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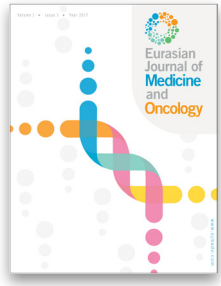

Review

Understanding Clinical Pharmacogenomics: A Descriptive Review

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Abstract

Pharmacogenomics (PGx) is the study of the correlation between an individual's genome and their response to specific medications. While different individuals respond differently to drugs, it has only been since the documentation of the human genome in 2003 that researchers have been able to make a tighter genetic connection with their metabolism. This study explores the current state of the PGx as of 2019 with an emphasis on its clinical usefulness. We analyzed data from the Food and Drug Administration (FDA), the Clinical Pharmacogenetics Implementation Consortium (CPIC) and PharmGKB, three key organizations that support pharmacogenomics in the US. A supported literature review was performed from PubMed and ClinCalc. We identified 27 drug-biomarker pairs on the highest ratings of confidence based on FDA, CPIC, and PharmGKB and chose 9 exemplary drugs to tabulate the association study (GWAS), PharmGKB dosing and FDA PGx actionability.

Keywords: Clinical implementation, description, pharmacogenomics, pharmacogenetics

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Pharmacogenomics (PGx) is the study of the linkage between an individual's genome and the specific medications. While most people respond differently to drugs, it has only been since the documentation of the human genome in 2003 that we have been able to make a tighter genetic connection with drug metabolism.[1] The potential usefulness stems from the ability to reasonably predict an individual's response to a medication before prescribing it for possible dose modification in regard to the adverse drug reactions. It initiates with the links of biomarkers to the specified drugs with subsequent development of dosing algorithms and drug label information.

Methods

The objective of this study is to assess the clinical usefulness of PGx in 2018. We compared and analyzed the data from the Food and Drug Administration (FDA), Clinical Pharmacogenetics Implementation Consortium (CPIC) and Pharmacogenomics Knowledgebase (PharmGKB), which represent the three key organizations in the United States (US) overseeing PGx. FDA[2] is a US government agency chartered to ensure the public safety by overseeing approval and guidelines for prescription drugs. CPIC[3] is a consortium of professionals from the medical, pharmacy, and research communities originated in 2009 by the Pharmacogenomics Research Network (PGRN) and PharmGKB. The CPIC informatics group was formed in 2014 to develop clinical decision support (CDS) standards to be implemented in personal health records (PHR). Likewise, PharmGKB[4] is the US government funded organization chartered to support the FDA with research and recommendations re-

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lated to the use of PGx. All three autonomous organizations maintain databases for PGx informatics and evaluate the same or other medications. But at times they evaluate each other's findings and maintain distinctive systems of evidence-based confidence levels of drug-gene pairs.

We also sampled nine drugs with PGx implications from the CPIC level of highest confidence for existing guidelines, recommendations, and prevalence in patient cohorts from genome-wide association studies (GWAS).[5] GWAS analyzes the individual genomic variation for associated traits including drug reactions. GWAS is used to develop a drug-gene pairs for these nine exemplary drugs. Dosing and guideline recommendations are taken from CPIC, PharmGKB, FDA and ClinCalc[6] for analysis to develop the current trend of progression. ClinCalc is an online tool to help medical professionals calculate medications dose and support the clinical decisions based on the current evidence.

Search Techniques

FDA, CPIC and PharmGKB databases were used for supporting the recommendations, drug-gene pair data, levels of confidence, and FDA PGx label indications and dosing formulations. PubMed' database was employed for locating GWAS and comparative analysis in the results and discussion sections. Studies exhibiting clinical application of pharmacogenomics were identified with the keywords: "Clinical pharmacogenomics" OR "Clinical use of pharmacogenomics" OR "Pharmacogenomic tests" to illustrate the state of tactical implementation of pharmacogenomics. Similarly, non specific combination of keywords used to identify studies for the nine exemplary drugs include: "Pharmacogenomics" OR "Pharmacogenetics" OR "GWAS" OR "Clinical significance of pharmacogenomics" OR "Clopidogrel Pharmacogenomics" OR "Codeine Pharmacogenomics" OR "Warfarin Pharmacogenomics" OR "Tacrolimus Pharmacogenomics" OR "Carbamazepine Pharmacogenomics" OR "Abacavir Pharmacogenomics" OR "Thiopurine Pharmacogenomics" OR "Statins Pharmacogenomics" OR "Phenytoin Pharmacogenomics" OR "Thioguanine Pharmacogenomics." Only the studies reporting incidence of drug-gene pairing within specific cohorts have been selected to illustrate the significance of applied pharmacogenomics with exemplary drugs.

Compilation of screening criteria used to identify articles of interest for this review for each exemplary drug (Fig. 1). Criteria were progressively filtered and refined from top to bottom.

Explanation of Analysis

A descriptive analysis was performed to determine the quantity and quality of PGx clinical data. As a prerequisite,

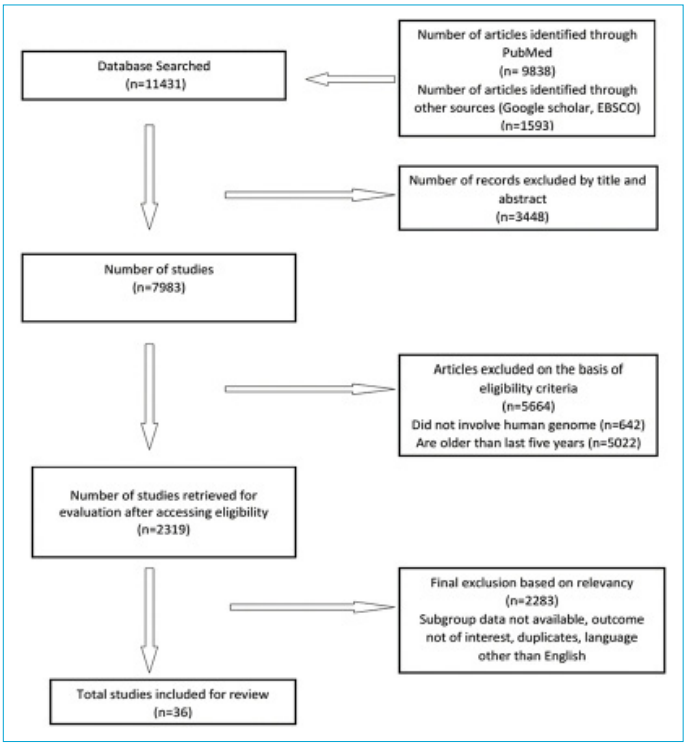

Figure 1. Flowchart showing the screening criteria to identify relevant articles for this descriptive review.

the rating systems are explained, and these levels represent the respective way to state their level of confidence in evidence to qualify their recommendations (Table 1).

Results

Data Analysis of Drug-Gene Pairs

292, 352 and 651 drug-biomarkers pairs with PGx interest were identified within FDA, CPIC and PharmGKB respectively (Table 2). CPIC and PharmGKB have tier system to quantify the extent of each organization's accounting for drug-gene pairs as well as the difference between their levels of confidence.

Drug Level

The strategic differentiation of drug-gene pairs was to establish a roster that demonstrated the highest level of confidence among these three organizations (Table 3). CPIC level A was the only level offering the confidence needed for clinical application as per their guidelines. It was used to select the best indications and subsequently compared to PharmGKB and FDA to develop a solid count.

Graded Confidence Levels

An analysis of drug-gene pairs mentioned above was performed as an indication of the overall confidence level after considering recommendations from FDA, CPIC and Phar-

Table 1. Explanation of PGx levels from Food and Drug Administration (FDA), Clinical Pharmacogenetics Implementation Consortium (CPIC) & Pharmacogenomics Knowledgebase (PharmGKB)

	FDA actionable PGx	
Advisory	**Interpretation**	
Test required	Requires test conducted to determine that patient's sensitivity to drug.	
Test recommended	The testing recommended but not required.	
Actionable PGx	Information given about dose or efficacy of a drug to patient subgroup without mention of a test.	
Informative PGx	A gene or protein is mentioned but no difference of response in patients having that difference is suggested.	
	PharmGKB evidence levels	
Level	**Interpretation**	
1A	Denotes PGx guideline from CPIC, PGRN site, other significant hospital, or medical society endorsement.	
1B	Based on more than one cohort showing significance with a lot of evidence and a significantly affected percent of patients.	
2A	Contains association with Very Important Pharmacogene (VIP) per PharmGKB.	
2B	Contains a moderate amount of evidence where the affected group may be small and statistical significance is less than 2A.	
3	Contains evidence of only a single study that has not been repeated or multiple studies that lack statistical significance.	
4	Contains evidence that comes from a study lacking statistical significance.	
	CPIC levels	
Level	**Interpretation**	**Evidence**
A	Prescription of drug should be changed.	High
B	Genetic based dosing may be indicated but dose is like non-genetic based dose.	Weak
C	No convincing genetic evidence exists. No changes are recommended.	Mixed
D	Few studies are published. No changes are recommended.	Mixed

Data derived from the FDA (www.fda.gov), CPIC (https://cpicpgx.org), and PharmGKB (www.pharmgkb.org).

Table 2. Comparison of databases from Food and Drug Administration (FDA), Clinical Pharmacogenetics Implementation Consortium (CPIC) & Pharmacogenomics Knowledgebase (PharmGKB) showing the number of drugs with PGx interest

Agency	**Drug-biomarker pairs**	**Tier†**					
		Tier 1	**Tier 2**	**Tier 3**	**Tier 4**	**Tier 5**	**Tier 6**
FDA‡	292	–	–	–	–	–	–
CPIC	352	48-A	87-B	12 -B/C	72- C	34-C/D	99-D
PharmGKB	641	46-1A	70-2A	–	59-3	6-4	64-None
		10-1B	91-2B				

Data derived from the FDA (www.fda.gov), CPIC (https://cpicpgx.org) and PharmGKB (www.pharmgkb.org). †: Tier quantifies the extent of each organization's accounting for drug-gene pairs as well as the difference between their levels of confidence; ‡: FDA does not have tiers.

mGKB (Table 4). 27 amongst them met the highest level of confidence, which were used as a selection pool for this study to provide nine exemplary drugs chosen by us.

Exemplary Drugs

Nine drug-gene pairs were selected from the 27 highest confidence levels given above based on their numerical impact upon total prescriptions and additional measure of clinical significance. We tabulated their uses, mechanisms of action (MOA), genomic associated alleles, dosing guidelines from PharmGKB and normal/actionable percent of cohorts extracted from GWAS (Table 5). The DNA biomarkers referenced in the following table consist of genes, single nucleotide polymorphisms (SNP) and alleles taken from GWAS. Genes are labeled with a text string of upper-case letters and numerals. SNPs, the most common type of genetic variant consisting of only one changed nucleotide, are labeled with a lower case of "rs" followed by numerals with each SNP having one unique identifier.[9] Alleles are documented with an asterisk (*) followed by a numeral, with each pair of alleles divided by a "/". Pairs of alleles containing the same numerals are homozygous and with dif-

Table 3. Comparison of Clinical Pharmacogenetics Implementation Consortium (CPIC), Pharmacogenomics Knowledgebase (PharmGKB) & Food and Drug Administration (FDA) levels for pharmacogenomic actionability of drug-gene pairs

Gene	Drug	CPIC Level	Pharm GKB Level	FDA Label Indicator	Gene	Drug	CPIC Level	Pharm GKB Level	FDA Label Indicator
HLA-B †	Abacavir	A	1A	Testing required	CYP2D6	ondansetron	A	1A	Informative PGx
HLA-B	Allopurinol	A	1A	No FDA indication	HLA-B	oxcarbazepine	A	1A	Testing recommended
CYP2C19	amitriptyline	A	1A	No FDA indication	CYP2D6	oxycodone	A	2A	No FDA indication
CYP2D6	amitriptyline	A	1A	Actionable PGx	CYP2D6	paroxetine	A	1A	Informative PGx
UGT1A1	Atazanavir	A	1A	No FDA indication	CYP2C9	phenytoin	A	1A	Actionable PGx
TPMT	azathioprine	A	1A	Testing recommended	HLA-B	phenytoin	A	1A	Actionable PGx
DPYD	capecitabine	A	1A	Actionable PGx	G6PD	rasburicase	A	1A	Testing required
HLA-A	carbamazepine	A	1A	Actionable PGx	CACNA1S	sevoflurane	A	3	Actionable PGx
HLA-A	carbamazepine	A	1A	Actionable PGx	RYR1	sevoflurane	A	3	Actionable PGx
HLA-B	carbamazepine	A	1A	Testing required	SLCO1B1	simvastatin	A	1A	Informative PGx
CYP2C19	clopidogrel	A	1A	Actionable PGx	CACNA1S	succinylcholine	A	3	Actionable PGx
CYP2D6	codeine	A	1A	Actionable PGx	CYP3A5	tacrolimus	A	1A	No FDA indication
CACNA1S	desflurane	A	3	Actionable PGx	CYP2D6	tamoxifen	A	1A	No FDA indication
RYR1	desflurane	A	3	Actionable PGx	CYP2D6	tamoxifen	A	1A	No FDA indication
DPYD	fluorouracil	A	1A	Actionable PGx	TPMT	thioguanine	A	1A	Actionable PGx
CYP2D6	fluvoxamine	A	1A	Actionable PGx	CYP2D6	tramadol	A	1B	Actionable PGx
UGT1A1	irinotecan	A	2A	Actionable PGx	CYP2D6	tropisetron	A	No PharmGKB indication	No FDA indication
CACNA1S	isoflurane	A	3	Actionable PGx	CYP2C19	voriconazole	A	1A	Actionable PGx
RYR1	isoflurane	A	3	Actionable PGx	CYP2C9	warfarin	A	1A	Actionable PGx
CFTR	ivacaftor	A	1A	Testing required	CYP4F2	warfarin	A	1B	No FDA indication
TPMT	mercaptopurine	A	1A	Testing recommended	VKORC1	warfarin	A	1A	Actionable PGx
CYP2D6	nortriptyline	A	1A	Actionable PGx	CYP2C19	citalopram	A	1A	Actionable PGx
IFNL3	peginterferon alfa-2b	A	1A	Actionable PGx	CYP2C19	escitalopram	A	1A	Actionable PGx
IFNL3	ribavirin	A	1A	No FDA indication	IFNL3	peginterferon alfa-2a	A	1A	No FDA indication

†Additional syntax for gene description used in this article follows the naming convention prescribed by the HUGO Gene Nomenclature Committee (HGNC).[7] The syntax follows. ["Group"-"Gene"*Allele group: protein: synonymous DNA in coding region: differences in noncoding region + suffix to show changes in expression]. An example of this syntax would is HLA-B-*01:102:01:03N.
[8] Data derived from the FDA (www.fda.gov), CPIC (https://cpicpgx.org) and PharmGKB (www.pharmgkb.org) was tabulated and analyzed to differentiate clinically actionable drug-gene pairs from those still being researched or regarded with ambivalent results.

Table 4. Summation of graded confidence levels based on Clinical Pharmacogenetics Implementation Consortium (CPIC), Pharmacogenomics Knowledgebase (PharmGKB) & Food and Drug Administration (FDA)

Confidence Level Criteria	Count
CPIC level A	48
PharmGKB level 1A	36
PharmGKB level 1B	2
PharmGKB level 2B	2
PharmGKB level 3	7
FDA label indicators	37
CPIC A, PharmGKB 1A and an FDA label indicator †	27
CPIC level A and PharmGKB level 1A, but no FDA label indication	8
CPIC level A and FDA label indicator but have the PharmGKB level of 3	7
CPIC A, a PharmGKB 2A and an FDA label indicator	1
CPIC A, PharmGKB 2A with no FDA label indicator	1
CPIC A, PharmGKB 1B and no FDA indicator	1
CPIC A, no PharmGKB and no FDA indicator	1
† Indicates the 27 highest confidence level	

Data derived from the FDA (www.fda.gov), CPIC (https://cpicpgx.org) and PharmGKB (www.pharmgkb.org).

ferent numerals are heterozygous.

Exemplary Drugs with FDA Labels

7, out of 9, exemplary drugs had FDA label summaries that were detailed well enough to illustrate further depth into the clinical application of genetic dosing algorithms. These exemplary drugs were tabulated with corresponding FDA labels to show additional depth of support for dosing recommendations (Table 6). FDA label summaries were derived from the original NIH public database[23] for placement into PharmGKB.

Biomarkers are grouped into normal and actionable categories. These genetically actionable/normal percentages are plotted to illustrate the significance of the application of pharmacogenomics for each of these exemplary drugs (Fig. 2). Specific actions are tied to different biomarkers which may consist of using an alternative drug, raising or lowering the dose depending on the dosing algorithms. The percent of individuals who are not having actionable drug-biomarkers are marked as normal and the rest as actionable. Prescription statistics are taken from ClinCalc.[6]

Warfarin

Finally, we chose warfarin from these exemplary drugs to show the wide variation on dosing algorithms based on its actionable allele combination (Fig. 3). 26% of the populations have normal alleles while 74% carry at least one actionable alleles (2% with three actionable alleles, 21% with two actionable alleles, and 51% with three actionable alleles).[13, 14] GWAS studies imply that over 70% of the population has genetically actionable drug-gene pairs for warfarin.

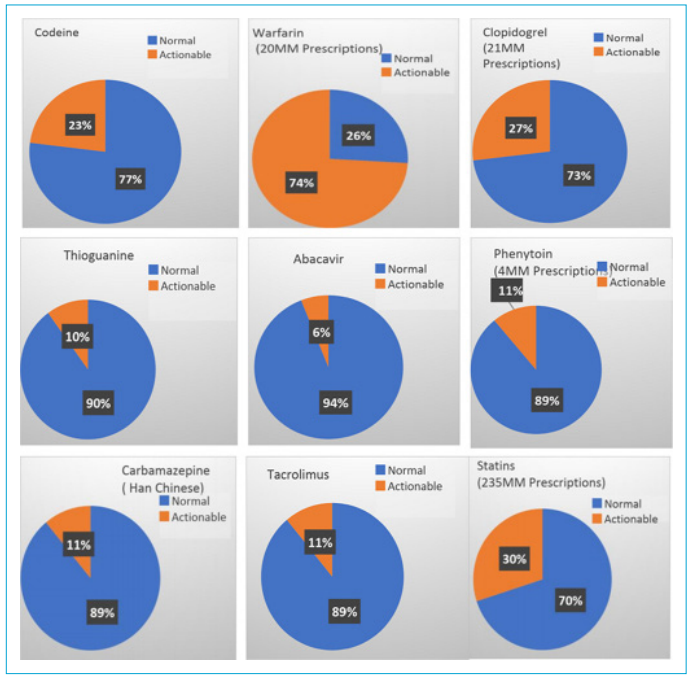

Figure 2. Figures showing the number of normal/actionable drug biomarkers prescriptions percentages for the nine exemplary drugs to show their quantitative effect.

Data derived from the FDA (www.fda.gov), CPIC (https://cpicpgx.org) and PharmGKB (www.pharmgkb.org).

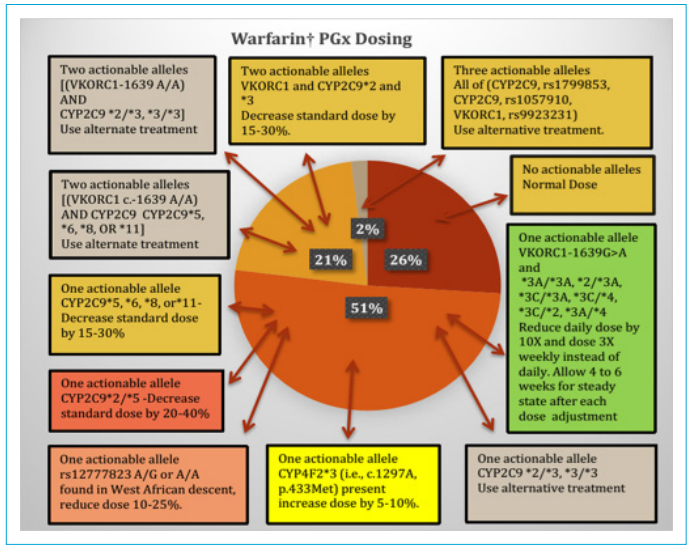

Figure 3. Pie chart showing the allelic variations in warfarin in relations to the PGx dosing algorithms.

†Warfarin dosing algorithm shows wide variation based upon the actionable allele combination. The percent distribution in the population shows 26% being normal, 2% having three actionable genes, 21% having two actionable genes, and 51% having three actionable genes.[13, 14]

Table 5. Exemplary medications chosen from 27 highest confidence level as per the Clinical Pharmacogenetics Implementation Consortium (CPIC), Pharmacogenomics Knowledgebase (PharmGKB) & Food and Drug Administration (FDA)

Drug	Gene	Haplotype, SNP	PharmGKB Guideline Summary	% Pop.
Codeine	CYP450 2D6	*1/*1,*1/*2,*2/*2,*1/*41, *1/*4,*2/*5, *10/*10	Use standard dosing.	77
	CYP450 2D6	*4/*10, *5/*41	Use standard dosing. If no response, consider alternatives.	12
	CYP450 2D6	*1/*1xN, *1/*2xN	Avoid codeine because of potential toxicity.	1-2
	CYP450 2D6	*4/*4,*4/*5, *5/*5,*4/*6, *5/*5,*4/*6	Codeine shows lack of efficacy and should be avoided.	5-10
Warfarin	CYP2C9, VKORC1	Lacks (CYP2C9 rs1799853, rs1057910 & VKORC1 rs9923231)	Use standard dosing.	26
	CYP2C9, VKORC1	VKORC1 and CYP2C9*2 and *3 OR CYP2C9*5, *6, *8, or*11	Decrease standard dose by 15-30%.	51
	CYP2C9	If CYP2C9*2/*5 present, OR if two variant alleles	Decrease standard dose by 20-40%.	21
	CYP2C9, VKORC1	All (CYP2C9 rs1799853, CYP2C9 rs1057910, VKORC1 rs9923231)	Use alternate treatment. Dosing algorithms vary widely for specific biomarkers in this group.	2.4
Clopidogrel	CYP2C19	Lacks rs4244285	Use standard dosing.	73
	CYP2C19	rs4244285, heterozygous 25%, homozygous 1-3% *1/*1,*1/*2,*1/*3,*2/*17, *2/*2,*2/*3, *3/*3	Use alternative antiplatelet therapy.	27
Thioguanine	TPMT	*1/*1	Start normal & adjusting in 2 weeks after steady state.	10
	TPMT	*1/*2,*1/*3A, *1/*3B,*1/*3C,*1/*4	Reduce normal dose by 30 to 50 % based on myelosuppression. Allow 2 to 4 weeks to reach steady state.	
	TPMT	*1/*3B,*1/*3C,*1/*4	Reduce daily dose by 10X. Dose 3X weekly. Allow 4-6 weeks for steady state after each dose adjustment.	
Tacrolimas (% for Han Chinese)	CYP3A5	rs776746, *1/*1	Increase starting doses 1.5 to 2 X normal starting dose.	11
CYP3A5	*1/*3, *1/*6, *1/*7	Do not exceed 0.3mg/kg/day for	NA starting dose. Apply drug monitoring	
	CYP3A5	*3/*3,*6/*6,7/*7,*3/*6,*3/*7,*6/*7	Initiate with recommended dose. Use drug monitoring for adjustments	
Carbamazapime	HLLA-A	Not HLA-A31:	If carbamazepine-naive don't use.	9-11
	HLA-A	HLA-A31:	If alternatives not available use with increased monitoring. Adverse reactions occur within three months	Han Chinese
Abacavir	HLA-B*57:01	NOT HLA-B*57:01	Use standard dose	94
		+ HLA-B*57:01	Do not use abacavir	6
Simvastatin	SLCO1B1	*1a/*1a, *1a/*1b, *1b/*1b	Normal myopathy risk. Start with and adjust with disease-specific guidelines	70
	SLCO1B1	*1a/*5, *1a/*15, *1a/*17, *1b/*5, *1b/*15, *1b/*17	Intermediate myopathy risk, use lower dose or other statin, use CK monitoring	30
	SLCO1B1	*5/*5, *5/*15, *5/*17, *15/*15, *15/*17, *17/*17	High myopathy risk, use lower dose or other statin, use CK monitoring	
Phenytoin	SCN1A	Test for TPMP status prior to dosing.	Test for TPMP status prior to dosing.	1-10

Data derived from the FDA (www.fda.gov), CPIC (https://cpicpgx.org) and PharmGKB (www.pharmgkb.org)

Table 6. Seven exemplary drugs with Food and Drug Administration (FDA) label summary

Exemplary medication	FDA label summary
Codeine	CYP450 2D6 variant of *1/*1xN, *1/*2xN associated with death in infants breast fed by mothers having this variant due to rapid metabolism conversion of codeine to morphine in milk.
Warfarin	VKORC1: G-1639A Variant indicates lower dose requirements in Asians and Caucasians. PROC and PROS1 gene variants for protein C and protein S are associated with tissue necrosis following warfarin administration. VKORC1 and CYP2C9 variants are associated with altered dose recommendations.
Clopidogrel	CYP2C19*2, CYP2C19*3 & other CYP2C9 variants are associated with low metabolism of clopidogrel which indicates using an alternative medication.
Thioguanine	Patients with certain TPMT variants, the gene that codes for thiopurine methyltransferase, can suffer from life threatening bone marrow suppression.
Phenytoin	Strong risk of Steven Johnsons Syndrome (SJS)/ Toxic epidermal Necrolysis (TEN) in Asian patients having the `HLA-B*1502 variant and taking carbamazepine.
Carbamazepine	HLA-A*3101 associated with hypersensitivity.
	HLA-B*1502 in Asians associated with fatal dermatological reactions.
Abacavir	Genetic testing for the HLA-B*5701 allele required.
	Hypersensitivity association.

Data derived from the FDA (www.fda.gov).

Discussion

Approximately, 4.5 million patients [24] report side effects to medications annually in the US and around 128,000 hospitalized patients [25] die each year from prescription based medications. There is a wider safety and financial implications of these adverse drug reactions to general public, and third-party insurance providers like, insurance companies, corporations that self-fund insurance plans and government organizations such as Medicare, Medicaid, and the Veterans administration. Johnson [26] implemented a pharmacogenomic panel test for five genes and showed that more than 90% patients had clinically actionable drug-gene pairs. This finding is also consistent with illustrations shown by O'Donnell PH et al., [27] which labels the pharmacogenomics as a summation of the outliers in the population unable to show normal drug responses.

We surveyed pharmacogenomics from several vantage points on this study. The first examination determined the concurrence of the FDA, CPIC and PharmGKB levels of confidence of guidelines. All three organizations play a high profile roles in a $215M initiative designed to alleviate more than 100.00 deaths per year directly related to adverse drug reactions (ADR), listed as the sixth leading cause of death in the US, known as the Precision Medicine Initiative (PMI).[28] In addition to these analyses, we profiled nine drugs that have guidelines, dosing algorithms and FDA label recommendations as a subset of many more with a conservative estimate of 27 meeting the highest levels of the three critical organizations. This is in unison to the study conducted by SD Mooney,[29] who described the use of GWAS and two exemplary actionable drugs: warfarin and tamoxifen.

Undeniably, there is a need for pharmacological genomic dosing algorithms for both economic and safety reasons. Clinical decision support system (CDS) has been successfully developed to represent the existing pharmacogenomic knowledge base, locate errors, assigns biomarkers to patients, provides pharmacogenomic recommendations, and identifies inconsistencies in dosing guidelines from different sources.[30] Feasibility of unfettered clinical use also depends upon supportive technology. One strategy is to build the CPIC guidelines into a unified model language system for PGx CDS.[31] But there are still many challenges to the successful implementation of PGx applications to the wider populations including the lack of awareness and tactical application, absence of proven associations between many drugs and biomarkers, immature development of supporting double-blind studies, and dosing algorithms that are not yet framed. [32] A collective effort is necessary for applying genomic technology to the greater public. The entire stakeholder, including the medical educators, students and clinicians needs to understand the state of this technology to have confidence for its full clinical interpretation and utilization.

Conclusion

PGx can be employed in all patients to significantly decrease adverse drug reactions while prescribing actionable drugs. It carries a strong clinical safety prospect and 27 drug-gene pairs have met the highest level of confidence from FDA, CPIC, and PharmGKB for PGx screening. There is a dire need for accompanying infrastructure with properly trained staff. We recommend that PGx should be clinically employed to the greater public and any existing objections for its application are removed to develop this field of medicine.

Learning points

1. PGx uses individual's genome to predict nonstandard reactions to a drug.
2. PGx has progressed continuously since the documentation of the human genome in 2003.
3. PGx screening is useful in patients who carry actionable drug-gene pairs.
4. PGx should be clinically employed in the field of medicine for optimal patient output.
5. A collective effort from all the concerned stakeholders is necessary for the effective clinical application of PGx.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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