Clinical and Translational Science

ARTICLE OPEN ACCESS

Pharmacogenetic Information on Drug Labels of the Italian Agency of Medicines (AIFA): Actionability and Comparison Across Other Regulatory Agencies

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Received: 21 October 2024 | **Revised:** 11 December 2024 | **Accepted:** 5 January 2025

Funding: Italian Ministry of Health (Ricerca Corrente) to E.C.

Keywords: AIFA | drug labels | level of actionability | pharmacogenetic testing

ABSTRACT

To plan future steps for the implementation and regulation of pharmacogenetic testing, any issue in the management of pharmacogenetic information by regulatory bodies must be identified. In this paper, an analysis of pharmacogenetic information in the summary of product characteristics (SmCPs) of drugs approved by Italian Drug Agency (AIFA) was conducted. Among 4214 SmCPs of 1063 active ingredients, 53.2% ($n = 2240$) included pharmacogenetic information in at least one section, most frequently for drugs in the Anatomical Therapeutic Chemical category "Antineoplastic and immunomodulatory agents". To contextualize these data in the international scenario, a pharmacogenetic level of actionability, based on AIFA SmCPs, was assigned to 608 drug/gene pairs included in FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels", according to PharmGKB (The Pharmacogenomics Knowledge Base). Approximately 67% of drug/gene pairs were deemed classifiable: Based on SmCPs phrasing, for half of them the genetic testing was cataloged as "required" or "recommended" (mainly tumor somatic variants), whereas 40% as "actionable" (mostly PK/PD-related germline variants). The comparison with other regulatory agencies highlighted a discordance in the assigned pharmacogenetic levels of actionability ranging from 1% to 14%. This discrepancy may also point out the need to rethink the language used in AIFA-approved SmCPs to clarify whether a pharmacogenetic test is necessary or not and for which subjects it has been recommended. For the first time, a detailed evaluation and comparative analysis of the pharmacogenetic information on Italian SmCPs was presented, placing it in an international context and laying the groundwork for rethinking pharmacogenetic indications in AIFA-approved SmCPs.

1 | Introduction

Both efficacy and safety of a pharmacological intervention are outcomes of complex multifactorial mechanisms [1]: In addition to the contribution of non-genetic factors, such as concomitant medications, comorbidity with other medical conditions, or the individual's sex and age, the importance of the personal genetic makeup is emerging with increasing strength [2].

Summary

- What is the current knowledge on the topic?
  - Pharmacogenetic information contained in drug labels approved by various regulatory agencies (such as FDA, EMA, or HCSC) is collected and classified for actionability by PharmGKB. To date, a similar assessment of drug labels approved in Italy is not available.
- What question did this study address?
  - What pharmacogenetic information is contained in the label of drugs approved in Italy? How is this information classifiable according to PGx levels defined by PharmGKB, and how does it align with other international drug regulatory agencies?
- What does this study add to our knowledge?
  - This is the first ever large-scale analysis of the pharmacogenetic information contained in the data sheets of drugs approved in Italy. To the best of our knowledge, this information had never been systematically analyzed before.
- How might this change clinical pharmacology or translational science?
  - Detailed knowledge of how pharmacogenetic information is structured in labels of drugs approved in Italy and how it compares to other countries is the starting point for the identification of problems and solutions in the road toward an implementation of pharmacogenetics in the Italian national health care system.

It is hardly surprising that genetic variability can influence how we respond to a medication: rare and common genetic variants can in fact influence the mechanism of action of a drug [3–8].

According to the DrugBank resource [9], a total of 2750 drug targets exist for marketed small molecules: 424 metabolizing enzymes, 276 transport proteins, and 72 carriers are involved in their metabolism. It is highly probable that the function of genes encoding these proteins may be altered by genetic variants, whose discovery, functional validation, and identification in different populations are the goals of pharmacogenetics (PGx). Only a small number of these genes have genuine biological significance [10].

Several studies have shown that the proportion of human genetic variability studied by PGx, which therefore qualitatively or quantitatively influences the action of pharmacogenes, affects nearly 100% of individuals in various populations [2, 11, 12].

Consequently, it is expected that the implementation of PGx in clinical decision-making may be a strategy to reduce the substantial burden of unanticipated drug reactions, which are still a major concern in healthcare. In line with this hypothesis, there is growing supporting evidence [13] that the frequency of adverse drug reactions (ADRs), which account for 10% to 20% of hospitalizations [14, 15], may be reduced through pharmacogenomic testing. A measure of the potential advantage of pharmacogenomics-based clinical best practices was the landmark result of the "Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions" (PREPARE) trial [16, 17]. In this multicenter study, the impact of a 12-gene PGx panel as a tool to inform prescription of 42 commonly prescribed drugs in 18 hospitals, 9 community health centers, and 28 community pharmacies in 7 European partner countries (including Italy) was evaluated. Participants with an "actionable" variant were treated according to the guidelines released by the Dutch Pharmacogenetics Implementation Working Group (DPWG), whereas patients in the control group received standard treatment. The results indicated that a genotype-guided treatment reduced by 30% the risk of clinically relevant ADRs and is feasible in different healthcare organizations and settings.

The power of a PGx-based personalized treatment is not only related to the clinical benefit of the patients but also to a more rational expenditure of health economic resources. It was previously demonstrated that patients with risky genotypes cost more to the National Health System (NHS) when treated according to the standard of care [18, 19], and that adjusting the dosage based on the PGx assessment is cost-effective in saving economic resources while improving patient's outcome [20].

PGx testing recommendation by drug agencies was demonstrated to be a key step in the process of testing implementation in the clinical practice [21]. However, the translation of such recommendations and the reporting of PGx information in drug labels (DLs) within NHSs is poorly standardized. Pharmacogenomics Knowledgebase (PharmGKB), an expert-curated knowledgebase, carefully revises PGx information contained in DLs creating a catalog reporting the level of recommendation for testing according to different national and international drug agencies [22, 23].

Several groups—with the aim to identify inconsistencies and to suggest potential improvements for the future—have compared information on PGx in the DLs of drugs authorized for marketing by different European agencies, such as Spain [24], Hungary [25], and Switzerland [26]; the Summary of Product Characteristics (SmCPs) generally aligns with EMA standards, however drugs which are previously approved through national marketing authorization process before joining the EU may have outdated PGx information.

To date, a similar assessment is lacking for the DLs and SmCPs available in Italy. In the Italian NHS, the regulatory body—Agenzia Italiana del Farmaco (AIFA [27])—authorizes the marketing of drugs and publishes their DLs and SmCPs.

The first aim of this study was to perform a systematic analysis of the sections of the Italian SmCPs containing PGx-relevant information, for evaluating the instructions provided to healthcare professionals. Additionally, the study aimed to classify Italian SmCPs according to the most recent PharmGKB PGx recommendation levels and to perform a comparative analysis with SmCPs authorized by agencies in other countries.

2 | Materials and Methods

2.1 | Study Design

The aims of this study were as follows: (i) to systematically review the information on PGx in SmCPs approved by AIFA; and (ii) to compare the level of recommendation of PGx biomarker tests (according to the classification proposed by PharmGKB) inferred from the analysis of Italian SmCPs with that of drug agencies in other countries.

Accordingly, the SmCPs of all Class A and H drugs (PDF format) were downloaded—when available—from the AIFA website [28] and analyzed.

Furthermore, the table with the full list of PharmGKB Drug Label Annotations was retrieved from the "downloads" page of the PharmGKB website (see below) [29].

2.2 | Systematic Review of PGx Information in SmCPs Approved by the Italian Medicines Agency

From the PDF file of each SmCP, the ATC code of the drug was extracted; all mentions of PGx markers for which there is at least one variant in PharmGKB with clinical evidence level of class 1A or 1B [30] were then identified, for a total of 26 pharmacogenes (Table S1). For each instance, the section of the SmCP where each marker is mentioned was recorded (Table S2). For hyperthermia related genes *CACNA1S* (calcium voltage-gated channel subunit alpha1 S) and *RYR1* (ryanodine receptor 1), not only mentions of the gene name but also of the keyword "hyperthermia" were searched.

In cases where more than one SmCP was available for the same active ingredient, only the SmCP with the highest number of distinct markers cited in the document for further analysis and statistical processing were kept.

2.3 | Comparison of PGx Biomarker Tests Level of Recommendation in SmCPs Approved by the Italian Medicines Agency With Other Countries

The table with the full list of Drug Label Annotations (file "Drug Label Annotations" in TSV format, comprising 608 drug/gene pairs)—with PGx information extracted from DLs approved by regulatory agencies (with PGx information extracted from DLs approved by the US Food and Drug Administration [FDA], European Medicines Agency (EMA), Swiss Agency of Therapeutic Products [Swissmedic], Pharmaceuticals and Medical Devices Agency, Japan (PMDA) and Health Canada [Santé Canada (HCSC)]) and manually curated by the PharmGKB team—was downloaded from the PharmGKB website [29].

For each drug/gene pair in the PharmGKB table, all the sentences mentioning the gene in the SmCP corresponding to the drug were manually extracted. Based on the analysis of these sentences, each SmCP was then classified according to the PGx Levels defined by PharmGKB [30] (namely: "Actionable PGx", APGx; "Informative PGx", IPGx; "No Clinical PGx", NoPGx; "Criteria not met", CNM; "Testing required", TReq; "Testing recommended", TRec) by the authors of this paper (M.F., A.S., and E.C.) independently and unbiased respect to the PharmGKB classification of EMA EPARs. For each SmCP, a consensus classification was reached (Table S3).

Furthermore, for all drug/gene pairs which reached a classification of testing different from CNM in the Italian SmCPs, PharmGKB was mined for the availability of published PGx guidelines for the application in the clinical practice by any international scientific consortium.

2.4 | Statistical Analysis

Agreement between regulatory agencies was assessed using Fleiss' kappa coefficient for overall concordance among all agencies, and Cohen's kappa coefficient for pairwise comparisons between AIFA and each other agency (1 indicates perfect agreement, 0 indicates agreement by chance, and values between 0.41–0.60, 0.61–0.80, and >0.80 represent moderate, substantial, and almost perfect agreement, respectively).

Analysis, creation of figures and tables were performed with R software version 4.4.1.

3 | Results

3.1 | PGx-Relevant Information in AIFA Drug Labels

The list of class A and H reimbursable medicinal products contains a total of 12,404 drugs in various dosages and formulations [28]. From the AIFA website, 5864 SmCPs (corresponding to 10,865 distinct pharmaceutical products), covering 1242 active ingredients (1539 SmCPs were not available on the AIFA website) were downloaded; after excluding drugs containing multiple active ingredients, 4214 SmCPs corresponding to 1063 active ingredients were retained: 53.2% of them ($n=2240$ SmCPs) included information on PGx biomarker(s) in at least 1 of the 13 SmCP sections.

A total of 26 different PGx biomarkers (i.e., genes with at least one variant with clinical evidence level of class 1A or 1B [30]) were searched for on each of the examined SmCPs (Table S1). After selection of a single representative product of each drug having multiple dosage forms or formulations, a final dataset of 562 SmCPs (refSmCPs) containing information on PGx biomarker(s) in at least one section was obtained (Table S2).

3.2 | Analysis of the Reference Dataset of Drug Labels (refSmCPs)

Drugs whose refSmCPs mentioned any PGx biomarkers were identified within all ATC areas, although PGx information was more frequent for ATC categories "Antineoplastic and immunomodulating agents" (category L, number of distinct refSmCPs $n=173$, 30.78%), followed by the "Nervous system" ($N=100$, 17.8%), "Alimentary tract and metabolism", "Cardiovascular

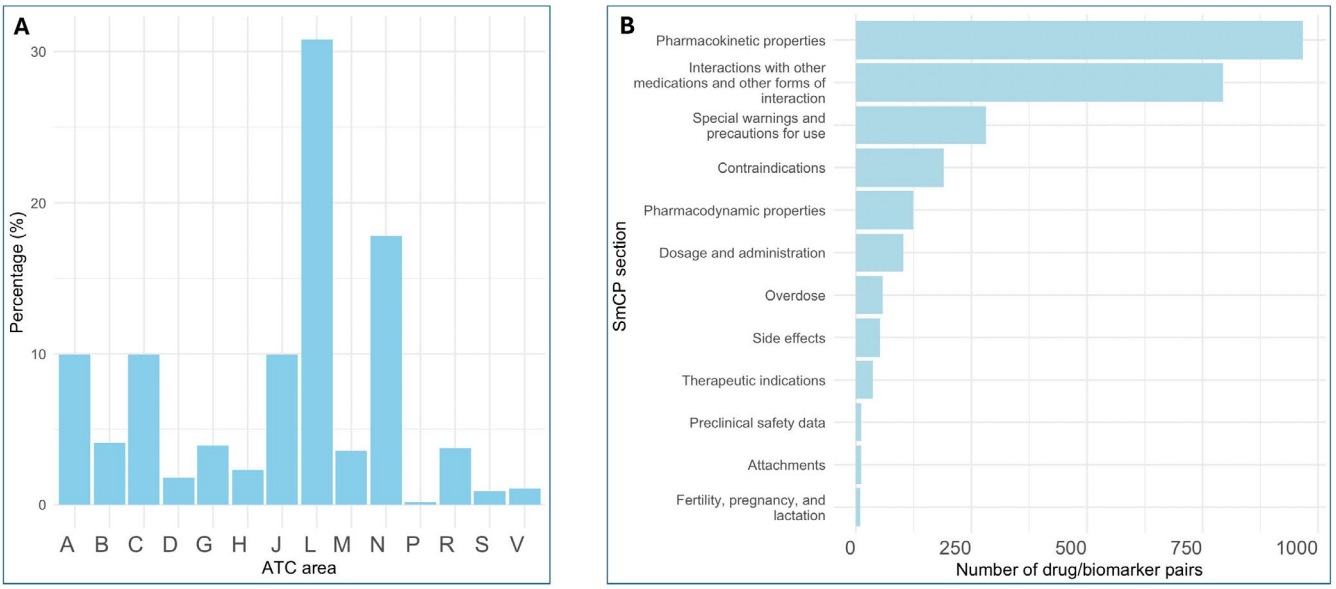

FIGURE 1 | (A) Percentage of drug SmCPs containing information on pharmacogenetic biomarker(s) in at least one section, grouped by ATC area, in the final dataset of 562 SmCPs (refSmCPs). (B) Distribution of Pharmacogenetic Biomarkers across SmCP Sections.

system" and "Antiinfectives for systemic use" ($N = 56$, 10% for each of these categories) (Figure 1A).

The most frequently cited PGx biomarker (Table S4) was *CYP3A4* ($N = 411$, 73.1% of the evaluated refSmCPs), followed by *CYP2C9* ($N = 260$, 46.3%), *CYP2D6* ($N = 254$, 45.2%), *CYP2C19* ($N = 232$, 41.3%), and *CYP2B6* ($N = 145$, 25.8%), all present in more than one hundred different refSmCPs.

A total of 2632 drug–biomarker associations were identified in the 562 selected refSmCPs. Of these, 124 (4.7%) were found in the "Pharmacodynamic properties" section and 962 (36.6%) in the "Pharmacokinetic properties" section of refSmCPs. In 794 instances (30.2%), biomarkers were found in the "Interactions with other medicines and other forms of interaction" section of SmCPs (Figure 1B).

Focusing on the "Pharmacokinetic properties" section (the one with most marker citations), the greatest number of occurrences concerns the family of cytochromes (especially *CYP3A4*) in all ATC areas, particularly in the area of antineoplastics and immunomodulators (ATC group "L", for which a relevant portion of associations concerns *UGT1A1* and *EGFR*), and in that of the nervous system ("N") (Figure 2A).

Regarding the "Pharmacodynamic properties" section, again the role of cytochromes is generally predominant, but the most frequent associations concern EGFR in the areas of antineoplastics and immunomodulators ("L") and of gastrointestinal system and metabolism ("A") (Figure 2B).

3.3 | Definition of the Level of Actionability and Comparison of PGx Annotations With Those of Other Drug Regulatory Authorities

PharmGKB regularly extracts PGx information from the labels of drugs approved by FDA, EMA, HCSC, or listed in the FDA's "Table of Pharmacogenomic Biomarkers in Drug Labels" [29] and assigns each DL a "PGx Level" (APGx, IPGx, NoPGx, CNM, TReq, and TRec). Labels from other regulatory agencies are noted as collaborations and are not routinely updated. All AIFA SmCPs for the drug/gene pairs mentioned in the FDA's table (PharmGKB version) were extracted to compare their contents with the PGx information reported in the drug summaries or labels of the above mentioned regulatory agencies.

It was possible to extract matched PGx information in about three quarters of 608 drug/gene pairs available in the FDA table ($N = 443/608$). All the AIFA SmCPs were then classified by the authors according to PGx level of actionability as defined in PharmGKB [31].

Excluding drug/gene pairs whose respective AIFA SmCPs were assigned by our team to a CNM PGx level, a total of 363 drug/gene pairs were considered for further analysis (Table S3).

Considering the type of genetic markers included in AIFA SmCPs (Figure 3A), half of them (190/363, 52%) were germline genetic markers with a potential impact on the PK or PD of the drug. Somatic variants, mainly related to the prescription of cancer drugs, covered another 35% of the labels of drugs with a genetic indication, whereas only a minority of labels (13%) contained germline genetic information related to the diagnosis of the disease for which the drug is prescribed (such as in the case of drugs for the treatment of Cystic Fibrosis). For 11 drug/gene pairs, the PGx indication could not be unambiguously classified.

The analysis pointed out that the vast majority of somatic and disease-related germline variants were classified as mandatory for the drug prescription. In contrast, information on PK/PD-related germline variants was mostly provided as *IPGx* or described as *APGx* without requesting or recommending analysis prior to treatment (Figure 3B).

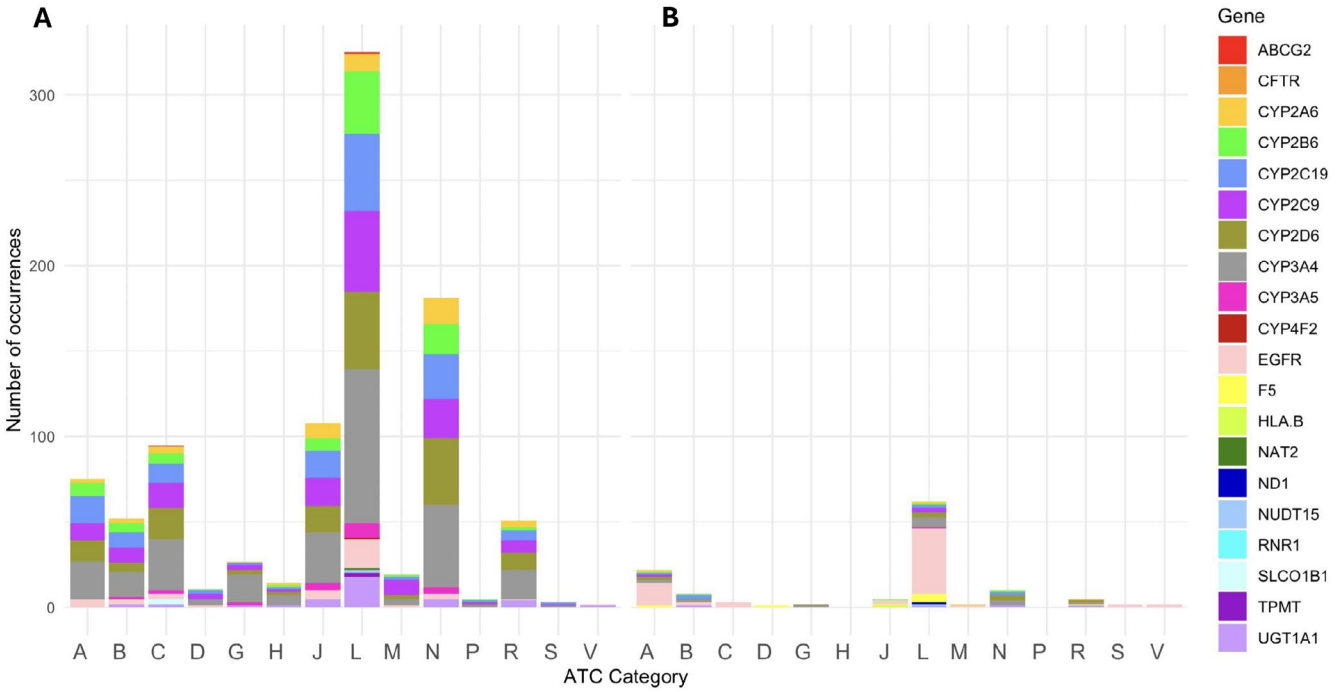

FIGURE 2 | Prevalence of key pharmacogenetic biomarkers across ATC categories: frequency of the most prevalent pharmacokinetic (A) biomarkers and frequency of the most prevalent pharmacodynamic (B) biomarkers.

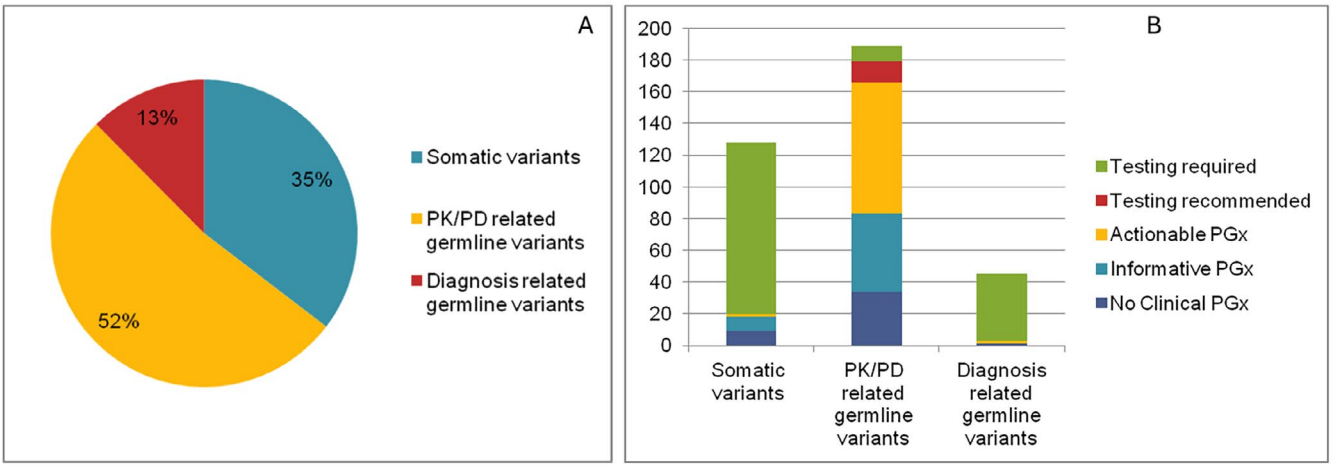

FIGURE 3 | Type of genetic variant mentioned in the AIFA drug label among 362 evaluable drug/gene pairs ("Criteria not met" level was not considered here) (A). Classification of recommendation by type of genetic variant (B).

With regard to the 245 out of 608 drug/gene pairs not classifiable for PGx actionability: (i) for 74 pairs the drug was not registered in the AIFA database; (ii) for 40 pairs the gene was not found in the SmCP; (iii) for 12 pairs the SmCP was not available on the AIFA website; and (iv) in 44 instances, the authors assessed that the label did *not currently meet* (*CNM*) the requirements to be assigned to one of the 5 PGx levels *APGx*, *IPGx*, *NoPGx*, *TReq*, and *TRec* (Figure 4).

In total, 24.2% of the 363 AIFA SmCPs ($N=88$) were classified as *APGx* (Table 1).

This percentage is discordant with that of EMA (23/146 classified as *APGx*, 15.8%), PDMA (29/49, 59.2%), and SwissMedic (89/127, 70.1%), although it is comparable to the FDA (95/325, 29.2%) and HCSC (41/174, 23.6%) values. Regarding the category *IPGx* the AIFA percentage (16%, $N=58/363$) is almost similar for all other regulatory agencies. Also for the *TRec* PGx level, the percentage in AIFA (3.6%, $N=13/363$) is slightly similar to that of all other agencies, whereas for the *TReq* level (44.1%, $N=160/363$) there is a strong discordance with EMA data (58.2%, $N=85/146$). On the other hand, it should be noted that FDA values are almost completely overlapping (Figure 4).

Overall (i.e., considering also *CNM*), out of 197 drug/gene pairs for which both AIFA and EMA classification are available, a total of 36 (18.3%) have discordant classification. Although the level of concordance is quite high, this non-negligible number of discordances is probably attributable to the difficult interpretation of some texts in the SmCPs. Twenty-two cases out

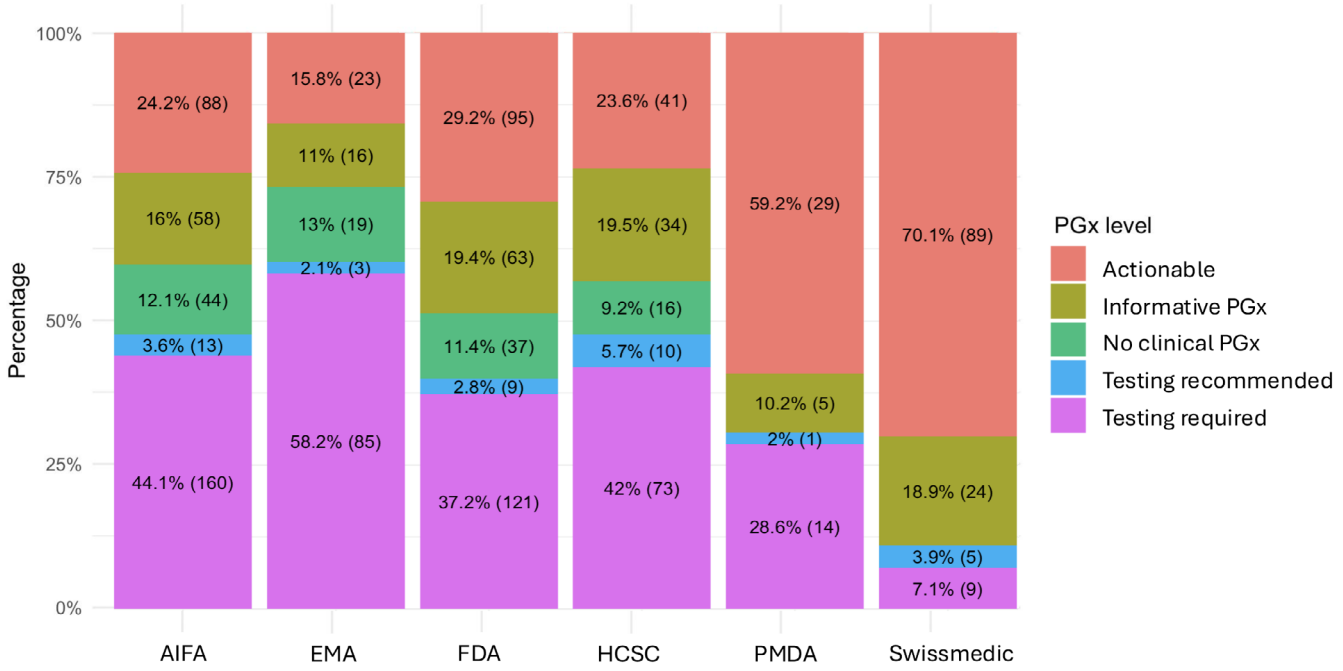

FIGURE 4 | Distribution of Classifications across Agencies: Percentage of PGx levels for each regulatory agency.

TABLE 1 | Comparative analysis of drug/gene pairs classifications for SmCPs of AIFA and other regulatory agencies.

	EMA, *N* (%)	FDA, *N* (%)	HCSC, *N* (%)	Swissmedic, *N* (%)	PMDA, *N* (%)	AIFA, *N* (%)
Actionable PGx	23 (15.75)	95 (29.23)	41 (23.56)	89 (70.08)	29 (59.18)	88 (24.24)
Informative PGx	16 (10.96)	63 (19.38)	34 (19.54)	24 (18.9)	5 (10.2)	58 (15.98)
No clinical PGx	19 (13.02)	37 (11.38)	16 (9.2)	0 (0)	0 (0)	44 (12.12)
Testing recommended	3 (2.05)	9 (2.78)	10 (5.75)	5 (3.94)	1 (2.05)	13 (3.58)
Testing required	85 (58.22)	121 (37.23)	73 (41.95)	9 (7.08)	14 (28.57)	160 (44.08)
Total	146 (100)	325 (100)	174 (100)	127 (100)	49 (100)	363 (100)

Note: Number (and percentage) of drug/gene pairs classified in each of the five PGx levels "Testing required," "Testing recommended," "Actionable PGx," "Informative PGx," or "No clinical PGx," for SmCPs of each regulatory agency (EMA, FDA, HCSC, Swissmedic, and PMDA classifications were provided in the PharmGKB website). Drug/gene pairs classified as "Criteria not met" were not considered.

of 36, where the EMA classification proposed by PharmGKB was CNM and the classification for AIFA's SmCP was instead TReq, were observed. These are cases such as "betaine and CBS, MMADHC, MTHFR" where diagnostic testing (thus not purely PGx) is required before administering a certain therapy.

For the other regulatory agencies, out of 311 drug/gene pairs for which both AIFA and FDA classifications were available, the discordance was moderate, with 112 discordant classifications (36%).

The level of agreement between AIFA and other regulatory agencies (EMA, FDA, HCSC, Swissmedic, and PMDA) was evaluated using Cohen's Kappa Index. The kappa values indicated fair agreement with EMA ($\kappa = 0.341$) and FDA ($\kappa = 0.267$), while agreement with HCSC ($\kappa = 0.260$), PMDA ($\kappa = 0.169$), and Swissmedic ($\kappa = 0.105$) was minimal. These findings highlight variability in actionable PGx classifications across regulatory agencies.

Finally, for the present analysis, a classification in the four major PGx levels was proposed for an additional 246 drug/gene pairs currently not covered by an EMA EPAR classification provided by PharmGKB. For 170 of these drug/gene pairs, an FDA label classification already exists in PharmGKB, with a concordance rate of 57.7% ($N = 98$).

3.4 | Analysis of PGx Variants Included in AIFA Drug Labels According to the Type of Variant and Clinical Pharmacogenetic Guidelines Availability

With regard to the above mentioned 363 AIFA SmCPs for which the drug/gene pairs were classified according to one of the five PharmGKB levels (*APGx, IPGx, NoPGx, TReq* and *TRec*) (Table S5), a strong stratification of the type of genetic variant according to the PGx actionability level was highlighted. 84 out of 88 drug/gene pairs classified as *APGx* (95.4%) were associated with germline testing (PK or PD related), whereas 108 out of 160

pairs classified as *TReq* (67.5%) were associated with somatic testing.

Focusing exclusively on the subset of AIFA SmCPs including germline genetic information regarding drugs PK or PD (Figure S1A), the majority of the retrieved drug/gene pairs had no supporting PGx clinical guideline (111/190, 58.4%). The remaining drug/gene pairs (79/190, 41.6%) had at least one guideline available among CPIC, DPWG, and others, as reported in PharmGKB. Supervised PGx guidelines were most frequently available for drug/gene pairs with a "required" or "recommended" test indication as reported in the AIFA DL, whereas variants reported as "actionable" or "informative" usually lack PGx guidelines (Figure S1B).

On the other hand, when considering the list of all the 573 drug/gene pairs highlighted by CPIC (https://cpicpgx.org/genes-drugs/) with a PharmGKB Level 1A ($N = 106/573$), 40 out of 106 drug/ gene pairs (37.7%) were observed, which are not mentioned in any drug label approved either by FDA, EMA, AIFA, Swissmedic or PMDA.

4 | Discussion

The introduction of PGx into the clinical practice of an NHS has the primary goal to make therapies safer for each patient and to adopt tools to aid the selection of the most appropriate drugs and dosages. The growing body of evidence supporting the role of genetics in drug response—coupled with the development of clinical guidelines for the translation of genetic information into clinical practice—is facilitating this process in several countries.

Although there are virtuous examples of implementation of pharmacogenetic testing in European NHSs, there is a certain discordance between the initiatives of individual countries and what is regulated by the EMA, as well as heterogeneity in the management of tests and clinical practices.

In the Italian NHS, PGx is not yet fully developed in its potential, partly because of a regulatory lacuna that does not support its dissemination and standardization [32]. To design an implementation strategy in Italy, it is first necessary to have a clear picture of the status quo. One of the first steps to be addressed is to understand how PGx information is currently organized in DLs and SmCPs of drugs approved for marketing in Italy. For this reason, the first systematic analysis of all mentions of genetic variants included in Italian SmCPs was performed. Some aspects of interest emerged from this analysis.

In this evaluation of the AIFA SmCPs, a classification system consisting of four "PGx levels" was applied to all drug/gene pairs reported in the FDA "Table of Pharmacogenomic Biomarkers in Drug Labels" and approved by AIFA for marketing in Italy (as provided by PharmGKB).

This analysis showed that about 72% of the drug/gene pairs in the FDA table include in their AIFA SmCPs genetic indications that are classifiable in the three PGx levels with a minimum level of actionability in PharmGKB (*APGx*, *TReq*, and *TRec*). For exactly two-thirds of these drug/gene pairs, the genetic test was deemed classifiable as *TReq* or *TRec*, whereas the remaining one-third was reported as *APGx*. These numbers are impressive and indicate how urgent it is to establish a regulatory and procedural framework.

It is worth noting that these proportions are quite variable when considering the typology of the genetic variants mentioned in each SmCP. *Tumor somatic variants*, which are mainly tested to identify tumors sensitive to specifically targeted drugs, are mostly mandatory (*TReq* and *TRec*) to allow drug prescription. This is clearly driven by the clinical need to increase treatment efficacy. However, it cannot be neglected that these drugs are very expensive, and the genetic test can be deemed cost-effective when considering the benefits for the patients as well as for a rational health economic resources expenditure [18–20]. On the other hand, many of the drug/gene pairs referring to *germline variants* impacting the drug PK/PD are classified as *APGx* on the basis of the evidence indicated in the SmCPs. These data highlight an urgent need to fill a regulatory gap through the issuance of clear indications for testing, at least for gene/drug pairs for which supporting international guidelines are available.

Despite large prospective clinical trials have demonstrated a clinical benefit of applying PGx testing for PK/PD-related variants in combination with DPWG guidelines [16], testing implementation in Italy is still restricted to few gene/drug interactions, such as *DPYD*/fluoropyrimidines or *UGT1A1*/irinotecan.

Another interesting aspect—related to pharmacoeconomic implications [33, 34]—which emerged from the analysis, is that the drugs belonging to the ATC categories A, C, J, L, and N (in particular L, "Antineoplastic and immunomodulating agents") are those with the highest content of PGx information and at the same time those with the highest expenditure impact for the NHS in Italy (about EUR 7.4 billion in 2023), according to the 2023 report of AIFA's National Observatory on the Use of Medicinal Products (OsMed 2023) [35]. Further investigation into the cost-effectiveness of a prospective PGx testing application would be desirable.

Another element of interest that emerged from this analysis is revealed by the albeit few instances of discordance among the authors of the present SmCPs revision work when assessing the classification of testing according to PharmGKB criteria. These discordances reveal that sometimes the language (terminology and phrases) used in SmCPs and referred to patient genetics in relation to therapy is not clear enough and easy to interpret.

In general, there is a need to rethink the language used in SmCPs to clearly define the priority for testing, which patients should be tested and when, if a PGx test is required, recommended, or suggested when administering a certain drug. This could be achieved by creating a standard "Pharmacogenetics" section within the SmCPs, and through the definition and standardization of the terminology to be used for indicating dose modulation and/or risk of adverse events. Moreover, this could help to select the most clinically relevant markers worthy of mention in the SmCPs. A prototype illustrative "Pharmacogenetics" section is proposed by the authors of this paper (formatted on the basis of the EMA product-information template [36] and provided as Text S1). As the present work points out, a number of SmCPs approved by

AIFA already contain unstructured Pgx information in various sections. It is interesting to note that a "Pharmacogenetics" paragraph is present in only 36 of the 4214 SmCPs analyzed (0.85%), for only five drugs (piroxicam, canagliflozin hemihydrate, clopidogrel, warfarin sodium, and acenocoumarol).

Another instrument that could help define the priority for testing would be the creation and adoption of Italian PGx guidelines. Currently, in Italy only PGx guidelines related to *UGT1A1*/IRI and *DPYD*/FP are available, and were jointly developed by the Italian Society of Pharmacology (SIF) and the Italian Association of Medical Oncology (AIOM) [37]. The interaction between different professional societies appears to be a robust strategy which, by exploiting different expertise, can help improving and accelerating the implementation of PGx into the clinical practice [38]. Indeed, this goal could only be achieved with the involvement of an interdisciplinary team including medical professionals, pharmacologists, geneticists and other stakeholders to regulate the procedures for PGx implementation and to give clinicians the possibility to refer to authoritative international guidelines such as those from CPIC and DPWG. In this context, the role of scientific societies in monitoring evidence and producing guidelines adapted to the Italian reality may be crucial in promoting the implementation of PGx tests in clinical practice [32]. Since the update of the Italian Livelli Essenziali di Assistenza (LEA), effective from 30 December 2024, significantly limits the possibility of prescribing PGx tests, the publication of national guidelines, developed by a joint working group of the Italian Society of Human Genetics (SIGU) and the SIF, is even more urgent.

Despite the meticulous work done to extract PGx information from the SmCPs of the drugs marketed in Italy, several limitations emerge from the data analysis. Firstly, the AIFA website does not provide SmCP documents for all commercialized drugs, thus some products cannot be included in the analysis. Moreover, the interpretation of the recommendations reported in the SmCPs is subjective, although the authors involved have tried to apply an unbiased approach, based on the suggestions provided by PharmGKB for interpreting labels. Indeed, as mentioned earlier, the formulas used in the paragraphs of the SmCPs are not always overlapping among different drugs, and the recommendations reported on PharmGKB may differ across various regulatory agencies.

An accurate study of the PGx information contained in SmCPs and the correlation of this with international recommendations collected by PharmGKB contributes to achieve a standardized approach that facilitates consultation and updating of these documents. This, consistent with the literature data, would support a wider spread of these tests in clinical practice with benefit to the NHS.

Our results showed that the drug classes with the highest number of PGx indications in SmCPs are among the top-selling product categories in Italy over the past year. However, not all pharmacogenes mentioned in SmCPs have equal clinical utility. In the case of PK/PD-related pharmacogenes, only a minority of tests can be considered required or recommended according to PharmGKB criteria. Integrating this information with national guidelines and recommendations of other regulatory agencies could also be useful to indicate the significance of the proposed PGx tests and to justify inclusion in the LEAs.

In conclusion, the agreement between the PGx information reported in AIFA SmCPs with the other regulatory bodies considered in this study is overall high. Nevertheless, the discordant cases highlight a lack of clarity in the terminology used, as well as a dearth of detailed information which, therefore, make these specific drug/gene pairs not informative for clinicians. This scenario is determined by several factors, among which a still incomplete understanding of the relationship between genes and drugs play a major role. The path toward an implementation of PGx testing will significantly benefit from clear and robust evidence of the clinical utility of the tests, a goal which could only be achieved with more efforts to perform large, randomized clinical trials, which are still limited in number in this field. Moreover, it appears clear that a synergy between different expertise is strongly warranted for a better understanding of the role of genetics in drug efficacy and safety. Such a multidisciplinary team would provide health professionals with the desirable knowledge and support to reach a standardized and reliable interpretation and implementation of PGx guidelines in the everyday clinical practice.

Author Contributions

M.F., E.C., and A.S. wrote the manuscript; M.F. and A.M. designed the research; M.F., E.C., M.M., A.S., and A.M. performed the research; and S.M., S.P., E.Z., D.B., D.S., and C.T. analyzed the data.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.