

# Role of cytochrome P450 genotype in the steps toward personalized drug therapy

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**Abstract:** Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, *P450* genotype results in decreased enzyme activity and an increased risk for adverse drug effects. For example, individuals with the *CYP2D6* loss-of-function genotype are at increased risk for ventricular arrhythmia if treated with usual doses of thioridazine. In other cases, *P450* genotype may influence the dose of a drug required to achieve a desired effect. This is the case with warfarin, with lower doses often necessary in carriers of a variant *CYP2C9*\*2 or \*3 allele to avoid supratherapeutic anticoagulation. When a prodrug, such as clopidogrel or codeine, must undergo hepatic biotransformation to its active form, a loss-of-function *P450* genotype leads to reduced concentrations of the active drug and decreased drug efficacy. In contrast, patients with multiple *CYP2D6* gene copies are at risk for opioid-related toxicity if treated with usual doses of codeine-containing analgesics. At least 25 drugs contain information in their US Food and Drug Administration-approved labeling regarding *P450* genotype. The *CYP2C9*, *CYP2C19*, and *CYP2D6* genes are the *P450* genes most often cited. To date, integration of *P450* genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine *P450* genotyping to assist in the treatment of their patients. Genotyping for *P450* variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, *P450* genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the *CYP2C9*, *CYP2C19*, and *CYP2D6* genes and the implications of this for drug efficacy and safety.

**Keywords:** cytochrome P450, polymorphism, allele, drug metabolism, genotype

## Introduction

It is well recognized that variation in the genes for cytochrome P450 (P450) enzymes contributes to interindividual differences in the plasma concentrations of drug substrates, resulting in interpatient variability in drug efficacy and safety. Functional polymorphism has been discovered for *CYP2A6*, *CYP1A2*, *CYP2C9*, *CYP2C19*, *CYP2D6*, and *CYP3A4/5*. At least 25 drugs now contain pharmacogenetic information related to P450 enzymes in their US Food and Drug Administration-approved labeling.<sup>1</sup> Examples of such drugs are provided in Table 1. The *P450* genes included in drug labeling are limited to *CYP2C9*, *CYP2C19*, and *CYP2D6*. Thus, this review will focus on genetic variation for the *CYP2C9*, *CYP2C19*, and *CYP2D6* enzymes and drug substrates for these enzymes.

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**Table 1** Examples of drugs with genotype information included in their US Food and Drug Administration-approved labeling<sup>1</sup>

Drug	Biomarker	Clinical implication
<b>Antidepressants, anxiolytics, and antipsychotics</b>		
Aripiprazole	CYP2D6	Increased drug exposure in CYP2D6 PMs; dose reduction is recommended
Atomoxetine	CYP2D6	Increased plasma concentrations in CYP2D6 PMs, which may increase the risk for adverse effects; dose adjustment is recommended
Clozapine	CYP2D6	Increased plasma concentrations possible in CYP2D6 PMs; clinical significance is unclear <sup>121</sup>
Diazepam	CYP2C19	Decreased enzyme activity may lead to increased sedation
Doxepine	CYP2D6	Increased plasma concentrations in CYP2D6 PMs; lower doses may be needed
Fluoxetine	CYP2D6	Increased plasma concentration of <i>S</i> -fluoxetine in PMs; clinical significance is unclear <sup>119</sup>
Protriptyline	CYP2D6	Increased plasma concentrations in CYP2D6 PMs; lower doses may be needed
Risperidone	CYP2D6	Increased plasma concentrations in CYP2D6 PMs; clinical significance is unclear <sup>121</sup>
Thioridazine	CYP2D6	Increased plasma concentrations in CYP2D6 PMs, which increases the risk for drug-induced QT-interval prolongation and arrhythmias. <sup>124</sup> Thioridazine is contraindicated in CYP2D6 PMs
Venlafaxine	CYP2D6	Increased plasma concentrations in CYP2D6 PMs; may increase the risk for adverse drug effects
<b>Analgesic drugs</b>		
Celecoxib	CYP2C9	Increased drug exposure with CYP2C9 reduced function alleles; use celecoxib with caution. Consider dose reduction in patients with the *3/*3 genotype
Codeine	CYP2D6	Decreased morphine plasma levels and analgesic effects in CYP2D6 PMs <sup>106–109</sup>
Tramadol	CYP2D6	Decreased <i>O</i> -desmethyltramadol plasma levels and analgesic effects in CYP2D6 PMs <sup>106–109</sup>
<b>Cardiovascular drugs</b>		
Carvedilol	CYP2D6	Increased plasma levels of <i>R</i> -carvedilol in CYP2D6 PMs; potential increased risk for adverse effects, such as dizziness
Clopidogrel	CYP2C19	Decreased antiplatelet effects in CYP2C19 PMs; may increase risk for adverse cardiovascular events, including stent thrombosis <sup>68,77</sup>
Metoprolol	CYP2D6	Increased plasma levels in CYP2D6 PMs; clinical significance is unclear <sup>125,126</sup>
Propafenone	CYP2D6	Increased plasma levels in CYP2D6 PMs; clinical significance is unclear
Propranolol	CYP2D6	Increased plasma levels in CYP2D6 PMs; clinical significance is unclear <sup>125,126</sup>
Warfarin	CYP2C9	Reduced <i>S</i> -warfarin clearance with a CYP2C9 reduced function allele; need for lower dose requirements; increased bleeding risk <sup>21,22,24,33</sup>
<b>Proton pump inhibitors</b>		
Omeprazole	CYP2C19	Potentially lower efficacy in CYP2C19 EMs compared to PMs <sup>92</sup>
Rabeprazole	CYP2C19	Potentially lower efficacy in CYP2C19 EMs compared to PMs <sup>93</sup>
<b>Other drugs</b>		
Cevimeline	CYP2D6	Increased plasma levels in CYP2D6 PMs; may increase risk for adverse effects; use with caution in patients with known or suspected deficiency in CYP2D6 activity
Nelfinavir	CYP2C19	Increased nelfinavir plasma levels with reduced-function CYP2C19 alleles; may reduce risk for virologic failure <sup>99</sup>
Tetrabenazine	CYP2D6	Increased plasma concentrations of the primary drug metabolites of tetrabenazine are expected in PMs compared to EMs, leading to an increased risk for adverse effects. Patients needing doses above 50 mg/day should be genotyped for <i>CYP2D6</i> variants. The maximum recommended dose if 50 mg/day, with no more than 25 mg administered in a single dose for PMs. The maximum recommended dose in EMs and IMs is 100 mg/day, with no more than 37.5 mg per dose
Tolterodine	CYP2D6	Increased plasma concentrations in CYP2D6 PMs; clinical significance is unclear

**Abbreviations:** PM, poor metabolizer; EM, extensive metabolizer; IM, intermediate metabolizer.

## CYP2C9 genotype

### Functionality of *CYP2C9* variants

The *CYP2C9* enzyme metabolizes approximately 15% of clinically used drugs, including some anticoagulants (eg, *S*-warfarin), hypoglycemics (eg, tolbutamide), angiotensin II receptor blockers (eg, losartan), antiepileptics (eg, phenytoin), and nonsteroidal anti-inflammatory drugs

(eg, diclofenac).<sup>2</sup> To date, 35 variants of the *CYP2C9* gene have been identified.<sup>3</sup> There are racial differences in the frequency of *CYP2C9* variants, as shown in Table 2.<sup>4–6</sup> The *CYP2C9*\*2 allele is common in Caucasians and results from the R144C substitution located on the exterior surface of the enzyme.<sup>7</sup> This allele leads to decreased *CYP2C9* enzyme activity in vitro, the magnitude of which ranges from 8% to

**Table 2** CYP2C9 allele frequencies by race<sup>4-6</sup>

CYP2C9 allele	Caucasians	African Americans	Asians
*2	0.13–0.14	0.02	<0.01
*3	0.06–0.11	0.01	0.02
*5	<0.01	0.01	<0.01
*6	<0.01	0.01	<0.01
*8	<0.01	0.06	<0.01
*11	<0.01	0.02–0.04	<0.01

94% depending on the CYP2C9 substrate (reviewed in Lee et al<sup>8</sup>). The CYP2C9\*3 allele is also common in Caucasians and results from the I359L substitution at the substrate recognition site of the enzyme.<sup>9</sup> This leads to a 71%–96% decrease in enzyme activity (also reviewed in Lee et al<sup>8</sup>). The decreased catalytic activities of CYP2C9\*2 and \*3 are in part due to enhanced uncoupling (ie, abortive catalytic cycle) of the reaction or a disruption of the water network in the variant enzymes.<sup>10</sup> The CYP2C9\*5, \*6, \*8, and \*11 alleles predominate in African populations, with decreased enzyme activity reported with the \*5, \*6, and \*11 alleles.<sup>11–13</sup> The CYP2C9\*8 allele is the most common of these alleles in African Americans and results from the R150H substitution in exon 3. Data on the effects of the CYP2C9\*8 allele on enzyme activity are inconsistent. Although an in vitro study showed increased tolbutamide metabolism with the CYP2C9\*8 variant compared with the wild type,<sup>13</sup> in vivo studies using phenytoin or losartan revealed decreased or no change in drug elimination in CYP2C9\*8 carriers.<sup>12,14</sup> This discrepancy may reflect substrate-specific effects of CYP2C9 variants on enzyme activity, as has been previously reported for the CYP2C9\*2 and \*3 alleles,<sup>8,15</sup> the underlying molecular mechanisms for which remain to be characterized.

### Impact of CYP2C9 genotype on warfarin response

Warfarin is the most commonly prescribed oral agent for the prevention of thromboembolism. Warfarin has a narrow therapeutic index and is dosed according to the international normalized ratio (INR), with an INR of two to three recommended for most indications.<sup>16</sup> The risk for thrombosis increases with subtherapeutic anticoagulation,<sup>17,18</sup> while the risk for bleeding increases significantly when the INR exceeds four.<sup>19</sup> Warfarin is a challenging drug to manage, largely because the dose required to achieve a therapeutic INR varies as much as 20-fold among individuals.<sup>20</sup>

Warfarin is a racemic mixture, and the more potent *S*-enantiomer is metabolized almost exclusively by CYP2C9 to the inactive 7-hydroxy metabolite. The clearance

of *S*-warfarin is reduced approximately 40% with the CYP2C9\*1/\*2 genotype, up to 75% with the \*1/\*3 genotype, and by as much as 90% with the \*3/\*3 genotype.<sup>21,22</sup> Accordingly, lower warfarin doses are generally required in the presence of a CYP2C9\*2 or \*3 allele.<sup>4,5,20,23–26</sup> For example, Taube et al<sup>27</sup> reported that patients with a variant CYP2C9\*2 or \*3 allele required between 61% and 86% of the dose needed by \*1 allele homozygotes.

Table 3 shows warfarin dose requirements by CYP2C9 genotype across racial groups according to data from the International Warfarin Pharmacogenetics Consortium, a collaboration of 21 research groups from four continents who have pooled genotype and phenotype data from over 5700 warfarin-treated patients.<sup>28,29</sup> As shown, CYP2C9 genotype influences warfarin dose requirements across racial groups. In genome-wide association studies in Caucasians, the CYP2C9\*2 and \*3 alleles were shown to explain 9%–12% of the total variability in warfarin dose requirements.<sup>30,31</sup>

African Americans are underrepresented in warfarin pharmacogenomic studies. However, recent data show significantly lower warfarin dose requirements among patients with a CYP2C9\*5, \*6, \*8, or \*11 allele compared to those with the \*1/\*1 genotype.<sup>5</sup> Specifically, among 226 African Americans, the warfarin maintenance dose was 18% lower in individuals with a CYP2C9\*5, \*6, \*8, or \*11 allele compared to those with the \*1/\*1 genotype (median dose of 5.0 mg/day versus 6.1 mg/day,  $P = 0.004$ ). The CYP2C9 genotype explained approximately 8% of the total variance in warfarin dose, just slightly less than that in Caucasians. In a recent targeted resequencing approach, Perera et al<sup>32</sup> found a novel CYP2C9 single nucleotide polymorphism in the African American genome that was associated with higher warfarin dose requirements. The 18786A > T single nucleotide polymorphism is located in intron three and occurs in 40% of African Americans. In a cohort of over 300 African

**Table 3** Median warfarin dose requirements by CYP2C9 genotype across racial groups, according to the data from the International Warfarin Pharmacogenetics Consortium<sup>29</sup>

CYP2C9 genotype	Warfarin dose requirements (mg/day)		
	Caucasians (n = 3062)	African Americans (n = 645)	Asian (n = 1063)
*1/*1	5.0	5.7	3.2
*1/*2	4.0	5.4	–
*1/*3	3.4	5.0	2.3
*2/*2	3.3	–	–
*2/*3	2.2	–	–
*3/*3	1.1	–	2.0

**Note:** The \*2 allele is rare in Asians, and the homozygous variant genotype is rare in African Americans.

Americans, investigators observed a 3.7 mg/week increase in warfarin dose requirements for each 18786T allele.

The *CYP2C9* genotype has also been implicated as a risk factor for over-anticoagulation and bleeding with warfarin.<sup>23,24,26,33</sup> Limdi et al<sup>33</sup> conducted one of the largest studies to examine bleeding risk according to *CYP2C9* genotype. Among 446 patients started on warfarin, including 227 African Americans, investigators observed 44 major bleeding events during a 2-year follow-up period. The variant *CYP2C9* \*2, \*3, \*5, \*6, and \*11 alleles conferred an increased risk of major bleeding, with an adjusted hazard ratio of 3.0 (95% confidence interval of 1.2–7.5). The bleeding risk was similar between Caucasians and African Americans. Interestingly, while the association between *CYP2C9* genotype and risk for bleeding was highest during warfarin initiation, it persisted after dose stabilization. These data suggest that bleeding should be closely monitored throughout warfarin therapy for patients with a variant *CYP2C9* allele. Based on the totality of data, *CYP2C9* variants appear to increase the bleeding risk with warfarin approximately twofold.<sup>34</sup>

There are data suggesting that *CYP2C9* gene expression changes during development, and this, in turn, may lead to age-related differences in the *CYP2C9* genotype-drug response phenotype.<sup>35</sup> In support of differential genotype effects by age, a recent study showed minimal influence of *CYP2C9* genotype on warfarin dose variability in pediatric patients.<sup>36</sup> Specifically, among 59 children (aged 1–19 years) treated with either warfarin or the vitamin K antagonist phenprocoumon, *CYP2C9* genotype explained <1% of the variability in vitamin K antagonist dose. Age was the most important predictor of dose requirement, explaining 28% of variance in dose.

Two small prospective trials and a comparative effectiveness study provide evidence of clinical benefit with genotype-guided warfarin dosing in adult populations.<sup>37–39</sup> Caraco et al<sup>37</sup> randomized 191 patients to warfarin dosing based on either clinical factors plus *CYP2C9* genotype or clinical factors alone. Genotype-guided dosing resulted in more rapid attainment of stable anticoagulation, more time spent within the therapeutic range, and a lower incidence of minor bleeding than dosing according to clinical factors alone. Similarly, Huang et al<sup>39</sup> reported that dosing based on genotypes for *CYP2C9* and vitamin K epoxide reductase complex 1 (*VKORC1*), which codes for the primary target of warfarin, improved the time to achieve stable dosing in a small Asian population.

Epstein et al<sup>38</sup> evaluated the effect of *CYP2C9* and *VKORC1* genotyping at the time of warfarin initiation on

clinical outcomes. In this comparative effectiveness study, the incidence of hospitalization was compared between a group of 896 patients offered free genotyping and a control group of nearly 2700 patients who started warfarin the previous year and were not offered genotyping. Genotype results were provided to each patient's physician with an interpretative report. Those who underwent genotyping had fewer hospitalizations for any cause and fewer hospitalizations for bleeding or thromboembolism during the 6-month follow-up period compared with controls.

Findings from these positive studies are tempered by findings from two small (n = 206–230) prospective trials of Caucasians showing no benefit with genotype-guided warfarin dosing in terms of time spent in the therapeutic INR range during the initial months of therapy.<sup>40,41</sup> Several large multicenter randomized-controlled clinical trials are underway to further assess the clinical utility of warfarin pharmacogenetics. One of the largest of these is the National Heart, Lung, and Blood Institute-sponsored Clarification of Optimal Anticoagulation Through Genetics trial.<sup>42</sup> This trial is targeting an enrollment of 1238 patients randomized to either a genotype-guided or clinical warfarin-dosing strategy. The study will assess the primary outcome of percent of time spent within the therapeutic range and is expected to be completed in early 2012.

In 2007, warfarin labeling was revised to include pharmacogenetic data. The label was further revised in 2010 to include a dosing table based on *CYP2C9* and *VKORC1* genotypes.<sup>43</sup> At least four US Food and Drug Administration-cleared genotyping assays are available for clinical use. There are also a number of published algorithms to assist clinicians with warfarin dosing when *CYP2C9* genotype is known.<sup>28,44–46</sup> However, a limitation of most genotyping assays and algorithms is that they do not include *CYP2C9* variants that are common in African Americans and thus may have lower utility in this population. Many clinicians and third-party payers are awaiting results of ongoing clinical trials before embracing genotype-guided warfarin dosing.

## *CYP2C19* genotype

### Functionality of *CYP2C19* variants

The *CYP2C19* enzyme metabolizes approximately 10% of clinically used drugs, including *S*-mephenytoin, proton pump inhibitors (PPIs), and nelfinavir. The *CYP2C19* enzyme is also responsible for biotransformation of clopidogrel to its pharmacologically active form. Genetic deficiency in *CYP2C19*-mediated *S*-mephenytoin elimination was first reported in 1979,<sup>47</sup> with the urinary excretion rate of

4-hydroxymephenytoin (a metabolite of *S*-mephenytoin produced by CYP2C19)<sup>48</sup> used to discriminate extensive metabolizers (EMs; possessing normal enzyme activity) from poor metabolizers (PMs; with reduced or absent enzyme activity) for CYP2C19 substrates.<sup>49,50</sup>

To date, 28 *CYP2C19* variants have been identified.<sup>51</sup> The *CYP2C19*\*1 allele is considered the wild-type allele, with normal enzyme activity. The *CYP2C19*\*2 allele is the primary allele responsible for the PM phenotype in Asians and Caucasians.<sup>52</sup> Other, less common, defective alleles leading to the PM phenotype include *CYP2C19*\*3 in Asians<sup>53</sup> and *CYP2C19*\*4, \*5, \*6, \*7, and \*8 in Caucasians.<sup>54</sup> The *CYP2C19*\*2 through \*8 alleles are deemed loss-of-function alleles. Both *CYP2C19*\*2 (c.681G>A) and \*3 (c.636G>A) produce a truncated nonfunctional protein. The *CYP2C19*\*2 allele results from a splicing defect in exon 5, while the *CYP2C19*\*3 allele results from a single base substitution leading to a premature stop codon in exon 4.<sup>52</sup> Various base-pair sequence changes in the *CYP2C19*\*4, \*5, \*6, \*7, and \*8 alleles negatively influence expression of the protein and catalytic activity.<sup>55</sup> However, the *CYP2C19*\*17 allele results from polymorphisms in the gene promoter region (c.99C>T and c.991A>G) and increases enzyme activity due to enhanced gene transcription. Thus, *CYP2C19*\*17 is deemed a gain-of-function allele.<sup>56</sup> *CYP2C19* genotype confers four phenotypes: extensive metabolism (\*1/\*1), poor metabolism (eg, \*2/\*2, \*2/\*3, or \*3/\*3), intermediate metabolism (eg, \*1/\*2), and ultrarapid metabolism (\*1/\*17, \*17/\*17). There are marked racial differences in the frequencies of *CYP2C19* phenotypes, as shown in Table 4, with Asians having the highest frequencies of the PM and intermediate metabolizer (IM) phenotypes.<sup>57,58</sup>

### Impact of *CYP2C19* genotype on clopidogrel effectiveness

Clopidogrel is an antiplatelet agent that is widely used in patients with cardiovascular disease. Clopidogrel, in combination with aspirin, has been shown to reduce morbidity and mortality in patients with an acute coronary syndrome

(ACS) who are either managed medically or with coronary revascularization.<sup>59–61</sup> Dual antiplatelet therapy with clopidogrel plus aspirin also reduces the risk for coronary stent thrombosis following percutaneous coronary intervention (PCI).<sup>62</sup> There is marked interpatient variability in clopidogrel's effectiveness, with approximately 25% of treated patients exhibiting residual ex vivo platelet aggregation.<sup>63</sup> These patients are at increased risk for major adverse cardiac events, including myocardial infarction and stent thrombosis.<sup>64</sup> The variability in clopidogrel response is largely attributed to interpatient differences in clopidogrel pharmacokinetics.

Clopidogrel requires hepatic bioactivation to its active thiol metabolite, which irreversibly binds to the platelet P2Y<sub>12</sub> receptor, thus inhibiting platelet activation and subsequent aggregation. Approximately 85% of the oral dose is inactivated by esterases, leaving only 15% available for hepatic bioactivation to the active metabolite. Bioactivation of clopidogrel is a two-step oxidative process, as shown in Figure 1. The CYP2C19 enzyme is involved in both oxidative steps. Reduced or absent CYP2C19 activity, secondary to either genetic polymorphism or interacting medication (eg, PPIs) results in decreased exposure to the active thiol metabolite, which, in turn, diminishes clopidogrel's effectiveness.

IMs and PMs produce approximately 30%–50% less of the active clopidogrel metabolite compared with EMs.<sup>65–68</sup> As a result, IMs and PMs may derive less protection from thrombotic events with clopidogrel. Genetic substudies of a number of large clinical trials have demonstrated a higher incidence of stent thrombosis and major adverse cardiovascular events (ie, cardiovascular death, myocardial infarction, or stroke) following ACS or PCI among clopidogrel-treated patients with the PM or IM phenotype compared with similarly treated EMs.<sup>68–76</sup>

Mega et al<sup>77</sup> conducted a meta-analysis of nine clinical trials including 9685 patients, of whom 54% had ACS and 91% underwent PCI. The hazard ratio for major adverse cardiovascular events was 1.55 (95% confidence interval 1.11–2.17) in carriers of one loss-of-function allele (IMs) and 1.76 (95% confidence interval 1.24–2.50) for carriers of two loss-of-function alleles (PMs), compared with noncarriers. Among patients who underwent PCI with stent placement, the hazard ratio for stent thrombosis was 2.67 (95% confidence interval 1.69–4.22) and 3.97 (95% confidence interval 1.75–9.02) in carriers of one or two loss-of-function alleles, respectively, compared with noncarriers.

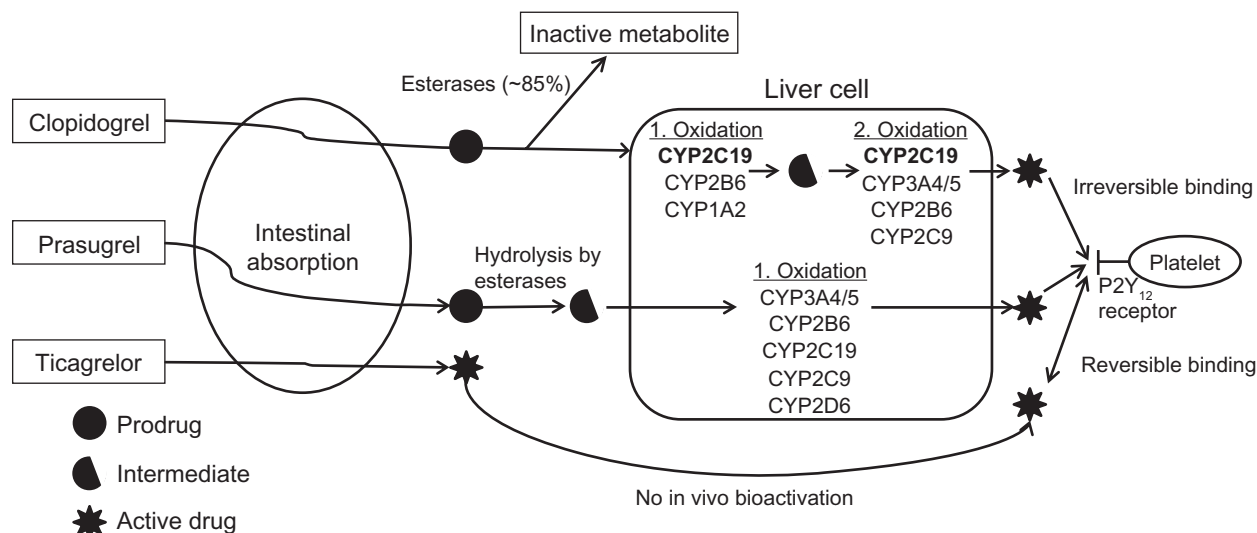
In contrast, a substudy of two large placebo-controlled trials showed no effect of *CYP2C19* loss-of-function

**Table 4** The frequency of *CYP2C19* phenotypes by race<sup>53,57,58</sup>

Race	<i>CYP2C19</i> phenotype		
	PMs	IMs	UMs
Caucasian	1%–7%	25%	40%
Asian	13%–23%	50%	<5%
African American	1%–7%	30%	45%

**Note:** Patients without the PM, IM, or UM phenotype are presumably EMs.

**Abbreviations:** PMs, poor metabolizers; IMs, intermediate metabolizers; UMs, ultrarapid metabolizers.



**Figure 1** Bioactivation and mechanism of action of clopidogrel, prasugrel, and ticagrelor. CYP2C19 (in bold) is the predominant enzyme in clopidogrel bioactivation. The P2Y<sub>12</sub> receptor on the surface of the platelet is the site of action of clopidogrel, prasugrel, and ticagrelor.

genotype on clopidogrel efficacy in the setting of ACS or atrial fibrillation.<sup>78</sup> However, there are two caveats with this substudy that are worth mentioning. First, fewer than 15% of patients with ACS underwent stent placement and none had ST segment elevation ACS. Secondly, the benefits of clopidogrel in the setting of atrial fibrillation are minimal.<sup>79</sup> Thus, while these data suggest that reduced *CYP2C19* activity does not impact clopidogrel efficacy in patients with lower-risk ACS who are predominately medically managed, an insufficient number of patients who underwent coronary revascularization were included to reach any conclusions in this higher-risk group.

There is some evidence suggesting an increased risk of bleeding with clopidogrel in ultrarapid metabolizers (UMs) with the *CYP2C19\*17* allele. Specifically, among over 1500 patients who underwent PCI and stent placement, carriers of a *CYP2C19\*17* allele had an increased risk for both major and minor bleeding with clopidogrel compared with noncarriers.<sup>58</sup> The risk for bleeding was greatest among *\*17* homozygotes, with an odds ratio of 3.27 (95% confidence interval 1.33–8.10) compared with noncarriers of the *\*17* allele.

The clopidogrel labeling was updated in March 2010 in response to reports of reduced efficacy with *CYP2C19* loss-of-function alleles.<sup>80</sup> The label warns of reduced effectiveness in PMs and states that genetic testing for reduced-function *CYP2C19* alleles is available. The label further advises health care professionals to consider alternative strategies in patients identified as PMs. However, the labeling falls short of providing recommendations on whom to genotype and what specific approaches to undertake in patients testing positive

for a loss-of-function allele. Additionally, the labeling does not address IMs, who are clearly at increased risk for adverse cardiovascular events compared with EMs, although at lower risk than PMs.

Recently, the National Institutes of Health-supported Clinical Pharmacogenetics Implementation Consortium published guidelines on genotype-guided antiplatelet therapy in cardiovascular disease.<sup>81</sup> These guidelines do not make firm recommendations about which patients should be genotyped but instead suggest two potential approaches. The first approach is to genotype all patients with ACS or undergoing PCI; the second is to target moderate-to-high-risk patients, such as those with a history of stent thrombosis, diabetes, renal insufficiency, or high-risk coronary angiographic features. In patients who have *CYP2C19* genotype data available, standard dose clopidogrel is recommended for EMs and UMs. Alternative therapy with prasugrel, ticagrelor, or cilostazol is recommended for IMs or PMs.

Similar to clopidogrel, prasugrel is a thienopyridine that irreversibly binds to the platelet P2Y<sub>12</sub> receptor and requires hepatic bioactivation (Figure 1). While CYP2C19 is involved in prasugrel bioactivation, *CYP2C19* genotype does not affect the generation of active metabolite or drug efficacy, probably because the reaction is not highly dependent on CYP2C19.<sup>66,67,82,83</sup> Ticagrelor is a recently approved reversible P2Y<sub>12</sub> antagonist that does not require hepatic bioactivation. As such, ticagrelor pharmacokinetics is not affected by *CYP2C19* genotype.<sup>84</sup> Cilostazol is a phosphodiesterase type III inhibitor shown to more effectively inhibit platelet aggregation than high-dose clopidogrel (eg, 150 mg/day) in

CYP2C19 IMs and PMs.<sup>85–87</sup> Use of high-dose clopidogrel (150 mg daily) is not recommended as an alternative therapy in PMs, based on recent data demonstrating no benefit with higher doses in patients with residual, ex vivo, platelet reactivity after PCI.<sup>81,88</sup>

**Impact of *CYP2C19* genotype on the efficacy of PPIs**  
PPIs, including omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole, are partially metabolized by CYP2C19. Loss-of-function *CYP2C19* alleles result in higher plasma concentrations of PPIs and greater suppression of gastric acid.<sup>89–91</sup> Consistent with these data, higher *Helicobacter pylori* eradication rates are achieved with both dual (PPI and amoxicillin) and triple (PPI, amoxicillin, and clarithromycin) therapy in patients with a defective *CYP2C19* allele. Specifically, reported cure rates with standard dose omeprazole (20 mg/day) plus amoxicillin were 100%, 60%, and 29%, in PMs, IMs, and EMs, respectively.<sup>92</sup> Rabeprazole 10 mg twice daily plus amoxicillin provided better *H. pylori* cure rates; although differences by genotype were observed (94%, 92%, and 61% in PMs, IMs, and EMs, respectively).<sup>93</sup> Using a higher dose of rabeprazole (10 mg four times daily) effectively eradicated *H. pylori* for EMs who failed initial therapy.<sup>93</sup> Triple therapy that included omeprazole 20 mg or lansoprazole 30 mg twice daily produced cure rates of 98%–100% for PMs but only 73%–86% in EMs.<sup>94,95</sup> Of EMs who failed triple therapy, a 97% *H. pylori* eradication was achieved with high-dose lansoprazole (30 mg four times daily) and amoxicillin.<sup>94</sup>

*CYP2C19* genotype also impacts the effectiveness of PPIs for gastroesophageal reflux disease. Among patients with gastroesophageal reflux disease treated with lansoprazole 30 mg daily for 8 weeks, cure rates of mucosal breaks were 85% in PMs, 60% in IMs, and 46% in EMs.<sup>96</sup> Those with the EM phenotype and the most erosive esophagitis achieved cure rates of only 17%.

Similar to *CYP2C9*, there is evidence that *CYP2C19* gene expression changes with development, with adult expression levels reached by age 10.<sup>35</sup> As a consequence, the *CYP2C19* genotype-PPI response relationship may differ between adult and pediatric patients. In support of this, a single-dose pharmacokinetic study in children showed no effect of *CYP2C19* genotype on omeprazole pharmacokinetics.<sup>97</sup> In contrast, *CYP2C19* genotype clearly impacts omeprazole levels in adults.<sup>91</sup>

Information regarding *CYP2C19* genotype is included in the drug interaction and clinical pharmacology sections of rabeprazole and esomeprazole labels.<sup>1</sup> The data suggest that

use of higher PPI doses will overcome reduced effectiveness in EMs.<sup>93,94</sup> Dosing strategies for PPIs based on *CYP2C19* genotype have been proposed for rabeprazole: 20 mg/day for PMs, 20 mg twice daily for IMs, and 10 mg four times daily for EMs.<sup>98</sup>

**Impact of *CYP2C19* genotype on nelfinavir response in human immunodeficiency virus (HIV)**

Nelfinavir is metabolized by CYP2C19 to the hydroxyl-tertbutylamide (M8) metabolite. *CYP2C19* genotype can influence the bioavailability of nelfinavir, with lower oral clearance with the \*2 allele.<sup>99</sup> Saitoh et al<sup>99</sup> examined the effect of *CYP2C19* genotype on antiviral response to nelfinavir in 152 children taking highly active antiretroviral therapy. At 24 weeks, presence of the *CYP2C19*\*2 allele was associated with a greater likelihood of achieving plasma HIV RNA < 400 copies/mL; 46%, 69%, and 63% of patients with the \*1/\*1, \*1/\*2, and \*2/\*2 genotypes, respectively, achieved concentrations <400 copies/mL. Others have reported a trend toward decreased virologic failure with the *CYP2C19*\*2 allele.<sup>100</sup> Information regarding *CYP2C19* genotype is included in the drug interaction and clinical pharmacology sections of the nelfinavir label. However, no recommendations are provided regarding genetic testing.

## CYP2D6 genotype

### Discussion of clinically relevant variants

The CYP2D6 enzyme metabolizes about 25% of clinically used drugs from many different drug classes including antidepressants, antipsychotics, antihypertensives, and analgesics. Since early reports of a population exhibiting defective metabolism of debrisoquine or sparteine (CYP2D6 substrates) as a result of genotype,<sup>101,102</sup> genetic polymorphisms leading to different CYP2D6 phenotypes have been extensively studied. Based on the extent of CYP2D6 substrate metabolism, the population is largely divided into four different groups, listed in order of decreasing CYP2D6 activity: UMs, EMs, IMs, and PMs. EMs carry at least one *CYP2D6* allele showing normal enzyme function, IMs carry one *CYP2D6* allele showing reduced function and another with no CYP2D6 function, and PMs carry two nonfunctional *CYP2D6* alleles.<sup>103</sup> UMs, however, carry multiple copies of functional *CYP2D6* genes.<sup>104</sup> The *CYP2D6*\*1, \*2, and \*4 alleles are the most common alleles associated with the gene duplication and multiduplication. There are racial differences in the frequency of *CYP2D6* alleles (Table 5). Ethiopian and Saudi Arabian populations have an unusually high (10%–16%) frequency of

**Table 5** Major *CYP2D6* variants

Allele	Gene mutation(s)	Consequence of mutation on <i>CYP2D6</i> activity	Allele frequency (%)		
			Caucasian	African American	Asian
<i>CYP2D6</i> *1	Wild type	Normal	22–32	29–36	43–55
<i>CYP2D6</i> *2	R296C, S486T	Normal	22	4–14	0–2
<i>CYP2D6</i> *4	Splicing defect	Absent	20–21	2–8	1
<i>CYP2D6</i> *5	<i>CYP2D6</i> deletion	Absent	2–7	4–6	6
<i>CYP2D6</i> *10	P34S, S486T	Decreased	1–2	2–6	38–70
<i>CYP2D6</i> *17	T107I, R296C, S486T	Decreased	0–1	16–35	0
<i>CYP2D6</i> *29	V136I, R296C, V338M, S486T	Decreased	0–1	5–8	NR
<i>CYP2D6</i> *41	–1584G > C, splicing defect	Decreased	8	2	0–2
<i>CYP2D6</i> xn	Gene duplication or multiduplication	Increased	1–5	2–5	0–1

**Note:** Data from Bradford et al,<sup>103</sup> Sim,<sup>141</sup> Cai et al,<sup>142</sup> and Sachse et al.<sup>143</sup>

**Abbreviation:** NR, not reported.

*CYP2D6* gene duplication when compared with populations in other African or Asian countries, the cause of which has not been elucidated.<sup>105</sup>

### Impact of *CYP2D6* genotype on response to opioid analgesics

Codeine and tramadol are prodrugs requiring conversion via *CYP2D6* to their therapeutically active metabolites, morphine and *O*-desmethyltramadol, respectively. Poor *CYP2D6* metabolizers achieve lower metabolite concentrations and experience minimal analgesic relief with usual doses of these drugs.<sup>106–109</sup> In contrast, patients with *CYP2D6* gene duplication and the UM phenotype are at risk for toxic plasma concentrations of the morphine and *O*-desmethyltramadol metabolites after taking codeine or tramadol, respectively.<sup>110–112</sup> Indeed, there are reports of severe respiratory depression and abdominal pain in patients treated with codeine-containing analgesics, who were subsequently found to have the UM phenotype.<sup>111,112</sup> In addition, serious opioid-related toxicity and even death have been reported in breastfed infants of mothers with the UM phenotype.<sup>113</sup> These data suggest that codeine- and tramadol-containing analgesics should be reserved for patients with the EM phenotype to avoid analgesic failure in PMs and toxicity in UMs.

### Impact of *CYP2D6* genotype on response to antidepressants and antipsychotics

The *CYP2D6* enzyme is involved in the metabolism of secondary (eg, protriptyline, nortriptyline) and tertiary (eg, doxepine) tricyclic antidepressants. The PM phenotype has been correlated with greater tricyclic antidepressant plasma concentrations and lower dose requirements.<sup>114,115</sup> In contrast, extremely low nortriptyline concentrations have been observed in patients with multiple *CYP2D6* gene copies.<sup>116</sup> Tricyclic antidepressant doses two to five times higher than normally

recommended may be necessary to achieve therapeutic plasma concentrations in UMs.<sup>117,118</sup> Pharmacogenetic information is included in the labeling of doxepine and protriptyline (Table 1). Lower doses of these drugs should be considered in patients with a reduced-function *CYP2D6* allele.<sup>1</sup>

The *CYP2D6* genotype has also been associated with plasma concentrations of various selective serotonin reuptake inhibitors (SSRIs), such as paroxetine and fluoxetine.<sup>119</sup> For example, Charlier et al<sup>120</sup> reported significantly higher steady-state plasma concentrations of paroxetine and fluoxetine among PMs compared with EMs. However, results from various pharmacokinetic studies are inconsistent, and there is no clear correlation between *CYP2D6* genotype and clinical response.<sup>119</sup> In a systematic review of 37 research articles, Thakur et al<sup>119</sup> concluded that data are insufficient to support *CYP2D6* genotyping to guide SSRI prescribing.

Evidence to support *CYP2D6* genotyping to predict efficacy of antipsychotic therapy is also limited.<sup>121</sup> However, there are data supporting an association between *CYP2D6* polymorphisms and antipsychotic toxicity. The *CYP2D6* enzyme extensively metabolizes the typical (eg, haloperidol, perphenazine, and thioridazine) and atypical (eg, risperidone, clozapine, and aripiprazole) antipsychotics. Higher plasma concentrations of antipsychotics, including perphenazine, haloperidol, thioridazine, and risperidone, are observed in individuals with reduced-function *CYP2D6* alleles compared with EMs.<sup>122,123</sup> In a meta-analysis of prospectively designed studies, Fleeman et al<sup>121</sup> reported that antipsychotic-treated patients with a nonfunctional *CYP2D6* allele were at higher risk for tardive dyskinesia (odds ratio of 1.83, 95% confidence interval 1.09–3.08) and parkinsonism (odds ratio of 1.64, 95% confidence interval 1.04–2.58) compared with EMs.<sup>121</sup> However, the authors concluded that the differences observed by genotype were small and probably not of clinical significance.



Pharmacogenetic information is included in the labeling of thioridazine, clozapine, and aripiprazole. The language is strongest for thioridazine, which has the potential to prolong the QT interval in a dose-dependent manner, thus increasing the risk for life-threatening ventricular arrhythmias. The CYP2D6 PM phenotype is correlated with greater QT interval prolongation during thioridazine therapy.<sup>124</sup> As such, thioridazine is contraindicated in patients known to have reduced CYP2D6 activity. Recommendations for other antipsychotics are shown in Table 1.

### Impact of CYP2D6 genotype on response to $\beta$ -blockers

Beta-blockers are metabolized by CYP2D6, and CYP2D6 polymorphisms have significant effects on  $\beta$ -blocker plasma concentrations.<sup>125,126</sup> However, data regarding the clinical significance of CYP2D6 genotype on  $\beta$ -blocker response are inconsistent. For example, Rau et al<sup>125</sup> reported significantly higher metoprolol plasma concentrations in PMs versus EMs (70 ng/mL versus 14 ng/mL), despite similar drug doses. This translated into greater reductions in heart rate and diastolic blood pressure in PMs. In contrast, Terra et al<sup>126</sup> found that, while S-metoprolol plasma concentrations differed significantly by CYP2D6 genotype among heart failure patients, genotype had no effect on  $\beta$ -blocker tolerability, heart rate, or systolic blood pressure response. Beta-blockers have a wide therapeutic index and thus genes affecting drug disposition may have minimal effects on drug response. Genes for drug target proteins may be more likely to be of clinical significance for  $\beta$ -blockers and other drugs with a wide therapeutic index. Indeed, polymorphisms in the gene encoding for the  $\beta_1$ -adrenergic receptor are associated with clinical response to  $\beta$ -blockers in both hypertension and heart failure.<sup>127,128</sup>

### Impact of CYP2D6 genotype on outcomes with tamoxifen therapy

Tamoxifen is widely prescribed for estrogen receptor-positive breast cancer. Tamoxifen requires biotransformation to its active 4-hydroxytamoxifen and endoxifen metabolites, which possess potent antiestrogenic effects. The CYP2D6 enzyme is a key enzyme in tamoxifen bioactivation. Tamoxifen metabolite levels are inversely correlated with the number of defective CYP2D6 alleles.<sup>129,130</sup> The CYP2D6 genotype is estimated to explain 39% and 9% of the variability in endoxifen and 4-hydroxytamoxifen plasma concentrations, respectively.<sup>129</sup>

The ability to metabolize tamoxifen has been associated with treatment outcomes.<sup>131</sup> In over 1300 patients with

estrogen receptor-positive breast cancer, treatment with tamoxifen resulted in greater disease recurrence in patients with a reduced or loss-of-function CYP2D6 allele compared with those with normal enzyme activity. The highest recurrence rates occurred in patients with two loss-of-function (\*3, \*4, or \*5) alleles (PMs), who had a nearly twofold higher incidence of recurrence (29% in PMs versus 14.9% in EMs). Similarly, patients with a reduced-function allele had worse event-free survival (hazard ratio 1.33, 95% confidence interval 1.06–1.68) and disease-free survival (hazard ratio 1.29, 95% confidence interval 1.03–1.61) than EMs. Other studies have shown similarly deleterious effects of CYP2D6 variant alleles on clinical outcomes with tamoxifen.<sup>132–134</sup> However, the data are inconsistent and, in one case, conflicting.<sup>135,136</sup> The discrepancies in the data may be secondary to factors other than CYP2D6 genotype influencing plasma concentrations of tamoxifen metabolites.<sup>130</sup> While data exist to support genotype-guided adjuvant endocrine therapy, the clinical utility of such an approach is currently unclear.<sup>137,138</sup>

## Clinical relevance of P450 polymorphism

The potential consequences of P450 polymorphisms range from serious toxicity to ineffective drug therapy. Genetically determined reductions in P450 enzyme activity may have important implications for narrow-therapeutic-index drugs such as warfarin, where increased plasma concentrations contribute to drug toxicity. For prodrugs, such as codeine and clopidogrel, deficient enzyme activity can prevent the attainment of therapeutic drug plasma concentrations and lead to treatment failure. However, CYP2D6 gene duplication can lead to toxic reactions with codeine due to accumulation of the active morphine metabolite. For drugs with a wide therapeutic index, such as SSRIs and  $\beta$ -blockers, the clinical implications of P450 gene variation are less significant.

To date, clinicians have been slow to embrace pharmacogenetics, despite the addition of pharmacogenetic information in the labeling for many drugs. Two notable exceptions include clopidogrel and opioid analgesics. Vanderbilt University Medical Center, Nashville, TN, recently announced efforts to genotype for CYP2C19 variants in all patients with a high likelihood of requiring potent antiplatelet therapy in the future.<sup>139</sup> Genotype results are placed in the electronic medical record so that they may be used to assist in choosing appropriate antiplatelet therapy in the event of an ACS or PCI. Similarly, clinicians at St Jude Children's Research Hospital, Memphis, TN, test patients for CYP2D6 genotype to individualize analgesic therapy.<sup>140</sup>

Genotypes for the CYP2C9, CYP2C19, and CYP2D6 enzymes have minimal implications for disease susceptibility, as opposed to drug response. Specifically, an inherited deficiency in CYP2C9 may go completely undetected during an individual's lifetime unless that individual is prescribed a narrow therapeutic index drug, such as warfarin, that relies on CYP2C9 for metabolism. Similarly, a person with inactive CYP2D6 may suffer no untoward effects unless exposed to a drug such as thioridazine that can produce deleterious cardiac consequences in CYP2D6 PMs. Thus, *P450* genotyping may pose less ethical concerns than genotyping for disease-associated variants. As such, *P450* genotyping is likely to lead the way in the clinical implementation of pharmacogenomics, as evidenced by current efforts at Vanderbilt University and St Jude Children's Hospital. Genotyping arrays that broadly detect variation in multiple *P450* genes are commercially available. Given the breadth of drugs that require P450 metabolism, use of such arrays may prove to be a feasible approach to broad implementation of *P450* genotype-guided drug therapy.

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