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Applied Pharmacogenomics in Cardiovascular Medicine

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Abstract

Interindividual heterogeneity in drug response is a central feature of all drug therapies. Studies in individual patients, families, and populations over the past several decades have identified variants in genes encoding drug elimination or drug target pathways that in some cases contribute substantially to variable efficacy and toxicity. Important associations of pharmacogenomics in cardiovascular medicine include clopidogrel and risk for in-stent thrombosis, steady-state warfarin dose, myotoxicity with simvastatin, and certain drug-induced arrhythmias. This review describes methods used to accumulate and validate these findings and points to approaches—now being put in place at some centers—to implementing them in clinical care.

Keywords

personalized medicine; genetics; polymorphisms; clopidogrel; warfarin; statin

INTRODUCTION

Half of all Americans take at least one prescription drug monthly (1). Variability in efficacy is nearly universal across drugs. Also variable is susceptibility to serious adverse drug reactions (ADRs), which have been implicated as a leading cause of death in the United States (2).

Pharmacogenomics is the science of understanding interindividual variation in drug response as a function of underlying genetic architecture. The field has its roots in traditional translational medicine—identifying the mechanisms of unusual responses to drug therapy in individual subjects. Recent advances in informatics, genetics, and sequencing throughput are increasing our understanding of the molecular, cellular, and genetic determinants of drug responses and hold the promise of realizing a vision of genome-enabled healthcare. Furthermore, discovery of genetic variants that modulate human physiology or drug

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RELATED RESOURCES

Pharmacogenomics knowledge resource: <http://www.pharmgkb.org>

A Catalog of Published Genome-Wide Association Studies: <http://www.genome.gov/gwasstudies/>

Pharmacogenomics Research Network (PGRN): <http://www.pgrn.org>

response can point to targets for development of new drugs. These advances are having an impact across multiple disciplines in medicine (see sidebar, Pharmacogenomics Beyond the Heart); the present review describes progress in understanding genomic variability in response to commonly used cardiovascular drugs (Figure 1), and how this knowledge may be used in clinical care.

PRINCIPLES

Hippocrates stated that “when a patient’s unique idiosyncrasia is known, then it is feasible to custom tailor the treatment” (3). Rather than a “one size fits all” approach, personalized medicine involves a tailoring of diagnostic and treatment strategies based on individual patient characteristics. Clinicians have been personalizing care for centuries in response to features such as patient attitudes, age, comorbid conditions and therapies, and educational levels. A modern vision of personalized medicine builds on these principles and incorporates genetic information into clinical decision making to improve the precision, safety, and efficacy of drug therapy.

Common modulators of variable drug responses include genes affecting a drug’s plasma or tissue concentrations (pharmacokinetics) or its effects (pharmacodynamics). In addition, variation in specific genes involved in the disease being treated can also affect drug outcomes. Two approaches are commonly used to identify the contribution of underlying genetic variation to a given drug-response phenotype. The first, a hypothesis-driven “candidate gene” approach, is one in which an understanding of underlying pharmacokinetics or pharmacodynamics drives selection of specific genes and variants to be tested for association with the variable drug response. The second, an agnostic “hypothesis free” approach, interrogates large sets of genomic variants without regard to a priori knowledge and tests these for association with the drug response. The most widely used hypothesis-free approach is the genome-wide association study (GWAS), in which a large number (now usually >1,000,000) of common single-nucleotide polymorphisms (SNPs) are genotyped in hundreds or thousands of patients and the association with a phenotype such as drug response analyzed. The emerging approach of resequencing whole genes, pathways, or genomes may identify rarer SNPs and other genetic variants associated with drug response.

ANTITHROMBOTICS

Warfarin

The widely used vitamin K antagonist warfarin is administered as a racemate, and the more potent (S)-enantiomer is bioinactivated by the cytochrome P450 (CYP) enzyme CYP2C9. Carriers of common *CYP2C9* SNPs that reduce enzymatic activity require lower average warfarin dose requirements (4, 5). In Caucasians, two common loss-of-function polymorphisms in *CYP2C9* are associated with impaired ability to metabolize warfarin (~30% impairment with *2, rs1799853 and ~90% with *3, rs1057910) compared with the *1 reference allele (6). Moreover, a higher risk of bleeding and lower warfarin dose requirements have been reported in carriers of the *2 or *3 alleles compared to noncarriers (5, 7, 8).

Vitamin K epoxide reductase subunit 1 (encoded by *VKORC1*) is the target protein with which warfarin interacts to produce its therapeutic effect. Two common SNPs, rs9923231 (–1639G>A) and rs9934438 (–1173C>T), located in the promoter region of the gene and in almost perfect linkage disequilibrium in Caucasians, modulate hepatic *VKORC1* mRNA transcript abundance, and individuals with lower *VKORC1* expression require lower warfarin dosages to achieve stable anticoagulation, whereas individuals with SNPs leading to greater expression require greater steady-state dosages (9–13). Up to 60% of the variability in a steady-state warfarin dose requirement can be explained by clinical factors plus common variants in *CYP2C9* and *VKORC1*. In addition, rare *VKORC1* polymorphisms that cause a change in the amino acid sequence of the protein (“nonsynonymous polymorphisms”) are associated with increased warfarin dose requirements (14).

Warfarin pharmacogenomics also highlights the critical role of ancestry in drug responses. Steady-state doses are generally lower in Asian subjects largely because the *VKORC1* reduced-function variants are common, whereas greater dosages are required in African subjects because increased-function *VKORC1* promoter variants are more common. In addition, *CYP2C9**2/*3 variants are less common in subjects of African descent and thus explain less of the overall dosing variability in these subjects than in Caucasians; other *CYP2C9* SNPs (*CYP2C9**5, *6, *8, and *11) may contribute in African subjects (15).

GWAS have also implicated the V433M variant in *CYP4F2* as an independent predictor of warfarin dosing variability (16, 17). *CYP4F2* catalyzes the metabolism of reduced vitamin K by removing vitamin K from the vitamin K cycle and acts as a counterpart to *VKORC1* in limiting excessive accumulation of vitamin K (18).

Two small randomized controlled trials (RCTs) (19, 20) and a nonrandomized cohort study using historical controls (21) have provided evidence of improved outcomes such as time to steady-state dosing when genetic information is incorporated into prediction algorithms compared to standard dosing (21–24). The National Heart Lung and Blood Institute has completed enrollment in COAG, an RCT comparing warfarin outcomes in patients treated conventionally and those treated with a pharmacogenomically driven algorithm; initial results should be available in late 2013 (25).

Newer factor Xa and direct thrombin inhibitors have been developed to improve efficacy, reduce bleeding risk, and increase convenience of dosing by eliminating a need for dose adjustment. One of these, dabigatran, is a prodrug bioactivated by carboxylesterase, and an analysis of genomic data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial has implicated a common variant in carboxylesterase 1 (*CES1*, rs2244613) as a modulator of bleeding risk (26).

Clopidogrel

Clopidogrel (Figure 2), widely used in diverse settings including percutaneous coronary intervention (PCI), is a prodrug that requires hepatic biotransformation via multiple CYPs, notably *CYP2C19*, to form the pharmacologically active metabolite(s) that binds irreversibly to the adenosine diphosphate receptor encoded by *P2RY12*, thereby inhibiting platelet aggregation (27).

Genetic variation within *CYP2C19* is consistently associated with variable clopidogrel response (28). The strongest evidence is related to the common loss-of-function allele *CYP2C19**2 [681 G>A, rs4244285, which encodes a cryptic splice variant with no enzymatic activity in vivo (29)]. *CYP2C19**2 is associated with impaired clopidogrel bioactivation (30–32), decreased antiplatelet activity (30, 33–36), and increased risk of adverse cardiac events (31, 37–41). A large meta-analysis (31) identified an increased risk of major adverse cardiovascular events in carriers of the *CYP2C19**2 variant undergoing PCI. Carriers of the *CYP2C19**2 allele had a greater risk of the composite endpoint of cardiovascular death, myocardial infarction, and stroke [heterozygous carriers: hazard ratio (HR)=1.55, 95% confidence interval (CI) 1.11–2.17; homozygous carriers: HR=1.76, CI 1.24–2.50] (39). The risk of in-stent thrombosis was especially increased [heterozygous carriers: HR=2.67, CI 1.69–4.22; homozygous carriers: HR = 3.97, CI 1.75–9.02]. Although this and some other studies have reported findings suggestive of a graded gene-dose relationship between the number of *CYP2C19**2 alleles and the risk of sustaining a cardiovascular event (31, 36, 37), others have not replicated the finding; this may reflect small study numbers, since homozygotes for the *2 allele are uncommon (~2%) in Caucasian populations (42, 43). Another large meta-analysis included more subjects but with diverse indications for clopidogrel, and did not identify a strong signal with *CYP2C19**2 (44). One possibility is that the effect of the drug is greatest in patients undergoing PCI, and therefore the effect of genomic variation is also most easily detected in this group (45). A GWAS in a large Amish population estimated that inhibition of platelet aggregation by clopidogrel was ~75% heritable but that *CYP2C19**2 accounted for only ~12% of the overall variation in platelet aggregation among clopidogrel-treated subjects (36). The extent to which the *3 (rs498693), *4 (rs28399504), and *5 (rs72552267) alleles contribute is unknown; these loss-of-function alleles have minor allele frequencies (MAFs) below 1% in Caucasians, but *3 is common in Asian populations (MAF 2%–9%). The *17 (rs1248560) variant has been implicated as a gain-of-function allele, and carriers exhibit increased *CYP2C19* activity, greater platelet inhibition, and possibly increased bleeding risk (46, 47). Variants in *ABCB1* and *P2YR12* (see Figure 2) have been associated with variable clopidogrel responsiveness, but the findings have been inconsistent or not reproduced. One very small study also associated *PON1* variants with impaired clopidogrel response, but multiple other reports have failed to replicate this finding (48).

In 2010, the US Food and Drug Administration (FDA) revised the clopidogrel label to include a black box warning of decreased efficacy in *CYP2C19**2 homozygotes. However, an American College of Cardiology/American Heart Association task force decided not to recommend routine *CYP2C19* testing (49), arguing the evidence was insufficient. Recognizing that genetic testing—including preemptive testing described below—is becoming increasingly widespread, the Clinical Pharmacogenetics Implementation Consortium (CPIC) provides guidelines, including for clopidogrel (48), on how to treat patients in whom genetic-variant data have already been obtained (Table 1).

CHOLESTEROL-LOWERING THERAPY

There is substantial interindividual variability in response to treatment with 3-hydroxy-3-methylglutaryl HMG-CoA reductase (HMGCR) inhibitors, commonly known as statins. One-

third of statin-treated patients do not obtain clinically desired reductions in low-density lipoprotein cholesterol (LDLc) (50). In addition, rare severe adverse drug reactions can occur (51). Important factors affecting statin outcomes include genetic variability, as well as environmental factors and compliance (52).

Variability in Statin Response

Variants in *HMGCR* and *LDLR* have been associated with a decrease in LDLc lowering (53–56). Variation in other genes has also been associated inconsistently with variability in statin responsiveness. These include *APOE*, encoding a protein that interacts with the LDL receptor; *CYP3A4*, encoding a key drug-metabolizing enzyme; and *ABCB1* and *ABCG2*, encoding drug transporters. Multiple reports associated a missense variant, Trp719Arg (rs20455), in kinesin-like protein 6 (encoded by *KIF6*) with increased risk of coronary events, improved LDLc response to pravastatin, and a ~30% reduction in relative risk of cardiovascular events compared to noncarriers who were also treated with pravastatin (57, 58). However, these associations have been questioned (59, 60). Rare variants in *PCSK9* have been associated with low LDLc and decreased coronary disease, and the protein is now being targeted to develop new cholesterol-lowering agents (61).

The most common ADR during statin therapy is muscle pain or myalgia (1%–5%), which is sometimes accompanied by increases in plasma creatine kinase (CK) levels. True statin-induced rhabdomyolysis is much rarer (incidence ~ 1/1,000,000) and carries a 10% mortality rate (52, 62). Risk factors include high statin doses (e.g., 80 mg/day simvastatin), drug interactions, and genetic factors. Early candidate studies implicated variants in *CYP3A5* (63) and *SLCO1B1* (64). *SLCO1B1* encodes the polypeptide organic anion transporter OATP1B1, involved in hepatic statin uptake (52). A GWAS that compared 85 individuals who developed myalgia and elevated CK while on high-dose simvastatin (80 mg/day) to 90 controls tolerating high doses identified a signal at genome-wide significance for a SNP near *SLCO1B1* that was in linkage disequilibrium with rs4149056, a previously studied nonsynonymous variant resulting in V174A (65). In an additive model, heterozygous carriers of the rs4149056 risk allele had an odds ratio (OR) of 4.5 (CI 2.6–7.7) per risk allele for developing myalgia over five years and homozygous carriers had an OR of 16.9 (CI 4.7–61.1), compared to noncarriers. Sixty percent of the myalgia risk identified was attributable to rs4149056, and most cases occurred in the first year of treatment. Subsequently, rs4149056 was also shown to influence simvastatin adherence, suggesting that some patients stop the drug due to myalgia (66). In 2011 the FDA announced an update to the simvastatin product label recommending that the 80-mg/day dose not be used because of the risk of myalgia.

Given the FDA warning against high-dose simvastatin unless the patient has tolerated >12 months of treatment, which is when the majority of simvastatin-related myalgia is encountered, routine screening for V174A prior to simvastatin initiation seems impractical. However, if genotype information is available before simvastatin initiation, the CPIC recommends that CK levels be monitored among heterozygous and homozygous risk allele carriers in conjunction with a reduced simvastatin dose (20 mg/day) (67). Alternatively,

carriers should be placed on another statin, as the evidence is strongest regarding simvastatin (68).

β-Blockers

Two common nonsynonymous polymorphisms in the β-1-adrenergic receptor gene (*ADBR1*), resulting in S49G (rs1801252) and R389G (rs1801253), are associated with the clearest evidence for modulating β-blocker action (69). In vitro, G49 is more susceptible to agonist-promoted downregulation than S49 (70), and the R389 form of the receptor couples more efficiently to G protein than does the G389 variant (71, 72). In vivo, one study reported that homozygous carriers of the R389 genotype experienced greater improvements in left ventricular ejection fraction following β-blocker therapy (carvedilol and metoprolol) than did individuals with other genotypes (73). Improved outcome in R389 homozygotes was also reported in the β-Blocker Evaluation of Survival Trial (BEST), a large study of bucindolol in heart failure patients (74, 75). As a result, a superiority trial designed to assess the safety and efficacy of bucindolol in ~3,200 homozygous R389 heart failure patients is planned. Improved antihypertensive response to β-blockers was also reported among homozygous R389 carriers (76, 77).

The β-2-adrenergic receptor is encoded by *ADBR2*. Two common *ADBR2* polymorphisms, R16G (rs1042713) and Q27G (rs1042714), are resistant to agonist-mediated downregulation (78). Associations between common *ADRB2* polymorphisms and altered clinical cardiovascular outcomes have been reported but have not been replicated (79, 80).

CYP2D6 metabolizes some commonly used β-blockers (e.g., propranolol, timolol, and metoprolol) and propafenone, an antiarrhythmic with β-blocking properties. There are many loss-of-function variants in the gene, and individuals who carry two loss-of-function alleles, ~7% of Caucasians and Africans, are termed poor metabolizers. Rarer individuals carry multiple functional copies of the gene and are termed ultrarapid metabolizers, and the remainder are extensive metabolizers. Poor metabolizers have higher metoprolol and propafenone concentrations than extensive metabolizers (81), a difference associated with increased risk for bradyarrhythmias or bronchospasm. There is some evidence that the poor metabolizers may be at increased risk for ADRs (82), and the FDA has added a statement to the metoprolol and carvedilol labels to this effect.

G protein–coupled receptor kinases (GRKs) desensitize β-adrenergic receptors. The L41Q variant in *GRK5* blunts the effects of catecholamines and is associated with improved outcomes in heart failure compared to noncarriers (Q41Q) (83). Although L41 is more common among individuals of African ancestry, the benefit associated with the polymorphism is seen across multiple ancestries (84).

ANTIHYPERTENSIVES

Among patients treated with angiotensin-converting enzyme inhibitors (ACEi), homozygous carrier status for a common insertion/deletion (I/D) (rs4646994) in *ACE* has been associated with improved 10-year outcomes compared to noncarriers (I/I), but this association has not been replicated (85, 86). ACEi-related angioedema is commoner in African than in

Caucasian subjects, and initial studies have implicated a variant in *XPNPEP2* (rs3788853, C-2399A), encoding aminopeptidase P (87). Among thiazide users, a common nonsynonymous variant in the adducin gene (*ADD1*, Gly460Trp) has been inconsistently associated with thiazide response (88). Genetic variants producing large signals for variability in responses to antihypertensives have not yet been identified, and so clinical implementation would be premature.

ARRHYTHMIAS

Exaggerated drug-induced QT interval prolongation is a predictor of the malignant arrhythmia torsades de pointes (TdP) and is a common cause of drug relabeling or withdrawal. Variation in genes associated with the congenital form of the long QT syndrome (cLQTS) appears overrepresented in acquired long QT cases (89–93). A large candidate-gene study found that the D85N variant in the potassium channel subunit gene *KCNE1* conferred an odds ratio of 9–12 for this ADR(90). Another study implicated variants in *NOS1AP*, a gene known to modulate baseline QT interval, as risk factors for amiodarone-induced TdP (94).

CONCLUSIONS

A rapidly growing set of data links genetic variation to variable drug responses. Key factors in establishing the strength of such associations are allele frequency, effect size, and population size (Figure 1). The strongest evidence is obtained when large numbers of subjects are studied, and this may not be possible for some drug-response phenotypes. Establishing an association between a drug response and a genetic variant may be especially problematic if the drug response is uncommon, like some ADRs, and the risk alleles are rare. Most studies to date have concentrated on subjects of Caucasian ancestry, although risk alleles may be different, and have different frequencies, in other ancestries. Once a potential association is identified, replication in larger numbers is desirable; networks using electronic medical records (EMRs) have been proposed as one potential approach (95). The advent of cheap sequencing technologies is showing that most human genetic variants are rare, and establishing the functions of rare variants will be a challenge to genomics and pharmacogenomics going forward.

A very appealing idea is that pharmacogenomic data can be used to individualize therapy. Physicians can select drugs and drug dosages based on anticipated therapeutic responses and risks for ADRs. It has been argued that this approach will be valid only after RCTs demonstrate its utility. A common counterargument is that for many decisions in clinical medicine, such as adjusting the dose of a renally excreted drug in a patient with renal dysfunction, RCTs have never been done to demonstrate utility; furthermore, expecting an RCT for each of hundreds or thousands of potentially actionable variants is unrealistic.

Logistics and cost are also considerations. Obtaining a genotype relevant to a single drug when that drug is prescribed may add considerably to the cost for all patients prescribed the drug, to potentially benefit only the few who carry a risk allele. An alternative is a preemptive strategy, such as the Vanderbilt PREDICT project (96). The idea is first to

identify subjects who are “at risk” for receiving drugs that have clinically important variable effects due to genetic variants. Efforts to identify subjects at risk can use informatics tools developed by examining large numbers of subjects (96) or can simply use the disease being treated, e.g., subjects about to undergo joint replacement are “at risk” for receiving warfarin and subjects about to have coronary arteriography are “at risk” for receiving clopidogrel. Once subjects are identified, they are genotyped on a platform that includes many pharmacogenomic variants relevant to many drugs, and the data are stored in a genetic archive. Those variants with the strongest levels of evidence (determined by CPIC guidelines and institutional oversight) are displayed in the EMR, and informatics-based decision support is delivered when a patient with a relevant genetic variant is prescribed a target drug. As new evidence accumulates, more drug-gene pairs are deployed from the archive into the EMR. This preemptive approach has the potential advantages of bringing down costs and recognizing that pharmacogenomic considerations will not be relevant for most patients receiving most drugs but that all patients carry potentially deleterious alleles, some of which will be highly relevant to some drugs.

New sequencing technologies have brought the cost of sequencing whole genomes below \$2,000, but how to use these data to better care for patients is an ongoing question (97). Although it seems likely that drug therapy will be one of the first areas to benefit from this genomic revolution, continued rigorous scientific discovery in individual subjects, families, and large cohorts remains the major challenge and opportunity in the field.

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Glossary

ADR	adverse drug reaction
CPIC	Clinical Pharmacogenetics Implementation Consortium

References

1. Gu Q, Dillon CF, Burt VL. Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. NCHS Data Brief. 2010:1–8.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998; 279:1200–1205. [PubMed: 9555760] Adverse drug effects may account for >100,000 deaths annually in the United States, making them the fourth to sixth leading cause of death.
3. Sykiotis GP, Kalliolias GD, Papavassiliou AG. Pharmacogenetic principles in the Hippocratic writings. J. Clin. Pharmacol. 2005; 45:1218–1220. [PubMed: 16239353]
4. Kim MJ, Huang SM, Meyer UA, et al. A regulatory science perspective on warfarin therapy: a pharmacogenetic opportunity. J. Clin. Pharmacol. 2009; 49:138–146. [PubMed: 19179293]
5. Aithal GP, Day CP, Kesteven PJ, et al. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet. 1999; 353:717–719. [PubMed: 10073515] One of the first studies to show that carriers of *CYP2C9**2 and

*3 require lower steady-state dosages and have an increasing risk of bleeding during long-term therapy; the latter observation remains unexplained.

6. Rettie AE, Haining RL, Bajpai M, et al. A common genetic basis for idiosyncratic toxicity of warfarin and phenytoin. *Epilepsy Res.* 1999; 35:253–255. [PubMed: 10413320]
7. Lindh JD, Holm L, Andersson ML, et al. Influence of CYP2C9 genotype on warfarin dose requirements—a systematic review and meta-analysis. *Eur. J. Clin. Pharmacol.* 2009; 65:365–375. [PubMed: 19031075]
8. Cooper GM, Johnson JA, Langaee TY, et al. A genome-wide scan for common genetic variants with a large influence on warfarin maintenance dose. *Blood.* 2008; 112:1022–1027. [PubMed: 18535201]
9. Ross KA, Bigham AW, Edwards M, et al. Worldwide allele frequency distribution of four polymorphisms associated with warfarin dose requirements. *J. Hum. Genet.* 2010; 55:582–589. [PubMed: 20555338]
10. Wadelius M, Chen LY, Lindh JD, et al. The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood.* 2009; 113:784–792. [PubMed: 18574025]
11. Wang D, Chen H, Momary KM, et al. Regulatory polymorphism in vitamin K epoxide reductase complex subunit 1 (VKORC1) affects gene expression and warfarin dose requirement. *Blood.* 2008; 112:1013–1021. [PubMed: 18523153]
12. Rost S, Fregin A, Ivaskevicius V, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature.* 2004; 427:537–541. [PubMed: 14765194]
Study of families with little anticoagulation at high warfarin dosages identified mutations in *VKORC1*. This finding led to the identification of *VKORC1* as the target protein for warfarin action.
13. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. *N. Engl. J. Med.* 2005; 352:2285–2293. [PubMed: 15930419] First study to identify variation in hepatic mRNA levels as a function of *VKORC1* promoter haplotype.
14. Scott SA, Edelmann L, Kornreich R, et al. Warfarin pharmacogenetics: CYP2C9 and VKORC1 genotypes predict different sensitivity and resistance frequencies in the Ashkenazi and Sephardi Jewish populations. *Am. J. Hum. Genet.* 2008; 82:495–500. [PubMed: 18252229]
15. Allabi AC, Gala JL, Horsmans Y. CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population. *Pharmacogenet. Genomics.* 2005; 15:779–786. [PubMed: 16220110]
16. Takeuchi F, McGinnis R, Bourgeois S, et al. A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS Genet.* 2009; 5:e1000433. [PubMed: 19300499]
17. Caldwell MD, Awad T, Johnson JA, et al. CYP4F2 genetic variant alters required warfarin dose. *Blood.* 2008; 111:4106–4112. [PubMed: 18250228]
18. Danese E, Montagnana M, Johnson JA, et al. Impact of the CYP4F2 p.V433M polymorphism on coumarin dose requirement: systematic review and meta-analysis. *Clin. Pharmacol. Ther.* 2012; 92:746–756. [PubMed: 23132553]
19. Anderson JL, Horne BD, Stevens SM, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). *Circulation.* 2012; 125:1997–2005. [PubMed: 22431865] An RCT suggesting that pharmacogenetically guided warfarin therapy provides superior outcomes compared to a clinical algorithm only.
20. Caraco Y, Blotnick S, Muszkat M. CYP2C9 genotype-guided warfarin prescribing enhances the efficacy and safety of anticoagulation: a prospective randomized controlled study. *Clin. Pharmacol. Ther.* 2008; 83:460–470. [PubMed: 17851566]
21. Epstein RS, Moyer TP, Aubert RE, et al. Warfarin genotyping reduces hospitalization rates: results from the MM-WES (Medco-Mayo Warfarin Effectiveness study). *J. Am. Coll. Cardiol.* 2010; 55:2804–2812. [PubMed: 20381283]
22. Finkelman BS, Gage BF, Johnson JA, et al. Genetic warfarin dosing: tables versus algorithms. *J. Am. Coll. Cardiol.* 2011; 57:612–618. [PubMed: 21272753]

23. Gage BF, Eby C, Johnson JA, et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. *Clin. Pharmacol. Ther.* 2008; 84:326–331. [PubMed: 18305455]
24. Johnson JA, Gong L, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin. Pharmacol. Ther.* 2011; 90:625–629. [PubMed: 21900891]
25. French B, Joo J, Geller NL, et al. Statistical design of personalized medicine interventions: the Clarification of Optimal Anticoagulation through Genetics (COAG) trial. *Trials.* 2010; 11:108. [PubMed: 21083927]
26. Pare G, Eriksson N, Lehr T, et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation.* 2013; 127:1404–1412. [PubMed: 23467860]
27. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab. Dispos.* 2010; 38:92–99. [PubMed: 19812348]
28. Hulot JS, Bura A, Villard E, et al. Cytochrome P450 2C19 loss-of-function polymorphism is a major determinant of clopidogrel responsiveness in healthy subjects. *Blood.* 2006; 108:2244–2247. [PubMed: 16772608] The first report to implicate variation in *CYP2C19* as a modulator of clopidogrel action.
29. Goldstein JA. Clinical relevance of genetic polymorphisms in the human CYP2C subfamily. *Br. J. Clin. Pharmacol.* 2001; 52:349–355. [PubMed: 11678778]
30. Kim KA, Park PW, Hong SJ, et al. The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance. *Clin. Pharmacol. Ther.* 2008; 84:236–242. [PubMed: 18323861]
31. Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. *N. Engl. J. Med.* 2009; 360:354–362. [PubMed: 19106084]
32. Umemura K, Furuta T, Kondo K. The common gene variants of CYP2C19 affect pharmacokinetics and pharmacodynamics in an active metabolite of clopidogrel in healthy subjects. *J. Thromb. Haemost.* 2008; 6:1439–1441. [PubMed: 18532997]
33. Fontana P, Hulot JS, De Moerloose P, et al. Influence of CYP2C19 and CYP3A4 gene polymorphisms on clopidogrel responsiveness in healthy subjects. *J. Thromb. Haemost.* 2007; 5:2153–2155. [PubMed: 17697139]
34. Brandt JT, Close SL, Iturria SJ, et al. Common polymorphisms of CYP2C19 and CYP2C9 affect the pharmacokinetic and pharmacodynamic response to clopidogrel but not prasugrel. *J. Thromb. Haemost.* 2007; 5:2429–2436. [PubMed: 17900275]
35. Frere C, Cuisset T, Morange PE, et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. *Am. J. Cardiol.* 2008; 101:1088–1093. [PubMed: 18394438]
36. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA.* 2009; 302:849–857. [PubMed: 19706858]
37. Collet JP, Hulot JS, Pena A, et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. *Lancet.* 2009; 373:309–317. [PubMed: 19108880]
38. Simon T, Verstuyt C, Mary-Krause M. Genetic determinants of response to clopidogrel and cardiovascular events. *N. Engl. J. Med.* 2009; 360:363–375. [PubMed: 19106083]
39. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA.* 2010; 304:1821–1830. [PubMed: 20978260] A meta-analysis defining the risk associated with loss of *CYP2C19* alleles in patients being treated for percutaneous coronary interventions.
40. Trenk D, Hochholzer W, Fromm MF, et al. Cytochrome P450 2C19 681G> A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. *J. Am. Coll. Cardiol.* 2008; 51:1925–1934. [PubMed: 18482659]

41. Delaney JT, Ramirez AH, Bowton E, et al. Predicting clopidogrel response using DNA samples linked to an electronic health record. *Clin. Pharmacol. Ther.* 2012; 91:257–263. [PubMed: 22190063]
42. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 2009; 361:1045–1057. [PubMed: 19717846]
43. Pare G, Mehta SR, Yusuf S, et al. Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N. Engl. J. Med.* 2010; 363:1704–1714. [PubMed: 20979470]
44. Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA.* 2011; 306:2704–2714. [PubMed: 22203539]
45. Johnson JA, Roden DM, Lesko LJ, et al. Clopidogrel: a case for indication-specific pharmacogenetics. *Clin. Pharmacol. Ther.* 2012; 91:774–776. [PubMed: 22513313]
46. Sibbing D, Koch W, Gebhard D, et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. *Circulation.* 2010; 121:512–518. [PubMed: 20083681]
47. Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet.* 2010; 376:1320–1328. [PubMed: 20801498]
48. Scott SA, Sangkuhl K, Gardner EE, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy. *Clin. Pharmacol. Ther.* 2011; 90:328–332. [PubMed: 21716271]
49. Holmes DR Jr, Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA “boxed warning”: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *Circulation.* 2010; 122:537–557. [PubMed: 20585015]
50. Davidson MH, Maki KC, Pearson TA. Results of the National Cholesterol Education (NCEP) Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey and implications for treatment under the recent NCEP Writing Group recommendations. *Am. J. Cardiol.* 2005; 96:556–563. [PubMed: 16098311]
51. Law M, Rudnicka AR. Statin safety: a systematic review. *Am. J. Cardiol.* 2006; 97:52C–60C.
52. Mangravite LM, Thorn CF, Krauss RM. Clinical implications of pharmacogenomics of statin treatment. *Pharmacogenomics J.* 2006; 6:360–374. [PubMed: 16550210]
53. Chasman DI, Posada D, Subrahmanyam L, et al. Pharmacogenetic study of statin therapy and cholesterol reduction. *JAMA.* 2004; 291:2821–2827. [PubMed: 15199031]
54. Krauss RM, Mangravite LM, Smith JD, et al. Variation in the 3-hydroxyl-3-methylglutaryl coenzyme A reductase gene is associated with racial differences in low-density lipoprotein cholesterol response to simvastatin treatment. *Circulation.* 2008; 117:1537–1544. [PubMed: 18332269]
55. Medina MW, Gao F, Ruan W, et al. Alternative splicing of 3-hydroxy-3-methylglutaryl coenzyme A reductase is associated with plasma low-density lipoprotein cholesterol response to simvastatin. *Circulation.* 2008; 118:355–362. [PubMed: 18559695]
56. Mangravite LM, Medina MW, Cui J, et al. Combined influence of LDLR and HMGCR sequence variation on lipid-lowering response to simvastatin. *Arterioscler. Thromb. Vasc. Biol.* 2010; 30:1485–1492. [PubMed: 20413733]
57. Iakoubova OA, Sabatine MS, Rowland CM, et al. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. *J. Am. Coll. Cardiol.* 2008; 51:449–455. [PubMed: 18222355]
58. Iakoubova OA, Tong CH, Rowland CM, et al. Association of the Trp719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary heart disease in 2 prospective trials: the CARE and WOSCOPS trials. *J. Am. Coll. Cardiol.* 2008; 51:435–443. [PubMed: 18222353]
59. Assimes TL, Holm H, Kathiresan S, et al. Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and coronary artery disease in 19 case-control studies. *J. Am. Coll. Cardiol.* 2010; 56:1552–1563. [PubMed: 20933357]

60. Hopewell JC, Parish S, Clarke R, et al. No impact of KIF6 genotype on vascular risk and statin response among 18,348 randomized patients in the heart protection study. *J. Am. Coll. Cardiol.* 2011; 57:2000–2007. [PubMed: 21458191]
61. Cohen JC, Hobbs HH. Simple genetics for a complex disease. *Science.* 2013; 340:689–690. [PubMed: 23661745] A narrative describing how identification of variants in *PCSK9* led to new drug development.
62. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003; 289:1681–1690. [PubMed: 12672737]
63. Wilke RA, Moore JH, Burmester JK. Relative impact of CYP3A genotype and concomitant medication on the severity of atorvastatin-induced muscle damage. *Pharmacogenet. Genomics.* 2005; 15:415–421. [PubMed: 15900215]
64. Pasanen MK, Neuvonen M, Neuvonen PJ, et al. *SLCO1B1* polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet. Genomics.* 2006; 16:873–879. [PubMed: 17108811]
65. Link E, Parish S, Armitage J, et al. *SLCO1B1* variants and statin-induced myopathy—a genomewide study. *N. Engl. J. Med.* 2008; 359:789–799. [PubMed: 18650507] A GWAS identifying an *SLCO1B1* risk allele conferring high risk for simvastatin-related myopathy.
66. Voora D, Shah SH, Spasojevic I, et al. The *SLCO1B1**5 genetic variant is associated with statin-induced side effects. *J. Am. Coll. Cardiol.* 2009; 54:1609–1616. [PubMed: 19833260]
67. Wilke RA, Ramsey LB, Johnson SG, et al. The Clinical Pharmacogenomics Implementation Consortium: CPIC guideline for *SLCO1B1* and simvastatin-induced myopathy. *Clin. Pharmacol. Ther.* 2012; 92:112–117. [PubMed: 22617227]
68. Puccetti L, Ciani F, Auteri A. Genetic involvement in statins induced myopathy. Preliminary data from an observational case-control study. *Atherosclerosis.* 2010; 211:28–29. [PubMed: 20347093]
69. Muthumala A, Drenos F, Elliott PM, et al. Role of beta adrenergic receptor polymorphisms in heart failure: systematic review and meta-analysis. *Eur. J. Heart Fail.* 2008; 10:3–13. [PubMed: 18158268]
70. Rathz DA, Brown KM, Kramer LA, et al. Amino acid 49 polymorphisms of the human beta1-adrenergic receptor affect agonist-promoted trafficking. *J. Cardiovasc. Pharmacol.* 2002; 39:155–160. [PubMed: 11791000]
71. Johnson JA, Liggett SB. Cardiovascular pharmacogenomics of adrenergic receptor signaling: clinical implications and future directions. *Clin. Pharmacol. Ther.* 2011; 89:366–378. [PubMed: 21289619]
72. Mason DA, Moore JD, Green SA, et al. A gain-of-function polymorphism in a G-protein coupling domain of the human beta1-adrenergic receptor. *J. Biol. Chem.* 1999; 274:12670–12674. [PubMed: 10212248]
73. Chen L, Meyers D, Javorsky G, et al. Arg389Gly-beta1-adrenergic receptors determine improvement in left ventricular systolic function in nonischemic cardiomyopathy patients with heart failure after chronic treatment with carvedilol. *Pharmacogenet. Genomics.* 2007; 17:941–949. [PubMed: 18075464]
74. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. *Proc. Natl. Acad. Sci. USA.* 2006; 103:11288–11293. [PubMed: 16844790] β -Blocker Evaluation of Survival Trial (BEST), a large study of bucindolol in heart failure patients.
75. Bristow MR, Murphy GA, Krause-Steinrauf H, et al. An alpha2C-adrenergic receptor polymorphism alters the norepinephrine-lowering effects and therapeutic response of the beta-blocker bucindolol in chronic heart failure. *Circ. Heart Fail.* 2010; 3:21–28. [PubMed: 19880803]
76. Karlsson J, Lind L, Hallberg P, et al. Beta1-adrenergic receptor gene polymorphisms and response to beta1-adrenergic receptor blockade in patients with essential hypertension. *Clin. Cardiol.* 2004; 27:347–350. [PubMed: 15237695]
77. Liu J, Liu ZQ, Yu BN, et al. Beta1-adrenergic receptor polymorphisms influence the response to metoprolol monotherapy in patients with essential hypertension. *Clin. Pharmacol. Ther.* 2006; 80:23–32. [PubMed: 16815314]

78. Green SA, Turki J, Innis M. Amino-terminal polymorphisms of the human beta 2-adrenergic receptor impart distinct agonist-promoted regulatory properties. *Biochemistry*. 1994; 33:9414–9419. [PubMed: 7915137]
79. de Groote P, Helbecque N, Lamblin N, et al. Association between beta-1 and beta-2 adrenergic receptor gene polymorphisms and the response to beta-blockade in patients with stable congestive heart failure. *Pharmacogenet. Genomics*. 2005; 15:137–142. [PubMed: 15861037]
80. Small KM, Wagoner LE, Levin AM, et al. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. *N. Engl. J. Med.* 2002; 347:1135–1142. [PubMed: 12374873]
81. Rau T, Heide R, Bergmann K, et al. Effect of the CYP2D6 genotype on metoprolol metabolism persists during long-term treatment. *Pharmacogenetics*. 2002; 12:465–472. [PubMed: 12172215]
82. Bijl MJ, Visser LE, van Schaik RH, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clin. Pharmacol. Ther.* 2009; 85:45–50. [PubMed: 18784654]
83. Liggett SB, Cresci S, Kelly RJ, et al. A GRK5 polymorphism that inhibits beta-adrenergic receptor signaling is protective in heart failure. *Nat. Med.* 2008; 14:510–517. [PubMed: 18425130]
84. Cresci S, Kelly RJ, Cappola TP, et al. Clinical and genetic modifiers of long-term survival in heart failure. *J. Am. Coll. Cardiol.* 2009; 54:432–444. [PubMed: 19628119]
85. Brugts JJ, Isaacs A, Boersma E, et al. Genetic determinants of treatment benefit of the angiotensin-converting enzyme-inhibitor perindopril in patients with stable coronary artery disease. *Eur. Heart J.* 2010; 31:1854–1864. [PubMed: 20538738]
86. Harrap SB, Tzourio C, Cambien F, et al. The ACE gene I/D polymorphism is not associated with the blood pressure and cardiovascular benefits of ACE inhibition. *Hypertension*. 2003; 42:297–303. [PubMed: 12925557]
87. Woodard-Grice AV, Lucisano AC, Byrd JB, et al. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet. Genomics*. 2010; 20:532–536. [PubMed: 20625347]
88. Johnson JA. Pharmacogenomics of antihypertensive drugs: past, present and future. *Pharmacogenomics*. 2010; 11:487–491. [PubMed: 20350127]
89. Paulussen AD, Gilissen RA, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J. Mol. Med. (Berl.)*. 2004; 82:182–188. [PubMed: 14760488]
90. Kaab S, Crawford DC, Sinner MF. A large candidate gene survey identifies the KCNE1 D85N polymorphism as a possible modulator of drug-induced torsades de pointes. *Circ. Cardiovasc. Genet.* 2012; 5:91–99. [PubMed: 22100668]
91. Ramirez AH, Shaffer CM, Delaney JT, et al. Novel rare variants in congenital cardiac arrhythmia genes are frequent in drug-induced torsades de pointes. *Pharmacogenomics J.* 2012; 13:325–329. [PubMed: 22584458]
92. Yang P, Kanki H, Drolet B, et al. Allelic variants in long-QT disease genes in patients with drug-associated torsades de pointes. *Circulation*. 2002; 105:1943–1948. [PubMed: 11997281]
93. Itoh H, Sakaguchi T, Ding WG, et al. Latent genetic backgrounds and molecular pathogenesis in drug-induced long-QT syndrome. *Circ. Arrhythm. Electrophysiol.* 2009; 2:511–523. [PubMed: 19843919]
94. Jamshidi Y, Nolte IM, Dalageorgou C, et al. Common variation in the NOS1AP gene is associated with drug-induced QT prolongation and ventricular arrhythmia. *J. Am. Coll. Cardiol.* 2012; 60:841–850. [PubMed: 22682551]
95. McCarty CA, Chisholm RL, Chute CG, et al. The eMERGE Network: a consortium of biorepositories linked to electronic medical records data for conducting genomic studies. *BMC Med. Genomics*. 2011; 4:13. [PubMed: 21269473]
96. Schildcrout JS, Denny JC, Bowton E, et al. Optimizing drug outcomes through pharmacogenetics: a case for preemptive genotyping. *Clin. Pharmacol. Ther.* 2012; 92:235–242. [PubMed: 22739144]
97. Manolio TA, Chisholm RL, Ozenberger B, et al. Implementing genomic medicine in the clinic: the future is here. *Genet. Med.* 2013; 15:258–267. [PubMed: 23306799]

PHARMACOGENOMICS BEYOND THE HEART

The scenarios outlined here for cardiovascular therapies are being repeated across multiple disciplines: varying levels of evidence and replication, common variants with modest to large effects, rarer variants with very large effects. HLA-B variants conferring high risk for serious adverse drug reactions have now been identified for allopurinol, carbamazepine, and abacavir. Cancer is a disease of genomic instability, and variants in tumor genomes are serving not only as biomarkers for prognosis but also as targets for new drugs that can provide surprising efficacy. Tumor genotyping is becoming standard of care for drug selection in certain cancers. The influence of the microbiome on development of a range of diseases—cancer, atherogenesis, obesity, and asthma and other immune conditions, to name a few—is only now being appreciated and exploited for individualized therapy. Pharmacogenomics is emerging from its adolescence and is poised to contribute to improved drug therapy across medicine.

SUMMARY POINTS

1. Interindividual variability in drug response exists for all types of drug therapy.
2. For some drugs, single common variants with large effect sizes contribute to variable drug actions.
3. Polymorphisms in *CYP2C19* modulate cardiovascular outcomes, particularly risk of instant thrombosis, among patients undergoing treatment with clopidogrel.
4. Polymorphisms in *VKORC1* and *CYP2C9* modulate steady-state warfarin dose requirements.
5. Polymorphisms in *SLCO1B1* are associated with myotoxicity among simvastatin-treated patients.
6. Genotyping for common variants modulating drug response is entering practice at some centers.
7. Pharmacogenomic signals may represent potential targets for drug discovery.

FUTURE ISSUES

1. Response to drug therapy is multifactorial. Examples to date focus on single common variants, and the warfarin example shows that variants in more than one gene can be analyzed. How can we predict the effects of multiple variants, especially if they have directionally differing predicted effects?
2. Serious adverse drug reactions are uncommon, and risk alleles may have large effect sizes but be rare. Thus, methods to accrue enough samples to identify these variants need to be refined.
3. The randomized controlled trial (RCT) is the gold standard for defining efficacy of new drugs or therapeutic approaches. However, RCTs in pharmacogenomics require participation by many subjects in order to identify the few who carry variants being evaluated. It seems unrealistic to propose RCTs for hundreds of target variants. Although potential advantages of implementation may seem self-evident, hidden risks (e.g., withholding an effective drug) also need to be evaluated. Thus, the optimal way in which to evaluate the utility of pharmacogenomic implementation remains in flux.

Figure 1.

The continuum from initial scientific discovery to evidence development and consolidation, with the ultimate goal of implementing new knowledge in clinical care. The position of the arrows is a rough indicator of progress for each of the listed drug responses. Abbreviations: LDLc, low-density lipoprotein cholesterol; ACEi, angiotensin-converting enzyme inhibitor.

Figure 2.

Pharmacogenomic basis for variability in clopidogrel action. (a) There is variability in the extent to which ADP results in platelet aggregation at baseline (*left*). With exposure of platelets to clopidogrel (*right*), the effect of ADP is blunted as expected, but variability in response persists. Reproduced from Reference 36 with permission. (b) Potential genetic mechanisms underlying variability in clopidogrel action. Clopidogrel is a prodrug and undergoes bioactivation in the liver using the enzymes shown, notably CYP2C19. The active metabolites interact with the ADP receptor on platelets to inhibit ADP-induced

platelet aggregation. (c) Data on distribution of loss-of-function variants (predominantly CYP2C19*2) in a cohort of 12,451 subjects in the Vanderbilt PREDICT program described in the text.

Table 1

Genotype-phenotype assignment and suggested clinical implications of common *CYP2C19* variants for clopidogrel therapy (adapted from Reference 46 with permission)

Carrier genotype	Inferred metabolizer phenotype	Implication	Clinical Pharmacogenetics Implementation Consortium guideline
2/*2, *2/*3, *3/*3	poor	significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events	*2/*2: prasugrel or other alternative therapy unless clinically contraindicated
*1/*2, *1/*3	intermediate	increased residual platelet aggregation;	*1/*2: prasugrel or other alternative therapy unless clinically contraindicated
*1/*1	extensive	normal platelet inhibition and residual platelet aggregation	standard dosing of clopidogrel
*1/*17, *17/*17	ultra-rapid	increased platelet inhibition; decreased residual platelet aggregation;	standard dosing of clopidogrel