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Review Article

Comprehensive Review of Clinically Relevant Drug-Gene Interactions in Pharmacy Practice: A UKBB Data Guide for Providers

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Abstract

The translation of pharmacogenomic insights into clinical practice faces a significant barrier stemming from the lack of knowledge and guidance within healthcare institutions for prioritizing genetic tests and drug-gene interactions. To address this critical challenge, we provide a single, simple, user-friendly, and comprehensive electronic database of all important drug-gene interactions (n =421) with summaries of clinical recommendations per association as classified into our simple triple classification system (A, B, or C) depending on their clinical relevance (https://c1abo933.caspio.com/dp/d81f70009de6d5055c2a44a5a970). The database can be looked at as a roadmap for healthcare providers in health care settings facilitating practicing pharmacogenomics in their institutions. To present how the database can be effectively utilized, we utilized the longitudinal prescribing data from across different UK health care institutions (the UKBB dataset) for ~ 230,000 participants to identify the most frequently prescribed drugs in the UK and linking them with our database. This enabled us to uncover the most frequently used drugs in the UK which have genotype-guided clinical recommendations. Then, we show, using a scoring approach, which specific drug-gene interactions should be prioritized over others in any given health care institution using an example from our analyzed UKBB data. Generally, we propose the genetic testing of 114 key genes covering all significant drug-gene associations. However, we specifically recommend prioritization of genetic testing for CYP2D6 and G6PD genes, acknowledging that they are involved in ~ 30% of all important drug-gene associations. This paper holds profound promise for advancing clinical practice and patient care.

Keywords: Pharmacogenomic, Pharmacy practice, Genetic tests, Drug-gene interactions, Healthcare institutions, Drug safety and efficacy, UKBB prescribing data, commonly prescribed drugs

INTRODUCTION

In contemporary clinical practice, prescribers often rely on clinical guidelines derived from population-based clinical trials to determine the most suitable treatment options for patients. However, the broad spectrum of factors influencing drug responses makes it challenging to ensure these guidelines are universally applicable to every individual. Individual patients are influenced by a unique combination of variables that set them apart from one another, resulting in distinct drug response experiences. These variables include age, weight, height, sex, liver and kidney function, drug interactions, both with other drugs and with food, interactions with pre-existing medical conditions, and crucially, interactions with an individual's genetic makeup. The pursuit of personalized medicine seeks to account for all these contributing factors to arrive at the optimal treatment for each individual. However, while most of these factors are routinely considered in current clinical practice, genetic variability remains a largely overlooked element in the decision-making process for healthcare providers. Previous research studies[1-5] have consistently demonstrated that the selection of drugs based on individual genetic profiles can significantly enhance the safety, efficacy, and economic outcomes of drug prescribing.

Pharmacogenomics (PGx) can be approached from multiple perspectives, including variants in genes influencing drug metabolizing enzymes or transporters (the pharmacokinetic pathway), genetic variability in drug targets (e.g., receptors or enzymes) (the pharmacodynamic pathway), and polymorphisms in genes unrelated to either pathway but impacting drug response. Additionally, PGx can be a crucial tool in infectious diseases where an individual's genetic makeup may render them either protected or vulnerable to bacterial or viral attacks. Furthermore, PGx can be used to identify genetic variants linked to diseases and guide treatment decisions accordingly, particularly in the field of cancer pharmacogenomics. Despite the immense clinical potential of PGx and its diverse applications, efforts to integrate PGx services into healthcare institutions have been relatively modest, primarily due to a lack of knowledge and awareness among healthcare providers worldwide, cost, and lack of straightforward plans regarding which PGx tests and drug-gene interactions should be considered in a given healthcare institution. These challenges can be clearly observed from a large number of studies conducted worldwide. Here, we present a quick overview from across the globe.

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America

In the United States, a study involving 282 physicians revealed that less than 10% felt familiar with pharmacogenetics[6], highlighting a substantial knowledge gap in developed countries. Similarly, a survey of 744 healthcare providers in North Carolina found that while the majority recognized the benefits of PGx testing, they rarely utilized it due to cost concerns and insufficient training[7]. In Canada, two separate studies underscored the limited PGx knowledge among pharmacists. In a sample of 74 pharmacists, only one-third had received any PGx education, and a mere 12.2% had applied PGx test results in their practice[8]. Another study in Quebec reported that only 22% of pharmacists felt confident in using PGx information, with 90.3% expressing a need for further training[9].

Europe

The situation in Europe mirrors that in North America. In Belgium, a study involving 201 healthcare providers, including both pharmacists and physicians, found that 78% were unfamiliar with the basic principles of PGx and its clinical applications[10]. In the United Kingdom, it has been reported that common barriers to PGx implementation included cost, workflow integration issues, and a lack of knowledge[11]. In Romania, most pharmacists (64.8%) demonstrated moderate PGx knowledge, yet there remains a significant gap to fill[12]. French healthcare providers also displayed limited knowledge, with only 11.2% achieving maximum knowledge scores, and 25.4% having prescribed or recommended PGx tests, indicating a clear need for more comprehensive training[13].

Asia and Middle East

Asian countries also face challenges in PGx knowledge and implementation. In Thailand, 46% of 600 surveyed pharmacists reported poor PGx knowledge[14]. In Japan, only 12.4% of 1,313 pharmacists had received PGx-specific education, and 26% were involved in PGx testing, with a majority citing lack of insurance coverage as a major barrier[15]. In China, over half of the 1,005 pharmacists surveyed rated their PGx knowledge as "average", with only 25% rating it as "good" or "excellent"[16]. A study in Jordan showed that younger healthcare providers had slightly better PGx knowledge scores compared to their older counterparts, but overall knowledge remained limited[17]. In the United Arab Emirates, key barriers to PGx implementation were cost, lack of training, and insurance coverage issues[18]. Similar trends were observed in Syria, where pharmacists had better PGx knowledge than physicians, though overall knowledge levels were still low[19]. In Saudi Arabia, only 29.8% of 671 pharmacists reported good PGx knowledge, underscoring the need for improved education and training[20] with other studies reporting similar findings in this region[21-22].

Africa

African countries exhibit significant PGx knowledge deficits as well. In Egypt, a study involving 184 pharmacists and physicians revealed low PGx knowledge (mean score = 41.7%), with barriers including lack of knowledge, testing devices, and funding[23]. In Zambia, 38% of 304 healthcare providers were found to have low PGx knowledge[24]. In Nigeria, only 25.5% of 161 pharmacists had prior PGx training, though 90.1% expressed interest in future training[25].

Australia

In Australia, a study of 107 pharmacists and medical practitioners revealed that few healthcare providers felt confident in identifying indications for PGx testing, ordering tests, or communicating results with patients. Major barriers included the lack of clinical practice guidelines and insufficient knowledge[26].

The global landscape of pharmacogenetics knowledge among healthcare providers is characterized by significant gaps and barriers. These issues are consistent across different continents, where insufficient training, lack of confidence, and major obstacles such as cost and the absence of clinical guidelines hinder the effective integration of PGx into clinical practice. In an attempt to address these challenges, in this paper we provide a simple comprehensive review of all clinically relevant PGx associations, as classified into 3 main categories based on their potential clinical relevance, in a single database to be readily utilized by health providers addressing knowledge gap and lack of confidence challenges. Then, by utilizing UK Biobank prescribing data as a real-world example, we demonstrate how this information can be used to identify the most critical PGx tests and drug-gene interactions to be considered within a given healthcare institution addressing PGx tests' costs-related challenges.

METHODS

Structure of the utilized sources from PharmGKB

Pharmacogenomic Knowledge Database (PharmGKB)[27] provides a clinical annotations section where drug-variant associations are classified based on the strength of scientific evidence into six levels. However, we focused on four levels that hold more significant clinical relevance:

1A: Drug-variant associations mentioned in clinical guidelines or FDA labels, supported by at least one publication.

1B: Drug-variant associations not mentioned in clinical guidelines or FDA labels but supported by a high level of evidence from at least two independent publications.

2A: Drug-variant associations in well-known pharmacogenes, supported by at least two publications, although some studies may present conflicting findings.

2B: Similar to 2A, but the variant is not located in a well-known pharmacogene.

PharmGKB also provides summaries of pharmacogenomic (PGx) recommendations found in drug labels approved by regulatory agencies such as the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), Health Canada (HCSC), the Swiss Agency of Therapeutic Products (Swissmedic), and the Pharmaceuticals and Medical Devices Agency (Japan)

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(PMDA). These PGx recommendations are categorized into three main groups:

1. Indicated or contraindicated: Specific genetic variants determine whether a patient should receive or avoid a drug.

2. Dose adjustment: Genetic variants necessitate a specified change in drug dosage (e.g., a 50% dose reduction) for carriers of specific variants.

3. Other general PGx recommendations: This category includes general instructions not fitting into the first two categories, such as 'use with caution,' 'monitor for side effects,' or 'dose reduction is recommended.'

Additionally, PharmGKB offers an extensive compilation of clinical recommendations sourced from various guidelines, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy, as well as other professional societies like the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and the French National Network of Pharmacogenetics (RNPGx). These guidelines mostly include information on genotype-based dosing guidelines and whether the drug is indicated or contraindicated based on the genotype.

Harmonizing Clinical Recommendation Data in PharmGKB

To streamline the classification, maintain consistency, and enhance clarity, we reclassified all drug-variant associations from the three above-mentioned categories, whether sourced from clinical annotations, drug labels, or guidelines into three simple categories:

Class A: Associations with clear clinical instructions directly applicable in practice (e.g., drug prescription or avoidance based on genetic variants, or specific dose adjustments).

Class B: Associations with general clinical instructions that lack clear clinical application guidance (e.g., use with caution, dose reduction, potential changes in efficacy, etc.).

Class C: Associations providing information about genetic influence on drug pharmacokinetics or pharmacodynamics but without explicit clinical instructions.

For reclassification of PharmGKB levels, data from the "clinical annotations" section were obtained from the PharmGKB website (https://www.pharmgkb.org/downloads). By linking the "clinical_ann_alleles" and "clinical_annotations" tables, downloaded from the website, using R programming language (R: RStudio, Boston, MA, USA, version 4.1.2), we combined drug names with their associated text annotations. This results in a table with 984 drug-variant associations. All of these associations were reviewed for each of them to be classified into A, B, or C classes according to our criteria. A total of 609 drug-variant associations were classified under class B (PharmGKB levels 1A,2A, 1B, or 2B) with the remaining (n=375) being classified under class C (PharmGKB levels 1A,2A, 1B, or 2B) (refer to Supplementary Table 1). These associations are linked with a total of 125 drugs.

For drug labels, these were accessible via the online PharmGKB

Table 1: List of the top ten most frequently used medications in UKBB longitudinal prescribing data with genotype-guided clinical instructions of class A (strong evidence + specific clinical instructions (i.e., indicated, contraindicated, or dose needs to be adjusted into a certain value)).

No	Drug	Genes	Phenotype	Genotype-Guided Clinical Instructions	Sub-clinical class*	Data source**	Total usage frequency in UKBB	UKBB Rank
1	codeine	CYP2D6	URM, PM	URMs & PMs: Codeine is Contraindicated	C	L/CPIC	180519	2
2	ibuprofen	CYP2C9	PMs , IMs	PMs: dose reduction by 25-50% of the lowest recommended dose. IMs: with activity score of 1: use the lowest recommended starting dose.	D	CPIC	112094	3
3	omeprazole	CYP2C19	URM,PM	URMs: increase the starting daily dose by 100%. IMs & PMs: dose reduction by 50% after achieving therapeutic efficacy.	D/D	CPIC	95995	4
4	flucloxacillin	HLA-B	HLA-B*57:01	select an alternative agent for patients carrying the HLA-B*57:01 variant and have elevated liver enzymes.	C	DPWG	92178	6
5	simvastatin	SLCO1B1	poor,	Prescribe an alternative statin or reduce the dose into < 20mg/day for patients with SLCO1B1 decreased function, possible decreased function or poor function phenotype.	C/D	CPIC		
6	lansoprazole	CYP2C19	URM,PM	URMs: increase the starting daily dose by 100%. IMs & PMs: dose reduction by 50% after achieving therapeutic efficacy.	D/D	CPIC	67597	11
7	atorvastatin	LDLR		Atorvastatin is Indicated for treatment of familial hypercholesterolemia.	I	L	46736	19
	atorvastatin	SLCO1B1	poor, decreased function	Prescribe ≤20mg for patients with SLCO1B1 poor function phenotype and ≤40mg for patients with SLCO1B1 decreased or possible decreased phenotype.	D	CPIC	46736	19

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8	amitriptyline	CYP2D6	URMs, IMs, PMs	URMs & PMs: use an alternative drug. If warranted for PMs: dose reduction by 50%. IMs: dose reduction by 25%. .	C/D	CPIC	44619	23
		CYP2C19	URMs, IMs, PMs	URMs & PMs: use an alternative drug. If warranted for PMs: dose reduction by 50%.	C/D	CPIC	44619	23
9	nitrofurantoin	G6PD	G6PD deficiency	Nitrofurantoin should be used with caution in G6PD deficient patients without chronic non-spherocytic hemolytic anemia (CNSHA) and completely avoided by G6PD deficient patients with CNSHA. Avoid breastfeeding of infants with G6PD deficiency.	C	L/CPIC	30537	39
10	tramadol	CYP2D6	URM, PM	URMs & PMs: use an alternative analgesic agent.	C	CPIC	30288	40

* I: Indicated; C: Contraindicated; D: Dose adjustment
** L: FDA Labels; CPIC, DPWG, CPNDS, or RNPGx: Clinical guidelines

database (https://www.pharmgkb.org/labelAnnotations) for 472 drugs. We reviewed all drug labels for these drugs and selected one drug label based on specific criteria. When multiple recommendations from different labels for the same drug conveyed similar meanings, one random recommendation was chosen. If a drug had one general recommendation from one label and a more specific or conservative recommendation from another label, the latter was selected (e.g., "reduce the dose by 50%" over the general statement "dose reduction is recommended," and "the drug is contraindicated" over "use with caution," etc.). Recommendations stating no significant difference between carriers and non-carriers of certain genotypes on drug response were excluded. The selected genotype-guided recommendations were then classified into Class A, B, or C (see Supplementary Table 2). In cases where a recommendation included both Class B and Class C components, it was classified as Class B.

Regarding PGx guidelines, these were available for 194 drugs at: https://www.pharmgkb.org/guidelineAnnotations. Guidelines for all of these drugs were reviewed and recommendations from a single guideline per drug was selected. Due to its more comprehensive, clear, and detailed clinical recommendations, CPIC guidelines are selected over other guidelines if they are available for the drug of interest. If not available, one of the other guidelines is selected in the following order (based on comprehensiveness and clarity of instructions): DPWG, CPNDS, and then RNPGx. Drugs with no specific genotyped-based recommendations in the guidelines have been excluded and the number of drugs has decreased into 108. The guidelines categorize all relevant information pertaining to these drugs within the confines of Class A (see Supplementary Table 3).

Finally, to create the final comprehensive database, data from PharmGKB levels, drug labels, and clinical guidelines, which were reclassified into the same clinical classification system (A, B, or C), were combined in a single database. This database contains the drug name, the affected gene, the specific variant or genotype, well-organized color-coded genotype-guided clinical instructions, our clinical classification (A, B, or C), and an

Table 2: List of the top ten most frequently used medications in UKBB longitudinal prescribing data with genotype-guided clinical instructions of class B and not mentioned in class A (strong evidence + general clinical instructions (i.e., increased toxicity/efficacy or decreased toxicity/efficacy).

No.	Drug	Genes	Variants/Phenotypes	Sub-clinical class*	Data source**	Total usage frequency in UKBB	UKBB Rank
1	**Paracetamol (acetaminophen)**	G6PD	G6PD deficiency	**IT**	L	62941	13
2	**erythromycin ethylsuccinate / sulfisoxazole acetyl**	G6PD	G6PD deficiency	**IT**	L	54663	14
3	**aspirin**	G6PD	G6PD deficiency	**IT**	L	49680	17
		HLA-DPB1	HLA-DPB1*03:01:01	**IT**	2B	49680	17
4	**atorvastatin**	APOE	rs7412	**BR**	2B	46736	19
5	**amlodipine / atorvastatin / perindopril arginine (triveram)**	G6PD	G6PD deficiency	**IT**	L	45137	22
		SLCO1B1	rs4149056	**IT**	L	45137	22
6	**lidocaine / prilocaine**	G6PD	G6PD deficiency	**IT**	L	33195	38
7	**ciprofloxacin**	G6PD	G6PD deficiency	**IT**	L	29879	42
8	**bisoprolol fumarate / perindopril arginine**	G6PD	G6PD deficiency		L	16657	71
9	**nicotine**	CHRNA5	rs16969968	**IT**	2B	11929	104
10	**tamsulosin**	CYP2D6	PMs	**IT**	L	11088	112

* IT: Increased Toxicity; BR: Better Response
** L: FDA Labels; 1A,1B,2A, or 2B: PharmGKB levels

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Table 3: List of the top 10 most frequently used medications in UKBB longitudinal prescribing data with genotype-guided clinical instructions of class C not mentioned in Class A or B (strong evidence + general pharmacokinetic information: increased/decreased metabolism or increased/decreased plasma drug concentration).

No.	Drug	Genes	Variants/phenotypes	Sub-clinical class*	Data source**	Total usage frequency in UKBB	UKBB Rank
1	diazepam	CYP2C19	NA	genetic variability affects metabolism-Direction not mentioned	L	35754	33
2	fluoxetine	CYP2D6	PMs	DM/IC	L	23490	55
3	clopidogrel	CES1	rs71647871	IC	2B	12733	98
4	nicotine	CYP2A6	CYP2A6*1A, CYP2A6*1B1, CYP2A6*1X2B, CYP2A6*2, CYP2A6*4A, CYP2A6*7, CYP2A6*9A, CYP2A6*10, CYP2A6*12, CYP2A6*17, CYP2A6*19, CYP2A6*20, CYP2A6*23, CYP2A6*24A, CYP2A6*25, CYP2A6*26, CYP2A6*27, CYP2A6*28A, CYP2A6*35	IM/DM	1B	11929	104
5	losartan	CYP2C9; CYP3A4	PMs	DM	L	9982	126
6	mirtazapine	CYP2D6	CYP2D6*1, CYP2D6*1xN, CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6	IM/DM	2A	8124	152
7	esomeprazole	CYP2C19	PMs	IC	L	7639	164
8	tolterodine	CYP2D6	PMs	IC	L	5561	219
9	rabeprazole	CYP2C19	CYP2C19*1, CYP2C19*2, CYP2C19*3, CYP2C19*17	IM/DM	2A	3227	306
10	duloxetine	CYP2D6	PMs	IC	L	2989	324

* DM: Decreased metabolism; IM: increased metabolism; IC: Increased concentration
** L: FDA Labels; 1A,1B,2A, or 2B: PharmGKB levels

indication of the source of information. The complete database is available in Supplementary Table 4.

The database has been also made available online as a user-friendly application at: https://c1abo933.caspio.com/dp/d81f70009de6d5055c2a44a5a970 . The user can search using a customized form by drug/variant/gene names, clinical recommendations, clinical class or source of information (Figure 1 shows the application's interface). Results are presented as either graphs showing number of records associated with each different clinical class or a detailed downloadable table (Figure 2 shows an example)

Identifying the Most Frequently Used Drugs from UKBB with Significant Genotype-Guided Clinical Instructions

The UK Biobank (UKBB) longitudinal prescribing data, comprising records for approximately 230,000 participants, offers more precise estimates of prescribed drugs per patient compared to the self-reported data from the 500,000 participants in the UKBB cross-sectional dataset. Consequently, we harnessed the UKBB longitudinal prescribing data to identify the most frequently prescribed drugs within the UKBB. Since certain drugs may be prescribed multiple times to a single patient, we employed the R programming language to ensure that only unique drug names per patient were considered. Initially, we calculated the raw frequencies for all drug names in the dataset, which included approximately 43,200 unique drug names (refer to Supplementary Table 5). However, this calculation provided frequencies for different formats of the same drug, resulting in multiple entries for the same drug. To address this issue, we refined the list of drug names, retaining only those with a frequency of no less than 100. This reduced the list of drug names from approximately 43,200 to around 4,100 unique drug names. For each of these distinct drug names, which might be represented in various formats, we identified a single equivalent generic name (see Supplementary Table 6). We then computed the final usage frequency for each unique drug among a total of 1,619 unique drugs by consolidating the different frequencies of the same drug (refer to Supplementary Table 7).

Subsequently, this list of drugs and their frequencies was linked with the previously produced table (Supplementary Table 4) containing reclassified PharmGKB drugs classified into classes A, B, or C. This linkage facilitated the creation of the final database (refer to Supplementary Table 8), enabling us to pinpoint the most frequently used drugs associated with significant genotype-guided clinical recommendations in the UK.

RESULTS

In our study, all drug-gene associations for a total of 421 drugs (highlighted in drug labels, clinical guidelines, or assigned under one of four strong PharmGKB levels of evidence) into our three distinct categories: A (n=281), B (n=181), or C (n=84) (see Supplementary Table 4) taking into account that some drugs are mentioned in more than one category. We have identified

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a total of 114 crucial genes covering all of these associations. CYP2D6 emerged as the most frequently reported gene, showing significant associations in 66 instances, impacting drug response and pharmacokinetics. Following closely is G6PD (n=46), with CYP2C19 (n=24), CYP2C9 (n=17), IFN3 (n=15), SLCO1B1 (n=12), HLA-B (n=12), UGT1A1 (n=11), and NAT2 (n=10). For a detailed breakdown of the frequencies of these genes, refer to Supplementary Table 9.

Regarding Class A drug-gene associations (i.e. have clear, well-established, and specific clinical instructions), these were from either drug labels or clinical guidelines. The majority of them were found in drug labels only but not guidelines (n= 178), followed by those in clinical guidelines only but not in drug labels (n= 62), and those found in both drug labels and clinical guidelines (n= 51) (See supplementary Table 10). The most frequently reported genes within Class A drug-gene associations are similar to the most frequently reported genes in our whole list of drug-gene associations mentioned above with CYP2D6 being in the top of the list followed by G6PD, CYP2C19, and CYP2C9.

Our investigation into the most frequently prescribed drugs within the UK Biobank (UKBB) longitudinal prescribing data unveiled amoxicillin as the top contender. This drug had been prescribed a staggering 205,367 times. It was followed by codeine-containing products (CCPs) at 180,519 prescriptions, ibuprofen at 112,094, omeprazole at 95,995, diclofenac sodium at 94,018, flucloxacillin at 92,178, trimethoprim at 72,685, simvastatin at 71,969, naproxen at 71,437, and salbutamol at 68,582. Supplementary Table 6 contains the complete list of drugs with usage frequencies of >= 100 times.

Within the domain of our primary findings, we pinpointed 63

Figure 1. The user-friendly interface of the developed application, designed to facilitate the search for clinically relevant drug-gene interactions. The interface includes features such as a search bar, result filters, and detailed interaction summaries.

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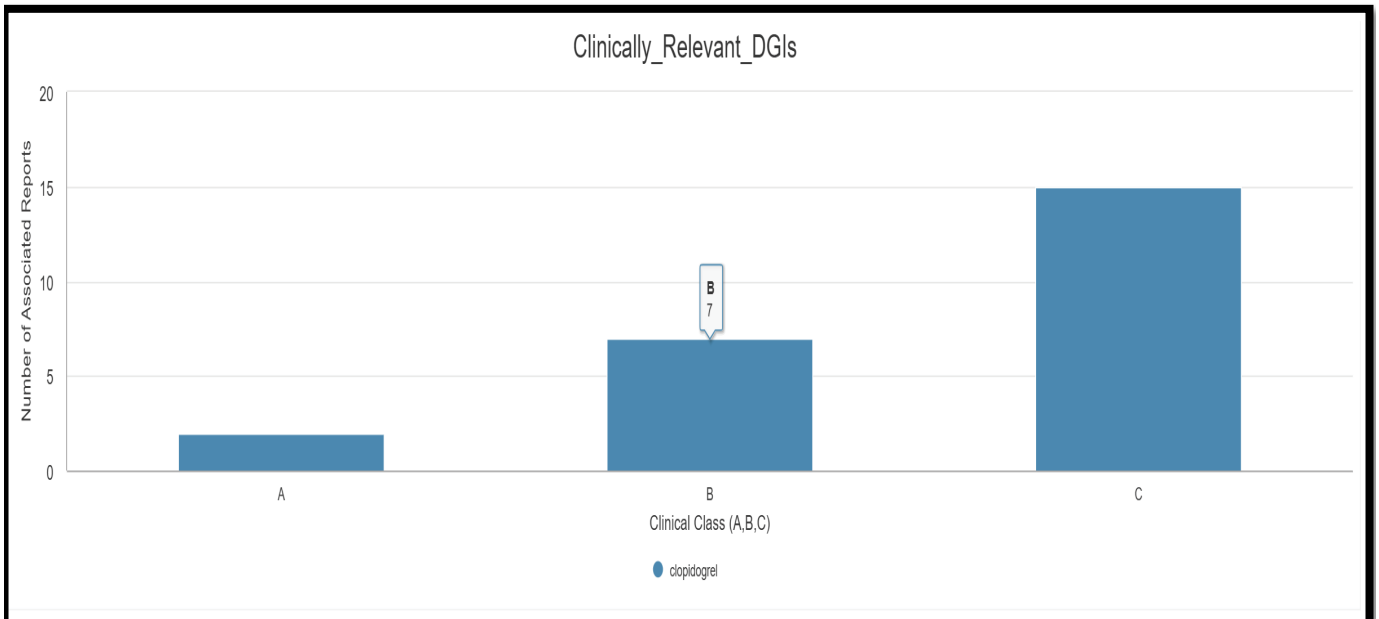

Download Data▼

Drug	Gene/s	Variants Phenotypes	Clinical Recommendations	Clinical Class	Source	
clopidogrel	CYP2C19	CYP2C19*1; CYP2C19*2; CYP2C19*3; CYP2C19*4; CYP2C19*5; CYP2C19*6; CYP2C19*7; CYP2C19*8	* Use higher clopidogrel doses. However, no dosing guidelines currently available. Therfore, use an alternative platelet P2Y12 inhibitor in CYP2C19 poor metabolizers due decreased clopidogrel efficacy.	A	L	View Details
clopidogrel	CYP2C19	PMs , IMs	The CPIC Dosing Guideline for clopidogrel recommends an alternative antiplatelet therapy for CYP2C19 poor or intermediate metabolizers (cardiovascular indications: prasugrel or ticagrelor if no contraindication; neurovascular indications: alternative P2Y12 inhibitor if clinically indicated and no contraindication.). For more details, see the table in : https://www.pharmgkb.org/guidelineAnnotation/PA166104948	A	CPIC	View Details
clopidogrel	CYP2C19	CYP2C19*1, CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*8, CYP2C19*17	The CYP2C19*2 allele is assigned as a no function allele by CPIC. Patients carrying the CYP2C19*2 allele in combination with a no, decreased, normal, or increased function allele who are treated with clopidogrel may have an increased risk for adverse cardiac and cerebrovascular events as compared to patients with two normal function alleles. However, conflicting evidence has been reported. Other genetic and clinical factors may also influence the risk for adverse cardiovascular events.	B	1A	View Details

Figure 2. An example of outputs shown after searching the database. Searching for "Clopidogrel", yielded 2,7, and 15 records belong to clinical classes A,B, and C respectively as shown in the graph. Detailed findings are presented in the downloadable table (part of it is presented).

commonly prescribed medications in the UKBB longitudinal prescribing data that were accompanied by genotype-guided clinical instructions classified under class A (see Supplementary Table 8). Among these, the predominant type of clinical guidance (n=47) stated that the drug should be contraindicated under certain circumstances for carriers of specific genetic variants. In contrast, recommendations regarding dose adjustments to specific values or the indication of the drug for carriers of specific genetic variants were reported 35 and 9 times, respectively. Zooming in on the top ten drug-gene associations identified under Class A (see Table 1), codeine stood out as the most frequently used medication (ranked 2nd in UKBB) with specific genotype-based clinical guidelines recommending using an alternative agent in CYP2D6 ultra-rapid metabolizers and poor metabolizers. Almost all top ten drug-gene associations have guideline-based clinical recommendations.

Under class B (strong evidence + general clinical instructions), we have recognized 64 commonly used medications in UKBB as demonstrated in Supplementary Table 8. The majority of drug-gene interactions are associated with increased toxicity (IT, n= 67), followed by decreased drug response (DR, n= 16), better response (BR, n= 9), and decreased toxicity (DT, n= 5). Focusing on the top ten associations identified in UKBB under Class B and not mentioned in Class A (see Table 2), paracetamol came first as to be correlated with increased risk of haemolytic anaemia in patients with G6PD deficiency.

Finally, we report 57 commonly used medications belong to class C (i.e., strong evidence on the influence of genetic variability on drug pharmacokinetic but not clinical outcomes, see Supplementary Table 8). The most frequently reported phenotype was "decreased metabolism (DM)" (n = 47),

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followed by "increased plasma drug concentration (IC)" (n= 27), "increased metabolism (IM)" (n= 25), and then "decreased plasma drug concentration (DC)" (n=3). Focusing on the top ten associations identified in UKBB under Class C and not mentioned in Class A or B (see Table 3), diazepam has emerged as the most prescribed drug in UKBB in this class.

DISCUSSION

This study represents a pioneering effort to provide a comprehensive database as a guide for healthcare providers, outlining the potential drug-gene interactions that need consideration when implementing pharmacogenomic testing in their healthcare institutions. We meticulously identified a total of 421 drug-gene associations sourced from drug labels, clinical guidelines, and PharmGKB's strongest levels of evidence and classified them into three classes, namely A, B, and C, based on the degree of applicability of genotype-guided clinical instructions. Of note, not all of Class A associations are found in clinical guidelines and, similarly, not all of them are in drug labels; combining both is essential to identify all important associations as what our study did. In this study, we pinpointed the necessity of testing a total of 114 significant genes to encompass all three classes of associations. Notably, CYP2D6 and G6PD genes emerged as particularly crucial, collectively accounting for approximately 30% of these drug-gene associations.

It's worth highlighting that the prioritization of specific genetic tests and drug-gene interactions may vary across different healthcare institutions. This variation hinges on various factors, such as whether a particular drug-gene association possesses a clear, specific, and directly applicable genotype-guided clinical recommendation, the extent of clinical impact, the frequency of drug usage within the institution, and the minor allele frequency (MAF) of the genetic variant in the institution's patient population. Our study, leveraging extensive longitudinal prescribing data from over 230,000 participants in the UK Biobank (UKBB), serves as an illustrative example of how our recommended approach to identifying crucial drug-gene associations can be applied. Furthermore, it presents findings that hold significance for healthcare institutions in the UK.

To initiate the recommended approach, users can begin by downloading Supplementary Table 4, specifically the first sheet, where all drug-gene associations backed by the best available scientific evidence are categorized into classes A, B, or C within the database. Subsequently, users should analyze prescribing data within their institutions to identify the most frequently prescribed medications. This list of commonly used drugs is then cross-referenced with the comprehensive genetic database obtained in the initial step, allowing for the recognition of all commonly used medications with genotype-guided clinical instructions.

We propose prioritizing drug-gene associations for consideration in healthcare institutions based on a composite score derived from four key criteria:

1. Class: a score of 3 points for Class A, 2 points for Class B, and 1 point for Class C.

2. Severity of Clinical Impact: Assigning 4 points if the drug is contraindicated, 3 points if the interaction is associated with increased toxicity, 2 points if dose adjustment is required, or the interaction results in decreased efficacy, and 1 point if the interaction is linked with better response, decreased toxicity, pharmacokinetic but not clinical parameters , or the drug is indicated in the presence of specific variants.

3. Frequency of Drug Usage in the Institution: Awarding 4 points for drugs among the top 25, 3 points for ranks 26-50, 2 points for ranks 51-75, 1 point for ranks 76-100, and 0 points for drugs with usage exceeding the top 100.

4. Minor Allele Frequency (MAF): Allocating points based on MAF - 0 points for less than 1%, 1 point for 1-4%, 2 points for 5-10%, 3 points for 11-20%, 4 points for 21-30%, 5 points for 31-40%, and 6 points for over 40%. If multiple variants are associated with the same phenotype of a specific drug, the total MAFs of all variants should be considered. For For example, if 3 unique variants (i.e., not in linkage disequilibrium) with MAFs of 4%, 13%, and 10% are linked with increased toxicity of drug X, then the total MAFs = 27% which deserve 4 points according to our criteria.

Based on this scoring approach, it is not necessary that all drug-gene associations under Class A are prioritized over those under Class B or C; in some cases, the reverse might be true or both associations could be equivalent in the overall clinical significance. For example, when applying our scoring approach to prioritize between the two drug-gene associations: nitrofurantoin-G6PD deficiency (Class A) and diazepam-CYP2C19 rapid, ultra-rapid, and poor metabolizers (RMs, URMs, and PMs) in the UK, both associations could be clinically equivalent. Clinical recommendations suggest avoidance of nitrofurantoin or using it with caution in G6PD deficient patients who represent only ~ 4% in the European ancestry[28]. On the other hand, diazepam's drug label mention that CYP2C19 genetic variability significantly affect pharmacokinetics of the drug. Recent studies demonstrate that CYP2C19 URMs, RMs, IMs, and PMs (~ 60 % in the European ancestry[29,30]) experienced statistically significant reduction or increase in the drug's plasma levels compared to normal metabolizers[31,32]. Considering our scoring approach, the nitrofurantoin-G6PD association would be ranked as follows: Class A (3 points (pts)) + clinical impact (4 pts) + usage frequency in the UK (3 pts) + MAF (1 pt) = 11 points in total. Regarding the diazepam-CYP2C19 associations: Class C (1 pt) + clinical impact (1 pt) + usage frequency in the UK (3 pts) + MAF (6 pts) = 11 pts in total as well.

When confronted with the challenge of genetic testing costs for all 114 genes encompassing essential drug-gene associations, our scoring system offers valuable guidance to discern the most critical associations that merit consideration in a given healthcare institution. Nevertheless, we firmly recommend that healthcare institutions in the UK prioritize genetic testing for specific genes such as CYP2D6, G6PD, CYP2C19, CYP2C9, and SLCO1B1. These genes exert substantial influence on the

safety and efficacy of the most frequently used drugs for which directly applicable or, at a minimum, general genotype-guided instructions are grounded in robust scientific evidence.

It is important to acknowledge the limitations of this study. The observed frequencies of drug usage in the UKBB dataset may not be entirely representative of real-world drug consumption. This discrepancy arises from the fact that a considerable number of over-the-counter (OTC) medications are obtainable without prescriptions, and these transactions are not comprehensively captured in the UKBB data. It is conceivable that the utilization of OTC medications significantly surpasses the figures presented in this study. Nevertheless, it remains intriguing that our analysis has identified amoxicillin as the most prescribed drug within the UK's healthcare institutions. Moreover, it's imperative to underscore the study's exclusive focus on drug-gene interactions. The dearth of research on drug-drug-gene interactions, as previously highlighted[33], steers this study towards its concentration on drug-gene interactions. This emphasis is justified given that a majority of pharmacogenomic research is predominantly constrained within this realm.

CONCLUSION

This study stands as a trailblazer, offering a clear and concise guide for healthcare providers aiming to implement pharmacogenomic services within their institutions. Significantly, our research addresses two critical challenges: firstly, it aids in the identification and prioritization of essential pharmacogenomic tests within healthcare settings, and secondly, it fills the existing knowledge gap in pharmacogenomics by presenting a user-friendly, comprehensive database of crucial genotype-guided clinical recommendations for practitioners. In light of these advancements, the present study holds tremendous potential for elevating clinical practice standards and enhancing patient care outcomes.

AUTHOR CONTRIBUTIONS

Mustafa Malki Conceptualization, Methodology, Formal analysis, Writing – original draft, review & editing.

CONFLICTS OF INTEREST

We report that there are no competing interests to declare.

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