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Emerging Clinical Applications in Cardiovascular Pharmacogenomics

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Over one fourth of the 36 million annual outpatient prescriptions filled in the United States are associated with known human genomic biomarker information impacting drug safety and efficacy, or both.¹ To date, we have not effectively used this valuable data to improve patient outcomes in clinical practice. Much of the difficulty stems from the hesitancy of the medical community to adopt and translate data gleaned in basic and translational research to clinical medicine. Claims of lack of adequate prospective studies showing superior outcomes, reduced toxicity, and cost savings with pharmacogenetic approaches are commonly used explanations.^{2–5} In addition, the false positive results that plagued early pharmacogenetic studies have further added to clinicians' cynicism.⁶

However, over the last three years, we have seen substantial improvements in genotyping that allow for simultaneous assaying of hundreds of thousands of common single nucleotide polymorphisms (SNPs) in an unbiased 'hypothesis-free' approach.^{7, 8} Such technology has leveraged information from the Human Genome Project and more recently the common tag SNPs identified by the HapMap Consortium.⁹ Genome-wide association studies (GWAS) using these SNPs have now identified and validated common variants that affect drug metabolism, response, and toxicity in a number of highly significant diseases.^{10–14} Most importantly, these results have been independently validated and replicated in thousands of subjects. Furthermore, unlike the modest odds ratios seen with susceptibility loci now linked to over one hundred complex traits, SNPs associated with drug efficacy and adverse events have been highly significant with risk ratios greater than 50 fold in particular cases.^{14, 15} Herein, we aim to detail the most clinically compelling and robust examples of pharmacogenomic algorithms emerging in the field of cardiovascular medicine and to hopefully foretell how cardiovascular disease will be approached in an era of pharmacogenomic medicine.

Pharmacogenetics versus Pharmacogenomics

Prior to embarking on a review of the clinical applications generated by pharmacogenomic studies, we must first understand the transition that has occurred from pharmacogenetics to pharmacogenomics. For the last several decades, genetic studies have selectively investigated polymorphisms in only single or multiple candidate genes based on known biologic activity of these variants.⁷ This pharmacogenetic-based process precludes the discovery of genes with yet unknown but potentially substantial impact on drug absorption, metabolism, excretion, and receptor affinity. It is this omission with the candidate approach to gene discovery that has frequently led to an inability to replicate findings across

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independent populations and hence numerous false positive results. On the other hand, with pharmacogenomic methods, we are able to simultaneously assay hundreds of thousands of SNPs across the entire genome for common variation that significantly alters drugs pharmacokinetic and pharmacodynamic responses. This methodology serves two vital purposes. First, it allows for discovery of polymorphisms in genes with novel mechanisms in drug response biology not previously known. Second, its agnostic approach to gene discovery has led to the unbiased identification of many genetic variants, which have subsequently been widely replicated in independent cohorts.

Going forward, the dramatic reduction in cost for DNA sequencing will provide yet another transformative change in genomic medicine. Extensive and rapid high-throughput sequencing of the genome in large cohorts will allow for pharmacogenomic studies that identify rare SNPs contributing to drug response. Together, these common and rare SNPs will be complementary and incremental with regards to prediction of efficacy and risk for toxicity when initiating therapy. Such SNP data should significantly bolster efforts to implement truly individualized medicine.

The Clopidogrel Story

The adjunctive use of the antiplatelet agent clopidogrel with aspirin has substantially reduced the risk of recurrent ischemia, stent thrombosis, and death in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI) with coronary stents.¹⁶⁻¹⁸ However, in 2006, a variable antiplatelet response from clopidogrel was noted in healthy individuals harboring hepatic cytochrome (CYP) 2C19 gene variants.¹⁹ Several large subsequent studies involving thousands of patients have since extended these initial findings to individuals with ACS.^{10, 20-22} Effects from the common loss-of-function variants include reduced active metabolite formation of clopidogrel leading to a significantly diminished antiplatelet effect and a corresponding three-fold increase in the risk for stent thrombosis and death. In addition recent data have now also linked common gain-of-function variants to close to a doubling in risk for bleeding.²³ Remarkably, these variants are present in over a third of Europeans with the loss-of-function alleles being present in close to half in those with African and Asian ancestry.

These results initially discovered using candidate gene approaches were confirmed when Shuldiner and colleagues conducted a GWA study to integrate and reconcile all existing data on clopidogrel responsiveness.¹⁰ Platelet aggregation was measured in over 400 individuals at baseline and within 1 hour following the last dose of clopidogrel on day 7. Subsequently, over 400,000 SNPs were assayed for association with platelet reactivity. Polymorphisms with the greatest impact (1.5×10^{-13}) on clopidogrel response were in high linkage disequilibrium with the known CYP2C19 variants. Most importantly, these SNPs did not impact platelet response prior to the administration of clopidogrel, thereby confirming the CYP2C19 locus as the major genetic mediator of clopidogrel response. Further, at one year, the investigators documented greater than a three-fold increase in the risk for stent thrombosis and death in CYP2C19 carriers, which closely mirrors results seen in previous genomic studies of clopidogrel response.

The most compelling aspect of this story is not only the heightened risk for adverse cardiovascular events associated with CYP2C19 genetic variants, but also the readily available alternatives to standard clopidogrel therapy that include doubling of the clopidogrel maintenance dose or administering multiple and higher loading doses.^{24, 25} Further, prasugrel, a recently approved thienopyridine similar to clopidogrel but without the variability in antiplatelet effect is another viable alternative.²⁶ However, the most promising emerging agent is the reversible platelet inhibitor, ticagrelor.²⁷

In a recent head-to-head study with clopidogrel, ticagrelor reduced the risk of stent thrombosis by 50%.²⁷ Most importantly, those taking ticagrelor also received a significant reduction in mortality, which is the first time such a benefit for dual antiplatelet therapy has been demonstrated. However, prior to deriving a final conclusion on ticagrelor's clinical superiority, several considerations regarding this trial must be addressed. Foremost, genotyping for CYP2C19 alleles was not performed prior to patient randomization to the clopidogrel arm of the study. Furthermore, the vast majority of participants were of European descent of which 30% or more carry resistant genotypes. Therefore, it is likely that the net clinical benefit of ticagrelor is conferred only in those individuals genetically predisposed to clopidogrel resistance. These facts and the anticipated generic availability of clopidogrel in 2011 will maintain clopidogrel's preferred status in those with wild type CYP2C19 alleles.

Clopidogrel therapy represents the prototypic example of a much needed pharmacogenomic algorithm in cardiovascular medicine. It is a highly prescribed medicine used in a procedure performed in millions of patients annually around the world.²⁸ Most importantly, readily available alternatives to clopidogrel can be easily integrated into pharmacogenetic algorithms that involve genotyping patients for susceptibility variants, which can then be followed with selecting the right antiplatelet agent for the right patient. Such a strategy could easily prevent the devastating clinical outcomes that accompany stent thrombosis, bleeding, and myocardial infarction.

Warfarin

Warfarin is the most commonly used blood thinner in the world with over 20 million prescriptions filled annually in the United States.²⁹ It is standard of care for the prophylaxis of thrombotic events in individuals with mechanical heart valves, atrial fibrillation, deep vein thrombosis, and host of hypercoagulable states. Unfortunately, its narrow therapeutic window and widely varying dosage (5-80mg) range has contributed to a large number of fatal and nonfatal bleeding events. On average, major bleeding events in those on warfarin occur at a rate of 1-2% placing hundreds of thousands of patients at heightened risk for significant morbidity and mortality.^{29, 30} Hence, there has been great interest in developing strategies to predict appropriate dosing and dose response in individual patients.

There are a multitude of variables known to impact warfarin dosing including diet, alcohol intake, body mass, coexisting illnesses and genes. Given the difficulty controlling the former variables, there has been increased interest in leveraging the individual's fixed genomic make-up. Common genetic polymorphisms in the hepatic cytochrome (CYP2C9) system and the enzyme vitamin K epoxide reductase (VKOR) have been implicated in warfarin response and in particular warfarin associated bleeding.³¹ Hepatic CYP2C9 mediates activation of warfarin from its inactive precursor with common variants (*2 and *3) conferring a three-fold increase in risk for bleeding. These common variants are present in approximately 30% of those of European descent and a much lower rate in those with African and Asian ancestry.³¹

On the other hand, VKOR regenerates the reduced form of vitamin K, which is essential for the carboxylation and activation of vitamin K dependent clotting factors II, VII, IX, and X (Figure 1).³² Warfarin effectively inhibits VKOR. Currently, over 10 polymorphisms in VKOR are represented by 2 common haplotypes (A,B) with the A haplotype individuals on average using lower mean maintenance doses (2.7 mg/d) of warfarin and the B haplotype higher doses (6.2 mg/d).³² Those of Asian descent more commonly carry the A haplotype versus the B haplotype, which is more common in those with European or African descent. Together, the VKORC1 and CYP2C9 genetic variants account for one-third of the

interindividual variation in warfarin dose requirements.^{3, 32} Most recently, Eckman and colleagues calculated an average hazard ratio of 3.01 for major bleeding in patients carrying both at-risk loci.³

At first glance, the data supporting pharmacogenetic algorithms in warfarin dosing appear incontrovertible. However, recent data from two elegantly conducted studies refute such an approach.^{3, 33} Klein and colleagues demonstrated that pharmacogenetic dosing conferred a net benefit only in those requiring extremes of dosing (< 21mg or > 49mg). Of those patients, only of minority (~35%) fell within 20% of the actual stable effective dose in the validation cohort compared to a clinical algorithm where 24% fell within the effective stable dose. In addition, the current estimate for pharmacogenetic-based algorithms for warfarin place the cost per quality adjusted life year at greater than \$170,000 – a number far beyond the traditionally accepted \$50,000.³ Advocates for routine warfarin genotyping may cite a recent Medco-Mayo comparative effectiveness study that demonstrated a significant reduction of hospitalizations for bleeding and thromboembolism in patients treated with a genotype-based algorithm.³⁴ However, the study design had significant flaws and has not adequately addressed many of the issues noted above. In particular, the use of a historical control group and the extremely long delay in turnaround of genotyping results (~ 30 days) prevent the extrapolation of these results to clinical settings.

Eckman and colleagues³ go on to suggest that a hybrid approach to dosing that includes initiation of warfarin based on clinical variables followed by refined dosing once genomic information returns may reduce the cost and improve outcomes. However, such genotyping results would have to be available within 24 hours and be much more inexpensive than today's standards. Such a scenario may certainly arise as the cost of genotyping drops rapidly and in-house genotyping becomes available. However, as newer agents surface that do not require monitoring and display little interindividual variability, such as dabigatran, pharmacogenetic algorithms for warfarin dosing will likely have limited to no clinical applicability.³⁵

The warfarin and clopidogrel scenarios exemplify both the promises of and challenges to implementing pharmacogenetic strategies in medicine. Not only must data implicating variants be validated in numerous cohorts, but also viable alternatives to therapy and rapid turnaround of genotyping results must be available. Further, the frequency and severity of the adverse outcomes must be sufficient to justify both the cost and time required to institute systematic genotyping, and finally, the results of genetic testing must yield tangible benefits in clinical studies.

Beta-Blockers in Heart Failure

Chronic stimulation of the β_1 subtype of the adrenergic receptor (AR) as a consequence of excess sympathetic tone from a failing heart results in compromised cardiac function and untimely death.^{36, 37} It is believed that interruption of this pathogenic neurohormonal process by β_1 receptor inhibition limits the myopathic process and forms the basis for β -blocker therapy in the management of chronic heart failure (HF).³⁸ However, despite their salutary effects, there is substantial variation in β -blocker response that isn't explained through baseline clinical features.³⁹ This key observation is what led to the genetic heterogeneity hypothesis of β -blocker response.

To further evaluate this hypothesis, Liggett and colleagues performed extensive resequencing of the β_1 AR in several human cohorts and found a common nonsynonymous SNP in the β_1 AR gene at position 1,165 of the open reading frame that results in an Arginine (Arg) for Glycine (Gly) substitution.⁴⁰ This is a highly conserved variant across species with only homo sapiens showing allelic heterogeneity (Figure 2) with the allele frequency of the

Arg variant being 0.62 in African Americans and 0.73 in those of European descent (50% homozygotes). Interestingly, the Arg variant conferred increased β_1 AR coupling to G_s and stimulation of adenylyl cyclase when compared to the Gly variant in human transfected fibroblasts. Further, the same polymorphism in explanted human failing and nonfailing right ventricular trabeculae resulted in increased contractile reserve with isoproterenol stimulation and an augmented negative inotropic response to bucindolol— a novel β -blocker with sympatholytic effects.

These findings led to retrospectively investigating the role of these gene variants in the β -blocker Evaluation of Survival Test (BEST) trial, which had evaluated bucindolol therapy in class III/IV HF patients.⁴⁰ Notably, bucindolol therapy conferred a selective survival benefit only in Arg variant hearts, while individuals harboring the Gly variant derived no benefit. These results have generated significant excitement; however, several variables should be addressed. First, in vitro data has shown that carvedilol – the first-line agent for treatment of HF – effects are independent of β_1 receptor genotype.⁴⁰ In addition, to our knowledge, no head-to-head trials demonstrating superiority of bucindolol to commonly used β -blockers have been published. Finally, no genome-wide study assessing β -blocker response in HF has been performed – a gold standard when evaluating common genetic mediators of complex trait susceptibility and treatment response. All these factors and the availability of more inexpensive generic β -blockers with a more universal morbidity and mortality benefit currently preclude the selective use of genotype based bucindolol therapy.

On the other hand, a pharmacogenomic approach involving β -blockers should emerge from recent data linking G-protein coupled receptor kinases (GRK) to an intrinsic “genetic β -blockade” in individuals harboring a specific allelic polymorphism.⁴¹ The β_1 AR is a member of the superfamily of heterotrimeric G-protein coupled 7 transmembrane spanning receptors that transduce cell signals from hormones, ions, and various additional stimuli. β_1 AR's through stimulatory G proteins act to increase adenylyl cyclase and intracellular cAMP, thereby culminating in increased contractility and progressive cardiomyopathy in patients with HF.^{36, 37, 40} Conversely, receptor downregulation, which commonly occurs during chronic HF appears to be protective.³⁷ This downregulation is principally mediated through GRK. Both GRK2 and GRK5 participate in downregulation through phosphorylation that leads to recruitment of β -arrestin and β AR uncoupling from G proteins (Figure 3).⁴²

Recently, Liggett et al. published data revealing a leucine (Leu) for glycine (Gly) substitution at position 41 in GRK5 resulted in more effective β AR uncoupling after isoproterenol stimulation than wild-type GRK5.⁴¹ More importantly, they showed the same GRK-Leu41 variant conferred a “genetic β -blockade” that improved survival in carriers and mirrored the survival benefit seen from β -blocker use in non-carriers of the loss-of-function allele. Further, they showed that individuals with HF that harbored the Leu41 variant derived no incremental benefit from addition of β -blockers. Notably, an approximate 40% of African Americans in contrast to 1% of European Americans are carriers of this allele, which provides a plausible biologic explanation for the heterogeneity in therapeutic response to β -blockers seen in African American populations. Going forward, systematic genotyping for GRK polymorphisms in African American patients requiring β -blockers for HF should be strongly considered given the established lack of benefit in carriers of Leu41 GRK5 variants.

Statin Pharmacogenomics

Polymorphisms in the apolipoprotein E (ApoE) gene have been the most robustly replicated genomic risk factor for dyslipidemia and CAD.⁵ Its biologic activity involves receptor-based

clearance of lipoproteins from the plasma.⁴³⁻⁴⁷ Notably, carriers of the E4 polymorphism (~25% of the population) have higher circulating cholesterol levels and a heightened risk for CAD (~40%) when compared to those harboring the more common E2 and E3 genotypes.⁵ Since its initial discovery in 1977, this ApoE4 link to dyslipidemia and CAD has been validated in over 50 studies involving tens of thousands of individuals.⁵ Most importantly, several recent GWA studies have now confirmed this effect.⁴⁸ In 2000, investigators took this association one step further when they found that E4 carriers after multivariate adjustment had reduced survival after myocardial infarction when compared to non-carriers.⁴⁹ Most importantly, simvastatin therapy abolished this heightened risk. Curiously, this reduction in cardiovascular death was not related to greater lipid lowering, thereby providing further support for the pleiotropic and yet to be fully discovered spectrum of *in vivo* statin activity. Based on existing data summarized here, intensive statin initiation for primary prevention in E4 carriers with moderate clinical risk could be justified. However, first we must address the ethical and social implications of disseminating information on E4 genotype given its strong link to Alzheimer's dementia.

A nonsynonymous SNP in the kinesin family member 6 (KIF6) gene that results in an arginine for tryptophan substitution has recently received a great deal of attention.⁵⁰⁻⁵² Three independent studies with cohorts consisting of individuals with and without CAD demonstrated that carriers of the mutation had an approximate 30% increase in the relative risk for CAD events, and most importantly, derived a ten-fold greater reduction in cardiovascular endpoints when treated with intense statin therapy.⁵⁰⁻⁵² These results have prompted calls for KIF6 based statin therapy initiation. In addition, a commercial assay has now been developed for KIF6 variants and is being aggressively marketed.⁵³ However, several concerns should be addressed. First, this variant, despite being present in over 30% of individuals, has not been found to be associated with CAD or dyslipidemia in the over 8 independent well conducted and highly statistically powered GWA studies performed to date.^{48, 54-61} In addition, the biased nature of candidate gene methods used to identify and validate this variant's effect adds to the skepticism.⁶² Finally, KIF6 is not highly expressed in the coronary tree and no plausible biologic explanation on how this variant mediates CAD has been provided.^{62, 63} Importantly, a major meta-analysis from multiple groups that have studied the genomics of coronary artery disease refutes any effect of KIF-6 on susceptibility to the trait. All these points are in distinct contrast to ApoE4 polymorphisms, which have been extensively validated through GWAS and the functional genomics well established.

Another rapidly evolving area for pharmacogenomic applications is in the space of adverse drug event prediction. Variants in genes responsible for antibiotic liver toxicity and cisplatin-based ototoxicity have been discovered using genome-wide technology in as few as 50 patients.^{12, 14} Most importantly the odd ratios (OR) for these serious adverse events have ranged from 10-50, which is far greater than the very modest OR's (1 – 1.5) traditionally seen in GWA studies for complex trait susceptibility that have required thousands of study subjects for adequate statistical power.⁷ Furthermore, these successes are now being extended to prediction of events in patients on commonly used cardiovascular agents.¹¹

Recently, a GWA study assaying over 316,000 SNPs in just 85 subjects with statin related myopathy and 90 controls yielded a strong signal ($p = 4 \times 10^{-9}$) on chromosome 12p12 implicating a nonsynonymous SNP in SLC01B1, which encodes the organic anion-transporting polypeptide OATP1B1.¹¹ Carriers of the at-risk allele (~13%) exhibited a 4-fold increase in risk and homozygotes a striking 16-fold increase in risk for statin related myopathy. In addition, clinical studies have noted a positive correlation between SLC01B1 variants and statin pharmacokinetics with blood levels notably higher in carriers of the at-risk alleles, while the WT allele has been associated with lower statin levels and reduced LDL lowering capability.^{11, 64}

To follow-up on the genome-wide scan, Ginsburg and colleagues prospectively studied the SLC01B1 variants impact on the much more common musculoskeletal side effects of statins.⁶⁵ Approximately 25 – 50% of patients with existing coronary artery disease discontinue statin therapy within a year with musculoskeletal side effects, which are seen in 5-10% of statin users, being a primary contributor. Composite adverse events (CAE) were described as drug discontinuation for any side effect, myalgia, or 3-fold elevation of muscle enzymes. At one year, 22% of the 452 subjects met at least 1 criterion for a CAE with female sex and the common SLC01B1*5 variant significantly associated with adverse events and drug discontinuation on multivariate analysis. Interestingly, the SLC01B1*5 variant conferred a risk for adverse events in simvastatin users only and not in those taking pravastatin or atorvastatin. Further, simvastatin metabolites were notably higher in SLC01B1*5 carriers, while metabolites from atorvastatin and pravastatin were not altered, thereby providing a plausible biologic mechanism for the variants selective impact in simvastatin treated individuals. Based on this data, changing therapy from simvastatin to an alternative statin may be useful in SLC01B1*5 carriers with musculoskeletal side effects and potentially prevent premature discontinuation of a therapy vitally important in the prevention and treatment of CAD.

Future Directions

All the illustrations covered within this review represent a snapshot of the most transformative changes occurring in the arena of cardiovascular pharmacogenomics. The highly validated clopidogrel scenario highlights the promises of pharmacogenomic technology, while the KIF6 story demonstrates its potential pitfalls. Going forward, we will continue to uncover predictive biomarkers of drug response enabled by studies using rapidly evolving ‘omic’ (genomics, proteomics, metabolomics) based technologies. The positive implications from these discoveries for society are enormous. With the anticipated global aging of the population and increases in the worldwide prevalence of diseases such as diabetes, various cancers, and cardiovascular disease, novel, more efficacious, and precise therapies must be developed. We can no longer afford to continue with the shotgun ‘one size fits all’ approach to medicine. Clinicians must be educated in the nuances and the benefits that can be derived from pharmacogenomic applications. In addition, investment in well-designed genomic studies and in the development of high-throughput and cost-effective methods for genotyping and sequencing must be continually enhanced. The potential to leverage the information on low frequency and rare variants from the ongoing era of whole genome sequencing will further potentiate the opportunities for the practice of individualized medicine.

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Figure 1. Genetic Variants in VKOR Impact Warfarin Dose Response

Vitamin K (vit K) epoxide reductase (VKOR) regenerates the reduced form of vit K, which is necessary for the carboxylation and activation of vit K dependent clotting factors II, VII, IX, and X. Warfarin inhibits VKOR thereby exerting its anticoagulant effect. Genetic polymorphisms in VKOR result in significant variability to warfarin response and a requirement for upward or downward dosage adjustment.

The β_1 -AR 389 polymorphism is within a highly conserved intracellular region. Amino acid sequences from diverse species are shown aligned with human residues 379-397, with differences indicated in red. The human polymorphism is located at position 389 (yellow) in patients treated with bucindolol. *Adapted with permission from the Proceeding of the National Academy of Sciences*³⁹

Figure 3. GRK Variant Confer a Genetic β -Blockade

Norepinephrine (NE) and Epinephrine (Epi) binding to the β -AR results in recruitment of heterotrimeric G-proteins, $G\alpha$ and $G\gamma$. This stimulates adenylyl cyclase activity, which results in downstream increases in myocardial contractility. G-protein coupled receptors kinases (GRK) uncouple the heterotrimeric proteins and limit persistent myocardial stimulation present in hyperadrenergic states. A gene variant in GRK 5 results in enhanced β -AR uncoupling and diminished response to adrenergic stimulation thereby conferring a “genetic β -blockade”