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ARTICLE

Pharmacogenomic biomarker information on drug labels of the Spanish Agency of Medicines and Sanitary products: evaluation and comparison with other regulatory agencies

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This work aimed to analyse the pharmacogenetic information in the Spanish Drug Regulatory Agency (AEMPS) Summary of Products Characteristics (SmPC), evaluating the presence of pharmacogenetic biomarkers, as well as the associated recommendations. A total of 55.4% of the 1891 drug labels reviewed included information on pharmacogenetic biomarker(s). Pharmacogenomic information appears most frequently in the "antineoplastic and immunomodulating agents", "nervous system", and "cardiovascular system" Anatomical Therapeutic Chemical groups. A total of 509 different pharmacogenetic biomarkers were found, of which CYP450 enzymes accounted for almost 34% of the total drug-biomarker associations evaluated. A total of 3679 drug–biomarker pairs were identified, 102 of which were at the 1A level (PharmGKB® classification system), and 33.33% of these drug-pharmacogenetic biomarker pairs were assigned to "actionable PGx", 12.75% to "informative PGx", 4.9% to "testing recommended", and 4.9% to "testing required". The rate of coincidence in the assigned PGx level of recommendation between the AEMPS and regulatory agencies included in the PharmGKB® Drug Label Annotations database (i.e., the FDA, EMA, SWISS Medic, PMDA, and HCSC) ranged from 45% to 65%, being 'actionable level' the most frequent. On the other hand, discrepancies between agencies did not exceed 35%. This study highlights the presence of relevant pharmacogenetic information on Spanish drug labels, which would help avoid interactions, toxicity, or lack of treatment efficacy.

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INTRODUCTION

Pharmacogenomics (PGx) is essential for transitioning from population-based treatment to individualized therapy. Although clinical testing for selected genes known to influence drug efficacy and/or toxicity is available, discordances between biomarker analyses and their utilization in therapeutic recommendations for accurate prescription still occur.

Approved drug labels (DLs) include the essential information in the appropriate sections, the recommended actions for health care professionals about the impact of genotype on the response to a drug through a description of relevant genomic markers, the functional effects of genomic variants, dosing recommendations based on genotype, and other applicable genomic information. Unfortunately, specific actions based on PGx biomarker information are not present [1].

The presence of information and recommendations on DLs about pharmacogenetic biomarkers, based on consistent knowledge, needs to be encouraged or required by major regulatory bodies, i.e., the U.S. Food and Drug Administration (FDA), the European Medicine Agency (EMA) and other national regulatory agencies [2, 3].

Additionally, discordances regarding the level of recommendation between agencies occur, thus representing a significant barrier to the clinical implementation of PGx, mostly due to the absence of a consensus among the stakeholders involved [4–10]. Additionally, medical, ethical, legal, social, or economic aspects represent other sources of discrepancies [6], as well as gaps in professional education and practice standards, doubts about the therapeutic relevance, regulatory and reimbursement challenges, and the viability of incorporating rapid-turnaround genetic testing into regular clinical practice may hinder such clinical implementation.

The Pharmacogenomics Knowledge Base (PharmGKB®) publishes data on PGx in DLs, as well as clinical implementation guidelines by the Clinical Pharmacogenomics Implementation Consortium and the Royal Dutch Association for the Advancement of Pharmacy–Pharmacogenetics Working Group. PharmGKB® encompasses information including clinical guidelines and drug labels, potentially clinically actionable gene-drug associations, and genotype-phenotype relationships, to be used as a reference for implementation [11]. In this sense, PharmGKB provides different categories to describe the PGx information present in DLs: testing required, testing recommended, actionable PGx and informative PGx. These categories may help healthcare professionals to assess the level of guidance and clinical relevance of the PGx information provided in DLs (https://www.pharmgkb.org/page/drugLabelLegend#pgx-level).

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Many studies have emphasized the importance of actionable PGx data in drug information sources for the clinical decision-making process [12–15]. Currently, the FDA and the EMA incorporate PGx information in the labelling of 15% of all their approved medications [3], and many DLs usually refer to more than one pharmacogene [4, 5, 16]. Likewise, the FDA publishes and maintains a list of substances whose DLs contain information about PGx biomarkers (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling) whereas the EMA develops and includes in PharmGKB®, European Public Assessment Reports of centrally approved medicinal products (MPs) containing PGx information [17, 18]. In Spain, DLs authorized by the National Spanish Agency of Medicines and Sanitary Products (AEMPS) are similarly organized into different sections, but no section concerning pharmacogenomics is included.

Ideally, regulations for drugs and diagnostics should not differ among countries, as the same scientific data generated are evaluated by regulatory authorities [19]. However, despite international efforts to obtain regulatory harmonization, differences regarding the implementation of pharmacogenomic information in official drug labelling occur worldwide [20]. Nevertheless, it is anticipated that national regulatory agencies within the European Union approve their product information based on the requirements specified in EMA guidelines and European Commission regulations, although there is no information about the implementation of PGx in nationally approved MPs. To date, no revision or analysis of PGx information present on the DLs of Spain has been carried out. Hence, the presence of PGx information and the level of implementation needs to be analyzed to summarize the current state of pharmacogenomic-related information in Spain.

Thus, this study aimed to provide a comprehensive repository including PGx information and to evaluate the PGx biomarker information present on Spanish DLs. A quantitative analysis of the data collected, the concordance and discrepancies, and their potential underlying causes in the corresponding recommendations for genome-informed drug treatment modalities with other international regulatory agencies are discussed, particularly focusing on drug-PGx biomarker associations with the highest level of evidence (1A) according to PharmGKB®, which compiles information from several regulatory agencies worldwide.

MATERIALS AND METHODS

The data presented here were collected in November 2021 from the database of the AEMPS (https://cima.aemps.es/cima/publico/buscadoravanzado.html) to identify biomarkers within the Technical Data Sheets of authorized medicines in Spain. The active ingredients were extracted and ordered by therapeutic groups according to the Anatomical Therapeutic Chemical (ATC) classification system.

The pharmacogenomic information was screened through all sections of the labels according to selection criteria that identified biomarkers referring to proteins or genes involved in pharmacokinetics, pharmacodynamics, hypersensitivity reactions, or other processes related to the drug response. Nonhuman genetic biomarkers, biomarkers used uniquely for diagnostic purposes or related to a drug other than the referenced drug (e.g., influences the effect of the referenced drug by interacting with another drug), were omitted. For drugs in multiple dosage forms, a single-representative product was listed, and drugs containing multiple active substances were excluded. The DL with the latest date of approval was included, and when the same date was detected more than once, the DL with the highest number of registrations was selected.

Data on biomarkers were collected in a database, including information referring to the biomarker, the sections of the DL in which it appears, and the role of each biomarker.

Drug-biomarker pairs classified as 1A level of evidence by PharmGKB® were selected to compare the recommendations included on the Spanish DLs with the FDA, EMA, Swiss Agency of Therapeutic Products (SwissMedic), Pharmaceuticals and Medical Devices Agency from Japan (PMDA) and Health Canada (Santé Canada, HCSC) DLs. PharmGKB® was also consulted to discuss the pharmacogenomics action level for each active principle that annotates DLs containing PGx information (https://www.pharmgkb.org/labelAnnotations).

Following the classification of PGx levels established by PharmGKB® indicating the level of action implied in each label (i.e., required test, recommended test, actionable information, informative note) and using the pharmacogenetic information contained in the DL, the current level of action for each 1A level drug-biomarker pair was discussed and compared with the aforementioned drug regulatory agencies [21].

RESULTS

Based on the 1891 drug labels reviewed in this study and approved by the AEMPS, 55.4% ($n = 1047$) include information on pharmacogenetic (PGx) biomarker(s) in different sections (Fig. 1A). An increasing trend of inclusion of PGx biomarkers and information related to PGx on DLs has been confirmed, particularly in the last decade (Table 1).

Drugs containing PGx biomarkers in their DL are included in all the ATC areas, although PGx information is more frequent for antineoplastic and immunomodulating agents ($n = 207$), followed by the nervous ($n = 196$), cardiovascular ($n = 128$), alimentary tract and metabolism ($n = 104$), and respiratory systems ($n = 75$) (Fig. 1B). Within each therapeutic class, oncology drug products showed the highest percentage of DLs with pharmacogenomic content (82.1%), followed by neurology and psychiatry drugs, and cardiology drugs. Moreover, there is a variable percentage of active principles within each ATC group (from 1.6% in group L to more than 15% in group P) that does not have a technical data sheet (Fig. 2).

A total of 509 different PGx biomarkers were found on the Spanish DLs reviewed. The most frequent PGx biomarker was *CYP3A4* (409), followed by *ABCB1*, *CYP2D6*, *CYP2C9*, *CYP1A2* and *CYP2C19*, all present on more than one hundred DLs (Table 2). CYP450 biomarkers account for almost 34% of the drug–biomarker associations listed [22]. Among the pharmacodynamic biomarkers, histamine H1 receptor (*HRH1*, $n = 48$), angiotensin-converting enzyme (*ECA*, $n = 44$), cyclooxygenase 2 (*PTGS2*, $n = 38$), dopamine receptor D2 (*DRD2*, $n = 38$), serotonin transporter (*SLC6A4*, $n = 28$) and β-2 adrenergic receptor (*ADRB2*, $n = 26$) were the most frequently found on the Spanish DLs reviewed (Table 2).

A total of 3679 drug–biomarker associations were identified. While psychiatric and neurologic drugs are mainly associated with CYP450 biomarkers and the transporters and/or receptors of neurotransmitters, biomarkers included for oncology drugs are not only associated with pharmacokinetics or linked to receptors (Fig. 3A, B) but also related to the tumour types involved, such as human epidermal growth factor receptor 1 (*HER1*) or human epidermal growth factor receptor 2 (*HER2/neu*).

Again, CYP450 biomarkers are highly present within DLs of cardiovascular drugs, together with pharmacodynamic biomarkers such as ACE, angiotensin II AT1 receptor (*AGTR1*) or both α- and β-adrenergic receptors. Interestingly, a remarkable frequency of *DRD-2*, *SLC6A4* and *SLC6A2*, as well as histamine H1 (*HRH1*) and serotonin receptors (*HTR1A*), is found within DLs of the nervous system, while vascular endothelial growth factor receptor 2 (*KDR*), c-kit tyrosine kinase CD117, *HER1* and *HER2* are frequent biomarkers within the L group (Fig. 3).

On the Spanish DLs, biomarkers were identified either related to pharmacokinetics ($n = 128$, 25.2%), pharmacodynamics ($n = 333$, 65.4%), or other unspecific features ($n = 48$, 12.4%). None of the DLs listing pharmacogenomic biomarker(s) included any specific PGx evidence for the Spanish population, neither for clinical endpoints nor pharmacokinetics.

A total of 102 individual drug-PGx biomarker associations, comprising 78 different drugs and 23 specific pharmacogenomic

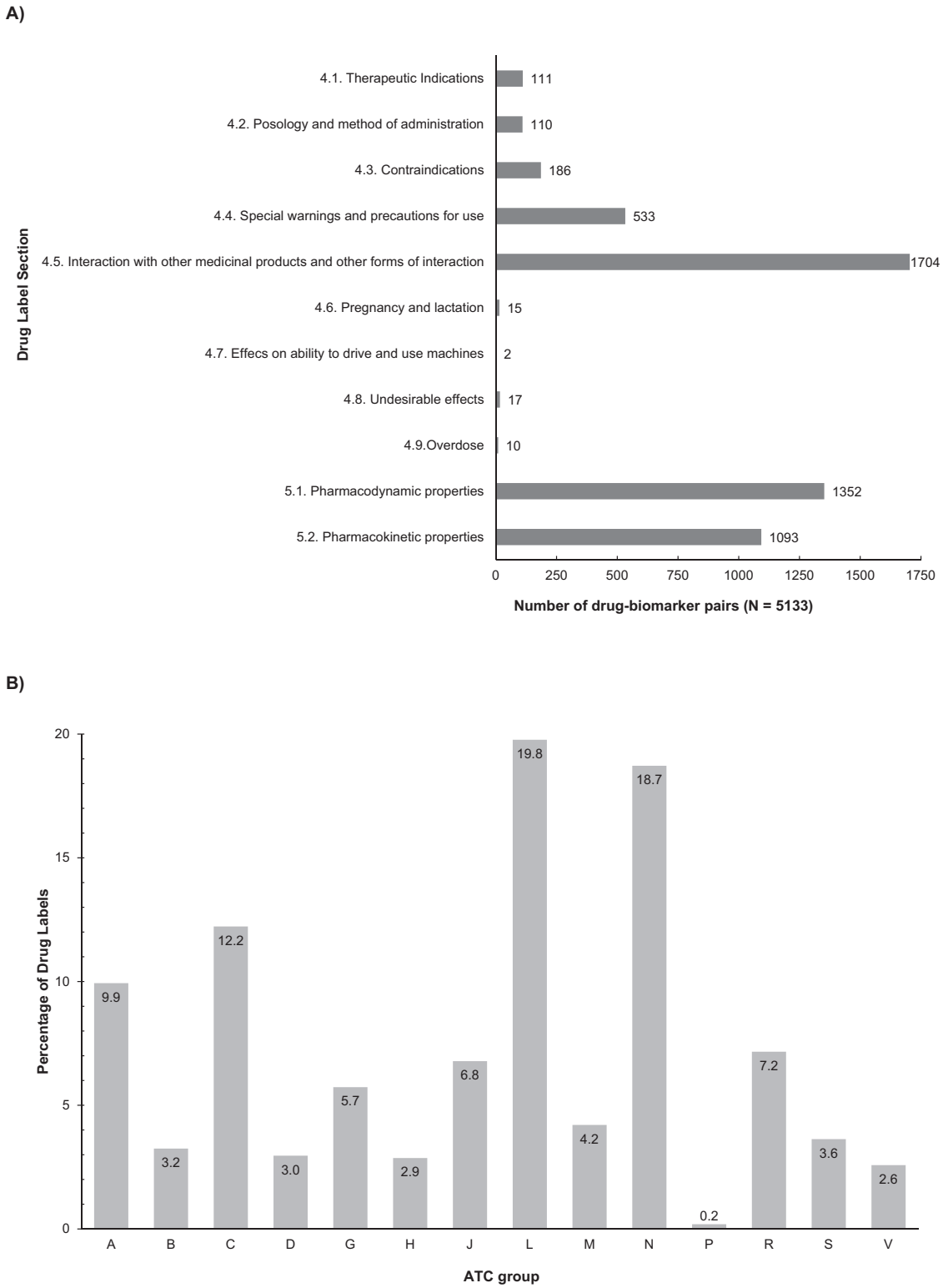

Fig. 1 Analysis of biomarker distribution and pharmacogenomics in Spanish drug labels. Distribution of biomarkers across DLs' sections for authorized medicinal products (**A**), and (**B**) distribution of drugs containing PGx biomarkers across therapeutic areas.

biomarkers, were classified as a 1A level of evidence in PharmGKB® (https://www.pharmgkb.org/page/clinAnnLevels). In Spain, 57 of these 1A drug-biomarker pairs were included on DLs approved by the AEMPS, including 49 drugs (62.8%) and 15 biomarkers. A total of 24.4% of drugs ($n = 19$) did not contain PGx information regarding these drug-PGx biomarker associations on their DLs, and 12.8% of drugs ($n = 10$) were not authorized or commercialized in Spain at that moment. Following the criteria established by PharmGKB®, it was found that 33.33% of these 1 A drug-PGx biomarker pairs were classified as "actionable PGx" and 12.75% as "informative PGx", while 4.9% and 4.9% were assigned to "testing required" and "testing recommended", respectively.

Table 1. Temporary evolution of the presence of pharmacogenomic biomarkers within drug labels authorized by the AEMPS.

ATC group	1945–1970	1971–1990	1991–2000	2001–2010	2011–2020
A	3	6	4	19	72
B	1	0	2	4	25
C	4	17	15	26	66
D	2	4	3	4	18
G	4	5	6	7	38
H	5	2	5	4	14
J	2	3	4	12	50
L	4	7	9	33	154
M	1	7	7	5	24
N	14	20	16	23	123
P	1	0	0	0	1
R	3	12	9	7	44
S	4	2	8	5	19
V	0	0	2	6	19
TOTAL	48	85	90	155	667

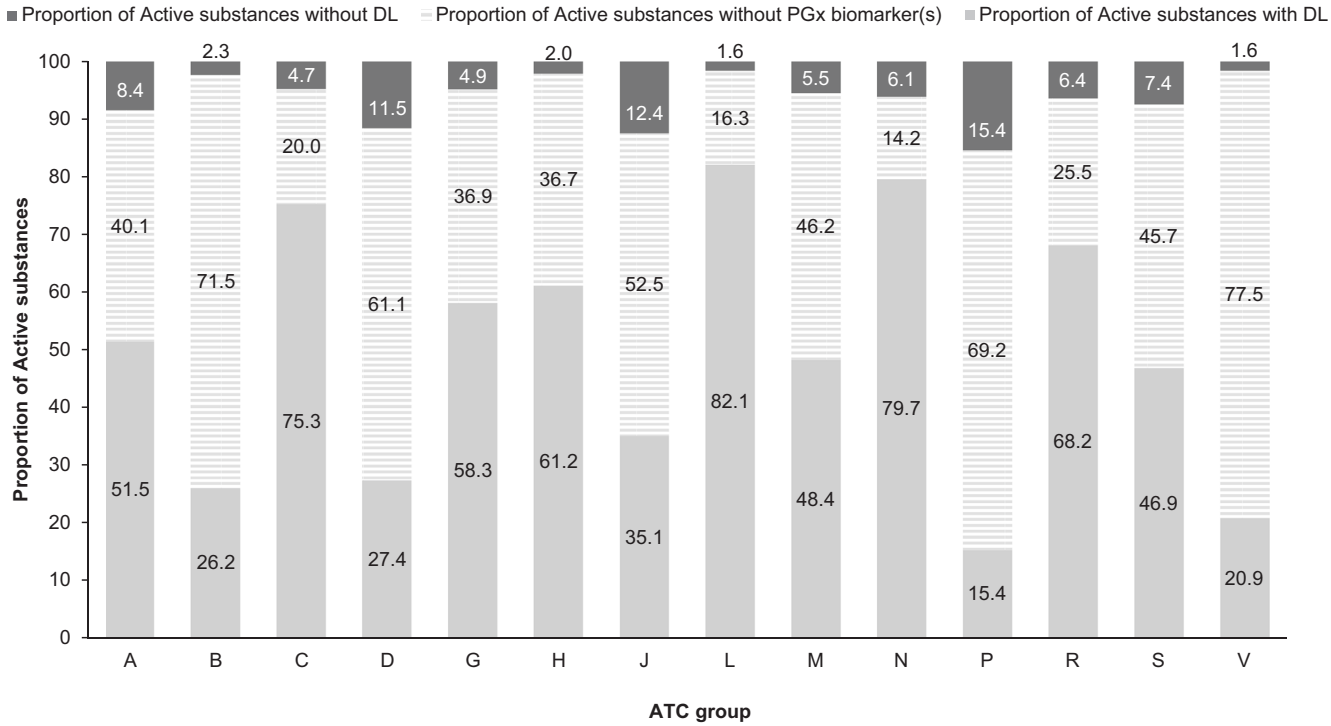

Fig. 2 Ratio of active substances and pharmacogenomic biomarkers in drug labels across ATC categories. Proportion of active substances containing drug labels, and of PGx biomarkers in DLs for each ATC group.

The rate of coincidence in the assigned PGx level between the AEMPS and the data provided by regulatory agencies registered in the PharmGKB® Drug Label Annotations database (https://www.pharmgkb.org/labelAnnotations) (i.e., the FDA, EMA, SWISS Medic, PMDA, and HCSC) ranged from 45% to 65%, with 'actionable level' being the most frequent. On the other hand, the discrepancies did not exceed 35%. Ten drug-PGx biomarker associations are included by other regulatory agencies but are not referenced on the Spanish DLs. In contrast, the PGx level of recommendation was assigned for 8 drug-biomarker pairs in Spain, but not by any of the other regulatory agencies (Table 3). Fourteen DLs containing PGx recommendations for 1A level drug-PGx biomarker pairs in PharmGKB® and/or by AEMPS additionally include recommendations for drug-PGx biomarker pairs with lower levels of evidence (Supplementary Table 1).

Summarizing the PGx recommendations annotated on Spanish DLs, the PGx level assigned as "actionable" was the most prevalent (Table 4). The anatomic Group N contains the highest number of any type of PGx recommendations for drug-biomarker pairs, most of which are actionable, while the highest proportion of "required" and "recommended" PGx recommendations is found within the L group.

DISCUSSION

The growing importance of pharmacogenomics for personalized drug prescription in Spain is confirmed by the increasing

Table 2. Distribution of the 25 most frequent specific PGx biomarkers among different ATC groups based on their presence in the Spanish DLs.

Biomarker (gene)	ATC Group														
	A	B	C	D	G	H	J	L	M	N	P	R	S	V	TOTAL
CYP3A4 (*CYP3A4*)	43	16	40	9	39	17	33	88	5	90	0	25	2	2	409
P-glycoprotein (*ABCB1*)	20	5	14	1	4	1	25	71	1	18	0	6	0	2	168
CYP2D6 (*CYP2D6*)	10	1	14	4	8	1	9	23	5	64	0	13	2	2	156
CYP2C9 (*CYP2C9*)	6	6	15	5	5	0	11	37	15	21	0	5	2	1	129
CYP1A2 (*CYP1A2*)	8	8	6	2	1	1	11	29	4	51	0	3	0	2	126
CYP2C19 (*CYP2C19*)	10	12	9	2	2	0	12	28	4	30	0	2	0	1	112
CYP2C8 (*CYP2C8*)	12	8	7	5	1	0	5	31	7	5	0	2	1	2	86
ATP-binding cassette super-family G member 2 (*ABCG2*)	7	4	4	0	3	0	8	42	1	2	0	0	0	2	73
CYP2B6 (*CYP2B6*)	2	9	2	0	0	0	8	23	1	12	0	1	0	1	59
Histamine H1 Receptor (*HRH1*)	0	0	0	3	0	0	0	1	0	15	0	21	8	0	48
Solute Carrier Organic Anion Transporter Family Member 1B1 (*SLCO1B1*)	4	3	7	0	0	0	9	20	1	1	0	0	0	1	46
Angiotensin converting enzyme (*ACE*)	0	0	37	0	0	0	0	4	1	0	0	0	0	2	44
CYP3A5 (*CYP3A5*)	5	3	2	0	4	0	2	17	0	8	0	1	0	1	43
Dopamine receptor D2 (*DRD2*)	4	0	0	0	2	0	0	0	0	32	0	0	0	0	38
Cyclooxygenase 2 (*PTGS2*)	0	0	12	0	0	0	0	0	21	3	0	1	1	0	38
UGT1A1 (*UGT1A1*)	2	1	2	0	1	0	7	18	2	1	0	3	0	1	38
Organic anion transporter 3 OAT3 (*SLC22A8*)	5	0	1	0	0	0	7	13	2	1	0	1	0	0	30
Serotonin transporter (*SLC6A4*)	0	0	0	0	1	0	0	0	0	26	0	0	0	1	28
Organic cation transporter 1 OCT1 (*SLC22A1*)	2	0	4	0	2	0	3	12	1	2	0	2	0	0	28
Beta 2 adrenergic receptor (*ADRB2*)	0	0	11	0	1	0	0	0	0	1	0	13	0	0	26
Noradrenaline/ Norepinephrine or NET transporter (*SLC6A2*)	0	0	0	0	0	0	0	0	0	24	0	0	0	0	24
Solute carrier organic anion transporter family member 1B3 (*SLCO1B3*)	2	1	2	0	0	0	7	9	1	1	0	0	0	1	24
Glucose-6-phosphate-dehydrogenase (*G6PD*)	6	0	0	0	0	0	9	0	0	2	2	1	0	2	22
Organic cation transporter 2 OCT2 (*SLC22A2*)	1	0	3	0	1	0	3	11	0	2	0	0	0	1	22
5-phosphodiesterase (*PDE5A*)	0	0	10	0	10	0	0	0	0	0	0	0	0	1	21

proportion of DLs listing PGx biomarkers, as well as the increasing number of active substances and PGx biomarkers relative to previous studies [18, 22–24]. For instance, only nine DLs authorized by AEMPS attributed the PGx level testing required or recommended: abacavir, carbamazepine, oxcarbazepine, ivacaftor, fluorouracil, gefitinib, mercaptopurine, siponimod and tegafur [22] (Table 4). Nevertheless, any direct comparison is limited by the criteria utilized in each study (e.g., the selection of the active principles included in every study).

It is worth noting the increase over time regarding the number and level of recommendations related to the presence of PGx biomarkers in DLs, and their particularly high frequency within the L, C and N ATC groups, for which personalized prescription is particularly important. The remarkable presence of PGx biomarkers in AEMPS is similar to studies from Japan [20], Hungary [24], Croatia [25], and Swissmedic [22], in which the PGx biomarkers are alternatively based on natural language processing (NLP), or the FDA [23].

Regarding the most frequent PGx biomarkers related to pharmacokinetics, similarities have been observed: CYP2D6, CYP2C19 and CYP2C9 are also highly present on DLs from Japan [20], the EMA [18], European national regulatory agencies [22, 24, 25], and the FDA [23]. On the other hand, the most frequent biomarkers linked to pharmacodynamics or other processes (i.e., *HRH1* and *ECA*, or *PTGS2, DRD2*, and *SLC6A4*) (Table 2) are diverse in studies on the FDA [23], Swissmedic [22] (G6PD, *HLA-A*), the Croatian [25] (DPYD, *HLA-A*), or the Hungarian regulatory agency (*ESR*, *PGR*, or G6PD) [24].

Previous studies have shown that almost everyone has one or more pharmacogenetic variations applicable to individualized drug therapy [26]. Indeed, ADRs, which represent approximately 3.5% of total hospital admissions, are mainly related to the central nervous system and gastrointestinal and cardiovascular systems [27], which is concordant with the higher frequency of PGx biomarkers present on the DLs of AEMPS within these ATC groups. PGx tests have been clinically available for more than 15 years, and studies have shown that PGx-guided therapy decisions for some medications can enhance clinical results [28]. Given this fact, as well as the high prescription rates of many medicines with pharmacogenetic relevance, pharmacogenomics adds valuable information and knowledge potentially influencing their dosing, effectiveness, and safety profile, thus becoming a key factor for improving personalized pharmacotherapy. Utilizing PGx information to guide rational drug therapy becomes essential to identify patients who are more likely to respond to a medication and those prone to experience an ADR. Consequently, pharmacogenetic testing and genotype-guided prescribing will undoubtedly help many patients [29].

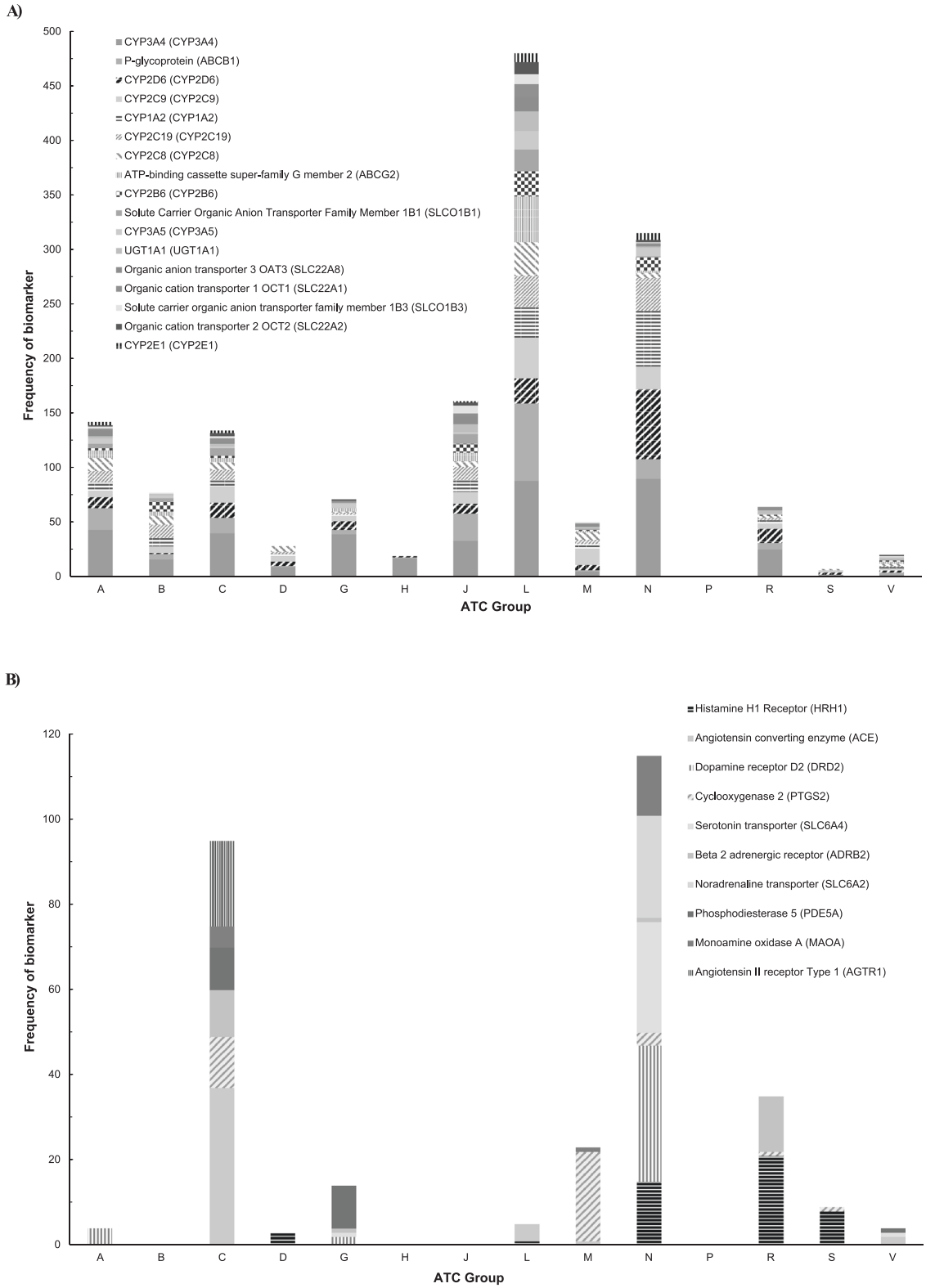

Fig. 3 Prevalence of key pharmacogenetic biomarkers in Spanish drug labels across ATC categories. Frequency of the most prevalent pharmacokinetic (**A**) and pharmacodynamic (**B**) biomarkers (present in a minimum of 20 DLs).

Likewise, including information and data related to PGx on DLs encourages physicians to consider testing these biomarkers before or during drug(s) treatment(s). Label revisions describing a group of individuals at increased risk that can be detected by genotyping may motivate increased pharmacogenetic testing [30–32]. The presence of this information was confirmed in this study based on the PGx biomarker frequency data observed on the DLs approved by the Spanish regulatory agency (Fig. 2). This trend was also confirmed in studies performed on PMDA [20] and EMA [18, 22, 23], even though the number of PGx biomarkers was

Table 3. Level of PGx recommendation included for each 1 A level drug-biomarker association, according to different regulatory agencies resumed in PharmGKB® and AEMPS*.

Drug-PGx Biomarker	AEMPS	FDA	EMA	Swissmedic	PMDA	HCSC
Abacavir-*HLA-B*	Required	Required	Required	Required	Informative	Required
Acenocoumarol-VKORC1	Actionable	NI	NI	NI	NI	NI
Allopurinol-*HLA-B*	Actionable	Recommended		Actionable	Informative	NI
Amitriptyline-CYP2C19	Actionable	NI	NI	NI	NI	NI
Amitriptyline-*CYP2D6*	Actionable	Actionable	NI	NI	NI	NI
Aripiprazole-*CYP2D6*	Actionable	Actionable	Actionable	Actionable	NI	Actionable
Atazanavir-UGT1A1	Informative	NI	NI	NI	NI	NI
Atomoxetine-*CYP2D6*	Actionable	Actionable	NI	Actionable	Actionable	Actionable
Atorvastatin-*SLCO1B1*	Actionable	Informative	NI	NI	NI	NI
Azathioprine-*TPMT*	Actionable	Recommended	NI	Actionable	Actionable	Actionable
Azathioprine-NUDT15	Actionable	Recommended	NI	Actionable	NI	NI
Boceprevir-*IFNL3*	NI	Informative	Actionable	NI	NI	Informative
Boceprevir-*IFNL4*	NI	NI	NI	NI	NI	NI
Capecitabine-*DPYD*	Actionable	Actionable	Recommended	Actionable	Actionable	Actionable
Carbamazepine-*HLA-A*	Actionable	Actionable	NI	Recommended	Actionable	Recommended
Carbamazepine-*HLA-B*	Required	Required	NI	Required	Actionable	Recommended
Celecoxib-*CYP2C9*	Actionable	Actionable	NI	Actionable	Actionable	Actionable
Citalopram-*CYP2C19*	Actionable	Actionable	NI	Actionable	NI	Actionable
Clomipramine-*CYP2D6*	Actionable	Actionable	NI	Actionable	NI	NI
Clomipramine-CYP2C19	Informative	NI	NI	NI	NI	NI
Clopidogrel-*CYP2C19*	Actionable	Actionable	Actionable	Actionable	Actionable	Actionable
Codeine-*CYP2D6*	Actionable	Actionable	NI	Actionable	Actionable	Actionable
Desflurane-*CACNA1S*	NI	Actionable	NI	NI	NI	Actionable
Desflurane-*RYR1*	NI	Actionable	NI	NI	NI	Actionable
Desipramine-*CYP2D6*	NI	Actionable	NI	NI	NI	NI
Dexlansoprazole-*CYP2C19*	NI	Actionable	NI	Actionable	NI	Actionable
Doxepin-*CYP2C19*	NDL	Actionable	NI	NI	NI	NI
Doxepin-*CYP2D6*	NDL	Actionable	NI	NI	NI	NI
Efavirenz-*CYP2B6*	Actionable	Actionable	Actionable	Actionable	Actionable	NI
Enflurane-*CACNA1S*	NI	Actionable	NI	NI	NI	NI
Enflurane-*RYR1*	NI	Actionable	NI	NI	NI	NI
Escitalopram-*CYP2C19*	Actionable	Actionable	NI	Actionable	Actionable	NI
Flecainide-CYP2D6	Informative	NI	NI	NI	NI	NI
Flucloxacillin-*HLA*-B	NI	NI	NI	Actionable	NI	NI
Fluorouracil-DPYD	Recommended	Actionable	NI	Required	Actionable	Actionable
Flurbiprofen-*CYP2C9*	NI	Actionable	NI	NI	NI	NI
Fluvoxamine-*CYP2D6*	Informative	Actionable	NI	Actionable	NI	NI
Gefitinib-*EGFR*	Required	Required	Required	NI	Required	Required
Gentamicin-*MT-ND1*	NI	NI	NI	NI	NI	NI
Gentamicin-*MT-RNR1*	NI	NI	NI	NI	NI	NI
Haloperidol-*CYP2D6*	Actionable	NI	NI	Actionable	NI	NI
Halothane-*CACNA1S*	NA	NI	NI	NI	NI	NI
Halothane-*RYR1*	NA	NI	NI	NI	NI	NI
Hydrocodone-*CYP2D6*	NA	NI	NI	NI	NI	NI
Ibuprofen-*CYP2C9*	NI	NI	NI	NI	NI	NI
Imipramine-CYP2C19	Informative	NI	NI	NI	NI	NI
Imipramine-*CYP2D6*	Informative	Actionable	NI	NI	NI	NI
Irinotecan-*UGT1A1*	Actionable	Actionable	Actionable	Actionable	Recommended	Actionable
Isoflurane-*CACNA1S*	NI	Actionable	NI	NI	NI	Actionable
Isoflurane-*RYR1*	NI	Actionable	NI	NI	NI	Actionable

Table 3. continued

Drug-PGx Biomarker	AEMPS	FDA	EMA	Swissmedic	PMDA	HCSC
Ivacaftor-*CFTR*	Required	Required	Required	NI	NI	Required
Lansoprazole-*CYP2C19*	Actionable	Informative	NI	Actionable	NI	NI
Lornoxicam-CYP2C9	Informative	NI	NI	NI	NI	NI
Meloxicam-*CYP2C9*	Informative	Actionable	NI	NI	NI	NI
Mercaptopurine-*NUDT15*	Recommended	Recommended	Actionable	Actionable	NI	NI
Mercaptopurine-*TPMT*	Recommended	Recommended	Actionable	Actionable	NI	Actionable
Methoxyflurane-*CACNA1S*	NI	NI	NI	NI	NI	NI
Methoxyflurane-*RYR1*	NI	NI	NI	NI	NI	NI
Metoprolol-*CYP2D6*	Informative	Informative	NI	Actionable	NI	Actionable
Nortriptyline-*CYP2D6*	NI	Actionable	NI	NI	NI	Actionable
Omeprazole-*CYP2C19*	Actionable	Actionable	NI	Actionable	Informative	Informative
Ondansetron-*CYP2D6*	Informative	Informative	NI	Informative	NI	NI
Oxcarbazepine-*HLA-B*	Recommended	Recommended	NI	Required	NI	Recommended
Pantoprazole-*CYP2C19*	Actionable	Actionable	NI	Informative	NI	NI
Paroxetine-*CYP2D6*	Informative	Informative	NI	NI	NI	NI
Pegylated interferon alfa-2a-*IFNL3*	NI	NI	NI	NI	NI	NI
Pegylated interferon alfa-2a-*IFNL4*	NI	NI	NI	NI	NI	NI
Pegylated interferon alfa-2b-*IFNL3*	NI	Actionable	NI	NI	NI	NI
Pegylated interferon alfa-2b-*IFNL4*	NI	NI	NI	NI	NI	NI
Phenprocoumon-*VKORC1*	NA	NI	NI	NI	NI	NI
Phenytoin-*CYP2C9*	Informative	Actionable	NI	Actionable	NI	NI
Phenytoin-*HLA-B*	Actionable	Actionable	NI	Actionable	NI	Recommended
Piroxicam-*CYP2C9*	Actionable	Actionable	NI	Actionable	NI	NI
Propafenone-*CYP2D6*	Actionable	Actionable	NI	Actionable	NI	Actionable
Rasburicase-*G6PD*	Actionable	Required	Actionable	Actionable	Actionable	Recommended
Risperidone-*CYP2D6*	Actionable	Informative	NI	Informative	NI	Informative
Ribavirin-*IFNL3*	NI	NI	NI	NI	NI	NI
Ribavirin-*IFNL4*	NI	NI	NI	NI	NI	NI
Sertraline-*CYP2C19*	NI	NI	NI	NI	NI	NI
Sevoflurane-*CACNA1S*	NI	Actionable	NI	NI	NI	Actionable
Sevoflurane-*RYR1*	NI	Actionable	NI	NI	NI	Actionable
Simvastatin-*SLCO1B1*	Actionable	Informative	NI	Recommended	NI	NI
Siponimod-*CYP2C9*	Required	Required	NI	NI	NI	NI
Streptomycin-*MT-RNR1*	NDL	NI	NI	NI	NI	NI
Succinylcholine-*CACNA1S*	NI	Actionable	NI	NI	NI	Actionable
Succinylcholine-*RYR1*	NI	Actionable	NI	NI	NI	NI
Tacrolimus-*CYP3A5*	NI	NI	NI	NI	NI	NI
Tamoxifen-*CYP2D6*	Actionable	Actionable	NI	Actionable	NI	Required
Tegafur-DPYD	Recommended	NI	NI	NI	NI	NI
Telaprevir-*IFNL3*	NA	NI	NI	NI	NI	NI
Telaprevir-*IFNL4*	NA	NI	NI	NI	NI	NI
Tenoxicam-*CYP2C9*	NI	NI	NI	NI	NI	NI
Tramadol-*CYP2D6*	Actionable	Actionable	NI	NI	NI	Actionable
Trimipramine-*CYP2C19*	NI	NI	NI	NI	NI	NI
Trimipramine-*CYP2D6*	NI	Actionable	NI	NI	NI	NI
Tropisetron-*CYP2D6*	NC	NI	NI	NI	NI	NI
Venlafaxine-*CYP2D6*	Actionable	Actionable	NI	Actionable	NI	NI
Voriconazole-*CYP2C19*	Actionable	Actionable	Informative	Actionable	Actionable	Actionable

Table 3. continued

Drug-PGx Biomarker	AEMPS	FDA	EMA	Swissmedic	PMDA	HCSC
Warfarin-*CYP2C9*	NI	Actionable	NI	NI	NI	Actionable
Warfarin-*CYP4F2*	NI	NI	NI	NI	NI	NI
Warfarin-*VKORC1*	Informative	Actionable	NI	NI	NI	Actionable
Zuclopenthixol-*CYP2D6*	Actionable	NI	NI	Informative	NI	NI

AEMPS Spanish Agency of Drug and Medicinal Products, *EMA* European Medicines Agency, *FDA* US Food and Drug Administration, *HCSC* Health Canada (Santé Canada), *PMDA* Pharmaceuticals and Medical Devices Agency, Japan; and Swissmedic: Swiss Agency of Therapeutic Products. *NA* not authorized, *NC* not commercialized, *NDL* drug label not registered, NI information not included in the corresponding DL. *Levels of recommendation assigned based on PharmGKB® criteria. **In bold, drug-PGx biomarker with CPIC guidelines**. Underlined, drug-PGx biomarker pairs exclusively present in DLs from AEMPS.

Table 4. ATC distribution of 1 A level drug-biomarker pairs contained in drug labels approved by AEMPS.

ATC group	Required	Recommended	Actionable	Informative	No Recommendation
A	0	0	3	1	2
B	0	0	2	1	3
C	0	0	3	2	0
D	0	0	0	0	1
G	0	0	0	0	1
H	0	0	0	0	0
J	1	0	2	1	7
L	3	4	5	0	4
M	0	0	3	2	4
N	1	1	14	6	19
P	0	0	0	0	0
R	1	0	1	0	2
S	0	0	0	0	0
V	0	0	1	0	0
TOTAL	5	5	34	13	45

substantially lower in these previous works. However, DLs approved by AEMPS on the same chemical substance show different information, especially due to their different dates of market admission. Obviously, this could affect the analysis of the assignment of a PGx level of recommendation for such active substances. Furthermore, some DLs include information about more than one individual biomarker, which could potentially result in more than one PGx level. Nevertheless, such information and all related data on DLs do not necessarily change physician decisions [33, 34]. Therefore, the DLs may indicate whether a test is necessary, recommendable, actionable, or merely informative. In this sense, various regulatory agencies (e.g., the FDA, the EMA, the PMDA, and HCSC) and AEMPS are increasingly including recommendations to perform a genetic test prior to the use of many drugs [21].

In Spain, the most frequent biomarkers found on DLs are those related to CYP450 enzymes, possibly due to their key function in the metabolism of over 90% of drugs [35], and the drug transporter P-glycoprotein, genetically encoded by *ABCB1*, which reflects the growing importance of these biomarkers for predicting drug response and safety, especially considering the high levels of polypharmacy currently noted in the aged population. Nevertheless, the clinical utility of PGx biomarkers is best determined by controlled prospective clinical outcome monitoring. Although randomized controlled trials are ideal, they are expensive and time-consuming, and their viability is likely to be influenced by disease prevalence and commercial possibilities [36]. That is, the general trend for the level of recommendation from AEMPS is the higher the level of evidence assigned, the higher the level of recommendation. Most of the PGx biomarkers included are assigned to levels 3-4 of evidence, while just a small percentage have a requirement for genetic testing before prescription (required level). However, the levels of recommended *testing required* and *actionable* increase when referring to 1A drug-biomarker pairs. There is a significant absence of recommendations for pharmacogenetic testing on DLs authorized by AEMPS, and the number of 1A pairs that possess *required* or *recommended* testing is still low (10–15%), thus reinforcing the need to perform research to consider the inclusion and/or application of such recommendations, as verification is required through retrospective studies and/or clinical trials prospectively stratifying patients based on biomarkers [22].

A DL is created by manufacturers and approved by AEMPS, and it reflects the collaborative involvement of regulators, drug manufacturers, and scientific experts. Drug labelling evolves in response to changing laws and increasing information while maintaining a consistent format to facilitate the safety and effectiveness of pharmaceuticals. However, local laws, cultures, differences in relevant allele frequencies, genetic test availability and variability in insurance coverage might influence regulatory decisions and, consequently, the observed differences in labelling among regulatory agencies [37]. It is worth noting that the FDA updates its table of PGx biomarkers for drug labelling on a regular basis, while this analysis is not yet performed by other international regulatory agencies [38]. Moreover, it should be determined whether their labelling languages are applicable or not in clinical practice [39]. Given that some DLs already recommend precise doses in specific populations, it is desirable not only to have clear language for dose recommendations of other drugs if appropriate but also for regulatory agencies to try to determine similarities and discrepancies to achieve true

harmonization. For instance, establishing harmonized structured product labelling, physician labelling rules and guidance for the industry on clinical pharmacogenomics information being prepared for labelling, as already established by the FDA, is recommended [40].

More than half of all drug labels approved by AEMPS contain PGx biomarker information, thus reflecting their relevance for drug prescription. However, no concordance regarding the prevalence and level of recommendation related to biomarkers exists among regulatory agencies worldwide and AEMPS. There is still much to do to move drug therapies towards individualized therapy and improve clinical outcomes in Spain: more information about potential biomarkers is required to enhance the current knowledge on the definitive role of PGx biomarkers to adjust their level of recommendation for each active substance. More pharmacogenomic-guided patient therapy and better outcomes will follow from the promotion of standardized and transparent pharmacogenomic information on prescription labels.

DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

REFERENCES

1. Schuck RN, Grillo JA. Pharmacogenomic biomarkers: An FDA perspective on utilization in biological product labeling. AAPS J. 2016;18:573–7.
2. Haga SB, Mills R, Moaddeb J. Pharmacogenetic information for patients on drug labels. Pharmgenomics Pers Med. 2014;7:297–305.
3. Lauschke VM, Ingelman-Sundberg M. How to consider rare genetic variants in personalized drug therapy. Clin Pharm Ther. 2018;103:745–8.
4. Lam YWF. Scientific challenges and implementation barriers to translation of pharmacogenomics in clinical practice. Omics Clin Pract: Genom Pharmacogenomics Proteom Transcriptom Clin Res. 2014;2013:95–133.
5. Relling MV, Evans WE. Pharmacogenomics in the clinic. Nature. 2015;526:343–50.
6. Gillis NK, Innocenti F. Evidence required to demonstrate clinical utility of pharmacogenetic testing: the debate continues. Clin Pharm Ther. 2014;96:655–7.
7. Koutsilieri S, Tzioufa F, Sismanoglou DC, Patrinos GP. Unveiling the guidance heterogeneity for genome-informed drug treatment interventions among regulatory bodies and research consortia. Pharm Res. 2020;153:104590.
8. Lauschke VM, Zhou Y, Ingelman-Sundberg M. Novel genetic and epigenetic factors of importance for inter-individual differences in drug disposition, response and toxicity. Pharm Ther. 2019;197:122–52.
9. Mukerjee G, Huston A, Kabakchiev B, Piquette-Miller M, van Schaik R, Dorfman R. User considerations in assessing pharmacogenomic tests and their clinical support tools. NPJ Genom Med. 2018;3:1–9.
10. Vivot A, Boutron I, Ravaud P, Porcher R. Guidance for pharmacogenomic biomarker testing in labels of FDA-approved drugs. Genet Med. 2015;17:733–8.
11. Whirl-Carrillo M, McDonagh EM, Hebert JM, Gong L, Sangkuhl K, Thorn CF, et al. Pharmacogenomics knowledge for personalized medicine. Clin Pharm Ther. 2012;92:414–7.
12. Reis-Pardal J, Rodrigues A, Rodrigues E, Fernandez-Llimos F. Comparing cytochrome P450 pharmacogenetic information available on United States drug labels and European Union Summaries of Product Characteristics. Pharmacogenomics J. 2017;17:488–93.
13. Tan-Koi WC, Lim ESH, Teo YY. Health regulatory communications of well-established safety-related pharmacogenomics associations in six developed countries: An evaluation of alignment. Pharmacogenomics J. 2017;17:121–7.
14. Imatoh T, Sai K, Saito Y. Pharmacogenomic information in the Warning section of drug labels: A comparison between labels in the United States and those in five other countries/regions. J Clin Pharm Ther. 2018;43:493–9.
15. Shimazawa R, Ikeda M. Pharmacogenomic biomarkers: Interpretation of information included in United States and Japanese drug labels. J Clin Pharm Ther. 2018;43:500–6.
16. Haga SB, Lapointe NMA. The potential impact of pharmacogenetic testing on medication adherence. Pharmacogenomics J. 2013;13:481–3.
17. PharmGKB. The Pharmacogenomics Knowledgebase. PharmaGKB. 2020. https://www.pharmgkb.org/.
18. Ehmann F, Caneva L, Prasad K, Paulmichl M, Maliepaard M, Llerena A, et al. Pharmacogenomic information in drug labels: European Medicines Agency perspective. Pharmacogenomics J. 2015;15:201–10.
19. Shimazawa R, Ikeda M. International differences in companion diagnostic approvals: How are we able to manage the differences? Expert Rev Mol Diagn. 2015;15:157–9.
20. Otsubo Y, Asahina Y, Noguchi A, Sato Y, Ando Y, Uyama Y. Similarities and differences between us and Japan as to pharmacogenomic biomarker information in drug Labels. Drug Metab Pharmacokinet. 2012;27:142–9.
21. Olivera G, Sendra L, Herrero MJ, Berlanga P, Gargallo P, Yáñez Y, et al. Pharmacogenetics implementation in the clinics: information and guidelines for germline variants. Cancer Drug Resist. 2019;2:53–68.
22. Jeiziner C, Suter K, Wernli U, Barbarino JM, Gong L, Whirl-Carrillo M, et al. Pharmacogenetic information in Swiss drug labels–a systematic analysis. Pharmacogenomics J. 2020. https://doi.org/10.1038/s41397-020-00195-4.
23. Mehta D, Uber R, Ingle T, Li C, Liu Z, Thakkar S, et al. Study of pharmacogenomic information in FDA-approved drug labeling to facilitate application of precision medicine. Drug Discov Today. 2020;25:813–20.
24. Varnai R, Szabo I, Tarlos G, Szentpeteri LJ, Sik A, Balogh S, et al. Pharmacogenomic biomarker information differences between drug labels in the United States and Hungary: implementation from medical practitioner view. Pharmacogenomics J. 2020;20:380–7.
25. Skvrce NM, Krivokapić S, Bozina N. Implementation of pharmacogenomics in product information. Pharmacogenomics. 2020;21:443–8.
26. Heise CW, Gallo T, Curry SC, Woosley RL. Identification of populations likely to benefit from pharmacogenomic testing. Pharmacogenet Genomics. 2020;30:91–95.
27. Khalil H, Huang C Adverse drug reactions in primary care: A scoping review. *BMC Health Serv Res.* 2020; 20. https://doi.org/10.1186/s12913-019-4651-7.
28. Roden DM, McLeod HL, Relling MV, Williams MS, Mensah GA, Peterson JF, et al. Pharmacogenomics. Lancet. 2019;394:521–32.
29. Pritchard D, Patel JN, Stephens L, Mc Leod HL Comparison of FDA Table of Pharmacogenetic Associations and Clinical Pharmacogenetics Implementation Consortium guidelines. *Am J Health-System Pharm* 2022;79:993–1005.
30. Feldman HL. Pushing drugs: genomics and genetics, the pharmaceutical industry, and the law of negligence. Washburn Law J. 2003;42:575–99.
31. Rothstein MA, Hoffman S. Genetic testing, genetic medicine, and managed care. Wake For Law Rev. 1999;34:849–88.
32. Howlett MJ, Avard D, Knoppers BM. Physicians and genetic malpractice. Med Law. 2002;21:661–80.
33. Van Grootheest ACK, Edwards IR. Labelling and 'Dear Doctor' letters: Are they noncommittal? Drug Saf. 2002;25:1051–5.
34. Guo JJ, Curkendall S, Jones JK, Fife D, Goehring E, She D. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf. 2003;12:295–301.
35. Fatunde OA, Brown SA. The role of CYP450 drug metabolism in precision Cardio-Oncology. *Int J Mol Sci* 2020; 21. https://doi.org/10.3390/ijms21020604.
36. Haga SB, Thummel KE, Burke W. Adding pharmacogenetics information to drug labels: Lessons learned. Pharmacogenet Genom. 2006;16:847–54.
37. Shimazawa R, Ikeda M. Differences in pharmacogenomic biomarker information in package inserts from the United States, the United Kingdom and Japan. J Clin Pharm Ther. 2013;38:468–75.
38. Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. Last Updated: 12/2021.
39. Yamazaki S. A retrospective analysis of actionable pharmacogenetic/genomic biomarker language in FDA labels. Clin Transl Sci. 2021;14:1412–22.
40. Fang H, Harris SC, Liu Z, Zhou G, Zhang G, Xu J, et al. FDA drug labeling: rich resources to facilitate precision medicine, drug safety, and regulatory science. Drug Discov Today. 2016;21:1566–70.

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AUTHOR CONTRIBUTIONS

Conceptualization: ALL. Methodology: ALL, FdA. Data retrieval, analysis, and curation: MEP, FdA, MCMM. Resources: ALL. Writing-original draft: FdA, MEP. Writing-review and editing: MEP, FdA, MCMM, ALL. Project administration: ALL. Funding acquisition: ALL. All authors have read and agreed to the published version of the paper.

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The authors declare no competing interests.

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