Received: 9 September 2020 | Accepted: 25 January 2021

DOI: 10.1111/cts.13000

ARTICLE

A retrospective analysis of actionable pharmacogenetic/genomic biomarker language in FDA labels

Shinji Yamazaki

Pharmacokinetics, Dynamics & Metabolism, Pfizer Worldwide Research and Development, San Diego, California, USA

Correspondence
Shinji Yamazaki, Drug Metabolism & Pharmacokinetics, Janssen Research & Development, Pharmaceutical Companies of Johnson & Johnson, San Diego, CA, USA.
Email: syamaza5@its.jnj.com

Present address
Shinji Yamazaki, Drug Metabolism & Pharmacokinetics, Janssen Research & Development, Pharmaceutical Companies of Johnson & Johnson, San Diego, California, USA

Funding information
This study was sponsored by Pfizer.

Abstract

The primary goal of precision medicine is to maximize the benefit-risk relationships for individual patients by delivering the right drug to the right patients at the right dose. To achieve this goal, it has become increasingly important to assess gene-drug interactions (GDIs) in clinical settings. The US Food and Drug Administration (FDA) periodically updates the table of pharmacogenetic/genomic (PGx) biomarkers in drug labeling on their website. As described herein, an effort was made to categorize various PGx biomarkers covered by the FDA-PGx table into certain groups. There were 2 major groups, oncology molecular targets (OMT) and drug-metabolizing enzymes and transporters (DMETs), which constitute ~70% of all biomarkers (~33% and ~35%, respectively). These biomarkers were further classified whether their labeling languages could be actionable in clinical practice. For OMT biomarkers, ~70% of biomarkers are considered actionable in clinical practice as they are critical for the selection of appropriate drugs to individual patients. In contrast, ~30% of DMET biomarkers are considered actionable for the dose adjustments or alternative therapies in specific populations, such as CYP2C19 and CYP2D6 poor metabolizers. In addition, the GDI results related to some of the other OMT and DMET biomarkers are considered to provide valuable information to clinicians. However, clinical GDI results on the other DMET biomarkers can possibly be used more effectively for dose recommendation. As the labels of some drugs already recommend the precise doses in specific populations, it will be desirable to have clear language for dose recommendation of other (or new) drugs if appropriate.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pharmacogenetic/genomic (PGx) biomarkers are increasingly being used for precision medicine to focus on maximizing therapeutic efficacy while minimizing adverse events. The US Food and Drug Administration (FDA) provides an updated summary table of PGx biomarkers in the labels of approved drugs (FDA-PGx table).

WHAT QUESTION DID THIS STUDY ADDRESS?

PGx biomarkers listed in the FDA-PGx table were analyzed to categorize into certain groups (e.g., as oncology molecular targets [OMTs] and drug-metabolizing enzymes and transporters [DMETs]), and then classify whether their labeling language could be actionable in clinical practice.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

There are 2 major groups in the FDA-PGx table, OMT and DMET biomarkers, accounting of ~70% of all biomarkers. Among them, ~70% of OMT biomarkers and ~30% of DMET biomarkers are considered actionable in clinical practice.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The gene-drug interaction results related to some DMET biomarkers can be used more effectively and practically for dose recommendation in specific populations. It will be therefore desirable to have clear labeling language on dose recommendation for other (or new) drugs if appropriate.

INTRODUCTION

Precision medicine is increasingly recognized as a promising approach to maximize therapeutic efficacy and minimize undesirable adverse events in patients.[1–4] Ultimately, the primary goal is to deliver the right drugs to the right patients at the right dose, through the right route at the right time. This approach can therefore effectively tailor medical therapies to individual patients. Identifying some variants in specific genes can be key for advancing the precision medicine successfully. The study of gene-drug interactions (GDIs) has emerged in support of investigations focused on how individual genomic profiles could affect a drug's pharmacokinetics, pharmacodynamics, efficacy, and safety in patients.[5–7] Recently published regulatory guidance documents covering pharmacogenetics/genomics (PGx) have undoubtedly accelerated the generation of clinical GDI results.[8–10] However, given several associated factors, such as the intrastudy and interstudy variabilities of drug responses, therapeutic indices (or safety margin), and availability of alternative dosages or therapies, it is not straightforward to extrapolate the observed GDI results to clinical practice in many cases. To make the extrapolation more reliable and precise, several initiatives and approaches are underway to provide the practical information including clinical GDI application. For instance, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have published their peer-reviewed guidance documents that focus translating clinically characterized GDI into actionable prescribing decisions for individual drugs.[11–15]

The GDI results on drug-metabolizing enzymes and transporters (DMETs) have initially been applied to account for the variability in pharmacokinetics.[16–18] Understanding the intersubject differences in drug exposures can guide individual dose adjustments (e.g., dosage amounts and frequency), when reflecting efficacy or safety profiles. Recently, precision medicine has become a focus area in anticancer therapy by linking PGx on oncology molecular targets (OMTs) to therapeutic responses of specific anticancer drugs, particularly molecularly targeted agents.[7,19,20] Because the detection of presence or absence of OMT is critical for the selection of appropriate drugs to individual patients, the associated biomarker assays should be validated to meet regulatory requirements.[20,21] These assays, companion diagnostic tests/devices (CDx), are integral components of precision medicine and most often developed in parallel with the corresponding drugs. The US Food and Drug Administration (FDA) periodically updates the list of FDA-cleared or approved companion diagnostic devices (FDA-CDx) on their website.[22] The table shows an increasing number of FDA-CDx developed to guide therapeutic treatments. Enhanced understanding of OMT as PGx biomarkers has enabled the accelerated development of precision medicines for patients with cancer, particularly in the last decade.[19,20]

Regulatory authorities, such as the FDA, the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency (PMDA), provide GDI information on their approved drugs in their labels.[23–25] According to the Code of Federal Regulations, Title 21, the FDA labels are intended to convey "a summary of the essential scientific information needed for the safe and effective use of the drug."[26] Thus, the labels should contain the essential information regarding GDI when a drug's efficacy or safety is influenced. The FDA regularly updates the table of PGx in drug labeling (FDA-PGx table) on their website.[27] This table covers all PGx biomarkers indicated in the labels of FDA-approved drugs. In the present study, the PGx biomarkers listed in the FDA-PGx table have been analyzed retrospectively to categorize into certain groups, and then classified whether the labeling language regarding PGx biomarkers of individual drugs could be actionable in clinical practice. The present results could therefore provide some perspective on how precision medicine is currently being implemented at the bedside in the United States.

METHODS

Data source

PGx biomarkers of approved drugs by the FDA were collected from the FDA-PGx table available on the FDA website (updated by December 2019).[27] The table consists of 275 drugs with 398 biomarkers, as some drugs possess multiple PGx biomarkers. For oncology drugs, FDA-CDx were collected from the list of FDA-cleared or approved companion diagnostic devices available on the FDA website (updated by January 2020).[22] The labels and letters of approved drugs on the FDA website (Drugs@FDA) were also used as necessary (https://www.accessdata.fda.gov/scripts/cder/daf/).

Label analysis

PGx biomarkers ($n = 398$) in the FDA-PGx table were first analyzed by the listed years and therapeutic areas. Following the categorization, 2 major PGx biomarker groups, OMT, and DMET, were further analyzed in detail. The OMT biomarkers are known targets of anticancer drugs, such as anaplastic lymphoma kinase (ALK), Philadelphia chromosome (BCR-ABL1), protooncogene B-Raf (BRAF), breast cancer gene (BRCA), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and hormone receptors (HR, including estrogen receptor [ESR] and progesterone receptor [PGR]) listed in Table S1. The OMT biomarkers were then classified into three groups based on the labeling language, largely with respect to the labeling sections, such as Indications and Usages and Dosage and Administration (particularly, Patient Selection):

1. IND1 (indication required for FDA-CDx): indication for drugs in specific patients based on OMT biomarkers detected by FDA-CDx,
2. IND2 (indication not required for FDA-CDx): indication for drugs in specific patients based on OMT biomarkers not required for FDA-CDx,
3. INF (information only): OMT biomarkers not related to drug selection for patients.

The labeling language for OMT biomarkers in IND1 and IND2 were considered actionable in clinical practice.

The DMET biomarkers are known enzymes and transporters involved in drug metabolism and transport, such as acetyltransferases, cytochromes P450 (CYPs), UDP-glucuronosyltransferases (UGTs), and solute carrier organic anion transporter 1B1 (SLCO1B1 also known as OATP1B1) listed in Table S2. The DMET biomarkers were then classified into seven groups based on the labeling language, largely with respect to the labeling sections:

1. IND (indication): indication or contraindication for drugs in specific populations based on DMET biomarkers,
2. WAR (warning): warning for drugs in specific populations based on DMET biomarkers, such as labeling language of "consider alternative therapies" and "withhold or discontinue drugs,"
3. REC (recommendation): dose recommendation in specific populations based on DMET biomarkers, such as dosage adjustment,
4. NRE (negative results): negative GDI results in specific populations (e.g., negligible changes in drug exposures) without dose recommendation,
5. PRE (positive results): positive GDI results in specific populations (e.g., fold-changes in drug exposures) without dose recommendation,
6. INF (information only): information on GDI in specific populations without clinical results, such as labeling language of "possible or expected changes in drug exposures of specific populations,"
7. NIN (no information): no information on GDI in specific populations.

Clinical GDI results in specific populations with DMET polymorphisms are mainly pharmacokinetic results with some exceptions for efficacy and safety as end points. The labeling language for DMET biomarkers in IND, WAR, and REC were considered actionable in clinical practice.

RESULTS

General analyses

The number of PGx biomarkers categorized by year is less than or equal to 4 per year from 1998 to 2013, 7 to 15 in 2014 to 2016, 57 in 2017, 153 in 2018, and 128 in 2019 (Figure 1). Thus, the majority of biomarkers (~70% of total 398) in the FDA-PGx table are present during 2018 to 2019. For the biomarkers categorized by therapeutic area, oncology is the major therapeutic area (~40%) followed by psychiatry (9%), infectious diseases (8%), neurology (7%), and hematology (7%; Figure 1). Of note, the biomarkers in oncology consist of ~45% and ~50% in 2018 and 2019, respectively.

Among all the biomarkers, there are 2 major groups, DMET (~35%) and OMT (~33%), constituting nearly 70% (Figure 2). The third and fourth groups are glucose-6-phosphate dehydrogenase deficient (G6PD; ~9%) and coagulation accelerating factors (CAFs; ~5%), such as F2 (prothrombin) and F5 (factor V Leiden). Each G6PD and CAF accounts for only less than one-third of either OMT or DMET biomarkers. G6PD varies across greater than or equal to 8 therapeutic areas whereas CAF are mainly in hematology (~70%). PGx biomarkers related to interferon

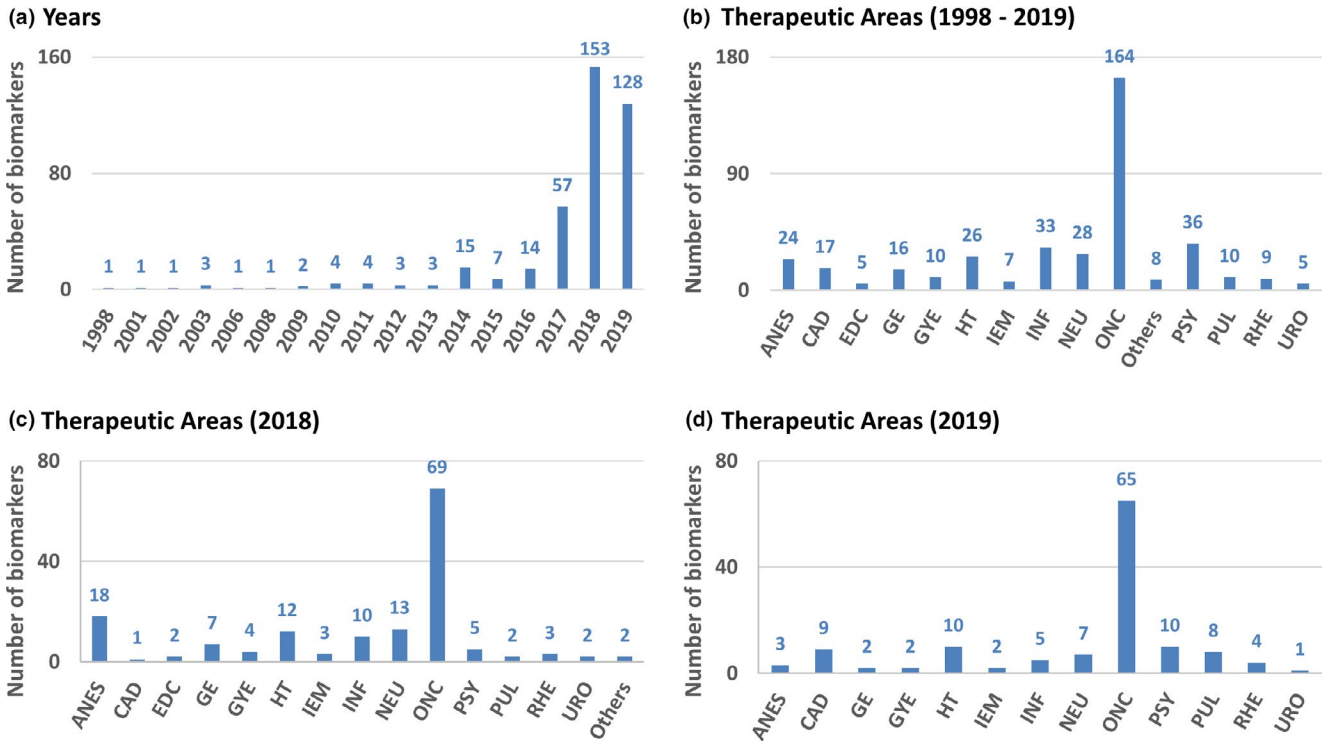

FIGURE 1 Categorization of pharmacogenetic/genomic biomarkers per year from 1998 to 2019 (a) and per therapeutic area in 1998–2019 (b), 2018 (c), and 2019 (d) listed in the US Food and Drug Administration-pharmacogenetic/genomic (FDA-PGx) table. Biomarkers on the labels were collected from the FDA-PGx table on the FDA website.[27] ANES, anesthesiology; CAD, cardiology; EDC, endocrinology; GE, gastroenterology; GYN, gynecology; HT, hematology; IEM, inborn errors of metabolism; INF, infectious diseases; NEU, neurology; ONC, oncology; PSY, psychiatry; PUL, pulmonary; RHE, rheumatology; URO, urology; Others (dental, dermatology, dermatology and gastroenterology, toxicology, and transplantation)

and interleukin are exclusively in infectious diseases. Consequently, the OMT and DMET biomarkers were further analyzed in detail.

Oncology molecular targets

The FDA-PGx table indicates 82 oncology drugs with greater than 30 different OMT biomarkers (n = 131), such as ESR/PGR (21), HER2 (17), EGFR (11), BCR-ABL (10), ALK (9), BRAF (8), and RAS (8) (Figure 2 and Table S1). Among these drugs, FDA-CDx are required for 32 drugs to detect 15 different biomarkers (n = 37 accounting for ~30% of OMT biomarkers), including BRAF (n = 6), EGFR (6), HER2 (5), BRCA (4), and ALK (3) (Figure 3). On the other hand, FDA-CDx are not required for 64 drugs with ~30 different biomarkers (n = 94 accounting for ~70% of OMT biomarkers). Among these OMT biomarkers, 11 biomarkers (e.g., ALK, EGFR, HER2, and RAS) are overlapped between with and without FDA-CDx, whereas only 3 biomarkers, BRCA (n = 6), FGFR (1), and PIK3CA (1), are exclusively listed as those required for FDA-CDx.

Regarding the labeling sections where biomarkers are specified, all the OMT biomarkers required for FDA-CDx (n = 37) are indicated in both the sections of Indications and Usage and Dosage and Administration on the labels (Table S3). In contrast, among the OMT biomarkers without FDA-CDx (n = 94), only ~20% are in both the sections whereas ~50% are in either section. In other words, nearly ~50% of the biomarkers without FDA-CDx are not indicated in either section because they are not directly related to the selection of anticancer drugs to patients. Additionally, all the OMT biomarkers except for four biomarkers are in the section of Clinical Studies (n = 127/131). The biomarkers not in this section are RAS for dabrafenib, trametinib, and vemurafenib, and ROS1 for lorlatinib. They are not directly related to their anticancer targets or indications, as the former three drugs are BRAF inhibitors and the latter is an ALK inhibitor.

Overall, all the biomarkers required for FDA-CDx (n = 37) are classified as IND1 because they are directly related to the drug selection for patients indicated in both the sections of Indications and Usage and Dosage and Administration (Table 1). Slightly over a half of the biomarkers (n = 49/94) among the OMT biomarkers without FDA-CDx are classified as IND2 because they are also related to the drug selection for patients, as indicated in Indications and Usage. The rest of the OMT biomarkers are classified as INF (n = 45) because they are not related to the drug selection for

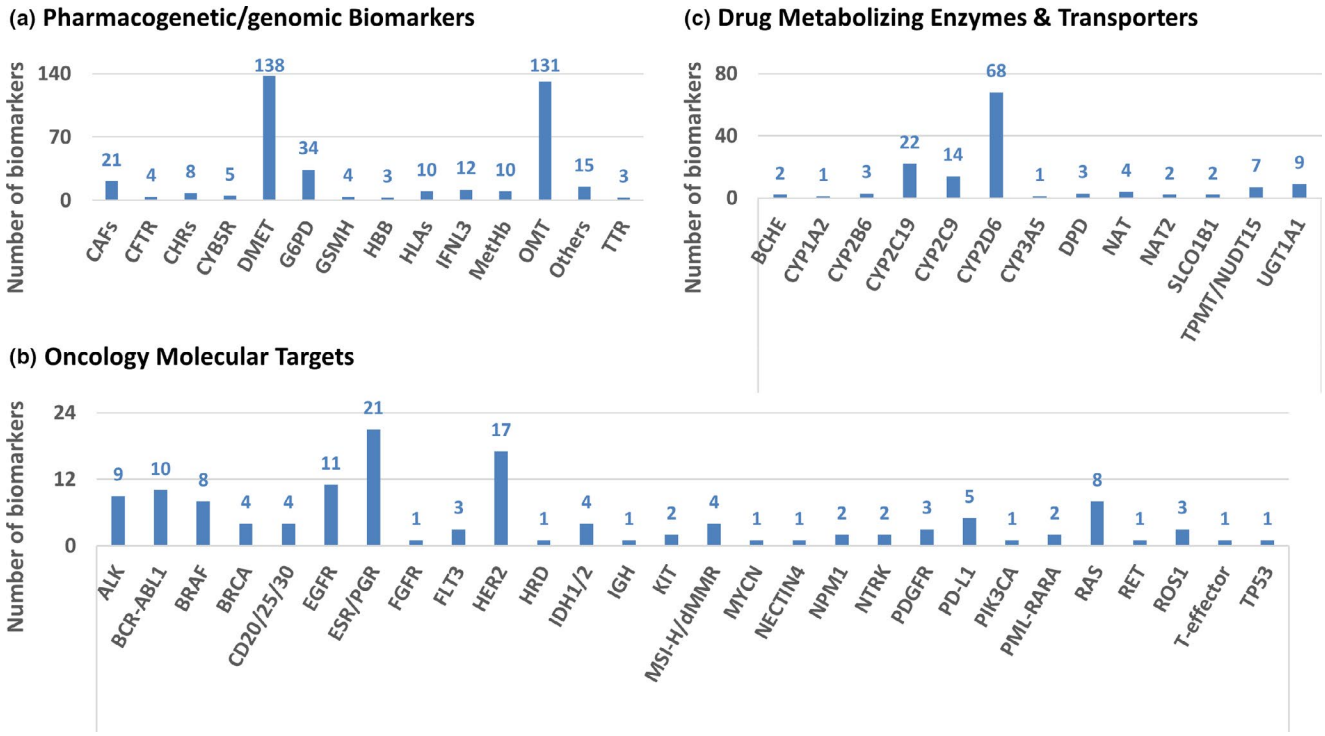

FIGURE 2 Categorization of pharmacogenetic/genomic biomarkers per subgroup (a), oncology molecular targets (b), and drug metabolizing enzymes and transporters (c), listed in the US Food and Drug Administration-pharmacogenetic/genomic (FDA-PGx) table. Biomarkers were collected from the FDA-PGx table on the FDA website.[27] (a) CAFs, coagulation accelerating factors; CFTR, cystic fibrosis transmembrane conductance regulator; CHRs, chromosomes 11q/13del/17p/5q/7del; CYB5R, cytochrome b5 reductase; DMET, drug metabolizing enzymes and transporters; G6PD, glucose-6-phosphate dehydrogenase; GSMH, nonspecific genetic susceptibility to malignant hyperthermia; HBB, hemoglobin subunit beta; HLAs, human leukocyte antigen A, B, DRB1, and DQA1; IFNL3, interferon L3/interleukin 28B; MetHb, nonspecific congenital methemoglobinemia; OMT, oncology molecular targets; TTR, transthyretin; others (amenable galactosidase alpha, Duchenne muscular dystrophy, calcium-sensing receptor, etc.). (b) ALK, anaplastic lymphoma kinase; BCR-ABL1, Philadelphia chromosome; BRAF, proto-oncogene B-RAF; BRCA, breast cancer gene; CD20/25/30, membrane spanning 4-domains A1 (MS4A1), interleukin 2 receptor subunit alpha (IL2RA), tumor necrosis factor receptor 8 (TNFRSF8); EGFR, epidermal growth factor receptor; ESR/PGR, estrogen receptor/progesterone receptor; FGFR, fibroblast growth factor receptors; FLT3, fms-related tyrosine kinase 3; HER2, erb-b2 receptor tyrosine kinase 2; HRD, homologous recombination deficiency; IDH1, isocitrate dehydrogenase 1; IGH, immunoglobulin heavy locus; KIT-D816 V, proto-oncogene receptor tyrosine kinase, D816 V mutation; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; MYCN, proto-oncogene, bHLH transcription factor; NECTIN4, nectin cell adhesion molecule 4; NPM1, nucleophosmin 1; NTRK, neurotrophic tyrosine receptor kinase; PDGFRA, platelet-derived growth factor receptor alpha; PD-L1, programmed death-ligand 1 (CD274); PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PML-RARA, promyelocytic leukemia-retinoic acid receptor alpha; RAS, proto-oncogene, GTPase; RET, ret proto-oncogene; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; T-effector, T-effector gene signature; TP53, tumor protein p53. (c) BCHE, butyrylcholinesterase; CYP1A2, cytochrome P450 1A2; CYP2B6, cytochrome P450 2B6; CYP2C19, cytochrome P450 2C19; CYP2C9, cytochrome P450 2C9; CYP2D6, cytochrome P450 2D6; CYP3A5, cytochrome P450 3A5; DPD, dihydropyrimidine dehydrogenase; NAT, nonspecific acetyltransferase; NAT2, N-acetyltransferase 2; SLCO1B1, organic anion transporting polypeptide 1B1 (OATP1B1); TPMT/NUDT15, thiopurine methyltransferase/nudix hydrolase 15; UGT1A1, UDP-glucuronosyltransferase 1A1

patients. Accordingly, nearly 70% of the OMT biomarkers (n = 86/131) in IND1 and IND2 are considered actionable.

Drug-metabolizing enzymes and transporters

The FDA-PGx table indicates 121 drugs with 138 DMET biomarkers consisting of 13 different DMET (e.g., CYP2D6 [n = 68], CYP2C19 [22], CYP2C9 [14], and UGT1A1 [9]) (Figure 2 and Table S2). They vary substantially across the therapeutic areas, such as psychiatry (n = 36), oncology (17), neurology (16), cardiology (13), and gastroenterology (11) (Figure 4). Remarkably, 33 of 36 biomarkers in psychiatry along with all 5 biomarkers in urology are CYP2D6.

Regarding the labeling sections for DMET biomarkers, CYP2D6 for eliglustat is the only one indicated in the section of Indications and Usage, which specifies that patients who are CYP2D6 ultra-rapid metabolizers may not achieve adequate therapeutic concentrations (Table S4). Eliglustat has been approved for adult patients (Gaucher disease

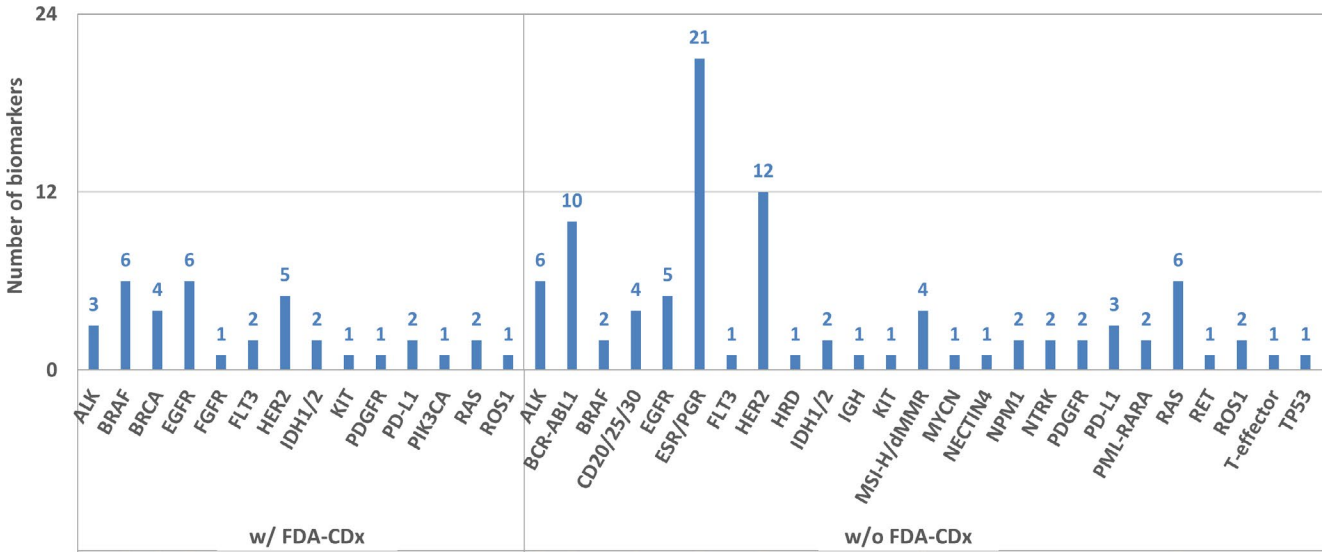

FIGURE 3 Categorization of oncology molecular targets required or not required for US Food and Drug Administration (FDA)-cleared or approved companion diagnostic devices (FDA-CDx) listed in the FDA-pharmacogenetic/genomic (PGx) table. Biomarkers with and without FDA-CDx were collected from the FDA-PGx table on the FDA website.[22,27] The abbreviations are listed in the legend of Figure 2

TABLE 1 Classification for oncology molecular targets listed in the FDA-PGx table

Class	Biomarker classification	Actionable	Drug (*n*)	Biomarkers (*n*)	Actionable (*n*)
IND1	Indication with FDA-CDx	Yes	32	37 (28%)	86 (66%)
IND2	Indication without FDA-CDx	Yes	38	49 (37%)	
INF	Information	No	32	45 (34%)	

The classification is described in the Methods section. The values in parentheses represent percent of all biomarkers related to oncology molecular targets. Biomarkers on the labels were collected from the table of pharmacogenomic biomarkers in drug labeling (FDA-PGx) on the FDA website.[22] FDA-CDx, FDA-cleared or approved companion diagnostic devices.

type 1) who are CYP2D6 normal (extensive), intermediate, or poor metabolizers, as detected by an FDA-CDx. This is also the only case where an FDA-CDx is required for DMET biomarkers; therefore, this is classified as IND (Table 2).

Forty-eight DMET biomarkers are indicated in sections of Contraindications, Boxed Warning, Warnings and/or Precautions (Table S4). Notably, three biomarkers are specified in Contraindications (i.e., CYP2D6 for eliglustat, dihydropyrimidine dehydrogenase [DPD] for fluorouracil [dermatology], and CYP2C9 for siponimod). The other three biomarkers are listed in Boxed Warning, CYP2C19 for clopidogrel, CYP2D6 for codeine, and CYP2D6 for tramadol. The former and latter are classified as IND and WAR, respectively (Table 2). Additionally, four biomarkers, TPMT and NUDT15 for azathioprine, DPD for capecitabine and fluorouracil (oncology), are also classified as WAR based on the labeling language in Warnings and Precautions.

In the section of Dosage and Administration, there are 27 drugs with 31 biomarkers consisting of 7 different DMET in the order of CYP2D6 (n = 16), TPMT (6), NUDT15 (6), CYP2C9 (3), CYP2C19 (2), NAT2 (2), and UGT1A1 (2) (Table S4). Among them, the labels of 23 drugs with 25 biomarkers specify recommended doses in specific populations (e.g., CYP2D6 poor metabolizers); therefore, they are classified as REC. Among the rest of the 6 biomarkers, 4 biomarkers (CYP2D6 for eliglustat, CYP2C9 for siponimod, and TPMT and NUDT15 for azathioprine) are already classified as IND or WAR (Table 2). The other two biomarkers are classified as INF (CYP2D6 for clozapine and valbenazine) because their labeling languages are "it may be necessary to reduce the dose" or "consider reducing the dose" in CYP2D6 poor metabolizers. Additionally, six biomarkers for six drugs are classified as RECs. These biomarkers include CYP2D6 (galantamine, gefitinib, and nefazodone), CYP2C19 (pantoprazole),

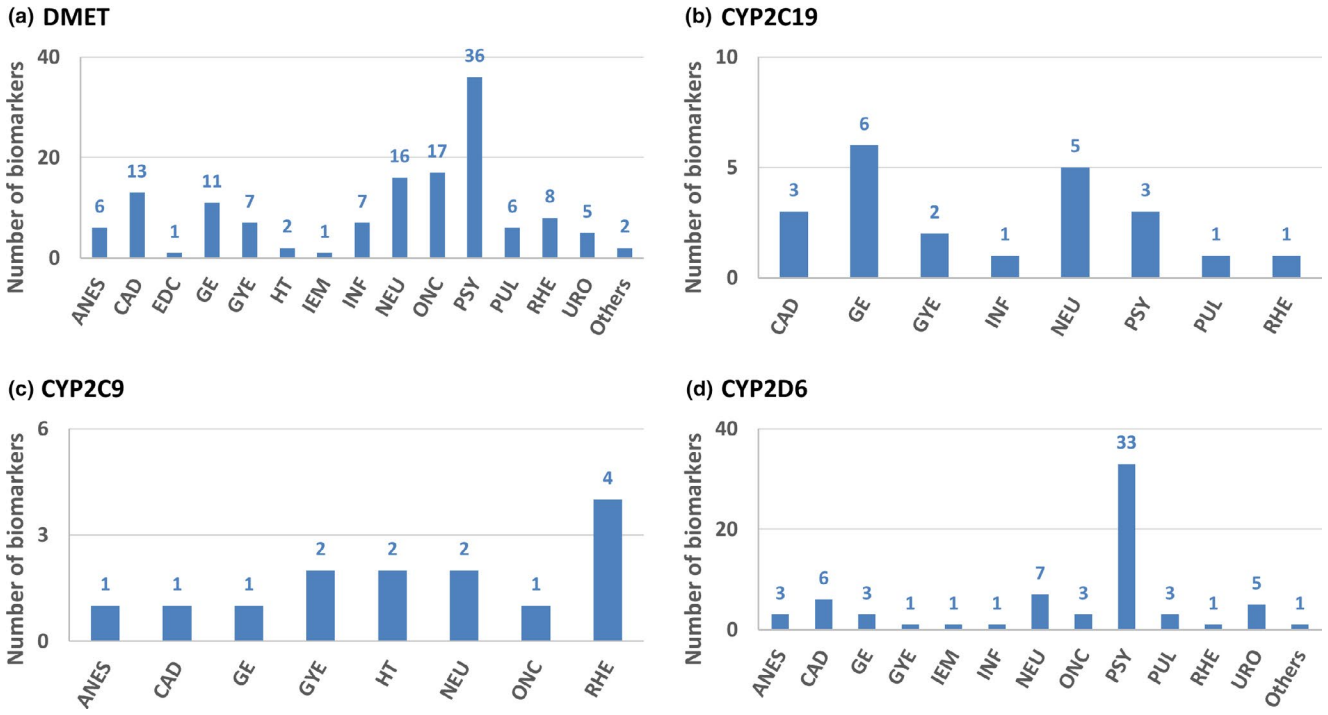

FIGURE 4 Categorization of drug metabolizing enzymes and transporters (a), CYP2C19 (b), CYP2C9 (c), and CYP2D6 (d) per therapeutic area listed in the US Food and Drug Administration-pharmacogenetic/genomic (FDA-PGx) table. Biomarkers were collected from the FDA-PGx table on the FDA website.[27] The abbreviations are listed in the legend of Figure 1

TABLE 2 Classification for drug metabolizing enzymes and transporters listed in the FDA-PGx table

Class	Biomarker classification	Actionable	Drug (*n*)	Biomarker (*n*)	Actionable (*n*)
IND	Indication or contraindication	Yes	3	3 (2%)	41 (30%)
WAR	Warning	Yes	6	7 (5%)	
REC	Recommendation	Yes	29	31 (22%)	
NRE	Negative results	No	23	28 (20%)	
PRE	Positive results	No	27	29 (21%)	
INF	Information	No	28	29 (21%)	
NIN	No information	No	8	11 (8%)	

The classification is described in the Methods section. The values in parentheses represent percent of all biomarkers related to drug metabolizing enzymes and transporters. Biomarkers on the labels were collected from the table of pharmacogenomic biomarkers in drug labeling (FDA-PGx) on the FDA website.[22]

and BCHE (mivacurium and succinylcholine). In the former two cases, the sections of Clinical Pharmacology or Precautions ultimately state no dose adjustments required for poor metabolizers because of minimal impacts on exposures in these populations. In the latter case, the section of Precautions recommends the initial or test doses in patients with reduced plasma cholinesterase activity. Accordingly, total 31 biomarkers of 29 drugs are classified as RECs.

A little over 75% of the DMET biomarkers are not indicated in either the section of Indications and Usage or Dosage and Administration. They are mainly in the section of Clinical Pharmacology. The labels of 23 drugs for 28 DMET biomarkers describe negative GDI results in specific populations without dose recommendation. They account for ~20% of DMET biomarkers and classified as NRE because of no dose recommendation. Of note, in the FDA-PGx table, there is only one case for each CYP1A2 (rucaparib) and CYP3A5 (prasugrel), that are in this class (Figure 2 and Table S2). In contrast, 27 drugs for 29 DMET biomarkers show positive GDI results in specific populations, whereas dose recommendation is not indicated in their labels. Therefore, they are classified as PRE accounting for ~20%. Last, the DMET biomarkers with and without some information regarding GDI account for ~20% (INF) and ~8% (NIN), respectively. The labels in INF do not describe any clinical results, but simply state "possible or expected increases in exposures in these

populations" in many cases. The labels in NIN do not present any information regarding GDI related to DMET biomarkers.

Overall, among 138 DMET biomarkers, 41 DMET biomarkers (~30%) for 38 drugs classified as IND ($n = 3$), WAR (7), and REC (31) are considered actionable because the labels indicate actionable clinical practice, such as dose adjustments in specific populations.

DISCUSSION

As described herein, ~70% of the OMT biomarkers and ~30% of the DMET biomarkers are considered actionable, whereas the GDI results related to some of the other OMT and DMET biomarkers are considered to provide valuable information to clinicians. This is the first report to extensively analyze PGx biomarkers in the latest FDA-PGx table based on labeling languages per section. The results could contribute to a better understanding of the current state of precision medicine in the United States. Consequently, the findings of the present analysis raise several issues that warrant further discussion.

The number of biomarkers per year listed in the FDA-PGx table rapidly increased to greater than or equal to 128 per year in 2018 and 2019 from less than or equal to 4 during 1998 to 2013 (Figure 1). This trend likely suggests the continued increases in the number of PGx in labels because the FDA has pursued to raise the visibility of PGx biomarkers in labels of drugs approved for the US market.[4] Oncology is the main therapeutic area for PGx biomarkers (e.g., ~50% in 2018 and 2019). These results appear to be in line with the number of recent drug approvals by the FDA, particularly oncology drugs (e.g., a record-breaking 59 new medicines in 2018 followed by 48 in 2019).[28,29] However, the years listed in the FDA-PGx table as label version date do not appear to be the date when the biomarkers are first indicated in their labels. For example, an oncology drug, crizotinib, was approved in 2011 for the treatment of patients with non-small cell lung cancer (NSCLC) that is ALK-positive, followed by an additional approval in 2016 for patients with NSCLC whose tumors are ROS1-positive. However, the FDA-PGx table indicates 2019 for both the biomarkers when the latest version of the label has been approved. In contrast, for some other drugs (e.g., abacavir, abemaciclib, and aripiprazole), the years in the FDA-PGx table are not the latest label version dates. Therefore, attention should be paid to interpret the number of biomarkers per year.

For OMT biomarkers, FDA-CDx are required for 32 drugs with greater than 10 different biomarkers (~30% of OMT biomarkers) (Figure 3). According to the FDA website, 38 CDx for 33 drugs have been cleared or approved by the FDA.[22] Several FDA-CDx were approved with multiple drugs or vice versa, whereas certain CDx were specifically approved for a single drug. In comparison, FDA-CDx are not required for 64 drugs with ~30 different biomarkers (~70%), even though some of them are critical to select appropriate drugs for specific patients (e.g., BCR-ABL1 and HR). One of the main reasons is that their measurements have already been a part of the standards for clinical practices because CDx implementation into the routine clinical practice generally presents significant challenges.[13,30] As an example, for the treatment of adult patients with BCR-ABL1 chronic myelogenous leukemia, bosutinib was approved without FDA-CDx for the patient selection. As another reason, FDA-CDx are not required for so-called second-generation ALK inhibitors, brigatinib and lorlatinib (both under accelerated approval), whereas those are required for so-called first-generation inhibitors, alectinib, ceritinib, and crizotinib. The former's indications are for patients who have progressed on or are intolerant to the previously treated first-generation ALK inhibitors. Therefore, the patients for the second-generation inhibitors have already been diagnosed with ALK-positive tumors. As the other notable examples, entrectinib was approved for patients with ROS1-positive tumors along with a postmarketing commitment to develop/validate CDx. This is the similar case of crizotinib that FDA-CDx for ROS1 was approved and added to the label after the approval for this indication. Regarding the biomarkers for microsatellite instability-high or mismatch repair-deficient, four drugs, ipilimumab, lenvatinib (negative for this biomarker), nivolumab, and pembrolizumab, have been approved recently as a single agent and/or in combination with other drugs (under accelerated approval). On these approvals, postmarketing commitments were issued to develop/validate CDx. Overall, total nearly 70% of OMT biomarkers (IND1 and IND2) are considered actionable (Table 1). Among the rest of the OMT biomarkers (INF), some of them can be considered valuable to understand drug characteristics on GDI, although they are not related to the drug selection for patients.

Regarding the DMET biomarkers, among three biomarkers classified in IND (i.e., CYP2D6 for eliglustat, DPD for fluorouracil [dermatology], and CYP2C9 for siponimod), CYP2D6 for eliglustat is the only one required for an FDA-CDx. This is indicated in both the sections of Indications and Usage and Dosage and Administration in a similar manner as the OMT biomarkers required for FDA-CDx. In contrast, it is noteworthy that the label of siponimod indicates "test patients for CYP2C9 variants to determine CYP2C9 genotype," followed by "an FDA-CDx for the detection of CYP2C9 variants is not currently available." The major lack of FDA-CDx for DMET biomarkers on the labels is the notable difference from the OMT biomarkers. This could lead to concerns about the current healthcare system (e.g., limited insurance coverage and reimbursement of testing).[31–33] Among six drugs with seven biomarkers classified in WAR, it is noted that there is a difference in the labeling languages of fluorouracil between the indications (i.e., dermatology and oncology).

The labeling language in dermatology is "fluorouracil should not be used in patients with DPD enzyme deficiency" in Contraindication. In contrast, that in oncology is "withhold or permanently discontinue fluorouracil based on the evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity" in Warnings and Precautions. The difference appears to be largely due to the disease nature for their indications.

For the DMET biomarkers classified as REC (29 drugs with 31 biomarkers), their labels recommend dose adjustments in specific populations. Among them, there are some notable languages (e.g., CYP2D6 poor metabolizers for aripiprazole, brexpiprazole, and metoclopramide, and CYP2C9 genotypes for warfarin). The labels of the former three drugs clearly state the recommended doses in CYP2D6 poor metabolizers (e.g., a half of usual doses in adult patients). They are comprehensively summarized in tables, including other dose recommendations related to drug-drug or drug-disease interactions. Specifically, the label of warfarin, originally approved in 1954, indicates three different dose ranges associated with genetic variants of CYP2C9 and vitamin K epoxide reductase complex subunit 1.[23] There are also other drugs that interact with multiple genes; however, it cannot easily take into account the effects of multiple GDI on dose-adjustments compared with warfarin having a long history of clinical use.

For other DMET biomarkers, the labels of 23 drugs with 28 biomarkers classified as NRE indicate negative GDI results in specific populations. They can possibly be classified as REC because of negligible to minimal GDI results. However, dose recommendations in specific populations are not indicated in their labels, which is different from the four cases for negative GDI in REC (i.e., no dose adjustments required for poor metabolizers of CYP2D6 and CYP2C19), as described in Results. The labeling languages of these biomarkers in NRE can still be useful in clinical practice, although it would be desirable to clearly indicate dose recommendation (e.g., no dose adjustment required). On the contrary, the labels of 27 drugs with 29 DMET biomarkers classified as PRE indicate positive GDI results in specific populations. However, their dose recommendations are not indicated in the labels. They are arguably the most controversial cases because these labels could potentially leave clinicians to make their own decisions. For instance, systemic exposures of several drugs (e.g., carisoprodol, carvedilol, dronabinol, flibanserin, and voriconazole) increased by greater than twofold in poor metabolizers, but the labels do not specify dose adjustments, such as half of the usual dose. Instead, some of them indicate "it should be used with caution," "consider dose reduction," or "clinical implication is unclear."

Additionally, PGx biomarkers in the FDA-PGx table were compared to 67 biomarkers of 57 drugs described in either the CPIC or DPWG guidelines.[11–13] Thirty-nine biomarkers in the CPIC/DPWG guidelines are in the FDA-PGx table. They consist of 31 DMET biomarkers followed by nonspecific genetic susceptibility to malignant hyperthermia (2) and human leukocyte antigens (2). Among them, 21 biomarkers are considered actionable in the present analysis (2 in IND, 7 in WAR, and 12 in REC). It is worth noting that OMT biomarkers in the FDA-PGx table are not in the CPIC/DPWG guidelines. This is largely due to the CPIC/DPWG guidelines that primarily focus on the dose adjustments or alternative therapies in patients with germline polymorphisms rather than the drug selection for patients with somatic mutations. Overall, there appears to be a lack of consensus between the actionable PGx biomarker in the FDA-PGx table and the CPIC/DPWG guidelines. The lack of consensus between the FDA-PGx and the CPIC/DPWG guidelines or the drug labels in other countries have also been reported recently.[30,34,35] One of the reasons could be due to the statistical power in clinical studies with a limited number of patients, particularly in clinical trials with patients carrying low-frequency variants before the drug approvals. Over the last decade with advances in

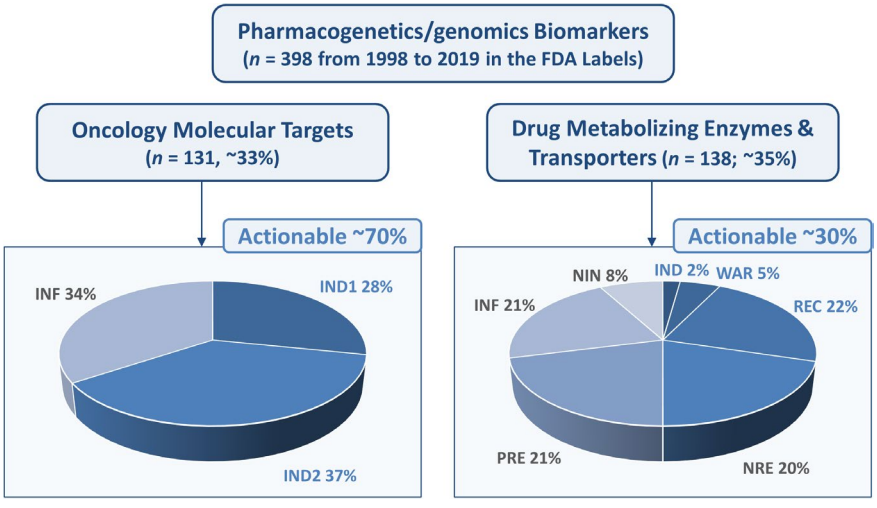

FIGURE 5 Summary of pharmacogenetic/genomic biomarker classification in the US Food and Drug Administration-pharmacogenetic/genomic (FDA-PGx) table. Biomarkers were collected from the FDA-PGx table on the FDA website.[27] The classification is described in the section of Methods.

technology of PGx testing, clinical evidence strongly supports the integration of PGx into clinical practice as therapeutic benefits.[1–4] The global consensus and harmonization of actionable GDI labels would be required to further overcome the current barriers to implement precision medicine in clinical practice effectively and efficiently.

Overall, as summarized in Figure 5, nearly 70% of OMT biomarkers in the FDA-PGx table are considered actionable in clinical practice as they are crucial for the selection of appropriate drugs to individual patients with cancer. In contrast, DMET biomarkers are not directly related to the selection of drugs for patients in most cases, but they are often critical to maintain appropriate therapeutic exposures in specific populations. In the FDA-PGx table, ~30% of DMET biomarkers are considered actionable in clinical practice for the dose recommendations in specific populations, such as CYP2C19 and CYP2D6 poor metabolizers. In addition, the GDI results related to some of the other DMET biomarkers, such as negative GDI results in NRE, can be considered valuable to provide the critical information to clinicians. However, the GDI results, particularly positive GDI results in PRE, can be used more effectively and practically for the dose adjustments in specific populations. Because the actionable drug labels clearly indicate the dose recommendation in specific populations based on the clinical GDI results, it will be desirable to have clear language for dose recommendation of other (or new) drugs, especially when their clinical GDI results are available. To further implement precision medicine into clinical practice, the labels should also be updated timely according to postmarketing experience.

ACKNOWLEDGMENTS

The author would like to thank Tomoko Hirohashi (Global Product Development, Oncology, Pfizer, New York, NY), Jean-Claude Marshall (Early Clinical Development, Pfizer, Groton, CT), R. Scott Obach and A. David Rodrigues (Pharmacokinetics, Dynamics and Metabolism, Pfizer, Groton, CT) for their fruitful comments on this manuscript.

CONFLICT OF INTEREST

S.Y. was an employee of Pfizer and is an employee of Johnson & Johnson and shareholder of Pfizer and Johnson & Johnson.

AUTHOR CONTRIBUTION

SY wrote the manuscript, designed and performed the research, and analyzed the data.

REFERENCES

1. Hockings JK, Pasternak AL, Erwin AL, Mason NT, Eng C, Hicks JK. Pharmacogenomics: an evolving clinical tool for precision medicine. *Cleve Clin J Med*. 2020;87:91-99.
2. Krebs K, Milani L. Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. *Hum Genomics*. 2019;13:39.
3. Lauschke VM, Ingelman-Sundberg M. Emerging strategies to bridge the gap between pharmacogenomic research and its clinical implementation. *NPJ Genom Med*. 2020;5:9.
4. Tutton R. Pharmacogenomic biomarkers in drug labels: what do they tell us? *Pharmacogenomics*. 2014;15:297-304.
5. Ahmed S, Zhou Z, Zhou J, Chen SQ. Pharmacogenomics of drug metabolizing enzymes and transporters: relevance to precision medicine. *Genom Proteomic Bioinform*. 2016;14:298-313.
6. Sim SC, Kacevska M, Ingelman-Sundberg M. Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects. *Pharmacogenomics J*. 2013;13:1-11.
7. Hess GP, Fonseca E, Scott R, Fagerness J. Pharmacogenomic and pharmacogenetic-guided therapy as a tool in precision medicine: current state and factors impacting acceptance by stakeholders. *Genet Res (Camb)*. 2015;97:e13.
8. European Medicines Agency (EMA). Guideline on good pharmacogenomic practice. Available from https://www.ema.europa.eu/en/good-pharmacogenomic-practice#current-effective-version-section. Accessed February 29, 2020.
9. International Conference of Harmonisation E15: Definitions for genomic biomarkers, pharmacogenomics, pharmacogenetics, genomic data and sample coding categories. Available at: https://www.ema.europa.eu/en/ich-e15-definitions-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-sample-coding#current-effective-version-section. Accessed February 29, 2020.
10. US Food and Drug Administration (FDA). Guidance for industry: clinical pharmacogenomics: premarket evaluation in early-phase clinical studies and recommendations for labeling. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacogenomics-premarket-evaluation-early-phase-clinical-studies-and-recommendations. Accessed February 29, 2020.
11. Pharmacogenomics Knowledgebase (PharmGKB). Drug Label Information and Legend. Available at: https://www.pharmgkb.org. Accessed February 29, 2020.
12. Relling MV, Klein TE. CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin Pharmacol Ther*. 2011;89:464-467.
13. Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte–an update of guidelines. *Clin Pharmacol Ther*. 2011;89:662-673.
14. Whirl-Carrillo M, McDonagh EM, Hebert JM, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther*. 2012;92:414-417.
15. Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. *Curr Drug Metab*. 2014;15:209-217.
16. Bahar MA, Setiawan D, Hak E, Wilffert B. Pharmacogenetics of drug-drug interaction and drug-drug-gene interaction: a systematic review on CYP2C9, CYP2C19 and CYP2D6. *Pharmacogenomics*. 2017;18:701-739.
17. Tremaine L, Brian W, DelMonte T, et al. The role of ADME pharmacogenomics in early clinical trials: perspective of the Industry Pharmacogenomics Working Group (I-PWG). *Pharmacogenomics*. 2015;16:2055-2067.

18. Conrado DJ, Rogers HL, Zineh I, Pacanowski MA. Consistency of drug-drug and gene-drug interaction information in US FDA-approved drug labels. *Pharmacogenomics*. 2013;14:215-223.
19. Lu DY, Lu TR, Xu B, Ding J. Pharmacogenetics of cancer therapy: breakthroughs from beyond? *Future Sci OA*. 2015;1:FSO80.
20. Jorgensen JT, Hersom M. Clinical and regulatory aspects of companion diagnostic development in oncology. *Clin Pharmacol Ther*. 2018;103:999-1008.
21. US Food and Drug Administration (FDA). Guidance for industry: developing and labeling in vitro companion diagnostic devices for a specific group of oncology therapeutic products. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/developing-and-labeling-vitro-companion-diagnostic-devices-specific-group-oncology-therapeutic. Accessed April 30, 2020.
22. US Food and Drug Administration (FDA). List of cleared or approved companion diagnostic devices (in vitro and imaging tools). Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed February 29, 2020.
23. Drozda K, Pacanowski MA, Grimstein C, Zineh I. Pharmacogenetic labeling of FDA-approved drugs: a regulatory retrospective. *JACC Basic Transl Sci*. 2018;3:545-549.
24. Ehmann F, Caneva L, Prasad K, et al. Pharmacogenomic information in drug labels: European Medicines Agency perspective. *Pharmacogenomics J*. 2015;15:201-210.
25. Ishiguro A, Sato R, Nagai N. Development of a new Japanese guideline on drug interaction for drug development and appropriate provision of information. *Drug Metab Pharmacokinet*. 2020;35:12-17.
26. US Food and Drug Administration (FDA). Code of Federal Regulations Title 21: Food and Drugs (revised as of April 1, 2019). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56s. Accessed February 29, 2020.
27. US Food and Drug Administration (FDA). Table of Pharmacogenomic Biomarkers in Drug Labeling, (updated on February 5, 2020). Available at: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. Accessed February 29, 2020.
28. Mullard A. 2018 FDA drug approvals. *Nat Rev Drug Discov*. 2019;18:85-89.
29. Mullard A. 2019 FDA drug approvals. *Nat Rev Drug Discov*. 2020;19:79-84.
30. Shekhani R, Steinacher L, Swen JJ, Ingelman-Sundberg M. Evaluation of current regulation and guidelines of pharmacogenomic drug labels: opportunities for improvements. *Clin Pharmacol Ther*. 2020;107:1240-1255.
31. Anderson HD, Crooks KR, Kao DP, Aquilante CL. The landscape of pharmacogenetic testing in a US managed care population. *Genet Med*. 2020;22:1247-1253.
32. Keeling NJ, Rosenthal MM, West-Strum D, Patel AS, Haidar CE, Hoffman JM. Preemptive pharmacogenetic testing: exploring the knowledge and perspectives of US payers. *Genet Med*. 2019;21:1224-1232.
33. Borden BA, Galecki P, Wellmann R, et al. Assessment of provider-perceived barriers to clinical use of pharmacogenomics during participation in an institutional implementation study. *Pharmacogenet Genomics*. 2019;29:31-38.
34. Varnai R, Szabo I, Tarlos G, et al. Pharmacogenomic biomarker information differences between drug labels in the United States and Hungary: implementation from medical practitioner view. *Pharmacogenomics J*. 2020;20:380-387.
35. Yoon DY, Lee S, Ban MS, Jang IJ, Lee S. Pharmacogenomic information from CPIC and DPWG guidelines and its application on drug labels. *Transl Clin Pharmacol*. 2020;28:189-198.

SUPPORTING INFORMATION

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

How to cite this article: Yamazaki S. A retrospective analysis of actionable pharmacogenetic/genomic biomarker language in FDA labels. *Clin Transl Sci*. 2021;14:1412–1422. https://doi.org/10.1111/cts.13000