# Personalized Pharmacogenomics: Predicting Efficacy and Adverse Drug Reactions

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## Keywords

pharmacogenomics, personalized medicine, drug efficacy, drug safety, biomarkers

## Abstract

Drug response varies between individuals owing to disease heterogeneity, environmental factors, and genetic factors. Genetic factors can affect both the pharmacokinetics and pharmacodynamics of a drug, leading to changes in local and systemic drug exposure and/or changes in the function of the drug target, altering drug response. Several pharmacogenetic biomarkers are already utilized in clinical practice and have been shown to improve clinical outcomes. However, a large number of other biomarkers have never made it beyond the discovery stage. Concerted effort is needed to improve the translation of pharmacogenetic biomarkers into clinical practice, and this will involve the use of standardized phenotyping and genotyping strategies, collaborative work, multidisciplinary approaches to identifying and replicating associations, and cooperation with industry to facilitate translation and commercialization. Acceptance of these approaches by clinicians, regulators, patients, and the public will be important in determining future success.

## INTRODUCTION

When a clinician prescribes a drug for a patient, he or she is trying to treat the patient's disease, with the aim of curing the condition or controlling symptoms without causing any adverse effects. The clinician should therefore carefully evaluate the benefit–risk relationship of prescribing a particular drug to a patient with a particular disease. However, this approach hampers physicians for several reasons.

First, it assumes that each patient's body will handle the drug in the same way. During drug development, dosing is based on mean values, only occasionally taking into account parameters such as body surface area. Variability in pharmacokinetics (absorption, distribution, metabolism, and excretion) is only superficially incorporated into dosing regimens.

Second, patients vary in age, weight, ethnicity, dietary habits, alcohol intake, smoking status, and any interacting medications they are taking. All of these factors can affect the pharmacokinetics of the drug and how it acts in the body, i.e., its pharmacodynamics. To a large extent, however, these factors are ignored.

Third, for most diseases, we are still using classifications that date back to the nineteenth century, when diseases were categorized by a gross and easily measurable phenotypic marker, such as blood pressure. However, we now know that diseases with the same phenotypic label can differ enormously, not only at the time of diagnosis but also in how they evolve. Recent insights into the molecular heterogeneity of diseases, particularly in cancer, have shown that this variability can have a marked effect on drug efficacy. As our insights into disease improve and we develop a new taxonomy of disease, we will be able to develop a stratification of disease and base the use of drugs on disease strata. At present, however, we have no choice but to treat every patient with the same "disease" in the same way.

It is therefore not surprising that there is large variability in drug response (both efficacy and toxicity) in current clinical practice between different patients treated with the same drugs for seemingly the same disease. To improve the personalization of medicine, it will be important to consider all three of the above aspects and integrate them into patient care (**Figure 1**). This task will not be easy, but it will be worth the effort to ensure that each patient receives the right drug at the right time at the right dose for the right disease (subtype). This review focuses on pharmacogenomics in particular, but, where necessary, it also considers other aspects to highlight the opportunities to improve drug therapy.

## VARIATION IN DRUG EFFICACY

That there is variation in the efficacy of almost every drug used in clinical practice has been known for a long time. However, this is not usually reported very well in published efficacy trials, which typically provide only the mean effects in the primary and secondary outcome measures. It is important for future trials that authors, and journal editors, include data on the variability observed in the response to a particular therapy.

Response rates to drugs vary from 10% to 90% (110). This is typified by asthma and the response to β2 agonists, which are the first line of therapy. Up to 50% of patients may not benefit optimally from these agents, with approximately 60% of the variability in treatment response being heritable (26). The famous quote from Allen Roses when he was a vice president at GlaxoSmithKline captures the problem well: "The vast majority of drugs—more than 90 per cent—only work in 30 or 50 per cent of the people. . . . Drugs out there on the market work, but they don't work in everybody" (15).

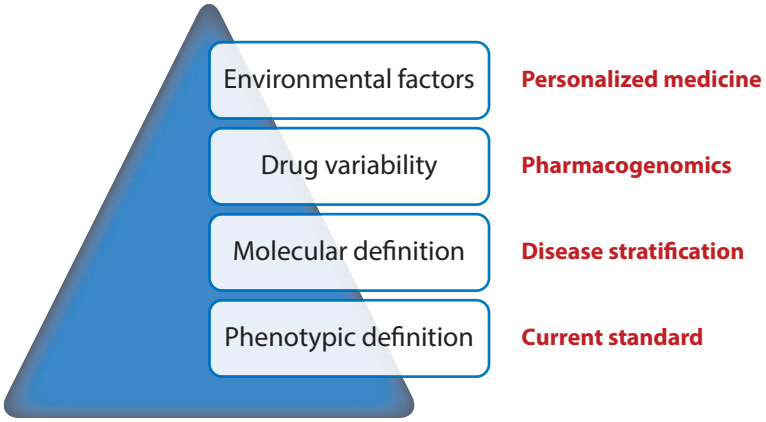


**Figure 1**

Different elements necessary to achieve the goal of personalized medicine (also termed stratified or precision medicine). Current disease classifications are based on gross phenotype, but as we dissect the molecular basis of disease, we will be able to identify disease strata in which the disease subphenotypes will have differential drug responses. However, variability in drug response within the strata will still be evident owing to both environmental and genetic factors. Taking all of these factors into account will be important in achieving the goal of personalized medicine.

## VARIATION IN DRUG SAFETY

Adverse drug reactions (ADRs) are a common issue during drug development, and they are an important reason for drug withdrawal early during development or soon after marketing. The most common ADRs leading to drug withdrawal include QT-interval prolongation and liver injury (128). ADRs also represent a huge burden on all health care systems. For example, a meta-analysis by Lazarou et al. (61) showed that ADRs were between the fourth and sixth most common cause of death in the United States in 1994. The cost is also enormous, estimated to be up to $4 billion per year in the United States (61) and £1 billion per year in the United Kingdom (20, 93). **Table 1** shows the overall burden of ADRs in both adults and children. Although these data relate to UK hospitals, they are likely representative of the burden worldwide.

Of course, not all ADRs are due to genetic factors. Many factors, ranging from poor prescribing to dietary and disease factors, contribute to a predisposition to ADRs. A systematic review of ADR-related hospital admissions in adults has shown that approximately 70% of ADRs may be avoidable through improved prescribing practices (43). Ingelman-Sundberg (48)

**Table 1 The burden caused by adverse drug reactions (ADRs) in UK hospitals**

| Study | Setting | Number of patients studied | Frequency of ADRs |
|---|---|---|---|
| **Adults** | | | |
| Pirmohamed et al. (93) | Hospital admissions | 18,820 | 6.5% |
| Davies et al. (20) | Hospital inpatients | 3,695 | 14.7% |
| **Children** | | | |
| Gallagher et al. (33) | Hospital admissions | 8,345 | 2.9% |
| Thiesen et al. (118) | Hospital inpatients | 16,601 | 17.7% |

suggested that up to 10–20% of ADRs may be due to genetic factors, either in whole or in part, but this is an estimate. The genetic contribution to an ADR likely varies with the drug and the type of ADR.

## REASONS FOR VARIABILITY IN DRUG RESPONSE

### Genetic Factors

What is the evidence that genetic factors play a role in determining variability in drug response? Unlike variability in disease, it is difficult to precisely determine the genetic contribution to variability in drug response. Twin studies have been used to assess the relative contributions of genetic and environmental factors to variation in drug response. For instance, in a study comparing the metabolisms of five pairs of monozygotic and dizygotic twins, Evans (29) showed that the metabolism of isoniazid was far less variable in the monozygotic twins than it was in the dizygotic twins. Vatsis et al. (121) subsequently related this finding to polymorphisms in the *N*-acetyltransferase gene that divide the population into slow and fast acetylators. Twin studies have also shown that genetic factors are the main determinants of the interindividual variation in the metabolism of antipyrine, phenytoin, halothane, and phenylbutazone (122). But metabolism, and variation within it, is only one component of the variability in drug response. Other factors, including pharmacodynamic elements (see below), are likely to contribute to variability, which leads to a situation akin to complex disease and thus poses challenges in developing predictive tests (82).

Determining the genetic contribution to ADRs is even more difficult, and research in this area has relied largely on case reports of the occurrence of ADRs, sometimes severe, in members of the same family (89). For instance, Edwards et al. (28) reported the occurrence of primary generalized epilepsy in identical twins, each of whom was treated with carbamazepine and subsequently developed hypersensitivity syndrome.

### Pharmacokinetics and Pharmacodynamics

Early work in pharmacogenetics focused largely on pharmacokinetic sources of variation (**Figure 2**). Most of the attention was directed specifically at drug metabolism and the variation caused by cytochrome P450 enzymes. The landmark discovery of variation in debrisoquine hydroxylase (which later became known as CYP2D6) was followed, after the advent of molecular biology, by the discovery of the genetic basis of this variation (88). This P450 isoform is responsible for the metabolism of 25% of drugs and has more than 75 allelic variants that can cause complete loss of enzyme activity or, conversely, through duplication, can lead to an increase in enzyme activity (48). Although *CYP2D6* is one of the most widely studied pharmacogenes, it has made little impact on clinical practice.

Pharmacodynamic drug targets have not been studied to the same extent as pharmacokinetic sources of variation. Drugs act largely on ion channels, receptors, enzymes, and nucleic acids to produce their therapeutic action (**Figure 2**). However, the identification of pharmacodynamic sources of variation has not been easy for several reasons: (*a*) We still do not completely understand the mode of action of many drugs, and often they interact with more than one target gene/protein; (*b*) interaction with a target is often accompanied by downstream effects that activate multiple genes and pathways, which cannot be easily measured; and (*c*) unlike pharmacokinetic processes, where it is possible to measure drug and metabolite concentrations, functional assessment of the effects of a drug on a target, particularly in vivo, has not been readily available. There is thus a need

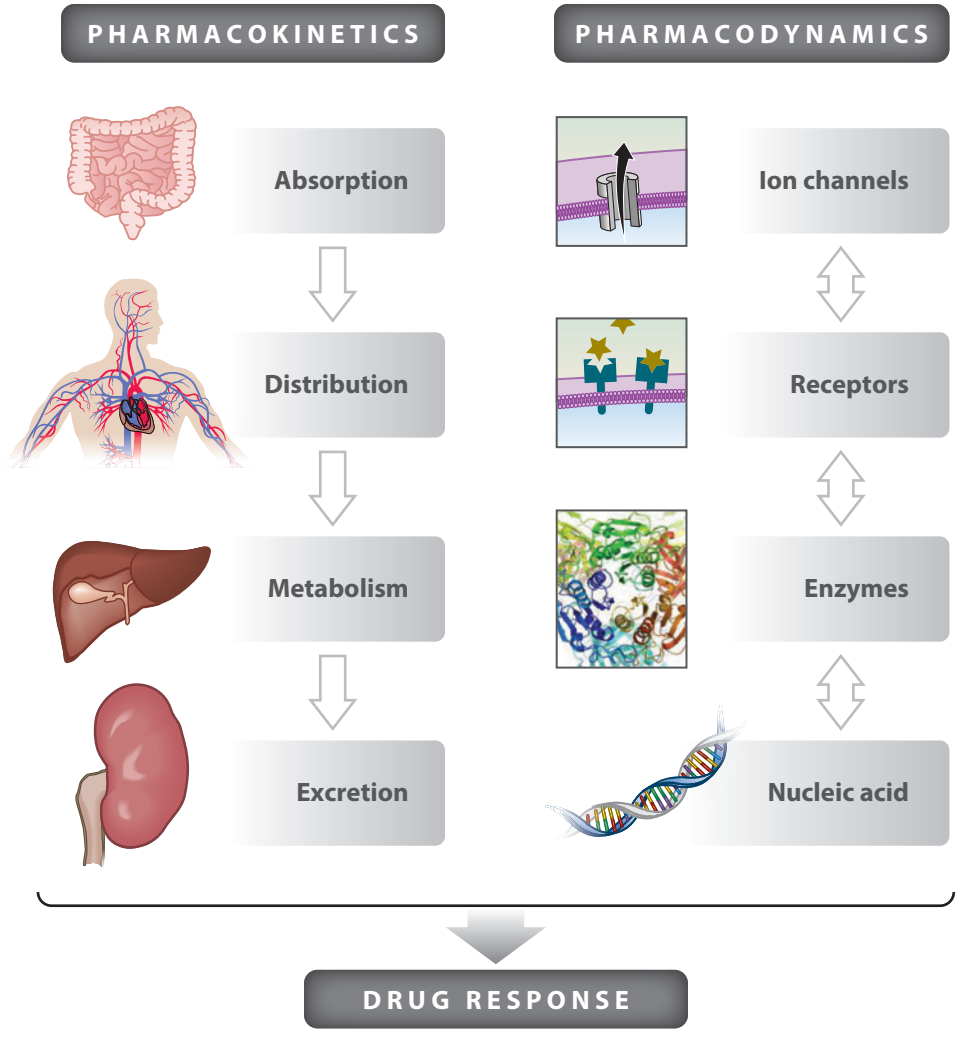


**Figure 2**

The pharmacokinetic and pharmacodynamic elements responsible for determining variability in drug response.

for future studies to evaluate drug targets as sources of variation in drug response; genome-wide approaches will, of course, help with this (see below).

## THE EVOLUTION OF PHARMACOGENETIC STUDIES

Studies in pharmacogenetics and pharmacogenomics have progressed from phenotypic analysis to sequencing-based studies (**Figure 3**). Clearly, the development of next-generation sequencing technologies has enabled investigators to identify individual rare and common variants more quickly than they could before. However, this technology does not exclude the use of slower techniques, including phenotyping, that focus on one gene/enzyme system. Indeed, the different techniques should be regarded as complementary rather than competitive.

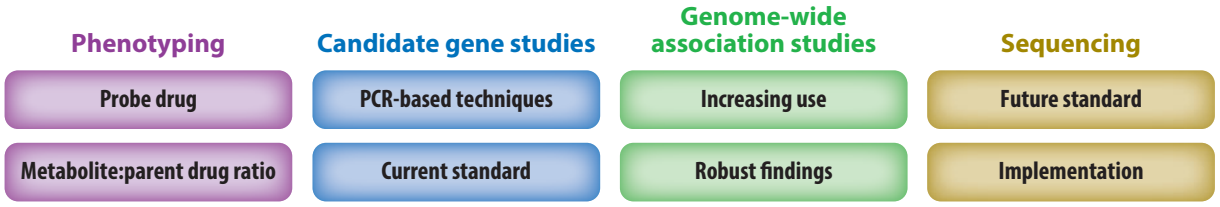


**Figure 3**

The evolution of pharmacogenetic research from phenotype testing to candidate gene studies, which have recently been enhanced by the availability of genome-wide and sequencing approaches. Abbreviation: PCR, polymerase chain reaction.



## Phenotyping

From the end of the 1950s to the end of the 1980s, phenotyping was utilized to assess variation in drug-metabolizing enzyme genes (77). This technique usually requires administering a probe drug and measuring the ratio between the probe drug and its metabolite, with the ratio then used to determine whether an individual has an absolute or partial deficiency of an enzyme (88); this methodology was used, for example, in the identification of CYP2D6 deficiency. Phenotyping is still used for research purposes—for example, to assess whether a genotype leads to functional variation. Furthermore, improvements in mass spectrometry have enabled the use of a cocktail of P450 probes, allowing for simultaneous assessment of the activities of multiple P450 isoforms (25).

In modern clinical practice, phenotyping tests are still used to determine individual variability in response to a drug. Three examples are detailed below.

**Thiopurine *S*-methyltransferase.** Thiopurine *S*-methyltransferase (TPMT) catalyzes the S-methylation of the thiopurine drugs azathioprine and 6-mercaptopurine. These drugs can cause bone marrow depression in patients with a deficiency of the TPMT enzyme (62, 112), which then leads to the increased formation of a cytotoxic 6-thioguanosine nucleotide metabolite via an alternative metabolism pathway. Approximately 86–97% of patients have the *TPMT*1/*1* (wild-type) genotype, conferring normal TPMT enzyme activity. Three polymorphisms—*TPMT*3C* (an A719G substitution on exon 10), *TPMT*3A* (a G460A substitution on exon 7 and an A719G substitution on exon 10), and *TPMT*2* (a G238C transition on exon 5)—account for 80–95% of the deficient TPMT activity in Caucasians, African Americans, and Asians. Approximately 3–14% of patients are heterozygous for the *TPMT* genotype, whereas the population prevalence of the homozygote variant ranges from approximately 1 in 178 to 1 in 3,736 patients (101). Patients with variant genotypes, in particular the homozygotes, benefit from dose reduction or alternative drug selection.

The TPMT phenotype test quantifies the level of enzyme activity in red blood cells. Phenotyping is considered to be more reliable for the detection of myelosuppression risk (105, 130). There are currently eight genotype tests available and no single gold standard. A systematic review concluded that genotype tests have lower sensitivity but greater positive predictive value than the TPMT phenotype test, as well as a wide range of sensitivity and specificity (23). The American College of Gastroenterology treatment guidelines prefer TPMT phenotyping over genotyping because phenotyping reports a quantitative level of the TPMT enzyme activity (59). In the United Kingdom, phenotyping is the preferred method for routine TPMT screening.

**Glucose-6-phosphate dehydrogenase.** Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme deficiency in the world, affecting more than 600 million

people. Numerous drugs (including primaquine, dapsone, sulfonamides, and rasburicase) can lead to red cell hemolysis in patients with G6PD deficiency, and for these drugs, the prescribing information requires testing before the use of the drug. Because there are more than 140 variants in the *G6PD* gene (8), testing for deficiency is usually undertaken using phenotypic assays, several of which are available. However, in resource-poor settings, phenotype testing may not be possible because of the lack of appropriate laboratory facilities. For instance, in many areas of the world, antimalarials containing the 8-aminoquinoline backbone (such as primaquine) are important for malaria control and elimination but have a propensity to cause hemolysis in G6PD-deficient patients (123). The importance of this is exemplified by the recent withdrawal of the combination antimalarial chlorproguanil-dapsone (Lapdap) because of a higher risk of anemia in G6PD-deficient patients in Africa (67).



**Platelet function.** Platelet function testing has been advocated as a biomarker to identify nonresponders to clopidogrel, an antiplatelet agent widely used in patients with ischemic heart disease. Clopidogrel is a prodrug that is converted to its active metabolite by various P450 isoforms, of which CYP2C19 seems to be the most important (132). A study in healthy Amish individuals given clopidogrel for 7 days showed that platelet response was highly heritable, with genome-wide association studies (GWAS) showing that it was linked to the *CYP2C* cluster on chromosome 10, although it accounted for only 12% of the variability (107). Numerous systematic reviews and meta-analyses have shown that individuals with the low-activity variants in *CYP2C19* have a higher risk of stent thrombosis but not of other cardiovascular end points (109). Because of the controversy associated with *CYP2C19* genotyping, some cardiologists advocate using platelet function testing to identify patients who have high on-treatment platelet reactivity after taking clopidogrel, and then changing these patients to an alternative antiplatelet agent (such as prasugrel or ticagrelor) (115). However, although platelet function testing may have the advantage of assessing overall platelet function ex vivo (thus taking into account the effects of many different gene products), the lack of testing standardization is a major disadvantage; many different tests are available, with a range of platform- and center-specific cutoff values to denote high platelet reactivity. Trials assessing both genotype and phenotype testing to identify poor responders to clopidogrel are under way.

## Candidate Gene Studies

Candidate gene studies are perhaps still the most widely used methodology in assessing genetic determinants of drug response. However, many pharmacogenetic markers discovered through candidate gene studies have failed to be replicated and remained in the discovery phase (87). The reasons for this include poor sample sizes, poor phenotyping strategies, concentration on one variant in a gene rather than evaluation of the genetic diversity of the whole gene, and incomplete knowledge of the drug's mechanism of action in terms of both efficacy and safety (88). These failures have led to a large amount of criticism of not only candidate gene studies but also pharmacogenomics as a whole, as a field of research (42, 51). However, it is important to remember that these issues are not specific to pharmacogenomics, but rather apply to the whole of genomics.

Furthermore, candidate gene studies have provided valuable insights into many important pharmacogenetic associations. Research on the *TPMT* genotype (described above) and its effects on thiopurine toxicity is a key example of the success of candidate gene studies. Another important example is abacavir hypersensitivity, where the predisposition was identified through candidate gene analysis of the human leukocyte antigen (HLA) region. In fact, the association

of *HLA-B*57:01* with abacavir hypersensitivity represents the best example of the translation of pharmacogenomics into clinical practice (85): This association is strong, has been replicated in numerous populations, and has been confirmed by a randomized controlled trial; the implementation of genetic testing is cost effective in at least three different health care settings; and the use of testing has been shown to improve clinical outcomes (89). More recently, the mechanistic basis of the association has been elucidated through crystallographic studies (6).

## Genome-Wide Association Studies

GWAS have been increasingly used over the past five years to identify pharmacogenetic predictors of response (for reviews, see 16, 17, 68). Although the total number of GWAS on complex diseases far outnumbers those on drug response (39), some of the most exciting associations, in terms of potential clinical applicability, have been found with the latter. GWAS of drug response are complicated by the fact that they require patients that not only have a particular disease but also have been treated with the same drug, and the phenotype being measured must be tractable. There have thus been concerns that it would not be possible to identify true associations because of the need for the large numbers that have been used in studies of complex diseases (68, 80). However, the effect size in drug response associations, particularly drug-related immune ADRs, seems to be much larger than that in complex diseases, making it possible to use small numbers of well-phenotyped patients (17). Furthermore, as with complex disease genetics (32), the identification of multiple loci that determine a drug response phenotype can allow investigators to define potential pathways that may be important in elucidating a drug's mode of action.

Nevertheless, as the field moves on, larger sample sizes (together with replication sets) will likely be needed to identify genetic predictors of drug responses that have smaller effect sizes. It will therefore be important for groups to collaborate to undertake multicenter patient recruitment to improve sample size. The use of standardized phenotypes (90) for the drug response being studied will be an important part of this effort.

It is perhaps also noteworthy to remember that associations that do not reach genome-wide significance should not be forgotten and may still be important. In such situations, functional assessment may help in determining the importance of a single-nucleotide polymorphism (SNP) or gene. Ingle et al. (49) showed this nicely in a GWAS with 293 cases and 585 controls on musculoskeletal adverse events associated with aromatase inhibitors in patients with breast cancer. Four SNPs that did not reach genome-wide significance were shown to be in the proximity of an apparently unrelated gene, *T-cell leukemia 1A* (*TCL1A*). However, functional studies showed that one of these SNPs created an estrogen response element, TCL1A expression was estrogen dependent, and this combination ultimately modulated cytokine and cytokine receptor expression (including IL-17, IL-17RA, IL-12, IL-12RB2, and IL-1R2) (64), providing insight into a novel mechanism for the musculoskeletal adverse events.

## Next-Generation Sequencing

Next-generation sequencing technologies have already started to make an impact on the identification of predictors of drug response. This work has been done largely in the cancer field, where sequencing of the somatic genome has allowed the identification of driver mutations, some of which have been druggable (see below). In the area of complex diseases, sequencing of the germline genome may also allow the identification of disease subphenotypes with differential responses to different drugs (120).

For serious ADRs, sequencing studies are ongoing to identify rare variants with large effect sizes. There are already examples of serious adverse effects that are due to rare variants and were identified because of familial aggregations of phenotypes (120). These include the associations between TPMT deficiency and thiopurine toxicity (described above) and between butyrylcholinesterase deficiency and prolonged apnea resulting from treatment with suxamethonium. At least 10% of cases of drug-induced torsades de pointes may be due to rare mutations in the congenital long QT syndrome genes, representing incomplete penetrance (5). A next-generation sequencing approach showed that 23% of Caucasian subjects with drug-induced torsades de pointes carried a variant within 22 congenital arrhythmia genes (which include the 13 congenital long QT syndrome genes), compared with a background rate of 1.7% in 60 control subjects from the 1000 Genomes CEU data (98).



## EFFICACY

### Cancer

Unlike the other areas discussed in this review, variation in response to anticancer drugs can be related to two genomes: the germline genome and the somatic genome. These have been discussed in two extensive reviews (75, 127) and so are discussed only briefly here. In the germline genome, a number of associations have been identified (for example, between TPMT and thiopurine toxicity, irinotecan-induced neutropenia, and CYP2D6 and tamoxifen efficacy), but apart from TPMT, none are used routinely in clinical practice (127). The role of CYP2D6 polymorphisms in determining tamoxifen efficacy in particular has been the subject of intense debate (96) that remains unresolved.

More successful has been the identification of driver somatic mutations, which has led to successful drug therapy (75). One of the most striking examples is the BCR-ABL translocation in chronic myeloid leukemia, which led to the development of the tyrosine kinase inhibitor imatinib (27). The earliest example of targeted therapy was actually in breast cancer, where typing for estrogen receptor status is routine as part of assessing whether drugs such as tamoxifen should be used. Clearly, therapeutics in breast cancer have since evolved with the use of HER2 typing to determine the use of trastuzumab (Herceptin), the further delineation of molecular subtypes, and the use of transcriptomic signatures to determine whether chemotherapy needs to be used (21). There have also been successes in colon cancer (EGFR expression and *KRAS* mutations and response to cetuximab) and lung cancer (*EGFR* mutations and response to gefitinib, and *ALK* mutations and response to crizotinib) (127).

The advantage of targeted therapy has also been evident in the regulation and licensing of some of these new drugs. For instance, it has been possible to conduct smaller pivotal trials that show efficacy only in patients with the relevant mutation, and approval from regulatory agencies such as the US Food and Drug Administration (FDA) has been rapid (1); for example, vemurafenib, which targets the V600E mutation in malignant melanoma (**Figure 4**), was approved by the FDA in only four months. However, despite the exciting developments of these targeted therapies, they do not necessarily lead to cures. This is perhaps best illustrated by vemurafenib in malignant melanoma: The median overall survival in previously untreated patients is 9.7 months among those treated with dacarbazine compared with 13.6 months among those treated with vemurafenib (104). Relapse occurs because of the development of resistance, and dual therapy with a MEK inhibitor and a BRAF inhibitor has shown some further success in improving survival rates (31). The challenge for treating melanoma as well as other tumors will be the development of targeted therapies that attack several key gene products in the pathway to produce sustainable improvements in survival and

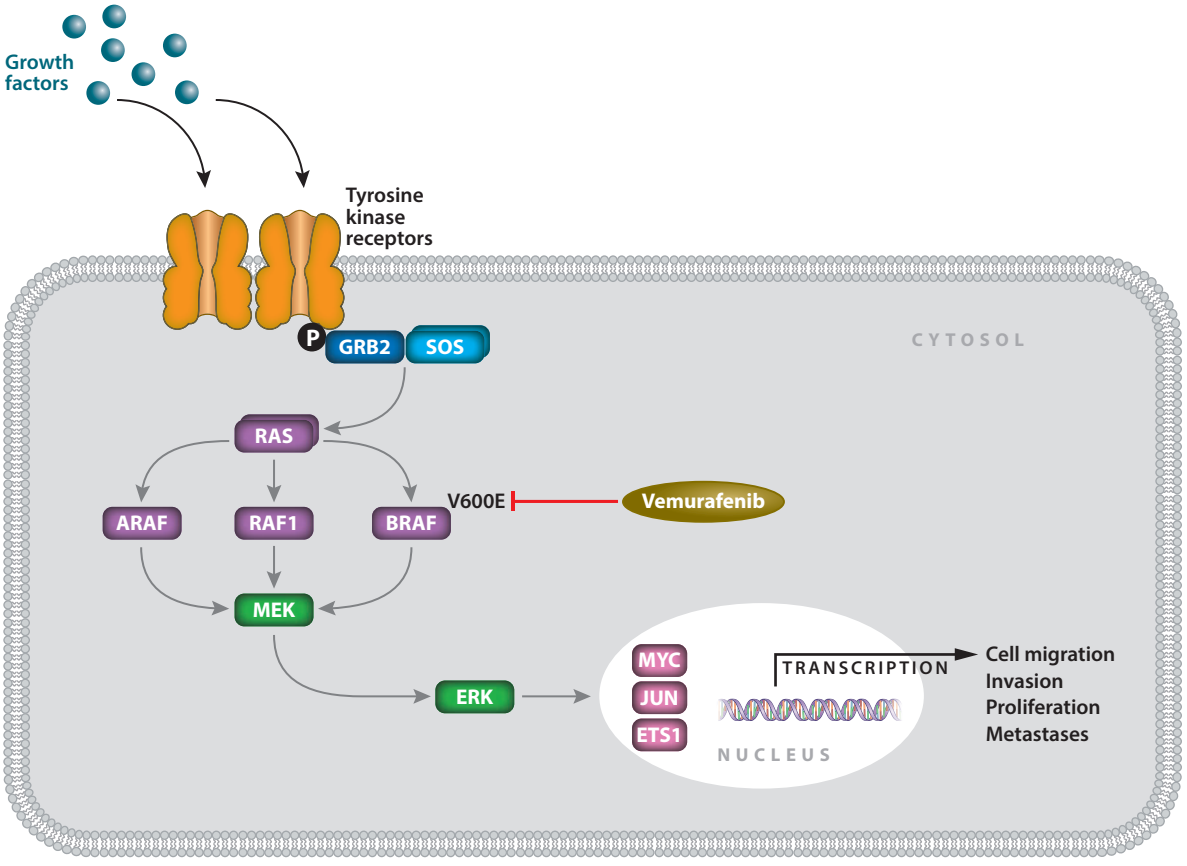


**Figure 4**

The molecular pathway involved in the mode of action of vemurafenib, which inhibits BRAF containing the V600E mutation. Adapted from PharmGKB (**https://www.pharmgkb.org/pathway/PA165980050**) with permission from PharmGKB and Stanford University. Copyright 2012 by PharmGKB.



reduce the occurrence of resistance. Lessons can be learned here from tuberculosis chemotherapy and anti-HIV treatments, where single agents were quickly replaced by combination therapy to effect either a cure (tuberculosis) or sustained suppression of viral (HIV) replication.

## IFNL3 and Response to Interferon-α in Hepatitis C

The response to treatment of hepatitis C with a combination of interferon-α and ribavarin is highly variable. Predictors of response include age, sex, weight, the presence of liver fibrosis, adherence to therapy, viral load, and hepatitis C virus (HCV) genotype (genotypes 2 and 3 have better responses than genotype 1) (2). In addition, patients of African ancestry are characterized by a poor response. Three GWAS in patients with hepatitis C virus genotype 1 infection implicated SNPs in the vicinity of the *IFNL3* (*IL28B*) gene on chromosome 19q13.13 in the response to interferon therapy (34, 113, 114). Patients with the *CC* genotype at rs12979860 have higher response rates to interferon-α (119), even when they are coinfected with HIV (99), and have higher spontaneous viral clearance rates (2). Treatment algorithms incorporating *IFNL3* genotyping have

been proposed and used in many clinics (60). *IFNL3* encodes a lambda type of interferon, which has antiviral activity, and the SNP at rs12979860 affects interferon-stimulated gene production as part of the innate immune response against hepatitis C, but the actual mechanism is unclear (2).

A recent study using primary human hepatocytes activated by viral RNA mimics (95) showed that a frameshift variant, ss469415590[ΔG], which is in linkage disequilibrium with rs12979860, was more strongly associated with viral clearance in individuals of African ancestry, whereas the effect in other ethnic groups was similar to that of rs12979860. The frameshift variant also created a new gene, *IFNL4*, reduced expression of which may be associated with reduced responsiveness of cells to interferon-α (95). Given these findings, there may be a need to include ss469415590 genotyping in the treatment decisions for interferon-α therapy in patients with HCV infection (66). Although interferon-α therapy is likely to be superseded by the new anti-HCV agents, some patients who are resistant to or intolerant of the new drugs will continue to need interferon-α therapy.



## DOSING

For most drugs, dosing schedules are rather crude. A one-dose-fits-all strategy is the norm rather than the exception. This leads to under- or overexposure to the drug, which in turn leads to either a reduction in efficacy or an increased risk of toxicity, respectively. The dose required by an individual for the optimal therapeutic effect of a drug is determined by many factors, both environmental and genetic.

Warfarin provides a good illustration. Warfarin is the most widely used anticoagulant, typically prescribed to approximately 1% of the population. Individual daily dose requirements vary from 0.5 mg/day to 20 mg/day, with overanticoagulation, as measured by the international normalized ratio (INR), predisposing to bleeding (125). This variability in dose has been attributed to both clinical factors and genetic factors. The clinical factors include age, body surface area, interacting medications, renal function, and nonadherence. The genetic factors affect (*a*) the metabolism of warfarin [the *CYP2C9*2* and *CYP2C9*3* polymorphisms, which are associated with reduced catalytic activity of CYP2C9, in particular account for approximately 15% of the variability in dose requirement (52)] and (*b*) the mode of action of warfarin through the inhibition of vitamin-K epoxide reductase complex. *VKORC1* genetic polymorphisms account for approximately 25% of the variability in dose requirements (52). Taken together, age, body surface area, and genetic factors can account for approximately 50% of the variation in daily dose requirements for warfarin (52), with most of this contribution coming from the genetic factors.

The role of *CYP2C9* and *VKORC1* genetic polymorphisms in determining warfarin dose variation has been extensively replicated in many different populations and patients of different ancestries, although the effect size of the variants varies with ethnicity (53). These results led to a change in the warfarin drug label by the FDA in 2007 and the subsequent introduction of dosing tables in 2010 (30, 63). Many dosing algorithms have also been developed, including the International Warfarin Pharmacogenetics Consortium algorithm, which represents a global collaborative effort (50). However, it is important to bear in mind that warfarin dosing in current clinical practice varies within and between countries, which may impact the utility of genetic factors in predicting starting and maintenance warfarin doses in individual patients. For example, some European Union countries initiate therapy using loading doses, whereas countries in other parts of the world initiate therapy with standard 5-mg doses. Furthermore, the frequency of INR measurements varies; some patients use home testing to determine INR values, whereas others attend anticoagulation clinics; and dosing during maintenance may be based on computer software packages or undertaken manually based on clinical experience (41).

Although warfarin has been regarded as the poster child for pharmacogenomics, the variability in clinical practice, the differences in the algorithms developed, the differential contributions of clinical and genetic factors in determining daily dose according to ancestry, and the variability in phenotypes used to assess warfarin outcomes in pharmacogenetic studies have meant that demonstrating clinical utility through conventional randomized controlled trials was always going to be difficult. Indeed, this has proven to be true with the recent publication of two trials that showed discordant results (56, 91). The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial showed that genotype-guided dosing was superior to standard clinical dosing in maintaining patients within an INR range of 2–3 over 3 months (91); the Clarification of Optimal Anticoagulation Through Genetics (COAG) trial, in contrast, showed no difference between genotype-guided dosing and standard clinical dosing in maintaining patients within an INR range of 2–3 over 1 month (56). The reason for the different outcomes is not entirely clear, but may have been related to the greater heterogeneity of patients in the COAG trial, the different algorithmic strategies used in the two trials, the underlying country differences in the quality of anticoagulant care, and the age differences in the two trials, with the EU-PACT trial having recruited an older age group with predominantly atrial fibrillation.

These results have created a great deal of confusion as to whether there is a need, or indeed an evidence base, for implementing genotype-guided dosing for warfarin in clinical practice. The clinical scenario is further complicated by the fact that four novel oral anticoagulants are now available. Anticoagulation is much more predictable with these novel agents, there is no need for monitoring, and the agents are equally as effective or more effective compared with warfarin (102). They do have disadvantages, however, including higher costs, lack of a pharmacodynamic biomarker, and lack of an antidote. Warfarin will still be needed in the future, but how it will be used is unclear. A stratified approach to anticoagulation is likely needed—particularly in atrial fibrillation—that takes into account not only warfarin but also how clinicians should choose between the four new agents.

## ADVERSE DRUG REACTIONS

### Immune-Mediated Adverse Drug Reactions

The association of serious immune-mediated ADRs—for example, those leading to serious skin or liver injuries—with the HLA genes represents an important advance in pharmacogenomics (89). The role of HLA in predisposing to immune-mediated ADRs has been of interest for a long time. For example, studies in the 1980s showed an association between HLA-DR4 and hydralazine-induced lupus (4). However, the field has been transformed by the availability of improved genotyping techniques and GWAS. Indeed, since the beginning of this century, a large number of HLA alleles have been associated with several serious ADRs (**Table 2**).

There does not seem to be a clear pattern: In some cases, the same HLA allele predisposes to different reactions with different drugs [for example, *HLA-B*57:01* predisposes to both abacavir hypersensitivity (69) and flucloxacillin-induced cholestasis (18)], and in other cases, HLA associations with the same drug show ethnic and phenotype-specific associations [for example, with carbamazepine hypersensitivity (131)]. Most of these associations have been identified using small sample sizes and, despite the use of GWAS approaches, have exceeded genome-wide significance thresholds (89). In many cases, it is difficult to be sure that the HLA alleles implicated represent the causal variants, because of the high degree of linkage disequilibrium in this part of the genome. However, the recent demonstration of novel mechanisms of how drugs can interact in an HLA-specific manner with T cells and lead to immune responses suggests that HLA alleles may be causal

**Table 2 Some of the notable HLA allele associations reported with serious adverse drug reactions since 2000**

| Drug | Class of drug | HLA allele | Phenotype | Reference(s) |
|---|---|---|---|---|
| Allopurinol | Uricosuric | *B*58:01* | HSS, SJS/TEN | 22, 47, 55, 116 |
| Carbamazepine | Antiepileptic | *B*15:02* | SJS/TEN | 14, 22, 46, 65, 72, 76, 117 |
| | | *A*31:01* | MPE, HSS, SJS/TEN | 74, 84 |
| Abacavir | Antiretroviral | *B*57:01* | HSS | 38, 44, 45, 69, 70, 103 |
| Nevirapine | Antiretroviral | *C*04:01* | SJS/TEN | 9 |
| | | *B*35:05* | HSS | 12 |
| Dapsone | Antimycobacterial | *B*13:01* | HSS | 133 |
| Flucloxacillin | Antibiotic | *B*57:01* | DILI | 18 |
| Ximelagatran | Antiplatelet agent | *DRB1*07:01 DQA1*02* | DILI | 57 |
| Lumiracoxib | COX-2 inhibitor | *DRB1*15:01 DQA1*01:02* | DILI | 108 |
| Co-amoxiclav | Antibiotic | *DRB1*15:01* | DILI | 37, 83 |
| Lapatinib | Anticancer | *DQA1*02:01* | DILI | 111 |
| Ticlopidine | Antiplatelet | *A*33:03* | DILI | 40 |
| Statins | Lipid-lowering agent | *HLA-DRB1*11:01* | Myopathy | 71 |

Abbreviations: DILI, drug-induced liver injury; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

(6). Pre-prescription genotyping is used for some drugs; for example, *HLA-B*57:01* genotyping is used in preventing abacavir hypersensitivity, and *HLA-B*15:02* genotyping is used in preventing carbamazepine-induced Stevens–Johnson syndrome in Southeast Asians (89). However, for the other HLA associations—for example, *HLA-A*31:01* and carbamazepine hypersensitivity, and *HLA-B*58:01* and allopurinol-induced serious cutaneous adverse reactions—pre-prescription genotyping is not currently recommended.

The nature of the evidence that will be required for implementation is currently unclear; prospective studies are under way for some of the HLA allele associations, but it seems unlikely that such studies will be possible (or affordable) for all the HLA allele associations reported (**Table 2**). It is also important to note that although prospective studies were performed for both abacavir (70) and carbamazepine (13), the results did not contradict data from the observational studies that preceded the prospective studies.

## Statin Myopathy

Statins are now widely used in clinical practice. However, some patients treated with statins can develop muscle toxicity, which in some cases can be severe enough to cause rhabdomyolysis and death. Indeed, cerivastatin, a highly potent statin, was withdrawn because of an unacceptably high incidence of muscle toxicity. Several clinical factors, including greater age, female gender, and low body mass index, predispose to statin-induced muscle toxicity (129). The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group (106) identified the rs4363657 SNP in *SLCO1B1*, an influx membrane transporter responsible for the transport of some statins, as a risk factor for simvastatin-induced myopathy. The association has been replicated by several other investigators (10, 24, 124) and seems to be associated with simvastatin and to lesser extent with atorvastatin but not with rosuvastatin or pravastatin (7, 19, 124).

**Table 3 Other -omics technologies and associations with drug response**

| Technology | Biomarker | Drug response | Reference |
|---|---|---|---|
| Epigenomics | Hypermethylation of $O^6$-methylguanine-DNA methyltransferase-encoding gene | Efficacy with temozolomide | 126 |
| | miR-24 | Methotrexate resistance | 79 |
| | miR-133a | Regulation of VKORC1 and potential effect on warfarin dosing | 86 |
| Transcriptomics | 21-gene expression array (Oncotype DX) | Prediction of breast cancer recurrence, stratification of chemotherapy use | 58 |
| Proteomics | HMGB1 isoforms | Risk of hepatic failure after acetaminophen overdose | 3 |
| Metabolomics | Metabolomic profile | Potential response to sertraline | 54 |
| Metagenomics | Digoxin inactivation by gut bacteria | Reduced response to digoxin | 35 |

*SLCO1B1* genotyping is not used in clinical practice before statin administration because the predictive accuracy is low, and more recently, other genotypic associations have been identified, including between *HLA-DRB1*11:01* and the subphenotype of immune-mediated necrotizing myopathy (71) and between the rs9806699 SNP in the *glycine amidinotransferase* (*GATM*) gene and modest protection against myopathy (73). These novel associations need to be replicated, and the role of multigene markers in predisposing to statin myopathy needs further evaluation.

## USE OF OTHER -OMICS TECHNOLOGIES

Although this review has focused on the role of genomics in predicting drug response, it is important to remember that other -omics technologies also have an important role. Indeed, these are not competitive but complementary to the use of genomics. In the future, multimarker methodologies that predict drug response may involve biomarkers derived from a number of -omics technologies. **Table 3** provides some examples. Systems approaches that integrate data from various sources (clinical and -omics data) will also identify new pathways for drug efficacy and toxicity and novel biomarker profiles for predicting drug response (78).

## FROM DISCOVERY TO IMPLEMENTATION

The major challenge facing researchers working in the field of personalized medicine is translating their discoveries into clinical practice. However, this challenge is not unique to this field; it is faced by every field of translational research. In an editorial, Poste (94) pointed out that we are good at discovering biomarkers, with more than 150,000 articles in the literature, but only 100 have made it to clinical practice. Four translational gaps have been identified: the basic discovery process, taking the discovery into populations, implementing the discovery into clinical practice, and assessing the impact of the discovery on public health (87). Bridging all four gaps will require multidisciplinary partnerships with complementary areas of expertise. A recent report from the Academy of Medical Sciences (1) includes the involvement of many stakeholders and the creation of collaborative partnerships as two of its key recommendations to accelerate the pace of progress. Other key recommendations include better developing and using informatics systems (in particular linking health records to biomedical informatics), incentivizing industry to develop stratified medicine products, and developing better processes to accelerate implementation and adoption into health care systems.

Robust evidence is important for the clinical implementation of any biomarker that predicts drug response. The introduction of a biomarker into clinical practice without such evidence can lead to unnecessary interventions that do not improve clinical outcomes. This is perhaps typified by the use of prostate-specific antigen as a screening test, which led to unnecessary prostate biopsies and prostatectomies (11); as a result, the US Preventive Services Task Force recently recommended against routine prostate cancer screening (81).

Although purists point to a hierarchy of evidence, with meta-analyses and randomized controlled trials as the highest levels of evidence and expert opinion as the lowest (36), randomized controlled trials may not always be possible, particularly for biomarkers for rare adverse events. An alternative view is that we need to embrace all forms of evidence rather than apply artificial hierarchies, and we should not have entrenched positions but rather should use judgment to interpret the evidence (100). It is the quality of the evidence that is important—after all, a badly designed randomized controlled trial is as useless as a badly designed observational study. Thus, for future pharmacogenomics research, there will be a need to conduct randomized trials in some instances but certainly not in all. Some of the issues that need to be tackled by researchers to improve the evidence have been highlighted previously (88). Furthermore, evidence that is now being gathered from genomic medicine programs, such as the one at Vanderbilt University Medical Center (97), will be important in developing pathways for implementation by providing evidence of effectiveness in real-world settings.

Allied to the quest for evidence from multiple sources is the requirement for better guidance on biomarker qualification, the type of evidence needed for such qualification, and harmonization among global regulatory agencies and with guideline developers to provide some clarity for researchers and clinicians. Particularly important will be treating genetic and nongenetic biomarkers in the same way, rather than requiring higher thresholds of evidence for genetic testing (92). All of this will also provide clearer routes for reimbursement and implementation within clinical practice. In the quest to implement personalized medicine, there will undoubtedly be mistakes, but there will also be successes. We need to learn from both our mistakes and successes. This is encompassed in a quote from the late Steve Jobs: "Sometimes when you innovate, you make mistakes. It is best to admit them quickly, and get on with improving your other innovations."

## CONCLUSION

Pharmacogenomics is one component of the quest for personalized medicine. Although there have been numerous successes in translating pharmacogenomics biomarkers into clinical practice, these have been greatly exceeded by biomarkers that are stuck in the discovery phase. Much work remains. We are fortunate to have so many resources that will contribute to likely successes in the future, including the free availability of detailed genomic information on populations; the availability of high-throughput yet affordable genotyping/sequencing technologies; the increasing use and availability of electronic medical records, which are increasingly being linked to biological archives and databases; and advances in mathematical techniques, combined with computer power, that allow us to pursue systems approaches. Equally important is the willingness of different stakeholders to acknowledge the need for personalized approaches in therapeutics, and the acceptance that we need to work together to achieve our ambitions.

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**Errata**

An online log of corrections to *Annual Review of Genomics and Human Genetics* articles may be found at http://www.annualreviews.org/errata/genom