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An evaluation of pharmacogenomic information provided by five common drug information resources

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Introduction: This study evaluated whether pharmacogenomic information contained in the Food and Drug Administration (FDA)–approved package inserts of sixty-five drugs was present in five drug information resources.

Methods: The study searched for biomarkers from the FDA package inserts in 5 drug information sources: American Hospital Formulary Service Drug Information (AHFS), Facts & Comparisons 4.0 (Facts), ePocrates Online Free (ePocrates Free), Lexicomp Online (Lexicomp), and Micromedex 2.0. Each resource had the *opportunity* to present biomarker information for 65 drugs, a total of 325 opportunities. A binary system was used to indicate presence or absence of the biomarker information. A sub-analysis was performed on the 13 most frequently prescribed drugs in the United States.

Results: Package insert biomarker information was available, on average, for 81.5% of the 65 FDA-listed drugs in 2011. Percent availability for the individual resources was: Lexicomp, 95.3%; Micromedex 2.0, 92.3%; Facts, 76.9%; AHFS, 75.3%; and ePocrates Free, 67.7%. The sub-analysis of the 13 top drugs showed Lexicomp and Micromedex 2.0 had the most mentions, 92.3%; ePocrates Free had the least, 53.8%.

Conclusion: The strongest resource for pharmacogenomic information was Lexicomp. The gap between Lexicomp and ePocrates Free is concerning. Clinicians would miss pharmacogenomic information 6.6 times more often in ePocrates Free than in Lexicomp.

Implications: Health sciences librarians should be aware of the variation in biomarker availability when recommending drug resources for licensing and use. Librarians can also use this study to encourage publishers to include pharmacogenomics information from the package insert as a minimum standard.

INTRODUCTION

The study of pharmacogenomics involves investigating the effect of genetic variation on drug response and has led to a movement toward ''personalized medicine.'' Pharmacogenomic studies have helped to identify genomic biomarkers. These biomarkers may be classified as gene variants, functional deficiencies, expression changes, or chromosomal abnormalities that cause changes in how the body reacts to medications [1]. Although pharmacogenomic studies are amassing at a greater rate every year, many health care practitioners have never received didactic instruction on pharmacogenomics, biomarkers, or even basic genetic concepts [2–5]. However, patients want pharmacogenomic information included in all stages of health care, including diagnosis, testing, and when their medications are prescribed and monitored [1, 6]. Health care practitioners should anticipate meeting the expectations of patients regarding pharmacogenomics. The medical library is an important partner in this process, by providing high-quality resources that include appropriate pharmacogenomic information.

A common misconception of many practitioners is that pharmacogenomics is not a clinical tool or that it is useful only in specialty areas like oncology or infectious diseases. Yet, studies have shown that about 25% of patients take a medication for which pharmacogenomic information is relevant [7, 8]. Lessons from research of the pharmacogenomics of warfarin therapy teach us that even old drugs benefit from new genetic information [9]. Utilizing the relevant cytochrome P450 subunit 2C9 (CYP2C9) and vitamin K epoxide reductase subunit 1 (VKORC1) genotypes, clinicians can achieve desired therapeutic levels more quickly and cause fewer bleeding events or thromboses in the process [9, 10]. The package insert for warfarin contains information on CYP2C9 and VKORC1, as well as a detailed genotype-guided dosing chart that performs better than the standard of care in selecting a patient's therapeutic warfarin dose [11].

With little didactic instruction, clinicians are relegated to identifying pharmacogenomic relationships and learning to apply the information from medical literature, colleagues, patient requests, the Internet, or drug information resources. The use of monographic drug resources by health care practitioners has not been quantified. However, a study by Stanek et al. found that published information in specialty physician guidelines, journal articles, and recommendations from the Food and Drug Administration (FDA) are all valued by a large majority of physicians [12]. Medical librarians can support efficient and appropriate use of pharmacogenetic information in clinical practice by advocating for the best information to be included in the resources that they select and manage as well as training health care practitioners in their use.

One major source of information for tertiary literature sources, such as drug monographs, is the FDA-approved package insert. Until 2005, the FDA did not require inclusion of pharmacogenomic information in

package inserts [7]. Before that time, the prevalence of any kind of genetic information in inserts was scant, with studies by Zineh et al. noting discordance between the available evidence from research and the inclusion of the genetic biomarker, available tests, or genetic implications in package inserts [13, 14]. In addition, Frueh et al. found that this information was scattered in several different locations in the drug labeling even after the FDA began requiring inclusion of pharmacogenomic information [7]. While this information is now required in package inserts, the authors could find no study determining if drug information resources commonly used by pharmacists have taken steps to include that information.

The study reported here was designed to evaluate whether the pharmacogenomics information, specifically, biomarker information contained in the package inserts of sixty-five drugs, was also present in five commonly used drug information resources. The authors hypothesized that all of the drug information resources would include, at a minimum, any information about the biomarkers that is provided in the prescribing information in the package inserts.

METHODS

The study compared the drug information mandated by the FDA for inclusion in package inserts with information found in five major sources of clinical drug information: American Hospital Formulary Service Drug Information (AHFS), ePocrates Online Free (ePocrates Free), Facts and Comparisons 4.0 (Facts), Lexicomp Online (Lexicomp), and Micromedex 2.0 (Micromedex). These five sources for clinical drug information were chosen based on accessibility of use among health care practitioners at major research institutions. All five are available online. AHFS, Facts, Lexicomp, and Micromedex are fee-based resources, while this version of ePocrates is free with individual registration. Previous studies comparing drug information resources for non-genetic information included Facts, Lexicomp, and Micromedex, with a few also including AHFS or ePocrates Free [15–18].

As of April 2011, the FDA had approved genetic information for twenty-six unique biomarkers for the package inserts of sixty-five drugs [1]. The FDA list of sixty-five drugs was used in this study. Data were collected in November 2011, providing a grace-period of seven months for the resources to add or update FDA-approved genetic information. The specific listed genes and location of genetic information in the package insert were noted.

The list of sixty-five drugs was divided among the four coauthors, a pharmacy librarian and three pharmacists, resulting in a list of sixteen to seventeen drugs to be searched in each of the five resources for each coauthor, or eighty to eighty-five monographs to be read per coauthor. The primary monograph for each drug was located in each resource. Every drug on the FDA list had one monograph in each resource; monographs for combination therapies were excluded from the search because there was a risk that combination therapies could have incomplete coverage of available information, which would complicate analysis. The authors used a keyword search on the specific package insert biomarker, including both the code and the name of the gene, and then scanned the entire monograph for mentions of additional genetic biomarkers. This process created consistency across each drug's analysis and allowed each coauthor to effectively compare the resources at the individual drug level.

Each of the 5 drug information resources had the *opportunity* to present package insert biomarker information in the drug monograph for each of the 65 drugs, for a total of 325 opportunities. If the biomarker was identified in the monograph for the drug information resource, it was termed a *mention*. Mentions included drugs for which the genetic information had known dosing implications (e.g., warfarin) and for which some genetic information was known, but implications were not discussed (e.g., terbinafine).

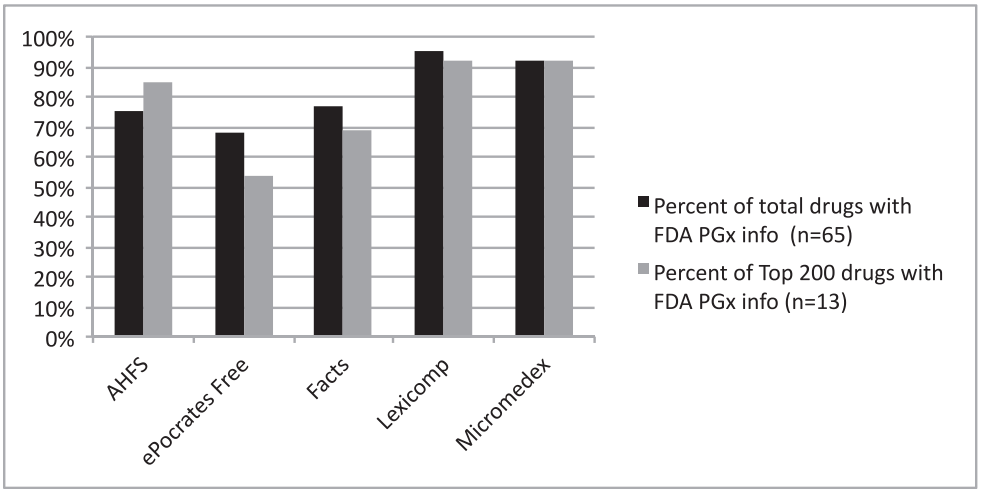
A binary system was used to indicate presence or absence of the known biomarker, and any additional biomarkers not included in the package insert. If the specific package insert biomarker was found, its location in the monograph was noted. In addition, monographs for the 13 drugs located on the 2010/2011 *Pharmacy Times* Top 200 Drug List, which reports the medications most frequently prescribed by physicians in the United States [19], were treated as a subgroup for analysis. Note that the content of information about each biomarker was not analyzed: for this initial study, only the presence or absence and location of information were collected. To highlight nuances in presentation of the package insert biomarker information, 1 commonly prescribed drug, warfarin, and 1 biomarker, the CYP2D6 gene, were assessed for differences in the number of mentions across the 5 drug resources.

RESULTS

Across the 5 resources, the average percentage of FDA package insert biomarkers that were identified in the drug monographs was 81.5% (265 mentions out of 325 opportunities). Percent identified in individual resources ranged from 95.3% (62 mentions/65 opportunities) for Lexicomp to 67.7% (44 mentions/65 opportunities) for ePocrates Free (Figure 1). Micromedex had 92.3% (60 mentions/65 opportunities) agreement, while Facts and AHFS were similar with 76.9% (50 mentions/65 opportunities) and 75.4% (49 mentions/65 opportunities), respectively.

Of the 65 drugs evaluated, 20% (13) were included on the 2010/2011 top 200 drugs list. ePocrates Free presented package insert biomarker information for 53.8% (7 mentions/13 opportunities) of the top 200 drugs, the least of any of the 5 resources. Lexicomp and Micromedex tied for the most mentions at 92.3% (12 mentions/13 opportunities). Lexicomp was also most likely to document additional biomarkers not

Figure 1
Percent availability of package insert biomarkers by drug resource



Black column represents the percent of drugs with Food and Drug Administration (FDA) pharmacogenomics biomarker information from the package insert that were available in the drug information resource (percent out of 65 drugs).
Gray column represents the percent of drugs from the top 200 list of medications from 2010/2011 for which there is biomarker information in the drug information resource (percent out of 13 drugs).

included in the package insert (84.6%, 11 mentions/13 opportunities).

The list of 26 biomarkers found in the FDA-approved package inserts is listed in Table 1. Two package insert biomarkers (NAT1 and NAT2, 7.7%) were not found in any resource, and 57.7% (15/26 biomarkers) were found in all the resources: C-Kit, CCR5, chromosome 5q, CYP2C9, CYP2C19, CYP2D6, EGFR, estrogen receptor, G6PD, Her2/Neu, HLA-B*5701, Philadelphia chromosome, PML/RARa translocation, TPMT, and UGT1A1. The biomarkers associated with the top 200 drugs were: CYP2C19, CYP2C9, CYP2D6, and LDL receptor. Of the 13 drugs listed on the top 200 drug list with biomarkers in the package insert, 6 (46.2%) had the FDA biomarker information included in all 5 drug resources. For warfarin, the CYP2C9 biomarker was included in all 5 resources.

When evaluating from the perspective of only 1 biomarker, CYP2D6 appeared in the prescribing information for the most drugs: 24 out of 65 drugs (36.9%). Of the 24 drugs with the CYP2D6 biomarker listed in the package insert, 11 (11/24 drugs, 45.8%) had the information included in all 5 resources. Lexicomp performed best with the information identified for 100% (23/23 drugs) of the drugs related to the CYP2D6 biomarker.

Table 1
Pharmacogenomic biomarkers identified in drug package inserts in April 2011 [1]

ARG
ASL
ASS
C-Kit
CCR5
Chromosome 5q
CPS
CYP2C9
CYP2C19
CYP2D6
DPD
EGFR
Estrogen receptor
G6PD
Her2/Neu
HLA-B*1502
HLA-B*5701
LDL receptor
NAGS
NAT1
NAT2
OTC
Philadelphia chromosome
PML/RARa translocation
TPMT
UGT1A1

Bold=Found in all 5 sources.
Italics=Found in none of the sources.

DISCUSSION

This study provides useful data on which drug information resources are most likely to contain pharmacogenomic information that impacts diagnosis and therapy. Of the 5 drug resources evaluated, ePocrates Free provided information on pharmacogenomic biomarkers from the package insert for the fewest drugs overall, as well as the fewest additional biomarkers not found in the package insert for drugs in the top 200 drug list (Figure 1). In contrast, Lexicomp mentioned package insert biomarkers most often. Lexicomp also mentioned additional genes not found in the package inserts for the greatest number of drugs on the top 200 list. Lexicomp tended to place all of the pharmacogenomics information into 1 section (Pharmacogenomic Genes of Interest). No other evaluated drug resource included a specific section for pharmacogenomic information.

From these results, the most consistent resource for FDA-approved pharmacogenomics information was Lexicomp, both for all drugs with known biomarkers and for the top 200 most commonly prescribed drugs in the United States. Micromedex included information for the next largest percentage of the drugs and biomarkers evaluated, followed by Facts and AHFS. Out of the 5 evaluated resources, ePocrates Free offered information for the fewest number of drugs with FDA-approved biomarker information. The large gap between Lexicomp and ePocrates Free is concerning. Clinicians would miss established pharmacogenomic information in 5% of the drugs examined in Lexicomp, whereas they would miss the same information 6.6 times more often in ePocrates Free (33% of the drugs in this study). This has implications not just for general practitioners who might not typically consult several resources, but for prescribers in economically disadvantaged areas, where practitioners might rely exclusively on free products for drug information, including pharmacogenomics. Among the subscription-based and free products, it is alarming that, on average across the resources, nearly 1 out of 5 (19%) drug monographs lacked potentially important genomic information that could impact prescribing and dispensing practice.

The likelihood that pharmacogenomic data would be included for the most commonly prescribed drugs, that is, those on the top 200 drug list, followed a similar pattern as for the total list of drugs. Lexicomp and Micromedex both performed well in the analyses, while ePocrates Free performed particularly poorly. This is particularly troublesome, as it would seem natural to include the most well-characterized and useful information in a drug monograph. Leaving out known information that could influence diagnosis and therapy is a problem regardless of the type of information: omitting the information for the most commonly prescribed products increases the chance of uninformed prescribing, including the potential for under- and overdosing, and extreme side effects due to drug-gene interactions.

This study had several limitations. While pharmacogenomic information was identified in the five resources, the biomarker information contained in the drug resources was not evaluated for quality. Criteria to evaluate the quality of pharmacogenomic drug information do not exist. Therefore, the simple binary system of presence or absence allowed identification of the availability of information but not of the accuracy, completeness, or usefulness to clinical care of the information. There are a number of additional resources that could be considered in further studies, including the subscribed version of ePocrates, other free online resources including RxList and WebMD, and other subscribed resources such as Clinical Pharmacology. The selected resources, however, are commonly available in the United States and have been studied when assessing the availability of specific drug information, such as renal dosing and information to describe drug use in pregnancy.

Drug resources should include information regarding pharmacogenomics from the drug package insert as a minimum standard. Omission of this information could contribute to adverse patient outcomes due to a health care practitioner's inability to access established recommendations in drug resources. When biomarker information is available, the clinician is still left with the responsibility to interpret the information and apply it to an individual patient. Gaps in information contained in trusted drug information resources, including those highlighted by this study, should be identified and rectified on an ongoing basis to ensure the best possible care for the public [4, 20]. In the authors' experience, pharmacists turn to drug resources, including the five studied here, first when evaluating therapies for patients. The quantity and quality of pharmacogenomic information included should be one of the criteria used by librarians to evaluate drug information resources for their communities.

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