Minireview

Biomarkers of adverse drug reactions

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Impact statement

- Genetic and circulating biomarkers present significant opportunities to personalize patient therapy to minimize the risk of adverse drug reactions. ADRs are a significant heath issue and represent a significant burden to patients, healthcare providers, and the pharmaceutical industry.
- This review details the current state of the art in biomarkers of ADRs (both genetic and circulating). There is still significant variability in patient response which cannot be explained by current knowledge of genetic risk factors for ADRs; however, we discussed how specific advances in genomics have the potential to yield better and more predictive models.
- Many current clinically utilized circulating biomarkers of tissue injury are valid biomarkers for a number of ADRs. However, they often give little insight into the specific cell or tissue subtype which may be affected. Emerging circulating biomarkers with potential to provide greater information on the etiology/pathophysiology of ADRs are described.

Abstract

Adverse drug reactions can be caused by a wide range of therapeutics. Adverse drug reactions affect many bodily organ systems and vary widely in severity. Milder adverse drug reactions often resolve quickly following withdrawal of the casual drug or sometimes after dose reduction. Some adverse drug reactions are severe and lead to significant organ/tissue injury which can be fatal. Adverse drug reactions also represent a financial burden to both healthcare providers and the pharmaceutical industry. Thus, a number of stakeholders would benefit from development of new, robust biomarkers for the prediction, diagnosis, and prognostication of adverse drug reactions. There has been significant recent progress in identifying predictive genomic biomarkers with the potential to be used in clinical settings to reduce the burden of adverse drug reactions. These have included biomarkers that can be used to alter drug dose (for example, Thiopurine methyltransferase (TPMT) and azathioprine dose) and drug choice. The latter have in particular included human leukocyte antigen (HLA) biomarkers which identify susceptibility to immune-mediated injuries to major organs such as skin, liver, and bone marrow from a variety of drugs. This review covers both the current state of the art with regard to genomic adverse drug reaction biomarkers. We also review circulating biomarkers that have the potential to be used for both diagnosis and prognosis, and have the added advantage of providing mechanistic information. In the future, we will not be relying on single biomarkers (genomic/non-genomic), but on multiple biomarker panels, integrated through the application of different omics technologies, which will provide information on predisposition, early diagnosis, prognosis, and mechanisms.

Keywords: Adverse drug reactions, drug safety, biomarkers, pharmacogenomics

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Introduction

An adverse drug reaction (ADR) is defined by the World Health Organization as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function".[1] The majority of ADRs fall into the two broad categories:

- Type A – Reactions which are predictable from the drug's known pharmacology and typically result from an augmented on-target pharmacological response when given at a usual therapeutic dose.
- Type B – Reactions which are also termed idiosyncratic and are not predictable from the known pharmacological actions of the drug. These are typically rare and safety signals are often not detected prior to marketing.

As demonstrated in Table 1, ADRs can affect a significant number of organ systems in the body and can range in

Table 1. Examples of immunogenetic biomarkers of ADRs by organ system.

System	ADR	Causal drug	Indication	Associated genetic variant	References
Skin	Hypersensitivity (SJS/TEN/DRESS/ maculopapular exanthem)	Carbamazepine	Epilepsy	*HLA-B*15:02* (Han Chinese)	2
		Phenytoin		*HLA-A*31:01* (Caucasian/Japanese)	3,4
				*HLA-B*15:02* (Han Chinese)	5
		Allopurinol	Gout	*HLA-B*58:01*	6
		Nevirapine	HIV	*HLA-C*04:01*	7
				*HLA-B*35:05* (Thai)	7
				*HLA-DRB1*01:01*	7
		Abacavir	HIV	*HLA-B*57:01*	8
Gastrointestinal	Hepatotoxicity	Flucloxacillin	Gram +ve bacterial infection	*HLA-B*57:01*	9
		Co-amoxiclav	Bacterial infection	*HLA-A*02:01, DRB1*15:01-DQB1*06:02*	10
		Nevirapine	HIV	*HLA-DRB1:01:01*	11
		Minocycline	Bacterial infection	*HLA-B*35:02*	12
		Lapatinib	Breast cancer	*HLA-DQA1*02:01/HLA-DRB1*07:01*	13,14
	Pancreatitis	Azathioprine	Rheumatoid arthritis, Crohn's disease	*HLA-DRB1, HLA-DQB1*	15
Renal	Nephrotoxicity	5-aminosalicylic acid	Inflammatory bowel disease	*HLA-DRB1*03:01*	16
Hematological	Agranulocytosis	Clozapine	Schizophrenia	*HLA-B/HLA-DQB1*	17
		Sulfasalazine	Inflammatory joint/ bowel disease	*HLA-B*08:01, HLA-A*31:01*	18
		Antithyroid drugs	Hyperthyroidism	*HLA-B*27:05* (Caucasian)	19
				*HLA-B*38:02,*	20
				*HLA-DRB1*08:03* (Han Chinese)	21
				*DRB1*08032* (Japanese)	
Musculoskeletal	Necrotizing autoimmune myopathy	Statins	Hypercholesterolemia	*HLA-DRB1*11:01*	22

ADR: adverse drug reaction; DRESS: drug reaction with eosinophilia and systemic symptoms; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

severity from mild reactions (e.g. skin rash or mild liver enzyme elevation) which resolve upon withdrawal of the causal drug to severe, life-threatening reactions including skin blistering reactions (Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)) and fulminant liver failure.

ADRs account for between 6.5% (hospital admissions) and 25% (primary care) of attendances for medical treatment, representing a significant burden on healthcare services.[23] This translates to a cost in excess of £1 billion every year in the UK (with equivalent figures in other countries).[24] Indeed, in the US, the figure has been estimated to be as high as $30.1 billion.[25] The financial burden on pharmaceutical research and development is also significant; between 1990 and 2013, 43 drugs were withdrawn from market due to severe ADRs.[26]

From both a patient and healthcare perspective, there are potential benefits in developing biomarkers for identifying individuals predisposed to ADRs prior to initiation of therapy. Biomarkers can also have a prognostic role in determining the likelihood of recovery postreaction and potentially in the development of severe sequelae (e.g. ophthalmic complications postreaction in SJS/TEN survivors) (Figure 1). This review covers the current knowledge base of biomarkers of ADRs (both genomic and non-genomic) and discusses potential advances and directions for the development and implementation of new biomarkers.

Genomic biomarkers

Pharmacodynamic/pharmacokinetic-related genetic biomarkers

Polymorphisms in genes encoding drug metabolizing enzymes or drug transporter proteins have been associated with a number of type A ADRs (Table 2). Indeed, clinical implementation guidelines exist for a number of drugs where pharmacokinetic genetic variation can be critical in determining the risk of an ADR. These include (but are not limited to) *TPMT* and azathioprine/mercaptopurine-induced bone marrow toxicity;[27,28] *CYP2D6* and codeine (morphine)-related respiratory depression;[29] and *SLCO1B1* and simvastatin-induced myotoxicity.[30] An interesting recent study has shown that a non-synonymous variant in the *SLCO2A1* gene, which encodes a prostaglandin transporter, is associated with thiazide-induced hyponatraemia.[31]

In addition to PK-related pharmacogenomic biomarkers, some type A ADRs are also associated with polymorphisms in genes encoding pharmacodynamic targets. Perhaps the most prominent example of this is the anticoagulant warfarin which is indicated in the treatment of atrial fibrillation, deep-vein thrombosis, and pulmonary embolism. The *CYP2C9*2* and *CYP2C9*3* polymorphisms in the gene-encoding P4502C9, which is responsible for the metabolism

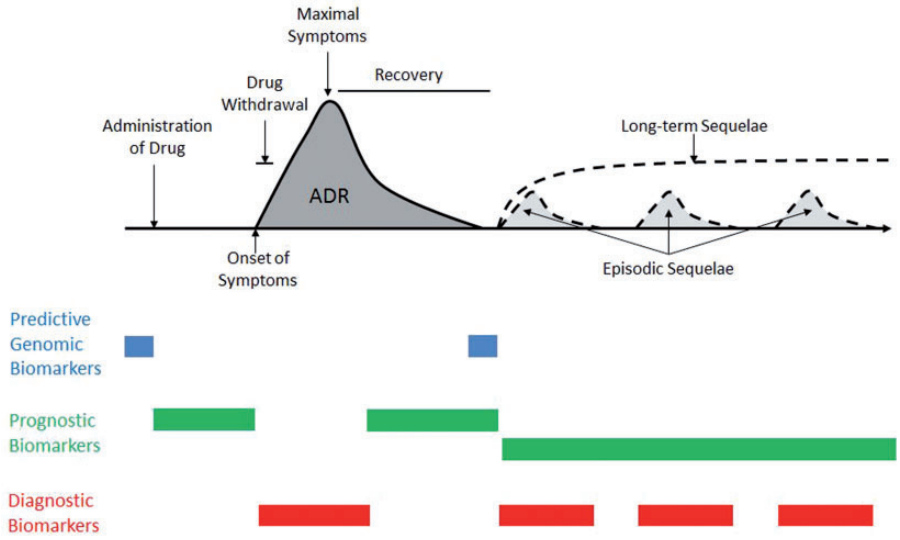

Figure 1. Schematic of a typical delayed onset idiosyncratic ADR and indicative points at which theoretical predictive, prognostic, and diagnostic biomarkers could be used for informing patient treatment decisions and care pathways. (A color version of this figure is available in the online journal.)
ADR: adverse drug reaction.

Table 2. Examples of pharmacokinetic/pharmacodynamic genetic biomarkers of ADRs by organ system.

System	ADR	Causal drug	Indication	Associated genetic variation	References
Skin	SJS/TEN	Phenytoin	Epilepsy	*CYP2C9*2/*3*	5
Gastrointestinal	Hepatotoxicity	Isoniazid	Tuberculosis	NAT2 slow acetylator	32
	Hyperbilirubinemia	Atazanavir	HIV	*UGT1A1*28*	33
CNS	Respiratory depression	Codeine (morphine)	Analgesia	CYP2D6 Ultrarapid metabolizer	29,34
Renal	Nephrotoxicity	Tacrolimus	Immunosuppressant	*CYP3A5*3/*6/*7*	35
Hematological	Bone marrow suppression	Azathioprine	Rheumatoid arthritis, Crohn's disease	*TPMT*2/*3A/*3C/*4*	27,28
	Neutropenia	Irinotecan	Colorectal cancer	*UGT1A1*28*	36
Cardiovascular	Bleeding	Warfarin	Anticoagulant	*CYP2C9*2/*3, VKORC1*	37
	Myocardial infarction, stroke, bleeding	Clopidogrel	Antiplatelet	*CYP2C19*2/*3/*17*	38,39
Musculoskeletal	Myopathy	Simvastatin	Hypercholesterolemia	*SLCO1B1*5*	30

ADR: adverse drug reaction.

of the active S enantiomer of warfarin, are a key determinant of daily dose requirement in patients. Additionally, a promoter region polymorphism (c.1639A > G) which reduces the hepatic expression of vitamin K epoxide reductase (VKORC1), the pharmacological target of warfarin, is also strongly associated with warfarin dose requirement. The combination of genetic polymorphisms in the *CYP2C9* and *VKORC1* genes in fact accounts for almost 50% of the variation in daily dose requirement.[40] The translation of these findings into clinical practice has been challenging,[41] but a randomized controlled trial in Europe has shown that genotype-guided dosing was superior to the current standard of care in improving overall anticoagulation control (including time in therapeutic international normalized ratio (INR) range and reducing overshoot to an INR > 4).[37]

Immunogenetic biomarkers

Many type B (idiosyncratic) ADRs, including SJS/TEN and drug-induced liver injury (DILI), have an immune pathogenesis. This is consistent with the fact that very strong genetic associations between such reactions and individual HLA genetic loci within the major histocompatibility complex region on chromosome 6 have been reported (Table 2). Indeed, for two of these associations (*HLA-B*57:01* and abacavir hypersensitivity; and *HLA-B*15:02* and carbamazepine-induced SJS/TEN in some SE Asian populations), prepresscription genotyping is recommended by most regulatory agencies including the FDA. This has been of clinical value since the incidence of these reactions has shown a marked decrease where the genetic test has been consistently implemented.[42,43]

An increasingly important issue to consider in the implementation of pharmacogenetic testing is the cost-effectiveness – this is vital to persuade the healthcare providers to pay for testing. There is now an increasing number of such studies being performed; this requires the collection of different types of data (including quality of life) which can then be incorporated into health economic models. Examples of tests which have been demonstrated to be cost-effective include *HLA-B*57:01* for abacavir hypersensitivity,[44] *HLA-B*15:02* and *HLA-A*31:01* for carbamazepine hypersensitivity,[45,46] and *TPMT* for azathioprine.[47] In other situations, even though a test result may be highly significant, the rarity of the ADR may make genetic testing cost-ineffective. For instance, the antibiotic flucloxacillin, which is widely used to treat Gram-positive bacterial infections, can lead to hepatotoxicity, which shows a strong association with the *HLA-B*57:01* allelotype.[9] However, the incidence of flucloxacillin-induced liver injury is approximately 8.5 cases per 100,000 individuals,[48] and it has been estimated that in order to prevent one case of hepatotoxicity, a total of 13,513 individuals would need to be tested.

Barriers to the clinical implementation of genomic biomarkers of ADRs

Very few genomic markers have been translated into clinical practice as pre-emptive screening tools to identify individuals at risk of ADRs. Although there is significant evidence for many genetic associations with ADRs (Table 1), lack of replication remains a key factor in hampering translation of genomic biomarkers. Two key reasons for the failure of genetic associations to progress beyond discovery stage are:

a. Heterogeneity of phenotype definition between independent studies: Many promising, biologically plausible genetic associations of ADRs fail replicate in part due to disparities in the clinical definition of the phenotype. In order to overcome this, in recent years a number of projects have been undertaken to standardize ADR phenotypes including cutaneous hypersensitivity,[49] liver injury,[50] Torsade de Pointes,[51] and statin-induced myopathy.[52] Such standardization will help not only for replication but also in undertaking meta-analyses of different studies.
b. Statistically underpowered studies: Many severe ADRs are rare and by virtue of this, identification of patients and recruitment to pharmacogenomic studies is challenging, requiring international collaborative initiatives. Because of this, many ADR studies tend to be small and statistically underpowered, particularly for replication purposes, where the odds ratio in the original discovery set may be inflated. Despite the smaller numbers of patients available, it is important to note that pharmacogenetic association traits, on average, have significantly larger effect sizes than complex disease associations,[53] and therefore may find significant associations despite relatively small (compared with complex disease studies) sample sizes.

It is perhaps also important to note that genomic biomarkers can also be used for purposes other than prediction. Our recent paper has outlined the case as to how genomic biomarkers can be used for diagnosis, selection of patients, pre-emptive genotyping, and for understanding mechanisms.[41] Pre-emptive genotyping is now being tested in several countries, and data on clinical outcomes are keenly awaited.[54] Indeed, as whole genome sequencing becomes more widespread, a wider perspective on how genetic tests can be used in practice will help to improve the benefit–risk ratio of medicine and in implementing precision medicine in its broadest sense.

Genomic biomarkers of ADRs: Opportunities

Common genetic variants represent the "low hanging fruit" as predictive risk factors for ADRs but it is clear that there is still a significant degree of interindividual variability in drug response that cannot be accounted for by our existing knowledge of genetic and non-genetic risk factors. Efforts in a number of research areas have the potential to shed light on this unexplained variability.

Rare variants

With the increased availability of sequencing technologies has come the ability to type patients for rare genetic variants (minor allele frequency <1%) and assess the role they may play in predicting ADRs. Warfarin is an example where pharmacogenetic (*CYP2C9* and *VKORC1*) and non-genetic determinants account for approximately 60% of the dose requirement,[55] with 40% of the variability unexplained. It is plausible that rare variants in both known and as yet unknown gene loci may play a role in warfarin response, particularly in individuals with extreme phenotypes, i.e. requirement of either very low or very high daily warfarin doses. Furthermore, twin studies of the pharmacokinetic variability of torsemide and metoprolol[56] have shown that only around 40% of the genetic variability can be explained by known genetic polymorphisms. Recent work by Kozyra et al.[57] has indicated that between 30% and 40% of the variability in pharmacogenes is due to rare variants.

Metagenomic risk factors for ADRs

There is growing interest in the role of the human microbiome in predicting drug response.[58] More than 50 drugs are known to be metabolized by the microbiome (by hydrolysis or reduction in the majority of cases).[59] Examples include soruvidine, lovastatin, and paracetamol. Theoretically, this could alter their disposition in the host and potentially lead to lack of efficacy or predisposition to adverse effects. Whether the microbiome, in the gut and other locations, has a significant role in explaining the missing variability with different drugs requires further study. For instance, with the antidiabetic agent metformin, there is evidence that modulation of the gut microbiome is

responsible, at least partly, for its therapeutic effects.[60] Whether disturbance in the gut microbiome is also responsible for its common adverse effect of GI intolerance requires further study.

Multiomics/systems biology approaches

Genomic biomarkers clearly still have much to offer for predicting ADRs. However, alternative but complementary omics technologies need to be considered both in insolation but also within an integrated multiomic/systems biology framework.[61] This will allow the identification of complexed multifaceted traits which predispose to ADRs but also uncover novel mechanistic biological pathways with the potential to yield novel biomarkers of both a genetic and non-genetic nature.

Circulating protein and nucleic acid biomarkers

Biomarkers of generalized tissue injury applicable to ADRs

A plethora of "traditional" circulating protein biomarkers which correlate with specific tissue injury, regardless of etiology, can be used for diagnosis of ADRs, and in some cases, for determining prognosis (Table 3). Typical examples include plasma alanine transaminase (ALT) and aspartate transaminase (AST) for liver injury and serum creatinine for kidney injury. While these markers of tissue injury have been used for many years, they can have limitations in terms of sensitivity (they become elevated only when a significant proportion of the organ is damaged) and specificity (they can be produced by multiple organ or multiple toxic insults). Additionally, in the context of ADRs, they are also limited in informing as to the specific mechanism of toxicity or the affected cell type within an organ system. A typical example is serum creatine kinase (CK) where a level of $>4\times$upper limit of normal (ULN) has been used for diagnosing muscle toxicity associated with the use of statins.[52] CK elevation can occur due to a number of commonly occurring events including strenuous exercise[62] and trauma.[63] In addition, other unrelated comorbidities such as myocardial infarction can also cause CK elevation.[64] Broadly speaking, CK elevation thus offers low specificity for diagnosing statin myopathy and gives little indication of the specific mechanisms of statin myopathy.

By contrast, recent advances in biomarkers for the detection of DILI serve as a paradigm for how novel markers can have significant advantages over traditional markers for diagnosing and understanding the etiology of an ADR. Of particular promise is serum miR-122, which has been shown to be a highly specific marker for acute hepatocyte injury in paracetamol overdose[82] and more sensitive than traditional liver function tests for early toxicity detection. However, further work is required to determine the utility of miR-122 as a diagnostic/prognostic marker of late-onset idiosyncratic DILI. Evidence for other miR as diagnostic tools for ADRs is currently low, although a number of other putative miR biomarkers have been reported, including miR-124[69] and miR-18a-5p[70] for SJS/TEN. Understanding how and when miRs become elevated also provides an opportunity to gain insight into the specific cell source and pathogenesis of the injury. This may also help in the future in drug development during both preclinical toxicology testing and early phase human trials.

Mechanistic biomarkers

The field of kidney injury research is perhaps the best example of how a new generation of biomarkers has the potential to provide not only early sensitive detection of renal toxicity but also provide information as to the specific site of injury within the nephron.[83] The additional information could have tremendous potential benefits to both drug development and healthcare professionals. This sort of mechanistic approach to biomarker discovery could certainly be applied to other tissues/organs commonly affected by ADRs where toxicity may be specific to particular cell types such as the liver and gastrointestinal (GI) tract.

High Mobility Group Box-1 (HMGB1) is a biomarker which has significant potential as a prognostic mechanistic biomarker for ADRs. HMGB1 is an example of a Damage Associated Molecular Pattern molecule, which is critical in linking cell death to inflammation and in the progression of disease. HMGB1 sits at the intersection between infectious and sterile inflammation. HMGB1 is actively released in an acetylated form from activated immune cells and passively released in the non-acetylated form during necrotic cell death.[84] Furthermore, the HMGB1 molecule can exist in three redox states, each of which infers a different physiological function related to the innate immune response. Disulfide HMGB1 has been demonstrated to engage with MD2 as part of the toll-like receptor 4 (TLR4) complex on monocytes in order to elicit cytokine induction[85] while the fully reduced isoform is thought to interact with CXCL12 to engage with CXCR4 to induce chemotaxis.[86] Work undertaken in patients with liver damage who have overdosed on acetaminophen has shown that early elevation of HMGB1, in patients with normal ALTs, was able to predict more severe forms of liver injury later during the course of the overdose.[82]

Total serum HMGB1 is also elevated in a number of immune-mediated type B ADRs including DRESS,[87] SJS/TEN,[68] and in principle DILI.[88] HMGB1 isoforms could theoretically be utilized for early distinction of hypersensitivity reactions leading to significant tissue injury (e.g. SJS/TEN) as opposed to milder phenotypes (maculopapular exanthem), but more work needs to be done on this.

Identifying and implementing diagnostic biomarkers which can predict the onset of ADRs (Figure 1) is clearly of benefit to both patients and healthcare professionals. However, in some examples, such as SJS/TEN, severe long-term sequelae can occur a significant time after the acute reaction and subsequent drug withdrawal.[89] Although at present no examples exist, the development of prognostic biomarkers for prediction of these sequelae, which can include vision loss, has the potential to provide tools to improve treatment decisions and clinical care pathways.

Table 3. Clinically utilized and putative biomarkers of ADRs.

System	ADR	Biomarker	Tissue/fluid	Indicative of	Currently utilized for diagnosis/ prognosis	References
Skin	Hypersensitivity (SJS/TEN/ DRESS/rash)	C-reactive protein	Serum	Non-specific inflammation	Y	65
		Granulysin	Blister fluid		N	66
		Interleukin-15	Serum	Innate immune response	N	67
		HMGB1	Serum	Sterile tissue injury/ innate immune response	N	68
		miR-124	Serum/skin	Unknown	N	69
		miR-18a-5p	Serum/skin	Unknown	N	70
Gastrointestinal	Hepatotoxicity	Alanine transaminase (ALT)/aspartate transaminase (AST)	Serum	Hepatocellular injury	Y	71
		Alkaline phosphatase (ASP)	Serum	Hepatic bile canaliculi cell injury	Y	71
		Bilirubin	Serum	Hepatic injury/biliary obstruction but also extrahepatic disorder	Y	72
		HMGB1	Serum	Sterile tissue injury/ innate immune response	N	73
		miR-122	Serum	Hepatocyte-specific cell injury	N	24,74
		Cytokeratin-18	Serum	Apoptotic/necrotic hepatic cell death	N	75
	Lower GI toxicity	C-reactive protein	Serum	Non-specific inflammation	Y	76
		Lactoferrin	Fecal	Inflammation	Y	77
		Calprotectin	Fecal	Inflammation	Y	78
Renal		Creatinine	Serum	Glomerular filtration rate and proximal tubular secretion	Y	79
		Cystatin-C	Serum	Glomerular filtration rate and proximal tubular secretion	Y	80
		NGAL	Urine	Proximal and distal tubule secretion	N	81
		KIM-1	Urine	Proximal Tubule	N	90
Musculoskeletal	Myopathy/ rhabdomyolysis	Creatine kinase	Serum	Skeletal muscle injury but also cardiac muscle injury	Y	52

GI: gastrointestinal; HMGB1: High Mobility Group Box-1; N: no; Y: yes.
N-GAL: Neutrophil gelatinase-associated lipocalin; KIM-1: kidney injury molecule 1.

Conclusions

While much progress has been made in identifying predictive genomic biomarkers of ADRs, only a small number have been translated to clinical practice. With the increasing use of sequencing technologies, greater focus is being placed on the role of rare variants in ADR predisposition. Additionally, other omics technologies are likely to yield significant biomarkers for ADRs in the future. A new generation of circulating biomarkers of ADRs, typified by miR-122 and HMGB1, have great potential as highly specific and sensitive diagnostic and/or prognostic markers. The example of renal toxicity highlights the potential of using panels of biomarkers as indicators of specific cellular or tissue sites of injury and provide greater mechanistic understanding of ADRs. Application of this mechanistic approach to other target organs of ADRs (liver, skin, GI tract) could yield substantial benefits in producing robust biomarkers for the benefit of patient care and future drug development pipelines. It is likely that in the future we will not be relying on single biomarkers (genomic/non-genomic), but on multiple biomarker panels, integrated through the application of different omics technologies, which will provide information on predisposition, early diagnosis, prognosis, and mechanisms. This is however likely to introduce huge complexity in terms of the evidence that will be required for regulation and clinical implementation, and in the interpretation of these complex tests for clinical care of patients. This will need to be aligned to studies of cost-effectiveness and inclusion in clinical guidelines, as well as education and training of new and existing healthcare professionals.

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