Impact of CYP2C19 Genetic Testing on Provider Prescribing Patterns for Antiplatelet Therapy After Acute Coronary Syndromes and Percutaneous Coronary Intervention

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Background—Patients treated with clopidogrel who have ≥1 loss of function alleles for CYP2C19 have an increased risk for adverse cardiovascular events. In 2010, the US Food and Drug Administration issued a boxed warning cautioning against the use of clopidogrel in such patients. We sought to assess the impact of CYP2C19 genetic testing on prescribing patterns for antiplatelet therapy among patients with acute coronary syndrome or percutaneous coronary intervention.

Methods and Results—Patients with recent acute coronary syndrome or percutaneous coronary intervention prescribed clopidogrel were offered CYP2C19 testing. Genotype and phenotype results were provided to patients and their physicians, but no specific treatment recommendations were suggested. Patients were categorized based on their genotype (carriers versus noncarriers) and phenotype (extensive, intermediate, and poor metabolizers). The primary outcome was intensification in antiplatelet therapy defined as either dose escalation of clopidogrel or replacement of clopidogrel with prasugrel. Between July 2010 and April 2012, 6032 patients were identified, and 499 (8.3%) underwent CYP2C19 genotyping, of whom 146 (30%) were found to have ≥1 reduced function allele, including 15 (3%) with 2 reduced function alleles. Although reduced function allele carriers were significantly more likely than noncarriers to have an intensification of their antiplatelet therapy, only 20% of poor metabolizers of clopidogrel had their antiplatelet therapy intensified.

Conclusions—Providers were significantly more likely to intensify antiplatelet therapy in CYP2C19 allele carriers, but only 20% of poor metabolizers of clopidogrel had an escalation in the dose of clopidogrel or were switched to prasugrel. These prescribing patterns likely reflect the unclear impact and evolving evidence for clopidogrel pharmacogenomics. (Circ Cardiovasc Qual Outcomes. 2013;6:694-699.)

Key Words: antiplatelet agents ■ pharmacogenetics ■ quality of health care

Clopidogrel, an irreversible ADP-receptor blocker, has been shown to reduce the risk of major adverse cardiovascular events in patients with an acute coronary syndrome (ACS) and those undergoing percutaneous coronary intervention (PCI). However, there is significant interindividual variability in the response to clopidogrel, and patients with higher levels of platelet reactivity after receiving standard doses of clopidogrel are at significantly increased risk for recurrent adverse cardiovascular events. Clopidogrel is a prodrug that requires bioactivation mediated by the cytochrome P450 enzyme system, and reduced function alleles in CYP2C19 may help explain the observed variability in platelet reactivity. Patients who are both heterozygous and homozygous for reduced function CYP2C19 alleles have reduced levels of the active metabolite of clopidogrel, diminished levels of platelet inhibition, and 55% to 76% relative increase in the risk of cardiovascular death, myocardial infarction, or stroke, as well as a 2.6- to 4.0-fold increase in the risk for stent thrombosis. However, several pharmacogenetic analyses of clopidogrel have not found a significant association between CYP2C19 genotype and clinical outcomes.

However, the US Food and Drug Administration (FDA) advised avoiding the use of clopidogrel in patients with impaired CYP2C19 function because of known genetic polymorphisms. More recently, the FDA modified this boxed warning for clopidogrel and advised healthcare professionals to consider the use of other antiplatelet medications or alternative dosing strategies for [clopidogrel] in patients with particular CYP2C19 genotypes. Potential therapeutic options for patients with a CYP2C19 loss of function allele

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WHAT IS KNOWN

- Clopidogrel is a prodrug that requires bioactivation mediated by the cytochrome P450 enzyme system.
- Carriers of reduced function CYP2C19 alleles have reduced levels of the active metabolite of clopidogrel, diminished levels of platelet inhibition, and an increased risk of major adverse cardiovascular events, including stent thrombosis.
- The US Food and Drug Administration issued a boxed warning for clopidogrel advising providers to avoid its use in patients who carry certain CYP2C19 alleles and are poor metabolizers.

WHAT THE STUDY ADDS

- Among clinically eligible patients, providers declined CYP2C19 genetic testing in ≥25% of cases, whereas <10% of patients who were offered genetic testing for CYP2C19 declined the test.
- In our real-world analysis of a clopidogrel-CYP2C19 genotyping program among patients with acute coronary syndrome or undergoing percutaneous coronary intervention, we found that only 1 in 5 patients who are poor metabolizers of clopidogrel and subject to the US Food and Drug Administration boxed warning had their antiplatelet therapy changed.

Testing Procedures

Potentially eligible patients were those who had been prescribed clopidogrel in the prior 12 months as determined using filled prescription drug claims data. Each patient’s prescribing physician was contacted to confirm that the patient had experienced an ACS or undergone PCI in the prior 12 months and, if so, to obtain consent for CYP2C19 testing.

Patients whose physicians had agreed to testing were then contacted by a pharmacist to explain and obtain verbal consent for the test. Patients were then sent a sample collection kit that contained a buccal swab, instructions on how to administer the test, a written consent form, responses to frequently asked questions, and a prepaid return envelope. The expense of this program was fully covered by the patient’s pharmacy benefit, and as a result, patients were offered testing free of charge.

CYP2C19 Testing

Samples (buccal) were evaluated by amplifying selected exons of the CYP2C19 gene via a process of multiplex polymerase chain reaction, single-nucleotide primer extension, and subsequent detection of fluorescent extension products on an automated DNA sequencing platform. After an average of 3 to 5 days, test results were faxed directly to the prescribing physician. After test results, a more detailed summary report was sent to the physician with information on the patient’s clopidogrel metabolizer status and the FDA boxed warning for clopidogrel11 (see the online-only Data Supplement). On March 1, 2012, clinical pharmacists also began telephone outreach to physicians 30 days after results were faxed to provide test result interpretation support.

Based on genotype, patients were categorized into clopidogrel metabolizer phenotypes as presented in Table 1.

Changes in Antiplatelet Prescribing

Changes in antiplatelet prescribing were monitored for ≤120 days after reporting of CYP2C19 genotype and phenotype results using prescription claims data. The primary outcome for the current study was intensification of antiplatelet therapy defined as either a dose escalation of clopidogrel or replacement of clopidogrel by prasugrel. When assessing changes to antiplatelet therapy, we excluded patients with an undefined phenotype (ie, carriers of 1 reduced function CYP2C19 allele and 1 ultrarapid CYP2C19 allele). Any changes to a patient’s course of treatment after testing were solely at the discretion of the prescribing physician, and test results were not used for any medication coverage decisions.

Statistical Analysis

Baseline demographic, clopidogrel prescription, and insurance coverage characteristics were compared using χ² testing for categorical variables.
variables and Mann–Whitney test for continuous variables. Changes in prescribing patterns for antiplatelet therapy were evaluated using $\chi^2$ or Fisher exact test if there were <5 observations. $P$ values <0.05 were considered significant.

Results

Program Adoption and Cohort Characteristics
During the study period, 6032 potentially eligible individuals filled a prescription for clopidogrel. The prescribing physicians of 2692 provided relevant clinical eligibility information, of whom 1291 patients underwent a PCI or were hospitalized for an ACS within the prior 12 months. Consent for testing was provided by 945 physicians, and 678 patients were successfully contacted and offered testing. Of these, 623 consented and 499 completed testing (Figure 1).

The baseline demographic characteristics, duration of insurance coverage and clopidogrel therapy, coprescribed medications, and specialty of ordering provider for all identified patients (n=6032) and the patients who ultimately underwent testing (n=499) are presented in Table 2. The median age was 61 years, 70% were men, the median duration of clopidogrel treatment before identification for study enrollment was 40 days, and patients were receiving a median of 7.0 additional medications. There were no significant differences between groups except for prescriber practice setting. Cardiology, internal medicine, and family practice represented the specialties of the majority of treating providers.

CYP2C19 Genotype and Clopidogrel Metabolism Phenotype
The CYP2C19 genotypes and phenotypes for the 499 subjects successfully undergoing genetic testing are shown in Figure 2. The majority of subjects (n=344; 69%) were noncarriers of reduced function alleles; 155 (31%) were carriers of ≥1 reduced function allele. In terms of clopidogrel metabolism phenotype, 16 (3.2%) were ultrarapid metabolizers, 328 (65.7%) were extensive metabolizers, 131 (26.3%) were intermediate metabolizers, 15 (3.0%) were poor metabolizers, and 9 (1.8%) were unknown given the presence of 1 reduced function allele and 1 ultrarapid allele. Baseline patient and provider characteristics by reduced function allele carrier status are shown in Table 2 and were well balanced across groups.

Clinical Action by Testing and CYP2C19 Genotype and Clopidogrel Metabolism Phenotype
Patients who underwent genetic testing were significantly more likely to have their antiplatelet regimen change and to continue clopidogrel as compared with patients not undergoing testing ($P<0.001$). Among patients identified as eligible for testing but who did not complete genetic testing, 51 (0.9%) had their antiplatelet agent changed from clopidogrel to prasugrel compared with 33 (6.6%) patients who were genotyped; of those not undergoing testing, 984 (17.8%) discontinued antiplatelet therapy compared with 46 (9.2%) patients who underwent testing.

The clinical action that occurred ≤120 days after the reporting of test results to providers and patients stratified by allele carrier status is shown in Figure 3. The primary outcome, intensification of antiplatelet therapy, occurred significantly more often in carriers of $CYP2C19$ reduced function alleles as compared with noncarriers (20.5% versus 1.7%; $P<0.001$). As compared with noncarriers of reduced function $CYP2C19$ alleles, carriers of ≥1 reduced function allele were significantly more likely to have their antiplatelet therapy changed from clopidogrel to prasugrel (17.8% versus 1.7%; $P<0.001$). Carriers of ≥1 reduced function allele were also significantly more likely to have an increase in their dose of clopidogrel when compared with noncarriers (2.7% versus 0%; $P=0.008$).

Figure 3 also shows the impact of genetic testing on provider prescribing patterns for antiplatelet therapy by the predicted phenotype of clopidogrel metabolism. The primary outcome occurred in 20.6% and 20% of intermediate and poor metabolizers, respectively, as compared with 1.7% of extensive and ultrarapid metabolizers ($P<0.001$ for each comparison versus extensive and ultrarapid metabolizers). As compared with ultrarapid and extensive metabolizers where 1.7% of patients had replaced clopidogrel with prasugrel, there was a step-wise increase in the percentage of patients with an escalation from clopidogrel to prasugrel in intermediate metabolizers (17.6%) and poor metabolizers (20%; $P<0.001$ for both groups compared with ultrarapid and extensive metabolizers). One of the 9 (11%) subjects with undefined phenotype had an escalation in their antiplatelet regimen from clopidogrel to prasugrel (data not shown).

Discussion
Our analysis of a commercial clopidogrel-$CYP2C19$ genotyping program demonstrates that about one third of patients are carriers of reduced function alleles. Although the carriers (intermediate and poor metabolizers of clopidogrel) were more likely to have an intensification of their antiplatelet therapy, only 20% of the highest risk patients had an intensification of their antiplatelet therapy. In addition, we found that a small proportion of extensive and ultrarapid metabolizers were changed to prasugrel.
To the best of our knowledge, our study is the first real-world analysis of a clopidogrel-CYP2C19 genotyping program among patients with ACS or PCI and provides insight into how other genetic testing programs for other drugs may function. Notably, in ≈50% of cases, providers failed to respond to initial outreach, despite being contacted numerous times by mail and phone. Even among clinically eligible patients, providers declined testing in ≈25% of cases. Provider discomfort at how best to integrate FDA boxed warnings and genotype information to their selection of the appropriate antiplatelet regimen may underlie our findings. In contrast, <10% of patients offered genetic testing for CYP2C19 declined the test, highlighting a potential gap between providers and patients in their desire for genetic testing, especially once the physicians had already approved the test. We also observed that the rate of discontinuation of clopidogrel was significantly lower among patients who underwent testing as compared with those who were eligible but did not undergo testing. However, in the current analysis, we are unable to further evaluate the impact of CYP2C19 genetic testing on medication adherence.

Our observation that 1 in 3 patients are carriers of reduced function alleles and ≈3% are homozygotes for reduced function CYP2C19 alleles is consistent with prior literature. Genetic epidemiology studies have demonstrated that common polymorphisms in the CYP2C19 gene are present in ≈30% of whites, 40% of blacks, and >50% of Asians. In an analysis from the TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) 38 trial, 27% of the study population was found to be carriers of ≥1 reduced function CYP2C19 allele. Still further, in the randomized ELEVATE-TIMI (Escalating Clopidogrel by Involving a Genetic Strategy-Thrombolysis in Myocardial Infarction) 56 trial, 26% of enrolled subjects were carriers of ≥1 reduced function CYP2C19 allele, with 2% of subjects being homozygous for reduced function alleles. In a proof-of-concept study using point-of-care genetic testing for CYP2C19 in 200 patients undergoing PCI for ACS or stable CAD, 24.5% were noted to be carriers of reduced function alleles.

Our analysis uniquely offers the ability to observe provider prescribing patterns for antiplatelet therapy in response to genetic testing. We observed that carriers of reduced function alleles overall, and intermediate and poor metabolizers of clopidogrel specifically, were significantly more likely to have their antiplatelet therapy changed from clopidogrel to prasugrel or have their dose of clopidogrel increased—a clinical action that is consistent with FDA guidance. However, only 1 in 5 patients with 2 reduced function alleles, poor metabolizers of clopidogrel who would be expected to be at the highest risk for adverse events, had an intensification of
their antiplatelet therapy. These findings may have resulted from the providers’ lack of understanding about how to interpret genetic test results or a belief that genetic testing has not been definitively established as a reliable approach to tailoring antiplatelet therapy. In addition, providers may have been reluctant to switch to one of the novel antiplatelet agents because of their relative lack of clinical experience with them. For instance, despite the FDA boxed warning, the American College of Cardiology/American Heart Association maintain that insufficient evidence remains for this warning.10 In addition, multiple studies have failed to demonstrate a benefit to platelet function testing–guided therapy.19–21 Although these studies focused on platelet function testing rather than genotyping, the inability to show the superiority of personalized therapy for clopidogrel may have dampened enthusiasm for CYP2C19 genotype-guided antiplatelet therapy.

It is important to note that our analysis used pharmacy claims data and included many patients who were established users of clopidogrel. The median duration of clopidogrel use before their identification for allele carriers was 106 days. Providers and patients may have been less willing to alter therapy in patients who had been clinically stable on standard dose clopidogrel therapy after ACS/PCI. Given that the risk of recurrent adverse cardiovascular events and stent-related complications is highest in the first 30 days after ACS or PCI,22,23 our findings likely underestimate the response to CYP2C19 genetic testing when it is used for patients with more acute coronary artery disease. Patient factors such as the higher cost of branded antiplatelet agents and the increased risk of bleeding complications with alternative antiplatelet therapy may have also contributed to our findings.

There are several important limitations to our study. First, our study included a relatively small number of patients for whom we had comprehensive pharmacy claims data but limited clinical information or provider-level characteristics. However, given that this was a real-world analysis, it offers important insights into clinical practice patterns that could not be gained with the use of a controlled study design. Second, during our analysis period, ticagrelor was not an FDA-approved therapy, so we cannot make any conclusions about the medication providers would have selected if they chose to intensify therapy for a particular patient if ticagrelor were available. Third, the results of genetic testing were reported to the providers and patients but were not coupled with an active intervention highlighting the salient test results and potential therapeutic alternatives. Rather, this was a passive transmission of results to the physician with minimal integration of educational information and decision support as the American Heart Association/American College of Cardiology do not offer any specific recommendations on managing patients with ≥1 loss of function CYP2C19 alleles. Although the test results are certainly less likely to influence provider prescribing behavior, they do offer important, unique insights into provider decision making that would be lost if a more directive intervention was used. Finally, we are unable to capture whether providers responded to the genotype results by referring patients for additional testing, including platelet function studies, and then based their prescribing decision on a more integrated assessment of platelet activity.

In conclusion, clopidogrel has been shown to reduce the rate of major adverse cardiovascular events among patients with ACS or undergoing PCI. Its efficacy has been shown in some studies to be attenuated in patients carrying reduced function CYP2C19 alleles, a critical enzyme involved in the bioactivation of the drug. Regulatory agencies, including the FDA and European Medicines Agency, have reacted to these data, and the FDA has issued a boxed warning cautioning against the use of clopidogrel in patients carrying certain CYP2C19 alleles. Although providers were significantly more likely to alter the antiplatelet regimen in CYP2C19 allele carriers, ultimately only 20% of those at highest risk after ACS or PCI were switched to prasugrel or had an increase in the
dose of clopidogrel. These prescribing patterns likely reflect the unclear impact and physician uncertainty with the rapidly evolving evidence for clopidogrel pharmacogenomics.

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**Disclosures**

None.

**References**


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SUPPLEMENTAL MATERIAL

Supplemental Methods

A sample, detailed summary report that would be sent to the prescribing physician of a patient who is a poor metabolizer of clopidogrel is included below. In addition, we have provided the “considerations” section that was included for each of the clopidogrel metabolism phenotype results (ultrarapid, intermediate, other, and extensive).

Please Review Results for CYP2C19 Genetic Test for Clopidogrel with Your Patient

«System Date»

Dr. «Prescriber First Name» «Prescriber Last Name»
«Prescriber Address Line 1»«Prescriber Address Line 2»
«Prescriber City»«Prescriber State»«Prescriber Zip»

RE: «Patient First Name» «Patient Last Name» / DOB: «Patient DOB»
PRESCRIPTION: «HCS Name» / EOC ID: «EOC ID»

Dear Dr. «Prescriber Last Name»:

We received a copy of «Patient First Name» «Patient Last Name»’s CYP2C19 genetic test results on «System Date». Enclosed for your convenience is a brief summary in addition to the full lab report. Please review the test results and discuss them with your patient. We encourage you to consider the risks and benefits of all available treatment options so you and your patient can make the most informed treatment decision.

We sent a letter to your patient indicating that the test has been completed and that the results have been sent to your office.

If you have questions or concerns about any of the information in this letter or the attached results summary, please contact a Generation Health registered pharmacist toll-free at 1-877-340-4363.

Sincerely,
Generation Health

Enclosures: Results Summary Report
Full CYP2C19 Clopidogrel Test Report

This program has been designed to be compliant with the Health Insurance Portability and Accountability Act (HIPAA) and the Genetic Information Nondiscrimination Act (GINA).
Please discuss these results with your patient. As with all therapies, we encourage you to consider the risks and benefits of available treatment options so you and your patient can make the most informed treatment decision. If a change in drug therapy is required based on this test result, please discuss the available treatment options with your patient and write a new prescription.

<table>
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**Indication for Testing:** Prescription request for clopidogrel

**Specific Test Assay:** CYP2C19 Genetic Test

**TEST RESULT:**

**CYP2C19 Poor Metabolizer (PM)**

**POSSIBLE TEST RESULT DEFINITIONS:**

- **Poor Metabolizer:** Homozygous for a loss of function allele; severely decreased CYP2C19 enzyme function or complete lack of CYP2C19 enzyme function
- **Intermediate Metabolizer:** Heterozygous for one normal CYP2C19 allele and one loss of function allele; decreased CYP2C19 enzyme function
- **Extensive Metabolizer:** Wild type, or homozygous for two normal function CYP2C19 alleles; normal CYP2C19 enzyme function
- **Ultrarapid Metabolizer:** One or more CYP2C19 alleles that have increased expression of an otherwise normal CYP2C19 gene; increased CYP2C19 enzyme function
- **Other Metabolizer**

One loss of function CYP2C19 allele and one CYP2C19 allele that has increased expression of an otherwise normal CYP2C19 gene; the resulting CYP2C19 enzyme activity status is currently unknown because the net effect of 2 alleles which act in opposite directions has not been adequately studied.
CONSIDERATIONS: Poor metabolizers have decreased CYP2C19 function. When treated with standard doses of clopidogrel, these patients may have decreased antiplatelet activity compared with extensive metabolizers. This may put them at risk of an increased rate of cardiovascular events following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI).

The CYP2C19 metabolizer status of this patient may have implications for other medications that your patient is prescribed. Generation Health and CVS Caremark recommend that prescribers review FDA labels routinely for any updates regarding pharmacogenomic information.

FDA information related to this test result:

**Black Box Warning**

“DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

“EFFECTIVENESS OF PLAVIX DEPENDS ON ACTIVATION TO AN ACTIVE METABOLITE BY THE CYTOCHROME P450 (CYP) SYSTEM, PRINCIPALLY CYP2C19. POOR METABOLIZERS TREATED WITH PLAVIX AT RECOMMENDED DOSES EXHIBIT HIGHER CARDIOVASCULAR EVENT RATES FOLLOWING ACUTE CORONARY SYNDROME (ACS) OR PERCUTANEOUS CORONARY INTERVENTION (PCI) THAN PATIENTS WITH NORMAL CYP2C19 FUNCTION. TESTS ARE AVAILABLE TO IDENTIFY A PATIENT’S CYP2C19 GENOTYPE AND CAN BE USED AS AN AID IN DETERMINING THERAPEUTIC STRATEGY. CONSIDER ALTERNATIVE TREATMENT OR TREATMENT STRATEGIES IN PATIENTS IDENTIFIED AS CYP2C19 POOR METABOLIZERS.”

**Additional Label Information**

“The relationship between CYP2C19 genotype and Plavix treatment outcome was evaluated in retrospective analyses of Plavix-treated subjects in CHARISMA (n=4862) and TRITON-TIMI 38 (n=1477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.”


For more detailed information about the CYP2C19 genetic test and clopidogrel, please refer to the FDA label for this drug at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16997.
CONSIDERATIONS: Ultrarapid metabolizers have increased metabolism of clopidogrel; the impact on clopidogrel effectiveness is unknown but is predicted not to be diminished. The patient should be monitored for increased risk of bleeding and a change in therapy should be considered for those at high risk for bleeding or at high risk from bleeding events.

The CYP2C19 metabolizer status of this patient may have implications for other medications that your patient is prescribed. Please keep this test result in mind for future prescribing. Generation Health and CVS Caremark recommend that prescribers review FDA labels routinely for any updates regarding pharmacogenomic information.
CONSIDERATIONS: Intermediate metabolizers have decreased CYP2C19 function, which may inhibit the metabolism of clopidogrel. When treated with standard doses of clopidogrel, these patients may have decreased antiplatelet activity compared with extensive metabolizers. This may put them at an increased risk of cardiovascular events following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI).

The CYP2C19 metabolizer status of this patient may have implications for other medications that your patient is prescribed. Generation Health and CVS Caremark recommend that prescribers review FDA labels routinely for any updates regarding pharmacogenomic information.

CONSIDERATIONS: Other (between poor and ultrarapid) metabolizers have unknown metabolism of clopidogrel due to uncertain net effect of one copy of the gene that predicts increased enzyme activity and another that predicts decreased enzyme activity.

The CYP2C19 metabolizer status of this patient may have implications for other medications that your patient is prescribed. Generation Health and CVS Caremark recommend that prescribers review FDA labels routinely for any updates regarding pharmacogenomic information.
CONSIDERATIONS: Extensive metabolizers have normal CYP2C19 function and antiplatelet activity when treated with standard doses of clopidogrel.

All patients are at risk of cardiovascular events following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI), but there is no evidence that these patients are genetically predisposed to have an increased risk of cardiovascular events compared to baseline when treated with standard doses of clopidogrel. The CYP2C19 metabolizer status of this patient may have implications for other medications that your patient is prescribed. Generation Health and CVS Caremark recommend that prescribers review FDA labels routinely for any updates regarding pharmacogenomic information.