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Review

The emerging era of pharmacogenomics: current successes, future potential, and challenges

Lee J.W., Aminkeng F., Bhavsar A.P., Shaw K., Carleton B.C., Hayden M.R., Ross C.J.D. The emerging era of pharmacogenomics: current successes, future potential, and challenges.
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The vast range of genetic diversity contributes to a wonderful array of human traits and characteristics. Unfortunately, a consequence of this genetic diversity is large variability in drug response between people, meaning that no single medication is safe and effective in everyone. The debilitating and sometimes deadly consequences of adverse drug reactions (ADRs) are a major and unmet problem of modern medicine. Pharmacogenomics can uncover associations between genetic variation and drug safety and has the potential to predict ADRs in individual patients. Here we review pharmacogenomic successes leading to changes in clinical practice, as well as clinical areas probably to be impacted by pharmacogenomics in the near future. We also discuss some of the challenges, and potential solutions, that remain for the implementation of pharmacogenomic testing into clinical practice for the significant improvement of drug safety.

Conflict of interest

The authors have applied for patents based upon some of the work related to predictive markers of ADRs to cisplatin and anthracyclines described in this review. The funding agencies had no role in study design; collection, analysis and interpretation of data; writing of the report; or the decision to submit the report for publication.

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Mounting evidence has showed that variation in a patient's genome can significantly affect inter-patient disparities in drug response (1). Pharmacogenomics aims to uncover genetic variants that influence drug response in order to tailor a patient's therapy based on their genetic make-up. Indeed, a significant limitation of evidence-based drug therapy is that clinical trials only provide information on the average response of drug therapies at standard doses in relatively small, specific populations. At the same dose, a group of patients can experience no therapeutic effect while others develop serious adverse drug reactions (ADRs). This can lead to expensive and potentially life-threatening consequences. Each year in the United States alone, approximately

2 million people suffer drug-related adverse events, accounting for 7% of all hospital admissions (2, 3). More importantly, serious drug toxicities cause over 100,000 deaths with costs estimated to be over $30–$100 billion dollars annually (2, 4).

Initial pharmacogenomic studies have focused on candidate genes that encode proteins hypothesized to be involved in the absorption, distribution, metabolism and excretion (ADME) of specific drugs. Completion of the Human Genome Project, combined with advances in high-throughput genotyping and DNA sequencing, has shifted the focus of pharmacogenomic studies to explore a broader, genome-wide spectrum of potential genetic contributions. These studies have uncovered novel genes and biological pathways that influence drug response. By understanding a direct relationship between an individual's genotype and drug response, pharmacogenomics has the potential to empower clinicians with the ability to optimize the effectiveness and safety of drug therapy.

In this review, we highlight examples of pharmacogenomics in clinical practice to illustrate the potential of personalized drug therapy, and we describe on-going research initiatives and remaining challenges as we move toward a paradigm of personalized medicine.

Current successes in pharmacogenomics

Codeine

Codeine is a widely used opioid drug indicated for the treatment of mild to moderate pain in children and adults. Codeine (3-methyl morphine) itself does not elicit a strong analgesic effect, but is converted in the liver to its pharmacologically active metabolite, morphine, which has an approximately 600-fold greater affinity to the opioid receptor than the prodrug (5). Recently, the use of codeine in young children has received scrutiny because of codeine-related toxicities. Neonates have developed serious or fatal adverse reactions after receiving breast milk from mothers taking standard prescribed doses of codeine for post-partum pain (6, 7). In addition, there have been reports of children who developed similar adverse effects from taking codeine for pain relief after tonsillectomies and adenoidectomies (8, 9). In these rare but serious cases, the mothers and patients were shown to carry genetic mutations that enhanced their ability to metabolize codeine, resulting in toxic levels of morphine in their blood (7, 8).

The enzyme responsible for the biotransformation of codeine to morphine [cytochrome P450 2D6 (CYP2D6)] is highly polymorphic, with over 100 genetic variants described in the *CYP2D6* gene (10). Specific combinations of these alleles result in a wide range of enzyme activities. Patients with three or more functional copies of *CYP2D6* are classified as ultra-rapid metabolizers (UM) and rapidly convert codeine to toxic levels of morphine, even at low doses. As a result, severe life-threatening adverse events such as respiratory depression, and in rare cases death, have been reported in individuals carrying these high activity alleles (*CYP2D6*1xN/*2xN/*17xN/*35xN;* where *N* represents copy number) (8, 11). Conversely, poor metabolic activity of CYP2D6 is because of genetic variants that disrupt enzyme function or cause *CYP2D6* deletions. Poor metabolizers (PM) are unable to effectively convert codeine into morphine, resulting in minimal analgesic effect and pain relief (12). Consequently, the amount of morphine produced from the parent drug codeine can be highly variable between individuals, ranging from 0% to nearly 75% of the total codeine dose (11). The frequencies of *CYP2D6* polymorphisms are highly variable based on genetic ancestry, contributing to population-specific differences in codeine response (13). In some populations the CYP2D6 duplication occurs in over 28% of the population, which may account for the identification of toxicity in multicultural cities, such as Toronto, Canada (14). Recently, polymorphisms in other genes involved in the metabolic pathway of codeine, including *UGT2B7* and *ABCB1,* have also been implicated with differences in codeine response (15, 16).

In light of these findings, the US Food and Drug Administration (FDA) has twice revised the codeine label to warn of the increased risk of morphine overdosing in individuals with the ultra-rapid metabolizing genotype. Despite these warnings, codeine is still widely used in some countries. Clinical practice guidelines have recently been developed to inform physicians on the use of genetic testing for safer and more effective codeine dosing, by identifying individuals who will not benefit from therapy or are at an increased risk for serious toxicity (10, 17).

Warfarin

For decades, warfarin has been the mainstay of therapy for prevention and treatment of venous thromboembolism. Warfarin functions as an anticoagulant by inhibiting the enzyme vitamin K epoxide reductase, encoded in *VKORC1*, and decreasing the amount of vitamin K available for synthesis of coagulation factors. The warfarin dose needed to achieve target anticoagulation has been shown to vary by as much as 20-fold between patients. Although highly effective, its narrow therapeutic window results in large numbers of adverse events, such as bleeding or thrombosis, because of inappropriate dosing in individuals (18).

Both clinical and genetic factors have been shown to significantly influence the required dose of warfarin. For example, genetic variants in *VKORC1* as well as the cytochrome P450 2C9 (*CYP2C9*) gene, which is primarily responsible for metabolizing the pharmacologically active *S*-warfarin isomer, confer an increased sensitivity to warfarin (19). Patients carrying these variants [*VKORC1* rs9923231, *CYP2C9* rs1799853 (**2*), rs1057910 (**3*)] require lower warfarin doses to achieve equivalent therapeutic effects (20, 21). Furthermore, these variants are associated with a higher incidence of above-range international normalized ratios (INRs) and a greater risk of warfarin-induced bleeding (22). Several other genes that are involved in the vitamin K pathway have also been shown to influence warfarin dose,

including cytochrome P450 4F2 (*CYP4F2*) and gamma glutamyl carboxylase (*GGCX*) (23, 24). However their impact on dose variability is relatively minor after accounting for *VKORC1* and *CYP2C9* variants. Recently, studies have also demonstrated significant associations between warfarin dose and *VKORC1*/*CYP2C9* genotypes in pediatric patients, providing evidence that these same genetic variants are also important for warfarin dosing in children (25–27).

Several pharmacogenetic-based dosing algorithms have been developed to more accurately predict the required warfarin dose for an individual patient (28, 29). The majority of these algorithms also account for patient-specific factors, such as age, gender and concomitant medications when estimating a therapeutic dose. Clinicians who are interested in using genetic information for patient management can access these algorithms online (for example, www.warfarindosing.org), or downloaded as smartphone applications (for example, iWarfarin) (30). In addition, the FDA has updated the warfarin (Coumadin) product label to include a dosing table with recommended dose ranges according to *VKORC1*, *CYP2C9*2* and **3* genotypes (31). Unfortunately, the clinical benefit of genetic testing to guide warfarin therapy continues to be debated. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has recommended dosing based on genotype (32), while other groups, such as the American College of Chest Physicians, have recommended against routine testing because of lack of evidence from randomized control trials showing a benefit (33). Research in warfarin pharmacogenetics is underway to determine the impact of genotyping on patient outcomes compared to current clinical practice.

Carbamazepine

Carbamazepine is an anticonvulsant indicated for the treatment of epilepsy, trigeminal neuralgia, bipolar disorder and other seizure disorders. It is one of the most frequently used antiepileptic drugs in both children and adults (34, 35). In some patients, carbamazepine causes severe and life-threatening cutaneous adverse reactions, including drug-induced hypersensitivity syndrome (HSS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (36). HSS is characterized by generalized skin eruptions, high fever and involvement of at least one internal organ, with a mortality rate of approximately 10%. Although rare, SJS and TEN are serious blistering reactions of the skin and mucous membranes that can be permanently disabling or fatal, with mortality rates up to 10% and 50%, respectively (37).

In both adults and children, carbamazepine-induced hypersensitivity reactions have been highly associated with genetic variants in the human leukocyte antigen (HLA) region. Patients carrying the *HLA-B*1502* variant are at significantly higher risk of SJS/TEN (38, 39) while the *HLA-A*31:01* allele is primarily predictive for HSS (37, 40). The genetic risk for carbamazepine-induced SJS/TEN is largely dependent on a patient's ancestry. The frequency of the *HLA-B*1502* variant is high (10–15%) across broad areas of Asia including China, Indonesia, Malaysia, Taiwan, Thailand and Vietnam but rare (<1%) in Japanese, Korean, African American, European and Hispanic populations (41, 42). As a result, the incidence of carbamazepine-induced SJS/TEN is significantly higher in Asian compared to other non-Asian populations (41). Recently the *HLA-A*31:01* haplotype was reported to be strongly associated with carbamazepine-induced adverse reactions including SJS/TEN and HSS in European populations (43).

Recently, a prospective, genotype-guided trial was shown to prevent carbamazepine-induced SJS/TEN in a Chinese population using *HLA-B*15:02* screening (44). In this study, none of the 4120 *HLA-B*15:02*-negative patients receiving carbamazepine or the 215 *HLA-B*15:02*-positive patients given an alternative drug developed SJS/TEN. It was estimated that selectively prescribing carbamazepine for non-*HLA-B*1502* carriers *vs* prescribing higher-cost alternative drugs for all patients would save the Taiwanese government 1 billion dollars per year (45). Pharmacogenomic testing for *HLA-B*15:02* is now standard practice in at least 50 hospitals in Taiwan and is currently recommended by the FDA for patients with ancestry in at-risk populations. Clinical practice guidelines are available for clinicians to make informed genotype-based decisions for patients with an indication for carbamazepine therapy (46, 47) (Table 1).

Future potential

Cisplatin

Cisplatin is a highly effective chemotherapeutic agent used for a variety of solid organ tumors in children and adults, with a cure rate of nearly 85% (48). Its use however is restricted by the high incidence of dose-limiting adverse reactions, which include irreversible bilateral hearing loss, nephrotoxicity, and peripheral neuropathy. Cisplatin-induced ototoxicity (CIO) is an especially pervasive problem as it affects up to 10–25% of adults and 26–90% of children (49, 50). Particularly in children, this can lead to significant and long-term consequences, as hearing loss at an early developmental age can hamper the speech, cognitive, educational and social development of a child (51).

Risk of CIO is dependent on a number of clinical factors, including dose, age, exposure to cranial irradiation and other ototoxic insults (52). However, it is widely recognized that these risk factors alone are insufficient predictors for CIO (53). Although only a few studies have examined the hereditary basis for CIO in children, several gene variants have been identified. Specifically, genetic variants in *TPMT*, *COMT*, *XPC*, *ABCC3*, *GSTs* and *LRP2* have been reported to influence the susceptibility to CIO (53–57). The clinical utility of the majority of these genetic markers is largely uncertain and requires replication in independent patient cohorts. Recently however, the association of CIO with loss-of-function *TPMT* alleles was replicated in an

Table 1. Examples of current pharmacogenomic biomarkers in clinical practice

Drug	Associated gene(s)	Associated variant(s)	Associated variant effect	Clinical practice recommendation	References
Codeine	CYP2D6	**1xN/*2xN/*35xN*	Increased activity; life-threatening CNS depressive adverse effect	Avoid codeine use because of potential for toxicity. Consider using alternative analgesic	(10, 17)
		**4xN/*3-*8/ *12/*15/*19/*20/ *40/*42/*44/*56*	No activity; impaired/greatly reduced analgesia	Avoid codeine use because of lack of efficacy. Consider using alternative analgesic	(10, 17)
		**9/*10/*11/*17/*29/ *41/*29/*50/*43/ *55/*59*	Reduced activity; reduced analgesia	Codeine used as per standard of care. If no response, consider using alternative analgesic	(10, 17)
Warfarin	CYP2C9	rs1799853 (**2*)	Decreased activity; reduced dose requirement	Use of pharmacogenetic algorithm-based dosing is recommended when possible. Initial dosing ranges for patients with different combinations of CYP2C9 and VKORC1 genotypes provided on drug label	(32, 33)
		rs1057910 (**3*)	Decreased activity; reduced dose requirement		
	VKORC1	rs9923231	Reduced expression; reduced dose requirement		
Carbamezapine	HLA	*B*1502*	Increased risk of carbamazepine-associated Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN)	Do not use carbamazepine in naïve-patients that are positive for *HLA-B*1502*. If patient used carbamazepine for longer than 3 months without incidence of adverse reactions, consider use with caution	(46, 47)
		*A*31:01*	Increased risk of carbamazepine-associated hypersensitivity syndrome (HSS)		

independent pediatric cohort (55). As a result of these findings, the FDA updated the cisplatin drug label to highlight the risk of CIO when treating children and includes information about the identified association of CIO in patients who carry *TPMT* *3B and *3C functional variants. Interestingly, it was recently reported that clinical factors, such as ototoxic cranial irradiation and otoprotective drug treatment (amifostine), can diminish these *TPMT* genetic associations with CIO. This finding needs to be replicated however, as the same study also found that a small cohort of patients who did not receive amifostine or cranial irradiation retained trends of association with loss-of-function *TPMT* alleles, although the patient sample size was insufficient to achieve statistical power (58). Moving forward, additional research with larger and well-characterized cohorts will help support the implementation of predictive pharmacogenetic tests for CIO in children.

Anthracyclines

Anthracyclines are a class of highly effective anticancer drugs that have contributed to the increased 5-year survival rates of many cancers from 30% in the 1960s to over 80% today (59). They are among the most commonly used agents for the treatment of adult and childhood cancers; at least 970,000 patients receive anthracycline each year in North America (60). As with cisplatin, their clinical utility is significantly limited by dose-dependent toxicity, specifically cardiotoxicity. This manifests as asymptomatic cardiac dysfunction in up to 57% of treated patients and restrictive or dilated cardiomyopathy resulting in congestive heart failure (CHF) in up to 16–20% of treated patients (61). With the increasing number of long-term cancer survivors, the number of patients experiencing cardiomyopathy and CHF will probably increase in the future. Therefore, understanding the causes and mechanisms, as well as being able to predict and prevent anthracycline-induced cardiotoxicity (ACT) is imperative for the improvement of long-term survivor outcomes.

Currently, the etiology and pathophysiology of ACT is not fully understood. Several clinical factors have been shown to influence risk, such as the cumulative dose, age, gender, cardiac irradiation and pre-existing cardiovascular disease (61, 62). However, the variability in incidence for ACT, even when accounting for these clinical risk factors, suggests an underlying genetic component. Several

candidate gene studies have identified ACT risk variants in *SLC28A3*, *ABC*, *NADPH*, *CBR*, *SULT2B1*, *GST*, *UGT1A6* and *CAT* (63–72). Replication of these associations in independent patient cohorts has been showed for variants in *SLC28A3* (*rs7853758* and *rs885004*) and *UGT1A6* (rs17863783) and these genetic markers have been shown to improve risk prediction beyond established clinical risk factors (63, 72). Therefore, personalized anthracycline therapy for individual patients holds significant promise.

Challenges and future directions

ADRs can cause lifelong problems and are associated with high morbidity and mortality, as well as increased health, social and economic burdens for patients, their families, and the healthcare system. Here, we have highlighted the significant potential of genotype-guided drug therapies to better stratify patients into low and high-risk categories for specific ADRs. In theory, these predictive tests would continue to allow low-risk patients to derive therapeutic benefit from drug use, while potentially preventing exposure of high-risk patients to the development of severe toxicities. In reality, pharmacogenetic testing is but one facet of clinical care decision-making and genetic information must be carefully incorporated within the current standards of care. Still, the potential benefit for pharmacogenetics is great but there remain many challenges for its implementation into clinical practice.

Clinical case definition for ADRs

A major challenge when comparing pharmacogenomic studies is differences in the clinical characterization of patients and their reactions. Different ADR grading criteria or variations in the extent of clinical characterization between research groups can confound results or impede replication efforts. Standardizing phenotypic characterization is crucial for replication; however, the evaluation of some ADR phenotypes is particularly challenging when there are no readily quantifiable phenotypic changes or existing grading schemes. For example, vincristine-induced peripheral neuropathy (VIPN) occurs in a subgroup of children undergoing chemotherapy with vincristine (73). VIPN symptoms such as numbness, tingling and neuropathic pain are difficult for young children to describe and thus have been challenging to appropriately quantify. Novel imaging techniques and biomarkers are now being investigated to improve the clinical classification of vincristine-induced ADRs, which will increase the likelihood of uncovering predictive genetic markers in the future.

Time of ADR onset is another important issue in ADR phenotyping. Although many ADRs occur during or shortly after the end of treatment, drug-induced toxicities may not become symptomatic until years after drug exposure. For example, hearing loss has been reported to manifest 11 years after the end of therapy in children treated with cisplatin (74). Similarly, anthracycline-induced cardiotoxicity may present in some form of structural or functional left ventricular abnormalities years after treatment (62). Variable follow-up time between studies and patients with sub-clinical disease could lead to false negatives in replication cohorts, and thereby hinder the establishment of a true, robust pharmacogenetic marker. However, achieving a feasible time course for monitoring and assessment often remains a key challenge because of financial costs and lack of active ADR surveillance systems.

Establishing causality, replication and functional validation of identified genetic markers

A major methodological challenge in pharmacogenomics is ascertaining the causality of identified variants. Current trends in pharmacogenetic studies use genotyping panels consisting of 100,000-5 million genetic variants that include rare mutations (<1%) as well as more common (>1%) single nucleotide polymorphisms (SNPs). Investigating more SNPs increases the density of genomic coverage but also presents several challenges. Statistically, this introduces multiple-testing correction that in turn requires sufficient statistical power to uncover SNPs associated with the drug-induced phenotype. Secondly, the majority of SNPs in the genome (>14 million total SNPs) are located in non-exonic sequences. Furthermore, these SNPs can be located within large linkage disequilibrium blocks and thus, the identified variant may only serve as a marker of the true causal variant. Thus, a major challenge in these studies is to identify the causal variant associated with the ADR prior to the initiation of *in vitro*/*in vivo* validation studies. This may necessitate sequencing large genomic regions in the vicinity of the associated marker to find coding SNPs that could potentially affect protein activity or expression. Moreover, the causal variant may be synonymous, with no change in amino acid structure, yet still affect gene transcription, splicing, mRNA transport, and translation (75).

To show clinical validity and reduce the likelihood of false positives, the association of pharmacogenomic biomarkers must be replicated in independent, similarly treated patient populations. Indeed, current trends for the publication of new pharmacogenomic discoveries require concomitant replication. Attaining a suitable replication cohort presents an inherent challenge as the division of existing patients between discovery and replication cohorts can diminish statistical power in the discovery cohort. Furthermore, the time required to prospectively obtain a suitable replication sample can delay the dissemination of potentially clinically relevant pharmacogenetic discoveries. One solution currently employed by complex disease researchers is to form consortiums that would pool patient populations and expedite both discovery and replication efforts (76).

Functional validation through *in vitro* genotype–phenotype studies and *in vivo* pharmacokinetic studies are equally important to support a mechanistic understanding of a pharmacogenetic association. Species-specific phenotypic differences can be a considerable caveat to studies employing non-human

models. In addition, technical challenges of large DNA transfer (>15 kb) into cultured cells and the ensuing loss of native genomic context complicate the study of pharmacogenomic variants identified in non-coding regions. Technical advances in the generation of human induced pluripotent stem cells (hiPSCs) and precision genome engineering are opening new avenues to investigate variants that were previously intractable to conventional study (77, 78). hiPSCs derived from somatic cells of patients suffering an ADR, or from matched controls, can be differentiated into relevant cell-types of interest (e.g. cardiac cells to study ACT) to facilitate functional validation. One key advantage of patient-derived hiPSCs is that they contain the ADR causal variant and thus, mechanistic studies can proceed without knowing the specific causal variant *a priori*. Similarly, advances in genomic editing using site-specific mutagenesis, e.g. CRISPR/Cas9 and TALEN technologies, will facilitate targeted approaches that not only preserve genomic context, but also validate the causality of a variant.

Conclusion

The emerging era of pharmacogenomics includes a growing number of successful changes to clinical practice and the increasing development of pharmacogenomic tests. While challenges remain, these are being addressed through improved study designs and the establishment of international collaborations to discover, replicate and validate predictive pharmacogenomic factors of significant clinical utility. Moving forward, educating clinicians on how to incorporate pharmacogenetic information will be crucial for implementation of genetic testing into clinical practice. This can be addressed with the development of accessible and concise pharmacogenetic clinical practice guidelines. Reimbursement for hospitals and clinical laboratories offering these tests also needs to be addressed by most health insurance schemes (79). Despite these challenges, pharmacogenomics shows tremendous promise to significantly improve the safety and effectiveness of medications in the future.

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