Pharmacogenomic Biomarker Information in Drug Labels Approved by the United States Food and Drug Administration: Prevalence of Related Drug Use

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Study Objectives. To review the labels of United States Food and Drug Administration (FDA)-approved drugs to identify those that contain pharmacogenomic biomarker information, and to collect prevalence information on the use of those drugs for which pharmacogenomic information is included in the drug labeling.

Design. Retrospective analysis.

Data Sources. The Physicians’ Desk Reference Web site, Drugs@FDA Web site, and manufacturers’ Web sites were used to identify drug labels containing pharmacogenomic information, and the prescription claims database of a large pharmacy benefits manager (insuring > 55 million individuals in the United States) was used to obtain drug utilization data.

Measurements and Main Results. Pharmacogenomic biomarkers were defined, FDA-approved drug labels containing this information were identified, and utilization of these drugs was determined. Of 1200 drug labels reviewed for the years 1945–2005, 121 drug labels contained pharmacogenomic information based on a keyword search and follow-up screening. Of those, 69 labels referred to human genomic biomarkers, and 52 referred to microbial genomic biomarkers. Of the labels referring to human biomarkers, 43 (62%) pertained to polymorphisms in cytochrome P450 (CYP) enzyme metabolism, with CYP2D6 being most common. Of 36.1 million patients whose prescriptions were processed by a large pharmacy benefits manager in 2006, about 8.8 million (24.3%) received one or more drugs with human genomic biomarker information in the drug label.

Conclusion. Nearly one-fourth of all outpatients received one or more drugs that have pharmacogenomic information in the label for that drug. The incorporation and appropriate use of pharmacogenomic information in drug labels should be tested for its ability to improve drug use and safety in the United States.

Key Words: biomarkers, pharmacogenomics, U.S. Food and Drug Administration, FDA, drug labels, pharmacy benefits manager.

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One of the major challenges in drug development and in the practice of medicine is the variability among individuals that affects clinical outcome. Although the current approach to this problem (i.e., the use of biomarkers to identify patients who are likely to experience benefit or toxicity) has been called “personalized medicine,” clinical practice has always been personalized
with respect to the use of the best information possible for the treatment of an individual patient.\textsuperscript{1} Whereas the definition of personalized medicine may vary, there is general agreement that we have not yet achieved its potential,\textsuperscript{2,3} and the debate continues as to whether the pace is glacial,\textsuperscript{4} inconsequential,\textsuperscript{5} or possibly even too rapid. In the past, the tools of medicine have been limited largely to physical diagnostic skills and laboratory tests. The development of genomic medicine is revolutionizing the tools available.

Genomic medicine, in the future, may provide a complex and more precise set of tools for clinicians to use for diagnosis and treatment. Currently, the use of genomic medicine is most extensive in the field of pharmacogenomics and its application to oncology. For example, the codevelopment of trastuzumab and testing for the overexpression of human epidermal growth factor receptor 2 (HER2) in breast cancer is a prime example of the application of pharmacogenomic biomarkers to patient care. Pharmacogenomic biomarkers have been identified for other drugs in many treatment areas, and information regarding their use has been provided to clinicians through drug labels approved by the United States Food and Drug Administration (FDA).

Pharmacogenomics and the characterization of genomic biomarkers have become a part of research and development for new therapeutics over the last decade. In 2005, the FDA issued a guidance for the pharmaceutical industry, which describes what type of pharmacogenomic information should be submitted to the agency during the drug development process.\textsuperscript{6} This guidance also addresses related labeling.

Pharmacogenomic biomarker information was included in some FDA-approved drug labeling before this guidance, but there were no systematic guidelines for developing or approving information of this type. Two studies have examined the availability of pharmacogenomics information in drug labels. In 2004, one group of authors reviewed all of the drugs in the electronic version of the Physicians' Desk Reference (PDR) and concluded that only 25 (0.7%) of 3382 package inserts in the database contained sufficient pharmacogenomic information to guide treatment decisions.\textsuperscript{7} In 2006, the same authors reviewed the pharmacogenomic information in drug labels and in the literature for the top 200 prescribed drugs.\textsuperscript{8} They found that although 71.3% of these drugs had published pharmacogenomic information in the literature, only three had package inserts with pharmacogenomic information that they thought was sufficient to guide dosing.

Given this background, the question of the potential impact of pharmacogenomic information in drug labels remains unanswered. The objectives of this study were, therefore, to conduct a comprehensive review of the labels of drugs that came to the market during 1945–2005 by using an array of search terms and multiple sources in order to identify the drugs that contain pharmacogenomic biomarker information in their labeling, and to collect prevalence information on the use of those drugs in current clinical practice.

**Methods**

**Analysis of Product Labels**

Different sources were used to identify drug labels that contain pharmacogenomic information: the electronic version of the PDR,\textsuperscript{9} the Drugs@FDA Web site,\textsuperscript{10} and the Web sites of drug manufacturers. No single source contains all of the pertinent drug labels, and each source has its limitations. For example, the PDR does not include discontinued drugs, whereas Drugs@FDA lists all approved drug labels, including those for discontinued drugs; however, labels for some biologic therapeutics are not yet listed on this site.\textsuperscript{11} The most recently approved label for each drug was selected for analysis, independent of when the drug was originally approved. Drugs that were approved between 1945 and 2005 were included in the analysis.

Drug labels were reviewed for pharmacogenomic biomarker information in two stages. In the first stage, the labels were screened for the occurrence of one or more of the following key words: gene,
genetic, DNA, RNA, variant, haplotype, polymorphism, deficiency, SNP, cytochrome, CYP, CYP2D6, CYP2C9, CYP2C19, G6PD, UGT1A, DPD, UCD, NAT, EGFR, HER2, and TPMT. In the second stage, labels containing these key words were then screened manually by one of the investigators (P.M.) to determine which key word appearances represented pharmacogenomic biomarker information. Manual screening was the method of choice since pharmacogenomic information was scattered in different sections of labels for the FDA-approved drugs over the last 60 years. The screening was based on a set of selection criteria that identified descriptions of human genetics or genomics (gene expression changes; gene deficiencies, deletions, or insertions; genetic polymorphisms or variations; or genetic mutations) that affected drug efficacy (responders and nonresponders) or safety (toxicity or adverse events), pharmacokinetics, pharmacodynamics, or dosage, as well as descriptions of microbial genetics that are related to drug resistance or susceptibility. Drugs with multiple formulations or multiple new drug applications were included only once in the overall count of labels and in the count of labels with pharmacogenomic information. The original new drug applications were not reviewed for the occurrence of pharmacogenomic information.

For all labels identified in this analysis, pharmacogenomic biomarker information was extracted manually and tabulated according to the context in which the biomarker was included in the label, and the therapeutic classification of the drug. Pharmacogenomic biomarker information was found in several sections of the labels, including the Clinical Pharmacology, Dosage and Administration, Precautions, Indications and Usage, and Warnings sections. The biomarker content was generally provided for information only, but in a few cases, testing was recommended or required for the use of the drug in treatment.

Prevalence of Use of Identified Drugs

Drug utilization data were derived from a prescription claims database maintained by a large pharmacy benefits manager (Medco Health Solutions, Inc., Franklin Lakes, NJ), which manages pharmacy benefits for more than 55 million insured individuals in the United States. Deidentified claims data were extracted for benefit plan members who were eligible for a drug benefit at any time in 2006. The final study sample comprised all eligible members who filled one or more prescriptions during 2006. Within this sample, claims data were screened for any use of the drugs that contain human genomic biomarker information in their labeling (as identified in the first part of the study).

The primary measure of interest was prevalence of use—the proportion of patients who used drugs with pharmacogenomic biomarker labeling during the 12-month study period. For the study sample as a whole, prevalence of use was defined as the proportion of members who filled one or more prescriptions for any of the drugs that include biomarker labeling. Prevalence of use was also calculated for each biomarker (the proportion of patients who used one or more drugs with the identified biomarker) and for each drug (the proportion of patients who used a specific drug).

Only drugs that were covered and adjudicated through patients' drug benefits were included in the analysis. Drugs that are administered in physician offices and hospitals are typically covered under the medical benefit, and they were not reflected in these estimates to any significant extent. Demographic variables available for the analyses were age and sex. All analyses were performed by using SAS, version 9.1 (SAS Institute Inc., Cary, NC).

Results

Pharmacogenomic Labeling

Based on the initial screening of drug labels for pharmacogenomic key words, 600 drug labels were identified from approximately 1200 labels. After manual screening against the more precise set of selection criteria, 121 drug labels were found to include pharmacogenomic biomarker information, accounting for about 10% of the total number of drug labels in the original search. Of these 121 labels, 69 referred to human genomic biomarkers, or information related to the genetics of normal or cancerous tissue. An additional 52 labels referred to microbial genomic biomarkers, or information based on the genetics of infectious agents and used in microbial typing. A summary of these human genomic biomarkers, the drug label context of use, and the associated drugs is available on the FDA Web site. For purposes of this study, our analysis focused primarily on the subset of drugs with human genomic biomarker information in the product labeling.
Figure 1 shows the distribution of human genomic biomarkers in FDA-approved drug labels. Biomarkers related to cytochrome P450 (CYP) enzymes were cited in 43 (62%) of the 69 identified labels; these enzymes are associated with genetic polymorphisms that are known to affect drug metabolism and drug response. The CYP enzymes identified most frequently were CYP2D6 (24 labels, 35%), CYP2C19 (12 labels, 17%), and CYP2C9 (7 labels, 10%). When the labels containing pharmacogenomic information were sorted by therapeutic class (after removing the antimicrobial drugs), oncology drug products showed the highest percentage of labels with pharmacogenomic content (22 labels, 32%) followed by cardiology drugs (18 labels, 26%), neurology and psychiatry drugs (12 labels, 17%), and drugs for other therapeutic areas (17 labels, 25%).

Although some pharmacogenomic information appears in the labeling of drugs approved before 1995, most of the drugs with human or microbial genomic biomarker labeling were approved after 1996. Figure 2 illustrates the rapid increase in the number of drug labels with pharmacogenomic information over the last 10 years of the study period.

Prevalence of Use

The final sample of patients receiving a prescription during 2006 was 36.1 million members. During 2006, 24.3% of patients (about 8.8 million) filled prescriptions for drugs that include information about human genomic biomarkers in the product labels. Data on the prevalence of use for specific biomarkers is summarized in Table 1. Many patients took more than one drug with a pharmacogenomic biomarker, which agrees with an earlier report in patients from primary care clinics. The most commonly used drugs with biomarker labeling were metoprolol (5.6%) and esomeprazole (4.8%).

The most frequently used categories of drugs with biomarker labeling are those whose pharmacokinetics are affected by variations in CYP enzymes: CYP2D6 (13.56% of patients), CYP2C19 (10.91%), and CYP2C9 (3.91%). The actual number of patients with prescriptions dispensed containing pharmacogenomic information for CYP2D6 was 5.50 million, for CYP2C19 was 4.45 million, and for CYP2C9 was 1.46 million.

In most cases, the identified drug labels provide pharmacogenomic information without recommending a specific action. However, a few labels recommend or require biomarker testing as a basis for reaching a therapeutic decision. For example, testing for HER2/neu and epidermal growth factor receptor expression is required before starting therapy with specific oncology...
The prevalence of use of drugs with genomic biomarker information was higher for adult patients than for pediatric patients. Among adult patients (age ≥ 19 yrs), 34.2% of women and 25.8% of men used drugs with pharmacogenomic labeling. In contrast, only 4.2% of female patients and 4.7% of male patients aged 18 years or younger received drugs with pharmacogenomic information in the labeling. Most prescriptions for drugs with pharmacogenomic labeling were written by primary care physicians (66%), whereas 26% of the prescriptions were written by specialists—including cardiologists (9.7%), psychiatrists (5.9%), and hematology or oncology specialists (1.5%).

**Discussion**

The impact of genetic variation on drug response has been recognized for many years. In the 1950s, a genetic variant of the enzyme butyrylcholinesterase was identified as the reason for slower recovery rates in some patients after surgical use of the muscle relaxant suxamethonium chloride. Investigators also discovered that genetic differences in N-acetyltransferase metabolism were the reason why patients tend to be slow acetylators or fast acetylators, with very different blood concentrations and adverse reactions to drugs such as isoniazid and procainamide.

Genetic predisposition may be a significant contributor to individual variations in how patients respond to drugs, along with other factors, such as diet, environment, and other drugs that the patient may be taking concurrently. In a review of drugs that are frequently cited in adverse drug reaction studies, 59% were found to be metabolized by at least one enzyme that is known to have a genetic variant for poor metabolism. Information about the impact of genetic variations on drug therapy can provide an additional tool for physicians to use when designing a treatment plan for a patient. The FDA plays a role in making this information available to clinicians through the inclusion of pharmacogenomic biomarker information in drug labels and the clearance of devices for genetic testing. Although many more drugs have published information on pharmacogenomics than have pharmacogenomic information in their label (published data vs Table 2), the level of evidence required to establish or change drug labeling means that some gap between these two measures will always exist.

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**Table 1. Prevalence of Use in 2006 for Drugs with Pharmacogenomic Biomarker Information in the Product Labeling**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>User Prevalence (%) (n=36.1 million)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Kit expression</td>
<td>Imatinib 0.01</td>
</tr>
<tr>
<td>CYP2C19 variants</td>
<td>Esomeprazole, omeprazole 10.91</td>
</tr>
<tr>
<td>CYP2C9 variants</td>
<td>Warfarin, celecoxib 3.91</td>
</tr>
<tr>
<td>CYP2D6 variants</td>
<td>Metoprolol, fluoxetine 13.36</td>
</tr>
<tr>
<td>DPD deficiency</td>
<td>Cepacibatine, fluourouracil 0.31</td>
</tr>
<tr>
<td>EGFR expression</td>
<td>Erlotinib, gefitinib 0.02</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Chloroquine, dapsone 0.09</td>
</tr>
<tr>
<td>HER2/neu overexpression</td>
<td>Trastuzumab &lt; 0.01</td>
</tr>
<tr>
<td>NAT variants</td>
<td>Rifampin, isoniazid 0.15</td>
</tr>
<tr>
<td>Philadelphia chromosome</td>
<td>Busulfan &lt; 0.01</td>
</tr>
<tr>
<td>PML/RAR $^a$ gene expression</td>
<td>Tretinoin 0.68</td>
</tr>
<tr>
<td>TMPT variants</td>
<td>Azathioprine, mercaptopurine 0.17</td>
</tr>
<tr>
<td>Urea cycle enzyme</td>
<td>Divalproe sodium, valpric acid 0.48</td>
</tr>
<tr>
<td>defect</td>
<td></td>
</tr>
<tr>
<td>UGT1A1 variants</td>
<td>Irinotecan &lt; 0.01</td>
</tr>
<tr>
<td>Overall</td>
<td>24.32</td>
</tr>
</tbody>
</table>

$^a$User prevalence is the percentage of patients in the study sample who used one or more drugs with the indicated biomarker.

$^b$Overall prevalence is less than the sum of the individual rates, since many patients used more than one drug and some drugs (e.g., warfarin) are associated with more than one biomarker. Average usage was 1.5 drugs/patient.

C-Kit = proto-oncogene tyrosine kinase Kit; CYP = cytochrome P450; DPD = dihydropyrimidine dehydrogenase; EGFR = human epidermal growth factor receptor; G6PD = glucose-6-phosphate dehydrogenase; HER2/neu = human epidermal growth factor receptor 2; NAT = arylamine-N-acetyltransferase; PML/RAR = promyelocytic leukemia/retinoic acid receptor; TPMT = thiopurine S-methyltransferase; UGT1A1 = uridine diphosphate glucuronosyl transferase 1A1.
In this study, we observed that approximately 10% of the labels for drug products approved between 1945 and 2005 contain pharmacogenomic biomarker information. Based on the analysis of prescription claims for a large population of insured Americans, we found that approximately 24.3% of 36.1 million patients received drugs that have human genomic biomarker information in their labeling. Drugs metabolized by polymorphic CYP enzymes were the most frequently used class of drugs in the study sample. Most prescriptions for these drugs are generated by primary care physicians, so it is important that these physicians, as well as specialists, have the information they need to incorporate pharmacogenomic considerations into day-to-day practice. An FDA-approved genetic test (AmpliChip CYP450; Roche Diagnostics, Palo Alto, CA) is already available to test for polymorphisms in the two most frequently noted enzyme pathways, CYP2D6 and CYP2C19.

The CYP2D6 isoenzyme is involved in the metabolism of many drugs, including β-blockers and antiarrhythmic, antidepressant, neuroleptic, and opioid agents. Early studies in the 1970s revealed that patients can be classified into four phenotypes based on differences in their level of CYP2D6 activity: poor metabolism (low activity), intermediate metabolism (reduced activity), extensive metabolism (normal activity), and ultrarapid metabolism (enhanced activity). Poor CYP2D6 metabolism can be associated with an increase in adverse reactions to drugs that are inactivated by that enzyme pathway. Ultrarapid CYP2D6 metabolism has been associated with decreased therapeutic response to a drug, which may require a dosage adjustment or a switch to an alternative therapy. The opposite pattern of reactions may occur in response to drugs that are activated by CYP2D6 metabolism. For poor metabolizers, these “prodrugs” may have little therapeutic effect, whereas for ultrarapid metabolizers the active form of these drugs can build to toxic levels. For example, codeine is metabolized into its bioactive form (morphine) through CYP2D6, so a poor CYP2D6 metabolizer may not get an appropriate analgesic effect from codeine, whereas an ultrarapid metabolizer could have a serious adverse reaction. Recently, a breast-fed infant died of morphine intoxication while the mother—an ultrarapid CYP2D6 metabolizer—was taking codeine.19

The involvement of CYP2D6 in drug efficacy has also been established in the use of tamoxifen for the treatment of women with breast cancer. Tamoxifen is first converted to N-desmethyltamoxifen, which is then converted by CYP2D6 to endoxifen—the bioactive form of the drug that has potent antiestrogenic activity. Genetic variations in CYP2D6 activity and the coadministration of CYP2D6 inhibitors can both have a significant impact on endoxifen plasma concentrations20 and therapeutic outcomes21 for patients who use tamoxifen. Lower levels of CYP2D6 activity are associated with a reduced time to recurrence of breast cancer and worse relapse-free survival.21

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Test1)</th>
<th>Drug Example (n=36.1 million)</th>
<th>User Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Recommended</td>
<td>Warfarin</td>
<td>2.0896</td>
</tr>
<tr>
<td>EGFR</td>
<td>Required</td>
<td>Cetuximab</td>
<td>0.0001</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Recommended</td>
<td>Dapsone</td>
<td>0.0257</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Recommended</td>
<td>Rasburicase</td>
<td>0.0000</td>
</tr>
<tr>
<td>HER2/neu overexpression</td>
<td>Required</td>
<td>Trastuzumab</td>
<td>0.0003</td>
</tr>
<tr>
<td>TPMT variants</td>
<td>Recommended</td>
<td>Azathioprine</td>
<td>0.1168</td>
</tr>
<tr>
<td>TPMT variants</td>
<td>Recommended</td>
<td>Mercaptопurine</td>
<td>0.0541</td>
</tr>
<tr>
<td>TPMT variants</td>
<td>Recommended</td>
<td>Thioguanine</td>
<td>0.0012</td>
</tr>
<tr>
<td>UGT1A1 variants</td>
<td>Recommended</td>
<td>Irinotecan</td>
<td>0.0002</td>
</tr>
<tr>
<td>Urea cycle enzyme deficiency</td>
<td>Recommended</td>
<td>Valproic acid</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>2.768</strong></td>
</tr>
</tbody>
</table>

CYP = cytochrome P450; EGFR = human epidermal growth factor receptor; G6PD = glucose-6-phosphate dehydrogenase; HER2/neu = human epidermal growth factor receptor 2; TPMT = thiopurine S-methyltransferase.
Metabolism by CYP2D6 does not ensure that pharmacogenomic information will be directly applicable to patient care. A recent review from the Centers for Disease Control and Prevention concluded that insufficient information was available to recommend or to not recommend genetic testing for CYP enzymes in the use of selective serotonin reuptake inhibitors. Therefore, additional clinical studies are needed with a number of drugs before a definitive recommendation to test or not to test for a pharmacogenomic biomarker can be made.

The labeling of drugs is performed in the context of the available knowledge and applicable standards at the time the labeling process takes place, and it is updated as new information becomes available. Drug approvals have only recently included more pharmacogenomic information (Figure 2). Consequently, few pharmacogenomic biomarkers (approximately 3% prevalence) have the status of required or recommended, as evidenced in Table 2. One study set an upper boundary on drugs with published pharmacogenomic information (70%) that will never be achieved in drug labeling.

The study population used in our prevalence analysis may limit the precision of the estimates provided, so it may result in an over- or under-estimation. Although this study is based on a large sample of Americans with prescription drug coverage, it does not include uninsured users of drugs, and it is limited to drugs that are covered and adjudicated under the benefit plans included in the sample.

Conclusion

Our increased understanding of how genetic factors affect drug treatment is reflected by the increasing frequency of inclusion of pharmacogenomic information in drug labeling, both in the labels of newly approved drugs and in updates to the labels of existing drugs. This analysis demonstrates that one fourth of all prescriptions are for drugs that contain pharmacogenomic information in their labeling. The impact of this information on patient safety and efficacy should be tested to provide a guide for improving drug therapy.

References