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ARTICLE

Prevalence of actionable pharmacogenetic variants and high-risk drug prescriptions: A Swiss hospital-based cohort study

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Abstract

Drug type and dosing recommendation have been designed and optimized based on average response in the general population. Yet, there is significant inter-individual variability in drug response, which results in treatment inefficacy or adverse drug reactions in a subset of patients. This is partly due to genetic factors that typically affect drug metabolism or clearance. To verify the relevance and applicability of international pharmacogenetic guidelines in the Swiss population, we genotyped 1533 patients from a hospital-based biobank who received at least 30 different drugs, as documented in their electronic health record. We then assessed the prevalence of clinically actionable variants in 13 high-risk pharmacogenes. We compared the allele frequencies obtained in the hospital-based cohort with those of a Swiss population-based cohort of 4791 individuals. The prevalence of clinically actionable variants was comparable between the two cohorts, with most study participants (97.3%) carrying at least one actionable pharmacogenetic variant. We then assessed the frequency of high-risk prescriptions due to actionable gene–drug interactions and observed that 31% of patients in the hospital-based cohort were prescribed at least one drug for which they carried a high-risk variant, and for which international guidelines recommend a change of drug or dosage. Our analysis confirms the high prevalence of actionable pharmacogenetic variants in the Swiss population. It also shows that a substantial minority of patients are exposed to drugs for which they carry potentially problematic variants. Implementing a genetically informed approach to drug prescribing could have a positive impact on the quality of healthcare delivery.

Preliminary results of this work have been previously presented as a poster at the 56th Annual Conference of the European Society of Human Genetics (ESHG), June 10–13, 2023, Glasgow, Scotland.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

There is considerable inter-individual variability in drug response, which can lead to complete inefficacy or potential adverse reactions. This variability can be influenced by genetic factors, highlighting the complex interplay between an individual's genetic makeup and their response to pharmacotherapy.

WHAT QUESTION DID THE STUDY ADDRESS?

The study provided the frequency of actionable pharmacogenetic variants in the Swiss population and the prevalence of high-risk prescriptions due to gene–drug interactions, thereby evaluating the potential utility of integrating pharmacogenetic testing into routine clinical practice to enhance personalized medicine and optimize drug safety and efficacy.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study showed a high prevalence of actionable pharmacogenetic variants among the Swiss population, with almost all participants carrying at least one actionable pharmacogenetic allele. Furthermore, it underscored the common occurrence of high-risk exposures to potentially harmful gene–drug interactions within hospital settings, emphasizing the need for integrating genetically informed approaches to drug prescribing.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The study's findings could drive a paradigm shift by supporting the integration of pharmacogenetic testing into routine patient care, leading to more personalized medication regimens and improved drug safety and efficacy. They could also fuel translational science efforts toward developing tailored testing panels and novel therapeutic approaches to optimize drug selection and dosing, ultimately enhancing patient outcomes.

INTRODUCTION

While most medical interventions have been developed around a target population representing the average individual, we are entering an era of personalized medicine where prescriptions and procedures are designed to benefit each individual in a unique way. A major application of this personalized approach to medicine is pharmacogenetics, which seeks to understand the impact of genetic factors on drug response. The aim is to improve the benefit/risk ratio of pharmacotherapy by adjusting drug selection and dosage to the unique genetic makeup of the individual.[1]

Drug dosage recommendations are optimized in dose-ranging studies based on the average response of clinical trial participants. Yet, there is significant inter-individual variability in drug actions, sometimes resulting in complete inefficacy or in dangerous adverse drug reactions (ADRs). This variability can be partly attributed to genetic factors that typically affect pharmacokinetics—that is, drug absorption, distribution, metabolism, or elimination—or pharmacodynamics.[2–4] Recent advances in genotyping and sequencing technology and in bioinformatics revealed a plethora of associations between genetic variants and drug responses using agnostic genome-wide analyses in large populations.[5] Two publicly available directories based on seminal references classify relevant gene–drug interactions to improve drug safety and efficacy: the Pharmacogenomics Knowledge Base (PharmGKB), a comprehensive database reporting gene–drug interactions, and the Clinical Pharmacogenetics Implementation Consortium (CPIC) that provides guidelines for the use of pharmacogenetic tests in clinical decision making and practice.[6,7]

Previous studies have shown that around 97%–98% of individuals carry at least one actionable variant in a gene of demonstrated pharmacological importance (pharmacogene), suggesting that genetically guided drug prescription could be more effective and less toxic than current standard-of-care based on one-fit-all approaches.[8–10] However, before they can be recommended and deployed in clinical practice, pharmacogenetic tests must meet standard criteria regarding their analytical validity (i.e., test accuracy), clinical validity (i.e., diagnostic performance), and clinical utility (i.e., risk/benefit ratio, alternative therapies, cost-effectiveness).[5] These criteria determine the actionability of a gene–drug

pair and help establish prescription guidelines. Currently, the list of gene–drug pairs with sufficient evidence to recommend clinical actions remains relatively short (about 200 gene–drug pairs with therapeutic recommendations based on significant evidence of actionability; see www.pharmgkb.org/guidelineAnnotations) and their routine testing in clinical practice is rare.[11] Clinical trials are needed to demonstrate which pharmacogenetic tests improve clinical outcomes.[12–14] In addition, the implementation of pharmacogenetics in healthcare systems will require the implementation of standardized workflows to automatically incorporate results into clinical electronic health records (EHR), training programs for physicians and pharmacists to become familiar with the associated prescribing recommendations, as well as decisions by policymakers regarding accreditation and reimbursement for such tests.

In Switzerland, progress has remained limited, and recent discoveries in pharmacogenetics have not been integrated into current practice.[15] To date, only five actionable drugs require testing, as recommended by the Swiss Society for Clinical Pharmacology and Toxicology (SSPTC, version 3.0 from July 2019—www.bag.admin.ch/ref), and are covered by Swiss health insurance: abacavir, carbamazepine, thiopurines (azathioprine, 6-mercaptopurine), fluoropyrimidines (fluorouracil and capecitabine), and irinotecan. We report a study specific to the Swiss population to (a) measure the frequency of actionable pharmacogenetic variants in local hospital- and population-based cohorts, and (b) assess the frequency of exposure to high-risk prescriptions due to actionable gene–drug interactions in highly medicated patients.

METHODS

Study participants

The Lausanne University Hospital (CHUV) Genomic Biobank (BGC), created by the CHUV and the University of Lausanne in 2013, is a hospital-based biobank that collects DNA samples for research purposes. BGC participants provide a general consent that allows the use of their coded health-related data and samples for research projects. The Ethics Committee of canton Vaud approved the BGC (ref 144/12).

CoLaus|PsyCoLaus is a longitudinal population-based study initiated in 2003 in Lausanne, Switzerland.[16] The study involves 6734 European ancestry participants who were randomly chosen from the general population of Lausanne. All participants signed a consent form and agreed to take part in longitudinal examinations. They provided detailed phenotypic information through questionnaires and interviews, as well as clinical and biological data. The Ethics Committee of canton Vaud approved the CoLaus|PsyCoLaus study (ref 16/03).

For this study, we selected (a) 1533 highly medicated participants from the BGC (i.e., with a history of at least 30 different drugs prescribed in their electronic health record (EHR)), and (b) 4791 individuals from the CoLaus|PsyCoLaus study with available genotyping data. The study protocol and all amendments were approved by the Ethics Committee of canton Vaud (study ID: 2020-00589). The study was conducted in accordance with the Declaration of Helsinki and the Swiss Human Research Act (RS 810.30).

Genome-wide genotyping data

BGC samples were genotyped using the Illumina Global Screening Array version 2 with a multi-disease drop-in panel (GSA-MD), designed specifically to genotype single-nucleotide polymorphisms (SNPs) across populations for genome-wide coverage of common variation and relevant disease loci. Raw genotyping data were then filtered using standard quality controls: exclusion of markers with missing data (call rates <90%), and deviation of allelic/genotypic frequencies from Hardy–Weinberg equilibrium (HWE, 1×10^{-10}). Once high-quality data were obtained, missing genotypes were phased with SHAPEIT4, and imputed with IMPUTE 5 using the 1000 Genomes phase 3 reference panel and a high imputation confidence (INFO score > 0.8).[17] CoLaus|PsyCoLaus samples were genotyped using the BB2 GSK-customized Affymetrix Axiom Biobank array. Quality control procedures and genotype imputation for these samples have been previously described.[18] After genotype imputation and quality control procedures, approximately nine million SNPs were available for analysis in both cohorts.

Pharmacogenetic allele calling

To assess the prevalence of known pharmacogenetic variants, we selected all pharmacogenes with demonstrated clinical relevance (i.e., established effect on protein functionality and available CPIC guidelines): Cytochrome P450 2B6 (*CYP2B6*), *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *F5*, *HLA-A*, *HLA-B*, *HLA-DRB1*, *SLCO1B1*, *TPMT*, and *VKORC1*.[19] We did not include *UGT1A1* because available genotyping data were not sufficient to accurately determine an individual's *UGT1A1* metabolizer phenotype.

For the genes covered by Stargazer (*CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*, *CYP3A5*, *DPYD*, *SLCO1B1*, and *TPMT*), a bioinformatics tool specifically designed to call star alleles from genotyping data using statistical haplotype phasing, we extracted information on functional consequences.[20] The term "star allele" refers to the different haplotypes of

certain pharmacogenes, each of which is identified with a unique star system (e.g., 1*/2*). These star alleles are listed on gene-specific tables that define each allele and are used to predict metabolizer status.[21] SNPs and insertion/deletion variants in the eight selected genes covered by Stargazer were extracted from the Variant Call Format (VCF) files using BCFtools (version 1.10.2) and phased using Beagle (version 4.1) and the 1000 Genomes Project haplotype reference panel.[20,22,23] Phased variants and insertion/deletions were then matched to star alleles based on their corresponding definition table. The star alleles were ultimately translated into functional metabolizing classes. This was achieved by assigning to each allele an "activity value" that reflects the function rate of the metabolic enzyme. Subsequently, the activity values of both alleles were aggregated to derive an activity score corresponding to individual metabolizing profiles, ranging from poor to ultrarapid.[24] The metabolizer status for *F5* and *VKORC1* genes was defined by the genotypes at the single causal SNPs, rs6025 (c.1601G>A) and rs9923231 (c.-1639G>A), using PLINK v2.0.[25] For *HLA-A*, *HLA-B*, and *HLA-DRB1* genes, we used SNP2HLA v1.0.3 with the T1DGC reference panel to impute human leukocyte antigen (*HLA*) alleles from SNP genotype data at 4-digit allelic resolution.[26]

Prevalence of actionable pharmacogenetic variants

We calculated the proportion of study participants carrying actionable variants in both the BGC and the CoLaus|PsyCoLaus datasets and performed Chi-squared tests of equal frequencies to compare the two cohorts. An "actionable" metabolizer status was defined as any metabolizer status that could lead to a change in the prescription of at least one drug, such as a drug change or dose adjustment, in accordance with CPIC guidelines. This definition fails to consider clinical factors beyond drug and genotype, such as age, organ deficiencies, and drug interactions that might significantly influence the application of pharmacogenetic results, but these aspects are not within the scope of this article. We also calculated the total number of actionable phenotypes for each study participant.

Evaluation of high-risk drug use

Phenotypic data from the BGC, including demographic information (age and sex), and drug prescriptions (ATC codes), were extracted from the EHR using the privacy-preserving tools developed by the Direction of Information Systems of the hospital.[27] The period covered for each patient spans the entire available EHR, which varies between patients but includes all available data from the first visit to the date of data extraction. ATC codes (here, used interchangeably with the term Drugs) are used to classify medications based on their therapeutic properties and anatomical areas of action. Typically, these drugs contain different active substances; however, there may be exceptions when drugs with different ATC codes contain the same active ingredient but are formulated differently or used for different indications or routes of administration. For this study, we selected all drugs known to interact with one or more of the 13 selected pharmacogenes with the highest level of evidence (level 1A) as defined by CPIC,[28,29] leading to the inclusion of 133 ATC codes (substance or combination of substances) covering 61 drugs in total. For each drug, we extracted prescription information from the EHR by matching ATC codes. Using CPIC recommendations, we then defined gene-status-drug trios to account for differences in guidelines at the drug and metabolizer status levels. For example, *DPYD* (gene) is a poor metabolizer (metabolizer status) exposed to Fluorouracil (drug). Additionally, we differentiated whether a change of medication (alternate drug) or a dose adjustment (adjust dosage) is recommended for these observations. This allowed us to calculate the proportion of participants who received high-risk prescription(s) due to potential pharmacogenetic interactions, that is, individuals who carry at least one variant predicted to alter drug metabolism and who were prescribed the drug for which CPIC guidelines recommend modifying the drug or adjusting the dose. Evaluation of guidelines for 13 genes led to categorization of actionability for 61 drugs, which included 71 gene–drug pairs and 135 gene-status-drug trios.

RESULTS

Demographic characteristics

We included a total of 1533 participants from the hospital-based BGC cohort. The demographic and clinical information is presented in Table 1. Participants were selected on the basis of the high number of distinct ATC codes listed in their hospital records (30 or more). On average, individuals were prescribed 53 distinct drugs, with a range from 30 to 143 drugs during the period covered by their EHR. The median age of the participants was 68 years, ranging from 20 to 90.

Prevalence of clinically actionable variants

As shown in Figure 1a, the pharmacogenes that fulfilled the inclusion criteria and met the indicated levels of association evidence were *CYP2B6*, *CYP2C9*, *CYP2C19*, *CYP2D6*,

TABLE 1 Demographic and clinical characteristics of study samples.

Variable	BGC cohort ($N=1533$)
Age (mean (SD))	68.05 (13.26); 257 unknown
Sex = Male (N (%))	885 (57.7%)
Ancestry (N (%)):	
European	1452 (94.7%)
Admixed	39 (2.5%)
African	30 (2.0%)
South Asian	7 (0.5%)
East Asian	5 (0.3%)
Drugs prescribed (mean (range))	53 (30–143)

CYP3A5, *DPYD*, *F5*, *HLA-A*, *HLA-B*, *HLA-DRB1*, *SLCO1B1*, *TPMT*, and *VKORC1*. The genetically predicted metabolizer status were categorized as (a) carrier or non-carrier (i.e., tested positive or negative) for *F5* and *VKORC1* variants, and HLA alleles, or (b) as genetically poor, intermediate, normal, rapid, and ultrarapid metabolizer for all other pharmacogenes. The number of actionable genes among BGC participants, and the specific frequencies of genotype-predicted metabolizer status for each of the 13 genes are presented in Figure 1a and Table 2, respectively. Among BGC participants, we observed that the most prevalent actionable genes were *CYP2C19* (54.73%), *CYP2B6* (44.02%), *CYP2D6* (40.28%), and *CYP2C9* (39.97%) (Figure 1a).

Almost all BGC participants (97.26%) carried at least one actionable pharmacogenetic allele as per CPIC guidelines, indicating that these individuals carry a variant for which there is sufficient evidence to support specific prescribing actions based on genetic information if exposed to relevant medications. Furthermore, 82.58% of individuals carried at least two actionable alleles, and 54.86% carried at least three. Two participants exhibited a maximum of seven actionable alleles. Details of the observed prevalences are shown in Figure 1b.

We then compared these prevalences to the ones of the population-based CoLaus|PsyCoLaus study. Baseline characteristics of the CoLaus|PsyCoLaus study participants are shown in Table S1. The prevalence of clinically actionable variants was found to be comparable between the hospital-based and the population-based cohorts. The most frequent actionable genes were *CYP2C19* (56.22%), *CYP2B6* (40.83%), *CYP2D6* (39.06%), and *CYP2C9* (38.41%) (Table S2). The Chi-squared tests of equal frequencies did not reveal significant differences in the frequencies of actionable phenotypes between the two cohorts, except for *CYP3A5* ($p=1.68\times10^{-4}$) and *CYP2B6* ($p=3.08\times10^{-2}$). In total, 96.81% of the genotyped participants of the CoLaus|PsyCoLaus

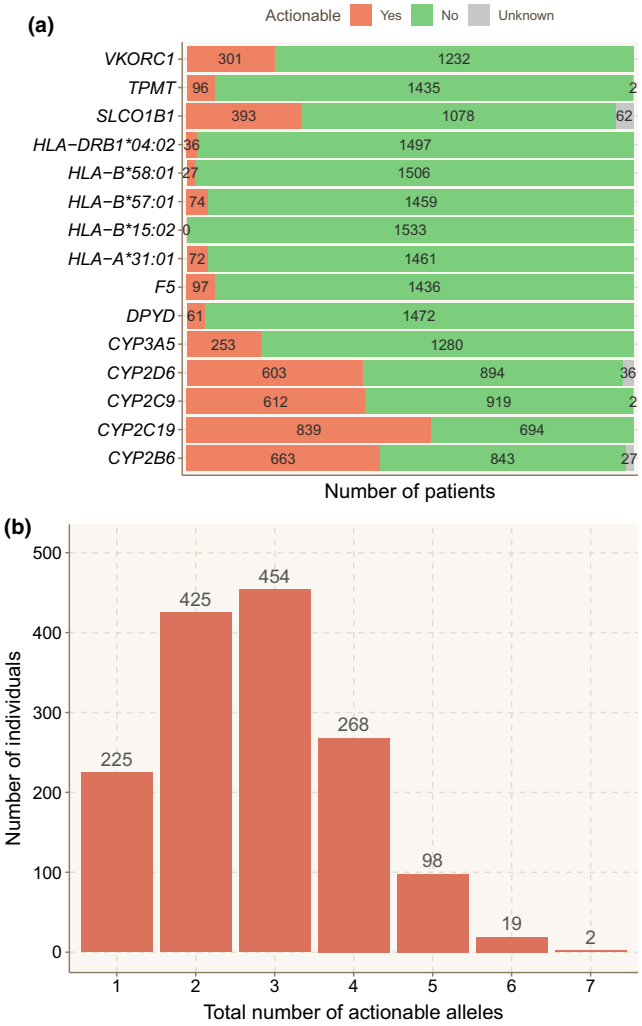

FIGURE 1 Prevalence of actionable alleles in the BGC cohort. (a) Proportion of participants carrying an actionable allele/abnormal metabolizer status for each gene. (b) Distribution and counts of total number of actionable alleles across participants.

study carried at least one actionable genotype, 81.38% carried at least two, and 50.26% carried at least three genotypes (Figure S1). Finally, the observed prevalences were also consistent with the reported actionable allele frequencies in European populations.[9,30,31]

(High-risk) drug prescriptions in the BGC

Of a total of 6977 prescriptions recorded in their EHR (a prescription corresponds to a unique combination of patient ID and drug name, that is, not including multiple prescriptions for the same drug, prescriptions followed by a change in dose or prescriptions for the same drug under different hospital stay number), tramadol (opioid analgesic) was the most frequently prescribed drug with a total of 1179 prescriptions, followed by ondansetron ($N=939$) (antiemetic medication) and pantoprazole ($N=569$) (proton pump inhibitor)

TABLE 2 Number and percentage of actionable phenotypes per gene in the BGC cohort.

Gene	Actionable	Poor	Intermediate	Normal	Rapid	Ultrarapid	Unknown
CYP2B6 (*N* = 1506)	663 (44.02%)	100 (6.64%)	563 (37.38%)	814 (54.05%)	27 (1.79%)	2 (0.13%)	27
CYP2C9 (*N* = 1531)	612 (39.97%)	NA	612 (39.97%)	919 (60.03%)	NA	NA	2
CYP2C19 (*N* = 1533)	839 (54.73%)	46 (3.00%)	340 (22.18%)	694 (45.27%)	386 (25.18%)	67 (4.37%)	0
CYP2D6 (*N* = 1497)	603 (40.28%)	84 (5.61%)	519 (34.67%)	894 (59.72%)	NA	NA	36
CYP3A5 (*N* = 1533)	253 (16.50%)	1280 (83.50%)	241 (15.72%)	12 (0.78%)	NA	NA	0
DPYD (*N* = 1533)	61 (3.98%)	2 (0.13%)	59 (3.85%)	1472 (96.02%)	NA	NA	0
SLCO1B1 (*N* = 1471)	393 (26.72%)	55 (3.74%)	338 (22.98%)	569 (38.68%)	509 (34.60%)	NA	62
TPMT (*N* = 1531)	96 (6.27%)	3 (0.20%)	93 (6.07%)	1435 (93.73%)	NA	NA	2
Gene	**Actionable**	**No risk**	**Increased risk**				
F5 (*N* = 1533)	97 (6.33%)	1436 (93.67%)	97 (6.33%)				
*HLA-A*31:01* (*N* = 1533)	72 (4.70%)	1461 (95.30%)	72 (4.70%)				
*HLA-B*15:02* (*N* = 1533)	0 (0.00%)	1533 (100.00%)	0 (0.00%)				
*HLA-B*57:01* (*N* = 1533)	74 (4.83%)	1459 (95.17%)	74 (4.83%)				
*HLA-B*58:01* (*N* = 1533)	27 (1.76%)	1506 (98.24%)	27 (1.76%)				
*HLA-DRB1*04:02* (*N* = 1533)	36 (2.35%)	1497 (97.65%)	36 (2.35%)				
VKORC1 (*N* = 1533)	301 (19.63%)	1232 (80.36%)	301 (19.63%)				

Note: Green cells represent non-actionable metabolizer status, and orange cells represent phenotypes considered actionable. The "Actionable" column represents the sum of actionable phenotypes. The last column shows the number of individuals that have not been classified.

(Figure 2). Other frequently prescribed drugs included atorvastatin, ibuprofen, acenocoumarol, and clopidogrel, with prescription numbers ranging from 534 to 404.

We next focused on high-risk prescription, referring to the prescription of a drug to an individual who carries an actionable gene variant that is known to interact with that specific drug and for which CPIC guidelines recommend modifying the drug or adjusting the dose. Of the 6977 prescriptions, nearly 10% (*N* = 657) were identified as high-risk prescriptions, with approximately one third (31.05%) of BGC participants prescribed at least one drug of concern (Figure 3a). The most frequently prescribed drugs with potential risks for adverse reactions due to individual genetic make-up were atorvastatin (132 times), clopidogrel (105 times), and simvastatin (90 times), all of which play a crucial role in the management of cardiovascular conditions. Atorvastatin and simvastatin are HMG-CoA reductase inhibitors, widely prescribed to lower cholesterol levels and thus the risk of cardiovascular events. Clopidogrel is an antiplatelet agent commonly used to prevent blood clots and thrombosis. These high-risk prescriptions may require substitution of the prescribed drugs for alternatives or adjustment of their dosage. A total of 205 individuals were prescribed at least one drug for which the guidelines recommend an alternative, 181 were prescribed at least one drug requiring a dosage adjustment, and 90 individuals were exposed to both (Figure 3b).

The three genes associated with the highest observed numbers of high-risk prescriptions were *SLCO1B1*, *CYP2C19*, and *CYP2D6* with 229, 198, and 106 high-risk exposures, respectively (Table 3). *SLCO1B1* encodes the solute carrier organic anion transporter family member 1B1 that is primarily expressed in the liver involved in the uptake of various substances and drugs, from the blood into the hepatocytes. *CYP2C19* and *CYP2D6* are both members of the cytochrome P450 enzyme family with a crucial role in the bioactivation of prodrugs into active forms.

Finally, we assessed exposure to the drugs that necessitate pharmacogenetic testing before being prescribed, as

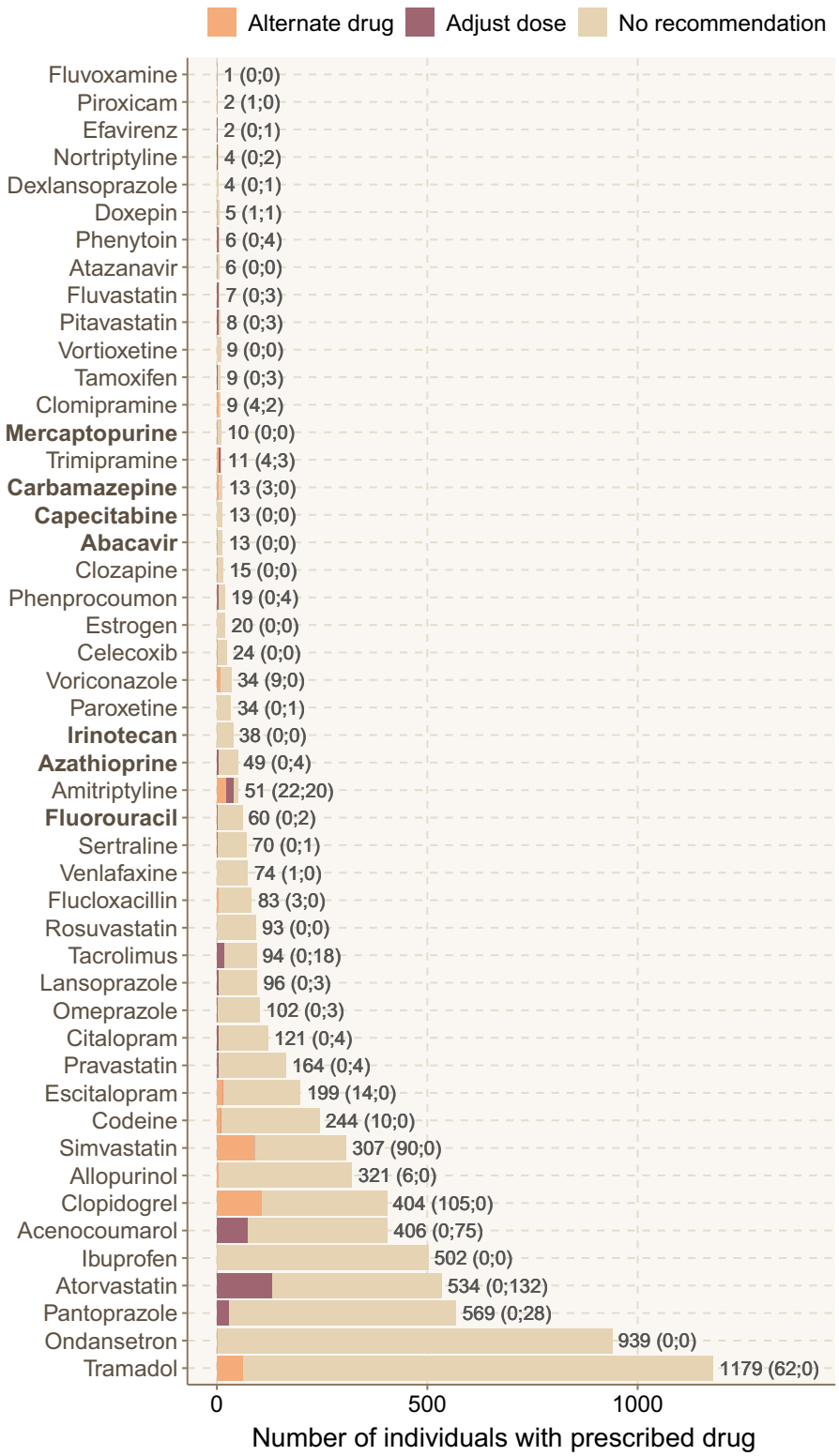

FIGURE 2 Number of (at-risk) prescriptions for drugs with CPIC guidelines. Barplot showing the total number of prescriptions (brown bars) and among these, the number of at-risk prescriptions requiring a change of drug (alternate drug) or dose (adjust dosage) for the 48 drugs with pharmacogenetic recommendations prescribed to individuals in the BGC cohort. Counts of total and respective at-risk prescriptions are indicated at the end of each bar as follows: *Total* (*alternate drug; adjust dosage*). Drugs that map to more than one ATC code were grouped. Drugs that require pharmacogenetic testing before being prescribed, as recommended by the Swiss Society for Clinical Pharmacology and Toxicology (version 3.9, dated July 2019) are highlighted in bold.

recommended by the Swiss Society for Clinical Pharmacology and Toxicology (SSPTC, version 3.0 from 11.07.2019-www.bag.admin.ch/ref): 5-fluorouracil (5-FU) (prescribed to $N=60$ individuals), azathioprine ($N=49$), irinotecan ($N=38$), abacavir ($N=13$), capecitabine ($N=13$), carbamazepine ($N=013$), and 6-mercaptopurine ($N=10$) (highlighted in bold in Figure 2 and Table 3). Of these, nine prescriptions were considered high risk: azathioprine was prescribed four times to patients with variants resulting in reduced TPMT catalytic activity, exposing them to an increased risk of acute myelosuppression if dosage is not adjusted accordingly. Carbamazepine was prescribed three times in association with the high-risk HLA allele *HLA-A**31:01 which increases the likelihood of developing severe hypersensitivity syndrome or mild maculopapular

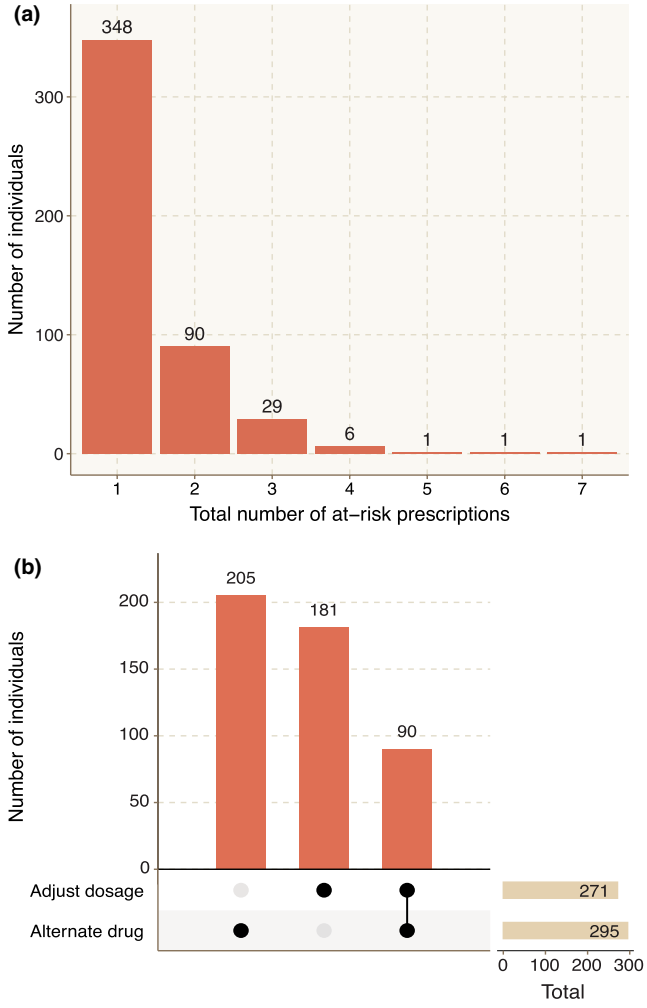

FIGURE 3 Distribution of individuals who have received high-risk prescriptions in the BGC. (a) Distribution and counts of total number of at-risk prescriptions in the cohort. (b) Upset plot showing the total number of individuals who received high-risk prescriptions, for which international guidelines recommend a change of drug or dosage. Individuals were separated according to whether they received at least one prescription requiring a drug change, at least one prescription requiring a dosage adjustment, or both. Individual counts for each category are shown.

rash, and therefore requires a change of drug. Fluorouracil was prescribed twice to individuals with a deficiency in the enzyme that catabolizes 5-FU (DPD), increasing their risk of severe or fatal drug toxicity if dosage is not adjusted accordingly.[32–34] Information on previous pharmacogenetic testing in relation to drug prescriptions was not available; thus, each individual may have been tested according to the guidelines at the time of prescription.

DISCUSSION

We conducted a comprehensive pharmacogenetic analysis of the prevalence of actionable variants in two different cohorts from Lausanne, Switzerland: the BGC, a hospital-based cohort, and the CoLaus|PsyCoLaus study, a population-based cohort. We found that 97.26% of BGC participants and 96.81% of CoLaus|PsyCoLaus participants carried at least one actionable pharmacogenetic variant. Similar to findings by Wittwer et al. using the Swiss Helsana database, the most frequently involved pharmacogenes were *CYP2C19*, *CYP2B6*, and *CYP2D6*.[35] A majority of participants carried two or three actionable variants.

The prevalence of virtually all actionable variants was comparable between the hospital-based and the population-based cohorts, which confirms that the findings could be used to estimate the potential benefit of pharmacogenetic implementation in the Swiss population. We observed prevalence differences only for *CYP2B6* and *CYP3A5*, which could be explained by minor variation in ancestry composition between the cohorts, or stochastic variation.[8,19] When comparing our results with international data, we found that the prevalence of actionable gene variants in the Swiss population is consistent with those reported in various global populations.[8,19,36] However, specific differences include, for example, a higher occurrence of the reduced-function allele of *CYP2D6* in Asian populations compared to Caucasians, a higher proportion of ultrarapid *CYP2D6* metabolizers in North African and Middle Eastern populations, a higher prevalence of *CYP2C19* poor and intermediate metabolizers in East Asians, South Asians, and Pacific Islanders, fewer *CYP3A5* poor metabolizers with a higher frequency of reduced-function alleles of *CYP2B6* in African populations compared to Caucasians.[37–40] These comparisons highlight both the shared and unique aspects of pharmacogenetic variation across different regions, underscoring the importance of considering ancestry and population diversity in pharmacogenetic research and implementation, and of identifying specific populations at higher risk of adverse reactions or treatment failure.

We also assessed the frequency of exposure to high-risk prescriptions in the hospital-based cohort. Our results showed a high prevalence of prescription schemes requiring particular attention, with over 30% of patients prescribed at least one high-risk drug. Most were prescribed at least one drug for which the guidelines recommend an alternative. Notably, patients carrying actionable pharmacogenetic variants in the *SLCO1B1* and *CYP2C19* genes were exposed to the highest numbers of hazardous prescriptions. Statins (atorvastatin and simvastatin) were the most frequently prescribed drugs in combination with actionable variants in *SLCO1B1*, and clopidogrel with actionable variants in *CYP2C19*. Altogether, this very high incidence of high-risk situations is cause of concern and calls for measures to identify at-risk individuals.

TABLE 3 List and number of high-risk prescriptions in the BGC cohort.

Genes	Drugs	*N*
CYP2B6	Efavirenz	1
CYP2C19	Amitriptyline	21
	Citalopram	4
	Clomipramine	4
	Clopidogrel	105
	Dexlansoprazole	1
	Doxepin	1
	Escitalopram	14
	Lansoprazole	3
	Omeprazole	3
	Pantoprazole	28
	Sertraline	1
	Trimipramine	4
	Voriconazole	9
CYP2C9	Fluvastatin	3
	Phenytoin	4
	Piroxicam	1
CYP2D6	Amitriptyline	21
	Clomipramine	2
	Codeine	10
	Doxepin	1
	Nortriptyline	2
	Paroxetine	1
	Tamoxifen	3
	Tramadol	62
	Trimipramine	3
	Venlafaxine	1
CYP3A5	Tacrolimus	18
DPYD	**Fluorouracil**	**2**
HLA-A*31:01	**Carbamazepine**	**3**
*HLA-B*57:01*	Flucloxacillin	3
*HLA-B*58:01*	Allopurinol	6
SLCO1B1	Atorvastatin	132
	Pitavastatin	3
	Pravastatin	4
	Simvastatin	90
TPMT	**Azathioprine**	**4**
VKORC1	Acenocoumarol	75
	Phenprocoumon	4

Note: The drugs are listed with their corresponding actionable gene and the number of times they were prescribed in high-risk situations in the BGC cohort. Drugs that require pharmacogenetic testing before being prescribed, as recommended by the Swiss Society for Clinical Pharmacology and Toxicology (version 3.0, dated July 2019) are highlighted in bold.

Our study has several limitations. First, heavily medicated individuals were included in the hospital-based cohort (>30 different drugs), resulting in a study population with a higher incidence of high-risk prescriptions than one would expect in the general population. Second, we identified 12% of individuals for whom the guidelines suggest a change in drug dosage. However, we could not verify whether the prescribed dose had been adapted to their metabolizer status prior to exposure in order to optimize treatment efficacy and safety. Third, using genotyping data instead of sequencing data in pharmacogenetics is associated with several limitations that can impact the accuracy and comprehensiveness of pharmacogenomic analyses. Indeed, genotyping arrays may overlook rare or novel variants outside the selected genotyped regions, potentially missing important genetic factors influencing drug metabolism and response. Additionally, genotyping does not capture information on structural variations, copy number variations, and some insertions/deletions, which can be crucial in understanding the complete genetic landscape relevant to pharmacogenetics. The *CYP2D6* gene locus is particularly challenging to genotype accurately, due to its high polymorphism and complex structural variation with duplications.

Our findings highlight the need for preemptive pharmacogenetic testing in the elderly, who are at higher risk of potentially preventable adverse events and are a key target population for improving healthcare outcomes. The very high prevalence of actionable pharmacogenetic variants and the large number of high-risk prescriptions observed in our study suggest a potential benefit of preemptive pharmacogenetic testing, that is, the generation of individual pharmacogenetic information in anticipation of future drug prescription. Reactive testing, conducted either at the time of prescription or after the occurrence of an adverse event, often using single-gene approaches, is likely to be less useful and more expensive.[41] The cost-effectiveness of different pharmacogenetic approaches depends on the costs of the assays and on the expected clinical utility in any clinical situation.[42] So far, in Switzerland, only targeted single-gene analyses are reimbursed by health insurances if they are prescribed by general practitioners or physicians without a pharmacologist specialty. The costs vary considerably depending on the assay and regional TARMED tariffs (i.e., the standardized fee schedule for medical services and procedures) for individual medical services, typically ranging from 80 to 190 CHF.[43] More comprehensive pharmacogenetic testing solutions using gene panels, genome-wide microarrays enriched for specific variants or low-coverage genome sequencing are being developed. Furthermore, advancements have been made in

professional pharmacogenomics communities and initiatives, offering enhanced frameworks for the integration of pharmacogenomics, demonstrating clinical effectiveness, and offering extensive resources for innovation.[44,45] The recent PREPARE study showed a remarkable 30% reduction in ADRs to commonly prescribed medications through the implementation of pharmacogenetic panel testing, providing compelling evidence for the potential benefits of preemptive pharmacogenetics.[19]

Although the genetic profile contributes significantly to the inter-individual variability in drug response, it does not fully account for it. The influence of other factors, such as age, organ dysfunction, and drug–drug interactions, can impact on drug efficacy and safety, and should be carefully considered in clinical practice.[46,47] For all these reasons, it is not recommended at this stage to abandon the use of monitoring tools and biomarkers, used to track circulating drug concentrations, and assess drug response and efficacy. These variables make it possible to integrate the non-genetic factors mentioned above and therefore play an essential role in guiding clinical decision-making processes, which should be combined with genetic tests, rather than replacing them.

AUTHOR CONTRIBUTIONS

F.H. and M.B.D.M. wrote the manuscript; F.H., M.B.D.M, C.W.T., C.R., P.V., F.G., and J.F. designed the research; F.H., M.B.D.M, and C.W.T. performed the research; F.H. and M.B.D.M analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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REFERENCES

1. Weinshilboum R, Wang L. Pharmacogenomics: bench to bedside. *Nat Rev Drug Discov*. 2004;3(9):739-748.
2. Hughes HB, Park Biehl J, Jones AP, Schmidt LH. Metabolism of isoniazid in man as related to the occurrence of peripheral neuritis. *Am Rev Tuberc*. 1954;70(2):266-273.
3. Carson PE, Larkin Flanagan C, Ickes CE, Alving AS. Enzymatic deficiency in primaquine-sensitive erythrocytes. *Science*. 1956;124(3220):484-485.
4. Lehmann H, Ryan E. The familial incidence of low pseudocholinesterase level. *Lancet*. 1956;268(6934):124.
5. Relling MV, Evans WE. Pharmacogenomics in the clinic. *Nature*. 2015;526(7573):343-350.
6. Hewett M, Oliver DE, Rubin DL, et al. Pharmgkb: the pharmacogenetics knowledge base. *Nucleic Acids Res*. 2002;30(1):163-165.
7. Relling MV, Klein TE. CPIC: clinical pharmacogenetics implementation consortium of the pharmacogenomics research network. *Clin Pharmacol Therapeut*. 2011;89(3):464-467.
8. Dunnenberger HM, Crews KR, Hoffman JM, et al. Preemptive clinical pharmacogenetics implementation: current programs in five US medical centers. *Annu Rev Pharmacol Toxicol*. 2015;55(1):89-106.
9. Nunez-Torres R, Pita G, Peña-Chilet M, et al. A comprehensive analysis of 21 actionable Pharmacogenes in the Spanish population: from genetic characterisation to clinical impact. *Pharmaceutics*. 2023;15(4):1286.
10. van der Wouden CH, Cambon-Thomsen A, Cecchin E, et al. Implementing pharmacogenomics in europe: design and implementation strategy of the ubiquitous pharmacogenomics consortium. *Clin Pharmacol Therapeut*. 2017;101(3):341-358.
11. Bank PCD, Caudle KE, Swen JJ, et al. Comparison of the guidelines of the clinical pharmacogenetics implementation consortium and the dutch pharmacogenetics working group. *Clin Pharmacol Ther*. 2018;103(4):599-618.
12. Ielmini M, Poloni N, Caselli I, et al. The utility of pharmacogenetic testing to support the treatment of bipolar disorder. *Pharmacogenom Personalized Med*. 2018;11:35-42.
13. Eadon MT, Rosenman MB, Zhang P, et al. The INGENIOUS trial: impact of pharmacogenetic testing on adverse events in a pragmatic clinical trial. *Pharmacogenomics J*. 2023;23(6):169-177.
14. Swen JJ, van der Wouden CH, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet*. 2023;401(10374):347-356.
15. Jaccard E, Redin C, Girardin F, Waeber G, Fellay J, Vollenweider P. Pharmacogenomics: a toolbox to improve drug prescription. *Rev Med Suisse*. 2020;16(716):2259-2263.
16. Firmann M, Mayor V, Marques-Vidal P, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord*. 2008;8:1-11.
17. Genomes Project Consortium, Auton A, Brooks LD, et al. A global reference for human genetic variation. *Nature*. 2015;526(7571):68-74.
18. Hodel F, Chong AY, Scepanovic P, et al. Human genomics of the humoral immune response against polyomaviruses. *Virus Evolution*. 2021;7(2):veab058.
19. Swen JJ, van der Wouden CH, Manson LE, et al. A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an

open-label, multicentre, controlled, cluster-randomised crossover implementation study. *Lancet*. 2023;401(10374):347-356.
20. Lee S-B, Wheeler MM, Thummel KE, Nickerson DA. Calling star alleles with stargazer in 28 pharmacogenes with whole genome sequences. *Clin Pharmacol Ther*. 2019;106(6):1328-1337.
21. Twesigomwe D, Wright GEB, Drögemöller BI, da Rocha J, Lombard Z, Hazelhurst S. A systematic comparison of pharmacogene star allele calling bioinformatics algorithms: a focus on CYP2D6 genotyping. *NPJ Genom Med*. 2020;5(1):30.
22. Danecek P, Bonfield JK, Liddle J, et al. Twelve years of SAMtools and BCFtools. *GigaScience*. 2021;10(2):giab008.
23. Browning SR, Browning BL. Rapid and accurate haplotype phasing and missing-data inference for whole-genome association studies by use of localized haplotype clustering. *Am J Hum Genet*. 2007;81(5):1084-1097.
24. Caudle KE, Sangkuhl K, Whirl-Carrillo M, et al. Standardizing CYP2D6 genotype to phenotype translation: consensus recommendations from the clinical pharmacogenetics implementation consortium and dutch pharmacogenetics working group. *Clin Transl Sci*. 2020;13(1):116-124.
25. Chen Z-L, Meng J-M, Cao Y, et al. A high-speed search engine plink 2 with systematic evaluation for proteome-scale identification of cross-linked peptides. *Nat Commun*. 2019;10(1):3404.
26. Jia X, Han B, Onengut-Gumuscu S, et al. Imputing amino acid polymorphisms in human leukocyte antigens. *PLoS One*. 2013;8(6):e64683.
27. Raisaro JL, McLaren PJ, Fellay J, et al. Are privacy-enhancing technologies for genomic data ready for the clinic? A survey of medical experts of the Swiss HIV cohort study. *J Biomed Inform*. 2018;79:1-6.
28. Altman RB. PharmGKB: a logical home for knowledge relating genotype to drug response phenotype. *Nat Genet*. 2007;39(4):426.
29. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92(4):414-417.
30. McInnes G, Lavertu A, Sangkuhl K, Klein TE, Whirl-Carrillo M, Altman RB. Pharmacogenetics at scale: an analysis of the UK biobank. *Clinical Pharmacology & Therapeutics*. 2021;109(6):1528-1537.
31. Lunenburg CATC, Thirstrup JP, Bybjerg-Grauholm J, et al. Pharmacogenetic genotype and phenotype frequencies in a large danish population-based case-cohort sample. *Transl Psychiatry*. 2021;11(1):294.
32. Lennard L, Van Loon JA, Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphism. *Clin Pharmacol Ther*. 1989;46(2):149-154.
33. Phillips EJ, Sukasem C, Whirl-Carrillo M, et al. Clinical pharmacogenetics implementation consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. *Clin Pharmacol Ther*. 2018;103(4):574-581.
34. Diasio RB, Harris BE. Clinical pharmacology of 5-fluorouracil. *Clin Pharmacokinet*. 1989;16:215-237.
35. Wittwer NL, Meier CR, Huber CA, Meyer zu Schwabedissen HE, Allemann S, Schneider C. Utilization of drugs with pharmacogenetic dosing recommendations in Switzerland: a descriptive study using the helsana database. *Pharmacogenom Personalized Med*. 2022;15:967-976.
36. Alshabeeb MA, Deneer VHM, Khan A, Asselbergs FW. Use of pharmacogenetic drugs by the dutch population. *Front Genet*. 2019;10:567.
37. Chanfreau-Coffinier C, Hull LE, Lynch JA, et al. Projected prevalence of actionable pharmacogenetic variants and level A drugs prescribed among US veterans health administration pharmacy users. *JAMA Netw Open*. 2019;2(6):e195345.
38. Ionova Y, Ashenhurst J, Zhan J, et al. CYP2C19 allele frequencies in over 2.2 million direct-to-consumer genetics research participants and the potential implication for prescriptions in a large health system. *Clin Transl Sci*. 2020;13(6):1298-1306.
39. Hustert E, Haberl M, Burk O, et al. The genetic determinants of the CYP3A5 polymorphism. *Pharmacogenet Genomics*. 2001;11(9):773-779.
40. Zhou Y, Lauschke VM. The genetic landscape of major drug metabolizing cytochrome P450 genes—an updated analysis of population-scale sequencing data. *Pharmacogenomics J*. 2022;22(5):284-293.
41. Ninomiya K, Saito T, Ikeda M, Iwata N, Girardin FR. Pharmacogenomic-guided clozapine administration based on HLA-DQB1, HLA-B and SLCO1B3-SLCO1B7 variants: an effectiveness and cost-effectiveness analysis. *Front Pharmacol*. 2022;13:1016669.
42. Girardin FR, Poncet A, Perrier A, et al. Cost-effectiveness of HLA-DQB1/HLA-B pharmacogenetic-guided treatment and blood monitoring in US patients taking clozapine. *Pharmacogenomics J*. 2019;19(2):211-218.
43. Office fédéral de la santé publique, Commission fédérale des analyses, moyens et appareils (CFAMA). Prestations et tarifs. Liste des analyses (LA) pour le 1er juillet. 2023 http://www.bag.admin.ch/dam/bag/fr/dokumente/kuv-leistungen/leistungen-und-tarife/Analysenliste/gesamtliste_analysenliste_010723.pdf [accessed October 2023]
44. van der Wouden CH, Swen JJ, Samwald M, Mitropoulou C, Schwab M, Guchelaar H-J. A brighter future for the implementation of pharmacogenomic testing. *Eur J Hum Genet*. 2016;24(12):1658-1660.
45. Girardin FR, Cohen K, Schwenkglenks M, Durand-Zaleski I. Pharmacoeconomics in the era of health technology assessment and outcomes research to prioritize resource use, innovation and investment. *Front Pharmacol*. 2023;14:1210002.
46. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1):6-14.
47. Palleria C, Di Paolo A, Giofrè C, et al. Pharmacokinetic drug-drug interaction and their implication in clinical management. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*. 2013;18(7):601-610.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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