und letzten Bereich des Interviews geht es um die Kosten der pharmakogenetischen Analyse.

Im Rahmen der Studie werden die Kosten durch Studiengelder abgedeckt. Somit müssen Sie natürlich nach wie vor nichts bezahlen. Wir möchten aber trotzdem die Zahlungsbereitschaft für eine pharmakogenetische Analyse erfragen.

Eine pharmakogeneitsche Analyse in der Apotheke würde alles in allem ungefähr 700 Franken kosten. Zu Beginn wird es der Patient selbst zahlen müssen. Ziel ist aber, dass diese Dienstleistung eines Tages von der obligatorischen Krankenversicherung bezahlt wird.

Die Kosten für den pharmakogenetischen Test im Labor betragen 390 Franken. Für die Beratungstätigkeit des Apothekers würden insgesamt etwa 300 Franken anfallen, darin enthalten sind unter anderem die Aufklärung und Beratung zum Thema Pharmakogenetik, die Probenentnahme und das Erstellen des Empfehlungsschreibens.

Wie beurteilen Sie den Preis von 390 Franken für den pharmakogenetischen Test?

Zu tief, angemessen oder zu hoch?

-

Wie beurteilen Sie den Preis von etwa 300 Franken für die Beratung?

Zu tief, angemessen oder zu hoch?

-

Falls Sie den Preis nicht als angemessen beurteilen: Wie viel wäre Ihnen die Beratung in der Apotheke wert?

Würden Sie die genannten 700 Franken selbst bezahlen für das Gesamtpaket: Pharmakogenetischer Test und Beratung?

☐ Ja

☐ Nein

Schluss

Wir sind nun am Ende des Interviews angelangt.

Haben Sie noch Anmerkungen zum Interview, oder sonst noch Fragen oder Anregungen?

Endzeitpunkt festhalten:

Ich möchte mich nochmals ganz herzlich für Ihre Teilnahme an der Studie bedanken und wünsche Ihnen noch einen schönen Tag/Abend und alles Gute für die Zukunft.

5

Project B4 – Guide for focus group discussion

Universität Basel

DEPARTMENT OF PHARMACEUTICAL SCIENCES

Diskussionsleitfaden Fokusgruppe Pharmakogenetische Analyse

Datum: 12.04.21
Ort: Online (Zoom ®)
Dauer: 1 Stunde

Forschungsteam:
- Chiara Jeiziner (Gesprächsleitung)
- Stefanie Mutter (Beobachterin)
- Prof. Kurt Hersberger (Beobachter)
- Prof. Henriette Meyer zu Schwabedissen (Beobachterin)

Teilnehmende Ärzte:
[redacted]

Begrüssung

(Folie 1)
Ich möchte Sie alle ganz herzlich begrüssen zur Fokusgruppendiskussion zum Thema pharmakogenetische Analyse.

(Folie 2)
Ich bin Chiara Jeiziner, Doktorandin bei Prof. Hersberger und werde Sie durch die Diskussion führen.

Neben mir sind noch drei weitere Personen aus der Forschungsgruppe als Beobachter anwesend. Sie bitte ich, das Mikrofon auf stumm zu stellen, die Kamera jedoch einzuschalten/anzulassen.
Damit Ihr wisst, wer die drei sind, stelle ich sie kurz vor:

Stefanie Mutter, Masterstudentin, welche am Anschluss an die Fokusgruppe die Diskussion transkribieren und auswerten wird.

Prof. Kurt Hersberger, Leiter der Studie.

Prof. Henriette Meyer zu Schwabedissen, Biomedizin?

Nun bitte ich Sie, geschätzte Ärztinnen und Ärzte, euch kurz selbst vorzustellen mit Name, Funktion und der ungefähren Anzahl der überwiesenen Fälle an uns.

Wer möchte beginnen? (...)

Spielregeln

(Folie 3)
Bevor wir mit der Diskussion beginnen, noch ganz kurz einige Spielregeln, damit die Diskussion auch virtuell klappt. Ich bitte alle, die nicht nur Beobachter sind, das Mikrofon und die Kamera einzuschalten. Für die Diskussion kann es hilfreich sein, wenn man alle beteiligten auf dem Bildschirm sieht. Ich empfehle euch darum die Galerieanschicht auszuwählen, wenn wir am Diskutieren sind.
Jede Meinung ist wichtig und jeder soll und darf zu Wort kommen. Es gibt kein Richtig oder Falsch.
Diese Fokusgruppe ist vertraulich. Die Diskussion wird aufgenommen zur Transkribierung. Nach der Transkribierung wird die Datei gelöscht.

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Rahmenbedingungen

(Folie 4)
Wir haben nun eine knappe Stunde Zeit, uns über die Dienstleistung der pharmakogenetischen Analyse auszutauschen. Der vorbereitete Leitfaden führt durch 3 Themenbereiche: Das Empfehlungsschreiben, die Liste der betroffenen Wirkstoffe und am Ende ein Zeitfenster zur allgemeinen Rückmeldung zur pharmakogenetischen Analyse. Wir haben zu jedem Thema jeweils eine bis drei kleine Zoomumfragen vorbereitet. Diese werden auf Ihrem Bildschirm aufpoppen und Sie dürfen dann jeweils eine Antwortmöglichkeit auswählen. Die Umfragenresultate werden im Anschluss direkt für alle freigeschaltet, so dass die Diskussion sogleich starten kann. Falls nötig, werde ich noch die eine oder andere Folgefrage stellen.

Thema 1: Empfehlungsschreiben

(Folie 5)
Starten möchte ich mit dem ersten Thema, dem Empfehlungsschreiben. Im Laufe der Studie hat sich dieses Schreiben stetig weiterentwickelt. Die aktuellste Version mit Farbcodierung ist folgendermassen aufgebaut: Medikamentenliste, Fragestellung, Resultate der pharmakogenetischen Analyse in Tabellenform (-> Verweis auf Legende), Beurteilung von Interkationen und am Schluss die Empfehlung aufgrund der pharmakogenetischen Analyse in Textform.

(Folie 6)
Hier könnt ihr ein zusammengeschnittenes Beispiel für Max Mustermann sehen: Die Medikamentenliste, die betroffenen Gene und die betroffenen Wirkstoffe gelistet nach Indikation.

(Folie 7)
Nun möchte ich gerne die erste Umfrage zur Darstellung des Empfehlungsschreibens starten.

Zoom-Umfrage 1 mit Antwortmöglichkeiten VAS (1-10)

- **Wie übersichtlich finden Sie die Darstellung des Empfehlungsschreibens auf einer Skala von 1-10?**
  Dabei bedeutet 1 «überhaupt nicht übersichtlich» und 10 bedeutet «voll und ganz übersichtlich»

(Zeit lassen für Beantwortung, danach Resultate zeigen. Diskussion eröffnen)

Folgefragen
- Was stört?
- Verbesserungsvorschläge?

Und gleich eine nächste Umfrage zum Umfang des Empfehlungsschreibens...

Zoom-Umfrage 2 mit Antwortmöglichkeiten VAS (1-10)

- **Wie angemessen finden Sie den Umfang des Empfehlungsschreibens auf einer Skala von 1-10?**
  Dabei bedeutet 1 «überhaupt nicht angemessen» und 10 bedeutet «voll und ganz angemessen»

(Zeit lassen für Beantwortung, danach Resultate zeigen. Diskussion eröffnen)

Folgefragen
- Inwiefern (un)angemessen? Zu lang?
- Welche Abschnitte sind für Sie besonders relevant, welche könnten weggelassen werden?

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Eher zu lang? -> Dies führt uns zur nächsten Frage, mit der wir herausfinden möchten, wie viel Zeit Ihr durchschnittlich für das Lesen der Empfehlungsschreiben aufbringen müsst.

Zoom-Umfrage 3 mit Antwortmöglichkeiten

- **Wie viel Zeitaufwand mussten Sie durchschnittlich aufbringen, um sich mit dem Empfehlungsschreiben auseinander zu setzten?**

Antwortmöglichkeiten
- Weniger als 10 Minuten
- 11-20 Minuten
- 21-30 Minuten
- Mehr als 30 Minuten

(Zeit lassen für Beantwortung, danach Resultate zeigen. Diskussion eröffnen)

Folgefragen
- Was war zeitaufwändig?
- Gut investierte Zeit?
- Wie **umsetzbar** sind Empfehlungen im praktischen Alltag?
- Haben Sie aufgrund unserer Empfehlung **Änderungen** in der Therapie vorgenommen?

Thema 2: Liste der betroffenen Wirkstoffe

(Folie 8)

Nun möchte ich zum zweiten Thema überleiten, zur Liste der betroffenen Wirkstoffe. Dabei handelt es sich um die zusammenfassende A4-Seite, auf der alle bisher bekannten pharmakogenetisch relevanten Wirkstoffe aufgelistet sind. Unterteilt werden die betroffenen Wirkstoffe in die drei Warnstufen: gelb (Hinweis), orange (Verdacht) und rot (Gefahr).

An dieser Stelle möchten wir gerne wissen, welcher Nutzen diese Liste für euch hat.

(Folie 9)

Zoom-Umfrage 4 mit Antwortmöglichkeiten VAS (1-10)

- **Wie hilfreich finden Sie die Liste der betroffenen Wirkstoffe in Ihrem klinischen Alltag auf einer Skala von 1 bis 10?**
  Dabei bedeutet 1 «überhaupt nicht hilfreich» und 10 bedeutet «voll und ganz hilfreich»

(Zeit lassen für Beantwortung, danach Resultate zeigen. Diskussion eröffnen)

Folgefragen
- Wie häufig greifen Sie auf die Liste zurück?
- Wie gehen Sie mit einem gelb kategorisierten Wirkstoff um?

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Thema 3: Pharmakogenetische Analyse allgemein

(Folie 10)

Zum Schluss interessiert uns noch allgemein Ihre Rückmeldung zur pharmakogenetischen Analyse. Bevor Ihr eure Meinungen darlegen könnt, möchte ich noch eine letzte Umfrage starten:

(Folie 11)

Zoom-Umfrage 5 mit Antwortmöglichkeiten VAS (1-10)

- **Wenn Sie an Ihre überwiesenen Fälle zurückdenken, wie relevant war die pharmakogenetische Analyse für die therapeutische Entscheidung auf einer Skala von 1 bis 10?**
  Dabei bedeutet 1 «überhaupt nicht relevant» und 10 bedeutet «voll und ganz relevant»

(Zeit lassen für Beantwortung, danach Resultate zeigen. Diskussion eröffnen)

Folgefragen:
- Wann hilfreich, wann nicht? Gründe?
- Wie empfanden Sie die Kommunikation mit uns/ interdisziplinäre Zusammenarbeit?
- Gibt es etwas, das wir aus Ihrer Sicht verbessern können?
- Haben Sie sonst noch ein Anliegen oder einen Kommentar?

Dank und Abschluss

Somit sind wir am Ende dieser Fokusgruppendiskussion angelangt. Vielen herzlichen Dank, dass Sie sich diese Stunde Zeit genommen haben! Euer wertvolles Feedback hilft uns enorm, die Dienstleistung der pharmakogenetischen Analyse weiter zu verbessern. Wir sind immer noch auf der Suche nach neuen Patienten und freuen uns deshalb auf weitere Überweisungen von euch.

Hat jemand noch ein Anliegen?

(...)

Danke nochmals und einen schönen Abend.

Project B4 – Transcript focus group discussion

Transkript Fokusgruppe Ärzte: Pharmakogenetische Analyse

Datum: 12.04.21
Ort: Online, Zoom-Meeting
Dauer: 56 Minuten
Teilnehmer:

- Moderator: Doktorandin, Pharmazeutin C.J.
- Arzt 1: Psychiater, T.J.
- Arzt 2: Rheumatologin, P.E.
- Arzt 3: Hausärztin, S.B.
- Arzt 4: Hausarzt, P.T.
- Beobachter 1: Studienleiter, Professor K.H.
- Beobachter 2: Pharmakologin, Professorin H.M.z.S.
- Beobachter 3: Masterstudentin Pharmazie, S.M

Moderator: Dann möchte ich schon einmal starten mit der Begrüssung. Herzlich willkommen zu dieser Fokusgruppendiskussion zum Thema pharmakogenetische Analyse. Es freut uns sehr, dass ihr euch jetzt alle bereit erklärt habt, mitzumachen. Ich starte gerade mit der Begrüssung. Und zwar stelle ich uns noch einmal kurz vor: Ich bin C.J., wir haben auch schon per Mail Kontakt gehabt. Meistens... Ich bin jetzt Doktorandin im dritten Jahr und beschäftige mich da mit dem Thema Pharmakogenetik. Ich werde sie jetzt dann auch durch die Diskussion leiten und dort gerade die erste Frage: Ist es in Ordnung, wenn ich Dialekt rede? (nicken der Ärzte) Gut. Dann mache ich gerade weiter. Ich würde auch gerne die anderen, die hinter der Kamera sind und vom Forschungsteam sind, kurz vorstellen. Das ist zum einen Professor K.H., er ist Leiter der Pharmaceutical Care Research Group und unter anderem auch Leiter von der Studie, von der Beobachtungsstudie, die wir da machen. Dann haben wir auch die Professorin H.M.z.S, sie ist Pharmakologin und sie ist Leiterin von der Biopharmazie, von der Biopharmaziegruppe am pharmazeutischen Departement von der Uni Basel. Mit ihr kollaborieren wir sehr eng in dem Thema Pharmakogenetik. Dann ist da auch noch die S.M., das ist aktuell die Masterstudentin bei mir. Da gerade schon mal einen grossen Dank, sie wird dann die Daten auch alle aufarbeiten, transkribieren und dann auswerten. Genau. Ja, jetzt würde ich euch kurz bitten, euch ganz kurz vorzustellen, am besten mit Name, Funktion, und vielleicht was dann auch interessant ist, wie viel von den pharmakogenetischen Fällen Ihr circa schon abgehandelt habt. Also ich mache kurz ein Beispiel: Ich bin die C.J., ich bin Apothekerin und habe jetzt schon im Rahmen der Beobachtungsstudie circa 67 Fälle abgehandelt. Genau. Vielleicht bevor wir zur Vorstellungsrunde kommen, noch einen kurzen Hinweis: Im Zoom gibt es die Funktion, dass man oben rechts unter Ansicht oder View, die Galerieansicht anwählen kann. Und im Rahmen der Diskussion ist es sehr empfehlenswert, damit man dann auch alle Gesichter sieht. Genau. Ja, wer würde gerne kurz starten?

Arzt 1: Ja, ich kann sonst gerade starten.

Moderator: Ja, sehr gerne.

Arzt 1: Mein Name ist T.I. Ich bin Psychiater, Chefarzt von der Psychiatrie im [...] bei den Spitälern [...], also Hauptsitz hier in [...]. Überwiesen in die Studie habe ich glaube drei Patienten, wenn es mir Recht ist. Wir sind ja ausserregional, das hat nachher dazu geführt, dass nicht mehr ganz alle

teilnehmen konnten. Bedarf hätten wir einen höheren gehabt, das wäre sehr beliebt gewesen bei unseren Patientinnen und Patienten. Wir haben aber auch schon mit anderen Anbietern und Labors zusammengearbeitet und haben deswegen natürlich mehr Erfahrung.

Moderator: Danke.

Arzt 2: Mein Name ist P.E., ich bin Rheumatologin in der Praxis und bin eigentlich durch S.B. darauf gestossen, auf die pharmakogenetische Abklärung. Sie stellt sich dann unten auch noch vor. Ehm, ich habe, ich weiss gar nicht wie viele, ich würde jetzt mal schätzen ungefähr 15 überwiesen, maximal.

Moderator: Ja, es waren noch mehr.

Arzt 2: Ah, noch mehr? (Lachen)

Moderator: Ja, noch mehr. (Lachen)

Arzt 2: Waren sehr spannende Rückmeldungen gekommen. Ja, nachher können wir noch ein paar Sachen diskutieren, denke ich.

Moderator: Sehr gerne, danke.

Arzt 3: Mein Name ist S.B.. Ich bin Hausärztin in [...] und ich weiss auch nicht wie viele ich schon eingeschleust habe, aber einige. Ja.

Moderator: Jawoll, sehr gut. Ja, vielen Dank. Deshalb ist es auch interessant für uns, wenn wir dann so eine Diskussion starten können. Genau, vielleicht bevor wir starten noch kurz ein paar Spielregeln. In so einer Diskussion ist es wichtig, dass man einen Rahmen hat. Grundsätzlich empfehle ich, das Mikrofon gerade angeschaltet zu lassen, dann kann man auch direkt reinsprechen. Die Kamera ist schon an, Soundcheck ist schon gemacht. Die Mitglieder von der Forschungsgruppe, welche ich vorgestellt habe, bleiben grundsätzlich im Hintergrund. Die würden nur intervenieren, wenn es notwendig ist. Jede Meinung zählt. Für uns ist jedes Feedback wertvoll und da gibt es kein Richtig und kein Falsch. Und ich versuche auch zu schauen, dass jeder einmal zu Wort kommt. Es kann sein, dass ich dann vielleicht sogar einmal unterbreche. Natürlich ist das ganze vertraulich. Die Diskussion wird aufgenommen. Das wird dann transkribiert und dann wird die Aufnahme gelöscht. Das zu den Spielregeln und vom Rahmen her: Es ist so, dass wir eine Stunde eingeplant haben und wir versuchen uns auch an den Rahmen dieser Stunde einzuhalten. Wir haben grundsätzlich drei Themen, die wir mit euch gerne besprechen möchten. Und jeweils einleitend machen wir eine kurze Umfrage im Zoom. Das ist so ein Fragetool, das es gibt. Das erkläre ich dann gerade, wenn es so weit ist. Genau, gut. Dann würde ich gerade mit dem ersten Themenblock starten:

Ich schaue dort gerade noch einmal, jawoll. Genau. Und hier geht es um das Empfehlungsschreiben, wo wir auch immer an Sie richten. Und dort ist es jetzt, dass hat sich im Laufe der Zeit immer wieder angepasst, haben wir immer wieder angepasst, haben wir es immer wieder versucht zu optimieren. Und der aktuelle Aufbau ist eigentlich so, dass wir kurz die Medikamente aufführen, nochmals die Fragestellung machen, dann die Resultate präsentieren. Und für diese Resultate haben wir da eine Legende gemacht, neuerdings mit einem Farbcode. Der lehnt sich eigentlich grösstenteils an das Ampelsystem von Stratipharm an, mit der zusätzlichen hellgrünen Farbe, wo Stratipharm rein gar keine Aussage machen kann. Und das haben wir noch wichtig gefunden, dass wir das auch so darlegen

können. Dann beurteilen wir Interaktionen und geben das dann natürlich auch am Schluss in Textform wieder. Das ist soweit an sich bekannt, und dann vielleicht hier nochmals kurz: Dort ist immer am Anfang eine Übersicht von den betroffenen Genen. Das sagt dann vielleicht auf den ersten Blick noch nicht so viel, aber deshalb gibt es dann die detaillierte Beurteilung, wo dann bei jedem Wirkstoff steht, welches Gen jetzt dort involviert ist und ist das grün oder ist das eben vielleicht gelb, orange oder sogar rot kategorisiert. Ja, ich möchte dort nicht zu sehr ins Detail gehen und schon zur ersten Frage kommen:

Und zwar möchten wir gerne ein bisschen abholen, wie übersichtlich Sie die Darstellung des Empfehlungsschreibens auf einer Skala von eins bis zehn finden. Wenn eins überhaupt nicht übersichtlich und zehn voll und ganz übersichtlich ist. Dazu würde ich gerade so eine Umfrage lancieren. Ehm, da poppt jetzt bei Ihnen ein Fenster auf und dann können Sie gerade, also dann auch hinunterscrollen bis zur zehn und dann können Sie gerade dort teilnehmen. Ich lasse Ihnen gerade ein paar Sekunden Zeit. Genau. Vielen Dank. Also, dann sehen wir das so: Es ist zweimal bei sieben gelandet und einmal bei zehn. Ja, dann möchte ich das gerne so in die Runde werfen. Ehm, was stört dann?

Arzt 1: Also ich hätte jetzt vielleicht weniger gesagt, dass etwas stört, sondern dass die Problematik ist, dass Ihr etwas Hochkomplexes darstellen müsst. Also ich sehe dort das Problem und ich hätte jetzt von dem her auch nicht genau Tipps, wie man es vereinfachen kann. Aber sehr viel komplexe Information.

Moderator: Ja, das wäre gerade die nächste Frage gewesen, ob es vielleicht eine Verbesserungsmöglichkeit gibt. Jetzt, wenn wir versuchen, das Empfehlungsschreiben möglichst kompakt zu machen... Gibt es da vielleicht noch einen anderen Input?

Arzt 2: Also ich finde es eigentlich im grossen und ganzen schon gut dargestellt. Also das man zuerst kurz informiert wird, wo die Probleme sind, bei dem Medikamentenabbau etc., Stoffwechsel. Zum Teil bei den Empfehlungen, wenn natürlich mehrere Wirkstoffe, oder aus verschiedenen Gruppen geprüft werden, wie zum Beispiel noch ein Magenschutz und so weiter, dann denke ich, muss man je nach dem aufpassen, dass man nicht noch zu viel Information einpackt bezüglich den Empfehlungen.

Moderator: Mhm. Also bei den Empfehlungen haben wir es grundsätzlich immer so gehalten, dass wir es nach Indikation zuordnen. Also oben die Tabelle und unten den Text. Und dann gibt es bei gewissen Medikamenten Wirkstoffe , welche dann noch zusätzlich sind oder in Reserve und so und das ist dann meistens einfach «andere Medikamente». Das haben wir jetzt so abgehandelt. Mhm. Genau.

Arzt 2: Aber ich denke auch, dass es relativ schwierig ist, da (lacht) eine optimale Darstellung zu machen, weil es wirklich kompliziert ist.

Moderator: Mmm, ja.

Arzt 2: Und man (versucht), möglichst viel Information auf möglichst wenig Papier darzustellen.

Moderator: Ja, grundsätzlich ist und das bewusst, dass es komplexe Information ist und deshalb haben wir auch immer versucht, dass zu optimieren. Im Moment ist es circa, je nach Patient natürlich

auch, ist es um drei bis fünf Seiten und da vielleicht kann ich schon überleiten zur nächsten Frage: Wie angemessen ist der Umfang? Oder, ich lanciere hier auch gerade wieder eine Umfrage.

Beobachter 1: Darf ich mich vielleicht hier ganz kurz einmischen. Und vielleicht ist eben auch ein Aspekt, dass wir in den Empfehlungen einerseits die aktuelle Therapie drin haben, dann vielleicht eine Therapie, die früher Probleme gemacht hat, aber wir gehen auch in die Zukunft und machen preemptive. Und das gibt natürlich immer mehr. Das wäre vielleicht dann noch eine Zusatzfrage, wie sehr das preemptive, wo wir irgendetwas annehmen: vielleicht kommt dort irgendwann mal ein Opiat bei der Person auch zum Spiel, aber heute ist es ja gar kein Thema, ob das zu viel des Guten ist... ?

Moderator: Ja genau. Also ich glaube das ist eine gute Überleitung zur nächsten Frage: Der Umfang, wo jetzt mit den drei bis fünf Seiten, wie angemessen finden Sie das jetzt auf einer Skala von eins bis zehn mit diesen drei bis fünf Seiten, je nach Patient?

Arzt 1: Kann man auch Halbpunkte wählen? (lacht)

Moderator: Ja das ist dann schwierig, oder... (lacht) Am besten ist dann, wenn man es aufrundet. (lacht)

Arzt 2: Mhm.

Moderator: Genau, vielen Dank. Dann beenden wir das schon. Okay, also es wird sicher eher tendenziell als angemessen angeschaut und klar gibt es immer Kürzungsbedarf. Oder.. Vielleicht, was für uns sicher noch wichtig ist zu wissen, welche Abschnitte sind für Sie jetzt überhaupt relevant?

Arzt 3: Also für mich ist relevant, welche Substanzen überhaupt nicht empfohlen sind. Also dort wo man sieht, Achtung das ist ganz eine schwierige Verstoffwechselung. Und manchmal ist es ein bisschen problematisch, wenn steht, welche Stoffe empfohlen sind, wenn es nicht gerade das trifft, was die aktuelle Fragestellung ist, aber ich denke, so wie der K.H. gesagt hat, manchmal ist es halt dann in der Zukunft doch relevant, dass diese Substanzen aufgelistet sind. Also das sind die Themata, wo wir in der Sprechstunde dann sehr eingehend zusammen anschauen, der Patient und ich.

Moderator: Mhm. Ja, vielen Dank. Ja, ich denke das mit dem preemptive oder das man in die Zukunft schaut... Also da schauen wir, da fragen wir nochmals beim Patienten nach, welche Medikamente sind ein Thema, wenn Sie Schmerzen haben, oder gibt es mit dem Schlaf und da, da kommt dann doch noch einiges an den Tag an Substanzen, wo schon einmal eingenommen worden sind, oder es eben auch sein könnte, dass es mal ein Thema wird. Genau.

Arzt 1: Wenn ich so schaue, was Patienten vor allem interessiert, dann ist halt die Frage, also da sehe ich vor allem Personen mit Therapieresistenz, wo in der Regel 11 Antidepressiva gehabt haben, vier Stimmungsstabilisatoren und ein Stimulans und dann ist natürlich die Hauptfrage, was könnte helfen. Und dort mehr Unterstützung zu haben, dass man das probiert mit einer höheren Wahrscheinlichkeit, dass macht natürlich sehr viel Sinn. Sie sind aber auch immer sehr interessiert daran, zurückzuschauen, zum Schauen warum etwas nicht helfen konnte. Dort habe ich auch gemerkt, dass es die Leute sehr entlastet, wenn sie nachher ein Muster sehen, wo für sie nachvollziehbar ist.

Moderator: Mhm.

Arzt 1: Bei mir ist es ja genauso gewesen. Paroxetin hat nicht gewirkt und jetzt weiss ich vielleicht ein bisschen mehr, warum.

Moderator: Ja...

Arzt 1: Wenn ich es den Leuten anpreise, in Anführungs- und Schlusszeichen, dann gebe ich auch immer den Hinweis, dass wird Ihnen aber auch Hinweise geben für die Zukunft, vielleicht auch für andere Medikamente. Also von dem her, schätze ich das sehr, dass die Leute dort eigentlich auch Hilfsmittel haben, wie sie vielleicht auch bei zukünftigen medizinischen Problemen bessere Entscheidungsgrundlagen haben.

Arzt 2: Mhm.

Arzt 1: Ich finde daher, es braucht viel Information. Also ich denke, wenn man es nachher auch schon macht, dann sollte man auch das Maximum herausholen können. Ich hätte jetzt 8.5 gegeben vom Umfang her.

Moderator: Jawoll.

Arzt 1: Wenn man jetzt mehr in die Breite gehen würde und jetzt wirklich Wald und Wissens-Psychiater und Psychiaterinnen anschauen würde, für die wäre es jetzt vielleicht effektiv ein bisschen zu viel. Dort wäre dann vielleicht eine bisschen kondensiertere Version gut.

Moderator: Mhm.

Arzt 1: Und eben auch gerade so mit indermediate metabolizer, also in diese muss man ja wie so ein bisschen hineinkommen und darum ist es nachher gerade sehr viel Information.

Moderator: Mhm, ja ich denke, dass sind sehr viele wichtige Punkte, welche Sie jetzt dort ansprechen, Herr T.I., und also zum einen macht es sicher Sinn, wenn man das Pannel schon hat, dass man in die Vergangenheit und in die Zukunft schaut. Und, ehm, dass es eben auch beides, wirklich beides, dem Patienten helfen kann. Und natürlich, dass ist uns bewusst, dass ist dann auch noch eine Frage, die wir gerne fragen möchten, einfach das interdisziplinär Setting, die Kommunikation, das muss gegeben sein, sonst kann ein Arzt dann vielleicht auch Nichts mit so einem Empfehlungsschreiben anfangen. Genau.

Arzt 2: Was noch wichtig ist, dass was wir natürlich machen, dass wir dem Patienten auch sagen, dass auch wenn die pharmakogenetische Toleranz da sein sollte, heisst das noch lange nicht, dass er nicht trotzdem Nebenwirkungen bei irgendwas machen kann. Das ist dann immer so, noch ein bisschen schwierig, oder... Und gleichzeitig, wenn es eben gelb ist, könnte man es sicher trotzdem einmal probieren als Option. Oder... Das heisst ja jetzt nicht, dass man das nicht einsetzten dürfte.

Moderator: Ja genau. Also zu den gelben Substanzen komme ich auch noch darauf zurück. Und, ja, das ist sicher so , dass muss man immer wieder klar kommunizieren, dass es ein Teil der Nebenwirkungen erklären kann oder der Nichtwirkung, dass es aber nur ein Puzzleteil ist. Das da, auch viele andere, das haben wir immer wieder auch mit Allergien, dass man das den Patienten erklären muss, dass wir eine allergische Reaktion nicht im pharmakogenetischen Profil voraussehen können. Ja, jetzt im Zusammenhang mit dem Empfehlungsschreiben, mit drei bis fünf Seiten, ist für

uns natürlich auch die Frage im praktischen Alltag, Wie viel Zeitaufwand müssen Sie jetzt dafür aufwenden, dass Sie die Änderungen, dass Sie das Empfehlungsschreiben, dass Sie sich damit auseinandersetzten können? Da starte ich auch gerade kurz eine Umfrage.

Arzt 1: Also nur das Empfehlungsschreiben, oder das ganze Paket, wo Ihr schickt?

Moderator: Ja, es ist jetzt Fokus auf das Empfehlungsschreiben. Sie müssen ja dies zuerst lesen und sich mit dem auseinandersetzten. Ja, eigentlich Fokus auf das Empfehlungsschreiben, weil sie haben ja nachher auch noch eine Konsultation mit dem Patienten und das jetzt mal aussen vor. Also wirklich wie viel Zeit brauchen Sie beim Empfehlungsschreiben. Ich lanciere das gerade...

Genau, super. So präsentieren sich die Resultate: Genau, ich sehe gerade, dass Herr P.T. noch gerade dazu gestossen ist. Guten Abend, schön konnten Sie sich auch noch Zeit nehmen. Ich mache einfach immer wieder eine Umfrage im Zoom und dann wird die Diskussion lanciert. Genau, also ich sehe die Mehrheit ist so zwischen 11 und 20 Minuten. Vielleicht die erste Frage, was ist das zeitaufwändige, ist es, wenn man jetzt so ein Empfehlungsschreiben liest?

Arzt 1: Ehhm... Es ist eine hohe Komplexität und ich muss danach innerlich auch immer den Abgleich machen mit der Patientin oder dem Patient. So dass ich das wie innerlich überprüfen muss. Ehm und es ist die Vorbereitung auf das Patientengespräch natürlich.

Moderator: Jawoll.

Arzt 1: Also es ist daher schon aufwändig neben Befunde, wie EEG- und MRI-Befunde. Aber es ist natürlich schon gerechtfertigt, weil es eben keine Routineuntersuchung ist.

Moderator: Mhm. Also würden Sie sagen, dass es gut investierte Zeit ist?

Arzt 1: Ja und eben auch die Leute, die ich schicke, die haben nicht drei Antidepressiva probiert. Dort wäre ich wesentlich schneller.

Moderator: Ja, das ist klar. Es kommt dann auch auf das Patientenbild drauf an und meistens handelt es sich dort auch um komplexe Fälle.

Ja, wenn ich vielleicht eine weitere Frage in die Runde werfen kann, wie umsetzbar sind die Empfehlungen im praktischen Alltag? Welche Sie jetzt so bekommen...

Arzt 2: Also ich denke, also für mich als Rheumatologin sind sie eigentlich gut umsetzbar, das einzige, dass mir aufgefallen ist, dass bei niemandem Methotrexat als verträglich empfunden ist (lacht). Also dort gibt es immer irgendwas, dass nicht funktioniert und das schränkt mich ein bisschen ein, da fange ich langsam ein bisschen an zu zweifeln... Ich weiss, dass viele Leute Probleme haben mit Methotrexat, aber dass es praktisch mit niemanden funktionieren soll... Das hat mich ein bisschen irritiert. Ja...

Moderator: Mhm, das ist uns auch schon aufgefallen, um nur kurz auf das zu kommen und da ist natürlich jetzt die Frage: Ist es jetzt das Patientensetting, wo eben diese Unverträglichkeiten vorweist, oder ist es die schwierige und komplexe Genetik des Methotrexats?

Arzt 2: Ja.

Moderator: Was halt auch einiges vorweist. Ja, aber das ist eine offene Frage. Ja... (lacht) Mhm.

Arzt 3: Für mich als Internistin, ich muss einfach, wenn ich die Empfehlungen anschaue, muss ich immer schauen, was steht jetzt gerade im Vordergrund, so dass ich nachher meine Anpassungen vornehmen kann. Meistens versuche ich nicht gerade alles umzusetzen, sonst kann ich auch keinen Verlauf mehr beurteilen.

Moderator: Ja, das ist klar.

Arzt 4: Also es ist auf jeden Fall sehr hilfreich, ist sehr ausführlich. Ich habe viele Patienten gehabt, wo vielleicht eher im Schmerzmittel-/Psychopharmaka- Bereich ihre Probleme hatten. Und ich war dann fast ein bisschen verloren, dann muss man, dann hat man ja fast eine A4-Seite mit Substanzen, wo man kann oder nicht brauchen kann. Wo ich mich gefragt habe, Umsetzbarkeit bei so einem Patient, gäbe es dort, gäbe es dort irgendeine App, wo die Daten drin wären, und dann könnte ich irgendetwas eingeben, z.B Methotrexat oder, und dann leuchtet es auf oder nicht, oder ehm es ist von der Umsetzbarkeit eigentlich super gewesen, weil man endlich Schwarz auf Weiss etwas festes hat, aber auch eine riesige Information an Daten, habe ich gefunden, und meistens am Schluss bei den Menschen, das geht vielleicht ein bisschen in das hinein, was P.E. gesagt hat, das was sie dann eigentlich vertragen, ist eigentlich noch auf einem kleinen Ort und vieles ist dann plötzlich irgendwie leicht gelb oder rötlich und umgekehrt sind dann Sachen auf einmal super verträglich, wo man denkt, die müssten eigentlich nicht verträglich sein. (Telefon klingelt)

Moderator: Ja klar, dass ist, also das mit der A4-Seite «Liste der betroffenen Wirkstoffe», das ist natürlich immer noch eine analoge oder sehr statische Sache. Wenn man jetzt den Zugang zu der Stratipharmsoftware nicht hat... Und das ist natürlich sehr wünschenswert, dass es dann irgendwo in einer elektronischen Version eingespeist werden kann. Dass das nicht nur eine einmalige Sache bleibt, sondern, dass auch in Zukunft immer wieder darauf zurückgegriffen werden kann. Genau...

Arzt 1: Eine Empfehlung im Kernbereich, wo es mir darum geht, bei den Antidepressiva, die erschienen mir sehr hilfreich, sehr genau das, was ich eigentlich gesucht habe. Manchmal hat es noch... also eigentlich ein Fall, nicht manchmal, (lacht) hat es noch Empfehlungen gehabt bezüglich einer Schlafmedikation, wo nachher Leitlinien ins Spiel kamen. Und das habe ich dann eine komische Vermischung gefunden, weil bei therapieresistenten Patienten sind die therapeutischen Leitlinien schon immer ausgeschöpft. Also da ist man weit... (lacht)

Moderator: Ja, das ist... Ja, danke für die Rückmeldung. Das war uns wahrscheinlich dort gar nicht so bewusst gewesen, dass man dort die Guidelines eher im Hintergrund lässt. Genau..

Arzt 1: Mhhm.

Moderator: Mhhm... Ja, ehm, die Frage, welche ich jetzt noch notiert habe, erübrigt sich jetzt wahrscheinlich, also: Haben Sie aufgrund der Empfehlung Änderungen in der Therapie vorgenommen? Ich denke, aufgrund von den Follow-up-Gesprächen, die wir auch mit den Patienten gemacht haben, haben wir doch gesehen, dass es dort immer wieder, dass dort auch immer wieder Änderungen vorgenommen worden sind. Hat dort noch jemand gerade einen Kommentar machen wollen? Sonst würde ich zum nächsten Thema übergehen...

Arzt 1: Also für mich ist ja das in der Regel genau der Grund, warum ich euch brauche. Weil ich für jemanden, für einen weiteren Schritt bei jemandem mit Therapieresistenz, eben Hilfe brauche, um zu entscheiden, was man als nächstes probieren könnte. Und dort ist dann meistens das genauso benützt worden. Mhm.

Moderator: Genau und deshalb braucht es das auch, also Sie müssen zuerst wissen, dass es die Möglichkeit gibt und dann auch die interdisziplinär Kommunikation, genau. Aber ja, dann würde ich das so mal stehen lassen und würde weitergehen. Jetzt habe ich gesehen, dass ich vor lauter Diskussion, mit den Folien nicht weitergegangen bin im Verlauf. Aber das haben wir ja alles schon abgehandelt. Dann würde ich mal weitergehen zum nächsten Punkt.

Und das ist die Liste der betroffenen Wirkstoffe. Das ist die Liste, die wir euch auch immer mitsenden in der Auswertung und das ist vor allem auch etwas, was wir dem Patienten auch immer sehr nahe legen, dass er das irgendwo bei sich hat, vielleicht eine Fotokopie, falls es eben in Zukunft zu einer neuen Therapie kommt, dass man das kurz checken kann. Und das ist ja, wie gesagt, Liste der betroffenen Wirkstoffen, das heisst, alle die grün sind, oder im Stratipharm, oder im pharmakogenetischen Profil nicht betroffen sind, sind nicht auf der Liste drauf. Sie sehen dort, Stand 16.04.19, das kann man also immer wieder machen, die Abfrage und in die Datenbank werden auch immer wieder neue Wirkstoffe eingespiesen. Und von der Kategorie her, dass ist Ihnen ja schon bestens bekannt. Mit gelb, wo es einen Hinweis gibt, orange, wo es eben doch einen Verdacht gibt mit entsprechender Anpassungsempfehlung oder Alternativmedikation und die Stufe rot, gibt es auch noch, das sehen wir aber sehr selten. Und bei diesem Wirkstoff, welcher jetzt in diesem Beispiel erwähnt ist, der ist zum Beispiel nicht erhältlich auf dem Schweizer Markt. Genau. Dann gehe ich dort gleich weiter. Ja jetzt uns interessiert so ein bisschen der Nutzen, wie Sie den so einschätzen.

Arzt 4: Darf ich noch etwas, darf ich noch schnell eine Frage stellen, Frau C.J.?

Moderator: Ja, auf jeden Fall.

Arzt 4: Das kann man immer wieder updaten? Aber wo kann man das updaten? Wo kann man wider einloggen und nach einem Jahr/zwei wieder irgendetwas herausholen? Das habe ich nirgends gesehen.

Moderator: Also, ja danke für die Frage. Also grundsätzlich ist es so, dass jede Apotheke und auch jeder Arzt sich bei der Stratipharm registrieren kann und ehm so, wie soll ich sagen, ein Benutzerkonto einrichten kann. Und dann kann man auch in die Daten hineinschauen. Jetzt, wenn Sie aber eine konkrete Frage haben zu einem, zu einem Patienten, wo bei uns in der Studie mitmachte, dann können auch wir das noch einmal, können wir nochmals eine aktuelle Anfrage machen. Also das ist jederzeit möglich. Aber das passiert innerhalb dieser Stratipharmsoftware. Genau.

Arzt 4: Aha.. Weil praktisch wäre es ja, wenn der Patient ein Login und ein Passwort hätte, wie für anderes auch und dann kann man ihm, nach einem Jahr loggt man dort noch einmal ein. Und dann gibt es dort ein Update: Brrrmp,100 neue Substanzen und so weiter. Das habe ich nicht gewusst, dass man das noch einmal machen könnte.

Moderator: Doch das könnte man, weil das ist in dem Sinne, die Gene verändern sich ja nicht und deshalb sind die Daten lebenslänglich gültig, in dem Sinn und die Patienten bekommen auch jeweils

ein Patientenkarte, mit dem Patientencode und mittels dem Code und unserem Zugang zur Software können wir da wieder in die Daten hineinschauen. Genau, das ist also möglich.

Ja, jetzt vielleicht nochmals kurz zu der Liste der betroffenen Wirkstoffe. Ehm, da, wie hilfreich finden Sie das im klinischen Alltag auf einer Skala von eins bis zehn? Eins ist überhaupt nicht hilfreich und zehn voll und ganz hilfreich. Ich starte hier gerade wieder eine Umfrage.

Genau, da haben wir also auf jeder Stufe etwas. (lacht) Sehr gut. Ehm.. Ja vielleicht gerade eine Anschlussfrage. Wie häufig greifen Sie auf die Liste zurück, Sie als behandelnder Arzt?

Arzt 1: Sehr häufig.

Moderator: Mhhm.

Arzt 3: Ich auch. Sehr häufig.

Arzt 2: Also es sind ja unterschiedliche Patienten. Diejenigen, wo wir vor allem am Anfang geschickt haben sind solche, bei denen viele Unverträglichkeiten aufgefallen sind. Und andere, wo wir gesagt haben, sogar vor Behandlungsbeginn mit einer sogenannten Basistherapie. Und dann, und die, die natürlich sowieso auf verschiedenes vorher schon reagiert haben, dort ist es natürlich erst recht sinnvoll, auf diese Liste zu schauen, wenn man ein neues Medikament einsetzten will.

Arzt 1: Es ist aber auch die Liste, die mir manchmal am meisten Kopfzerbrechen bereitet... (allgemeines Lachen)

Moderator: Ja genau...

Arzt 1: Weil dort habe ich nachher oft Schwierigkeiten, also ich sehe zwar den Namen, bei irgendwelcher Farbe und nachher muss man überlegen, wieso ist es jetzt hier... Weil zum Beispiel Interaktionen nützen wir zum Teil bewusst aus in der Psychiatrie. Also es gibt Kombinationen, welche nachher zur besseren Wirksamkeit führen, also dass wo nachher eigentlich als negativ gilt vom System her, aber eigentlich ein positives Kriterium ist. Und dort muss ich nachher immer wieder überlegen, ist es jetzt ein Problem oder das, was ich gerade will?

Moderator: Mhhm... Ja das ist so... Oder, das ist, das müssen wir auch immer ganz gut schauen. Wir haben zum einen die Genetik, die mitspielt und zum anderen die Interaktionen, die auch ein Faktor machen und dann, muss man dann immer die Analyse über das Ganze machen, oder...

Arzt 1: Mhhm.

Moderator: Und wenn es dann im Psychiatriesetting noch dazu kommt, dass man eine Interaktion noch ausnützen möchte, dann ist es halt speziell wertvoll, wenn man den genetischen Hintergrund auch kennt. Mhm. Aber ja, Sie haben, Sie sagen richtig, es ist eine lange Liste, vor allem die gelb kategorisierten Wirkstoffe. Das sind doch einige Wirkstoffe und dort vielleicht ganz konkret die Frage, wie gehen Sie mit den gelb kategorisierten Wirkstoffen um?

Arzt 2: Also ich probiere sie aus. Vor allem dann, wenn ich je nach dem schon andere Sachen ausprobiert habe, die nicht funktioniert haben.

Moderator: Mhm. Also Sie sagen, wenn, also gelb kategorisierte Substanzen lieber nicht?

Arzt 2: Ja, wenn ich die Abhandlung habe. Aber je nachdem muss ich trotzdem und dann würde ich halt, je nachdem was steht, eher tief anfangen oder so und langsam. Ja..

Moderator: Mhm. Jawoll. Und wie machen es die anderen?

Arzt 3: Manchmal hat man halt nicht so viel Wahl... bei der Polypharmazie, dann wechsle ich diese sicher nicht als erste aus. Aber wenn ich kann und muss eine neue Substanz einsetzten, dann nehme ich keine, welche auf der gelben Liste ist, versuche...

Moderator: Mhm.

Arzt 3: Aber ich denke, die gelbe Liste ist diejenige, welche uns am meisten Schwierigkeiten bereitet.

Arzt 2: Mhm.

Moderator: Ja, das ist genau richtig. Denn schlussendlich ist es ein Hinweis und dann müssen wir immer gut schauen, auch im Patientensetting, was machen wir jetzt mit dem Hinweis, oder... Ist es womöglich gerade das, was entscheidend ist und wo besser ist, dass wir das vermeiden oder ist das jetzt einfach lebensnotwendig und wir beobachten es sorgfältig. Genau..

Arzt 1: Bei vielen Leuten komme ich um die gelbe Liste gar nicht herum. Weil es gar nicht mehr, weil man alles grüne durchprobiert hat, was es gibt. Und dort ist nachher schon noch oft die Schwierigkeit, das Gelb löst wie ein Nocebo-Effekt aus. Also ich möchte selbst auch kein Medikament, dass Gelb aufleuchtet... Und das, was wir häufig haben mit den Apotheken, wenn sie dann Interaktionschecks machen, wenn nachher, dass verunsichert nachher den Patienten recht, wenn er dort die Mitteilung bekommt, dass es problematisch ist, was er nimmt. Ehm...

Arzt 2: Ja.

Arzt 1: Es hat immer auch so einen... Transparenz ist ganz wichtig, aber eben, es macht es nachher auch nicht einfacher.

Moderator: Ja, das ist sicher ein wichtiger Aspekt, das mit dem Nocebo-Effekt. Ich denke vor allem im Setting mit Psychiatriepatienten muss man da sicher noch eine Stufe vorsichtiger sein, wie man das dann kommuniziert.

Arzt 1: Mhm...

Moderator: Genau.

Beobachter 1: Darf ich dort vielleicht doch noch rasch dazukommen? Ich glaube, das ist ja eine sehr grobe Einteilung in das Gelbe und Orange. Und wenn wir im Detail bei einer gelben Substanz nachschauen gehen, dann sehen wir natürlich viel vertiefter. Ist das jetzt noch hellgelb oder noch dunkelgelb. Also dort gibt es also auch noch mal Nuancen. Und es gibt ganze Klassen, ich denke jetzt da zum Beispiel an Statine, wo zwar zum Teil gleich gelabelt kommen können, aber im Profil würden

wir sehen, das eine ist jetzt ist jetzt ein bisschen heller gelb oder dunkelgelb. Also das ist schon plakativ auf dieser Liste und es könnte sich lohnen, im Zweifelsfall bei uns nochmals nachzufragen. Ehm, sie müssen eins von den gelben, a, b oder c, alle drei sind gelb, welches wäre jetzt noch das günstige? Das dürften Sie nachfragen.

Moderator: Ja genau. Das ist auf jeden Fall möglich. Ja wenn es dort zur Liste keine Anmerkung gibt, dann würde ich gerade schon weitergehen zum letzten und wahrscheinlich auch wichtigsten Punkt.

Genau und dort möchten wir noch einmal gerne allgemein über die pharmakogenetische Analyse reden. Genau, ja, wenn Sie jetzt an die Fälle zurückdenken, wo sie bis anhin schon überwiesen haben, stelle ich ganz konkret die Frage: Wie relevant ist die pharmakogenetische Analyse für die therapeutische Entscheidung gewesen? Da lanciere ich auch nochmals gerne eine Umfrage. Auch wieder mit der Skala von eins bis zehn. Das ist immer superschnell, vielen Dank. Genau, also durchschnittlich wird das mit neun bewertet. Genau, also, wenn Sie jetzt nochmals konkret an die verschiedenen Fälle, wo sie gehabt haben, denken, können Sie vielleicht je ein Beispiel nennen, wo es hilfreich gewesen ist und wo es vielleicht nicht unbedingt so hilfreich gewesen ist?

Arzt 2: Also ich denke, was noch wichtig ist, ist auch die Kommunikation. Sie informieren ja die Patienten auch, was herausgekommen ist. Und dann muss man manchmal auch sehr aufpassen, weil es doch auch ängstliche Leute gibt. Und wenn man dann von einer Spritze redet, zum Beispiel, dass es dann klar, dass es sich um eine konkrete Substanz handelt und nicht um Spritzen allgemein, etc. Oder halt vielleicht gar nicht so viel dazu sagen und dann lieber uns die Information weiterleiten. Ich finde es zwar schon gut, dass Sie es auswerten, weil Sie nehmen sich ja auch viel Zeit, aber ich denke da muss man im Zweifelsfall, also Sie haben ja das auch mitbekommen, ich habe zum Teil Patienten gehabt, wo extrem komplizierte Hintergründe haben und dann ist es manchmal gut, wenn man vorher nochmals kurz Kontakt aufnimmt.

Moderator: Mhm. Ja, das ist sehr gut. Danke für den Input. Das ist natürlich immer auch eine Möglichkeit, dass die Kommunikation mit uns und den Ärzten auch schon parallel immer passiert. Oder, wenn man das Resultat jetzt hat und sieht, okay das Methotrexat kann ich jetzt nicht geben, dann gibt es jetzt noch die Möglichkeit ,dass man das noch kurz abspricht, bevor man es mit dem Patient macht. Aber grundsätzlich ist unsere Idee immer, dass wir dem Patient zeigen, das ist das Resultat der Analyse, das wäre jetzt eine Möglichkeit, aber es ist der Entscheid vom behandelnden Arzt. Oder.. Einfach zum Kommunizieren, das ist dabei herausgekommen, das wären jetzt die Möglichkeiten und dann die Information noch in schriftlicher Form weiterzuleiten. Genau.

Arzt 1: Also meine Patienten haben die Rückmeldungsgespräche enorm geschätzt. Dort ist sehr ein gutes Feedback gekommen von ihnen. Es hat auch etwas technisches sehr menschlich gemacht. Also die (Signalstörung) haben wie ein Gesicht bekommen, was wie die Angst nimmt bei den Patienten vor dem Ganzen. Ich habe mich dort auch gefragt, wieso bin ich dort eigentlich nicht mit dabei? Könnte man das nicht auch zu dritt machen? Das hätte ich sehr geschätzt. Da hätte man auch gerade auch das Ganze noch einmal anschauen können: Warum hat dann Wellbutrin früher nicht funktioniert und dann hätte es, also würde dort würde es gewisse Risiken von so einer Beratung eigentlich aus dem Weg räumen, dass nachher wirklich gemeinsam wie ein weiterer Weg skizziert werden kann.

Moderator: Mhm. Ja. Reden Sie nur.

Arzt 1: Wegen der Frage, ich habe eine Patient gehabt, dort ist das Resultat der Analytik völlig im Widerspruch gewesen zu seiner bisherigen Erfahrung. Also die Medikamente, auf die er in der Vergangenheit angesprochen hat, waren gerade die gewesen, welche man nicht geben durfte und diejenigen, die man geben sollte, auf die hat er genau nicht angesprochen. Ich habe dort auch eine Patientin gehabt, die hat wirklich, ja 20 Präparate durchprobiert und dort ist es wirklich wie die Faust auf das Auge gewesen. Das hat so gepasst. Also das heisst, es hat Leute gegeben, bei denen habe ich wirklich noch einmal schauen müssen. Was heisst jetzt das, stimmt etwas bei der Diagnostik nicht? Wobei diese in der Psychiatrie ja sowieso sehr ungenau ist. Aber es hat wirklich auch Leute gegeben, wo es nachher wirklich sehr hilft, gut auswählen zu können.

Moderator: Mhm, ja ich denke, dass was wir auch immer beobachten: Es gibt Fälle, wo wir einen sehr konkreten Verdacht haben und der sich dann auch bestätigt, aber es gibt auch die Fälle, bei denen man dann doch nichts findet in der Genetik. Oder, und dann ist es in der Kommunikation auch nochmals eine Herausforderung, das dann mit den Patienten zu besprechen.

Beobachter 1: Darf ich dort vielleicht eine Idee einfach aufnehmen, welche ich jetzt noch genommen habe vom Herr T.I.. Wenn Sie sagen zusammen, wäre das natürlich ideal. Wir wären dann quasi in einem Dreiergespräch. Sie als Arzt, wir, die die Analyse gemacht haben plus der Patient. Wir haben ja jetzt sehr häufig covidbedingt das sogar über Zoom gemacht mit den Patienten. Und das ist natürlich jetzt eine neue Möglichkeit, wo wir sehr einfach, und damit niederschwelliger sich zu dritt finden zu können. Wäre das für sie noch hilfreich als Option, dass Sie bei der Überweisung sagen könnten, jetzt bei dieser Patientin möchte ich auch schon beim Gespräch, dass wir führen nach Vorliegen der Resultate, dabei sein, wäre das für Sie eine wünschenswerte Option?

Arzt 1: Für mich wäre das sehr wünschenswert und als Bergler liebe ich natürlich Technologie, dass wir Leute nach Basel schicken können, das ist natürlich vorher, natürlich immer der grosse, also wäre jetzt die Studie nur vor Ort gewesen, wäre es schwieriger gewesen, Leute zu motivieren. Die haben das enorm geschätzt, dass sie von hier aus das machen konnten. Und eben, es bietet sich die Möglichkeit, solche Konferenzgespräche mit wenig Aufwand zu machen. Was sonst logistisch natürlich immer sehr schwierig ist, dass das nachher irgendwie klappt.

Moderator: Mhm.

Arzt 2: Ich finde es auch einen guten Vorschlag, dass man das online machen könnte und durch das sicher sehr viel einfacher ist, als ein Termin vor Ort.

Arzt 3: Ich glaube es wäre ein hervorragendes Tool, weil die Patienten, auch wenn es um rein internistische Angelegenheiten/ Fragestellung geht, haben sich enorm ernstgenommen gefühlt und die wünschen sich ja, dass wir interaktiv miteinander kommunizieren und wenn das in so einem Zoommeeting während der Sprechstunde wäre, wäre natürlich hervorragend. Ich habe beobachtet, dass insbesondere die kardiologischen Medikamente wirklich wahnsinnig gutes Ansprechen gezeigt haben. Wenn ich dort etwas wechseln konnte, wo wir gesehen haben, dass es nicht gematched hat, dort ist es für mich am eindrücklichsten gewesen bei den Patienten.

Moderator: Okay, ja, vielen Dank für die Rückmeldung. Das ist natürlich immer positiv, denn wir haben jetzt verschiedenste Fälle angeschaut. Mit Herr Dr. T.I. sind es Fälle aus der Psychiatrie gewesen, aber eben mit Ihnen Frau S.B. im internistischen Setting und ja Kardiologie, ist , am

Startpunkt sind wir uns nicht so sicher gewesen, wie viel wir dann aus dem Profil mitgeben können, darum ist das sicher eine wertvolle Rückmeldung.

Arzt 3: Ich kann vielleicht noch ganz kurz sagen, ich habe ja jemanden aus Bern geschickt, also nein besser gesagt aus Steffisburg (lacht) und die Rheumatologen aus Bern, also an der Insel, die sind miserabel gestimmt gewesen... (lacht) nach dem sie die Daten bekommen haben. Ich denke, Interprofessionalität ist jetzt etwas, was an der Uni gefordert ist und ich denke, gerade wenn wir so arbeiten könnten, dass man eben mittels Zoomkonsultationen bessere Transparenz zustande bekommt, wäre das sehr gut.

Moderator: Ja, das ist, also ich glaube diese Frage ist schon auf eine Art ein bisschen beantwortet worden, wie Sie das empfunden haben mit der Kommunikation mit uns und die interdisziplinäre Zusammenarbeit. Möchte dort noch jemand etwas hinzufügen oder anmerken?

Arzt 2: Ich möchte euch einfach Dankeschön sagen für die Initiative, die Sie ergriffen haben, das aufzugleisen. Ehm.. Also eben im Grossen und Ganzen denke ich auch, es bringt wirklich viel, sowohl für die Betroffenen, als auch für mich und ich, ehm, also ich habe vorher nicht Kritik ausüben wollen an den Gesprächen, einfach dass es zum Teil halt heikel ist. Aber das wäre ja dann genau so ein Zusammenhang, wo man sagen könnte, hey dort könne man dann die Sachen noch ein bisschen anders bringen.

Moderator: Ja genau. Dafür sind wir hier. Vielen Dank Frau P.E.. Herr Dr. P.T., Sie haben, glaube ich, vorher noch die Hand aufgehoben?

Arzt 4: Ja, ich habe gefunden, das ist eigentlich die Zukunft. Also wenn ich jetzt dort in einer Konsultation wäre mit meinem Patient und sage: «Ou dort habe ich jetzt wirklich noch eine Frage, Moment schnell, ich schalte schnell ein. Ah ja, Frau Jeiziner, grüetzi, wie geht es Ihnen? Ja, wir haben noch schnell eine Frage zum Thioridazin.» Ich glaube, das wäre die Zukunft, oder? Wenn wir natürlich Konferenzen machen müssen, um uns zu sehen, wird das natürlich fast wie in der Geriatrie mit den Riesenkonferenzen und dann wird es mühsam. Also ich glaube, der way to go ist sicher irgendwie digital, einschalten zu können, aber auch on time, on spot zu sein, dass weiss ich nicht wie das geht, dann müsste man vielleicht sogar einen Chatpot haben oder irgendein Tool, das einem dort hilft. Aber das Vernetzten und das Big Data-Wissen wo wir dort zusammenkriegen finde ich, ist super. Wer von uns würde schon noch bei einer Schwangeren ohne irgendwas zu konsultieren, irgend ein Medikament verschreiben. Niemand, oder? Und das haben wir schon seit Jahrzehnten drin und ich denke auch, dass wir dort für das Blutplättchen für die Phenylketonurie, wo man bei den Babies abnimmt, könnte doch auch gerade das Blutplättchen für 15 000 verschiedene Enzymmarker sein, wo man in Zukunft könnte laufen lassen und der Mensch wäre digitalisiert. Also ich finde es grossartig in den Möglichkeiten, allerdings, Gespräche geht immer noch von einem menschlichen Hirn zum anderen und das braucht immer noch Zeit und so Konferenzen wären sehr aufwändig aber für den Patienten sicher sehr hilfreich. Ich persönlich bin noch froh gewesen, dass Sie die Patienten kompetent abgeholt haben und ich nicht auch noch Dreiviertel oder eine Stunde dabeisitzen und mitbesprechen musste, was geht, sondern ich habe nachher eine zweite Runde machen können und nochmals daraus Fragen beantworten können. Das ist für mich als Hausarzt noch praktisch gewesen, was der zeitliche Ablauf betrifft. Ehhm aber ganz sicher, dass ist ein Zukunftsmodell und ich hätte sehr, sehr gerne bei viel mehr Patienten bereits so einen genetischen, gläsernen Mensch dahinter, der mir wie eine Datenbank sagt: «Halt! Nimm nicht Wellbutrin, nimm irgendetwas anders.» Ich darf vielleicht noch kritisch sagen. In der Erfahrung von meinen Patienten hat es ja nicht immer funktioniert. Glaube, die

S.B. hat das auch schon gesagt, also gewisse Medikamentengruppen haben super funktioniert, andere nicht. Bei anderen hat man genau das gemacht, was die Genanalyse sagt und es ist trotzdem nicht ganz so gut herausgekommen. Also ich bin noch fasziniert gewesen, wie vielfältig dann trotzdem noch die Pharmakodynamik gewesen ist, unabhängig von den paar Genmarkern, wo wir da hatten. Und wie viel man trotzdem noch improvisieren musste, im gelben Bereich oder nicht, und so. Ehm, eigentlich spannend das eben die ganze Therapie nicht machbar ist. Ehm. Nicht machbar ist, sie so zuzuschneiden, dass man nur noch künstliche Intelligenz braucht. Also tolle Sache, Zukunft ja, ehm unbedingt einbauen und so die schnellen Plop-ins von Wissenssachen oder von Konferenzen wären für die Zukunft sicher, sicher möglich und sicher wünschbar, so dass wir in Zukunft nicht nur Patienten dort haben, wo wir wohnen, sondern in Steffisburg, im Tessin, in Tokio, in London... Grossartig! Wie wenn wir sonst nichts zu tun hätten... Also es ist super! Ich bin ganz begeistert von dem Zeugs. Es ist eine spannende Sache.

Moderator: Ja, vielen Dank für die Rückmeldung Herr P.T.. Ich denke, dass ist grundsätzlich auch unsere Idee. Es ist eine Information, wo möglich ist, diese heutzutage abzurufen und deshalb müssen wir diese Information auch berücksichtigen. Und es verlangt eine gewisse Sorgfältigkeit und vor allem das interdisziplinäre Setting. Und ja, digital ist der Weg. Ich denke, dass sehen wir in der aktuell Zeit mehr als je. Und so ein Zweitgespräch mit oder ohne Ärzte, das kann man natürlich auch dann immer optional gestalten. Aber das wäre sicher eine gute Möglichkeit. Genau. Ja, gibt es sonst gerade noch eine Anmerkung, Kommentar oder irgendwas, was wir noch verbessern könnten?

Es bleibt still. Gut. Dann komme ich auch schon langsam zum Abschluss in meiner Präsentation. Also, erst einmal vielen Dank für die wertvolle Zeit, die sie jetzt dort eingesetzt haben und für das Feedback, das ist wirklich sehr wertvoll für uns, wenn wir jetzt das so bei euch abholen können und entsprechend auch die pharmakogenetische Analyse als Dienstleistung optimieren können. Also auch für mich, und ich denke auch für die, die im Hintergrund zugeschaut haben, ist es sehr spannend gewesen und interessant und wir freuen uns natürlich auf die weitere Zusammenarbeit und auch allenfalls auf weitere Überweisungen. Genau.

Beobachter 1: Darf ich dort das Stichwort übernehmen C.J.? Ehm einfach, dass sie das noch wissen. Die Studie geht jetzt sicher noch weiter, noch mindestens bis Ende Jahr. Wir hoffen sogar, dass das noch viel länger weiter gehen kann. Es ist immer ein bisschen ein Ressourcenproblem, aber für den Moment sind wir noch voll dabei. Und die Ideen, von wie könnte man die ganze Rückmeldungsgeschichte besser gestalten, ich glaube dort gehen wir jetzt in uns, jetzt wir da von der Uni Basel und Sie werden von uns hören, wie wir das ausprobieren könnten, die Möglichkeiten, dass man die Besprechung zu dritt mit dem Patienten machen könnte. Also das nehme ich sicher auf und dort werden sie von uns wieder hören, auch bezüglich dem, was wir jetzt gelernt haben in dieser Stunde. Auch ich sage: «Ganz herzlichen Dank! Ist ganz toll, es freut mich sehr, dass wir diese Zusammenarbeit erleben dürfen.»

Beobachter 2: Darf ich auch noch mich bedanken. Ich, ehm, man kommt so aus dem Hintergrund, das tut mir leid. Ich habe sehr, wir lernen sehr, sehr viel in dem Prozess, den wir bisher gemacht haben mit Ihnen und mit den Patienten. Und ich bin wahnsinnig dankbar, dass wir mit Ihnen zusammen das Lernen dürfen und optimieren müssen. Es ist nämlich, oder dürfen... Es ist nämlich sehr wichtig, dass man diese Empfehlungen, dass wir die an das anpassen, was die Realität ist. Und, ehm, ich hoffe Sie haben gelernt, dass wir auch gelernt haben in der Zwischenzeit. (lacht) Vielen herzlichen Dank!

Arzt 1: Darf ich nochmals kurz die Frage stellen: Das ist aber weiterhin so, dass aber Berneroberländer-Patienten nicht an der Studie teilnehmen können?

Moderator: Also, es ist einfach so: Die Studie ist von der Ethik Nordwestschweiz genehmigt, aber es ist nach wie vor die Situation: Wenn der Patient die Möglichkeit hat, für eine Konsultation nach Basel zu kommen, dann kann man das machen, ja.

Arzt 1: Mhhm. Okay.

Moderator: Mhhm. Ja

Arzt 1: Dann ist gut.

Moderator: Auf jeden Fall.

Beobachter 1: Aber wir können auch diskutieren, ob man dies ausweitet. Man kann ein Amendment machen bei der Ethikkommission und dann ist Bern dabei. Also in dem Sinne machen wir die Türe nicht zu ins Berner Oberland. Müssten wir vielleicht noch mal bilateral besprechen.

Arzt 1: Mhhm.

Moderator: Ja dann denke ich, war das das Schlusswort und wünsche euch allen ganz einen schönen Abend!

Arzt 2: Danke gleichfalls!

Arzt 1: Danke gleichfalls.

Arzt 4: Danke, ade.

Kollektives Verabschieden.

Curriculum Vitae

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Scientific contributions

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Abstract & Poster: Pharmacogenetic testing and consultation in Pharmaceutical Care - development of a new pharmaceutical care service

10/2021 European Society of Clinical Pharmacy (ESCP) Symposium “Clinical Pharmacy, working collaboratively in mental health care”, virtual event due to COVID-19

Workshop Leader: Pharmacogenetic testing in clinical pharmacy practice - a hands-on workshop focusing on psychiatry indications

02/2021 12th Pharmaceutical Care Network Europe (PCNE) Working Conference “Partnering for better patient outcomes - challenges and opportunities”, Basel, virtual event due to COVID-19

Participation & Workshop Coordinator

01/2021 Tag der Klinischen Forschung vom Departement für Klinische Forschung (DKF) Universität Basel, virtual event due to COVID-19

Abstract & Poster: Enriching medication review with a pharmacogenetic profile - a case of tamoxifen adverse drug reactions

01/2020 Tag der Klinischen Forschung vom Departement für Klinische Forschung (DKF) Universität Basel, Basel, Switzerland

Abstract & Poster: HLA-associated adverse drug reactions – what do Swiss drug labels include?

01/2020	Evidence-based Medicine (EbM) Congress, Basel, Switzerland
	Poster: HLA-associated adverse drug reactions - Scoping Review and Analysis of the Swiss Drug Labels
10/2019	European Society of Clinical Pharmacy (ESCP) Symposium "The digital revolution", Ljubljana, Slovenia
	Poster & Oral Communication: Pharmacogenetic Information in Summaries of Product Characteristics: Analysis by Natural Language Processing
02/2019	11th Pharmaceutical Care Network Europe (PCNE) Working Conference "Tailoring pharmaceutical care", Egmond aan Zee, The Netherlands
	Abstract & Poster: "Pharmacogenetic information: Large heterogeneity in drug labels"
08/2018	Swiss Pharma Science Day (SPhSD), Bern, Switzerland
	Participation