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Review

Genomics of Adverse Drug Reactions

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Adverse drug reactions (ADRs) are common, are associated with morbidity and mortality, and are costly to healthcare systems. Genomic factors predispose to ADRs, but these vary depending on the drug, patient, and disease. Genomic testing can not only help to 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

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 USA [1–4]. 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 ~45% of patients discontinue the antipsychotic medication clozapine within 2 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 3 months of treatment and, interestingly, it was more commonly clinician-led rather than patient-initiated [5]. Discontinuation of effective treatment is detrimental either in the short-term or long-term. For cardiovascular medications, withdrawal can increase the risk of cardiovascular events and death [6]. For example, with statins, poor adherence due to ADRs increases the risk of future cardiovascular events by approximately twofold in patients with known coronary artery disease [7].

Genetic Factors Contribute to Adverse Drug Reactions

Genetic factors contribute to ADRs; however, the degree of contribution varies according to 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. However, it has been estimated that approximately 20–30% of ADRs could be prevented by pharmacogenetic testing [8]. More importantly, in this era of precision medicine we do not need to focus on the nature versus nurture debate, and should evaluate genetic factors

Trends

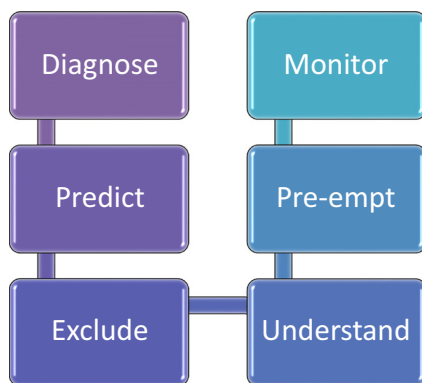
Genomic testing can help to predict and prevent adverse drug reactions.

Genomic tests can also be used for drug selection, diagnosis, more enhanced monitoring of at-risk populations, and pre-emptive genotyping, as well as for elucidating the mechanisms of adverse drug reactions.

As more individuals are characterized by whole-genome or whole-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.

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Trends in Pharmacological Sciences

Figure 1. Different Ways in which Genomic Testing Can Be Used in the Clinical Management of Adverse Drug Reactions.

alongside clinical, behavioral, and environmental factors 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 ~20 genes that affect approximately 80 medications have been shown to be actionable in the clinic [9]. There are many possible reasons for the lack of implementation, previously covered by many different authors [4,10–13]. 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].

Another factor in the area of drug safety pharmacogenetics which may have hampered implementation is the focus on ADR prediction. This is clearly important because 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 ADR diagnosis, excluding the use of a drug in an individual patient, and 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 the 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 is 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



Trends in Pharmacological Sciences

Figure 2. Time from Discovery of an Association Between Polymorphisms in the Cytochrome P450 Drug-Metabolizing Enzyme (*CYP2C9*) [77] and Vitamin K Epoxide Reductase (*VKORC1*) [78] Genes and Warfarin Dosing Requirements to Implementation of Point-of-Care Testing for *CYP2C9*2*, *CYP2C9*3* and *VKORC1* in the Clinic [34] To Prevent Bleeding and Thromboembolic Events.

can cause death. This association was first demonstrated using observational study designs in three countries [15–17], its utility demonstrated in a randomized controlled trial [18], its predictive accuracy assessed in different ethnic groups [19–23], and its cost-effectiveness shown in several different healthcare settings [16,24–27]. Pre-prescription genotyping for *HLA-B*57:01* has been included in the drug label by many different regulatory agencies worldwide, and has also been recommended in clinical guidelines [28–30]. Its success has been documented through follow-up studies which have shown a marked reduction in the incidence of abacavir hypersensitivity [18,23,26].

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 methyltransferase (TPMT) genetic polymorphism. Approximately 3–14% of patients are heterozygous for the *TPMT* variant genotype, whereas homozygote variant frequency ranges from approximately 1 in 178 to 1 in 3736 patients [31]. TPMT catalyzes 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-center 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 hematologic ADRs in variant carriers where dose was reduced, without a reduction in efficacy [32].

The importance of dose prediction has also been shown with warfarin [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]. 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 randomized controlled trials conflicted with each other [34,35]. The reasons for this have been discussed elsewhere [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].

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–clavunilate (43 in 100 000) has been estimated from epidemiological studies [38]. Flucloxacillin-induced DILI is strongly associated with *HLA-B*57:01* [odds ratio (OR) = 108] [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]. 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]. 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]. Clinically, a patient presenting with liver disease will need a full diagnostic work-up; if the patient has been exposed to flucloxacillin, but also has another possible etiology 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 because it will ensure the patient has the right diagnosis and is not falsely labeled as 'penicillin-allergic' with its attendant risks in the future to use more-expensive non- β -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) [39,42–45].

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 randomized 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 [46,47]. 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]. Despite evidence for the effectiveness of *HLA-B*15:02* genetic testing in carbamazepine-induced SJS [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]. 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]. After withdrawal, the company applied to the European Medicines Agency (EMA) 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*01:02* gene variant sufficiently reduced this risk' (of liver toxicity) [79].

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]. Our analysis showed that this association has a PPV and NPV of 43% and 92%, respectively, and a negative *HLA-A*31:01* test would reduce the probability of hypersensitivity from 5.0% to 3.8% (1:26 ratio) [54,55]. 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 because it is known for hypersensitivity reactions that 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 such that those at risk have more frequent monitoring while those who are not at risk have no or little monitoring. Electrocardiogram (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 [56,57].

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]. 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].

An important issue is to provide guidance on what needs to be done when patients have actionable genotypes. The National Institutes of Health (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]; 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 produced guidelines for more than 30 drugs (Table 1).

Table 1. Gene–Drug Combinations with Actionable Pharmacogenetics^{a,b}

Drug	Gene/allele	ADR
Abacavir	<i>HLA-B*57:01</i>	Hypersensitivity
Acenocoumarol, phenprocoumon	<i>CYP2C9, VKORC1</i>	Bleeding
Allopurinol	<i>HLA-B*58:01</i>	Hypersensitivity
Atazanavir	<i>UGT1A1</i>	Jaundice
Azathioprine, mercaptopurine, thioguanine	<i>TPMT</i>	Myelotoxicity
Azathioprine	<i>HLA-DRB1, HLA-DQB1</i>	Pancreatitis
Capecitabine, fluorouracil, tegafur	<i>DPYD</i>	Neutropenia, mucositis, neuropathy
Carbamazepine	<i>HLA-B*15:02, HLA-A*31:01</i>	SJS, hypersensitivity
Clopidogrel	<i>CYP2C19</i>	Myocardial infarction, stroke, bleeding
Clozapine	<i>HLA-B*158 T, HLA-DQB1*05:02</i>	Agranulocytosis
Codeine	<i>CYP2D6</i>	Respiratory depression
Daunorubicin, doxorubicin	<i>RARG, SLC28A3</i>	Cardiotoxicity
Oral hormonal contraceptives	Factor V (<i>FV</i>) <i>Leiden</i>	Venous thromboembolism
Irinotecan	<i>UGT1A1</i>	Neutropenia, diarrhea
Phenytoin	<i>CYP2C9, HLA-B*15:02</i>	Hypersensitivity
Rasburicase	<i>G6PD</i>	Acute hemolytic anemia
Simvastatin	<i>SLCO1B1</i>	Muscle toxicity
Tacrolimus	<i>CYP3A5</i>	Supratherapeutic concentrations, hypertension and nephrotoxicity
Thioridazine	<i>CYP2D6</i>	QT prolongation
Warfarin	<i>CYP2C9, VKORC1</i>	Bleeding

^aGuidelines for 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-Uncancer), the Canadian Pharmacogenomics Network for Drug Safety Clinical Recommendation Group, and other professional societies (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.

^bAbbreviations: CYP, cytochrome P450; DPYD, dihydropyrimidine dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; HLA, human leucocyte antigen; RARG, retinoic acid receptor γ ; SJS, Stevens–Johnson syndrome; SLC, solute carrier transporter; TPMT, thiopurine methyltransferase; UGT1A1, UDP glucuronosyltransferase family 1A.

Pre-emptive genotyping has been investigated in the Vanderbilt University Medical Centre (USA), where 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 [60,61]. 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 1000 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 performed 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 at 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]. 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, even when only 12 pharmacogenes with at least one known actionable variant are considered, that over 97% of the USA population has at least one high-risk diplotype [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 that 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].

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 seven European countries (The Netherlands, Spain, UK, Italy, Slovenia, Austria, and Greece) which have diverse public healthcare systems, with each site being randomized 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 cost-effectiveness as well as 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 CYP2D6 metabolizers have an increased risk of hepatotoxicity and peripheral neuropathy [64,65]; inability to metabolize perhexiline leads to higher systemic exposure and subsequent trapping of perhexiline within peripheral nerves and liver, leading to toxicity [66]. Similarly, genetic variation in the transporter gene *SLCO1B1* leads to a 200% increase in AUC (area under the curve) for simvastatin, which in turn increases systemic and muscle exposure, thereby increasing the risk of muscle toxicity [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 of 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 can induce hypersensitivity, and the possibility that this may be due to heterologous immunity arising from pre-existing viral infections [68–72].

Some further examples of how genetic associations have highlighted novel mechanisms [73,74] 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

Table 2. Genetic Associations Have Highlighted Novel Mechanisms of Adverse Drug Reactions; Several Examples Are Given where Genetic Risk Factors Have Indicated Novel Mechanisms of Drug Toxicity^a

Drug	Adverse drug reaction	Gene/allele	Mechanism
Abacavir	Hypersensitivity	<i>HLA-B*57:01</i>	Altered repertoire model with peptide binding displacement and heterologous immunity
Aromatase inhibitors	Muscle pain	<i>TCL1A</i>	TCL1A-mediated regulation of cytokine expression
Lumiracoxib	Hepatotoxicity	<i>HLA-DQA1*01:02</i>	Identification of the HLA predisposition highlighted an immune mechanism, which was not expected from the timecourse of liver injury seen clinically
Methotrexate	Mucositis and infection	<i>SLC01B1</i>	Systemic exposure increased as a result of low activity variant
Perhexiline	Neuropathy and hepatotoxicity	<i>CYP2D6</i>	Higher systemic exposure and subsequent trapping of perhexiline within liver and peripheral nerves
Ribavirin	Anemia	Inosine triphosphatase (<i>ITPA</i>)	Ribavirin depletes erythrocyte guanosine triphosphate and ATP levels, but is protected by higher levels of inosine triphosphate
Simvastatin	Muscle toxicity	<i>SLC01B1</i>	Increase in systemic and muscle exposure in patients with variant allele

^aAbbreviations: CYP, cytochrome P450; HLA, human leukocyte antigen; SLC, solute carrier; TCL1A, T cell leukemia 1A.

adequately evaluated. A recent systematic review of published economic evaluations for the prevention of ADRs [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 before 6-mercaptopurine and azathioprine, *VKORC1* and *CYP2C9* before warfarin therapy, and *MTHFR* before methotrexate treatment [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 workplan for any genomic test that is being implemented such 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 numbers 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] 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 the drugs we use today, as well as the drugs of the future.

Outstanding Questions

How readily will clinical, environmental, and other omics data be amenable to integration with genomic factors in preventing ADRs?

Who will provide, monitor, and quality-assure the education of patients and healthcare providers about genomics that will be crucial for implementation in 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 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 uptake into the healthcare system?

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