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ORIGINAL RESEARCH

Utilization of Drugs with Pharmacogenetic Dosing Recommendations in Switzerland: A Descriptive Study Using the Helsana Database

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Purpose: In Switzerland 167 drugs on the market contain information about pharmacogenetics in their drug label (PGx drug). Preemptive pharmacogenetic testing is reimbursed by health care insurance for only seven drugs (abacavir, carbamazepine, 6-mercaptopurine, azathioprine, 5-fluorouracil, capecitabine, and irinotecan) although, it is proposed to be a cost-effective approach to personalized medicine. The aim of this study was to describe the use of PGx drugs and their corresponding genes in Switzerland.

Methods: We identified 90 drugs with dosing recommendations from the Pharmacogenetic Knowledgebase involving 24 genes. We assessed the utilization of those drugs between 2016 and 2020, using claims data from a large Swiss insurance company (Helsana).

Results: Of 841 491 persons with drug claims during the whole study period, 78.7% were exposed to PGx drugs. Ibuprofen, pantoprazole, and tramadol had the highest number of users. Seven genes (*CYP2C19, CYP2C9, CYP2D6, SLCO1B1, HLA-B, MT-RNR1*, and *VKORC1*) were responsible for over 95% of all potential drug-gene interactions.

Conclusion: The prevalence of PGx drug prescriptions is high in the Swiss population. Therefore, intensified preemptive testing may be a useful option as a substantial amount of the Swiss population might benefit.

Keywords: PGx, drug use, claims data, pharmacoepidemiology

Introduction

Drug-gene interactions (DGIs) are associations between a drug and a genetic variant that can alter the response to a treatment, as opposed to drug-drug interactions (DDIs), which signify a change in how a drug effect changes when taken with another drug.[1–3] DDIs may result from pharmacokinetic alterations in absorption, distribution, metabolism, or elimination as well as from pharmacological effects that are either complementary or antagonistic (pharmacodynamics).[3] Genetic influences on pharmacodynamics or pharmacokinetics in DGIs might induce individual variability, which may result in treatment failure or toxicity.[1,2] So pharmacogenomics aims to improve an individual's drug response by a more patient- tailored and thus more effective and safer treatment.[4] Although the prevalence of gene variants in genes encoding for drug metabolizing enzymes (such as the cytochrome P450 *(CYP) 2C9, CYP2C19*, and *CYP2D6*) or transporters (such as the solute carrier organic anion transporter family member 1B1 *(SLCO1B1)*), and drug targets (such as the vitamin K epoxide reductase complex subunit 1 (*VKORC1)*) is high, the integration of pharmacogenetic (PGx) testing into clinical practice is progressing rather slowly worldwide.[5–8] Depending on the studied population, 91.0% to 99.5% of the population had clinically actionable variants in at least one gene.[5,7,9] Actionable variants are defined as a phenotype that requires a change in dosage or type of medication. A small study in two Swiss hospitals based on 135 selected patients

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even found a minimum of one actionable variant in all patients (100%) using a 16-gene panel test.[10] Studies from other countries such as Denmark or the Netherlands suggest that up to 25% of the population might benefit from preemptive PGx testing, as they had actionable DGIs.[11–14]

PGx testing can be done preemptively to inform prescribing decisions in order to prevent toxicity or inadequate treatment.[15] Reactive PGx testing, on the other hand, is used in cases of insufficient treatment response or adverse drug reactions (ADRs).[16] PGx testing has been shown to reduce ADRs, reduce the frequency of hospital admissions, and to improve treatment response.[17–20] In Switzerland, preemptive PGx testing is only reimbursed by basic health care insurances in the context of a pharmacotherapy with abacavir (human leukocyte antigen (*HLA*) *-B*5701*), carbamazepine (*HLA-A*3101* and *HLA-B*1502*), 6-mercaptopurine and azathioprine (thiopurine S-methyltransferase *(TPMT)*), 5-fluorouracil and capecitabine (dihydropyrimidine dehydrogenase *(DPYD)*), and irinotecan (UDP glucuronosyltransferase *(UGT) 1A1*28*).[21] Even though the insurers are private companies, the Federal Office of Public Health dictates, which services and medications they have to cover in the basic health care insurance. In addition, it is mandated by law for all inhabitants to have basic health care insurance.[22] Other PGx tests are only reimbursed by basic health care insurance if they are reactive and prescribed by a physician with a specialization in clinical pharmacology and toxicology.[23] As a result, PGx testing seems to be not commonly implemented into primary care in Switzerland, although 167 drugs on the Swiss market contain information on PGx in their drug label, of which 93 are deemed to be actionable.[24]

To the best of our knowledge, detailed population-based information on the utilization of PGx drugs in Switzerland is currently not available. Therefore, the aim of this study was to assess the prevalence of PGx drug prescriptions in the Swiss population and to identify the most commonly used PGx drugs and thereby the most relevant PGx genes.

Materials and Methods

We conducted a retrospective, descriptive study using claims data from the Swiss health care insurance company Helsana.

Helsana is one of the leading health care insurance companies in Switzerland, covering approximately 1.2 million people (15% of the Swiss population) of all age groups with basic health care insurance across all 26 cantons of Switzerland.[25]

Helsana provides information on demographics as well as on claims for diagnostic evaluations and treatment in the outpatient setting. Information on over-the-counter (OTC) medication, life-style, or laboratory results are not available. Information on drugs is recorded using the Anatomical Therapeutic Chemical Classification System (ATC). The Helsana database has repeatedly been used for studies on drug utilization and drug safety.[26–29]

Helsana granted us access to an anonymized dataset from the database located at Helsana. The dataset covered demographics and drug claims for the period from January 1, 2016, to December 31, 2020. We selected PGx drugs using PGx dosing guidelines accessible on the Pharmacogenetic Knowledgebase (PharmGKB) in December 2021.[30] We excluded three dosing guidelines (for HMG CoA reductase inhibitors, hormonal contraceptives for systemic use, and antidepressants), for the analysis of the drugs with the highest user numbers, genes with the highest user numbers, and potential DGIs, as they did not focus on specific drugs, but rather on drug groups. Furthermore, we excluded 48 guidelines for drugs without recommendations.

We identified 90 drugs associated with variants in 24 genes as PGx drugs. Of these drugs, 19 were associated with multiple genes (Table 1).

We assessed PGx drug exposure in all registered persons, stratified by age and sex during the study period, for the individual years (2016, 2017, 2018, 2019, 2020) as well as for the entire five-year period 2016–2020. The term "five-year period" is used only in regard to individuals present in the study population for all five years.

We calculated absolute and relative numbers of PGx drug exposure, and ranked the drugs and their associated genes based on the number of exposed persons. Moreover, we calculated the mean number of any drug and PGx drugs claimed by each person.

We stratified the PGx drug claims by anatomical groups. The anatomical groups are based on the first level of the ATC. Furthermore, we ranked the PGx drugs and associated genes by number of persons with claims for these drugs. All

Table 1 PGx Drugs with Their Corresponding Genes

Gene	Gene Name	Drug
CACNA1S	Calcium voltage-gated channel subunit alpha1 S	Desflurane, enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine
CFTR	Cystic fibrosis transmembrane conductance regulator	Ivacaftor
CYP2B6	Cytochrome P450 2B6	Efavirenz
CYP2C9	Cytochrome P450 2C9	Acenocoumarol, celecoxib, fluindione, flurbiprofen, fosphenytoin, ibuprofen, lornoxicam, meloxicam, phenytoin, piroxicam, siponimod, tenoxicam, warfarin
CYP2C19	Cytochrome P450 2C19	Amitriptyline, citalopram, clomipramine, clopidogrel, dexlansoprazole, doxepin, escitalopram, imipramine, lansoprazole, omeprazole, pantoprazole, sertraline, trimipramine, voriconazole
CYP2D6	Cytochrome P450 2D6	Amitriptyline, aripiprazole, atomoxetine, brexipiprazole, clomipramine, codeine, desipramine, doxepin, eliglustat, flecainide, fluvoxamine, haloperidol, hydrocodone, imipramine, metoprolol, nortriptyline, ondansetron, paroxetine, pimozide, propafenone, risperidone, tamoxifen, tramadol, tropisetron, venlafaxine, zuclopenthixol
CYP3A4	Cytochrome P450 3A4	Tacrolimus
CYP3A5	Cytochrome P450 3A5	Tacrolimus
CYP4F2	Cytochrome P450 4F2	Warfarin
DPYD	Dihydropyrimidine dehydrogenase	Capecitabine, flucytosine, fluorouracil, tegafur
G6PD	Glucose-6-phosphate dehydrogenase	Rasburicase
HLA-A	Human leukocyte antigen A	Carbamazepine
HLA-B	Human leukocyte antigen B	Abacavir, allopurinol, carbamazepine, flucloxacillin, fosphenytoin, oxcarbazepine
IFNL3	Interferon lambda 3	Peginterferon alfa-2a, peginterferon alfa-2b, ribavirin
MT-RNR1	Mitochondrially encoded 12S RNA	Amikacin, gentamicin, kanamycin, paromomycin, plazomicin, streptomycin, tobramycin
NUDT15	Nudix hydrolase 15	Azathioprine, mercaptopurine, thioguanine
RARG	Retinoic acid receptor gamma	Daunorubicin, doxorubicin
RYR1	Ryanodine receptor 1	Enflurane, halothane, isoflurane, methoxyflurane, sevoflurane, succinylcholine
SLC8A3	Solute carrier family 8 member A3	Daunorubicin, doxorubicin
SLCO1B1	Solute carrier organic anion transporter family member 1B1	Atorvastatin, simvastatin
TPMT	Thiopurine S-methyltransferase	Azathioprine, cisplatin, mercaptopurine, thioguanine
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1	Atazanavir, irinotecan
UGT1A6	UDP glucuronosyltransferase 1 family, polypeptide A6	Daunorubicin, doxorubicin
VKORC1	Vitamin K epoxide reductase complex subunit 1	Acenocoumarol, fluindione, phenprocoumon, warfarin

registered persons were divided into age groups based on their age at the end of 2020 for the five-year period 2016–2020. For the individual years, the age at the end of the particular year was taken into account.

We extrapolated our results for the Helsana study population to the Swiss population Appendix Tables 1–3. The extrapolation factor (ef) is based on age, gender, and canton of residence of the person. It is provided annually by the

joint facility KVG and is individual for each person. The ef is used for risk balance among Swiss mandatory basic health insurances, therefore it is based on the total number of insured individuals of all Swiss insurance companies.[31]

All analyses were conducted using SAS 9.4 Software (SAS Institute Inc., Cary, NC).

According to article 22 of the Swiss Federal Law on data protection, ethics approval was not required, because the analyses were retrospective and anonymous.[32]

Results

Study Population

We identified 1 626 058 persons who were registered at Helsana for at least one year during the study period, with 885 866 (54.5%) of them being registered for the whole five-year period (2016–2020). Persons who were registered for the whole five-year period were aged between 0 and 109 years, with a mean age of 48.5 (±24.0) years. The majority (53.9%) of persons over the entire five-year period were 40 to 79 years old, and 52.4% were women. Details on the characteristics of the population for the individual years, as well as for the five-year period, are displayed in Table 2 and Appendix Table 1.

PGx Drugs

Drug claims were available for 95.0% of persons; of those, 74.7% were exposed to at least one PGx drug. During the five-year period, each person claimed 19.8 (±16.8) different drugs on average, including 2.0 (±2.1) PGx drugs on

Table 2 Characteristics of the Study Population

Prescribing Period	1-Year Periods					5-Year Period
	2016	2017	2018	2019	2020	2016–2020
Persons	**Number of persons [N, %]**					
All	1,169,302	1,105,027	1,138,659	1,198,081	1,315,606	885,866
Women	602,403, 51.5	571,944, 51.8	588,495, 51.7	617,015, 51.5	673,540, 51.2	464,064, 52.4
Men	566,899, 48.5	533,083, 48.2	550,164, 48.3	581,066, 48.5	642,066, 48.8	421,802, 47.6
Age	**Number of persons [N, %]**					
0–19 years	237,016, 20.3	220,720, 20.0	227,884, 20.0	242,712, 20.3	268,821, 20.4	140,200, 15.8
20–39 years	285,437, 24.4	258,500, 23.4	273,961, 24.1	297,492, 24.8	342,892, 26.1	177,612, 20.0
40–59 years	310,533, 26.6	292,866, 26.5	301,233, 26.5	317,953, 26.5	353,191, 26.8	244,634, 27.6
60–79 years	247,648, 21.2	243,628, 22.0	245,240, 21.5	248,473, 20.7	257,420, 19.6	233,076, 26.3
80–99 years	88,200, 7.5	88,858, 8.0	89,864, 7.9	90,963, 7.6	92,709, 7.0	89,779, 10.1
100–119 years	468, <0.1	455, <0.1	477, <0.1	488, <0.1	573, <0.1	565, 0.1
Persons with drug claims	**Number of persons [N, %]**					
Any drug	884,947, 75.7	839,290, 76.0	865,916, 76.0	908,307, 75.8	966,705, 73.5	841,491, 95.0
≥1 PGx drug	504,327, 43.1	480,033, 43.4	493,608, 43.3	517,873, 43.2	522,726, 39.7	662,157, 74.7
≥2 PGx drugs	234,601, 20.1	225,871, 20.4	230,863, 20.3	241,062, 20.1	239,530, 18.2	441,140, 49.8
≥3 PGx drugs	107,381, 9.2	103,207, 9.3	104,304, 9.2	108,384, 9.0	105,641, 8.0	281,862, 31.8
≥4 PGx drugs	45,679, 3.9	44,023, 4.0	43,663, 3.8	45,506, 3.8	43,308, 3.3	175,802, 19.8
≥5 PGx drugs	17,938, 1.5	16,997, 1.5	16,838, 1.5	17,647, 1.5	16,229, 1.2	106,255, 12.0
≥10 PGx drugs	85, <0.1	86, <0.1	79, <0.1	83, <0.1	56, <0.1	5960, 0.7
	Mean per person ± sd					
Drugs	6.2±7.3	6.4±7.4	6.4±7.4	6.3±7.3	5.8±7.0	19.8±16.8
PGx drugs	0.8±1.1	0.8±1.2	0.8±1.2	0.8±1.2	0.7±1.1	2.0±2.1

Abbreviations: N, number of persons; %, percentage of all persons present in the respective observation period; sd, standard deviation; PGx, pharmacogenetic.

average. The average number of PGx drug claims in the individual years remained largely stable at approximately 0.8 different PGx drugs per person.

Of the 90 assessed drugs with PGx recommendations (PGx drugs) (Table 1), 73 had been claimed at least once during the study period. Of the 17 remaining PGx drugs, 11 were not approved in Switzerland. The total number of PGx drug users present during the whole five-year period varied from one for imipramine to 423 442 for ibuprofen. The top three PGx drugs in regard to user numbers during the whole five-year period were ibuprofen, pantoprazole, and tramadol with 423 442, 313 206, and 129 217 users, respectively. Table 3 shows the number of users and the percentage of all persons in the respective observation period for the top 15 PGx drugs. The results for all assessed PGx drugs are available in the Appendix (Appendix Table 2).

Grouping the drugs according to their anatomical group revealed that, at least 9 of 10 PGx drug users were exposed to drugs of the musculo-skeletal system (31.0%), the alimentary tract and metabolism (26.9%), or the nervous system (20.7%) (Figure 1).

Genes Associated with PGx Drugs

Ranking the genes associated with the PGx drugs showed, *CYP2C9, CYP2C19*, and *CYP2D6* to be the genes with the highest numbers of persons exposed to at least one associated PGx drug during the whole five-year period (Table 4 and Appendix Table 3). No drug claim was associated with *CYP4F2*, as it is not involved in the metabolism of drugs approved on the Swiss market. *CYP2C19, CYP2C9, CYP2D6, SLCO1B1, HLA-B*, mitochondrially encoded 12S RNA *(MT-RNR1)*, and *VKORC1* were accountable for at least 95% of all potential DGIs throughout all time-periods (Figure 2).

Discussion

In this study, we determined the percentage of persons using PGx drugs, to provide evidence for a rational discussion on potential preemptive PGx testing in the Swiss population. Based on extrapolations from the Helsana population in this study, which includes 15% of the Swiss population, we estimated that 74.7% of the Swiss population were exposed to PGx drugs in a five-year period. PGx drugs with the highest number of exposed persons included non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, proton pump inhibitors (PPIs) such as pantoprazole or omeprazole, and

Table 3 Top 15 PGx Drugs Stratified by Prescribing Periods 2016–2020

Drug	1-Year Periods					5-Year Period
	2016	2017	2018	2019	2020	2016–2020
	Number of persons [N, %]					
Ibuprofen	206,159, 17.6	195,631, 17.7	210,627, 18.5	231,131, 19.3	220,863, 16.8	423,442, 47.8
Pantoprazole	160,042, 13.7	153,933, 13.9	159,591, 14.0	167,148, 14.0	173,956, 13.2	313,206, 35.4
Tramadol	50,396, 4.3	46,230, 4.2	45,027, 4.0	45,015, 3.8	44,768, 3.4	129,217, 14.6
Codeine	34,778, 3.0	31,906, 2.9	32,137, 2.8	36,777, 3.1	29,379, 2.2	100,312, 11.3
Atorvastatin	60,349, 5.2	60,752, 5.5	61,474, 5.4	63,140, 5.3	66,423, 5.0	88,948, 10.0
Omeprazole	27,361, 2.3	23,862, 2.2	22,337, 2.0	21,675, 1.8	21,398, 1.6	50,206, 5.7
Metoprolol	38,042, 3.3	36,872, 3.3	36,727, 3.2	36,764, 3.1	37,456, 2.8	49,893, 5.6
Escitalopram	25,322, 2.2	24,589, 2.2	25,579, 2.2	26,654, 2.2	27,874, 2.1	46,775, 5.3
Ondansetron	12,915, 1.1	13,566, 1.2	14,152, 1.2	16,965, 1.4	15,358, 1.2	44,673, 5.0
Tobramycin	9131, 0.8	9170, 0.8	8939, 0.8	10,009, 0.8	8138, 0.6	29,799, 3.4
Allopurinol	18,021, 1.5	17,775, 1.6	18,037, 1.6	18,258, 1.5	18,806, 1.4	26,433, 3.0
Simvastatin	23,139, 2.0	20,853, 1.9	18,869, 1.7	17,250, 1.4	16,425, 1.2	25,038, 2.8
Celecoxib	8793, 0.8	8478, 0.8	8449, 0.7	8534, 0.7	8627, 0.7	24,480, 2.8
Clopidogrel	12,629, 1.1	12,301, 1.1	12,423, 1.1	12,586, 1.1	12,563, 1.0	23,359, 2.6
Trimipramine	8381, 0.7	7488, 0.7	7352, 0.6	7344, 0.6	7660, 0.6	17,121, 1.9

Note: The drugs are ranked by the number of exposed persons in the 5-year period 2016–2020.
Abbreviations: N, number of persons in the respective observation period; %, percentage of all persons present in the respective observation period; PGx, pharmacogenetic.

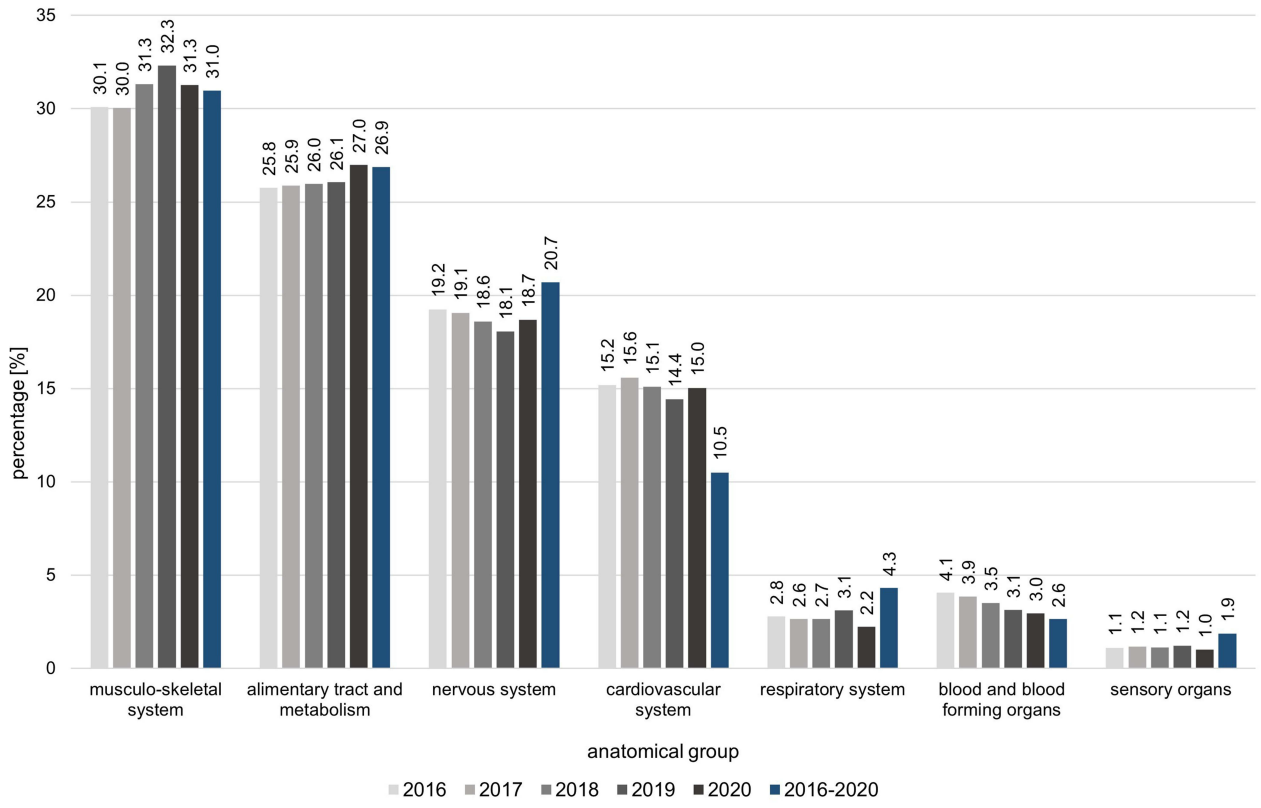

Figure 1 Percentage of persons with PGx drug claims stratified by anatomical groups for the five-year period 2016–2020 and stratified by year. The anatomical groups are ranked by the proportion of persons with PGx drug claims in the 5-year period 2016–2020.

Notes: Anatomical groups excluded, because ≤1.0%: antineoplastic and immunomodulating agents, dermatologicals, antiinfectives for systemic use, various, genitourinary system and sex hormones, systemic hormonal preparations, excl. sex hormones and insulins and antiparasitic products, insecticides and repellents. As persons may use multiple drugs, they can appear in several groups.

Abbreviation: PGx, pharmacogenetic.

weak opioids such as tramadol or codeine. Seven genes (*CYP2C19, CYP2C9, CYP2D6, SLCO1B1, HLA-B, MT-RNR1*, and *VKORC1*) were responsible for 95% of all potential DGIs.

Recent studies from the United Kingdom (UK), the United States of America (USA), the Netherlands, Denmark, and Singapore underpin our results.[11,12,33–37] Kimpton et al studied 63 PGx drugs in a five-year period in English primary care data of patients older than 50 years. There, 71% were exposed to at least one, 47% to at least two, and 7% to at least five PGx drugs. Each person used an average of 1.7 PGx drugs.[33] A study in medical home patients in the USA found that 64.8% of patients used at least one PGx drug, 40% at least two, and 5.9% at least five.[35] Our results showed comparable percentages in a larger and younger population, although we observed a higher proportion of persons taking multiple PGx drugs (12.0% with at least 5 PGx drugs). Youssef et al assessed 56 PGx drugs in primary care in the UK and observed that four genes (*CYP2C19, CYP2D6, SLCO1B1*, and *HLA-B*) were associated with more than 95% of all potential DGIs.[34] Kimpton et al found that only three genes (*CYP2D6, CYP2C19*, and *SLCO1B1*) accounted for over 95% of all potential DGIs.[33] In our study, seven genes (*CYP2C19, CYP2C9, CYP2D6, SLCO1B1, HLA-B, MT-RNR1*, and *VKORC1*) were responsible for 95% of all potential DGIs. Compared to other studies, *CYP2C9* ranked higher in our study because ibuprofen has recently been added to the list of drugs associated with *CYP2C9*, and we therefore included it in our list.[33] In earlier studies the ibuprofen-*CYP2C9* interaction was not included. Since ibuprofen is a commonly prescribed drug, this might explain the rather substantial differences we observed for this gene in comparison to previous studies. The mitochondrial gene *MT-RNR1* is considered a relevant pharmacogene, as genetic variants are linked to an increased risk of hearing loss associated to the use of aminoglycoside antibiotics.[38,39] The *MT-RNR1* gene ranked high in our list due to the large numbers of tobramycin claims. Those claims, however, were mainly ophthalmological

Table 4 Genes Associated with PGx Drugs

Gene	1-Year Periods					5-Year Period
	2016	2017	2018	2019	2020	2016–2020
	Number of persons [N, %]					
CYP2C9	223,029, 44.2	210,415, 43.8	224,331, 45.4	243,763, 47.1	231,868, 44.0	442,352, 97.6
CYP2C19	227,805, 45.2	216,496, 45.1	221,405, 44.9	229,097, 44.2	236,603, 45.3	379,656, 83.8
CYP2D6	144,502, 28.7	137,438, 28.6	137,843, 27.9	145,186, 28.0	139,557, 26.7	271,755, 60.0
SLCO1B1	82,288, 16.3	79,884, 16.6	78,470, 15.9	78,392, 15.1	80,662, 15.4	103,334, 22.8
HLA-B	21,776, 4.3	21,349, 4.4	21,525, 4.4	21,714, 4.2	22,200, 4.2	31,877, 7.0
MT-RNR1	9186, 1.8	9193, 1.9	8970, 1.8	10,035, 1.9	8170, 1.6	29,898, 6.6
VKORC1	20,087, 4.0	17,307, 3.6	15,099, 3.1	13,103, 2.5	11,365, 2.2	18,223, 4.0
CYP3A4	5324, 1.1	5256, 1.1	5523, 1.1	6013, 1.2	6341, 1.2	14,986 3.3
CYP3A5	5324, 1.1	5256, 1.1	5523, 1.1	6013, 1.2	6341, 1.2	14,986 3.3
CACNA1S	3975, 0.8	4074, 0.8	4390, 0.9	4380, 0.8	4360, 0.8	14,380, 3.2
RYR1	3783, 0.8	3888, 0.8	4200, 0.9	4167, 0.8	4123, 0.8	13,673, 3.0
DPYD	2452, 0.5	2294, 0.5	2432, 0.5	2541, 0.5	3187, 0.6	7802, 1.7
HLA-A	2356, 0.5	2192, 0.5	2096, 0.4	2076, 0.4	2037, 0.4	3133, 0.7
TPMT	2034, 0.4	1901, 0.4	1914, 0.4	1866, 0.4	1842, 0.4	3088, 0.7
NUDT15	1836, 0.4	1734, 0.4	1750, 0.4	1693, 0.3	1614, 0.3	2589, 0.6
RARG	394, 0.1	358, 0.1	352, 0.1	362, 0.1	427, 0.1	1093, 0.2
SLC8A3	394, 0.1	358, 0.1	352, 0.1	362, 0.1	427, 0.1	1093, 0.2
UGT1A6	394, 0.1	358, 0.1	352, 0.1	362, 0.1	427, 0.1	1093, 0.2
CYP2B6	399, 0.1	321, 0.1	243, <0.1	172, <0.1	129, <0.1	369, 0.1
IFNL3	161, <0.1	120, <0.1	71, <0.1	65, <0.1	71, <0.1	234, 0.1
UGT1A1	185, <0.1	123, <0.1	91, <0.1	70, <0.1	48, <0.1	170, <0.1
CFTR	0, 0.0	0, 0.0	0, 0.0	1, <0.1	18, <0.1	16, <0.1
G6PD	1, <0.1	4, <0.1	4, <0.1	8, <0.1	5, <0.1	6, <0.1
CYP4F2	0, 0.0	0, 0.0	0, 0.0	0, 0.0	0, 0.0	0, 0.0

Notes: The genes are ranked by the highest number of persons with claims for associated drugs in the 5-year period 2016–2020. Percentages can add up to over 100%, as some people were exposed to more than one PGx drug.

Abbreviations: N, number of persons; %, percentage of all persons with PGx drug claims in the respective observation period; PGx, pharmacogenetic.

preparations which have a limited systemic availability and therefore have only a decreased risk for hearing loss. Thus, a limitation of our current study is that, we did not account for differences in formulations or by route of application, which certainly impacts the relevance of a potential DGI.

The majority of PGx drug users received their PGx drugs due to pain, inflammation, or cardiovascular, gastrointestinal, or psychiatric/neurologic problems. This is consistent with findings of many other studies.[12,34,36,37] In a Danish population-based study, the top six drugs regarding number of users were simvastatin, contraceptives with estrogens, pantoprazole, metoprolol, tramadol, and atorvastatin.[11] With the exception of estrogens, which have a limited availability in our data because hormonal contraceptives are not reimbursed by Swiss basic health care insurances,[40] these drugs were also prevalent in our population. In general, differences in the reported results often emerged from different numbers of included PGx-drug combinations and from changes in recommendations over time. The CPIC Guideline for *CYP2C9* and Nonsteroidal Anti-inflammatory Drugs published in 2020, for example, provided new dosing recommendations for ibuprofen.[41] Studies published prior to this change did not include ibuprofen. In addition, different drugs are on the market in different countries. For example, warfarin, associated with *CYP2C9, CYP4F2*, and *VKORC1*, is not approved in Switzerland but in Denmark, the UK, and the USA. Thus, warfarin was one of the most prevalent PGx drugs in studies in these countries.[11,33–36]

It is a strength of our study that we included different sources for PGx recommendations to allow a comprehensive analysis, but we restricted the analysis to drugs with PGx guidelines with recommendations to assure that they are relevant for current clinical decision making. Our analysis relies on claims data and is therefore affected by the

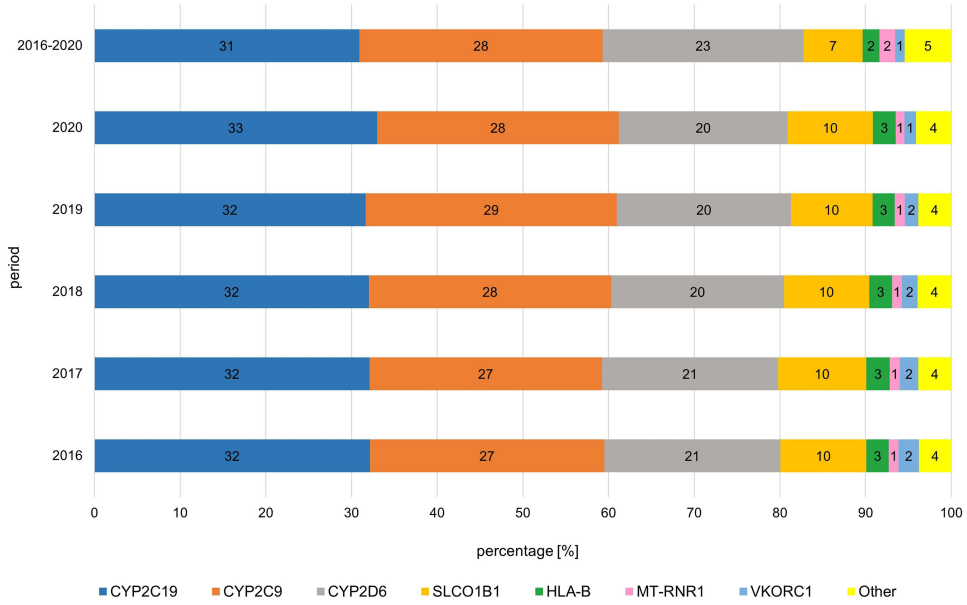

Figure 2 Proportion of all potential drug-gene interactions, stratified by prescribing periods 2016–2020. The potential drug-gene interactions are ranked by the highest proportion of all potential drug-gene interactions in the 5-year period 2016–2020. Other includes *CYP3A4, CYP3A5, CACNA1S, RYR1, DPYD, HLA-A, TPMT, NUDT15, RARG, SLC8A3, UGT1A6, CYP2B6, IFNL3, UGT1A1, CFTR, G6PD*, and *CYP4F2*.

limitations associated with claims data. We had no information on OTC use. Out of the 90 identified PGx drugs, five (codeine, flurbiprofen, ibuprofen, omeprazole, and pantoprazole) are available as OTC drugs but also as prescription drugs in Switzerland.[42] Therefore, our results for drugs which can be prescribed but are also available as OTC drugs will most likely be underestimated. Furthermore, we did not have information on drugs taken in hospitals because they are billed at a case rate. Our study probably underestimated the use of drugs that are typically used in hospitals. In addition, there is a certain (small) amount of out-of-pocket payment on an annual basis before the health care insurance starts to reimburse the bills in Switzerland. As out-of-pocket payment affects acute medication more than chronic medication, we might have missed a small amount of drug claims, again leading to a slight underestimation of acute medication in our results. Moreover, health care claims data do not provide evidence on whether or not the medication was actually taken by the persons. The exposure to PGx drugs is therefore likely to be lower in reality if the medication was not taken.

We provided the results for the Helsana population and extrapolated to the Swiss population, as we were interested in the potential for preemptive PGx testing in the Swiss population. The extrapolated results were similar to the ones of the Helsana population, but the fluctuation during the five-year period was marked, and only about 50% of persons registered in 2016 were still registered in 2020. Since Swiss insurances are private companies, the prices for basic insurance vary every year. Swiss people are free to choose and to switch their insurance on an annual basis.[22] As a result, some people indeed change their insurance every year, leading to this fluctuation. Compared to the persons in individual year groups, the persons present for the whole five-year period generally tended to have more different drugs on average (19.8 drugs vs 5.8–6.4 drugs) as well as more PGx drugs (2.0 drugs vs 0.7–0.8 drugs). During the one-year periods, the percentage of persons with drug claims was lower (73.5–76.0%) than during the five-year window (95.0%). The proportion of persons with drug claims was slightly lower in the year 2020. The Covid-19 pandemic and the resulting lockdowns with postponed doctor's appointments could be a reason for this finding. Czeisler et al found that 41% of adults in the USA postponed or evaded doctor's appointments during Covid-19.[43] A delay in drug claims registration might be another reason.

Conclusion

As far as we know, this is the first study that assessed the exposure of PGx drugs using Swiss health care claims data on a population level. Our findings demonstrated that the prevalence of PGx drug prescriptions is high and that a large proportion of the Swiss population could benefit from preemptive PGx testing, as more than 78% of persons with drug

claims during a five-year period were exposed to PGx drugs. The most commonly used PGx drugs included NSAIDs, PPIs, and weak opioids. Because we identified a number of relevant genes such as *CYP2C19, CYP2C9, and CYP2D6*, we propose a preemptive testing panel rather than single-gene testing. The assessment of the clinical impact of preemptive PGx testing on a population level was beyond the scope of this study. However, it will be a necessary step that requires further studies when evaluating the potential risks and benefits of PGx for the Swiss population.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to confidentiality requirements issued by Helsana. Analysis codes and datasets can be made available by the corresponding author (s.allemann@unibas.ch) upon reasonable request and with permission of Helsana.

Ethics Approval

According to article 22 of the Swiss Federal Law on data protection, ethics approval was not required, because the analyses were retrospective and anonymous.[32]

Disclosure

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