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Differences in pharmacogenomic biomarker information in package inserts from the United States, the United Kingdom and Japan

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SUMMARY

What is known and objective: **The provision of pharmacogenomic information in drug package inserts (PIs) has become more common in recent years. The content of PIs can be tailored to meet specific requirements of the target populations. Our objective was to identify, assess and report on differences in pharmacogenomic information in PIs from the United States (USA), the United Kingdom (UK) and Japan.**

Methods: **Package inserts were obtained from the US Food and Drug Administration (FDA) Table of Pharmacogenomic Biomarkers in Drug Labels on 1 October 2012. Corresponding PIs were obtained concurrently from Japan and the UK. We compared the pharmacogenomic information included, where the information was located, the therapeutic class of the drug, the type and purpose of the biomarker and the initial US approval year.**

Results and discussion: **One hundred eighteen PIs were included in the FDA table. Of the 118 PIs, 29 provided information on drug targets, 69 on metabolizing enzymes and 20 on other aspects. Genomic biomarkers were described in 71 PIs from the UK and 44 from Japan. Consistency in labelling across the three jurisdictions was greater in the 'Indications' section of the PIs than that in the 'Precautions' section. There appears to be greater concordance across countries for the biomarker information in the 'Indications' sections (UK 65% and Japan 48% relative to the US information) than that in the 'Precautions' sections (UK 41% and Japan 17%).**

What is new and conclusion: **There are substantial differences in the pharmacogenomic information included in PIs from the USA, the UK and Japan. The differences varied according to the PI sections, and type and purpose of the biomarkers. The differences appeared to vary according to the strength of the evidence supporting use of the biomarkers. Further analyses are necessary to determine the causes of these differences.**

WHAT IS KNOWN AND OBJECTIVE

Individual differences in drug efficacy and patients' susceptibility to adverse effects are well recognized. Studying the genomic basis of these differences can help clinicians to optimize therapy and reduce adverse drug reactions.

The United States (US) Food and Drug Administration (FDA) released their 'Guidance for Industry: Pharmacogenomic Data Submissions' document in March 2005 to help drug developers understand the agency's policies and processes for accepting and using pharmacogenomics data.[1] Similarly, the FDA created a 'Genomics' web portal, providing up-to-date regulatory and background information on genomics in relation to drug efficacy, safety, pharmacokinetics, pharmacodynamics and dosage.[2] Among other regulatory activities, the FDA attempts to incorporate genomic information into drug labels by requiring the revision of existing labels on the basis of clinical findings or the inclusion of appropriate wording in drug labels of new products. A list of pharmacogenomic biomarkers identified in the context of approved drug labels can be found on the FDA's website.[3] The FDA's European counterpart, the European Medicines Agency (EMA), has similarly published a variety of scientific guidelines on pharmacogenomics.[4]

Drug package inserts (PIs) represent the most fundamental tool for providing information on approved drugs to healthcare professionals and for promoting proper use of the drugs. The contents of PIs can be tailored to meet the requirements of the target populations and take local guidance into consideration.

The availability of pharmacogenomic information presented in PIs has been investigated in recent years in the United States, Europe and Japan.[5–10] Findings showed that 121 of the 1200 PIs from the United States released over the period 1945–2005 contained pharmacogenomic information.[5] In the European Union, the PIs from approximately 20% of the 584 products reviewed by EMA as of 2011 contained genomics information to personalize their use.[10] In Japan, 32 of 199 PIs (16%) reviewed by the Pharmaceutical Medical Device Agency (PMDA) from 2002 to 2006 included pharmacogenomic information.[8] However, there have been few comparisons of the pharmacogenomic information in PIs between countries.[9] We selected the United States, the United Kingdom (UK) and Japan for our comparison because of similarities in their drug regulations, as all three are members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The UK, like Japan, has a national health service that controls drug cost reimbursement.[11]

The aim of the current study was to investigate differences in information on genomic biomarkers in PIs from the United States, the UK and Japan. The findings should provide a basis for further regulatory standardization and highlight justifiable population-specific differences in pharmacogenomic information in PIs.

METHODS

A list of pharmacogenomic biomarkers in PIs from the United States is available from the FDA website.[3] PIs from the United

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States were obtained from Drugs@FDA[12] and DailyMed,[13] whereas PIs from the UK (Summaries of Product Characteristics; SPCs) were obtained from the Electronic Medicines Compendium (eMC).[14] Japanese PIs were obtained from the PMDA website.[15] 'PI is not available' indicates that PIs were not available from the eMC in the UK or the PMDA in Japan, for yet-to-be approved or discontinued products.

Because the lists of pharmacogenomic biomarkers and PIs are updated from time to time at irregular intervals, results are subject to changes over time but were current on 1 October 2012. We chose to manually screen genomic biomarker information because it was scattered throughout different sections of PIs approved by the respective regulatory authorities.[16–19] Our screening was based on a set of selection criteria that identified descriptions of genomic biomarkers (genotype and/or phenotype) that affected drug efficacy, safety, pharmacokinetics, pharmacodynamics or dosage.

In the present study, a set of drugs and biomarkers was counted as one PI. For all PIs identified in this analysis, genomic biomarker information was extracted manually, according to the context in which the genomic biomarkers were included in the PIs. We divided PI sections in the three countries into five categories (Table 1). UK PI sections had no counterpart for the 'Warning' section. When genomic biomarker information was scattered throughout more than one section (e.g. 'Indications' and 'Dosage'), the upper-categorized section in Table 1 (e.g. 'Indications') was assigned priority.

In addition, we analysed associated factors, including type of biomarker, purpose of biomarker, therapeutic area and initial approval year of the drug in the United States. Biomarkers were categorized into three types (drug target, metabolizing enzyme and others), with two groups for 'purpose' (efficacy and safety). Therapeutic areas were designated according to the FDA table.[3]

RESULTS AND DISCUSSION

Characteristics of pharmacogenomic biomarkers in PIs

118 sets of drugs and genomic biomarkers in PIs (106 as drugs) were included on the FDA list as of 1 October 2012. The 39 individual genomic biomarkers on the list were tabulated by biomarker type and purpose (Table 2). Cytochrome P450 (CYP) 2D6 was the most frequent biomarker found in PIs (37 PIs, 31%). More than half of the biomarkers (69 PIs, 58%) were classified as metabolizing enzymes, and safety-related biomarkers constituted 69% (81 PIs). Numbers of PIs, stratified by therapeutic area and initial approval year in the United States, are shown in Table 3.

Table 1. Package insert section categories for analysis

	PI sections in the USA, the UK and Japan		
Section categories for analysis	USA	UK	Japan
Indications	Indications and usage	4·1 therapeutic indications	Indications Precautions for indications
Warning	Boxed warning	Not applicable	Warning
Dosage	Dosage and administration	4·2 posology and method of administration	Dosage and administration Precautions for dosage
Contraindications	Contraindications	4·3 contraindications	Contraindications
Precautions	Others	Others	Others

Table 2. Type and purpose of genomic biomarkers in the FDA list

Type (number of PIs)	Purpose	Biomarker (number of PIs)
Drug target (29)	Efficacy	ALK (1), BRAF (1), C-Kit (1), CCR5 (1), CD20 antigen (1), CD25 (1), CD30 (1), CFTR (1), EGFR (4), ER (2), ER &/PgR (2), FIP1L1-PDGFRα (1), Her2/neu (4), PDGFR (1), Ph chromosome (4), PML/RARα (2), VKORC1 (1)
Metabolizing enzyme (69)	Safety	CYP1A2 (1), CYP2C19 (14), CYP2C9 (3), CYP2D6 (37), DPD (2), G6PD (3), NAT1/NAT2 (2), TPMT (4), UGT1A1 (3)
Others (20)	Efficacy (8)	ApoE2 (1), chromosome 5q (1), IL28B (3), KRAS (2), LDLR (1)
	Safety (12)	AT III (1), factor V Leiden (2), HGPRT (1), HLA-B*1502 (2), HLA-B*5701 (1), prothrombin mutations (1), Rh genotype (1), UCD (3)

ALK, anaplastic lymphoma kinase; ApoE2, apolipoprotein E2; AT III, antithrombin III; BRAF, v-raf murine sarcoma viral oncogene homologue B1; C-Kit, v-kit Hardy–Zuckerman 4 feline sarcoma viral oncogene homologue; CCR5, chemokine receptor type 5; CD, cluster of differentiation; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P450; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; FDA, Food and Drug Administration; FIP1L1, FIP1 like 1; G6PD, glucose-6-phosphate dehydrogenase; Her2/neu, human epidermal growth factor receptor 2; HGPRT, hypoxanthine–guanine phosphoribosyltransferase; HLA, human leucocyte antigen; IL28B, interferon-lambda-3; KRAS, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue; LDLR, low-density lipoprotein receptor; NAT, N-acetyltransferase; PDGFR, platelet-derived growth factor receptor; PDGFRα, platelet-derived growth factor receptor, alpha polypeptide; Ph, Philadelphia; PgR, progesterone receptor; PML/RARα, promyelocytic leukaemia/retinoic acid receptor alpha; TPMT, thiopurine S-methyltransferase; UCD, urea cycle disorder; UGT1A1, UDP glucuronosyltransferase 1 family, polypeptide A1; VKORC1, vitamin K epoxide reductase complex, subunit 1.

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Table 3. Package inserts stratified by therapeutic area and initial approval year in the USA

	Number of PIs (%)
Therapeutic area	
Analgesics	3 (3)
Antiarrhythmic	1 (1)
Antifungals	2 (2)
Antiinfectives	2 (2)
Antivirals	5 (4)
Cardiovascular	8 (7)
Dermatology and dental	4 (3)
Gastroenterology	8 (7)
Haematology	5 (4)
Metabolic and endocrinology	2 (2)
Musculoskeletal	1 (1)
Neurology	6 (5)
Oncology	36 (31)
Psychiatry	27 (23)
Pulmonary	2 (2)
Reproductive	1 (1)
Reproductive and urologic	2 (2)
Rheumatology	2 (2)
Transplantation	1 (1)
US initial approval date	
1940s	1 (1)
1950s	9 (8)
1960s	11 (9)
1970s	9 (8)
1980s	7 (6)
1990s	26 (22)
2000s	44 (37)
2010s	11 (9)

The largest therapeutic area was oncology, followed by psychiatry. Sixty-nine per cent of the oncology group PIs (25/36 PIs) included drug target biomarkers, whereas 96% (26/27 PIs) of the psychiatry group PIs provided metabolizing enzyme polymorphisms, notably CYP isoenzymes. 75% (27/36 PIs) of the oncology drug PIs referred to biomarkers to highlight efficacy issues. In contrast, all 27 psychiatric drug PIs provided the information to comment on the drugs' safety. For initial US drug approvals, more than two-thirds (81 PIs, 69%) of the PIs with genomic biomarker information were approved from 1990 onwards. Of the 29 PIs with drug target biomarkers, the majority (26 PIs, 90%) were initially approved in 1990 or later, whereas 59% (41/69 PIs) of metabolizing enzyme biomarkers were approved after 1990.

The cross-sectional study design we used provides results specific to a time point. For example, the information on Rh genotype was deleted from the clomiphene PI from the United States on 22 October 2012. In addition, changes in the classification of the type and purpose of biomarkers may also vary over time. For example, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (KRAS), not usually a direct target of drugs, may become so over time.[9]

Number of PIs containing pharmacogenomic biomarkers in the three countries

The numbers of PIs containing pharmacogenomic information from the United States, the UK and Japan by PI section, as categorized in Table 1, are shown in Fig. 1, along with types of biomarkers. With respect to the number of PIs that contained genomic information, those from the United States contained all 118 PIs, followed by the UK (71 PIs, 60%) and Japan (44 PIs, 37%). PIs classified as 'Precautions' were the most common PI sections cited in all three countries, followed by 'Indications' and 'Dosage'.

For the United States, information in the 'Indications' section typically comment on drug target biomarkers (25/31 PIs, 81%), whereas the 'Dosage' and 'Precautions' sections mainly included information on metabolizing enzyme biomarkers (14/15 PIs, 93% and 50/64 PIs, 78%, respectively). The genomic biomarker information in the 'Indications' section of the PIs was limited to seven therapeutic areas (antivirals, dermatology and dental, gastroenterology, haematology, metabolic and endocrinology, oncology, pulmonary), of which oncology predominated 77% (24/31 PIs). The 'Precautions' section of the PIs with genomic information included all 19 therapeutic areas, but 31% (20/64 PIs) of the PIs related to psychiatry.

For the UK and Japan, 21 (18%, 20 drugs) and 34 (29%, 32 drugs) of drugs with PIs that included genomic information in the United States were not approved or were discontinued. Of these, 18 PIs (15%, 17 drugs) were not available in either the UK or Japan. Relevant biomarkers were not described in 26 (22%) and 40 (34%) PIs from the UK and Japan, respectively, and 21 of these PIs (18%) did not mention relevant biomarkers in either the UK or Japan. As with the United States, the majority of the 'Indications' section PIs from the UK (18/23 PIs, 78%) and Japan (12/16 PIs, 75%) described drug targets. In contrast, no metabolizing enzyme biomarkers appeared in the 'Indications' section in any of the three countries. The 'Precautions' section mainly contained metabolizing enzyme information in the UK (27/38 PIs, 71%) and Japan (15/25 PIs, 60%); however, some PIs recommended or required a specific action according to the effect of the metabolizing enzyme in the 'Warning', 'Dosage' and 'Contraindication' sections. PIs from the UK had no counterpart to the 'Warning' section. The majority of the 'Indications' section PIs belonged to the area of oncology, both in the UK (19/23 PIs, 83%) and Japan (13/16 PIs, 81%), similar to those in the United States. On the other hand, only 18% (7/38 PIs) and 8% (2/25 PIs) of the 'Precautions' section PIs were in psychiatry in the UK and Japan, respectively. Most PIs of psychiatric drugs did not state relevant biomarkers or were not available in the UK (17/27 PIs, 63%) or in Japan (23/27 PIs, 85%).

Figure 1 shows that the United States was the country most likely to include pharmacogenomic information in PIs, followed by the UK and then Japan. The number of Japanese PIs that provided information on genomic biomarkers was small (44 PIs) compared with those of the United States (118 PIs) and the UK (71 PIs). The notorious 'drug lag' in Japan may have partly contributed to this.[20,21] Another reason for this discrepancy might be ethnic differences, such as differences in allele frequencies in the populations concerned. For example, factor V Leiden, which has an incidence of 5% among Caucasians in North America, is extremely rare in people of Asian descent.[22] The frequencies of CYP2D6 poor metabolizers (PMs), which was the most frequent biomarker found in PIs, are approximately 1% in Asians and approximately 5–10% in Caucasians. CYP2C19 PMs have prevalences of 15–30% in Asians and 3–6% in Caucasians.[23,24] Ethnic factors may therefore account for some of the differences seen in Japanese PIs relative to the other blocks.

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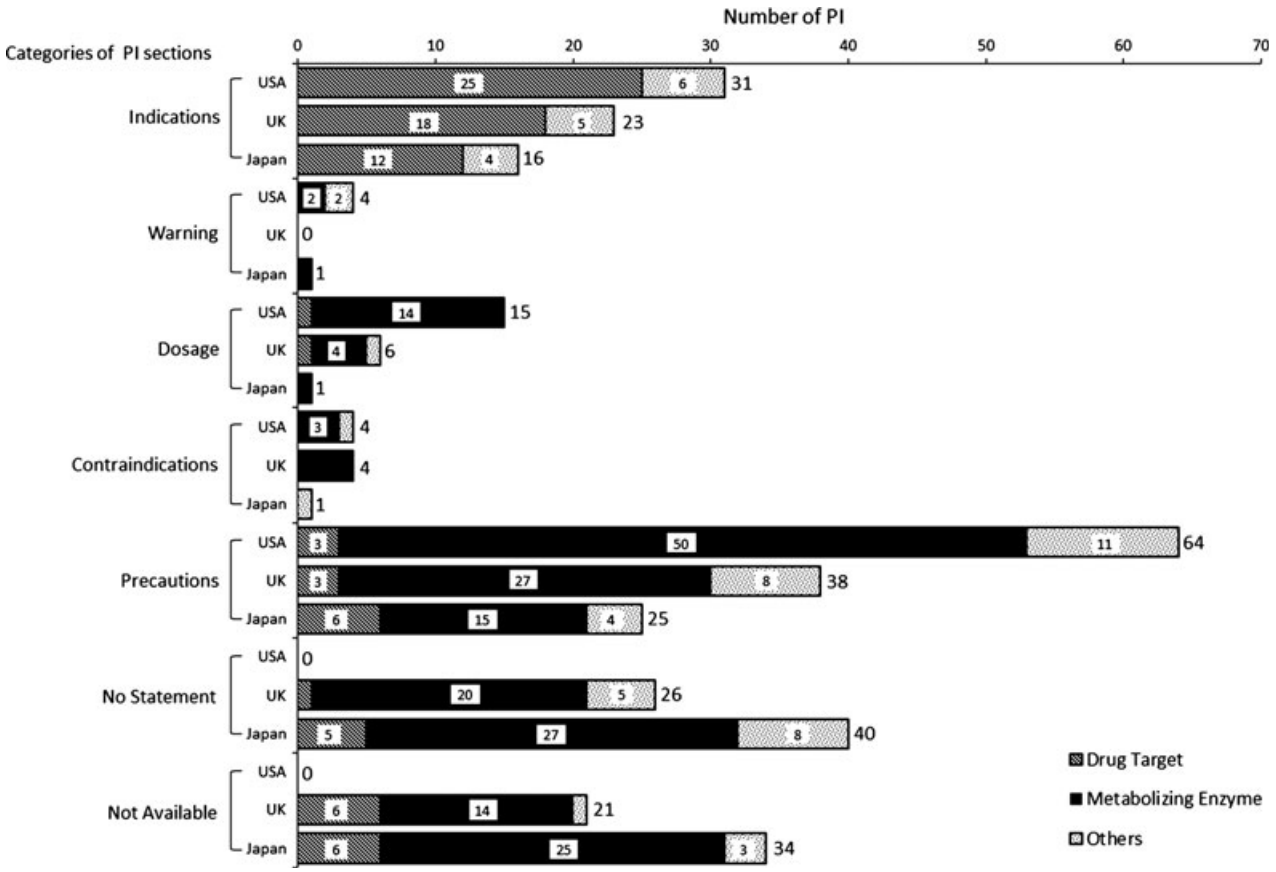

Fig. 1. Package insert sections for pharmacogenomic information in the USA, the UK and Japan.

Another reason for the difference is likely related to variations in the guidance issued by the different drug regulators for inclusion of pharmacogenomic information in PIs. The FDA and EMA provide instructions on how pharmacogenomic information should be incorporated into PIs,[17,19,25–27] whereas the Japanese regulatory guidelines have not been updated since 1997[18] and do not mention pharmacogenomics. In the United States, applicants have the option of creating a separate 'Pharmacogenomics' subsection in the Clinical Pharmacology section, if appropriate.[26] The establishment of guidelines and support from regulatory agencies would facilitate the translation of pharmacogenomic knowledge into routine clinical practice.

Comparisons of genomic biomarkers in PIs among the three countries

Details of the pharmacogenomic information in the 118 PIs from the United States, the UK and Japan are compared in Tables S1–S3 (online only), based on PI sections in the United States. Tables S1–S3 provide PI information on the 'Indications' section, 'Precautions' and sections other than 'Indications' and 'Precautions', respectively. Analyses of PI section differences between the United States and the UK, the United States and Japan, and the UK and Japan are shown in Tables 4–6, respectively. The 'not available' (NA) column was introduced to the tables between the United States and the UK or Japan (Tables 4 and 5) because 21 (18%) and 34 (29%) PIs were not available in the UK and Japan, respectively. The three tables show that there was significant disconcordance in the PI sections among the three countries, even though the regional authorities regulated the same product with considerable discussions on harmonization. We observed that the differences were stratified by PI section in the United States (Tables 4 and 5) or the UK (Table 6), type of biomarker, purpose of biomarker, therapeutic area and initial US approval period.

Stratification by PI section

The 'Indications' section showed higher concordance rates between countries (UK/USA 65%, Japan/USA 48% and Japan/UK 61%) than those of the 'Precaution' section (UK/USA 41%, Japan/USA 17% and Japan/UK 37%). As Fig. 1 demonstrates, PI section was linked to type of biomarkers, and the majority of the 'Indications' section PIs described drug targets in all three countries.

Stratification by type and purpose of biomarker

In the PIs from both the UK and Japan, the genomic information appeared more consistently in the same section relative to the US PIs for drug targets (UK 55%, Japan 41%) than that for metabolizing enzyme (UK 36%, Japan 14%). In this study, pharmacogenomic information in the PIs was classified roughly as describing the drug's pharmacological target (mainly efficacy oriented) or the drug's

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Table 4. Analysis of differences in information in package inserts between the USA and the UK

Stratified factor (number of PIs)	Number of PIs: Differences between the USA and the UK: Concordant (51)	Different (46)	NA in UK[a] (21)
PI section in the USA			
Indications (31)	20	4	7
Precautions (64)	26	26	12
Others (23)	5	16	2
Type of biomarker			
Drug target (29)	16	7	6
Metabolizing enzyme (69)	25	30	14
Others (20)	10	9	1
Purpose of biomarker			
Efficacy (37)	20	11	6
Safety (81)	31	35	15
Therapeutic area			
Oncology (36)	18	13	5
Psychiatry (27)	7	13	7
Others (55)	26	20	9
Initial US approval period			
Before 1979 (30)	6	18	6
1980–1999 (33)	20	11	2
After 2000 (55)	25	17	13

[a]PI was not available in the UK.

Table 5. Analysis of differences in information in package inserts between the USA and Japan

Stratified factor (number of PIs)	Number of PIs: Differences between the USA and Japan: Concordant (29)	Different (55)	NA in Japan[a] (34)
PI section in the USA			
Indications (31)	15	8	8
Precautions (64)	11	32	21
Others (23)	3	15	5
Type of biomarker			
Drug target (29)	12	11	6
Metabolizing enzyme (69)	10	34	25
Others (20)	7	10	3
Purpose of biomarker			
Efficacy (37)	16	14	7
Safety (81)	13	41	27
Therapeutic area			
Oncology (36)	14	16	6
Psychiatry (27)	4	11	12
Others (55)	11	28	16
Initial US approval period			
Before 1979 (30)	2	20	8
1980–1999 (33)	7	18	8
After 2000 (55)	20	17	18

[a]PI was not available in Japan.

metabolizing enzymes (mainly safety oriented). A drug target can be used to stratify a disease into two or more distinct illnesses or syndromes based on their biological characteristics, and clinical trials are increasing designed with the use of genomic biomarkers for inclusion eligibility. The majority of genomic biomarkers in the 'Indications' section consisted of drug targets in all three countries examined. The four biomarkers that were not drug targets, included in the 'Indications' section, were chromosome 5q (USA, Japan), KRAS (all), low-density lipoprotein receptor (LDLR, all) and urea cycle disorder (UCD, USA and UK). Chromosome 5q, KRAS and LDLR are not direct targets of drugs but are markers of efficacy. UCD is a safety biomarker for valproic acid but an efficacy biomarker for sodium phenylbutyrate. Differences in drug target descriptions in the PIs among the three countries were mainly related to whether the relevant indication was approved.

Compared with drug target biomarkers, polymorphisms of metabolic enzymes affect drug pharmacokinetics and usually have more modest impacts on drug response. The present study shows that inclusion of information on a metabolic enzyme's genomics is more inconsistent across the three countries when with drug target information. Interindividual variability in drug pharmacokinetics is caused by several factors, including sex, age, weight, renal and hepatic function and genetics. Therefore, pharmacokinetic variability does not necessarily influence drug safety and/or efficacy significantly. The inclusion of information on genomic biomarkers in the PIs for clopidogrel, tamoxifen and warfarin illustrates this issue well. The FDA updated the clopidogrel PI to include, in the 'Warning' section, information stating that the patient's genotype for CYP2C19 could affect the antiplatelet activity of the drug.[28] The warning recommends alternative medications for CYP2C19 PMs. On the other hand, the UK and Japanese PIs provide information on CYP2C19 PM in the 'Precautions' sections (Table S3). The American College of Cardiology Foundation and the American Heart Association published a Clinical Alert that emphasized that information regarding the predictive value of genetic testing is still very limited and that current evidence is insufficient to recommend routine genetic function testing at the present time.[29] Current evidence also does not support personalized treatment with clopidogrel tailored to the CYP2C19 genotype.[30]

In contrast, although several studies of tamoxifen have addressed the association between CYP2D6 genotype and clinical outcome,[31–38] only the UK PI includes information about CYP2D6 pharmacogenomics in the 'Precautions' section. A possible reason for this discrepancy could be differences in the results of relatively small and mostly retrospective studies.[39–41]

The information on genomic biomarkers for tamoxifen was more consistent as there was no information described in only one country.

The warfarin's PI included genomic information on both drug target (VKORC1; vitamin K epoxide reductase complex, subunit 1) and metabolizing enzyme (CYP2C9). A number of retrospective studies have reported a strong association between the presence of VKORC1 and CYP2C9 variants and warfarin dosing, and polymorphisms in VKORC1 have been shown to be more important than those in CYP2C9.[42–44] However, prospective evidence for any clinically relevant benefit of VKORC1 and/or CYP2C9 testing is limited or of uncertain clinical relevance.[45–49] The US warfarin PI provided dosing schedules according to a combination of

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Table 6. Analysis of differences in information in package inserts between the UK and Japan

	Number of PIs	
	Differences between the UK and Japan	
Stratified factor (number of PIs)	Concordant (68)	Different (50)
PI section in the UK		
Indications (23)	14	9
Precautions (38)	14	24
Others (10)	1	9
No statement (26)	21	5
Not available (21)	18	3
Type of biomarker		
Drug target (29)	19	10
Metabolizing enzyme (69)	38	31
Others (20)	11	9
Purpose of biomarker		
Efficacy (37)	25	12
Safety (81)	43	38
Therapeutic area		
Oncology (36)	23	13
Psychiatry (27)	16	11
Others (55)	29	26
Initial US approval period		
Before 1979 (30)	14	16
1980–1999 (33)	18	15
After 2000 (55)	36	19

VKORC1 and CYP2C9 genotypes, whereas the PI from the UK gave information only on genetic variability of VKORC1 and CYP2C9. The Japanese PI only presented information on the existence of CYP2C9 polymorphism (Table S3).

The way in which genomic information was described in the PIs depended on the strength of the available data and on the efficacy and expected safety consequences. When the biomarker is a drug target, there is preliminary evidence that the genomic biomarker was associated with drug response prior to initiating the clinical trials. Confirmatory trials were then undertaken for prospective validation of the biomarker. Differences in PIs occurred when there was a lack of strong evidence to provide clear information and recommendations to the prescriber and when the safety or efficacy consequences differed according to subpopulations considered.

Some of the differences may result from differences in health insurance provisions between the three countries. For example, the national health services of the UK and Japan do not reimburse CYP genotyping tests. In the United States, some payers have championed personalized approaches, even if reimbursement is limited.[50] This might lead to some US PIs (e.g. iloperidone, pimozide, tetrabenazine) strongly recommending CYP2D6 genotyping to individualize dosing, whereas there were no recommendations in the PIs from the UK and Japan (Table S3).

Stratification by therapeutic area

The present study showed contrasting results between oncology and psychiatry. The majority of the PIs with genomic information in the 'Indications' section were of the oncology area for all three countries (USA 77%, UK 83%, Japan 81%). In cancer treatment, diagnostic tests are available and pharmacogenomic approaches are already implemented in clinical practice in all three countries. On the other hand, molecular personalized medicine is still not common in psychiatry. Pharmacogenomic studies with concrete results in psychiatry have largely been on genes encoding metabolic enzymes because most psychiatric drugs are metabolized by CYP isoenzymes.

Stratification by initial approval year in the United States

The PIs from the UK and Japan were more likely to differ from PIs from the United States for drugs approved prior to 1980 (Tables 4 and 5). PIs with drug target biomarkers tended to be approved in the United States later than PIs with biomarkers for metabolizing enzymes.

WHAT IS NEW AND CONCLUSION

The United States was the country most likely to introduce genomic information into PIs, followed by the UK and Japan. Pharmacogenomic information in PIs differed among the three countries depending on type of biomarkers and therapeutic area. These differences appeared to vary according to the strength of the evidence supporting use of the genomic biomarkers and on the practicability of translating pharmacogenomic knowledge into PIs. Guidance by drug regulators on appropriate presentation of pharmacogenomic data in PIs should help facilitate the wider use of such information.

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CONFLICT OF INTEREST

The authors report no conflict of interests in this work.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Pharmacogenomic information in the 'Indications' section of the package inserts (PI) of products marketed in the US, UK and Japan.

Table S2 Pharmacogenomic information in the 'Precautions' section of the package inserts (PI) of products marketed in the US, UK and Japan.

Table S3 Pharmacogenetic information in sections, other than 'Indications' and 'Precautions' sections of the package inserts (PI) of products marketed in the US, UK and Japan.

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