TIPS-Commissioned review

**Genomics of Adverse Drug Reactions**

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**Abstract**

Adverse drug reactions (ADRs) are common, are associated with morbidity and mortality and are costly to healthcare systems. Genomic factors predispose to ADRs, but this varies depending on the drug, patient and disease. Genomic testing can help predict and prevent ADRs, but can also be used in other ways (diagnosis, closer monitoring of those at risk, pre-emptive genotyping, and understanding of mechanism), all of which will be important in the future to improve the benefit-risk ratio of drugs. In the era of precision medicine, such genomic data will need to be integrated with other forms of data to develop a comprehensive and integrated approach to improve responses to medicines used in patients.

**Adverse Drug Reactions**

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality, and they represent a huge burden for healthcare systems worldwide. Their annual cost has been estimated to be £1 billion in the UK and $4 billion in the US [[1-4](#_ENREF_1)]. ADRs in general can be classified into two basic types: (i) **Type A (on-target)** reactions are predictable from the known pharmacology of the drug, and show a clear dose-response relationship; and (ii) **Type B (off-target)** reactions that are difficult to predict from the known pharmacology of the drug, are often detected after the drug is licensed, and show no clear dose-response relationship. The pathogenesis is complex and can include both metabolic and immune-mediated factors.

Prevention of ADRs is important, not only to reduce morbidity and mortality, but also to improve compliance with medications. Patients are more likely to stop their drugs or take them less frequently if they develop an ADR, no matter how mild the ADR is. For instance, a recent study showed that approximately 45% of patients discontinue the antipsychotic medication clozapine within two years despite its efficacy, with the reason being an ADR in more than half of the cases. The risk of discontinuation was the highest in the first three months of treatment and interestingly, it was more commonly clinician-led, rather than patient initiated [[5](#_ENREF_5)]. Discontinuation of effective treatment is detrimental either in the short-term or long-term. For cardiovascular medications withdrawal can increase risk of cardiovascular events and death [[6](#_ENREF_6)]. For example, with statins, poor adherence due to ADRs increases the risk of future cardiovascular events by approximately two-fold in patients with known coronary artery disease [[7](#_ENREF_7)].

**Genetic factors contribute to adverse drug reactions**

Genetic factors contribute to ADRs; however the degree of contribution will vary between the drug, patient and disease process. This complexity makes it difficult to estimate in quantitative terms the contribution of genetic factors relative to other non-genetic factors in predisposing to specific ADRs. It has however been estimated that approximately 20-30% of ADRs could be prevented by pharmacogenetic testing [[8](#_ENREF_8)]. More importantly, in this era of precision medicine, we do not need to focus on the nature *vs* nurture debate, and should evaluate genetic factors alongside clinical, behavioural and environmental factors in order to develop comprehensive methods for preventing ADRs.

At least 10% of drug labels in the EU and USA contain information on genetic factors determining drug response. However, very few genetic tests are currently used in clinical practice. Indeed, after several decades of gene-ADR association research, only approximately 20 genes that affect approximately 80 medications have been shown to be actionable in the clinic [[9](#_ENREF_9)]. There are many possible reasons for the lack of implementation, previously covered by many different authors [[4](#_ENREF_4), [10-13](#_ENREF_10)]. Clearly evidence is key in implementing a genetic test, but the level of evidence required in different settings is often not clear. For instance, if a randomized controlled trial is required for using a genetic test to determine the efficacy of a drug, will the same paradigm be applied for preventing an ADR, even when it is rare? If genetic factors are identified in one ethnic group, how will they be implemented in different ethnic groups, particularly when the population prevalence of the risk allele varies according to ethnicity? Other factors identified as barriers to pharmacogenetic testing include the limited number of accredited genetic laboratories, lack of knowledge of pharmacogenetics in healthcare providers and patients, complexity of interpretation of pharmacogenetic testing results, and lack of computerized decision support [[14](#_ENREF_14)].

Another factor in the area of drug safety pharmacogenetics which may have hampered implementation is the focus on prediction of the ADR. Clearly this is important, as individuals with the risk allele can be provided with an alternative drug, or the dose can be modified. However, genomic testing can also be used clinically in different ways including for diagnosis of an ADR, for excluding the use of a drug in an individual patient, and for identifying patients that need closer monitoring. In addition, with the increasing availability of genomic testing and sequencing, it is also important to consider the use of genetic information pre-emptively. Finally, genomic information also provides insight into mechanisms of ADRs. It is important to note that these different uses are not mutually exclusive, but taken together, will help in the overall clinical management of ADRs – a framework for this is shown in Figure 1, and discussed further in the article.

**Genotyping to predict and prevent adverse drug reactions**

As indicated, the holy grail has been to identify genetic predisposing factors which have adequate predictive accuracy to be used prospectively to prevent the ADR through either drug choice or drug dose. In terms of translation, the best example of this is the use of *HLA-B\*57:01* genetic testing to prevent abacavir hypersensitivity, a serious ADR that in some circumstances can cause death. This association was first demonstrated using observational study designs in 3 countries [[15-17](#_ENREF_15)], its utility demonstrated in a randomised controlled trial [[18](#_ENREF_18)], its predictive accuracy assessed in different ethnic groups [[19-23](#_ENREF_19)], and its cost-effectiveness shown in several different healthcare settings [[16](#_ENREF_16), [24-27](#_ENREF_24)]. Pre-prescription genotyping for *HLA-B\*57:01* has been included in the drug label by many different regulatory agencies worldwide, and it has also been recommended in clinical guidelines [[28-30](#_ENREF_28)]. Its success has been documented through follow-up studies which have shown a marked reduction in the incidence of abacavir hypersensitivity [[18](#_ENREF_18), [23](#_ENREF_23), [26](#_ENREF_26)].

Genetic testing can also be used to predict dose rather than determine drug choice. One of the best examples of this is with the thiopurine methyl transferase (TPMT) genetic polymorphism. Approximately 3-14% of patients are heterozygous for the *TPMT* genotype while homozygote variant frequency ranges from approximately 1 in 178 to 1 in 3,736 patients [[31](#_ENREF_31)]. TPMT catalyses the *S*-methylation of the thiopurine drugs azathioprine (AZA) and 6-mercaptopurine (6-MP). Patients with variant genotypes, in particular the homozygotes, benefit from dose-reduction with these drugs. A recent multi-centre study in the Netherlands in patients with inflammatory bowel disease was able to show that screening for TPMT variants led to a 10-fold reduction in haematologic ADRs in variant carriers where dose was reduced, without a reduction in efficacy [[32](#_ENREF_32)].

The importance of dose prediction has also been shown with warfarin [[33](#_ENREF_33)], where an algorithm that incorporates clinical factors (age, body mass index, interacting drugs) and genetic factors (*CYP2C9* and *VKORC1* genetic polymorphisms) has been shown to predict individual variation in the daily dose of warfarin [[34](#_ENREF_34)]. This is one of the most highly replicated genotype-phenotype associations in the literature, but despite this, implementation can take decades and can still be patchy (Figure 2). The implementation of warfarin pharmacogenetics into clinical practice has been complicated by the fact that the results of two randomised controlled trials conflicted with each other [[34](#_ENREF_34), [35](#_ENREF_35)]. The reasons for this have been discussed elsewhere [[36](#_ENREF_36)], and highlight that the use of genetic testing needs to take into account the clinical context of how the drug used in different geographical settings. It is also important to note that no trial has been powered to show that pre-prescription genotyping before the use of warfarin can prevent warfarin-related bleeding. However, all studies have used time in therapeutic range for the international normalized ratio (INR), which is an acceptable surrogate. Furthermore, an analysis by Mega *et al*. performed as part of the ENGAGE AF-TIMI 48 trial was able to show that bleeding risk with warfarin was greater in those patients who had variants in both the *CYP2C9* and *VKORC1* genes [[37](#_ENREF_37)].

**Genotyping for clinical diagnosis**

Severe drug-induced liver injury (DILI) is rare: the prevalence of DILI for some commonly used drugs such as flucloxacillin (8.5 in 100,000) and amoxicillin-clavunalate (43 in 100,000) has been estimated from epidemiological studies [[38](#_ENREF_38)]. Flucloxacillin-induced DILI is strongly associated with *HLA-B\*57:01* (OR=108) [[39](#_ENREF_39)]. Given the very low prevalence of DILI associated with flucloxacillin, it has been estimated that a large number of individuals (>13,500) would need to be tested to prevent one case [[40](#_ENREF_40)]. Therefore, predictive testing for flucloxacillin-induced DILI would not be cost-effective, and it would also deny many patients an effective anti-staphylococcal antibiotic. However, although the positive predictive value (PPV) is low (0.12%), the negative predictive value (NPV) is almost 100% [[40](#_ENREF_40)]. This provides an opportunity to use *HLA-B\*57:01* testing as part of the diagnostic criteria used when patients present to their clinicians with evidence of liver disease. This is important because an audit conducted in 2013 showed that DILI accounted for approximately 15% of all hepatocellular jaundice cases (N=881 consecutive patients) in the UK [[41](#_ENREF_41)]. Clinically, a patient presenting with liver disease will need a full diagnostic work-up, and if the patient has been exposed to flucloxacillin, but also has another possible aetiology for the liver disease, the use of *HLA-B\*57:01* testing may allow the clinician to exclude flucloxacillin as a cause. This is important clinically as it will ensure the patient has the right diagnosis and is not falsely labelled as “penicillin-allergic” with its attendant risks in the future to use more expensive non beta-lactam antibiotics and antimicrobial resistance. Such diagnostic usage may also be relevant for other drug-induced liver injuries, for example *HLA-DRB1\*15:01* testing in amoxicillin-clavulanic acid-induced DILI (99% NPV), and *DRB1\*07:01* and highly correlated *DQA1\*02:01* lapatinib-induced DILI (99% NPV) [[39](#_ENREF_39), [42-45](#_ENREF_42)].

**Genotyping to exclude the use of a drug**

For diagnosis, the genetic test is undertaken at the time of the ADR, rather than prospectively. However, the high NPV of a test can also be used to avoid the use of a particular drug in an at-risk population. It can be distinguished from a predictive test by the fact that the predictive value may not be high (because of the rarity of the ADR), and it may thus not be possible to conduct a randomised trial to show the utility of genetic testing.

The best examples of this approach are for *HLA-B\*15:02* and *HLA-B\*58:01* genetic testing particularly in South-East Asian populations to prevent carbamazepine-induced Stevens-Johnson Syndrome (SJS) and allopurinol-induced serious cutaneous adverse reactions, respectively [[46](#_ENREF_46), [47](#_ENREF_47)]. In both cases, the initial demonstration of the association in observational studies has been followed up by replication in many different studies, highlighted through meta-analyses, and clinical significance assessed through prospective cohort studies where pre-prescription genotyping was able to reduce the incidence of these serious reactions compared with historical controls by avoiding the use of the drug in at-risk populations [[48-51](#_ENREF_48)]. Despite the evidence of the effectiveness of *HLA-B\*15:02* genetic testing for carbamazepine-induced SJS [[48](#_ENREF_48)], its uptake in clinical practice seems to be patchy. For instance, in Hong Kong, despite the fact that the government included genetic testing in its guidelines and agreed to pay for it, clinicians decided to avoid the use of carbamazepine altogether, and instead switched patients over to lamotrigine and phenytoin. The net result was that although SJS induced by carbamazepine decreased in incidence, SJS due to phenytoin or lamotrigine increased, and the overall incidence of SJS did not change over the years after introduction of *HLA-B\*15:02* genetic testing [[52](#_ENREF_52)]. This example provides a salutary lesson of the difficulties in implementing genetic testing despite acceptance of the test by regulators.

The same approach was suggested for lumiracoxib, a COX-2 inhibitor that was withdrawn from the market because of DILI. The DILI has been shown to be associated with HLA *DRB1\*15:01/DQA1\*01:02* [[53](#_ENREF_53)]*.* After withdrawal, the company applied to the European Medicines Agency to use lumiracoxib in those individuals who did not carry the risk allele, *HLA-DQA1\*01:02.*  However, this was not approved because the EMA “was not convinced that screening patients for the DQA1\*0102 gene variant sufficiently reduced this risk” [of liver toxicity] (http://www.ema.europa.eu/docs/en\_GB/document\_library/Medicine\_QA/2011/05/WC500106727.pdf).

The main issues to consider when using a genetic test in this way include the high NPV of the test, the availability of alternative drugs to use in those who carry the risk allele, the availability of testing, the clinical context in which the test and drug are likely to be used (for example, it may be more difficult to use genetic testing in primary care than in a specialist setting) and the health economics of testing.

**Closer clinical monitoring of patients with risk alleles**

For many gene/drug pairs, despite the evidence of an association and replication in different populations, the genetic risk factor may predispose to both mild and serious ADRs, and it may not have a NPV that reaches 100%. In such situations, and also when no other alternative drug is available, genetic testing may still have value because it can be used for risk stratification and closer monitoring in the at-risk population. For instance, for carbamazepine hypersensitivity reactions in Northern European patients, *HLA-A\*31:01* increases the risk of mild maculopapular exanthems, the more severe hypersensitivity syndrome and the potentially fatal SJS [[54](#_ENREF_54)]. Our analysis showed that this association has a PPV and NPV of 43% and 92%, respectively, and negative *HLA-A\*3101* test would reduce the probability of hypersensitivity from 5.0% to 3.8% (1:26 ratio) [[54](#_ENREF_54), [55](#_ENREF_55)]. In such cases, an individual who was positive for *HLA-A\*31:01* could either avoid carbamazepine or still be prescribed the drug if it was felt to be the best therapeutic option, but through risk stratification approaches, undergo closer clinical monitoring with discontinuation of the drug on the first occurrence of the ADR. This is important as it is known that for hypersensitivity reactions, the earlier the discontinuation of the drug, the better the prognosis.

The nature of clinical monitoring could vary from pure clinical observation (i.e. first occurrence of a mild skin eruption) to laboratory testing. For instance, more frequent INR monitoring could be used in patients on warfarin with at-risk variants. Similarly liver function monitoring which is sometimes required for drugs with a high incidence of liver dysfunction could be stratified so that those at risk have more frequent monitoring while those who are not at risk have no or little monitoring. ECG monitoring for QT-interval prolongation could be stratified based on dose of drug, gender of the patient, and the presence of rare genetic variants which are known to predispose QT-interval prolongation and torsades de pointes with some drugs. More frequent echocardiographic monitoring could be instituted in patients with novel genetic variants associated with anthracycline-induced cardiotoxicity [[56](#_ENREF_56), [57](#_ENREF_57)].

**Pre-emptive genotyping**

The current approach to pharmacogenetic testing usually involves genotyping when initiating a treatment regimen. Such an approach is particularly ineffective when immediate drug treatment is required and clinical decisions cannot be deferred. In addition, single tests of individual genes are ordered to guide a single therapeutic decision. However, as we enter the era of gene panel testing and whole genome sequencing, it is likely that genomic information will already be available at the time the drug needs to be prescribed. Indeed, genotyping multiple genes in a single test is more cost effective, makes better use of DNA, and allows for pre-emptive availability of genetic test information [[9](#_ENREF_9)]. Consistent with this, we are also currently developing a panel that contains 23 HLA alleles across the six HLA loci implicated in immune-mediated ADRs [[58](#_ENREF_58)].

An important issue is to provide guidance on what needs to be done when patients have actionable genotypes. The NIH-funded Implementing Genomics in Practice (IGNITE) Network, is an innovative collaboration aiming to enhance the translation of validated actionable genomic information into clinical settings [[59](#_ENREF_59)]; three of the six projects in IGNITE focus on pharmacogenomics implementation, and provide guidance on how to use genomic information. One of the IGNITE projects focuses on clopidogrel pharmacogenetics, where despite data on thousands of patients, adoption has been slow. The development of clinical guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC) also aims to provide guidance for prescribers if an individual carries an at-risk allele – to date, this group has produce guidelines for more than 30 drugs (Table 1).

Pre-emptive genotyping has been investigated in the Vanderbilt University Medical Centre (USA), where out of nearly 53,000 individuals over a median follow-up of 3 years, 64.7% of individuals were prescribed at least one and 12% were prescribed four or more medications with actionable pharmacogenomic variants [[60](#_ENREF_60), [61](#_ENREF_61)]. Using the calculator created at Vanderbilt University (http://data.vanderbilt.edu/rapache/Case4PG) that estimates the number of preventable adverse events from user defined data inputs extracted from literature, we calculate that at least 47 skin rashes in 1,000 patients treated with carbamazepine could be prevented if genotyping for *HLA-A\*31:01* was conducted, or 67 cases in Asian populations if genotyping was done for *HLA-B\*15:02*.

Pre-emptive genotyping programs in the USA have already started at several early adopter sites. The Translational Pharmacogenetic Program formed by the Pharmacogenetics Research Network aims to implement genotype-guided prescribing into routine clinical practice in eight sites including the Mayo Clinic, Ohio State University, St. Jude Children's Research Hospital, University of Florida, University of Maryland, Vanderbilt University Medical Center, University of Chicago and Brigham and Women's Hospital [[62](#_ENREF_62)]. The pharmacogenetic approach varies across the sites; they use between 34 (VeraCode ADME core panel) and 230 (Affymetrix DMET Plus array) gene panels containing actionable variants. It is important to note that even when only 12 pharmacogenes with at least one known actionable variant are considered, over 97% of the USA population has at least one high risk diplotype [[62](#_ENREF_62)]. The key issue for pre-emptive genotyping apart from the availability of a genotype panel is the ability to embed the genotype data into an electronic medical record, which is linked to a clinical decision support system which provides information for prescribers on possible alternative therapeutic options in patients with risk alleles.

An important area where pre-emptive genotyping may be particularly important is in patients on polypharmacy, which is of course more common in the elderly. Polypharmacy has been associated with an increased risk of adverse drug reactions, drug-drug interactions, medication nonadherence and increased health care costs. A recent study in 205 patients over the age of 65 years showed that testing for P450 gene polymorphisms was able to reduce the hospitalization rate from 16.1% to 9.8%, with a potential mean cost saving of $218 per patient [[63](#_ENREF_63)].

The pre-emptive genotyping approach is also being investigated in Europe by the EU Horizon 2020-funded Ubiquitous Pharmacogenomics (U-PGx) Consortium (http://upgx.eu). A panel of important pharmacogenomic variants is going to be combined with clear clinical guidelines embedded into electronic health record systems. The project will be undertaken in 7 European countries (The Netherlands, Spain, UK, Italy, Slovenia, Austria and Greece) which have diverse public healthcare systems, with each site being randomised to either current clinical care or the availability of genetic test results. The primary outcome measure will focus on prevention of ADRs, and will be combined with an assessment of the cost-effectiveness and ethical, legal and social issues.

**Understanding Mechanisms of ADRs**

Genomic testing may also have clinical benefits indirectly by improving our understanding of the mechanism of the ADR. This is relevant for both pharmacokinetic and pharmacodynamic gene variants. For example, in patients who have loss of function polymorphisms, systemic exposure may increase leading to an ADR. This was shown with the antianginal drug perhexiline, which is metabolized by CYP2D6. Patients who are poor metabolisers for CYP2D6 have an increased risk of hepatotoxicity and peripheral neuropathy [[64](#_ENREF_64), [65](#_ENREF_65)]; inability to metabolise perhexiline leads to higher systemic exposure and subsequent trapping of perhexiline within peripheral nerves and liver leading to toxicity [[66](#_ENREF_66)]. Similarly, genetic variation in the transporter gene *SLCO1B1* leads to a 200% increase in AUC for simvastatin, which is turn increases systemic and muscle exposure increasing the risk of muscle toxicity [[67](#_ENREF_67)]. Such information has been used clinically to avoid drug-drug interactions by identifying inhibitors of enzyme/transporter systems, which may have an effect similar to that observed through the genetic polymorphism. For pharmacodynamic gene variants, the identification of the association of *HLA-B\*57:01* with abacavir hypersensitivity led to crystallographic studies which have defined a novel mechanism (peptide binding displacement) by which abacavir may induced hypersensitivity, and the possibility that this may be due to heterologous immunity arising from pre-existing viral infections [[68-72](#_ENREF_68)].

Some further examples of how genetic associations have highlighted novel mechanisms [[73](#_ENREF_73), [74](#_ENREF_74)] are shown in Table 2.

**Cost-effectiveness**

The implementation of genetic testing to prevent ADRs will also require demonstration of the health economics of genetic testing. Clearly, every healthcare system is resource-constrained and therefore it is important to make sure that the cost-effectiveness of genetic testing has been adequately evaluated. A recent systematic review of published economic evaluations for the prevention of ADRs [[75](#_ENREF_75)] concluded that testing to prevent hypersensitivity reactions to abacavir (HLA-B\*57:01), carbamazepine (B\*15:02 and A\*31:01) and allopurinol (B\*58:01) was cost-effective, while one non-HLA pharmacogenomic marker, CYP2C19, was found to be cost-effective in patients taking clopidogrel to prevent myocardial infarction, stroke or death. Inconclusive evidence was found for genotyping of TPMT alleles prior to 6-mercaptopurine and azathioprine, VKORC1 and CYP2C9 prior to warfarin therapy and MTHFR prior to methotrexate treatment [[75](#_ENREF_75)]. However, it is important to note that many evaluations of cost-effectiveness published in the literature have used inadequate data sources. It is therefore important to ensure that health economic analysis is included in the work plan for any genomic test that is being implemented. so that industry feels it is worth investing in innovative approaches to prevent ADRs, healthcare payers feel it is cost-effective for them to pay for these technologies to allow uptake into their healthcare system, and patients feel that the money they pay for their healthcare, either directly or indirectly, is being spent in the most efficient and effective manner

**Concluding Remarks**

Genomic factors predispose to many different types of adverse drug reactions, mild and serious, localized and systemic, and in every therapeutic area affecting all ethnicities. While prediction of ADRs and selection of alternative agents in those at-risk is a goal of research in this area, it may not be possible in many circumstances, because the predictive accuracy of the genomic test may not be clinically acceptable. In this article, we have provided a framework for how genomic tests for ADRs can be used beyond prediction and selection. We are entering the era of precision medicine, and increasing number of individuals will already have genomic data, and we believe our framework will assist in using these data efficiently for clinical benefit. We have only focused on genomic tests. Clearly we need to also take into account all the other technologies which are becoming available (see outstanding questions), including those that measure environmental factors such as sensor technologies, and utilize integrative techniques [[76](#_ENREF_76)] to identify and implement biomarkers (which may be single or most likely, multiple biomarker panels, incorporating both genomic and non-genomic data) to improve the benefit-risk ratio of drugs we use today, and drugs of the future.

**Trends Box (900 characters)**

* Genomic testing can help to predict and prevent adverse drug reactions
* Genomic tests can also be used for drug selection, diagnosis, more enhanced monitoring of at-risk populations and pre-emptive genotyping, as well as elucidating mechanisms of adverse drug reactions
* As more individuals have whole or exome sequencing, genetic data will become increasingly available, sometimes embedded in electronic medical records. These data can be used pre-emptively to improve both precision choice and dose of drug.

**Outstanding Questions Box**

* How readily will clinical, environmental and other omics data be amenable to integration with genomic factors in preventing adverse drug reactions?
* Who will provide, monitor and quality assure the education of patients and healthcare providers about genomics that is going to be crucial for implementation into clinical practice?
* How will mobile technologies be used in improving the benefit-risk ratio of drugs, and will this lead to increased shared decision making between clinicians and patients?
* How will innovative clinical decision support tools be developed, integrated into electronic medical records and accepted by prescribers in order to ensure that knowledge about genomics and other precision medicine initiatives are available for patient care in a timely and accurate manner?
* What health economic data will need to be provided by industry and researchers to ensure that the payers are willing to pay for pharmacogenetic testing, and hence allow for uptake into the healthcare system?

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**Conflict of Interest**

The authors do not have any conflicts of interest.

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**Legends**

**Table 1. Gene-drug combinations with actionable pharmacogenetics.** Guidelines on genetic testing have been issued by the Clinical Pharmacogenomics Implementation Consortium (CPIC), the Royal Dutch Pharmacists Association-The Pharmacogenetics Working Group, the French joint working group comprising the National Pharmacogenetics Network (RNPGx) and the Group of Clinical Onco-pharmacology (GPCO-Unicancer), the Canadian Pharmacogenomics Network for Drug Safety clinical recommendation group, and other professional societies (<https://www.pharmgkb.org/view/dosing-guidelines.do>). These are examples of potentially preventable adverse drug reactions where a genotype is already available or undertaken specifically before a patient is started on the drug.

**Table 2. Genetic associations have highlighted novel mechanisms of adverse drug reactions.** Several examples where genetic risk factors have indicated novel mechanisms of drug toxicity

**Figure 1.** Different ways in which genomic testing can be used in the clinical management of adverse drug reactions.

**Figure 2**. Time from discovery of an association between the polymorphisms in the cytochrome P450 metabolising enzyme *CYP2C9* [[77](#_ENREF_77)] and vitamin K epoxide reductase (*VKORC1*) [[78](#_ENREF_78)] genes and warfarin dosing requirements to implementation of the point-of-care test for *CYP2C9\*2*, *CYP2C9\*3* and *VKORC1* in the clinic [[34](#_ENREF_34)] to prevent bleeding and thromboembolic events

**Table 1**

|  |  |  |
| --- | --- | --- |
| Drug | Gene/Allele | ADR |
| abacavir | HLA-B:57:01 | hypersensitivity |
| acenocoumarol, phenoprocoumon | CYP2C9 | bleeding |
| allopurinol | HLA-B:58:01 | hypersensitivity |
| atazanavir | UGT1A1 | jaundice |
| azathioprine, mercaptopurine, thioguanine | TPMT | myelotoxicity |
| azathioprine | HLA-DRB1, HLA-DQB1 | pancreatitis |
| capecitabine, fluorouracil, tegafur | DPYD | neutropenia, mucositis, neuropathy |
| carbamazepine | HLA-B\*15:02, HLA-A\*31:01 | SJS, hypersensitivity |
| clopidogrel | CYP2C19 | myocardial infarction, stroke, bleeding |
| clozapine | HLA-B\_158T, HLA-DQB1\*05:02 | agranulocytosis |
| codeine | CYP2D6 | respiratory depression |
| daunorubicin, doxorubicin | RARG, SLC28A3,  | cardiotoxicity |
| Oral hormonal contraceptives  | Factor V Leiden | venous thromboembolism |
| irinotecan | UGT1A1 | Neutropenia, diarrhea |
| phenytoin | CYP2C9, HLA-B\*15:02 | hypersensitivity |
| rasburicase | G6PD | acute haemolytic anemia |
| simvastatin | SLCO1B1 | muscle toxicity |
| tacrolimus | CYP3A5 | supratherapeutic concentrations, hypertension and nephrotoxicity |
| thioridazine | CYP2D6 | QT prolongation |
| warfarin | CYP2C9, VKORC1 | bleeding |

*CYP: Cytochrome P450; DPYD-dihydropyrimidine dehydrogenase; G6PD-glucose-6-phosphate dehydrogenase; HLA: human leucocyte antigen; RARG-retinoic acid receptor gamma; SLC-solute carrier transporters; TPMT-thiopurine methyltransferase; UGT1A1-UDP glucuronosyltransferase family 1A.*

**Table 2**

|  |  |  |  |
| --- | --- | --- | --- |
| Drug | Adverse drug reaction | Gene/allele\* | Mechanism |
| abacavir | hypersensitivity | *HLA-B\*57:01* | altered repertoire model with peptide binding displacement and heterologous immunity |
| aromatase inhibitors | muscle pain | *TCL1A* | TCL1A- mediated regulation of cytokine expression |
| lumiracoxib | hepatotoxicity | *HLA-DQA1\*01:02* | Identification of the HLA predisposition highlighted an immune mechanism, which was not expected from the time course of liver injury seen clinically |
| methotrexate | mucositis and infection | *SLC01B1* | systemic exposure increased as a result of low activity variant |
| perhexiline | Neuropathy and hepatotoxicity | *CYP2D6* | higher systemic exposure and subsequent trapping of perhexiline within liver and peripheral nerves |
| ribavarin | anemia | *Inosine triphosphatase* | Ribavirin depletes erythrocyte guanosine triphosphate and ATP levels, but is protected by higher levels of inosine triphosphate |
| simvastatin | muscle toxicity | *SLC01B1* | increase in systemic and muscle exposure in patients with variant allele |

\*CYP – cytochrome P450; HLA- human leucocyte antigen; SLC – solute carrier; TCL1A – T-cell leukemia 1A.