Characterizing the Strength of Evidence in FDA Labels for Pharmacogenomic Biomarker-Guided Medication Use

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Abstract

There is great heterogeneity in drug treatment response that is thought to be due to individual-level allelic variation in pharmacogenomic biomarkers. FDA Drug Labels provide information to guide pharmacogenomic biomarker use. Yet, the strength of evidence for clinical validity and clinical utility is lacking. We characterized the strength of evidence and treatment recommendations contained in FDA Drug Labels as of December 2015. Pharmacogenomic biomarker information was provided for 137 drugs, involving 49 pharmacogenomic biomarkers, constituting 166 drug-biomarker pairs. Convincing/adequate evidence of clinical validity was found for 46% of pairs, of clinical utility for 29% of pairs, and of both, for 27% of pairs. Despite evidence of convincing/adequate validity/utility, no treatment recommendation was provided for 37% of pairs. Germline biomarkers represented nearly three-quarters of all drug-biomarker pairs, however, only 29% and 16% of pairs had convincing/adequate evidence for clinical validity and clinical utility, respectively. Separately, somatic biomarkers that serve as molecular targets for targeted therapies, had convincing/adequate evidence for 95% of pairs for clinical validity, and for 67% for clinical utility. The strength of evidence for pharmacogenomic biomarker use is low, underscoring the need for additional research to achieve the promise of precision medicine.

Introduction

Inter-individual differences at the genomic level may produce variable treatment responses through an interplay of polymorphisms, altered pharmacokinetics and pharmacodynamics. Precision medicine aims to optimize therapeutic interventions using patient-specific factors by improving efficacy through appropriate medication selection and dose adjustments; and avoidance of serious adverse events (AEs). For example, to achieve their pharmacologic activity, targeted therapies generally target somatic biomarkers, defined as polymorphisms in tumor or cancerous cells. These agents rely on the presence of somatic polymorphic variants for therapeutic efficacy. On the other hand, individuals who carry specific germline pharmacogenomic variants may be at an increased risk for toxicity if the variant is involved with drug metabolism. Over one-third (37%) of enzymatic drug metabolism involves cytochrome P450 (CYP) enzymes, which are highly polymorphic. CYP variants are implicated in 66 drug labels as potential pharmacogenomic biomarkers for testing, as specific variants may predispose carriers to serious AEs due to narrow therapeutic indices, or accumulation of toxic metabolites. However, evidence for the clinical utility for various CYP phenotypes is poor.

Despite the rapid growth of published literature, availability of knowledge bases, and initiatives of consortia supporting the use of pharmacogenomic testing in clinical practice, use of testing is largely limited to a few specialized centers that support clinical research programs. One barrier to implementation is providers’ lack of pharmacogenomics education. In the largest survey of US physicians conducted to date, most providers (98%) agreed that pharmacogenomic variants could affect patient outcomes, while only 13% reported either ordering or recommending a pharmacogenomic test within the previous six months. This further underscores the apparent disconnect between available pharmacogenomic evidence and its real world applicability. A second barrier is the varying strength of evidence contained within labels. The US Food and Drug Administration (FDA) prescribing information (drug labels) remains a top source of pharmacogenomic information for providers, yet supporting evidence of clinical validity (e.g., ability to detect a clinical condition or disease) and utility (e.g., ability to impact clinical outcomes) is lacking, further highlighting the fact that existing evidence is often insufficient to translate into meaningful patient outcomes.
In previous work\(^7\), we assessed the strength of evidence (clinical validity and clinical utility) and described treatment recommendations based on mechanism of action (MoA) or drug-biomarker associations for pharmacogenomic-guided medication use for medications in 107 FDA drug labels, using 39 pharmacogenomic biomarkers, comprising 119 drug-biomarker pairs as of September 2013. The objective of the current study was to update our previous work by characterizing all drug-biomarker pairs as of December 2015. Specifically, we characterized the landscape of all current drug-biomarker pairs, provided an assessment of strength of evidence for clinical validity and utility, and described treatment recommendations. In addition, with a focus on the newly added drug-biomarker pairs, we compared and contrasted the recent information with that summarized in our earlier study. Finally, for both germline and somatic biomarkers, we identified the three biomarkers mentioned in the greatest number of FDA drug labels, cumulatively, between 1998 and December 2015 (‘top three’), and assessed trends in the strength evidence for clinical validity and utility of these over time.

**Methods**

We identified drug-biomarker pairs using the FDA Table of Pharmacogenomic Biomarkers\(^3\) publically available on the FDA website, and used a companion database on the FDA website (Drugs@FDA) that lists dates of regulatory approval and records labeling changes that take place over time\(^8\). As all data were publically available, the study did not constitute human subjects research and therefore did not require approval by the University of Washington Institutional Review Board.

As each biomarker can be associated with more than one medication, and each medication-specific label can include more than one biomarker, we used the drug-biomarker pair as the unit of analysis.

We adopted methods from our previous study, and identified all new drug-biomarker pairs added to the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling between September 20, 2013 and December 8, 2015\(^3,7\). We evaluated the earliest drug label that mentions the biomarker, adopting the reasoning from our previous work that this was when evidence supporting the inclusion of pharmacogenomic data and any testing recommendations were first provided to healthcare providers. To find the drug label that first mentioned the biomarker, we started with the current label, and worked in reverse chronologic order to identify the earliest label with first mention of the biomarker. When this information was unavailable from the FDA website, we referenced labels cited in PharmGKB\(^9\). PharmGKB is a manually curated knowledge base funded by the National Institutes of Health (NIH)/National Institute of General Medical Sciences (NIGMS) that presents evidence-based testing recommendations for drug-pharmacogenomic biomarker pairs based on primary literature, alongside other relevant information from FDA drug labels and international organizations such as the Clinical Pharmacogenetics Implementation Consortium. We then appended the information about the newly added drug-biomarker pairs to the data from our previous work\(^7\) to create an updated summary.

Four authors (LC, SB, KK, and JP) independently evaluated the strength of evidence provided in labels to determine the clinical validity and utility of biomarkers based on the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group’s criteria\(^10\). Pharmacogenomic evidence was classified as convincing, adequate, or incomplete according to the supporting study design and strength of evidence provided in the FDA label. If evidence from more than one study was mentioned in the FDA label, the most robust data were used to evaluate the strength of evidence of clinical validity and utility. Each author identified an excerpt of evidence from the label that supported his/her assessment of the drug-biomarker pair’s clinical validity and utility, whether a recommendation for testing was present, and if present, the type(s) of treatment recommendation suggested (mechanism of action; indication; contraindication/avoid use; dosage adjustment; drug interactions; follow-up lab testing; monitoring). Discrepancies were discussed verbally until consensus was reached. Targeted therapies were assigned a clinical utility grade of convincing if the relevant biomarker is required for efficacy (e.g. mechanism of action). We limited our review to information contained in each FDA label and did not review the primary literature, reasoning that busy clinicians will do the same.

We used descriptive statistics to characterize the number of drug-biomarker pairs and to categorize each included medication into its FDA-designated therapeutic class. To compare the clinical validity and utility of the updated list of drug-biomarker pairs, we collapsed the convincing and adequate evidence grades into one category, as this best represented the presence of adequate or stronger pharmacogenomic supporting evidence within FDA label. We collapsed treatment recommendations into one of three categories: mechanism of action (including indications); drug-biomarker association (including contraindication/avoid use, dosage adjustment, drug interactions, follow-up...
lab testing, monitoring), herein after termed safety; and absent (lack of treatment recommendation in labeling).
Lastly, stratifying by germline and somatic biomarkers, we selected the three biomarkers mentioned in the greatest number of FDA drug labels, cumulatively, between 1998 and December 2015 (‘top three’), and assessed the strength of evidence for clinical validity and utility, year over year.

Results
As of December 8, 2015, there were a total of 166 drug-biomarker pairs in the FDA Table of Pharmacogenomic Biomarkers in Drug Labeling, representing 137 unique medications and 49 pharmacogenomic biomarkers. In seven instances (amitriptyline-CYP2D6; dabrafenib-BRAFV600E/K; dabrafenib-G6PD; dapsone-G6PD; fluorouracil-DPYD; mafenide-G6PD; methylene blue-G6PD), either the label history or label with earliest mention of the biomarker was unavailable from the FDA, so a label from PharmGKB was used. We categorized each medication into one of seven FDA-designated therapeutic classes: oncology (n=54 [33%]), neurology (37 [22%]), infectious disease (ID) (18 [11%]), cardiovascular (CVD) (15 [9%]), gastroenterology (GI) (9 [5%]), endocrinology (7 [4%]), and Other (26 [16%]). These seven classes accounted for the greatest number of drug-biomarker pairs. The Other category encompassed therapeutic categories that contained fewer than ten drug-biomarker pairs. These were: analgesics, dermatology, hematology, inborn errors of metabolism, metabolic and endocrine, musculoskeletal, reproductive, urology, rheumatology, toxicology, and transplantation.

Of the 166 drug-biomarker pairs, 76 (46%) contained convincing or adequate evidence of clinical validity, while 48 (29%) provided convincing or adequate evidence of clinical utility. Among the 49 pharmacogenomic biomarkers, 31 (63%) were germline biomarkers, and 18 (37%) were somatic. All 18 (100%) somatic biomarkers were classified as efficacy biomarkers. Interestingly, only 7 (23%) germline biomarkers were related to efficacy, but 28 (90%) were classified as safety biomarkers; 4 (13%) germline biomarkers (CYP2C19; CYP2D6; LDLR; NAGS) were classified as both efficacy and safety biomarkers in separate, unique instances of different drug-biomarker pairs.

Only 36 (29%) of germline pairs were found to have convincing/adequate evidence for clinical validity and 20 (16%) for clinical utility. Treatment recommendations were provided for 59 (48%) pairs. In contrast, 40 (95%) somatic pairs had convincing/adequate validity evidence, while 28 (67%) pairs had convincing/adequate utility evidence. A treatment recommendation was provided within the label for 41 of 42 (98%) somatic drug-biomarker pairs.

Figure 1. Clinical validity evidence for pharmacogenomic biomarkers by therapeutic class.
Onc=oncology; ID=infectious diseases; Endo=endocrinology; CVD=cardiovascular disease; GI=gastrointestinal; Neuro=neurological
Figure 1 characterizes clinical validity and is summarized by the number and proportion of total drug-biomarker pairs that provide convincing/adequate versus incomplete evidence, by therapeutic class. Oncology medications contained the largest number (45) and highest proportion (83%) of labels with convincing or adequate evidence, followed by ID (8, 44%), endocrinology (3, 43%), CVD (6, 40%), GI (2, 22%), and neurology (5, 14%). In the combined Other category, 7 pairs, approximately 25%, contained convincing or adequate evidence.

Figure 2 characterizes clinical utility of drug-biomarker pairs by therapeutic class, and is summarized similarly. Oncology medications contained the greatest number (31) and highest proportion (57%) of labels with convincing or adequate evidence, followed by endocrinology (3, 43%), ID (6, 33%), CVD (2, 13%), neurology (2, 5%), and GI (0). In the combined Other category, 4 pairs, approximately 15%, contained convincing or adequate evidence.

In total, 88 (53%) drug-biomarker pairs provided inadequate evidence of both validity and utility (not shown in graphs).
Figure 3 illustrates the distribution of treatment recommendations, by therapeutic class, again summarized by number and proportion within each therapeutic class. A treatment recommendation was provided for 106 (64%) of drug-biomarker pairs.

Among the seven therapeutic classes, a treatment recommendation was provided for all 7 (100%) endocrinology drug-biomarker pairs, for 46 (85%) of oncology pairs, 11 (61%) of ID pairs, 19 (51%) of neurology pairs, 4 (44%) of GI pairs, 5 (33%) of CVD pairs, and for 14 (54%) of pairs categorized as Other. All drug labels for neurology and CVD with treatment recommendations were based on safety.

Even though 88 (53%) drug-biomarker pairs provided both inadequate evidence of validity and utility, 39/88 (44%) of these contained a treatment recommendation. Most of these recommendations, 37/39 (95%) were based on safety (not shown in graphs).

Table 1. Comparison of drug-biomarker pairs in drug labels identified through September 20, 2013 and through December 8, 2015

|                  | Pairs (n) | Drugs (n) | Biomarkers (n) | Oncology Drug-Biomarkers | Complete/Adequate Validity Evidence | Complete/Adequate Utility Evidence | Complete/Adequate Validity & Utility Evidence |
|------------------|-----------|-----------|----------------|--------------------------|---------------------------------|----------------------------------|-----------------------------------------------|
| Through 9/20/2013| 119       | 107       | 39             | 31%                      | 47%                             | 15%                              | 14%                                           |
| Through 12/8/2015| 166       | 137       | 49             | 33%                      | 46%                             | 29%                              | 27%                                           |

|                  | Treatment Recommendation: MoA | Complete or Adequate Validity & Utility Evidence and no Treatment Recommendation | Treatment Recommendation (yes) | Complete/ Adequate Validity & Utility Evidence and Treatment Recommendation | Complete/ Adequate Validity Evidence | Complete/ Adequate Utility Evidence | Treatment Recommendation: Safety |
|------------------|--------------------------------|-----------------------------------------------|---------------------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------|
| Through 9/20/2013| 51%                            | 37%                                           | 14%                             | 37%                             | 29%                              | 23%                              |                                  |
| Through 12/8/2015| 64%                            | 37%                                           | 27%                             | 37%                             | 41%                              | 34%                              |                                  |
Table 1 compares the two cumulative sets of drug-biomarker pairs assessed in our first analysis and in this study. Although the proportion of biomarkers that were oncology biomarkers and the proportion of drug-biomarker pairs with complete/adequate evidence of clinical validity remained largely the same over time, the proportion of pairs for which there was complete/adequate evidence of clinical utility increased from 15% to 29%. Similarly, the proportion of pairs that had complete/adequate evidence of both clinical validity and utility increased from 14% to 27%. The proportion of pairs that included a treatment recommendation increased from 51% to 64%. Each pair that had complete/adequate evidence of clinical validity and utility was also accompanied by a treatment recommendation, 14% and 27%, respectively. However, the same percentage (37%) of cumulative drug-biomarker pairs contained a treatment recommendation in the absence of complete or adequate validity and utility evidence in both analyses. In both analyses, a greater proportion of treatment recommendations were classified as being relevant to MoA than for safety. Of all therapeutic classes, oncology agents accounted for the highest proportion of pairs that contained a treatment recommendation of MoA in both the first (76%) and second analyses (72%) (not shown in table).

Fifty-six drug-biomarker pairs were identified since our last publication and nine pairs were removed between our first and second analysis to total the current 166 pairs. The 56 new pairs are characterized by 49 medications and 26 biomarkers. In total, the new pairs constitute 34% of the total number of drug-biomarker pairs listed on the FDA labels. Nineteen of 56 pairs (34%) represent oncology agents. Thirty (54%) of the new pairs have convincing or adequate evidence of clinical validity and 30 (54%) pairs have convincing or adequate evidence of utility; 29 (52%) new pairs have both convincing or adequate evidence of validity and utility. Fifty of the new pairs (89%) contain a treatment recommendation: 20 (36%) are associated with MoA, 30 (54%) with safety. Six (11%) do not contain a treatment recommendation (data not in table).

Figure 4 illustrates the trends in strength of evidence for the three germline biomarkers most frequently identified in 137 FDA drug labels.

Figure 4 indicates the trends in strength of evidence for the three germline biomarkers mentioned in the greatest number of FDA drug labels, cumulatively, between 1998 and 2015; these are cytochrome P450 2D6 (CYP2D6), glucose-6-phosphate dehydrogenase (G6PD), and cytochrome P450 C19 (CYP2C19). The number of labels in which CYP2D6 is mentioned increased from 3 in 1998 to 40 in 2015. Convincing or adequate clinical validity was first provided in 8% of labels (2001), and increased to 15% (2015). Convincing or adequate clinical utility was first

MoA=mechanism of action

Figure 4.
provided in 5% of labels (2013), and increased to 10% (2015). For G6PD, the number of labels increased from 1 in 2001 to 20 in 2015. Convincing or adequate clinical validity and utility was first provided in 14% of labels (2013), and increased to 15% (2015). For CYP2C19, the number of labels increased from 1 in 2000 to 16 in 2015. Convincing or adequate clinical validity was first provided in 10% of labels (2009), and increased to 25% of labels (2015). Convincing or adequate clinical utility has not been provided for any drug paired with CYP2C19 over the 1998-2015 time period.

By the end of 2015, while CYP2D6 was mentioned in the greatest number of FDA labels (n=40), the proportion of labels containing convincing or adequate evidence of clinical validity and utility were the lowest (clinical validity=15%; clinical utility=10%) of the top three. On the other hand, by the end of 2015, labels mentioning G6PD or CYP2C19 contained the highest proportion of convincing or adequate clinical validity and clinical utility, respectively (clinical utility=15%; clinical validity=25%).

**Figure 5.** Trends in the strength of evidence for the three somatic biomarkers most frequently identified in 137 FDA drug labels.

Figure 5 characterizes the trends in strength of evidence for clinical validity and utility for the three somatic biomarkers most frequently identified in the FDA labels. These are the Philadelphia chromosome (BCR/ABL1), proto-oncogene ERBB2 (ERBB2), and the epidermal growth factor receptor (EGFR). For BCR/ABL1, the number of labels increased from 1 in 2001 to 7 in 2015. Convincing or adequate clinical validity was first provided in 100% of labels (2001), and decreased to 86% (2015). Convincing or adequate clinical utility was first provided in 5% of labels (2013), and increased to 43% (2015). For ERBB2, the number of labels increased from 1 in 1998 to 5 in 2015. Convincing or adequate clinical validity and utility were first provided in 100% of labels (1998), and both consistently remained at 100% through 2015. For EGFR, the number of labels increased from 2 in 2004 to 4 in 2015. Convincing or adequate clinical validity and utility were first provided in 100% of labels (2004), and also consistently remained at 100% through 2015.

**Discussion**

Of the 166 drug-biomarker pairs in our analysis, we found that the strengths of evidence for clinical validity and clinical utility are highly variable, with under half of drug-biomarker pairs having convincing/adequate evidence of clinical validity and one-third for clinical utility. Despite the lack of evidence for clinical validity and utility, a treatment recommendation was provided for more than 60% of pairs.
Compared to the oncology therapeutic class, most labels for the neurology and GI therapeutic classes had incomplete evidence for clinical validity and utility. The reasons for incomplete evidence of validity in the neurology category are due to lack of relevant studies, that is, the availability of only case reports/case series or clinical laboratory data, and inability to classify study design from the information provided in the FDA label. The primary reason for incomplete evidence of utility was the lack of relevant studies. In the GI category, the primary reason for incomplete evidence of validity was the availability of only clinical laboratory data; the primary reason for incomplete evidence of utility was the lack of mention of any relevant studies.

Sixty (36%) drug-biomarker pairs did not provide a treatment recommendation in the label of first mention of the biomarker. Among the drug-biomarker pairs for which there were no treatment recommendations, 42 (70%) were based on CYP enzymes. Polymorphisms in CYP enzymes confer altered phenotypes that may affect drug metabolism\textsuperscript{11}. In many instances where a testing recommendation was not provided, the most likely rationale is the lack of evidence of a substantial effect of the CYP enzyme on drug metabolism. For example, in the drug label for doxepin, CYP2D6 is identified as one of the pharmacogenomic biomarkers with evidence for clinical testing. CYP2D6 poor metabolizers may experience reduced clearance of the parent drug and its metabolite when compared to extensive or ultrarapid metabolizers, however, the clinical utility of the effect of this association with established outcomes is lacking\textsuperscript{12}.

An informal look at updated labels revealed that some labels are updated over time as more rigorous evidence becomes available to support testing and use of a pharmacogenomic biomarker. For example, the July 2009 label for panitumumab first mentioned the KRAS biomarker, and stated that retrospective analyses had not demonstrated benefit in patients with KRAS mutations\textsuperscript{13}, but this information was updated in August 2012 to suggest that this agent is not indicated for use in patients with the KRAS mutation\textsuperscript{14}. Conversely, some updated labels have completely removed any identification of the pharmacogenomic biomarker and evidence for its association with the drug. Between our first analysis and the end of our second analysis, nine drug-biomarker associations were removed from the FDA’s Table of Pharmacogenomic Biomarkers. This underscores the need for clinicians to routinely evaluate FDA drug labels for updates on pharmacogenomic testing information to improve patient care.

There were 119 drug-biomarker pairs in our first publication, representing 107 medications and 39 biomarkers. Thirty-seven (31%) drug-biomarker pairs were for oncology agents. In the present study, oncology drugs also constituted approximately one-third of the drug-biomarker pairs. This proportion remained constant even with the addition of new drug-biomarker pairs after 2013\textsuperscript{7}. This observation was surprising, since cancer pharmacotherapy has shifted away from the traditional empirical approach toward individualized pharmacotherapy based on driver mutations. Based on PhRMA’s most recent pipeline report, the sheer number of oncology pipeline agents is more than four-fold the number of pipeline agents in the second leading therapeutic area, ID\textsuperscript{15}.

Compared to our first analysis and the cumulative total set of drug-biomarker pairs, the subset of new pairs for our second analysis contained almost 2-fold stronger evidence for both clinical validity and clinical utility\textsuperscript{7}. The proportion of cumulative drug-biomarker pairs with complete or adequate validity in the first and second studies remained constant at less than 50%, while the proportion of pairs with complete or adequate utility evidence and the proportion of pairs with both convincing or adequate validity and utility evidence nearly doubled. Since the first study, the proportion of labels with a treatment recommendation also increased; there was an equal increase in the proportion of treatment recommendations for MoA and safety.

Over time, the strength of evidence for both clinical validity and clinical utility increased for the three germline biomarkers most frequently mentioned in the FDA labels, but the overall proportion with convincing or adequate clinical validity and utility of these biomarkers remains ≤ 25%. The sheer number of germline biomarkers identified in drug labels for potential pharmacogenomic testing is greater than the number of somatic biomarkers mentioned in labels. However, of the three somatic biomarkers most frequently mentioned in FDA labels, the validity and utility hovers above 50%, with much stronger evidence for clinical validity and utility in practice. Upon first identification of both ERBB2 and EGFR in their respective drug labels, the clinical validity and utility evidence were either convincing or adequate. Each subsequent drug label that mentioned ERBB2 and EGFR through the end of our second analysis also contained both convincing or adequate validity and utility evidence. It is important to note that oncology agents comprised a majority of targeted agents for somatic biomarkers and a majority of the MoA treatment recommendations contained within labels\textsuperscript{7}. Germline biomarkers, while more frequently identified in drug
labels, are often supported by pharmacogenomic evidence from laboratory studies, case reports, or observational studies rather than randomized controlled trials or large subgroup analyses, which lack clinical validity and utility due to the limited knowledge surrounding clinical implications\textsuperscript{16}. This stark contrast in the validity and utility between somatic and germline biomarkers, based on supporting evidence, supports the need for more rigorous and clinically meaningful pharmacogenomic studies to be conducted to support inclusion in drug labels.

Strengths of this study include the consistency of our methods with our first analysis of drug-biomarker pairs. This characterizes trends over time in the strength of pharmacogenomic evidence published in the earliest label with mention of the biomarker. Moreover, by using EGAPP Working Group methods to classify strengths of evidence in drug labeling, we standardized the FDA’s repository of pharmacogenomic evidence contained within labels\textsuperscript{10}. The fact that we used the label with first mention of the biomarker may be considered a limitation of our study, but certainly underscores the need for clinicians to routinely evaluate FDA drug labels to identify updates about pharmacogenomic testing information to improve patient care. Future research should help define appropriate clinical trial designs for demonstrating the clinical utility of pharmacogenomic biomarkers based on treatment recommendation. Randomized controlled trials may be appropriate for targeted agents when efficacy relies on the presence of a specific pharmacogenomic biomarker, but may not be necessary to support the clinical utility of drug-biomarker pairs associated with an AE. Such drug-biomarker pairs may be supported by evidence from high-quality observational studies. This could promote the development of regulatory guidance documents to standardize inclusion of pharmacogenomic biomarker evidence available to healthcare providers and the general public.

Due to the variable strength of pharmacogenomic evidence contained in drug labels, in combination with vague and sometimes absent treatment recommendations, the labels do not always suggest clear, actionable measures for various pharmacogenomic biomarkers and variants. This makes it difficult for providers to assess and use these labels in clinical practice. Yet, providers do not have enough time to seek out this information from other sources, but rather, need a concise, ‘go-to’ source of information to inform their treatment decisions at the point of care. The FDA labels could be this source, especially because they are updated over time.

**Conclusion**

Based on these findings, there is a demonstrated need for higher strengths of evidence (e.g. well-designed and conducted studies in representative population(s)) to support the use of biomarkers alongside drug therapies. The EGAPP Working Group has provided a framework for the evaluation of pharmacogenomic testing, but drug manufacturers must also provide the relevant information necessary to facilitate translation of pharmacogenomic evidence into clinical practice\textsuperscript{10}. Moreover, the FDA should implement more stringent guidelines for evidence inclusion in labels. Manufacturers and the agency must work together to ensure appropriate evidence-based treatment of patients. With the aging US population\textsuperscript{17}, and rising healthcare costs due to targeted therapies\textsuperscript{18}, it is imperative to maximize therapeutic efficacy and minimize costs by utilizing appropriate pharmacogenomic testing and biomarkers with validated clinical utility.

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