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Cardiovascular Pharmacogenomics: The Future of Cardiovascular Therapeutics?

Dan M. Roden, M.D.

Departments of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville

Abstract

Responses to drug therapy vary from benefit to no effect to adverse effects which can be serious or occasionally fatal. Increasing evidence supports the idea that genetic variants can play a major role in this spectrum of responses. Well-studied examples in cardiovascular therapeutics include predictors of steady-state warfarin dosage, predictors of reduced efficacy among patients receiving clopidogrel for drug eluting stents, and predictors of some serious adverse drug effects. This review summarizes contemporary approaches to identifying and validating genetic predictors of variability in response to drug treatment. Approaches to incorporating this new knowledge into clinical care, and the barriers to this concept, are addressed.

It is an accepted feature of contemporary drug therapy that individual patients vary in responses. Some display gratifying clinical responses to low or therapeutic drug dosages, others require high dosages to achieve efficacy, some never achieve efficacy, and adverse effects are common. There is a substantial and increasing body of work that supports the idea that some of this variability is genetically determined. To date, well-studied examples among cardiovascular therapies include predictors of steady-state warfarin dosage, predictors of reduced efficacy among patients receiving clopidogrel for drug eluting stents, and predictors of some serious adverse drug effects. The lessons that have been learned, and are being learned, in understanding the genetics of variable drug responses are applicable across the spectrum of cardiovascular and other treatments. The hope of modern genome science is that identification of robust associations between genomic variants and human traits can inform underlying mechanisms, lead to new biomarkers, improve therapies by targeting drugs and doses to those most likely to benefit and least likely to suffer adverse effects, and identify targets for new drug development.

Genomic approaches have been used to predict both efficacy as well as adverse drug effects. Variability in response to therapy is an especially important feature for drugs with narrow margins between those associated with efficacy and those associated with toxicity; anticoagulant and antiarrhythmic therapies have therefore been a particular focus in cardiovascular pharmacogenomics. This review will summarize contemporary approaches to identifying and validating genetic predictors of variability in response to cardiovascular drug therapies. The methods by which populations for pharmacogenomic study can be ascertained will be presented followed by a discussion of the candidate gene and the

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Correspondence: Dan M. Roden, M.D., Professor of Medicine and Pharmacology, Director, Oates Institute for Experimental Therapeutics, Assistant Vice-Chancellor for Personalized Medicine, Vanderbilt University School of Medicine, 1285 Medical Research Building IV, Nashville, TN 37232, Telephone: 615-322-0067, Fax: 615-343-4522, dan.roden@vanderbilt.edu.

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genome-wide association study paradigms for identifying robust relations between genomic variants and variable drug actions. Finally, the idea of incorporating this new knowledge into clinical care, and the barriers to this concept, will be addressed. While this review focuses on cardiovascular drugs, the cardiovascular practitioner must also be sensitive to the fact that variability in response to many “non-cardiovascular” drugs in widespread use may also include a genetic component.

Approaches to identifying patients for genomic study

Adding genomic studies into a large randomized trial

A key requirement for any study that seeks to identify genetic variation as a source of variable drug effects is ascertainment of sets of patients with drug exposures, documentation of drug response phenotypes, and availability of genomic data. One approach to accumulating study subjects is to conduct genomic substudies in large investigator or industry-sponsored randomized clinical trials of drug efficacy. Analyses of large datasets gathered in this fashion identified robust associations between the *2 allele in *CYP2C19* (encoding a key enzyme modulating clopidogrel metabolism from its prodrug ingested form to active metabolites¹) and reduced ability of clopidogrel to prevent recurrent coronary events after treatment of acute coronary syndrome (ACS).^{2–4} A drawback to this design is that not all subjects enrolled in the main trial may be willing to provide DNA samples. In addition, because the genetic analyses are often secondary to the main thrust of the study, the randomization does not occur by genotype. That is, the analysis generally examines outcomes by genotype among patients randomized to a treatment arm and a control arm (placebo or other drug). While the power of such a design to detect the impact of genetic variants on outcome may be large, the actual ability to determine the potential impact of a genetic variant on clinic practice is limited. A more optimal design is to randomly assign patients to standard therapy or genotype-guided therapy and then to assess the impact of adding genotyping to clinical practice to assess outcome. This is the design of the NHLBI's COAG trial to examine the impact of genotyping on outcome of warfarin therapy.⁵

Consortium Approach: Warfarin

The International Warfarin Pharmacogenomics Consortium (IWPC) represents another approach to accumulating large numbers of patients with drug exposures, drug response phenotypes, and genomic information.⁶ The initial publication from the IWPC used data from 5052 subjects from 21 research groups to establish mechanisms underlying ancestry dependent variation in steady warfarin dose and to demonstrate that the accuracy of clinical algorithms to predict dose were improved by the addition of information on genomic variation. The improvement was especially notable in those subjects with unusually high or low warfarin dosages, consistent with the idea that much variability in drug response may be predicted by clinical factors (age, disease, ancestry, etc) and that genetic factors may be especially useful in subjects with high or low dose requirements. This consortium approach has also been extended to other areas in pharmacogenomics,⁷ including accumulation of cohorts of subjects with rare adverse drug reactions.⁸

Meta-analyses and Endophenotypes: Clopidogrel

Meta-analyses have been used to analyze the results of multiple individual trials examining, generally in the retrospective fashion described above, the impact of genetic variation on outcome of drug therapy in these designs. A meta-analysis of clopidogrel outcome after treatment of ACS showed a significant increase in risk of thrombosis-related events among patients with one or copies of *CYP2C19**2.⁹ By contrast, another meta-analysis, including not only patients with acute coronary syndrome but patients treated with clopidogrel for multiple other indications, detected only a very modest effect of *CYP2C19* genotype on

outcome during clopidogrel therapy and suggested that the initial result was due to publication bias (publishing only positive results) and was heavily weighted toward studies with small numbers of subjects.¹⁰ An alternative explanation for the latter result is that including patients in whom clopidogrel itself produces only modest efficacy will necessarily blunt the impact of any genetic variant on outcome.¹¹

Another study design useful in assessing the role of genetic variation in drug outcome is examination of a drug-related “endophenotype” or intermediate phenotype. For example, clopidogrel bioactivation leads to metabolites that bind irreversibly to the platelet P2Y₁₂ receptor and thereby inhibit ADP-induced platelet aggregation. Shuldiner and colleagues¹² examined ADP-induced platelet aggregation *ex vivo* at baseline and during clopidogrel therapy in a group of 429 subjects, all of Amish descent. Analysis of this dataset by the genome-wide association study (GWAS) paradigm discussed below and elsewhere in this issue revealed a strong association signal at the *CYP2C19* locus, and further analysis indicated that the signal was driven by the *CYP2C19**2 genotype.

Adverse reaction analysis: the statin example

The study of adverse drug reactions presents special challenges in ascertainment. If an adverse outcome is common (e.g. failure of efficacy during clopidogrel therapy), or if an adverse event represents the extension of a drug’s known pharmacologic actions (bleeding during anticoagulant therapy or hypotension during hypertensive therapy), clinical trial data may suffice. However, some adverse drug effects appear to be “off-target” (i.e. unrelated to the drug’s known primary therapeutic pharmacologic effects) and these are often termed “idiosyncratic”, a word that transmits the seemingly unpredictable nature of such adverse effects. Because rare life-threatening adverse drug reactions may occur in a random and highly unpredictable fashion, a genetic predisposition may be invoked.

The study of rare adverse drug events may require special efforts to identify and subsequently verify cases. This generally requires collaboration among multiple institutions and then presents special challenges in ensuring uniform case definitions. On occasion, multicenter drug trials have prospectively defined rare adverse drug events, enabling subsequent genomic analysis. A very nice example of the latter approach is the SEARCH Trial which used prospective definitions of definite or incipient statin-related myopathy to identify a small number of cases among those treated with high dose simvastatin.¹³ A GWAS using this set identified variants in *SLCO1B1*, encoding a hepatic uptake drug transporter, as conferring up to twenty-fold increased risk for myopathy among homozygotes.

Registries and electronic medical records

Another source of potential patient information is subjects accrued in the course of routine practice. This can be accomplished by community based studies or prospective registries¹⁴ that attempt to ascertain all subjects meeting a specified case definition (e.g. the Vanderbilt atrial fibrillation registry), and then enable intensive follow up of their clinical course, including presenting subsequent symptoms, and response to various drug or other therapies. Another mechanism to ascertain large numbers of patients is through electronic medical record systems (EMR).^{15,16} These approaches can accrue large numbers of “real-world” subjects, but the disadvantage is that these approaches are observational, and do not allow treatments to be directly compared as in a randomized clinical trial.

Associating genetic variants with drug responses

Two broad categories of study design have been used to identify and subsequently validate genotype-phenotype associations for traits like disease susceptibility or drug response: a

candidate gene approach and an unbiased approach. In both cases, if an initially positive study identifies an association between the trait and one or more polymorphisms, validation is required. This can occur by replication of the association in independent and larger datasets and by studies that identify and validate the underlying biologic mechanism.

The candidate gene approach

Candidate genes and common disease—The candidate gene approach uses *a priori* knowledge to implicate a specific pathway, gene, or variants within that gene or pathway as modulators of variability in a trait such as disease susceptibility or drug response. Sufficiently large numbers of patients are then phenotyped for the trait and genotyped for the candidate variant(s) and the relationship assessed. While the choice of the specific variant to be assessed is often driven by previous physiologic studies and thus “makes physiologic sense”, this approach has been disappointing for identifying genetic variants conferring susceptibility to common disease, since initial association often fail to replicate.^{17,18} This could reflect publication bias (only positive initial studies are published), or a failure of study design, such as not replicating the work in the same patient population. In fact, a major lesson for the last decade in genome science has been that common variants with large effect sizes are very unusual when the target phenotype is susceptibility to common diseases. One plausible explanation for this finding is that evolutionary pressure would rapidly eliminate common susceptibility alleles for a serious condition arising before or during reproductive age.

Candidate genes and pharmacogenomics—An exception to this common variant generalization is in pharmacogenomics, where single variants with large and reproducible effect sizes on drug response phenotypes have been identified. One explanation for this exception may be that, until recently, there has been little or no evolutionary pressure on such variation because drug therapy is a modern invention. A second explanation is that study of the pathways of drug disposition and drug effects have identified key molecular “choke points” at which variable protein function can generate large variability in drug actions. These choke points reflect sites at which genetic factors or acquired conditions like disease or drug interactions produce very large effects on drug concentrations or the interaction between drugs and their target molecules. This concept explains the large and reproducible effects of variants in *CYP2C19* on clopidogrel’s platelet inhibiting effect^{1,12} and its clinical actions in patients with acute coronary syndrome^{2–4} and in *CYP2C9* and *VKORC1* on warfarin dose requirement.^{19–21} A non-pharmacokinetic set of examples is provided by studies demonstrating that single HLA-B variant haplotypes can explain a very high proportion of risk for immunologically-mediated adverse drug reactions such as severe skin rashes or hepatotoxicity.^{22–27} Pathways of susceptibility to common diseases are generally multifactorial and thus such choke points are more unusual.

Variation in drug effects due to drug metabolism and transport genes

CYP2C19: One category of genes in which variation can confer large effects is in those mediating variable concentrations of drug or active metabolites delivered to target sites of action. As mentioned above, clopidogrel is a prodrug and its bioactivation is mediated largely by *CYP2C19*-mediated metabolism.¹ *CYP2C19*2* is a common single nucleotide polymorphism (SNP) that alters the splicing of the gene, results in a nonfunctional enzyme, and has been associated with reduced clopidogrel efficacy following treatment of ACS. As in the case of other drug metabolizing enzymes, allele frequencies vary by ancestry. Poor metabolizers are commoner among Asian subjects than among Caucasians or African-American subjects; a second loss-of-function allele, *CYP2C19*3*, is also prevalent among Asians. The *CYP2C19*17* allele has been associated with increased activity and, in some

reports, may be associated with an increased susceptibility to bleeding,²⁸ perhaps reflecting increased generation of active metabolites from the parent drug.

CYP2C9: Common variants in *CYP2C9*, that encodes the enzyme responsible for the bioinactivation of S-warfarin, are associated with elevated warfarin concentrations, decreased steady-state dose requirements, and susceptibility to bleeding complications.^{29,30} The major variants in *CYP2C9* reported in Caucasian subjects are non-synonymous SNPs (i.e. those changing an amino acid) termed *2, a reduction-of-function allele, and *3, a loss-of-function allele. In African-American populations, these variants are less common, while other SNPs (e.g. resulting in *6, *8, *11) – not seen in Caucasians – have been reported to modulate warfarin dose requirement.^{30,31} *CYP2C9* is responsible for the bioactivation of losartan³² and other angiotensin receptor blockers, and so it is reasonable to suggest that loss-of-function variants could also result in decreased antihypertensive effect.³³

CYP2D6: Another enzyme that is important in the disposition of many cardiovascular and other drugs is *CYP2D6*.³⁴ Here, the poor metabolizer trait, present in 5–10% of Caucasian and African subjects (and much less common among Asians), is present when loss-of-function variants are present on both alleles; that is, poor metabolizers are homozygotes or compound heterozygotes for loss-of-function polymorphisms. Further, and again unlike the situation with *CYP2C9* and *CYP2C19*, there are dozens or hundreds of variants – some of which are large insertions and deletions – reported for *CYP2D6*, and there is very high sequence homology with an adjacent pseudogene. Thus, assignment of expected metabolizer phenotype from genetic testing can be challenging.

CYP2D6 poor metabolizers have increased concentrations of metoprolol and of propafenone, and may thus display increased bradycardia and bronchospasm.^{35,36} Some reports have implicated the *CYP2D6* poor metabolizer trait in bioinactivation of the antipsychotic drug thioridazine, and an increased incidence of drug-induced torsades de pointes with this agent among poor metabolizers.³⁷ *CYP2D6* is also responsible for the metabolism of many antidepressants and the bioactivation of tamoxifen and codeine.

Drug transporters: Drug uptake by and efflux from cell interiors is in many cases an active process controlled by cell-, domain- and drug-specific transport molecules.^{38,39} The physiology of drug transport is a key determinant of processes such as absorption, bioavailability, renal and biliary drug excretion, and penetration of drugs into brain and other tissues. These specific transport functions can be modulated by drug interactions and by genomic variation. For example, *MDR1* (also known as *ABCB1*) encodes the key drug efflux transporter P-glycoprotein in gut, liver, kidney, and the blood-brain barrier. Many drugs (amiodarone, erythromycin, quinidine, verapamil, among others) inhibit P-glycoprotein and thus modulate tissue uptake and penetration of substrate drugs like digitalis glycosides. A common *ABCB1* SNP that does not change the predicted amino acid sequence (and is thus termed “synonymous”) has been associated with variable concentrations of substrate drugs like digoxin⁴⁰ or clopidogrel.³ The mechanism whereby a synonymous variant exerts this effect is uncertain; it may be a marker for a functional SNP or conceivably be functional (e.g. by altering translation).⁴¹ As discussed above, *SLCO1B1* encodes a hepatic drug uptake transporter (known as OATP1B1) and a common non-synonymous SNP in the gene modulates risk of myotoxicity during simvastatin therapy.^{13,42}

Variation in drug effects due to interactions with drug targets—Drugs interact with specific molecular targets to exert their effects, and variation in genes encoding drug target molecules is another source of variability in drug action. For example, a common non-synonymous SNP in the beta-1 adrenergic receptor gene has been associated with variability in response to the beta-blocker bucindolol in patients treated for heart failure.⁴³ This variant

has also been associated with variable responses to rate control therapies in atrial fibrillation.⁴⁴

While warfarin has been used for over 50 years as an anticoagulant, it was only in 2004 that studies in kindreds with the rare syndrome of warfarin resistance (no change in anticoagulation with extremely high drug dosages) identified *VKORC1* as the target for the drug's action.⁴⁵ Subsequent studies have described common variants in the promoter of *VKORC1* and these result in variability in mRNA transcripts in liver.⁴⁶ Among patients with reduced promoter activity, steady state warfarin dose requirement is decreased. These promoter variants are especially common among Asian subjects (and less common among African-American subjects) compared to Caucasians, and contribute importantly to the ancestry-dependence of warfarin steady-state dose requirements, which are highest among African-American subjects, lowest among Asian subjects, and intermediate in Caucasians.^{6,47}

Clinicians sometimes encounter patients in whom anticoagulation with warfarin requires unusually high dosages. The usual explanation is non-compliance, but in occasional subjects, plasma concentrations demonstrate that the patients are compliant and thus display true warfarin "resistance". Rare non-synonymous variation in the coding region of *VKORC1* has been implicated in such cases.^{48,49} One such variant, resulting in D36Y, has a 5% frequency among Ashkenazi Jews, again emphasizing the important role of ancestry in mediating the genetic contribution to variable drug actions.

Almost all drugs that cause torsades de pointes block one repolarizing current, I_{Kr} , encoded by the *KCNH2*.⁵⁰ However, variation in *KCNH2* causing predisposition to drug-induced long QT Syndrome (diLQTS) is unusual. Occasional patients with variation in *KCNE2*, implicated as a modulator of *KCNH2* function, have been reported in diLQTS.⁵¹ More generally, cardiac repolarization is accomplished by multiple potassium currents (I_{Kr} and I_{Ks}) as well as waning of inward currents, primarily through L-type calcium channels, and variation in the genes encoding I_{Ks} have been reported in patients with diLQTS.^{52–56} The likely mechanism is that the genetic effect probably remains subclinical (because repolarization can be accomplished by I_{Kr} alone) but becomes manifest and clinically important when an I_{Kr} -blocker is administered. One study identified a variant in *KCNE1*, which encodes a function modifying protein important for I_{Ks} activity, in 9% of subjects with diLQTS, compared to 1–2% among population controls.⁵⁷

Genome-wide Association Studies (GWAS) and pharmacogenomics

GWAS Principles

GWAS SNPs are signposts, and are usually not functional—The GWAS paradigm searches for associations between genomic loci, tagged by common SNPs, and phenotypic traits such as disease susceptibility or drug response.⁵⁸ The GWAS paradigm is much less than a decade old, and has been enabled by human genome sequences and maps of common variations across those sequences. Thus, SNPs identified by GWAS are rarely functional, but rather identify regions of the genome at which truly functional variants drive variability in the phenotype under study. Experimental approaches to identify the truly functional variants that drive the association may include resequencing candidate loci to identify causative (as opposed to tagging) polymorphisms or determining function in *in vitro* and animal model experiments.^{59–61}

An initial hope of GWAS was that the loci identified would explain large amounts of heritability in common traits such as susceptibility to cancer, type 2 diabetes, or atherosclerosis. In general, this expectation has not been met, since loci identified by GWAS

explain only small amounts of variable heritability of such traits, despite the fact that these diseases are often known to be highly heritable. Nevertheless, the approach has been spectacularly successful in identifying new genomic loci – often heretofore unsuspected – associated with common diseases.

Small sample sets may be informative for some drug responses—In general, studying traits such as disease susceptibility has required, and has been enabled by, the development of very large datasets (thousands or tens of thousands of cases and controls), adequately powered to identify SNPs only modestly associated with the trait under study. A striking exception to this general rule has been in some pharmacogenomic studies, where datasets as small as a few dozen cases have succeeded in identifying very strong signals, notably for adverse drug reactions. Examples include the very strong associations between variants in the HLA-B locus and Stevens-Johnson Syndrome or hepatotoxicity during carbamazepine^{24,25} or flucloxacillin,²⁷ and between variants in *SLCO1B1* and susceptibility to myotoxicity occurring with high dose simvastatin.¹³

Studies of variable drug efficacy using the GWAS paradigm have also occasionally resulted in relatively strong signals in small studies. One example is the endophenotype of inhibition of ADP-induced platelet aggregation by clopidogrel discussed above.¹² Another is the identification of *VKORC1*, *CYP2C9* and *CYP4F2* as modulators of warfarin steady state dose requirement.^{20,21}

Loci predicting disease or endophenotypes may also predict drug response—

GWAS has been applied to study determinants of physiologic traits or disease susceptibility, and the results are now being used to predict clinical events, including drug response. Variants at the 4q25 locus near the transcription factor *PITX2* have been repeatedly associated with susceptibility to atrial fibrillation,^{14,62} and studies have now reported associations between 4q25 AF susceptibility SNPs and outcome of antiarrhythmic drug therapy⁶³ or catheter ablation.⁶⁴ These data, if replicated, support the notion that SNPs at 4q25 locus identify a mechanistically distinct subset in atrial fibrillation. Variants in *NOS1AP* have been repeatedly associated with variability in baseline QT interval.^{65–67} Since those discoveries, variants in *NOS1AP* have been associated with susceptibility to sudden death,^{68–70} and to variability in the clinical course of the long QT syndromes.^{71,72}

How much heritability do GWAS results predict?—Many conditions analyzed by GWAS are known to be highly heritable. However, common polymorphisms, with incontrovertible statistical associations, paradoxically may explain only a small proportion of variability in the trait. This problem of “missing heritability”⁷³ applies especially to common complex traits, when single variants contributing more than 1–2% to trait variability are unusual. Pharmacogenomic variants can make much larger contributions to variability in a trait, yet even here common polymorphisms can leave much trait variability unexplained. For example, change in platelet aggregation following exposure to clopidogrel is highly heritable (approximately 73%) but the contribution to that heritability by clinical factors (10%) and by *CYP2C19**2 (12%) leaves much of the trait variability unexplained.¹² Similarly, variants in *CYP2C9* and *VKORC1* can explain up to 40–50% of variability in warfarin dose;^{19–21} this is a very large genetic effect, but even after correction for clinical covariates there is still substantial variability unexplained. A number of explanations have been advanced to explain the problem of missing heritability.⁷³ One possibility is that the heritability of the phenotypes under study is overestimated by current methods. A second is that the heritability arises from modest contributions of many genetic loci, and possibly by interactions between genetic variants at such loci. Identifying such variation requires extraordinarily large datasets.

An emerging story around rare variation and common traits—A third possibility to explain missing heritability is that multiple rare variants, each contributing substantially to heritability in individual small kindreds, but not across a population, may be responsible. The development of very cheap methods to resequence large swaths of the human genome will enable tests of this hypothesis, although the statistical methodology to analyze such very large datasets and to confidently identify individual variants tracking with variability in a disease trait, remain to be developed. A number of examples in cardiovascular pharmacogenomics highlight the potential role for rare variants in mediating drug responses. The identification of rare variants in *PCSK9* associated with low LDL cholesterol especially in African-Americans^{74,75} (and leading to development of *PCSK9*-targeted drug therapies^{76,77}) is one example. Another is work with diLQTS that has suggested that a high proportion of patients carry rare variants in congenital long QT syndrome disease genes, or other arrhythmia susceptibility genes.⁷⁸ A third is the example of rare individuals with true warfarin resistance arising from non-synonymous SNPs in *VKORC1*,⁴⁹ presumably the mechanism here is inhibition of warfarin binding to this target protein.

The Pathway to Implementation

Moving validated associations ready into clinical practice

The identification of statistically significant, validated, and biologically plausible associations does not imply that these are suitable for clinical implementation: effect sizes may be small, the clinical consequences of the variant polymorphism may be unimportant, or alternate therapies may be unavailable. Further, genetic variants are generally contributors to, but not absolute determinants of, most phenotypes including drug responses and there are very few well-powered randomized clinical trials that support the idea that including genomic information in clinical decision making improves outcomes: one difficulty is that trials need to study very large numbers of patients to identify believable variant response data in small subsets with potential at risk polymorphisms. It has also been argued that the data are sufficiently compelling in some cases (e.g. clopidogrel and *CYP2C19* in patients with coronary stents) that equipoise has been lost.⁷⁹ The field is grappling with the best way to generate sufficient evidence to support such implementation. Short of randomized clinical trials for each set of variants – which seems unrealistic – approaches that have been considered include alternate trial designs and combining multiple levels of evidence (such as biologic, statistical genetic, expression, clinical significance, alternate therapies); combining genetic information with functional studies such as INR for warfarin or platelet reactivity for clopidogrel^{80,81} is one example. Clinically important drug outcomes that have been reproducibly associated with specific genotypes are listed in Table 1; these potentially actionable associations represent the starting point for an implementation strategy discussed further below.

Personalizing care

The development of ever increasing large datasets⁸² relating genomic variation to important human diseases and drug responses raises the tantalizing possibility that these data may be used to “personalize” routine care in some instances. This philosophy has now been adopted as part of the strategic plan of the US National Human Genome Research Institute.⁸³ As the sheer volume of information relating genomic variants to clinical phenotypes continues to accumulate, the likelihood that these can be implemented in any way outside an electronic medical record system seems increasingly remote: healthcare providers simply cannot keep track of individual variants and their known or suspected roles in clinical medicine without such assistance.

There are a number of key questions that should be addressed as such a personalized genomic approach to care evolves. These include

- Does the trait under study display clinically important variability, and is there evidence that such variability is genetically determined?
- What is the level of evidence that links a specific genomic variant to a phenotype such as disease susceptibility or drug response? Have the results been replicated? Have experiments been conducted to explain the underlying biology? Do the data apply across ancestries?
- If such variability is genetically determined, does it arise from a small number of variants with large effect sizes? Or a very large number of variants with small to modest effect sizes? How robust are the assays for the genetic variants under consideration?
- If genotypes are determined in target patient populations, is there evidence to inform how care should be altered? How strong is this evidence?
- Are electronic medical record systems in place that can accrue data, deliver advice to health care providers at the point of care, and track outcomes as decision support is adopted?
- For some drug/genotype pairs, such as clopidogrel/*CYP2C19**2 or warfarin/*CYP2C9-VKORC1*, point of care genotyping platforms capable of delivering genotype data within an acceptably short time window, have been developed and are being deployed at early adopter medical centers.⁸⁰ An alternate model is to identify large populations of patients who are “at risk” for receiving drugs with actionable pharmacogenetics information (e.g. those in Table 1) and to preemptively embed relevant genotypes in the EMR.⁸⁴ This deposit is then coupled to advanced informatics systems capable of delivering informed advice to providers when a drug is prescribed to a patient with a variant genotype. The costs of sequencing individual genomes are now dropping so rapidly⁸³ that it may be possible to couple genome sequence data with advanced informatics to tailor aspects of clinical care to an individual’s genomic variants (Figure 1). The development of large sets of individual EMRs coupled to embedded genomic information may also serve as a resource for discovery in genome science,⁸⁵ thereby serving to further propel this vision.

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Figure 1.

A “future-tense” view of genome-enabled medicine. The rapidly dropping costs of whole genome sequencing raise the possibility that this will become part of medical practice. However, since the functional significance of most genomic variation is still unknown, it seems unrealistic to deposit all information into a patient’s record. In the scheme outlined above, only selected variants would be available to the electronic medical record. These would be used to counsel individuals at especially high risk of preventable disease and in selection of drugs and drug doses, when needed.

Table 1

Drug response variants potentially ready for clinical implementation

Gene	Drug	Comment
CYP2C19	clopidogrel	Best evidence after acute coronary syndrome
CYP2C9 VKORC1 CYP4F2	warfarin	Algorithms to predict steady state dose improved with addition of genetic data to clinical variables Frequencies of specific polymorphisms vary by ancestry.
SLCO1B1	simvastatin	Variants predict myotoxicity especially at higher dosages
TPMT	6-MP, azathioprine	Poor metabolizer status predicts risk for severe bone marrow suppression
CYP2D6	codeine, tamoxifen	PM status predicts decreased response
CYP2D6	some SSRIs	PM status predicts intolerance of effective dosages.
IL28R	Hepatitis C therapy	Genotypes predicting decreased response commoner in African American subjects
HLA-B*5701	abacavir	Serious skin reactions near-eliminated by avoiding abacavir in patients with <i>HLA-B*5701</i>
HLA-B	carbamazepine	<i>HLA-B*1502</i> predictive of hypersensitivity reactions in Asian subjects and <i>HLA-B*3101</i> in Europeans
HLA-B*5801	allopurinol	Hypersensitivity reactions