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Clinical and Regulatory Considerations for Pharmacogenetic Testing

Robert N. Schuck, Pharm.D., Ph.D., Elizabeth Marek, Pharm.D., Hobart Rogers, Pharm.D., Ph.D., and Michael Pacanowski, Pharm.D., M.P.H.

Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

Abstract

Purpose: Both regulatory science and clinical practice rely on best available scientific data to guide decision-making. However, changes in clinical practice may be driven by numerous other factors such as cost. In this review, we reexamine noteworthy examples where pharmacogenetic testing information was added to drug labeling to explore how the available evidence, potential public health impact, and predictive utility of each pharmacogenetic biomarker impacts clinical uptake.

Summary: Advances in the field of pharmacogenetics have led to new discoveries about the genetic basis for variability in drug response. The United States Food and Drug Administration (FDA) recognizes the value of pharmacogenetic testing strategies and has been proactive about incorporating pharmacogenetic information into the labeling of both new drugs and drugs already on the market. Although some examples have readily translated to routine clinical practice, clinical uptake of genetic testing for many drugs has been limited.

Conclusion: Both regulatory science and clinical practice rely on data-driven approaches to guide decision making; however, additional factors are also important in clinical practice that do not impact regulatory decision making, and these considerations may result in heterogeneity in clinical uptake of pharmacogenetic testing.

Keywords

Pharmacogenetics; Drug Labeling; Genetic Testing

Introduction

Pharmacogenetic approaches to drug therapy have the potential to improve patient outcomes by allowing clinicians to preemptively adjust doses or choose alternative agents based on the expected response of a given genotype, potentially resulting in greater effectiveness and/or fewer adverse events. Over the past decade, major advances in the field of pharmacogenetics

Address correspondence to: Robert Schuck, Pharm.D., Ph.D., Food and Drug Administration, Office of Clinical Pharmacology, 10903 New Hampshire Avenue, White Oak, Building 51, Room 3104, Silver Spring, MD 20993, Phone: 301-796-8184, Fax: 301-847-8720, robert.schuck@fda.hhs.gov.

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have led to new discoveries about the genetic basis for variability in drug response. In some clinical settings, most notably in the setting of cancer, genetic testing has become a routine part of medical care.¹ However, despite the successful discovery of pharmacogenetic biomarkers in other therapeutic areas, retrofitting new biomarkers to the use of approved drugs has generally been slow and many barriers to clinical implementation remain.^{1, 2}

The United States Food and Drug Administration (FDA) recognizes the value of pharmacogenetic testing strategies and has been proactive about incorporating pharmacogenetic information into the labeling of both new drugs and drugs already on the market.³ In fact, genetic testing is essential (i.e., bearing indications or contraindications that are based on the results of a genetic test, so called companion diagnostics) for the clinical use of some drugs. However, the labeling for many drugs provides explicit instructions on dosing or warns about potential risks for genetically-defined subsets of patients should genetic test results be available,⁴ even if testing is not essential, in order to provide prescribers with information to safely and effectively use the drug. Despite this, clinical uptake of genetic testing for these nonessential scenarios has been limited.^{5, 6}

Many sources of evidence are considered when determining whether or not pharmacogenetic testing information is included in drug labeling; however, changes in clinical practice may be driven by additional factors. In this review we deconstruct historical examples that readily translated into clinical practice, and examine the available evidence, potential public health impact, and predictive utility of each pharmacogenetic biomarker. Our goal is to revisit noteworthy FDA labeling updates to assess clinical uptake and discuss factors impacting labeling and clinical use.

Case Studies:

Abacavir: Exceptional Evidence—Abacavir is a nucleoside reverse transcriptase inhibitor used to treat human immunodeficiency virus (HIV) in combination with other antiretroviral agents. However, potentially fatal hypersensitivity reactions characterized by rash, fever, gastrointestinal symptoms, respiratory symptoms and lethargy occurred in approximately 5% of patients initiated on abacavir.⁷ In 2002, two retrospective studies identified an association between a genetic variant in the human leukocyte antigen B (HLA-B*5701) and higher prevalence of hypersensitivity reactions to abacavir.^{8, 9} HLA-B*5701 is found in European and Asian populations with a minor allele frequency of 6–7% and 20%, respectively.¹⁰ Subsequently, a prospective, randomized, double-blind trial was conducted to determine if screening patients for HLA-B*5701 prior to treatment with abacavir could reduce the occurrence of hypersensitivity reactions.¹¹ Prospective screening was found to eliminate immunologically confirmed hypersensitivity reactions (0% vs. 2.7% in the control group, $P<0.001$) and significantly reduce clinically diagnosed hypersensitivity reactions (3.4% vs. 7.8% in the control group, $P<0.001$).¹¹ Based on these data, the abacavir labeling was updated in 2008 to include information describing the high risk of hypersensitivity reactions in patients who carry the HLA-B*5701 allele.

Among pharmacogenetic tests, abacavir is relatively unique in having prospective clinical outcome data supporting the clinical utility of testing. In addition, the potential impact of testing on public health is substantial due to the relatively high frequency of the drug-related

adverse event, the severity of the reaction, and the high frequency of the risk allele. The performance characteristics of the HLA-B*5701 test have been published, and both the specificity and negative predictive values are over 95% based on clinical diagnosis.¹¹ Thus, patients without the HLA-B*5701 polymorphism are at low risk for a hypersensitivity reaction and better candidates for abacavir. Conversely, HLA-B*5701 variant allele carriers are at significant risk for experiencing a hypersensitivity reaction to abacavir. While abacavir is an effective drug in the treatment of HIV, several viable alternatives also exist. Therefore, conducting the pharmacogenetic test prior to initiation of abacavir therapy is prudent to ensure that the patient is receiving a therapy that is likely to be safe and effective. However, clinicians may instead choose to prescribe a drug that does not have HLA associated risks, thus circumventing the need for pharmacogenetic testing. In the case of abacavir, the high level of evidence provided by a prospective randomized controlled trial, high predictive utility of the test, and the availability of alternative agents has resulted in the incorporation of HLA-B*5701 screening into routine clinical practice prior to the prescribing of abacavir. Indeed, multiple guidelines on the use of anti-retroviral therapy now recommend the routine use of HLA-B*5701 screening prior to initiation of therapy.¹²

Mercaptopurine: Pharmacokinetics Matter—Mercaptopurine is a purine antagonist that inhibits deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis, it is used in the maintenance treatment of acute lymphoblastic leukemia (ALL) and numerous inflammatory diseases. The enzyme thiopurine methyltransferase (TPMT) metabolizes mercaptopurine to the inactive metabolite methyl-6-MP, which leaves substrate available for conversion to active thioguanine nucleotides. *TPMT* is highly polymorphic, with three genetic variants (*TPMT*2*, *TPMT*3A*, and *TPMT*3C*) accounting for 80–95% of intermediate or low activity alleles.¹³ Approximately 3–14% of patients are heterozygous for loss of function alleles, while about 0.03–0.06% have two loss of function alleles.¹⁴ Individuals with loss of function alleles accumulate higher cellular concentrations of the active thioguanine nucleotides,¹⁵ resulting in higher risk of myelosuppression and potentially fatal neutropenia.¹³ Patients who have two non-functional *TPMT* alleles are at 100% risk for life-threatening myelosuppression with chronic dosing of mercaptopurine at conventional doses and require drastic dose reductions or use of alternative therapies.¹⁴ Heterozygotes also have a higher incidence of moderate to severe myelosuppression and require moderately reduced starting doses compared to wild-type individuals.¹⁴ The mercaptopurine labeling was updated in 2004 to include specific information about the high risk of myelosuppression in patients with *TPMT* genetic polymorphisms who are treated with standard doses of mercaptopurine.

There are no randomized clinical trials demonstrating that *TPMT* genotyping reduces myelosuppression; however, there is substantial evidence from preclinical studies and retrospective analyses indicating that *TPMT* genotype is associated with mercaptopurine toxicity and that reducing mercaptopurine dose improves tolerability.^{16–19} Moreover, there is a clear relationship between *TPMT* genotype and cellular concentrations of the active thioguanine nucleotides.¹⁵ The clear impact on pharmacokinetic properties provides supportive evidence that *TPMT* genotype impacts risk of this exposure-mediated toxicity. Myelosuppression is a severe and potentially fatal adverse event, meaning that strategies to

reduce mercaptopurine-induced myelosuppression could have a large impact on individual patients. Although the presence of two non-functional *TPMT* alleles is rare, genetic (or phenotypic) testing and preemptive dose reduction is important for the safe use of mercaptopurine in these patients because of the 100% lifetime risk of myelosuppression with conventional mercaptopurine dosing and the lack of therapeutic alternatives devoid of this toxicity. In addition, individuals who are heterozygous for non-functional alleles are much more common, and are also at a higher risk for adverse events and benefit from a genotype- or phenotype-tailored dosing strategy. There is substantial evidence supporting the clinical utility of *TPMT* genotype guided mercaptopurine dosing to prevent a severe and relatively common adverse event.¹⁴ Consequently, *TPMT* genetic information is included in drug labeling, and genotype- or phenotype-tailored dosing for ALL has seen substantial clinical uptake; however, recommendation of tailored thiopurine dosing in clinical guidelines developed by professional societies has been limited. Moreover, *TPMT* testing in other therapeutic areas prior to use of azathioprine has not been consistent.²⁰

Cetuximab/Panitumumab: Retrospective Evidence, but Strong Biology—

Cetuximab and panitumumab are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing activation by epidermal growth factor and other ligands. These agents are used in the treatment of EGFR-expressing metastatic colorectal cancer to prevent EGFR-mediated cell survival, proliferation, and metastasis, and have demonstrated benefits on progression free survival. Kirsten rat sarcoma viral oncogene homolog (*KRAS*) is a small GTP binding protein downstream of EGFR in the signaling cascade, and activating mutations *KRAS* codons 12 and 13 result in constitutive activity. *KRAS* mutations are frequent in numerous cancers and occur in approximately 40% of colorectal cancers.²¹ Multiple retrospective substudies of clinical trials demonstrate that patients with *KRAS* mutations have higher rates of treatment failure and lower rates of progression free survival in colorectal cancer populations treated with cetuximab and panitumumab, despite varying degrees of *KRAS* mutation status ascertainment and methodological issues.^{22, 23}

Colorectal cancer is one of the most common cancers in both men and women and a leading cause of death in the United States.²⁴ Therefore, improving our ability to identify effective treatments for every patient could have a significant public health impact. The 40% prevalence of *KRAS* mutations in metastatic colorectal cancer patients is high, and although the studies supporting the impact of *KRAS* mutations on the efficacy of anti-EGFR monoclonal antibodies primarily rely on retrospective analyses, there is convincing evidence that patients with *KRAS* mutations in codon 12 or 13 have high rates of treatment failure. In addition, there are treatment alternatives to anti-EGFR monoclonal antibodies for metastatic colorectal cancer. In 2009, FDA updated the labeling for cetuximab and panitumumab to indicate that these anti-EGFR agents are not recommended in metastatic colorectal cancer patients with *KRAS* mutations in codon 12 or 13. Because the patient population these agents are indicated for is based on the test result, *KRAS* testing is considered essential prior administration cetuximab and panitumumab, and clinical testing is routine. In addition, the American Society of Clinical Oncology (ASCO) guidelines state that all patients with metastatic colorectal cancer who are candidates for anti-EGFR antibody therapy should have their tumor tested for *KRAS* mutations prior to initiating therapy.²⁵

A New Era: Targeted Therapies, Companion Diagnostics, and Prerequisite

Testing—More recently, genomic factors have been prospectively incorporated into drug development programs, and pharmacogenetic testing information has been included as part of the indication with the initial approval of numerous drug products (Table 1). Although many kinds of pharmacogenetic information have been included in drug labeling, the most notable change has been the increase in approvals of targeted therapies, which work only in a subset of patients, usually identified by testing for a biomarker (e.g., HER2 protein expression for trastuzumab or certain *CFTR* mutations for ivacaftor). Most targeted therapy drug development has been in oncology products; however, other fields are seeing increasing activity in this space.

Unlike pharmacogenetic testing for most of the examples discussed above, for most targeted therapies pharmacogenetic testing using a companion in vitro diagnostic device is required in order to determine whether or not a patient is eligible to receive the drug. For many targeted therapies it is highly anticipated that genetic factors will impact the efficacy of the drug, based on biological properties or initial clinical studies. Therefore, the clinical trials supporting safety and efficacy of the drug often restrict enrollment based on genetic testing, and little is known about efficacy of the drug in an untested population. As such, pharmacogenetic testing as a prerequisite to receiving these drugs has not only been readily implemented clinically, but the concept of developing targeted therapies for genetic subsets of disease has been widely adopted in the oncology community, and the advent of targeted therapies been lauded as a major medical breakthrough.

Factors Driving Clinical Implementation of Pharmacogenetic Testing

Heterogeneity in clinical uptake of pharmacogenetic testing is likely the result of many factors. Potential determinants include the strength of evidence supporting pharmacogenetic testing, the consequences of the adverse event or treatment failure, cost-effectiveness, test accessibility and turnaround time, professional society positions, the availability of alternative agents or dosing strategies, and the predictive utility of the test. However, unlike dose adjustment for drug interactions and special populations, the pathways for establishing the evidence base and utility of testing common markers such as drug metabolizing enzyme variants are unclear.

The adequacy of the evidence base is clearly a major determinant of whether new technology or treatment modality are adopted, particularly pharmacogenetic testing. Genetic screening for HLA-B*5701 prior to abacavir use is unequivocally supported by a prospective randomized trial demonstrating that genetic testing reduces the incidence of hypersensitivity reactions. This type of evidence is the exception rather than the rule for practical reasons. Evidence from planned analyses of adequate and well-controlled trials also represents a solid source of data to make inferences about clinical utility. The FDA and clinical community have relied on alternative streams of evidence in some cases. For example, screening for *TPMT* polymorphisms prior to initiation of mercaptopurine has not been evaluated in prospective randomized trials, although numerous observational studies have demonstrated that *TPMT* genotype is associated with myelosuppression and dose adjustment reduces the risk.¹⁴ More importantly, in the case of mercaptopurine, exposure is

guidelines for treatment of percutaneous coronary intervention.⁶ Similarly, many studies have demonstrated that dosing algorithms that include *VKORC1* and *CYP2C9* genetic information more accurately predict stable warfarin doses compared to algorithms relying on clinical factors alone.^{36, 37} However, prospective randomized trials evaluating genotype guided warfarin therapy have produced mixed results^{38, 39} and warfarin has a reliable pharmacodynamic endpoint that can be used to monitor response and titrate to a safe and effective dose. Furthermore, the current American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis guidelines recommend against routine pharmacogenetic testing.⁵ These scenarios suggest that prospective trials may be necessary in some cases to facilitate implementation of pharmacogenetic testing into standard clinical practice.

Considerations in Labeling and Clinical Practice

While the FDA is responsible for overseeing approval of drug marketing applications and post-marketing labeling updates, the way in which drugs are used clinically is ultimately driven by clinicians in the course of their clinical practice. We have highlighted multiple examples of drugs for which labeling was updated to include pharmacogenetic information based on various sources of data. In some cases, pharmacogenetic testing was readily implemented into patient care, indicating that the factors prompting the FDA to update drug labeling were well-aligned with the clinical considerations for testing. However, in other cases clinical implementation of pharmacogenetic testing is not observed following the labeling update, indicating that in some cases additional factors (e.g., cost, availability of alternative therapies) may impact clinical use.

To explore the factors impacting regulatory decision making compared to clinical uptake, we must first look at the purpose of drug labeling, which is to help provide information to the health care provider that aids in safe and effective use of the product. Therefore, pharmacogenetic information that helps describe pharmacokinetic and pharmacodynamic properties or risk of a serious but rare adverse event may be considered useful to include in drug labeling, even if testing is not a prerequisite for safe and effective use of the drug. To support inclusion of information in labeling, FDA relies on many studies including nonclinical toxicology studies (to help inform the toxicity profile), clinical pharmacology studies (to adequately describe drug disposition and mechanism of action), clinical trials (which provide data regarding drug effects), and other data. In some cases clinical pharmacology data along with other data such as retrospective analyses or mechanistic data may be relied on to better inform the safe and effective use of the drug in individual patients (e.g., poor renal function, low body weight, poor metabolizers).

Clinical practice is impacted by myriad factors including physician expectation and interpretation of the evidence from the clinical trials, availability of therapeutic agents, practice guidelines, economic factors, and others. Therefore, changes in drug labeling may not always result in immediate changes to clinical practice. Moreover, changes in clinical practice are generally driven by prospective clinical trials demonstrating that an intervention improves clinical outcomes. As such, data from sources such as clinical pharmacology studies or replicated retrospective analyses of clinical trials may be sufficient to indicate that

pharmacogenetic information may be useful to prescribers, and thus warrant inclusion in labeling, but not immediately result in ubiquitous clinical implementation of pharmacogenetic testing.

Population Enrichment

The utility of pharmacogenetic testing is constantly evolving as new pharmacogenetic tests are developed and new drugs are approved. In addition, the clinical utility of a pharmacogenetic test can be altered depending on how clinical testing is implemented. Two key factors driving the predictive utility of a pharmacogenetic test are the prevalence of the genetic biomarker and the frequency of the event that the biomarker is associated with. Testing in populations that have a high prevalence of the genetic biomarker or a high frequency of the adverse event, “population enrichment”, can improve the predictive utility of the genetic test. Therefore, limiting clopidogrel/*CYP2C19* screening to individuals with higher minor allele frequency (e.g. Asian populations) or patients at very high risk for cardiovascular events (e.g. individuals with multiple risk factors or recent acute coronary syndrome) could possibly improve the predictive utility of the test. Similarly, given that there are substantial differences in prevalence of HLA-B*1502 and HLA-A*3101 risk alleles across geographic regions, the predictive utility and cost effectiveness of pharmacogenetic biomarker guided carbamazepine use may be higher if a population enrichment strategy is utilized.⁴⁰ This is reflected in the FDA issued alert on HLA-B*1502 and risk of carbamazepine induced SJS and TEN, which states “Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine.”⁴¹ Similarly, clinical practice guidelines for percutaneous coronary intervention state that “genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel.” These statements indicate that testing the most appropriate patients is both an important regulatory consideration and an important clinical consideration.

Looking Towards the Future of Pharmacogenetic Testing

In recent years, there have been major advances in drug development and genetic testing, and these advances have in turn brought about changes in clinical practice.^{1, 42} Most notably, we have seen a shift towards “precision medicine” approaches to treatment of many diseases and the development and approval of numerous molecularly targeted therapies. In contrast to the retrofitting of new biomarkers to the use of approved drugs, which has often been met with resistance, most targeted therapies require molecular testing prior to use, which has been more readily accepted. The use of precision medicine approaches will likely continue to grow across all medical disciplines in the coming years, likely leading to broader implementation of preemptive screening approaches and integration of genetic information into the medical record, resulting in increased acceptance and use of pharmacogenetic testing in the clinical setting.

Conclusions

Both regulatory science and clinical practice rely on best available scientific data to guide decision making. Nevertheless, we have seen that regulatory updates to drug labeling do not always result in uniform clinical uptake. The examples discussed herein indicate that a higher level of evidence (e.g., prospective clinical trials demonstrating improved clinical outcomes) generally translates to greater clinical uptake; however the mercaptopurine and cetuximab/panitumumab examples demonstrate that prospective data are not always necessary to facilitate extensive clinical use. Although both regulatory science and clinical practice rely on scientific data to guide decisions, additional factors are important in clinical practice that do not impact regulatory decision making and these considerations may, in part, explain heterogeneity in clinical uptake of pharmacogenetic testing following labeling updates. Future developments in pharmacogenetic testing, such as adaptation of precision medicine approaches, use of population enrichment strategies, development of point-of-care genetic tests, and preexisting genotype data in patient medical records will likely help define the role and clinical utility pharmacogenetic testing in health care.

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Key Points

- Both regulatory science and clinical practice rely on the best available scientific data to guide decision making.
- Pharmacogenetic labeling updates do not always result in uniform clinical uptake.
- Potential factors leading to heterogeneity in clinical uptake may include: the strength of evidence supporting pharmacogenetic testing, the consequences of the adverse event or treatment failure, cost-effectiveness, test accessibility and turnaround time, professional society positions, the availability of alternative agents or dosing strategies, and the predictive utility of the test.

Table 1.
Selected Drugs Approved in 2015 with Targeted Indications or Tailored Dosing

Drug	Indication
Palbociclib	Estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer
Lumacaftor/Ivacaftor	Cystic fibrosis transmembrane conductance regulator (CFTR) F508 deletion mutation-positive cystic fibrosis
Daclatasvir	Genotype 3 chronic hepatitis C virus infection
Mepolizumab	Eosinophilic asthma
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide	Human immunodeficiency virus (HIV)-1 infection
Cobimetinib	B-Raf proto-oncogene, serine/threonine kinase (BRAF) V600E or V600K positive metastatic melanoma
Osimertinib	Epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer
Alectinib	Anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer
Brexiprazole	Schizophrenia, with cytochrome p450 (CYP)2D6-based dosing
Aripiprazole Lauroxil	Schizophrenia, with CYP2D6-based dosing