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Relating Human Genetic Variation to Variation in Drug Responses

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Abstract

Although sequencing a single human genome was a monumental effort a decade ago, more than one thousand genomes have now been sequenced. The task ahead lies in transforming this information into personalized treatment strategies that are tailored to the unique genetics of each individual. One important aspect of personalized medicine is patient-to-patient variation in drug response. Pharmacogenomics addresses this issue by seeking to identify genetic contributors to human variation in drug efficacy and toxicity. Here, we present a summary of the current status of this field, which has evolved from studies of single candidate genes to comprehensive genome-wide analyses. Additionally, we discuss the major challenges in translating this knowledge into a systems-level understanding of drug physiology with the ultimate goal of developing more effective personalized clinical treatment strategies.

Keywords

Pharmacogenomics; genome-wide association studies; next-generation sequencing; 1000 genome project; personalized medicine

Genetic variation likely contributes substantially to the variation in drug response observed across human populations. The field of pharmacogenomics, which seeks to relate genetic variability to variability in human drug response, has evolved considerably from candidate gene studies to studies of variation across whole genomes of human populations containing individuals who exhibit a range of responses to different drugs. The initial successes in the field often identified genetic variants within drug metabolizing genes that had large effects on sensitivity to a given drug. The field has since broadened in scope to encompass regulatory mutations, and refined techniques have allowed the identification of mutations with smaller effect sizes. Whereas early pharmacogenomics studies sought primarily to identify associations between common genetic variation and drug response, more recent

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approaches have begun to identify mRNAs, microRNAs, and other downstream events that are influenced by genetic variation and may underlie variation in pharmacologic responses.

A primary aim of pharmacogenomics has been to uncover novel human genetic variants that affect therapeutic response phenotypes and to identify the genes responsible for those phenotypic differences. The ultimate goal of the field has been to use an understanding of these relationships to devise novel personalized pharmacological treatment strategies that maximize the potential for therapeutic benefit and minimize the risk of adverse side effects for any given medication. The potential cost savings (via increased drug efficacy) and decreased morbidity and mortality (via increased drug safety) is immense. Advances in DNA sequencing and polymorphism characterization technologies have driven the field from a hypothesis-driven approach to a discovery-oriented, genome-wide approach that requires few assumptions regarding which variants are most relevant for outcome. Candidate gene approaches resulted primarily in the identification of genetic variants in drug metabolizing genes with large effects on toxicity or response [1], however, many genome-wide association studies (GWAS) have identified novel associations between drug response and genetic variants with unknown functional relevance and often with relatively small effect sizes [2]. The recent development of high-throughput sequencing techniques has allowed researchers to begin to examine the contribution of rare variants to drug sensitivity [3]. Although many important discoveries have been made, several challenges remain before the dream of personalized medicine will be realized. First, we must move from collecting large numbers of identified genetic variants to systematically analyzing them. Second, we must find ways to turn this systematic biological understanding into clinical strategies for treatment. The aim of this review is to provide an overview of recent exciting trends towards meeting these challenges.

Evolution of analytical methods for pharmacogenomic discovery

As shown in Figure 1, candidate gene approaches aim to study the relationship between either a single gene or a group of pathway-related genes and a drug-related phenotype. The single gene approach offers the advantage that highly relevant genes can be prioritized and tested first. This approach places greater burden on the researcher to choose good candidates. The pathway gene approach involves studying several candidate genes that function together to carry out related functions. Examples of pathways are genes related to drug metabolism (pharmacokinetics) or to drug responses (pharmacodynamics). A primary advantage of the candidate pathway gene strategy is the ability to identify effects of an aggregate of genes on a phenotype in circumstances where individual genes have small effects on the downstream phenotype. In addition, the association information of gene pathways may be more immediately understandable than single genes with regard to the mechanism of drug action [4]. However, the potential always exists that important unknown genes will be missed because only genes which are thought a priori to be involved in drug response are included in the study. Obviously, the success of this approach is heavily dependent on the assumptions underlying the selection of genes to be studied. Unexpected genes that play an important role in the pharmacokinetics and pharmacodynamics of the drugs would remain undiscovered.

Technologies for DNA genotyping and sequencing have undergone several evolutionary, if not revolutionary, steps of advancement. Genotyping of single nucleotide polymorphisms (SNPs) can now be performed at high density relatively cheaply with microarrays. At the same time, the rapidly decreasing cost of sequencing allows for entire genomes to be sequenced much more economically than before, thus enabling novel polymorphisms and rare mutations to be characterized. Thus the pharmacogenetic studies of yesterday (that relied heavily on candidate gene approaches) have evolved into pharmacogenomics studies

(using genome-wide analysis approaches). Generally, the limitations of candidate gene approaches have been solved by genome-wide approaches, which offer a more complete and unbiased picture of significant genome relationships. Several discovery and replication GWAS have successfully identified variants associated with pharmacogenomic phenotypes [2].

GWAS are not without problems, however, and these problems are not unique to pharmacogenomics. GWAS are generally insensitive to both structural and rare variants [5], although these are not likely to be a significant proportion of the total variation. Furthermore, the high number of false positive results is a substantial problem that continues to plague GWAS. Because it is difficult to functionally validate the large number of GWAS hits, results of replication cohorts are essential for building confidence in identified associations, narrowing the number of hits to be followed up on [5]. Additionally, large sample sizes are required to generate enough statistical power to overcome the multiple hypotheses that are often tested in GWAS [5]. Finally, even once a variant is identified, there is often little information to suggest its functional relevance [5]. Several approaches were developed to mitigate this last problem including the use of more biologically relevant endophenotypes, intermediate outcomes between the genotype and phenotype (Box 1).

Box (1)

The endophenotype concept

The term “endophenotype” was coined in 1966 to distinguish between exophenotype (external) and endophenotype (internal) [72]. Gottesman and Shields [73] defined an endophenotype to be “an internal phenotype discoverable by microscopic examination or biochemical test”. Endophenotype is referred to as an intermediate outcome that is generally closer to the phenotype than to the genotype [74]. In general, an endophenotype must meet the following criteria [75]: (i) it must be linked with an illness in a population, (ii) it must be heritable, (iii) it must manifest itself whether or not the illness is active, and (iv) it must co-segregate with an illness in families. The endophenotype concept has been extensively utilized in studies of psychiatric disorders (reviewed in [76]). This might have been because of the difficulty in precisely quantifying psychiatric disorder criteria. Recently, the endophenotype concept has been applied more broadly in genetic analyses of complex diseases [77]. For pharmacogenomic studies, one of the reasons for the introduction of this concept was the complexity of the processes that affect drug response and toxicity. It is generally easier to focus on a small group of genetic variants that have a large effect on the endophenotype, such as myotoxicity, the most common side effect of statins. The pathophysiology of this toxicity is not fully understood. Therefore, toxicity is defined in clinical trials by looking at a proxy, creatine kinase levels, which, if greater than 10 fold the normal value, indicates toxicity [78]. Similarly, the read out for the toxic effect caused by inhibitors of the vascular endothelial growth factor (VSP) signaling pathway (e.g., sorafenib) is hypertension [79]. Quantitative changes in blood pressure rather than elevation above a pre-defined threshold is used as an endophenotype in this case. The use of ambulatory blood pressure monitoring has allowed more confident measurements than office checks as it can provide 40–100 measurements/day [80]. This could help in the selection of the proper VSP inhibitor and its appropriate dose [79]. Another example of an endophenotype is an increase in alanine transaminase [81], which is indicative of drug-induced liver dysfunction. A non-TT genotype at GGH (gamma-glutamyl hydrolase), T16C, is associated with significant risk of liver failure in Japanese patients, as the C allele may alter the activity of the GGH enzyme [81]. To help further assess drug responses, the Phenotype Standardization Project (PSP) was initiated in order to define in detail three different types of adverse

drug reaction: drug-induced liver injury, drug-induced skin injury, and drug-induced torsade de pointes that were used in GWAS [82].

The candidate gene approach still plays a role even in the era of GWAS [6]. For example, this approach will be needed when looking at polymorphisms with low allele frequency. Additionally, it will be needed in the post-GWAS phase to follow up with functional validation studies or for deeper resequencing of interesting candidate genes that showed convincing association in earlier GWAS [6]. Another potential useful function of a candidate gene approach is to validate a GWAS by being “found” within the GWAS. Examples of this include a GWAS that identified the aspartate metabolism pathway as a contributing factor in asparaginase sensitivity [7] and the presence of variants in DNA repair and glutathione genes in a GWAS focused on platinating agents [8].

It is clear that the trend towards GWAS will continue, and likely even accelerate, although these studies may be aided by candidate approaches. Table 1 shows a list of published pharmacogenomics GWAS between 2010 and 2012. One recent successful GWAS examined adverse reactions induced by flucloxacillin, which is an antimicrobial agent used to treat gram-positive infections that works by inhibiting the synthesis of bacterial walls. The major adverse reaction to flucloxacillin is drug-induced liver injury (DILI). A GWAS was carried out using 51 cases and 282 controls matched for ancestry and sex [9]. The study showed that a SNP in complete linkage disequilibrium with *HLA-B*5701* is associated with DILI. This was then confirmed in flucloxacillin-tolerant controls and replicated in a second cohort [9].

The continued evolution of next-generation sequencing (NGS) platforms has resulted in a dramatic drop in both the time and cost for genome sequencing [10], leading to a rapid increase in its usage in pharmacogenomics. The 1000 Genomes Project uses these state-of-the-art high-throughput sequencing technologies for the in-depth characterization of human genome sequence variation. The goal for this project is to describe more than 95% of the variants with an allele frequency of at least 1% in each of five major populations [11]. As many of the samples in the 1000 Genomes Project were also International HapMap lymphoblastoid cell lines (LCLs) the project will provide a comprehensive resource for studying the relationship between genotype and cellular phenotype [12].

One of the problems associated with GWAS is that they have thus far been unable to detect the effect of rare SNPs on drug response and toxicity. The size of the pharmacogenomics GWAS has dramatically limited their statistical power. In order to increase the power of GWAS with smaller sample sizes, a new method was developed that incorporates rare variants. It examines the degree of correlation between uncommon alleles and drug response. If these genes are associated with an atypical drug response, then they are considered predictive pharmacogenes [13]. Applying this method on warfarin GWAS data [14] resulted in the identification of *VKORC1* and *CYP2C9* as warfarin pharmacogenes, although the original study reported only *VKORC1* as significant [13]. Pharmacogenomic studies have begun to use data from the 1000 Genomes Project. A recent application showed that the imputation of 1000 Genomes Project SNPs in pathways identified by pharmacometabolomic data can improve and accelerate pharmacogenomics studies [15]. In cell-based studies (described below), the 1000 Genomes Project data can provide valuable information regarding rare variants that contribute to cellular pharmacologic phenotypes.

Examples of pharmacogenomic gene-drug pairs

Personalized drug therapy is especially desirable where the therapeutic index is narrow (i.e., having little difference between toxic and therapeutic doses) and when the consequences of

drug toxicity are life-threatening [16]. These drugs (including antineoplastics, anticoagulants, and anti-HIV therapeutics) are often administered at maximally tolerated doses, which are typically chosen from population averages, resulting in up to one-third of treated patients developing toxicity and a significant proportion of treated patients exhibiting poor or no response. Drugs modulating hemostasis, such as clopidogrel and warfarin, have narrow therapeutic indexes, and genetic variability in the cytochromes P450 (*CYPs*) can influence outcome [17, 18]. Warfarin remains the most widely used anticoagulant [19], and the identification of genetic variants associated with toxicity of this drug is particularly important because high levels of this drug can cause internal bleeding. Variance in warfarin toxicity can be explained by heritable differences in *CYP2C9* and in the vitamin K oxidoreductase complex-1, *VKORC1*, an enzyme involved in the drug's mechanism of action. Genetic testing is estimated to reduce risk of hospitalization by as much as 30% [20]. The United States Food and Drug Administration (FDA) changed the label for warfarin twice; in 2007 the FDA indicated that genotyping of *CYP2C9* and *VKORC1* may be useful in the determination of the initial dose [21]. In 2010, the label was updated to include recommended dosage ranges [22].

Another example of a well-characterized gene-drug pair is clopidogrel, a drug used in combination with aspirin to prevent atherothrombosis after acute myocardial infarction [23]. It requires the transformation to an active metabolite by CYP enzymes [24]. The active metabolite then binds to adenosine diphosphate P2Y₁₂, which inactivates the fibrinogen receptor, which is involved in platelet aggregation [23]. Early studies showed that patients with the allelic variant *CYP2C19**2 had generally lower levels of the active metabolite, which led to reduced platelet inhibition activity and higher rates of cardiac events, particularly thrombosis, compared to controls [24]. Several studies have confirmed these results and further linked other loss-of-function *CYP2C19* allelic variants to undesirable cardiovascular system effects following treatment with clopidogrel [17, 23, 25]. A recent study showed that if the patient was a *CYP2C19**2 heterozygote, then tripling the maintenance dose could achieve platelet inhibition results similar to noncarriers that were administered the regular dose [26]. Surprisingly, another study showed that *CYP2C19* loss-of-function did not alter the safety and efficacy of clopidogrel in patients with acute coronary syndromes [27]. An alternative to clopidogrel is ticagrelor, which is a new-generation antiplatelet agent that reversibly, directly, and noncompetitively antagonizes the P2Y₁₂ receptor. Recently, it was shown that the efficacy of ticagrelor was not affected by the *CYP2C19* genotype. Ticagrelor was more efficacious than clopidogrel even in individuals predicted to be clopidogrel responders [28]. There may be other unknown variants that could affect the efficacy of ticagrelor. Identifying these variants would allow clinicians to better individualize treatment according to the needs of the each patient.

Lastly, recent statistics have indicated that more than 170 million individuals worldwide are chronically infected with hepatitis C virus (HCV) [29]. Complications of this infection include liver cirrhosis, hepatic injury, and hepatic fibrosis [30]. Over the last decade, peginterferon has been used alone or in combination with ribavirin for 24–48 weeks as the standard of care for the treatment of this infection [30]. Patients who respond to this standard of care achieve a sustained virologic response (SVR) that is associated with good quality of life [30]. Several independent GWAS showed that genetic variation in *IL28B* was associated with the positive response to this combination of drugs [29, 31, 32]. This genetic variation was also able to predict treatment response in the HCV patients co-infected with HIV [33] [34]. These are just a few examples of drug-gene pairs of significance to the healthcare community.

Cell-based models to complement clinical studies

Clinical studies, like those described above, contributed greatly to the success of pharmacogenetics discoveries [35]. According to the clinicaltrials.gov website, there are more than 650 clinical trials that involve pharmacogenomics and many of them are still recruiting patients. Although humans are the most relevant model, there are problems with accruing large numbers of patients receiving the same dose of drug without confounders such as concomitant medications, diet, and other variables. Large clinical trials are extremely expensive and require the coordination of many individuals. Some of the challenges with clinical trials can be circumvented by using cell-based models for either discovery or replication of pharmacogenomic findings.

One cell-based model that has emerged as a promising model system in the study of the genetics of drug response is the use of human Epstein-Barr virus-transformed lymphoblastoid cell lines (LCLs). The cells provide a cost-effective testing system in which environmental factors can be controlled [36]. Combining this with information from *HapMap* LCLs, which includes publicly available genotype and sequencing data, enables GWAS between *HapMap*/1000 Genomes Project variants and pharmacologic phenotypes measured in the LCLs after drug or radiation treatment such as cell growth inhibition, changes in gene expression, intracellular concentration of drug/metabolite, and apoptosis. Recent studies from a number of groups using preclinical cell-based models have taken top GWAS hits (i.e., SNPs with lowest P-values) from these models and validated them in prospective clinical trials [37–39].

Cell lines can also be employed for follow-up functional studies because the genetic architecture and expression environment of the International *HapMap* LCLs is known. The most commonly used phenotypes in cell based models are the following: cell growth inhibition (IC₅₀) [40], apoptosis [41], gene expression either at baseline or after treatment [42], and transport of drug molecules[43]. However, there are some drawbacks to using cell-based models. For example, important CYP450 enzymes are not expressed in LCLs, there may be *in vitro* confounders, and the generation of these cell lines from a limited number of tissues are the major limitations of this model [36].

Nevertheless, cell-based models have been applied successfully to various aspects of pharmacogenomics, including pharmacogenomics discovery [44], transcriptional profiling and expression quantitative trait loci (eQTL) studies [45], studies of interethnic differences in drug response [46, 47], and heritability analyses [48–50]. Additionally, discoveries using cell-based models have been translated into clinical findings. For example, to understand the inter-individual differences in asparaginase sensitivity in patients treated for childhood acute lymphoblastic leukemia (ALL), the results obtained via genome-wide pathway analysis in *HapMap* LCLs were validated in ALL leukemic blast samples [7]. Both indicated that SNPs in the aspartate metabolism pathway were associated with asparaginase sensitivity in patients [7]. Another example is that one of the top SNPs from a GWAS of carboplatin sensitivity in *HapMap* LCLs was replicated in an initial analysis of patients receiving carboplatin and paclitaxel but was not significant in patients from multiple cohorts [38]. This study emphasizes the need for extensive validation in patients for predictors discovered via a cell-based approach. Additionally, to understand the genetic basis of variability in the response to platinum-based chemotherapy in lung cancer patients, both LCLs and lung cancer patients were examined [51]. A GWAS for cisplatin cytotoxicity in 283 LCLs resulted in a list of 157 top SNPs, of which nine and 10 were correlated with overall survival in non-small cell lung cancer and small cell lung cancer patients, respectively [51]. Unfortunately, these SNPs were not significant after adjusting for multiple testing but follow-up studies confirmed the functional effect of genes correlated with these SNPs in

cisplatin response *in vitro*. Additional replicates in independent samples of patients are still needed to validate the findings.

The advantage of GWAS is the simultaneous, unbiased testing of millions of SNPs; the challenge is that functional information is absent for the vast majority of loci that are implicated in a particular phenotype. To overcome this challenge, the LCL model can be used to study the function of the identified variants. In addition to the genetic data, baseline expression data using Affymetrix exon [52] and Illumina expression arrays [53], miRNA data using Exiqon arrays [54], and DNA methylation patterns [55] are available. This data can be combined to assign endophenotypes, which can then be used to reduce the complexity of GWAS (Box 1). Protein data will also be highly valuable in determining the function of variants. Pharmacologic GWAS results are enriched for eQTLs [56], providing a starting point for investigating the function of the pharmacologically associated variants in cell-based models.

Implementation of pharmacogenomic discoveries

There is a growing consensus that pharmacogenomic biomarkers will be a chief player in health care [57]. Although a large number of studies on pharmacogenomic discoveries have appeared in the literature, the majority have not migrated into clinical laboratories. This is due in part to the lack of reproducibility of some gene/drug pairs and the questionable utility of the findings in a large population [58]. This problem is aggravated in countries with developing or emerging economies, as the evidence for pharmacogenomics testing is often based on a population different than their own [59]. Evidence from large-scale prospective randomized clinical trials is lacking, but several are currently in progress [58]. PREDICT is an example of a double-blind prospective randomized trial of a pharmacogenetic test to prevent side effects [60]. It demonstrated the utility of *HLA-B*5701* screening for the prediction of the incidence of immunologically-confirmed hypersensitivity reaction in patients administered abacavir [60]. Abacavir is now one of the most successful examples of pharmacogenomics testing integrated into clinical practice, indicating the efficacy of this type of trial.

A second hurdle to using pharmacogenomics in the clinic is economic [61]. Many physicians feel the costs of genotyping outweigh its potential benefits [62]. However, the notion that genotype-guided therapy is not cost-effective may be incorrect. For example, a recent study showed with mathematical modeling that genotype-guided clopidogrel therapy for specific patients was more cost-effective than prescribing it or its alternative, prasugrel, for all patients [63]. Other issues holding up wide-spread use of pharmacogenomics related to the clinical laboratory include the need for genotyping accuracy and trained clinicians with adequate expertise to interpret test results [64]. A recent survey indicated that the lack of physician knowledge and awareness is a major challenge for the implementation of pharmacogenomics testing [59]. Finally, privacy concerns and electronic tracking of diagnostic information also pose a challenge to this new era of medicine [61].

Developing companion diagnostic tests in conjunction with therapeutics allows the design of better clinical trials and eventually better implementation of pharmacogenomics testing [65]. In July 2011 the FDA released draft guidelines that required companion diagnostic tests to be approved simultaneously with their accompanying therapies if necessary for safe and effective use of the medication [65]. A recent survey showed that an average of 30–50% of drugs under development have an accompanying biomarker program, but only 10% of them are expected to be launched with a companion diagnostic in the next 5–10 years [61]. Examples of drugs approved recently by FDA with their companion tests are listed in Table 2.

Consortiums to move pharmacogenomics forward

As a result of substantial advances in the field of pharmacogenomics, the FDA has begun to update the labels of many drugs to include information about pharmacogenes to guide therapeutic strategies. A complete list of the drug genotype pairs cited by FDA mandated labels can be found online (<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>). In terms of research dedicated to this field, the National Institute of Health initiated the Pharmacogenomics Research Network (PGRN) to implement studies in basic, translational, and clinical science to advance pharmacogenomics in 2000 (<http://www.nigms.nih.gov/Research/FeaturedPrograms/PGRN/>). PharmGKB, the premier public site that curates knowledge about the impact of genetics on drug response for clinicians and researchers works closely with PGRN to disseminate knowledge gained within and outside of this network (<http://www.pharmgkb.org/>). Another offshoot of the PGRN network is the Clinical Pharmacogenetic Implementation Consortium (CPIC), which has the goal of gathering evidence for clinical implementation of drugs [66]. CPIC was formed in late 2009 in order to solve issues preventing the implementation of pharmacogenomics [66]. To date, CPIC has provided guidelines for *HLA-B*/abacavir [60], *CYP2D6*/codeine [67], *TPMT*/thiopurines [68], *CYP2C9* and *VKORC1*/warfarin [22], and *CYP2C19*/clopidogrel [69]. Outside the United States, the Pharmacogenetics Working Group within the Royal Dutch Association for the Advancement of Pharmacy is working to develop pharmacogenetics-based therapeutic recommendations [70, 71]. Finally, the Personalized Medicine Coalition (PMC) was launched in 2004 to build the foundation that underpins the advancement of personalized medicine as a viable solution to the challenges of efficacy, safety, and cost (www.personalizedmedicinecoalition.org).

Concluding remarks

Pharmacogenomic studies over the last three decades have resulted in an overwhelming amount of evidence that genetic variation plays a major role in drug response variability. Over the last few years, GWAS provided some interesting findings mainly due to the large effects of these genes on drug response and toxicity. Over the next few years more comprehensive studies involving genome-wide associations and NGS are likely to dominate the field. Finally, the Achilles heel of this field is the implementation of findings into regular clinical practice. This being tackled by several large academic centers focused on the implementation of pharmacogenomics discoveries into routine clinical care to help guide clinical decisions. However, the true challenge will be in the adoption of these tests by mainstream physicians.

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Figure 1. The evolution of pharmacogenomics

The diagram depicts the different advantages and disadvantages for candidate gene approaches, candidate pathway genes approaches, genome-wide association studies (GWAS), and next-generation sequencing. New techniques (e.g., GWAS) do not necessarily replace old strategies (e.g., candidate gene approach). Examples of the candidate gene approach include the gene/drug pairs (*UGT1A1*/Irinotecan). Examples of GWAS include the gene/drug pairs (*IL28B*/Peginterferon alfa-2b).

Table 1
List of published pharmacogenomics genome wide association studies between years 2010–2012

Drug	Response/toxicity	Number of cases	Genome-wide significance/replication	Lowest P- value	significant gene(s)	Refs.
5-fluorouracil (5-FU), either alone or in combination with oxaliplatin (FOLFOX)	Diarrhoea, haematologic, mucositis, nausea/vomiting, neuropathy (FOLFOX only)	221, 791	No/Yes	$P=1.076 \times 10^{-45}$	None	[83]
Antipsychotics (Olanzapine, Perphenazine, Quetiapine, Risperidone and Ziprasidone)	QT prolongation	738	Yes/No	1.54×10^{-7}	<i>SLC22A23</i>	[84]
Pegylated interferon and ribavirin (PEG-IFN/RBV)	Thrombocytopenia	303, 391	Yes/Yes	$8.17 \times 10^{-9}/5.29 \times 10^{-17}$ (combined)	<i>DDR6K1</i>	[85]
Cisplatin	Cytotoxicity	283 ethnically diverse LCLs, 222 small cell lung cancer (SCLC) and 961 non-SCLC (NSCLC) patients	No/Yes	1.66×10^{-7}	None	[86]
Nevirapine	Rash	149,233	Yes/Yes	$1.6 \times 10^{-4}, 2.6 \times 10^{-5}$	<i>CCHCR1</i>	[87]
Aromatase inhibitors	Musculoskeletal adverse events (MS-AEs)	878	Yes/No	6.67×10^{-7}	<i>TCL1A</i>	[88]
Carboplatin	Carboplatin sensitivity (cell model), progression-free survival (PFS) (patients)	87 (discovery), 54 (replication), Phase I validation (377), Phase II validation (1326)	Yes/Yes	9.84×10^{-6}	<i>ALDH2</i>	[89]
Inhaled corticosteroids	Difference in forced expiratory volume in 1 second (FEV1)	418,407	Yes/Yes	2.09×10^{-6} 6.13×10^{-6} (Combined p value)	T-gene	[90]
Inhaled glucocorticoids	Difference in FEV1	118, 935	Yes/Yes	7×10^{-4}	<i>GLCCI1</i>	[91]
Carbamazepine	Cutaneous adverse drug reactions (cADRs)	935, 60	Yes/Yes	1.18×10^{-13} 3.64×10^{-15}	<i>HLA-A</i>	[92]
Gemcitabine plus either bevacizumab or placebo	Overall survival	351	Yes/No	9.51×10^{-7}	<i>(IL)17F</i>	[93]
Antipsychotics	Extrapyramidal symptoms (EPS)	409	No/No	8.953×10^{-6}	None	[94]
Citalopram	Clinical scoring for response in depression	1,948	No/No	5×10^{-7} (response) 4×10^{-7} (remission)	None	[95]
Epirubicin	Leukopenia	473, 48	Yes/Yes	1.59×10^{-7} 2.27×10^{-9} (combined)	microcephalin 1	[96]

Drug	Response/toxicity	Number of cases	Genome-wide significance/replication	Lowest P- value	significant gene(s)	Refs.
Lamotrigine- and phenytoin	Hypersensitivity reactions	1386	No/No	None was significant	None	[97]
Fenofibrate	Systematic inflammation	1092	No/No	None was significant	None	[98]
Allopurinol	Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN)	1005	Yes/No	2.44×10^{-8}	<i>BAT1</i> , <i>HCP5</i> , and <i>MICC</i>	[99]
Lumiracoxib	Liver injury	217, 503	Yes/Yes	4.4×10^{-12} 6.8×10^{-25}	<i>HLA</i>	[100]
Aspirin	Aspirin intolerant asthma	180,592	Yes/Yes	6.0×10^{-5} 3×10^{-5}	<i>CEP68</i>	[101]
Angiotensin- converting enzyme (ACE) inhibitors	Blood pressure response	1023, 428	Yes/Yes	3.0×10^{-25} 2.3×10^{-10}	ABO gene	[102]
Amoxicillin- clavulanate	Drug-induced liver injury	733,396	Yes/Yes	4.8×10^{-14} 5×10^{-10}	<i>HLA</i>	[103]
Carbamazepine	Hypersensitivity reaction	4052, 145	Yes/Yes	3.5×10^{-8} 1.1×10^{-6}	<i>HLA</i>	[104]
Bisphosphonate	Osteonecrosis of the jaw	107	Yes/No	7×10^{-8}	<i>RBMS3</i>	[105]

Table 2

The most recently FDA approved drugs with their companion diagnostics tests

Drug name	Cancer type	Mechanism	Companion diagnostic	Approval date
Zelboraf (Vemurafenib)	BRAF V600E mutation - positive, inoperable or metastatic melanoma.	a BRAF inhibitor, blocks the function of the V600E-mutated BRAF protein.	Cobas 4800 BRAF V600 Mutation Test (Roche)	August 2011
Xalkori (Crizotinib)	Late-stage, non- small cell lung cancers (NSCLC) expressing the abnormal anaplastic lymphoma kinase (ALK) gene.	Blocking certain kinases, including the protein produced by the abnormal ALK gene	Vysis ALK Break Apart FISH Probe Kit	August 2011