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Novel genetic and epigenetic factors of importance for inter-individual differences in drug disposition, response and toxicity

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ABSTRACT

Individuals differ substantially in their response to pharmacological treatment. Personalized medicine aspires to embrace these inter-individual differences and customize therapy by taking a wealth of patient-specific data into account. Pharmacogenomic constitutes a cornerstone of personalized medicine that provides therapeutic guidance based on the genomic profile of a given patient. Pharmacogenomics already has applications in the clinics, particularly in oncology, whereas future development in this area is needed in order to establish pharmacogenomic biomarkers as useful clinical tools. In this review we present an updated overview of current and emerging pharmacogenomic biomarkers in different therapeutic areas and critically discuss their potential to transform clinical care. Furthermore, we discuss opportunities of technological, methodological and institutional advances to improve biomarker discovery. We also summarize recent progress in our understanding of epigenetic effects on drug disposition and response, including a discussion of the only few pharmacogenomic biomarkers implemented into routine care. We anticipate, in part due to exciting rapid developments in Next Generation Sequencing technologies, machine learning methods and national biobanks, that the field will make great advances in the upcoming years towards unlocking the full potential of genomic data.

Contents

Abbreviations: 5caC, 5- Carboxylcytosine; 5fC, 5- Formylcytosine; 5hmC, 5-hydroxymethylcytosine; ABC-HSS, Abacavir hypersensitivity syndrome.; ALL, Acute lymphoblastic leukemia; CAT, Catalase; CFTR, Cystic fibrosis transmembrane conductance regulator; ChIP, Chromatin immunoprecipitation; CNVs, Copy number variations; CPIC, Clinical Pharmacogenetics Implementation Consortium; DHR, Drug hypersensitivity reactions; DIHS, Drug-induced hypersensitivity syndrome.; DILI, Drug-induced liver injury; DNMTs, DNA methyltransferases; DPWG, Dutch Pharmacogenetics Working Group; DRESS, Drug rash with eosinophilia and systemic symptoms; eQTL, Quantitative trait locus; GPCR, G-protein coupled receptor; GST, Glutathione-S-transferase; HDACs, Histone deacetylases; MAF, Minor allele frequencies; MPE, Maculopapular exanthema; MS, Multiple sclerosis; PM, Poor metabolism; oxBS-seq, Oxidative bisulfite sequencing; PRC2, Polycomb repressive complex 2; PTMs, Posttranslational modifications; RA, Retinoic acid; SCAR, Severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; SNVs, Single nucleotide variations; TAB-Seq, TET-assisted bisulfite sequencing; TEN, Toxic epidermal necrolysis; UM, Ultrarapid metabolism.

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1. Introduction

The phenomenon that individuals differ in their response to pharmacological therapy has been known for a long time. The early beginnings of the field can be traced back to the identification of interindividual variability of fava bean poisoning by Pythagoras in the 6th century BC an effect much later shown to be linked to polymorphisms in the *G6PD* gene. Subsequent important contributions were made by Werner Kalow (Kalow & Gunn, 1957) and Bill Evans (Evans, Manley, & McKusick, 1960) identifying the polymorphism in butyrylcholinesterase and isoniazid metabolism, respectively. Seminal twin studies conducted by Sjöqvist and colleagues found that monozygotic and dizygotic twins differed significantly in nortyptiline pharmacokinetics (Alexanderson, Evans, & Sjoqvist, 1969). Contemporaneously, similar observations were made by Vesell and Page for antipyrine (Vesell & Page, 1968a), dicoumarol (Vesell & Page, 1968b) and phenylbutazone (Vesell & Page, 1968c). While these studies clearly demonstrated the extent of heritability of pharmacokinetic variation, the genetic basis remained elusive.

Another important milestone in pharmacogenetic research was the identification of the genetic polymorphisms underlying differences in debrisoquine and sparteine metabolism by Bob Smith and Michel Eichelbaum in an autosomal locus, which later turned out to be *CYP2D6* (Eichelbaum, Spannbrucker, & Dengler, 1979; Eichelbaum, Spannbrucker, Steincke, & Dengler, 1979; Mahgoub, Idle, Dring, Lancaster, & Smith, 1977). Subsequently, characterization of the responsible enzymes and their corresponding genes was only achieved more than a decade later in the 1980s and 1990s. A major development was the true biochemical purification of different cytochrome P450 (CYP) enzymes from liver that allowed the subsequent, often antibody assisted cDNA cloning. These breakthroughs allowed for the identification of the most common polymorphic variants using in vivo phenotype-to-genotype strategies and set the stage for modern pharmacogenetic research. For a comprehensive review about the historical origins of pharmacogenetics, we recommend the review by Lesko and Schmidt (Lesko & Schmidt, 2012).

Completion of the Human Genome Project in the early 2000s opened important new possibilities for pharmacogenetic biomarker discovery and set the stage for a plethora of studies that investigated associations between specific genetic polymorphisms and drug response, drug adverse reactions and disease risks. As a result, >200 pharmacogenomic biomarkers have been identified to date that can provide actionable information for clinicians and guide the choice and dosage of pharmacological therapy tailored for a specific patient. However, the societal benefits of these tests and their socioeconomic impacts are in most cases still uncertain and only nine pharmacogenetic biomarkers have received strict boxed warnings (abacavir, carbamazepine, clopidogrel, codeine, lenalidomide, pegloticase, rasburicase, tramadol and valproic acid). In addition, the literature is overwhelmed with a large number of inconclusive association studies that could not be replicated, primarily due to insufficient power to detect associations using agnostic approaches or incomplete phenotypic characterization of the analyzed patient cohorts.

In order to provide support for the further implementation of pharmacogenomic biomarkers, there is a clear need for more randomized, prospective clinical trials. However, as compared to clinical trials for newly developed medicines, the incentive for financing expensive trials that evaluate the added value of companion diagnostics is often rather low because the drugs in question have lost their patents, reducing the incentive to fund expensive trials that validate their use. The most successful example has been the identification of pharmacogenetic tests prior to initiation of abacavir therapy, funded by GlaxoSmithKline. In addition, few trials have been funded by governmental grants, such as the CoumaGen-II (Anderson et al., 2012), COAG (Kimmel et al., 2013) and EU-PACT (Pirmohamed et al., 2013) trials pertaining to warfarin treatment; however, with mixed results.

In this contribution we first provide a regulatory and clinical perspective of the current status of pharmacogenetic biomarkers (Section 2), highlight and comprehensively review emerging associations and critically reflect on the potential for the clinical implementation of these tests (Section 3), discuss the opportunities and challenges associated with the increasing application of Next Generation Sequencing technologies, and highlight exciting opportunities for pharmacogenomic research enabled by national biobank programs (Section 4). In addition, we provide an update of recent developments in pharmacoepigenetics (Section 5) and lastly give our view of current frontiers of pharmacogenomic research that aim to translate academic findings into clinical and societal benefits (Section 6).

2. Clinical implications of pharmacogenetic biomarkers

2.1. Current status of germline biomarkers

Most pharmacogenetic biomarkers with clinical importance reside in genes involved in drug pharmacokinetics and pharmacodynamics as well as in loci related to immune response. Genetic variability is generally analyzed in the germline genome of the patient of interest using non-invasive or minimally invasive methods to obtain the required DNA. In contrast, in oncological therapy, most biomarkers pertain to mutations within the neoplasm, i.e. the somatic genome, and thus require the genetic analysis of tumor biopsies.

Pharmacogenomic biomarkers in the germline genome mostly relate to genetic variants in loci affecting drug pharmacokinetics, including drug metabolizing enzymes and drug transporters. The clinical use of pharmacokinetic germline variants for preemptive guidance of therapy is most widespread in oncology, where variations in *DPYD*, *TPMT* and *UGT1A1* are analyzed for the prediction of adverse reactions to fluoropyrimidines, mercaptopurines, and irinotecan, respectively (Lauschke, Milani, & Ingelman-Sundberg, 2017). While the frequency of defective *TPMT* and *DPYD* alleles is low, their clinical effects are remarkably high. *TPMT* genotype-guided dosing is already widely applied in clinical practice and is mandatory before commencing mercaptopurine therapy in childhood leukemia (Lennard, 2014). Also the NUDT15 genotype is recommended by the Clinical Pharmacogenetics Implementation Consortium (CPIC) to be considered in this type of anticancer therapy Relling et al., 2018. Implementation of preemptive *DPYD* genotyping into routine care is lagging behind despite firm evidence supporting lower incidences of severe toxicities while maintaining fluoropyrimidine exposure levels in the therapeutic range, as well as reduced health care costs (Deenen et al., 2016; Henricks et al., 2018). Furthermore, pharmacogenetic testing is implemented in the clinics for genetic variants in *CYP2D6*, *CYP2C19*, *CYP2C9* and *VKORC1* for guidance of drug treatment in cardiology and psychiatry.

The only germline variation in a pharmacodynamic gene that has received pharmacogenetic labels, pertains to variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*, *ABCC7*) gene that cause cystic fibrosis (CF) and genotype-guided CF therapy already constitutes clinical reality. Here, >1900 different genetic variants have been identified that affect CFTR function, 1000 of which occur in fewer than five people in all cohorts studied to date (Oliver, Han, Sorscher, & Cutting, 2017). Depending on the functional consequences of the variants found in a given patients, different drugs can be prescribed including ivacaftor for patients that harbor variants resulting in gating defects (*CFTR* class III variants) or lumacaftor for patients with CFTR folding defect mutations. Thus, for CF, preemptive pharmacogenetic testing is already of fundamental importance for successful treatment and about 60% of CF patients can benefit from such tailored therapies.

Genetic variability in *ADRB2*, the gene encoding the β2-adrenergic receptor, has long been considered as a promising biomarker to predict the response to β-agonists in the management of asthma (Kersten & Koppelman, 2017; Ortega & Meyers, 2014). However, results of different trials were conflicting and could, if at all, only explain a minor

fraction of the observed variability in drug response (Israel et al., 2004; Wechsler et al., 2009; Wechsler et al., 2015). Thus, the implementation of genotype-guided therapies for asthma utilizing β2-adrenergic receptor variants in the near future appears unlikely. Recent evaluation of sequencing data from 60,000 individuals revealed a surprisingly large number of rare variants in this class of receptors, many potentially important for altered ligand binding or ligand effects (Hauser et al., 2018). Combined, these data indicate the importance to consider such rare receptor variants for drug response predictions.

2.2. Current status of somatic biomarkers

At present oncology is the most important therapeutic area for preemptive prediction of drug outcomes. This area is the subject of very intensive research and in total > 268,000 publications are indexed in PubMed that concern oncological biomarkers, including genomic and epigenomic variants, but the work also encompasses a variety of other molecules, such as non coding RNAs, proteins, peptides and metabolites.

In addition to the aforementioned germline variants in *DPYD*, *TPMT* and *UGT1A1* that affect the pharmacokinetics of chemotherapeutic agents, somatic mutations in various pharmacodynamic genes open possibilities for the treatment with therapeutics that specifically target the affected pathways. Examples for such targeted cancer drugs that require specific somatic mutations for their effectiveness include the EGFR inhibitors gefitinib, erlotinib and osimertinib, the BRAF inhibitors dabrafenib and vemurafenib and the ERBB2 targeting agents lapatinib, pertuzimab and trastuzumab. In addition, whole genome sequencing (WGS) of the somatic cancer genome is becoming more common, allowing to individualize oncological treatment beyond common mutations. We anticipate that these developments will further accelerate and establish WGS as an integral instrument in the area of anticancer therapy.

Current pharmacogenomic analyses are primarily focused on treatment with small molecules and biomarkers to predict treatment response to emerging biologics constitutes an important frontier. This need is exemplified by treatment outcomes of nivolumab, an antibody-based inhibitor of PD1, in melanoma. While nivolumab significantly improved overall survival compared to conventional dacarbazine chemotherapy, only 20–30% of patients responded to nivolumab and the reasons for the lack of response in the remaining patients remain unknown (Ascierto & Long, 2016). Similar response rates were observed for monoclonal antibodies for CTLA4, such as ipilimumab (Carreau & Pavlick, 2018).

2.3. Pharmacogenomic drug labels and guidelines

One instrument to support the application of genetic variations in the clinics are pharmacogenomic drug labels. These labels are prepared by the drug manufacturers and submitted for approval to the responsible regulatory agency, such as European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for Europe and the US, respectively. Where applicable, they recommend the genotyping of specific genes or variants to guide drug and dose selection, predict treatment outcomes or adverse reactions, or inform about potential effects on drug-drug interactions. By 2018, FDA has approved a total of 69 labels that carry information regarding indications, contraindications or dosage recommendation in relation to patient genotype, whereas about 107 have correspondingly based labels have been identified by EMA (Table 1 and Fig. 1a). In addition, pharmacogenomic advice is provided by guidelines from pharmacogenetic experts workgroups, such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG).

There are differences between drug labels and recommendations by the different regulatory agencies and consortia (Fig. 1). The majority of EMA labels (52%) refer to pharmacokinetic genes mainly in oncology, whereas the majority of FDA labels (66%) pertain to mutations or genomic rearrangements in the somatic genome of tumors and only 22% of labels refer to pharmacokinetic germline variations (Fig. 1b). Notably, as published in 2015, several of the EMA labels merely refer to drug-drug interactions rather than to genetic variation. In addition it is important to emphasize that EMA labels only concern drugs approved by EMA, which was founded in 1995, whereas labels in older drugs are provided by the different EU National Medical Product Agencies.

Recommendations from expert consortia are focused exclusively on the genetic variation in the germline genome and a recent comparison between theses therapeutic recommendations concluded that CPIC and DPWG pharmacogenetic guidelines were overall in good agreement (Bank et al., 2018). However, their alignment with drug labels is rather poor. Of 44 EMA labels with pharmacogenetic information referring to germline variants, only four (9%) overlap with CPIC or DPWG recommendations (abacavir and HLA-B, aripiprazole and CYP2D6, capecitabine and DPYD, ivacaftor and CFTR) (Fig. 1f). Alignment for FDA labels is higher and 18 out of 45 labels (40%) are supported by independent expert recommendations. Abacavir constitutes the only drug for which EMA and FDA labels, as well as CPIC and DPWG guidelines concordantly recommend genotype-guided therapy. Overall, there is thus a need to critically reflect upon the different recommendations by regulators and expert groups to reach a consensus view on the role of preemptive genotyping in the clinics.

The regulatory agencies also provide guidelines for the integration of pharmacogenomic analyses into early and later phases of drug development (https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacogenomic-practice-first-version_en.pdf, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf). Furthermore, EMA and Industry (EBE and EFPIA) have worked out specific guidance concerning the use of NGS as an instrument for pharmacogenomic advice (https://www.ema.europa.eu/documents/scientific-guideline/guideline-good-pharmacogenomic-practice-first-version_en.pdf, https://www.ebe-biopharma.eu/publication/ebe-efpia-position-paper-on-next-generation-sequencing-ngs/). This includes early identification of patients with extreme drug response phenotypes (outlier patients), the possibility to stratify patient groups based on their genetic makeup, methodological advice pertaining to genomic and phenotypic analyses, and planning of follow-up trials based on the pharmacogenomic experience in early phases. During this process also the incorporation of pharmacogenomic advice into the drug label must be considered. In line with a more genetically tailored drug therapy, the number of drugs released on the market with such labels has increased considerably in recent years (Ehmann et al., 2015).

3. Emerging pharmacogenomic biomarkers

In the following section, we synopsize recent promising progress and updates in the field of pharmacogenomic biomarkers to predict safety and efficacy of pharmacological therapies.

3.1. Drug hypersensitivity associated with HLA variations

3.1.1. HLA biomarkers

Drug hypersensitivity reactions (DHR) are the most common idiosyncratic adverse events. DHRs can manifest immediately within the first hours after drug administration or have a delayed onset of weeks to months (Romano et al., 2011). Prospective studies found that DHRs occurred with an overall prevalence of 0.2–0.8% of all hospitalized patients, of which >95% had cutaneous manifestations (Albala et al., 2003; Hernandez-Salazar et al., 2006; Park et al., 2008; Thong, Leong, Tang, & Chng, 2003). Delayed DHRs can manifest as severe cutaneous adverse reactions (SCARs) that encompass Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, the latter involving also internal

Table 1
Comparison of medications with associated pharmacogenomic biomarkers by EMA and FDA. EMA labels were reviewed in Ehmann et al. (Ehmann et al., 2015) and only encompass drugs registered after the foundation of EMA in 1995. FDA labels were extracted from https://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm [Accessed 01.11.2018]. Only the sections describing therapeutic indications, posology and contraindications were considered. BW = boxed warning.

Compound	Gene	Indication	Posology	Contraindication	Indication
Abacavir	*HLA-B*	EMA	FDA	FDA (BW)	HIV infection
Abemaciclib	*ESR*	FDA			Advanced or metastatic breast neoplasms
	ERBB2	FDA			
Afatinib	*EGFR*	EMA & FDA	EMA & FDA		Non-small cell lung cancer
Alectinib	*ALK*	FDA	FDA		Non-small cell lung cancer
Aliskiren	*ABCB1*			EMA	Hypertension
Anastrozole	*ESR, PGR*	FDA			Breast neoplasms
Aripiprazole	*CYP2D6*		EMA & FDA		Bipolar disorder, schizophrenia
	CYP3A4		EMA		
Arsenic trioxide	*PML-RARA*	EMA & FDA			Acute promyelotic leukemia
Atazanavir sulfate	*CYP3A4*			EMA	HIV infection
Atezolizumab	*CD274*	FDA			Lung cancer
Atomoxetine	*CYP2D6*		FDA		Attention deficit hyperactivity disorder
Axitinib	*CYP3A4*		EMA		Renal cell carcinoma
	CYP3A5		EMA		
Azathioprine	*TPMT*		FDA		Kidney transplantation, rheumatoid arthritis, Crohn's disease, ulcerative colitis
Belinostat	*UGT1A1*		FDA		T-cell lymphoma
Binimetinib	*BRAF*	FDA	FDA		Melanoma
Blinatumomab	*BCR-ABL*	FDA			Acute lymphoblastic leukemia
Boceprevir	*CYP3A4*			EMA	Chronic hepatitis C
Bosutinib	*BCR-ABL*	EMA & FDA	EMA		Myelogenous leukemia
Brentuximab vedotin	*CD30*	EMA			Hodgkin disease, non-Hodgkin lymphoma
Brexpiprazole	*CYP2D6*		FDA		Schizophrenia, depression
Brigatinib	*ALK*	FDA			Non-small cell lung cancer
Cabazitaxel	*CYP3A4*		EMA		Prostatic neoplasms
Cabozantinib	*CYP3A4*		EMA		Thyroid neoplasms
Capecitabine	*DPYD*			EMA	Colorectal neoplasms, colonic neoplasms, stomach neoplasms, breast neoplasms
Carbamazepine	*HLA-B*			FDA (BW)	Epilepsy, schizophrenia, bipolar disorder
Carglumic acid	*NAGS*	FDA			Hyperammonaemia
Celecoxib	*CYP2C9*		FDA		Treatment of inflammation and pain in various conditions
Ceritinib	*ALK*	FDA	FDA		Non-small cell lung cancer
Cerliponase alpha	*TPP1*	FDA			Neuronal ceroid lipofuscinosis
Cetuximab	*EGFR*	EMA & FDA	FDA		Colorectal neoplasms, head and neck neoplasms
	RAS	EMA & FDA	EMA & FDA	EMA	
Citalopram	*CYP2C19*		FDA		Major depression
Clobazam	*CYP2C19*		FDA		Epilepsy, acute anxiety
Clopidogrel	*CYP2C19*			FDA (BW)	Peripheral artery disease, stroke prevention
Clozapine	*CYP2D6*		FDA		Schizophrenia
Cobimetinib	*BRAF*	FDA	FDA		Melanoma
Codeine	*CYP2D6*			FDA (BW)	Treatment of pain
Crizotinib	*ALK*	EMA & FDA	EMA & FDA		Non-small cell lung cancer
	ROS1	FDA	FDA		
Dabrafenib	*BRAF*	EMA & FDA	EMA & FDA		Melanoma
	RAS		FDA		
Darifenacin hydrobromide	*CYP2D6*			EMA	Urinary Incontinence, overactive urinary bladder
	CYP3A4			EMA	
Darunavir	*CYP3A4*			EMA	HIV infection
Dasatinib	*BCR-ABL*	EMA & FDA	EMA & FDA		Chronic myelogenous leukemia, precursor cell lymphoblastic leukemia-lymphoma
Denileukin difitox	*IL2RA*	FDA			Cutaneous T-cell lymphoma
Deutetrabenazine	*CYP2D6*		FDA		Chorea
Dronedarone	*CYP3A4*			EMA	Atrial fibrillation
Efavirenz	*CYP3A4*			EMA	HIV infection
Eliglustat	*CYP2D6*	FDA	FDA	FDA	Gaucher's disease
Elosulfase	*GALNS*	FDA			Morquio-Brailsford syndrome
Enasidenib	*IDH2*	FDA	FDA		Acute myeloid leukemia
Encorafenib	*BRAF*	FDA	FDA		Melanoma
Erlotinib	*EGFR*	EMA & FDA	FDA		Non-small cell lung cancer, pancreatic neoplasms
	CYP3A4		EMA		
Eteplirsen	*DMD*	FDA			Duchenne muscular dystrophy
Everolimus	*ERBB2*	EMA & FDA	FDA		Renal cell carcinoma, pancreatic neoplasms, breast neoplasms
	ESR	FDA	FDA		
Exemestane	*ESR, PGR*	FDA	FDA		Breast neoplasms
Fampridine	*SLC22A2*			EMA	Multiple sclerosis
Fesoterodine	*CYP3A4*		EMA	EMA	Overactive urinary bladder
Fluorouracil	*DPYD*			FDA	Colorectal neoplasms, stomach neoplasms, pancreatic neoplasms, breast cancer, cervical neoplasms, esophageal neoplasms
Fosamprenavir	*CYP3A4*			EMA	HIV infection
Fulvestrant	*ERBB2*	FDA			Breast neoplasms
	ESR, PGR	FDA			

(continued on next page)

Table 1 (*continued*)

Compound	Gene	Indication	Posology	Contraindication	Indication
Gefitinib	*EGFR*	EMA & FDA	FDA		Non-small cell lung cancer
	CYP2C9		EMA		
	CYP2D6		EMA		
Ibrutinib	Chromosome 17p	FDA			B-cell lymphomas
Iloperidone	*CYP2D6*		FDA		Schizophrenia
Imatinib	*BCR-ABL*	EMA & FDA	EMA & FDA		Chronic myelogenous leukemia,
	KIT	EMA & FDA	FDA		myelodysplastic-myeloproliferative diseases,
	FIP1L1-PDGFRA	EMA & FDA	FDA		dermatofibrosarcoma,
	PDGFRB	FDA	FDA		precursor cell lymphoblastic leukemia-lymphoma, hypereosinophilic syndrome
Indinavir	*CYP3A4*			EMA	HIV infection
Irinotecan	*UGT1A1*		FDA		Colorectal neoplasms, pancreatic neoplasms, small cell lung cancer
Ivabradine	*CYP3A4*			EMA	Angina pectoris
Ivacaftor	*CFTR*	EMA & FDA	EMA		Cystic fibrosis
	CYP3A4		EMA		
Lapatinib	*ERBB2*	EMA & FDA	EMA & FDA		Breast neoplasms
	ESR, PGR	FDA	FDA		
Lenalidomide	Chromosome 5q	FDA		FDA (BW)	Myelodysplastic syndrome, multiple myeloma
Letrozole	*ESR, PGR*	FDA			Breast neoplasms
Lomitapide	*ABCB1*			EMA	Hypercholesterolemia
Lurasidone	*CYP3A4*		EMA	EMA	Schizophrenia
Maraviroc	*CYP3A4*		EMA		HIV infection
Mercaptopurine	*TPMT*		FDA		Acute lymphocytic leukemia, chronic myeloid leukemia, Crohn's
	NUDT15		FDA		disease, ulcerative colitis
Methylene blue	*G6PD*			FDA	Methemoglobinemia
Midostaurin	*FLT3*	FDA	FDA		Myelodysplastic syndrome
Nebivolol	*CYP2D6*		FDA		Hypertension
Nelfinavir	*CYP3A4*			EMA	HIV infection
Neratinib	*ERBB2*	FDA			Breast neoplasms
Nilotinib	*BCR-ABL*	EMA & FDA	FDA		Chronic myelogenous leukemia, acute myeloid leukemia, systemic mastocytosis
Nivolumab	*BRAF*	FDA			Melanoma, non-small cell lung cancer, renal cell carcinoma
Olaparib	*BRCA*	FDA	FDA		Breast neoplasms, ovarian neoplasms, prostate neoplasms
Osimertinib	*EGFR*	FDA	FDA		Non-small cell lung cancer
Palbociclib	*ERBB2*	FDA			Breast neoplasms
	ESR	FDA			
Panitumumab	*RAS*	EMA & FDA	EMA & FDA	EMA	Colorectal neoplasms
Parathyroid hormone	*CASR*	FDA			Osteoporosis
Pegloticase	*G6PD*			FDA (BW)	Gout
Pembrolizumab	*CD274*	FDA	FDA		Unresectable or metastatic solid tumors
Pertuzumab	*ERBB2*	EMA & FDA	EMA		Breast neoplasms
Pimozide	*CYP2D6*		FDA		Schizophrenia
Ponatinib	*BCR-ABL*	EMA & FDA			Lymphoid leukemia, myeloid leukemia
Posaconazole	*CYP3A4*			EMA	Aspergillosis, coccidioidomycosis, candidiasis, mycoses
Primaquine	*G6PD*			FDA	Malaria and Pneumocystis pneumonia
Propafenone	*CYP2D6*		FDA		Arrhythmias
Quinine sulfate	*G6PD*			FDA	Malaria and babesiosis
Ranolazine	*CYP3A4*		EMA	EMA	Angina pectoris
Rasburicase	*G6PD*			FDA (BW)	Tumor lysis syndrome
	CYB5R			FDA (BW)	
Ribociclib	*ERBB2*	FDA			Breast neoplasms
	ESR, PGR	FDA			
Ritonavir	*CYP3A4*			EMA	HIV infection
Rituximab	*MS4A1*	FDA	FDA		Rheumatoid arthritis, hematological cancers
Rucaparib	*BRCA*	FDA	FDA		Ovarian neoplasms
Ruxolitinib	*CYP3A4*		EMA		Myeloproliferative disorders
Sildenafil	*CYP3A4*		EMA	EMA	Pulmonary hypertension
Sirolimus	*CYP3A4*		EMA		Kidney transplantation, graft rejection
Sunitinib	*CYP3A4*		EMA		Neuroendocrine tumors, gastrointestinal stromal tumors, renal cell carcinoma
Tamoxifen	*ESR, PGR*	FDA			Breast neoplasms
Telaprivir	*CYP3A4*			EMA	Chronic hepatitis C
Telithromycin	*CYP3A4*			EMA	Community-acquired infections, chronic bronchitis, sinusitis, tonsillitis, bacterial pneumonia, pharyngitis
Tetrabenazine	*CYP2D6*		FDA		Hyperkinesia
Thioguanine	*TPMT*		FDA		Acute myeloid leukemia, acute lymphocytic leukemia, and chronic
	NUDT15		FDA		myeloid leukemia
Thioridazine	*CYP2D6*			FDA	Schizophrenia
Tipranavir	*CYP3A4*			EMA	HIV infection
Tramadol	*CYP2D6*			FDA (BW)	Treatment of pain
Trametinib	*BRAF*	FDA	EMA & FDA		Melanoma
Trastuzumab	*ERBB2*	EMA & FDA	EMA		Stomach neoplasms, breast neoplasms
Trastuzumab emtansine	*ERBB2*	EMA & FDA	EMA		Breast neoplasms
Tretinoin	*PML-RARA*	FDA			Acute promyelocytic leukemia
Valbenazine	*CYP2D6*		FDA		Tardive dyskinesia

Table 1 (*continued*)

Compound	Gene	Indication	Posology	Contraindication	Indication
Valproic acid	*POLG*			FDA (BW)	Epilepsy, bipolar disorder
Vandetanib	*RET*	EMA			Thyroid neoplasms
Vardenafil	*CYP3A4*		EMA	EMA	Erectile dysfunction
Vemurafenib	*BRAF*	EMA & FDA	EMA & FDA		Melanoma
Venetoclax	Chromosome 17p	FDA	FDA		Chronic lymphocytic leukemia
Voriconazole	*CYP3A4*			EMA	Aspergillosis, candidiasis, mycoses
Vortioxetine	*CYP2D6*		EMA & FDA		Major depressive disorder
Warfarin	*CYP2C9*		FDA		Deep vein thrombosis, pulmonary embolism, stroke prevention
	VKORC1		FDA		
Zonisamide	*CYP3A4*		EMA		Partial epilepsies

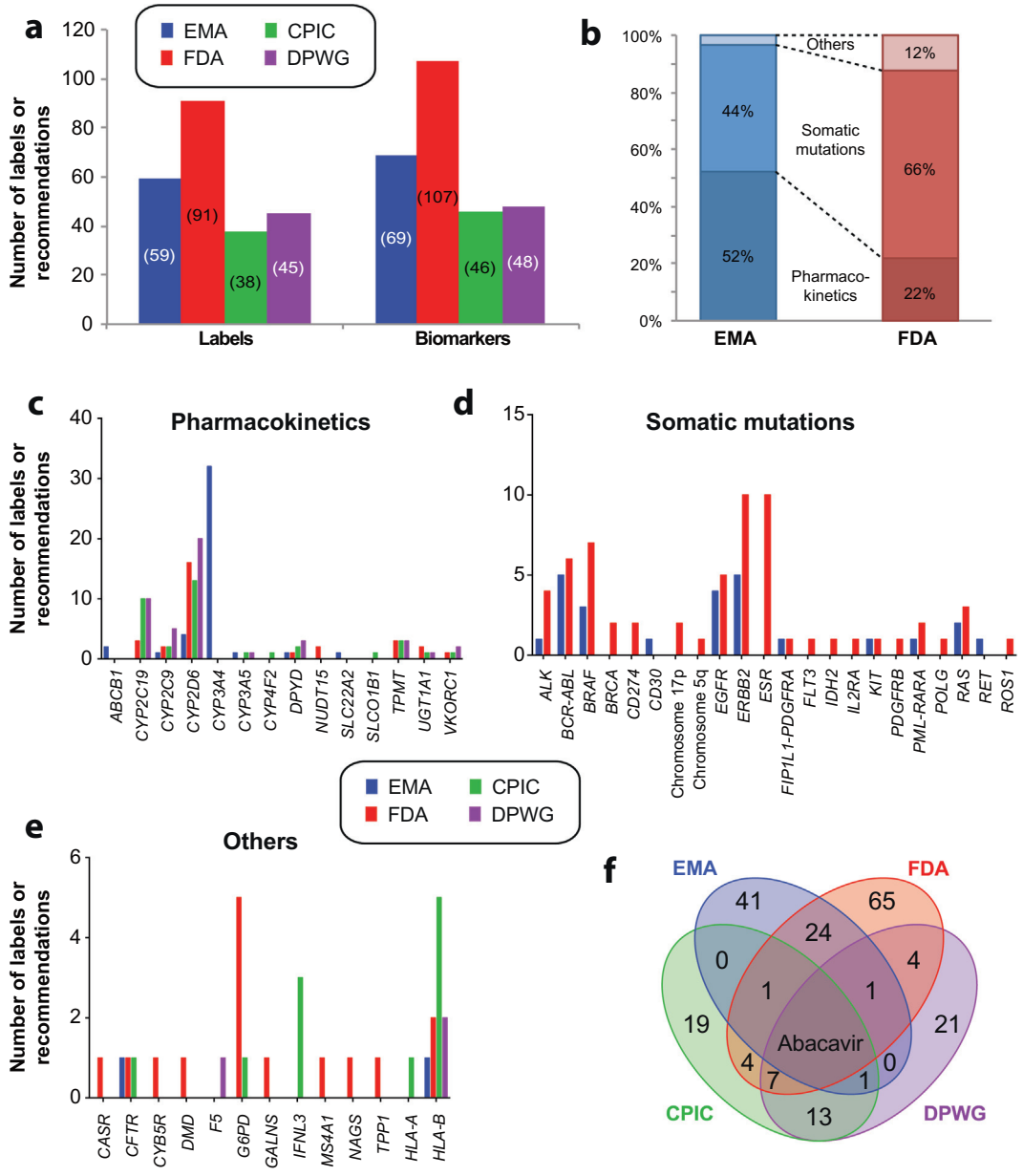

Fig. 1. Overview of drug labels and pharmacogenetic expert guidelines. a, Overview of the number of drug labels by EMA and FDA and recommendations by CPIC and DPWG, respectively. Note that some labels and guidelines contain references to more than one biomarker. b, The majority of EMA labels refer to pharmacokinetic germline variants, whereas FDA approved labels primarily pertain to variations in the somatic genome. Only the indication, contraindication and posology sections were considered. c-e, Overview of the number of drug labels and pharmacogenetic recommendations, stratified into germline variations that impact drug pharmacokinetics (c), somatic mutations in tumors (d) and other germline variants (e). f, Venn diagram depicting the overlap of pharmacogenetic guidance from EMA (blue) and FDA (red) approved drug labels and recommendations by CPIC (green) and DPWG (purple). EMA label information was reviewed in Ehmann et al. (Ehmann et al., 2015) and only encompasses drugs registered after the foundation of EMA in 1995, which creates some lack of coherence in the comparison. FDA labels were extracted from https://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. CPIC and DPWG guidelines were obtained from https://cpicpgx.org/guidelines and https://www.pharmgkb.org/guidelines, respectively. All sources were accessed Nov 1st 2018.

organs, such as liver (75–94% of patients), kidney (12–40% of patients) and heart (4–27% of patients) (Y.-T. Cho, Yang, & Chu, 2017). Agents most commonly implicated in SCARs are sulfonamides, phenytoin, allopurinol, carbamazepine and non-steroidal anti-inflammatory drugs (NSAIDs) of the oxicam class (Mockenhaupt et al., 2008; Roujeau et al., 1990; Rzany et al., 1996; Schöpf et al., 1991; Yamane, Aihara, & Ikezawa, 2007). In addition, DHRs can manifest as drug-induced liver injury (DILI), with β-lactam antibiotics and NSAIDs as the major culprit drugs. Further manifestations include abacavir systemic hypersensitivity and clozapine-induced agranulocytosis.

Genetic predisposition constitutes the most important risk factor for both immediate and delayed hypersensitivity reactions. Immediate reactions to β-lactams and NSAIDs have been consistently associated with polymorphisms in pro-inflammatory cytokine and IgE signaling (Oussalah et al., 2016). In addition, immediate hypersensitivity to NSAIDs was reproducibly associated with genetic variations in multiple arachidonic acid and leukotriene pathway genes, such as *ALOX15*, *PTGDR, PTGER4, TBXAS1* and *CYSLTR1* (Cornejo-García et al., 2012; Kim, Choi, Holloway, et al., 2005; Palikhe et al., 2012; Vidal et al., 2013). Anaphylactic reactions to both β-lactams and NSAIDs have also been associated with polymorphisms in class II *HLA* genes. A Spanish study with 387 patients that experienced immediate allergic reactions upon treatment with β-lactams and 1124 tolerant controls found multiple significant protective effects of *HLA-DRA* variations with odds ratios (ORs) around 0.6 that replicated in an Italian cohort of 299 patients and 362 control subjects (Guéant et al., 2015). In contrast, the *HLA-DRB1*11* and *HLA-DRB1*1302* alleles predisposed patients to NSAID-induced anaphylaxis and urticaria with ORs of 4 to 7.3 (Kim, Choi, Lee, et al., 2005; Quiralte et al., 1999).

For delayed hypersensitivity reactions >25 medications have been associated with MHC variability to date (Tables 2–4). The most extensively reproduced *HLA* biomarkers pertain to the antiretroviral abacavir, the antihyperuricemic allopurinol and the antiepileptics carbamazepine, phenytoin and lamotrigine. Hypersensitivity to abacavir is strongly associated with a single genetic risk allele, *HLA-B*5701* (Table 2). Prospective genotyping for *HLA-B*5701* was found to significantly reduce the incidence of abacavir hypersensitivity syndrome (ABC-HSS) in a single center cohort study with no cases of ABC-HSS among 148 *HLA-B*5701* negative patients compared to 5–8% in historic controls (Rauch et al., 2006). These encouraging results were confirmed in the prospective multicenter double-blind randomized PREDICT-1 trial in which the authors confirmed significantly lower incidence of ABC-HSS in the genotype arm (3.4% vs. 7.8% in the control group, $p < .001$) (Mallal et al., 2008). As a result, testing of *HLA-B*5701* has been recommended by both FDA and EMA before commencing abacavir therapy in abacavir-naïve patients.

For antiepileptics, the strongest associations have been identified for carbamazepine-induced SJS/TEN and *HLA-B*1502* in South and East Asian populations, including Chinese, Koreans, Thai, Malaysians and Indians, with odds ratios between 10 and 2500 (Table 3). In contrast, *HLA-A*3101* predicts SCARs in Koreans, Japanese and Europeans and a recent prospective cohort study with 1130 Japanese patients showed significantly reduced incidence of carbamazepine-induced cutaneous adverse reactions in the genotyped group (2% vs. 3.4–5.1% in historic controls)(Mushiroda et al., 2018). Moreover, *HLA-B*1511* and *HLA-B*1521* were implicated as additional risk alleles in various Asian populations (Table 3 and (Jaruthamsophon et al., 2017)). *HLA* biomarkers for phenytoin-induced SCARs have to our knowledge only been reported in Asian populations. The strongest risk factor has been found for *HLA-B*1502* with moderate odds ratios between 5 and 20, aligning with pharmacogenetic carbamazepine associations for these populations. However, the largest case-control study published to date in Thailand could not replicate this association and rather identified a multitude of other significantly associated HLA alleles, such as *HLA-B*3802*, *HLA-B*5602* and *HLA-C*1402* (Tassaneeyakul et al., 2016). For lamotrigine, various HLA associations have been reported, of which *HLA-B*1502* and *HLA-A*2402* have been reproduced. Combined, the existing data provide irrefutable evidence for associations between HLA alleles and SCARs related to antiepileptics. Carbamazepine is consistently associated with *HLA-B*1502* and *HLA-A*3101*. In contrast, risk factors for cutaneous adverse reactions to phenytoin and lamotrigine appear more heterogeneous.

Adverse cutaneous reactions following treatment with the xanthine oxidase inhibitor allopurinol, used for the treatment of gout and other conditions associated with an excess of uric acid, have been consistently linked with *HLA-B*5801* across ethnicities with odds ratios between 40 and 580 (Table 4). Furthermore, a prospective multicenter study in Taiwan with 2910 Han Chinese participants found that preemptive genotyping eliminated SCARs due to allopurinol when *HLA-B*5801* patients were instead referred to an alternate treatment (Ko et al., 2015). In addition, one study in 25 Korean allopurinol SCAR patients and 57 tolerant controls indicated a strong protective effect of *HLA-A*0201* (0/25 cases, 17/57 controls; OR = 0.04). However, this interesting observation requires further validations.

Cases of idiosyncratic DILI are generally much more rare than cases of adverse cutaneous reactions, which has made the identification of genetic factors predisposing to DILI difficult. Importantly, the establishment of large networks that collect and consolidate DILI cases, such as DILIN in the US and the DILIGEN study in the UK, have provided a significant step forward, increasing the study power and resulting in the identification of multiple HLA biomarkers in recent years. Notable examples include associations between flucloxacillin and *HLA-B*5701* (OR = 80.6) (Daly et al., 2009), terbinafine and *HLA-A*3301* (OR = 40.5) (Nicoletti et al., 2017), minocycline and *HLA-B*3502* (OR = 29.6) (Urban et al., 2017) and flupirtine with the *DRB1*1601-DQB1*0502* haplotype (OR = 18.7)(Nicoletti et al., 2016).

3.1.2. Molecular mechanisms of drug hypersensitivity

The molecular and immunological mechanisms underlying drug hypersensitivity are diverse and drug specific. Abacavir hypersensitivity is restricted exclusively to carriers of the *HLA-B*5701* allele with a negative predictive value of 100%. The abacavir parent compound binds specifically to the F-pocket of the peptide-binding groove of HLA-B*5701 and alters the repertoire of presented self-peptides, driving polyclonal alloreactive autoimmune responses (Illing et al., 2012; Norcross et al., 2012; Ostrov et al., 2012). Mechanistically similar immune activation has been suggested for nevirapine in some studies (Hirasawa et al., 2018), whereas others did not observe alterations in the repertoire of presented peptides in nevirapine exposed cells (Pavlos et al., 2017). In contrast, carbamazepine has been shown to activate carbamazepine-reactive CD8+ T-cells in the absence of loaded peptides by directly interacting with the HLA variant *HLA-B*1502* (Wei et al., 2012). Similar direct HLA binding and T-cell activation has been reported for ticlopidine (Usui et al., 2018) and the allopurinol metabolite oxypurinol (Yun et al., 2014). Whereas carbamazepine and oxypurinol interact non-covalently with the MHC, hypersensitivity reactions to β-lactam antibiotics involve covalent protein binding. Specifically, flucloxacillin binds covalently to lysine residues on albumin and the resulting flucloxacillin haptens are high affinity binders at HLA-B*5701 (Monshi et al., 2013). Lastly, sulfamethoxazole has been suggested to directly affect T-cell receptor conformation, thereby modulating HLA recognition and autoimmunity (Watkins & Pichler, 2013). For a more detailed overview of the mechanistic underpinnings of drug hypersensitivity, we refer the interested reader to excellent recent reviews on this topic (Bharadwaj et al., 2012; Chen et al., 2018; Pavlos et al., 2015).

3.1.3. Clinical implications

Routine clinical implementation of pharmacogenetic tests requires not only a strong association with severe adverse events but also various other conditions need to be considered, including the availability, efficacy and safety of alternative drugs, supportive clinical and experimental data, permissive environmental factors, sufficiently high

Table 2
Overview of genetic variations in the major histocompatibility complex associated with hypersensitivity to antiretrovirals and antibiotics. SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, DRESS = drug rash with eosinophilia and systemic symptoms, SCAR = severe cutaneous adverse reaction, DILI = drug-induced liver injury, ABC-HSS = abacavir hypersensitivity syndrome.

Allele	Ethnicity	Odds ratio	Adverse reaction	Cases	Controls	Study
Abacavir						
*HLA-B*5701*	Australian	960	ABC-HSS	18	230 tolerant controls	(Martin et al., 2004)
		117	ABC-HSS	18	167 tolerant controls	(Mallal et al., 2002)
	White	55.7	ABC-HSS	202	486 tolerant controls	CTR Summary for MDC - GSK Clinical Study Register (2007)
		30.4	ABC-HSS	61	657 tolerant controls	(Mallal et al., 2008)
	Spanish	44.3	ABC-HSS	22	70 tolerant controls	CTR Summary for MDC - GSK Clinical Study Register (2007)
		19.1	ABC-HSS	26	27 tolerant controls	(Rodríguez-Nóvoa et al., 2007)
	Caucasian	7.9	ABC-HSS	13	51 tolerant controls	(Hughes et al., 2004)
	Self-identified white	1945	ABC-HSS	42	202 tolerant controls	(Saag et al., 2008)
	Black	8.4	ABC-HSS	21	67 tolerant controls	CTR Summary for MDC - GSK Clinical Study Register (2007)
	Self-identified black	900	ABC-HSS	5	206 tolerant controls	(Saag et al., 2008)
	Thai	263.6	ABC-HSS	7	102 tolerant controls	CTR Summary for MDC - GSK Clinical Study Register (2007)
	Multiethnic group	23.6	ABC-HSS	84	113 tolerant controls	(Hetherington et al., 2002)
		6.9	ABC-HSS	9	41 tolerant controls	(Stekler et al., 2006)
Nevirapine						
*HLA-B*1402*	Sardinian	14.6	DRESS	13	36 tolerant controls	(Littera et al., 2006)
*HLA-B*35*	Asian	3.5	SCAR	71	227 tolerant controls	(Yuan et al., 2011)
	Thai	5.7	SCAR	52	173 tolerant controls	(Yuan et al., 2011)
*HLA-B*3505*	Thai	19	CAR	143	181 tolerant controls	(Chantarangsu et al., 2009)
*HLA-B*5801*	South African	3.15	DILI	53	106 tolerant controls	(Phillips et al., 2013)
*HLA-C*0401*	Sub-Saharan African	4.8	SJS/TEN	267	250 tolerant controls	(Carr et al., 2017)
	Malawian	17.5	SJS/TEN	36	155 tolerant controls	(Carr et al., 2013)
*HLA-DRB1*0101*	Australian	17.7	DRESS	14	221 tolerant controls	(Martin et al., 2005)
*HLA-DRB1*0102*	South African	4.3	DILI	54	103 tolerant controls	(Phillips et al., 2013)
*HLA-DRB1*01*	French	70	CAR	6	15 tolerant controls	(Vitezica et al., 2008)
	White	3	DILI	57	277 tolerant controls	(Yuan et al., 2011)
*HLA-Cw*04*	Thai	3.2	CAR	78	120 tolerant controls	(Likanonsakul et al., 2009)
		2.4	SCAR	52	179 tolerant controls	(Yuan et al., 2011)
	Asian	2.6	SCAR	71	233 tolerant controls	(Yuan et al., 2011)
	Black	5.2	SCAR	27	77 tolerant controls	(Yuan et al., 2011)
	White	1.9	SCAR	77	277 tolerant controls	(Yuan et al., 2011)
*HLA-Cw*08*	Japanese	6.2	DRESS	12	29 tolerant controls	(Gatanaga et al., 2007)
Sulfamethoxazole						
HLA-A30	Turkey	3.9	Fixed drug eruption	67	2378 general population	(Ozkaya-Bayazit & Akar, 2001)
*HLA-B*1502*	Thai	3.9	SJS/TEN	43	91 tolerant controls	(Kongpan et al., 2015)
*HLA-B*3801*	European	4.3	SJS/TEN	25	1822 general population	(Lonjou et al., 2008)
*HLA-B*3802*	European	76	SJS/TEN	25	1822 general population	(Lonjou et al., 2008)
*HLA-C*0602*	Thai	11.8	SJS/TEN	43	91 tolerant controls	(Kongpan et al., 2015)
*HLA-C*0801*	Thai	3.4	SJS/TEN	43	91 tolerant controls	(Kongpan et al., 2015)
Dapsone						
*HLA-B*1301*	Thai	60.8	DRESS	11	29 tolerant controls	(Tempark et al., 2017)
		40.5	SJS/TEN	4	29 tolerant controls	(Tempark et al., 2017)
	Chinese	122.1	DRESS	20	102 tolerant controls	(Wang et al., 2013)
		49.6	DRESS	7	677 general population	(Chen et al., 2018)
		20.5	DRESS	76	1034 general population	(Zhang et al., 2013)
*HLA-B*1502*	Thai	28	SJS/TEN	4	29 tolerant controls	(Tempark et al., 2017)
Amoxicillin-clavulanate						
*HLA-DRB1*07*	British	0.18	DILI	61	40 tolerant controls	(Donaldson et al., 2010)
*HLA-DRB1*1501*	Scottish	9.3	DILI	20	134 tolerant controls	(O'Donohue et al., 2000)
	Belgian	7.6	DILI	35	60 general population	(Hautekeete et al., 1999)
*HLA-DQB1*0602*	Belgian	12	DILI	35	60 general population	(Hautekeete et al., 1999)
	European	4.2	DILI	177	219 general population	(Lucena et al., 2011)
Flucloxacillin						
*HLA-B*5701*	European	80.6	DILI	51	64 tolerant controls	(Daly et al., 2009)
Minocycline						
*HLA-B*3502*	Caucasian	29.6	DILI	25	6835 general population	(Urban et al., 2017)
Erythromycin						
*HLA-A*3301*	European	10.2	DILI	10	10,588 general population	(Nicoletti et al., 2017)
Terbinafine						
*HLA-A*3301*	European	40.5	DILI	14	10,588 general population	(Nicoletti et al., 2017)

Table 3
Overview of genetic variations in the major histocompatibility complex associated with hypersensitivity to antiepileptics. SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, MPE = maculopapular exanthema, DRESS = drug rash with eosinophilia and systemic symptoms, SCAR = severe cutaneous adverse reaction, DIHS = drug-induced hypersensitivity syndrome.

Allele	Ethnicity	Odds ratio	Adverse reaction	Cases	Controls	Study
Carbamazepine						
Carbamazepine and *HLA-B*1502*						
*HLA-B*1502*	Thai	75.4	SJS/TEN	34	40 tolerant controls	(Kulkantrakorn et al., 2012)
		54.8	SJS/TEN	42	42 tolerant controls	(Tassaneeyakul et al., 2010)
		25.5	SJS/TEN	6	50 tolerant controls	(Locharernkul et al., 2008)
		7.27	MPE	17	271 tolerant controls	(Sukasem et al., 2018)
	Chinese	2504	SJS/TEN	44	101 tolerant controls	(Chung et al., 2004)
		1357	SJS/TEN	60	144 tolerant controls	(Hung et al., 2006)
		184	SJS/TEN	8	50 tolerant controls	(Wu et al., 2010)
		152	SJS/TEN	17	21 tolerant controls	(Zhang et al., 2011)
		114.8	SJS/TEN	9	80 tolerant controls	(Wang et al., 2011)
		97.6	SJS/TEN	112	152 tolerant controls	(Hsiao et al., 2014)
		89.3	SJS/TEN	26	135 tolerant controls	(Cheung et al., 2013)
		58.1	SJS/TEN	53	72 tolerant controls	(Genin et al., 2014)
		12.4	SJS/TEN	56	179 tolerant controls	(Shi et al., 2017)
	Hongkong Chinese	89.3	SJS/TEN	26	135 tolerant controls	(Kwan Ng, & Lo, 2014)
	Korean	40.3	SJS/TEN	7	485 general population	(Kim et al., 2011)
	Malaysian	16.2	SJS/TEN	16	300 tolerant controls	(Chang Too, Murad, & Hussein, 2011)
	Vietnamese	33.8	SJS/TEN	35	25 tolerant controls	(Nguyen et al., 2015)
	Indian	71.4	SJS/TEN	8	10 general population	(Mehta et al., 2009)
	Multiethnic group	168	SJS/TEN	6	7 tolerant controls	(Then Rani, Raymond, Ratnaningrum, & Jamal 2011)
Carbamazepine and *HLA-A*3101*						
*HLA-A*3101*	European	57.6	DRESS	10	257 tolerant controls	(Genin et al., 2014)
		25.9	SJS/TEN	12	257 general population	(McCormack et al., 2011)
		12.4	DRESS	27	257 general population	(McCormack et al., 2011)
		8.3	MPE	106	257 general population	(McCormack et al., 2011)
	Chinese	23	DRESS	10	72 tolerant controls	(Genin et al., 2014)
		17.5	MPE	18	144 tolerant controls	(Hung et al., 2006)
		6.4	DIHS	13	144 tolerant controls	(Hung et al., 2006)
	Japanese	33.9	SJS/TEN	6	420 tolerant controls	(Ozeki et al., 2011)
		9.5	SCAR	77	420 tolerant controls	(Ozeki et al., 2011)
	Korean	12.4	HSS	17	485 general population	(Kim et al., 2011)
		10.3	SCAR	24	485 general population	(Kim et al., 2011)
		6.5	SJS	7	485 general population	(Kim et al., 2011)
Carbamazepine and other class I HLAs						
*HLA-A*0201*	Chinese	3.6	MPE	40	52 tolerant controls	(Li et al., 2013)
*HLA-A*2402*	Chinese	2.3	SJS/TEN	56	178 tolerant controls	(Shi et al., 2017)
HLA-A31	Japanese	11.2	SJS/TEN or DIHS	15	33 tolerant controls	(Niihara et al., 2012)
*HLA-B*1511*	Chinese	30.8	SJS/TEN	56	179 tolerant controls	(Shi et al., 2017)
	Japanese	9.8	SJS/TEN	11	493 general population	(Kaniwa et al., 2010)
	Korean	18.4	SJS	7	485 general population	(Kim et al., 2011)
*HLA-B*1521*	Thai	9.5	SJS/TEN	16	271 tolerant controls	(Sukasem et al., 2018)
*HLA-B*4001*	Chinese	0.16	DRESS	23	152 tolerant controls	(Hsiao et al., 2014)
		0.22	SJS/TEN	112	152 tolerant controls	(Hsiao et al., 2014)
*HLA-B*4801*	Chinese	14.4	DRESS	23	152 tolerant controls	(Hsiao et al., 2014)
*HLA-B*5101*	Chinese	4.9	MPE	51	152 tolerant controls	(Hsiao et al., 2014)
		3.9	DRESS	23	152 tolerant controls	(Hsiao et al., 2014)
*HLA-B*5801*	Thai	7.6	DRESS	5	271 tolerant controls	(Sukasem et al., 2018)
	Chinese	0.24	MPE	40	52 tolerant controls	(Li et al., 2013)
*HLA-C*0801*	Chinese	11.8	SJS/TEN	55	177 tolerant controls	(Shi et al., 2017)
Carbamazepine and other class II HLAs						
*HLA-DRB1*0101*	Chinese	14	SJS/TEN	54	176 tolerant controls	(Shi et al., 2017)
*HLA-DRB1*0301*	Chinese	0.22	MPE	40	52 tolerant controls	(Li et al., 2013)
*HLA-DRB1*1202*	Chinese	11.4	SJS/TEN	60	144 tolerant controls	(Hung et al., 2006)
		3.4	SJS/TEN	54	176 tolerant controls	(Shi et al., 2017)
*HLA-DRB1*1405*	Chinese	22.1	MPE	40	52 tolerant controls	(Li et al., 2013)
*HLA-Cw*0801*	Chinese	86.8	SJS/TEN	60	144 tolerant controls	(Hung et al., 2006)
Phenytoin						
*HLA-B*1502*	Thai	18.5	SJS	4	50 tolerant controls	(Locharernkul et al., 2008)
	Malaysian	5.7	SJS/TEN	13	32 tolerant controls	(Chang et al., 2017)
	Multiethnic group	5	SJS/TEN	48	130 tolerant controls	(Chung et al., 2014)
*HLA-B*5101*	Thai	4.8	SJS/TEN	39	92 tolerant controls	(Tassaneeyakul et al., 2016)
		5.2	DRESS	21	92 tolerant controls	(Tassaneeyakul et al., 2016)
*HLA-A*0201*	Thai	3.9	SCAR	60	92 tolerant controls	(Tassaneeyakul et al., 2016)
	Chinese	11.7	SJS/TEN	13	40 tolerant controls	(Shi et al., 2017)
*HLA-A*2402*	Chinese	6	SJS/TEN	13	40 tolerant controls	(Shi et al., 2017)
*HLA-A*3303*	Thai	2.7	SJS/TEN	39	92 tolerant controls	(Tassaneeyakul et al., 2016)
*HLA-B*1513*	Malaysian	59	DRESS	3	32 tolerant controls	(Chang et al., 2017)
		11.3	SJS/TEN	13	32 tolerant controls	(Chang et al., 2017)

Table 3 (*continued*)

Allele	Ethnicity	Odds ratio	Adverse reaction	Cases	Controls	Study
Carbamazepine						
*HLA-B*3802*	Thai	3.2	SCAR	60	92 tolerant controls	(Tassaneeyakul et al., 2016)
*HLA-B*5602*	Thai	8.3	SCAR	60	92 tolerant controls	(Tassaneeyakul et al., 2016)
*HLA-B*5801*	Thai	3.2	SJS/TEN	39	92 tolerant controls	(Tassaneeyakul et al., 2016)
*HLA-C*1402*	Thai	5.9	SCAR	60	92 tolerant controls	(Tassaneeyakul et al., 2016)
Oxcarbazepine						
*HLA-B*1502*	Thai	49	SJS	3	99 general population	(Chen et al., 2017)
	Chinese	27.9	SJS	17	101 tolerant controls	(Chen et al., 2017)
		6.4	MPE	9	9 tolerant controls	(Hu et al., 2011)
*HLA-B*1501*	Korean	0.18	MPE	40	70 tolerant controls	(Moon et al., 2016)
*HLA-B*3802*	Chinese	3.2	MPE	28	56 tolerant controls	(Lv et al., 2013)
*HLA-B*4002*	Korean	4.3	MPE	40	70 tolerant controls	(Moon et al., 2016)
*HLA-DRB1*0403*	Korean	14.6	MPE	40	70 tolerant controls	(Moon et al., 2016)
Lamotrigine						
*HLA-A*0207*	Thai	7.8	SCAR	15	50 tolerant controls	(Koomdee et al., 2017)
*HLA-A*2402*	Spanish	49	DRESS	3	10 tolerant controls	(Ramírez et al., 2017)
	Chinese	4.5	SJS/TEN	22	102 tolerant controls	(Shi et al., 2017)
	Korean	4.1	MPE	21	29 tolerant controls	(Moon et al., 2015)
*HLA-A*3001*	Chinese	14.3	MPE	43	44 tolerant controls	(Li et al., 2013)
*HLA-A*3101*	Korean	11.4	SCAR	18	29 tolerant controls	(Kim et al., 2017)
*HLA-B*1502*	Thai	4.9	SCAR	15	50 tolerant controls	(Koomdee et al., 2017)
	Chinese	3.3	SJS/TEN	6	30 tolerant controls	(Cheung et al., 2013)
		4.2	SJS/TEN	9	123 tolerant controls	(Shi et al., 2011)
*HLA-B*1302*	Chinese	14.3	MPE	43	44 tolerant controls	(Li et al., 2013)

prevalence of hypersensitivity and high positive predictive value of the test (Phillips & Mallal, 2010). Furthermore, test rollout depends on monetary considerations and various health economic studies have addressed whether pharmacogenetic testing constitutes a cost-effective use of healthcare resources. Testing of *HLA-B*5701* prior to initiation of abacavir is suggested to be cost-effective in the UK (Hughes et al., 2004) and Germany (Wolf et al., 2010). Similarly, genotyping of *HLA-A*3101* and *HLA-B*1502* before starting carbamazepine therapy is likely cost-effective in the UK (Plumpton et al., 2015; Yip et al., 2012), whereas its cost-effectiveness is dependent on patient ethnicity in Singapore due to differences in population allele frequencies (Dong, Sung, & Finkelstein, 2012). Furthermore, a recent study suggested the cost-effectiveness of restricting long-term hematologic monitoring of patients with treatment-resistant schizophrenia on clozapine to carriers of the HLA-DQB1 (126Q) and HLA-B (158 T) variants (Girardin et al., 2018). In contrast, preemptive testing of *HLA-B*5801* and *HLA-B*5701* prior to initiation of allopurinol and flucloxacillin therapy, respectively, has not been found to be cost-effective (Phillips & Mallal, 2013; Plumpton, Alfirevic, Pirmohamed, & Hughes, 2017).

Based on the considerations and data highlighted above, recommendations for pharmacogenetic testing of the respective *HLA* risk alleles have been incorporated into current guidelines for abacavir (Aberg et al., 2009; Gazzard et al., 2008; Martin et al., 2014) and carbamazepine therapy (Phillips et al., 2018), whereas other associations have not yet been implemented into clinical practice (Fig. 2).

3.2. Anthracycline-induced cardiotoxicity

Anthracyclines are commonly used in chemotherapy regimens for the treatment of a variety of solid tumors and hematological malignancies in both pediatric and adult patients. However, depending on gender, age, cumulative dose and measured endpoints, 9–27% of patients experience cardiotoxicity that manifests in structural changes and left ventricular dysfunction after 1 year of follow-up (Cardinale et al., 2015; Hequet et al., 2004; Thavendiranathan et al., 2013) and up to 5% suffer from congestive heart failure (Swain, Whaley, & Ewer, 2003). Mechanisms underlying anthracycline-induced cardiotoxicity are complex and include oxidative and nitrosative stress, perturbation of myocardial calcium signaling and energy metabolism, as well as DNA damage (Mordente et al., 2009). Identification of biomarkers that can identify patients prone to anthracycline-induced cardiotoxicity therefore represents an important strategy to maximize the clinical utility of anthracyclines and to personalize the choice of chemotherapy-regimen. Recent research implicated variations in >20 genes in anthracyclin-induced cardiotoxicity (Table 5).

Carbonyl reductases metabolize anthracyclines to their alcohol metabolites and seminal studies demonstrated that these metabolites are potent inhibitors (up to 80-times more potent then the parent molecule) of sarcoplasmatic calcium handling and mitochondrial F-type proton ATPases that accumulate specifically in the heart after long-term anthracycine treatment (Boucek et al., 1987; Olson et al., 1988). The V244M variant of CBR3 exhibits 2.6-fold reduced metabolism per unit of time and multiple studies have associated the corresponding polymorphism rs1056892 with cardioprotective effects in pediatric (Blanco et al., 2008; Blanco et al., 2012; Volkan-Salanci et al., 2012) and adult patients (Hertz et al., 2016), whereas other studies did not reproduce this association (Aminkeng et al., 2015; Armenian et al., 2013; Lubieniecka et al., 2012; Visscher et al., 2012).

Multiple genes involved in redox signaling and detoxification of reactive oxygen species have been implicated in anthracycline-induced cardiotoxicity risk in multiple cohorts. These include the *CYBA*, *RAC2* and *NCF4* subunits of the NADPH oxidase complex, catalase (*CAT*) as well as the glutathione-S-transferase (GST) *GSTP1* (Table 5). Strikingly, NADPH oxidase deficient mice were fully protected from anthracycline-induced cardiotoxicity, further strengthening the link between ROS and myocardial dysfunction (Wojnowski et al., 2005). However, preconditioning of patients with antioxidants, such as coenzyme Q10 or *N*-acetylcysteine did not result in patient benefits (Iarussi et al., 1994; Myers et al., 1983), and treatment with the iron chelator dexrazoxane remains the only cardioprotective treatment with regulatory approval. Thus, while pharmacogenetic associations between genes involved in redox signaling and anthracycline-induced cardiotoxicity have been consistently reported, their low odds ratios (OR < 6) preclude their application for the guidance of therapy.

In addition to genes involved in anthracycline metabolism and redox signaling, pharmacogenetic studies implicated multiple transporter

Table 4
Overview of genetic variations in the major histocompatibility complex associated with hypersensitivity to other medications. SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, DRESS = drug rash with eosinophilia and systemic symptoms, SCAR = severe cutaneous adverse reaction, DILI = drug-induced liver injury, SLE = systemic lupus erythematosus.

Allele	Ethnicity	Odds ratio	Adverse reaction	Cases	Controls	Study
Allopurinol						
*HLA-B*5801*	European	80	SJS/TEN	27	1822 general population	(Lonjou et al., 2008)
	Portuguese	39.1	SCAR	25	23 tolerant controls	(Gonçalo et al., 2013)
	Thai	348.3	SJS/TEN	27	54 tolerant controls	(Tassaneeyakul et al., 2009)
	Chinese	580.3	SCAR	51	135 tolerant controls	(S.-I. Hung et al., 2005)
	Japanese	65.6	SJS/TEN or erythema exudativum multiforme	7	25 tolerant controls	(Niihara et al., 2013)
		40.8	SJS/TEN	20	986 general population	(Kaniwa et al., 2008)
	Korean	97.8	SCAR	26	57 tolerant controls	(Kang et al., 2011)
HLA-B58	Korean	179.2	SCAR	9	432 tolerant controls	(Jung et al., 2011)
*HLA-A*0201*	Korean	0.04	SCAR	26	57 tolerant controls	(Kang et al., 2011)
*HLA-A*3303*	Korean	20.5	SCAR	26	57 tolerant controls	(Kang et al., 2011)
HLA-A33	Korean	8.3	SCAR	9	432 tolerant controls	(Jung et al., 2011)
HLA-DR3	Korean	11.4	SCAR	9	432 tolerant controls	(Jung et al., 2011)
HLA-DR13	Korean	5.5	SCAR	9	432 tolerant controls	(Jung et al., 2011)
HLA-Cw3	Korean	19.4	SCAR	9	432 tolerant controls	(Jung et al., 2011)
*HLA-Cw*0302*	Korean	82.1	SCAR	26	57 tolerant controls	(Kang et al., 2011)
Lumiracoxib						
*HLA-DRB1*1501*	Multiethnic	7.5	DILI	137	577 tolerant controls	(Singer et al., 2010)
*HLA-DRB5*0101*	Multiethnic	7.2	DILI	137	577 tolerant controls	(Singer et al., 2010)
*HLA-DQA1*0102*	Multiethnic	6.3	DILI	137	577 tolerant controls	(Singer et al., 2010)
*HLA-DQB1*0602*	Multiethnic	6.9	DILI	137	577 tolerant controls	(Singer et al., 2010)
Aspirin						
*HLA-DRB1*0301*	Korean	9.7	Asthma	76	73 tolerant controls	(Choi et al., 2004)
*HLA-DRB1*0901*	Korean	2.3	Asthma	76	73 tolerant controls	(Choi et al., 2004)
*HLA-DRB1*1302*	Korean	4	Urticaria	188	152 tolerant controls	(Kim, Choi, Lee, et al., 2005)
*HLA-DQB1*0609*	Korean	5.6	Urticaria	188	152 tolerant controls	(Kim, Choi, Lee, et al., 2005)
*HLA-DPB1*0301*	Swiss	5.3	Asthma	59	57 tolerant controls	(Dekker et al., 1997)
	Korean	5.2	Asthma	76	73 tolerant controls	(Choi et al., 2004)
Feprazone						
HLA-B22	Italian	48	Fixed drug eruption	40	215 general population	(Pellicano et al., 1997)
HLA-Cw1	Italian	13.9	Fixed drug eruption	40	215 general population	(Pellicano et al., 1997)
Oxicam NSAIDs						
*HLA-B*7301*	European	152	SJS/TEN	14	1822 general population	(Lonjou et al., 2008)
Clozapine						
HLA-B38	Ashkenazi Jew	50	Agranulocytosis	15	32 general population	(Yunis et al., 1995)
HLA-B (158 T)	European	3.1	Agranulocytosis	161	4300 general population	(Goldstein et al., 2014)
HLA-DR4	Ashkenazi Jew	23.3	Agranulocytosis	15	32 general population	(Yunis et al., 1995)
*HLA-DRB1*0402*	Ashkenazi Jew	6.8	Agranulocytosis	24	54 general population	(Yunis et al., 1995)
*HLA-DRB1*11*	Ashkenazi Jew	0.06	Agranulocytosis	24	54 general population	(Yunis et al., 1995)
*HLA-DQA1*0301*	Ashkenazi Jew	3.1	Agranulocytosis	24	54 general population	(Yunis et al., 1995)
*HLA-DQB1*0302*	Ashkenazi Jew	4.9	Agranulocytosis	24	54 general population	(Yunis et al., 1995)
HLA-DQB1 (126Q)	European	0.19	Agranulocytosis	161	4300 general population	(Goldstein et al., 2014)
Sertraline						
*HLA-A*3301*	European	29	DILI	5	10,588 general population	(Nicoletti et al., 2017)
Hydralazine						
HLA-DR4	British	5.6	SLE	26	113 general population	(Batchelor et al., 1980)
Enalapril						
*HLA-A*3301*	European	34.8	DILI	4	10,588 general population	(Nicoletti et al., 2017)
Methazolamide						
*HLA-B*5901*	Chinese	305	SJS/TEN	8	30 tolerant controls	(Yang et al., 2015)
	Korean	249.8	SJS/TEN	5	485 general population	(Kim et al., 2010)
Ticlopidine						
*HLA-A*3301*	European	163.1	DILI	5	10,588 general population	(Nicoletti et al., 2017)
*HLA-A*3303*	Japanese	13	DILI	22	85 tolerant controls	(Hirata et al., 2008)
Thionamides						
*HLA-B*3802*	Chinese	12.3	Agranulocytosis	42	1202 general population	(Chen et al., 2015)
*HLA-B*3803*	Chinese	4.4	Agranulocytosis	42	1196 general population	(Chen et al., 2015)
Lapatinib						
*HLA-DQA1*0201*	European	9	DILI	24	155 tolerant controls	(Spraggs et al., 2011)
Flupirtine						
*HLA-DRB1*1601*	German	18.7	DILI	6	39,689 general population	(Nicoletti et al., 2016)
Methyldopa						

Table 4 (*continued*)

Allele	Ethnicity	Odds ratio	Adverse reaction	Cases	Controls	Study
*HLA-A*3301*	European	97.8	DILI	4	10,588 general population	(Nicoletti et al., 2017)
Fenofibrate *HLA-A*3301*	European	58.7	DILI	7	10,588 general population	(Nicoletti et al., 2017)

genes in cardiac dysfunction due to anthracylines, but only associations with *ABCC1* (Semsei et al., 2012; Vulsteke et al., 2015), *ABCC2* (Aminkeng et al., 2015; Armenian et al., 2013; Wojnowski et al., 2005) and *SLC28A3* (Visscher et al., 2012; Visscher et al., 2013) have been replicated. *ABCC1* (MRP1) and ABCC2 (MRP2) have been shown to transport anthracyclines (Cole et al., 1994; Folmer, Schneider, Blum, & Hafkemeyer, 2007). Most supportive data are available for rs8187710 in *ABCC2* that encodes a C1515Y amino acid exchange in MRP2 and results in reduced uptake of MRP2 substrates (Elens et al., 2011), whereas rs3743527 resides in the untranslated region of *ABCC1* and no direct effects of this variant on MRP1 have been reported. *SLC28A3* has to our knowledge not been demonstrated to be an anthracycline uptake transporter and thus the pharmacogenetic association lacks mechanistic support.

Retinoic acid (RA) signaling mediated at least in part by its nuclear receptor RARG is essential for cardiac development, coronary vasculogenesis and cardiomyocyte proliferation (Merki et al., 2005; Romeih et al., 2003; Xavier-Neto et al., 2015). Furthermore, levels of Raldh2, the central enzyme in RA biosynthesis, increased in the epicardium and the RA precursor retinol accumulates at the ischemic site in mouse models for myocardial infarction, resulting in significant activation expression of RA target genes (Bilbija et al., 2012; Kikuchi et al., 2011; Zhou et al., 2011). Combined this data suggest that RA signaling might contribute to tissue repair in post ischemic hearts. Importantly, the missense variant rs2229774 encoding an S427L amino acid exchange in RARG is strongly associated with anthracycline-induced cardiotoxicity in cohorts of European, African, Aboriginal Canadian, Hispanic and East Asian ancestry with odds ratios (OR) between 4.1 and 7 (Aminkeng et al., 2015). RARG binds to the *TOP2B* promoter (Delacroix et al., 2010) and represses its transcription in cardiomyocytes in vitro (Aminkeng et al., 2015). TOP2B is necessary for intercalation of anthracyclines into DNA (Tewey, Rowe, Yang, Halligan, & Liu, 1984) and cardiomyocyte-specific ablation of Top2b protects mice from anthracycline-induced cardiotoxicity (Zhang et al., 2012). Importantly, the repressive effect of RARG on *TOP2B* expression is diminished when the S427L RARG variant was transfected (Aminkeng et al., 2015), thereby providing a mechanistic link between the identified polymorphism, TOP2B expression and anthracycline-induced cardiotoxicity.

Fueled by these insights and the tremendous clinical relevance of anthracycline-induced cardiotoxicity, a variety of mechanistically diverse cardioprotective adjuvant therapies have been proposed. Of these dexrazoxane (relative risk [RR] = 0.35, $p < .00001$), inhibition of adrenergic beta receptors (RR = 0.31, $p = .001$), or HMG-CoA reductase (RR = 0.31, $p = .01$) and angiotensin antagonists (RR = 0.11, $p < .0001$) are most extensively studied and were found to significantly prevent cardiotoxicity in a large meta-analysis (Kalam & Marwick, 2013). Furthermore, the substantial available evidence has resulted in the development of clinical practice guidelines that recommend prospective genotyping of pediatric patients with an indication for anthracycline therapy and adjustment of frequency and aggressiveness of monitoring by genotype as well as off-label prescription of the cardioprotective agent dexrazoxane to high-risk patients (Aminkeng et al., 2016).

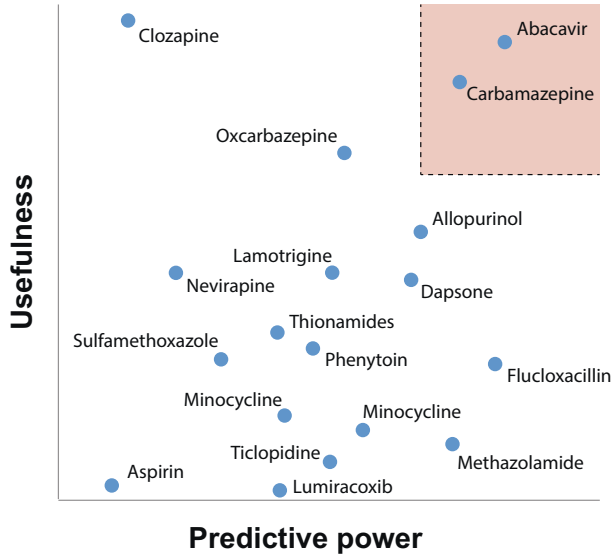

Fig. 2. Overview of the utility of HLA biomarkers for the prediction of hypersensitivity reactions to different medicines. The abscissa (predictive power) refers to the strength of association between a HLA variant alleles and adverse drug reactions. We refer to Tables 2-4 for details about the specific variant alleles of importance for the listed medications. The ordinate estimates the usefulness of a test that considers various practical aspects, including cost-effectiveness, availability of alternative treatments and severity of the adverse event. The box shaded in light red highlights the space that supports clinical implementation of the companion diagnostic.

3.3. Corticosteroid-induced osteonecrosis

The use of glucocorticoids prednisone and dexamethasone in the treatment of acute lymphoblastic leukemia (ALL) constitutes an essential component of ALL chemotherapy regimens and has contributed to significantly increased cure rates (Inaba & Pui, 2010). However, corticosteroid therapy can cause debilitating adverse reactions, including osteonecrosis, which occurs in 6% to 9% of pediatric and up to 20% of adolescent ALL patients and can result in life-long arthritis and pain in cancer survivors (Mattano, Sather, Trigg, & Nachman, 2000; te Winkel et al., 2011). Mechanisms underlying osteonecrosis due to glucocorticoids are believed to be thrombophilia, hyperlipidemia, intraosseous accumulation of lipids and fat embolism, that together result in reduced intramedullary blood flow, bone marrow ischemia and osteonecrosis (Shah, Racine, Jones, & Aaron, 2015). Furthermore, glucocorticoids might directly induce apoptosis of osteoblasts (Yun, Yoon, Jeong, & Chung, 2008).

Pharmacogenomic studies spearheaded primarily by the St. Jude Children's Research Hospital have implicated a variety of genetic factors in corticosteroid-induced osteonecrosis (Table 6). While these candidate studies raised hopes to find genetic biomarkers that could efficiently stratify patients by osteonecrosis risk, results from two agnostic genome-wide association studies (GWAS) were chastening and none of the associations could be replicated. Instead, the first GWAS revealed variants in the *ACP1-SH3YL1* locus to be associated with osteonecrosis ($p = 1.2^{*}10^{-6}$, OR = 5.8), whereas associations with *TYMS*, *VDR* and *SERPINE1* were again not replicated (Kawedia et al., 2011). While not reaching genome-wide significance (threshold

Table 5
Overview of genetic factors associated with anthracycline-induced cardiotoxicity.

Process	Gene	Variant	Ethnicity	Odds ratio	Study type	Cohort	Study
Anthracycline metabolism	*CBR3*	rs1056892 (V244M)	Multiethnic cohort	8.2	Candidate gene study	30 cases and 115 tolerant controls	(Blanco et al., 2008)
			Multiethnic cohort	3.3	Candidate gene study	170 cases and 317 tolerant controls	(Blanco et al., 2012)
Anthracycline transport	*SLC22A7*	rs4149178 (Intronic)	Canadian	0.45	Candidate gene study	122 cases and 398 tolerant controls	(Visscher et al., 2015)
	SLC22A17	rs4982753 (Regulatory)	Canadian	0.5	Candidate gene study	122 cases and 398 tolerant controls	(Visscher et al., 2015)
	SLC28A3	rs7853758 (L461 L)	Multiethnic cohort	0.35	Candidate gene study	121 cases and 319 tolerant controls	(Visscher et al., 2012)
			Multiethnic cohort	0.36	Candidate gene study	124 cases and 397 tolerant controls	(Visscher et al., 2013)
		rs885004 (Intronic)	Multiethnic cohort	0.34	Candidate gene study	124 cases and 397 tolerant controls	(Visscher et al., 2013)
	ABCC1	rs246221 (V275 V)	Belgian	1.6	Candidate gene study	153 cases and 724 tolerant controls	(Vulsteke et al., 2015)
		rs45511401 (G671 V)	German	3.6	Candidate gene study	44 cases and 363 tolerant controls	(Wojnowski et al., 2005)
	ABCC2	rs8187710 (C1515Y)	German	2.3	Candidate gene study	44 cases and 363 tolerant controls	(Wojnowski et al., 2005)
			Multiethnic cohort	4.3	Candidate gene study	77 cases and 178 tolerant controls	(Armenian et al., 2013)
	ABCG2	rs2231142 (Q141K)	Spanish	5.3	Candidate gene study	45 cases and 180 tolerant controls	(Megías-Vericat et al., 2017)
Redox signaling	*CYBA*	rs4673 (Y72H)	German	2	Candidate gene study	44 cases and 363 tolerant controls	(Wojnowski et al., 2005)
			Spanish	0.3	Candidate gene study	32 cases and 192 tolerant controls	(Megías-Vericat et al., 2018)
	RAC2	rs13058338 (Intronic)	Multiethnic cohort	2.8	Candidate gene study	77 cases and 178 tolerant controls	(Armenian et al., 2013)
			German	2.6	Candidate gene study	44 cases and 363 tolerant controls	(Wojnowski et al., 2005)
			Multiethnic cohort	2.3	Candidate gene study	56 cases and 94 tolerant controls	(Reichwagen et al., 2015)
	NCF4	rs1883112 (Regulatory)	German	2.5	Candidate gene study	44 cases and 363 tolerant controls	(Wojnowski et al., 2005)
			Spanish	5.2	Candidate gene study	32 cases and 193 tolerant controls	(Megías-Vericat et al., 2018)
	CAT	rs10836235 (Intronic)	Caucasian	0.28	Candidate gene study	43 cases and 33 tolerant controls	(Rajić et al., 2009)
Retinoic acid signaling	*RARG*	rs2229774 (S427 L)	Multiethnic cohort	4.7	GWAS	73 cases and 383 tolerant controls	(Aminkeng, et al., 2015)
Phase II metabolism	*UGT1A6*	rs17863783 (V209 V)	Multiethnic cohort	4.3	Candidate gene study	124 cases and 397 tolerant controls	(Visscher, et al., 2013)
	GSTM1	Whole gene	Italian	0.4	Candidate gene study	13 cases and 35 tolerant controls	(Vivenza et al., 2013)
	GSTP1	rs1695 (I105V)	Multiethnic cohort	9.4	Candidate gene study	16 cases and 39 tolerant controls	(Windsor et al., 2012)
Iron transport	*HFE*	rs1799945 (H63D)	Multiethnic cohort	2.5	Candidate gene study	77 cases and 178 tolerant controls	(Armenian et al., 2013)
		rs1800562 (C282Y)	Multiethnic cohort	9.2	Candidate gene study	11 cases and 168 tolerant controls	(Lipshultz et al., 2013)
CYP regulation	*POR*	rs2868177 (Intronic)	Multiethnic cohort	1.9	Candidate gene study	10 cases and 81 tolerant controls	(Lubieniecka et al., 2013)
		rs13240755 (Intronic)	Multiethnic cohort	3.2	Candidate gene study	10 cases and 81 tolerant controls	(Lubieniecka et al., 2013)
Extracellular matrix	*HAS3*	rs2232228 (A93A)	Non-Hispanic white	56.5	GWAS	93 cases and 194 tolerant controls	(Wang et al., 2014)
Splicing	*CELF4*	rs1786814 (Intronic)	Non-Hispanic white	10.2	GWAS	112 cases and 219 tolerant controls	(Wang et al., 2016)
Golgi homeostasis?	*GOLGA6L2*	rs28714259 (Intergenic)	Multiethnic cohort	4.2	GWAS	24 cases and 298 tolerant controls	(Schneider et al., 2017)

$p < 1*10^{-7}$), the implication of ACP1 as a key regulator of osteoblast differentiation (Zambuzzi et al., 2008) provides biological plausibility to the role of *ACP1* in corticosteroid-induced osteonecrosis. The second and so-far largest GWAS study into corticosteroid adverse reactions encompassing 2285 children in the discovery cohort identified two loci encoding glutamate receptor subunits (*GRIN3A* and *GRIK1*) on separate chromosomes as their top two associations and replicated these associations using a candidate approach in two independent cohorts with OR pivoting around 2 and meta-analysis *p*-values of $2.7*10^{-8}$ and $1.3*10^{-6}$ (Karol et al., 2015). Thus, while a variety of loci with biologically plausible effects have been identified, the absence of replication in independent cohorts indicates that pharmacogenetic testing of variants, which can predict the risk of developing osteonecrosis following corticosteroid therapy, can currently not result in actionable outcomes and thus do not warrant clinical implementation in the near future.

Table 6
Overview of genetic factors associated with corticosteroid-induced osteonecrosis. Variant support was defined as follows: Replication = identification of the same association in multiple (≥2) independent cohorts. Mechanistic support = Contextualization of the gene in question with corticosteroid pharmacokinetics, pharmacodynamics or bone development. Pathway = multiple significant associations in the same biological pathway. Experimental = in vitro evidence that the variant alters the functionality of the respective gene product.

Gene	Variant	Ethnicity	Odds ratio	Study type	Cohort	Study	Support			
							Replication	Mechanistic	Pathway	Experimental
VDR	rs2228570 (Altered start codon)	Multiethnic cohort	4.5	Candidate gene study	25 cases and 39 tolerant controls	(Relling et al., 2004)		x		
TYMS	Enhancer tandem repeat	Multiethnic cohort	7.4	Candidate gene study	25 cases and 39 tolerant controls	(Relling et al., 2004)		x		x
SERPINE1	rs6092 (A15T)	Multiethnic cohort	2.9	Candidate gene study	46 cases and 246 tolerant controls	(French, et al., 2008)		x		
ACP1	rs12714403 & rs10167992 (Intronic)	Multiethnic cohort	5.6	GWAS	69 cases and 263 tolerant controls	(Kawedia et al., 2011)		x		
GRIN3A	rs10989692 (Regulatory)	Multiethnic cohort	2	GWAS, 2 replication cohorts	250 cases and 2035 tolerant controls	(Karol et al., 2015)	x	x	x	
GRIK1	rs2154490 (Intronic)	Multiethnic cohort	1.3	GWAS, 2 replication cohorts	250 cases and 2035 tolerant controls	(Karol et al., 2015)	x	x	x	
BCL2L11	rs2241843 (Intronic)	Caucasian	2.4	Candidate gene study	32 cases and 272 tolerant controls	(Plesa et al., 2017)		x		x
	rs724710 (I155I)	Caucasian	5.5	Candidate gene study	14 cases and 166 tolerant controls	(Plesa et al., 2017)		x		x

3.4. L-asparaginase hypersensitivity

In addition to corticosteroids, asparaginase constitutes a cornerstone of the therapy of ALL and other hematologic malignancies since the 1970s. While normal human cells can synthesize asparagine from aspartate and glutamine, many cancers have deficiencies in asparagine biosynthesis and rely on external asparagine supply to fulfill their demands (Balasubramanian, Butterworth, & Kilberg, 2013). Asparaginase exerts its anti-leukemic effect by catalyzing the degradation of asparagine in the circulation, thereby depriving cancer cells of needed asparagine, blunting tumor growth and inducing apoptosis. While treatment is overall effective, 20–30% of patients experience hypersensitivity reactions with anaphylaxis, rash, erythema, urticaria, pruritis, pain, respiratory problems and edema that require modification or discontinuation of the treatment regimen of choice (Panosyan et al., 2004; Pieters et al., 2011).

The glutamate receptor gene *GRIA1* was identified as the top hit in a GWAS encompassing 485 children (Chen et al., 2010) and was independently replicated in two additional cohorts of 576 and 146 pediatric patients (Kutszegi et al., 2015; Rajić, Debeljak, Goričar, & Jazbec, 2015). These findings align with the association of the glutamate receptor subunits *GRIN3A* and *GRIK1* with corticosteroid-induced osteonecrosis (compare Table 7 and previous section). In addition, variations in the glutamate receptor *GRIA2* and the glutamate decarboxylase *GADL1* were also strongly implicated in the pharmacogenetics of lithium therapy in bipolar disorder (Chen et al., 2014; Perlis et al., 2009), providing evidence for an interesting broader implication of glutamate signaling in drug response phenotypes.

The adaptive immunity has been strongly implicated in asparaginase hypersensitivity and antibodies against asparaginase are detectable in >50% of patients (Liu et al., 2012). In line with these clinical observations, multiple studies point at associations of immune response-related genetic variations with adverse effects of therapy. The class II HLA allele *DRB1*0701* was found to correlate anti-asparaginase antibodies (OR = 2.9) and with incidence of hypersensitivity (OR = 1.6) in GWAS study of a cohort of 1870 pediatric ALL patients from St. Jude Children's Research Hospital (Fernandez et al., 2014). The effect of *HLA-DRB1*0701* on hypersensitivity risk was

Table 7
Overview of genetic variations associated with asparaginase hypersensitivity.

Gene	Variant	Ethnicity	Odds ratio	Study type	Cohort	Study
GRIA1	rs4958351 (Intronic)	Caucasian	1.7	Candidate gene study	72 cases and 74 tolerant controls	(Rajić et al., 2015)
		Hungarian	0.05	Candidate gene study	66 cases and 398 tolerant controls	(Kutszegi et al., 2015)
	rs4958381 (Intergenic)	Multiethnic cohort	1.8	Candidate gene study	204 cases and 281 tolerant controls	(Chen et al., 2010)
	rs4958676, rs6889909 and rs6890057 (all intronic)	Caucasian	1.6	Candidate gene study	72 cases and 74 tolerant controls	(Rajić et al., 2015)
	rs10070447 (Intronic)	Caucasian	1.7	Candidate gene study	72 cases and 74 tolerant controls	(Rajić et al., 2015)
	rs2055083 (Intronic)	Hungarian	0.2	Candidate gene study	298 cases and 192 tolerant controls	(Kutszegi et al., 2015)
	rs707176 (I187I)	Hungarian	3	Candidate gene study	292 cases and 185 tolerant controls	(Kutszegi et al., 2015)
HLA-DRB1	rs17885382 (R54Q)	Multiethnic cohort	1.6	GWAS	589 cases and 2719 tolerant controls	(Fernandez et al., 2015)
*HLA-DRB1*0701*		Multiethnic cohort	1.6	Candidate gene study	363 cases and 1844 tolerant controls	(Fernandez et al., 2014)
		Hungarian	2.9	Candidate gene study	321 cases and 38 tolerant controls	(Kutszegi et al., 2017)
ASNS	rs3757676 and rs3832526 (both intronic)	Caucasian	0.4	Candidate gene study	45 cases and 240 tolerant controls	(Ben Tanfous et al., 2015)
NFATC2	rs6021191 (Intronic)	Multiethnic cohort	3.1	GWAS	589 cases and 2719 tolerant controls	(Fernandez et al., 2015)

moreover replicated (OR = 2.9) and an additional link with *HLA-DQB1*0202* identified (OR = 3) in a Hungarian candidate study encompassing 359 pediatric ALL patients (Kutszegi et al., 2017). Additionally, the largest study published to date in which a total of 3308 patients of diverse ancestry were enrolled, validated *HLA-DRB1*0701* as a risk factor with an OR of 1.6 (Fernandez et al., 2015). Furthermore, the authors identified the intronic variant rs6021191 in *NFATC2* to be associated with asparaginase hypersensitivity at genome-wide significance with an OR of 3.1 (Fernandez et al., 2015). *NFATC2* encodes a transcriptional modulator that impacts on the transcriptional program in regulatory T-cells (Pan, Xiong, & Chen, 2013) and Nfatc2-deficient mice showed reduced cytokine levels in models of experimental chronic inflammation (Weigmann et al., 2008). Thus, the available data provide convincing evidence that genetic variations in both glutamate receptor signaling and immune response modulate asparaginase hypersensitivity risk. However, the predictive power of these associations is generally low, precluding their routine implementation as therapeutic biomarkers.

3.5. Liver injury due to interferon-β

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, hallmarked by degradation of myelin sheaths and inflammation (Reich, Lucchinetti, & Calabresi, 2018). MS onset and progression is believed to be caused by autoimmune reactions and genetic studies suggest multifactorial etiology with most risk alleles residing in genes related to immune response, such as HLA type II (Haines et al., 1996). No cure for MS is available and therapy is currently restricted to an inhibition of disease progression. Interferon-β constitutes the most widely used agent in MS therapy. However, 30–60% of interferon-β treated patients show increased liver enzyme levels and 1.4% experienced de novo liver injury with aminotransferases elevations >20 the upper limit of normal (Francis et al., 2003; Tremlett, Yoshida, & Oger, 2004).

Importantly, a recent 2-stage GWAS of MS patients of European ancestry identified variant rs2205986, an expression quantitative trait locus (eQTL) for the interferon regulatory factor *IRF6*, as a genetic risk factor for interferon-β-induced DILI (Kowalec et al., 2018). The *IRF* gene family encodes transcription factors involved in the regulation of immune responses (Tamura, Yanai, Savitsky, & Taniguchi, 2008) and some evidence had been presented that implicates *IRF6* in interferon-β response (Baranzini et al., 2015). The association was robustly detected irrespective of the adjustment for covariates with an OR of 8.3. Furthermore, the authors demonstrate that inclusion of this variant significantly improved the prediction of DILI compared to clinical factors alone. Strength and significance of the presented association suggest that rs2205986 might constitute a promising predictive biomarker for patient stratification in interferon-β therapy. However, further replication studies are needed before clinical implementation can be advocated.

3.6. Vincristine neurotoxicity

The natural vinca alkaloid vincristine is an antineoplastic agent used in multiple chemotherapy regimens for hematologic malignancies and solid tumors. Vinca alkaloids irreversibly bind to microtubule ends and prevent microtubule polymerization (Dumontet & Jordan, 2010). As a result formation of the mitotic spindle is inhibited, which blocks the activation of the anaphase promoting complex, thus causing arrest of dividing cells in metaphase. Furthermore, vinca alkaloids can cause apoptosis independent of cell cycle arrest by activation of NF-κB (Huang et al., 2004). The clinical utility of vincristine is limited by often-irreversible peripheral sensorimotor neuropathies that vary in incidence from 20% in adult patients with myeloma (Johnson et al., 2011) to 70–80% of pediatric ALL patients (Lavoie Smith et al., 2015; Tay et al., 2017).

Multiple cohort studies indicated that the neurotoxic effects of vincristine are dose-related (Desai, van den Berg, Bridges, & Shanks, 1982; Verstappen et al., 2005), prompting a focused search for pharmacogenomic biomarkers in genes related to vincristine pharmacokinetics (Table 8). Vincristine is metabolized by CYP3A isoenzymes and, notably, the intrinsic clearance of CYP3A5 is 10-fold higher than that for CYP3A4 (Dennison, Jones, Renbarger, & Hall, 2007). In individuals of European ancestry, around 90% of individuals are homozygous for the splicing defect *CYP3A5*3* and do not express functional CYP3A5 compared to approximately 30% of non-expressers in African populations (Zhou, Ingelman-Sundberg, & Lauschke, 2017). Indeed, presence of the *CYP3A5*3* allele was found to impact vincristine clearance and reduced CYP3A5 expression was associated with reduced vincristine-induced neuropathy risk in two multiethnic cohorts of 533 and 107 pediatric ALL patients (Aplenc et al., 2003; Egbelakin et al., 2011). In addition, variants in the vincristine transporter *ABCB1* (MDR1) associated with incidence of neurotoxicity (Ceppi et al., 2014). However, other smaller studies did not replicate these associations (Guilhaumou et al., 2011; Hartman et al., 2010; Moore et al., 2011; Plasschaert et al., 2004).

Besides pharmacokinetic associations, multiple studies implicated cytoskeletal proteins in vincristine neurotoxicity (Table 8). Ceppi et al. found variations in the actin network related genes *ACTG1* and *CAPG* (Ceppi et al., 2014); however the mechanism behind these associations remained elusive. In addition, a recent study in 321 children implicated an eQTL variant (rs924607) in the promoter of the gene encoding the centrosomal protein *CEP72* in vincristine-related toxicity (Diouf et al., 2015). The risk variant creates a binding site for the transcriptional repressor NKX6-3 and results in decreased *CEP72* expression.

Table 8
Overview of genetic variations associated with vincristine-induced neuropathies.

Biological process	Gene	Variant	Ethnicity	Odds ratio	Study type	Cohort	Study
Vincristine metabolism	*CYP3A5*	rs776746 (*CYP3A5*3*; Splicing defect)	Multiethnic cohort	0.05	Candidate gene study	105 cases and 2 tolerant controls	(Egbelakin et al., 2011)
			Multiethnic cohort	0.13	Candidate gene study	27 cases and 506 tolerant controls	(Aplenc et al., 2003)
Vincristine transport	*ABCB1*	rs4728709 (Intronic)	Caucasian	0.3	Candidate gene study	63 cases and 214 tolerant controls	(Ceppi et al., 2014)
Cytoskeleton	*CEP72*	rs924607 (Intronic)	Multiethnic cohort	2.4	GWAS	64 cases and 158 tolerant controls	(Diouf et al., 2015)
	ACTG1	rs1135989 (A310A)	Caucasian	2.8	Candidate gene study	38 cases and 214 tolerant controls	(Ceppi et al., 2014)
	CAPG	rs2229668 (V41I)	Caucasian	2.1	Candidate gene study	39 cases and 214 tolerant controls	(Ceppi et al., 2014)
		rs3770102 (Intronic)	Caucasian	0.1	Candidate gene study	39 cases and 214 tolerant controls	(Ceppi et al., 2014)

Furthermore, knock-down of *CEP72* increases vincristine toxicity in human stem cell-derived neurons and primary leukemia cells from homozygous rs924607 carriers showed increased vincristine sensitivity (Diouf et al., 2015), providing strong support for the hypothesis that reduced CEP72 levels sensitize patients to vincristine-related neuropathies.

3.7. CYP2C19 genotype and efficacy of antidepressant and antithrombotic treatment

One of the most polymorphic drug metabolizing enzymes is CYP2C19, which is principally involved in the metabolism of antithrombotic drugs, antidepressants and antipsychotics. The most prevalent *CYP2C19* variant alleles are the loss-of-function variant *CYP2C19*2* (minor allele frequencies [MAF] between 10 and 35% across populations) and the regulatory variant *CYP2C19*17* (MAF 1.5 to 25%) that results in ultrarapid metabolism (UM) (Zhou et al., 2017). In addition, the population-specific stop-gain variant *CYP2C19*3* is relevant in East Asians (MAF = 6%).

Much research has been devoted to understand the association between these genotypes and the effectiveness of antidepressant therapy. A recent study leveraged pharmacokinetic data and information pertaining to the switching of antidepressant medication within one year after commencing treatment of >2000 patients (Jukić, Haslemo, Molden, & Ingelman-Sundberg, 2018). Importantly, the authors found that *CYP2C19* genotype strongly affected the pharmacokinetics of the commonly used antidepressant escitalopram and only 60% of patients classified as CYP2C19 UM reached recommended therapeutic exposure levels (25 nM). In total 29% of the patients with UM genotype switched antidepressant medicine, likely because of lack of efficacy due to being underdosed. In contrast, CYP2C19 poor metabolizers (PM) experienced serum drug concentrations higher than the recommended range, resulting in 31% of PM patients switching likely due to adverse events. In comparison, only 11–14% of patients with the genotypes encoding normal CYP2C19 enzyme activity (extensive metabolizers) switched medicines. Preemptive *CYP2C19* genotyping would allow to adjust the initial doses to 5 mg in PMs and 20 mg in UMs (compared to 10 mg as current standard-of-care), thereby increasing escitalopram treatment efficacy. Given the important role of CYP2C19 in the metabolism of many antidepressants, we anticipate that *CYP2C19* genotype-guided dosing might provide patient benefits for a considerable number of the 216 million patients diagnosed with major depressive disorder worldwide (GBD 2015).

A *CYP2C19* genotype-dependent outcome was also seen in a recent survey monitoring suicides of Finnish citalopram users (Rahikainen et al., 2018) The study compared the genotypes of 349 citalopram-positive completed suicide cases and 855 general population controls and found that PMs and UMs were significantly enriched in the suicide cases. This finding is in accordance with another study where high CYP2C19 enzymatic capacity was associated with higher suicidality in depressed suicide attempters (Jukić et al., 2017). Based on these findings, we conclude that psychiatry presents a promising and clinically important arena for an increased implementation of preemptive genotyping.

The clinical endpoint of drug switching was also recently used to evaluate the influence of *CYP2C19* polymorphisms on antiplatelet treatment in 603 acute coronary syndrome patients (Gross et al., 2018). The authors found that 38% and 67% of patients carrying one or two loss-of-function *CYP2C19*2* alleles, respectively, switched from clopidogrel to prasugel due to insufficient platelet inhibition, whereas only 27% and 0% of patients switched medicine that carried one or two copies of the gain-of-function allele *CYP2C19*17*, respectively. Indeed, it appears evident that monitoring of drug switching might constitute an easily accessible, feasible and relevant endpoint to examine the influence of genetic polymorphisms on the success of drug therapy.

4. Pharmacogenomics and next-generation sequencing

4.1. Genetic determinants of drug disposition and response

Genetic factors are important modulators of the metabolism of medications and can influence their efficacy and toxicity. Overall, 20–30% of the inter-individual differences in drug-response are estimated to be due to genetic variations (Lauschke & Ingelman-Sundberg, 2016a; Sim, Kacevska, & Ingelman-Sundberg, 2013). Yet, seminal twin studies in the 1960s and 70s indicated that this fraction can be even substantially higher with pharmacokinetic heritability estimates ranging from 80%–99% for most evaluated medications, including antipyrine, dicoumarol, nortryptiline and halothane.

However, results from more recent investigations are more heterogeneous. While additive genetic factors explain around 90% of differences in the pharmacokinetics of metoprolol and torsemide (Matthaei et al., 2015), the clearance of metformin (Stage et al., 2015) and talinolol (Matthaei et al., 2016) is mostly governed by environmental factors. Importantly however, even for metoprolol and torsemide whose pharmacokinetics appear hereditary, common genetic polymorphisms in the genes involved in their metabolism and transport, explain only less than half of this heritability (Matthaei et al., 2015). These findings imply that a major fraction of heritable factors governing drug pharmacokinetics are currently missing and remain to be identified.

4.2. Pharmacogenes harbor a plethora of rare population-specific variants

In recent years considerable interest focused on the role of rare variants in the heritability of disease risk and complex traits. Rare genetic variants with minor allele frequencies (MAF) below 1% in the general population are commonly not interrogated in GWAS analyses. However, it has long been postulated that such rare variants with large effect sizes could contribute towards narrowing the gap between explained and expected heritability of complex traits (Manolio et al., 2009).

Only in the last decade or so was it possible to systematically characterize the inventory of rare genetic variants, primarily fueled by spectacular technological advances in Next Generation Sequencing (NGS) methods that allowed comprehensive sequencing of individuals on a population-scale (The 1000 Genomes Project Consortium, 2010; Drmanac et al., 2010). Importantly, these groundbreaking projects revealed a vast repertoire of rare genetic variants across the human genomes. Since these seminal findings, multiple studies focused their analyses on rare genetic variability specifically in genes involved in absorption, distribution, metabolism and excretion (ADME) of drugs (Table 9). In the largest study of its kind published to date encompassing 60,706 unrelated individuals from five global human populations >98% of all identified variants in drug transporters, drug metabolizing enzymes and nuclear receptors were found to be rare with MAF < 1% (Ingelman-Sundberg, Mkrtchian, Zhou, & Lauschke, 2018). Besides single nucleotide variations (SNVs) and small indels (insertions or deletions spanning <50 base pairs), most pharmacogenes harbor moreover copy number variations (CNVs), which account for >5% of all loss-of-function alleles in 87 out of 208 pharmacogenes analyzed (Santos et al., 2018). Similar findings were reported for important human drug targets, such as the G-protein coupled receptor (GPCR) family (Hauser et al., 2018).

Furthermore, around 80% of pharmacogenetic variants were found to be population-specific (Fujikura, Ingelman-Sundberg, & Lauschke, 2015; Kozyra, Ingelman-Sundberg, & Lauschke, 2017; Zhang & Lauschke, 2018). Population-specific variations were of particular importance in populations with pronounced founder effects and repeated bottlenecks, such as Ashkenazi Jews, where their aggregated frequency exceeded 20% (Zhou & Lauschke, 2018). Combined, these studies demonstrate that the pharmacogenetic landscape is complex and that pharmacogenes harbor a plethora of rare variants that are not

Table 9
Studies evaluating the prevalence of rare pharmacogenetic variants.

Study	Cohort size	Populations	Number of loci	Sequencing method	Exonic SNVs	Intronic SNVs
(Nelson et al., 2012)	14,002	3 global populations	2002	Targeted sequencing	39,647	11,177
(Mizzi et al., 2014)	482	12 global populations	231	WGS	26,807 in exons and proximal regulatory sequences	382,157 in introns and surrounding regions
(Gordon, et al., 2014)	6503	2 global populations	12 *CYP* genes	WES & WGS	1006	Not analyzed
(Fujikura et al., 2015)	6503	2 global populations	Human *CYP* gene family (57 genes)	WES & WGS	4254	1911
(Bush et al., 2016)	5639	5 populations from the US	82	Targeted sequencing	13,194	5231
(Kozyra et al., 2017)	6503	5 global populations	146	WES	12,152	7176
(Han et al., 2017)	376	Koreans	122	Targeted sequencing	4573	1079
(Ahn & Park, 2017)	12,844	5 global populations	48	WES	Around 9550	Not analyzed
(Zhou & Lauschke, 2018)	5076	Ashkenazi Jews	17	WES & WGS	327	Not analyzed
(Wright, Carleton, Hayden, & Ross, 2018)	2504	26 global populations	120	WGS	12,084	
(Ingelman-Sundberg et al., 2018)	60,706	Global	208	WES	69,923	Not analyzed
(Zhang & Lauschke, 2018)	138,632	7 global populations	Human *SLCO* gene family (11 genes)	WES & WGS	9811	3877

considered in conventional association studies with potential importance for inter-individual differences in drug disposition and response.

4.2.1. Functional interpretation of rare pharmacogenetic variants

The tremendous genetic complexity and abundance of rare genetic variants in pharmacogenomic loci directly raises the question about the functional and phenotypic relevance variability (Drögemöller, Wright, & Warnich, 2014; Lauschke & Ingelman-Sundberg, 2016b, 2016c, 2018). The functional impact of genetic variants is generally studied using heterologous in vitro expression systems coupled to a quantitative characterization of appropriate endpoints, such as clearance of different substrates per unit of time in the case of metabolic enzymes or activation of downstream signaling cascades for drug targets. Additionally, the functional impacts of variants on drug disposition or response can be analyzed in sufficiently powered cohort studies. Examples for the latter are effects of *VKORC1* and *CYP2C9* variants on warfarin dose requirements (Johnson & Cavallari, 2015) and impacts of *CYP2C19* genotype on escitalopram serum concentrations and treatment efficacy (Jukić et al., 2018).

However, the low throughput and high costs of in vitro assays for the interrogation of variant functionality do not permit a systematic characterization of the tens of thousands of rare variants identified in population-scale sequencing projects. Furthermore, in vivo rare variant association studies are anticipated to fail to identify significant variant-phenotype relationships due to the, by definition, low frequency of allele carriers. Lastly, when applied in a clinical scenario, neither aforementioned in vivo nor in vitro methods would allow to inform about putative functional consequences of the genetic makeup of a given patient sufficiently fast to support pharmacogenetic testing.

Driven by this lack of experimental strategies for the functional assessment of rare pharmacogenetic variants compatible with the sheer scale of the problem, much research has focused on the optimization of computational prediction methodologies. For an overview of methods available for the computational interpretation of pharmacogenomic NGS data we refer the interested reader to a recent comprehensive review (Zhou, Fujikura, Mkrtchian & Lauschke, 2018). Most attention has been centered on the evaluation of variants that result in amino acid exchanges (missense variants). However, this scope widened in recent years to also include the assessment of variations in enhancers, promoters, splice sites and untranslated regions. To infer the functional consequences of missense variations, most currently used algorithms base their predictions on evolutionary conservation of the respective residues, as well as structural information of the corresponding gene product. The most frequently used algorithms for missense variant interpretation include SIFT (Ng & Henikoff, 2001), PolyPhen-2 (Adzhubei et al., 2010), MutationAssessor (Reva, Antipin, & Sander, 2011) and PROVEAN (Choi et al., 2012).

Genetic variation in non-coding regions that account for >99% of the human genome has been proposed to substantially contribute to inter-individual variability in gene expression by modulating the activity of promoter and enhancer elements (Gloss & Dinger, 2018; Zhang & Lupski, 2015). By integrating molecular evolution patterns with functional genomic data, such as genome-wide maps of chromatin accessibility (Boyle et al., 2008), genome segmentation (Ernst & Kellis, 2012; Hoffman et al., 2012), transcription factor binding (Johnson, Mortazavi, Myers, & Wold, 2007) and histone modifications (Zhang et al., 2010), computational methods are now in a position to predict the phenotypic relevance of non-coding variations with acceptable reliability. Notable methods for the functional interrogation of non-coding variation include GWAVA (Ritchie, Dunham, Zeggini, & Flicek, 2014), CADD (Kircher et al., 2014), Basset (Kelley, Snoek, & Rinn, 2016) and LINSIGHT (Huang, Gulko, & Siepel, 2017). As predictions based on the regulatory logic underlying gene expression are highly cell type and context specific they rely on biologically appropriate training sets. In addition, a plethora of focused tools have been presented that analyze the impact of genetic variants on a multitude of diverse features and parameters, including splicing (Harmanci, Sharma, & Mathews, 2011; Mort et al., 2014; Woolfe, Mullikin, & Elnitski, 2010), non-sense mediated decay (Hsu, Lin, & Chen, 2017), miRNA binding (Barenboim, Zoltick, Guo, & Weinberger, 2010; Deveci, Catalyürek, & Toland, 2014; Ryan, Werner, Howard, & Chow, 2016) and translational efficiency (Zhang et al., 2014).

Importantly, functional interpretation of pharmacogenomic variant data is attended by specific challenges. Firstly, the use of conservation as a metric to predict variant functionality might be problematic due to overall low evolutionary constraints in pharmacogenes (Jin et al., 2018). Secondly, most algorithms are not designed to detect functionality but rather pathogenicity and fitness consequences associated with a given variant. Whereas altered functionality and pathogenicity overlap for regions of the genome that are directly associated with human disease, this association is less clear for pharmacogenes in which deleterious variants are generally not pathogenic. Lastly, training of machine learning methods with inaccurately annotated data sets translates into reduced predictive performance. One example of such a problem is the non-curated use of genetic variants that are common in the general population as functionally neutral training data. While these common variants are likely non-pathogenic, they can have pronounced functional consequences, particularly in pharmacogenes, as exemplified by the common functionally important pharmacogenetic polymorphisms rs1057910 (*CYP2C9*2*), rs4244285 (*CYP2C19*2*), rs3892097

(*CYP2D6*4*), rs34983651 (*UGT1A1*28*) and rs4149056 (*SLCO1B1*5*). Similarly, utilization of all phenotype associated GWAS polymorphisms as functional training data results is problematic as only 5% of GWAS index SNPs are estimated to be mechanistically responsible for the observed phenotypic consequences, i.e. have direct functional consequences (Farh et al., 2015).

To overcome these problems, we have recently developed and cross-validated an algorithm trained specifically on pharmacogenetic variants with comprehensive and high-quality functional annotations (Zhou, Mkrtchian, Kumondai, Hiratsuka, & Lauschke, 2018). This method outcompeted preexisting methods achieving 93% for both sensitivity and specificity. Importantly, the score provided by this prediction framework not only dichotomously classifies variants into functionally deleterious and neutral variants but rather provides estimates about the quantitative effects of the variant on the function of the gene product in question. We envision that such models can be useful for the prediction of phenotypic consequences pertaining to drug disposition and response in a personalized medicine framework.

4.2.2. Putative impact of rare pharmacogenetic variants on drug metabolism and response

The methodological toolbox presented above provides a sound basis to estimate the consequences of pharmacogenetic variation on drug disposition and response. Rare genetic variations in pharmacokinetic are enriched in variants with putative functional consequences and we (Ingelman-Sundberg et al., 2018; Kozyra et al., 2017) and others (Ramsey et al., 2012) have estimated that rare variants contribute around 10–40% to the entire genetically encoded functional variability in those loci. Importantly, the relevance of rare genetic variations was found to be highly gene-specific (Table 10).

Using this information as a template we estimated the impact of rare genetic variability on pharmacokinetics and response of specific drugs with well-characterized pharmacology (Ingelman-Sundberg et al., 2018). Depending on the genes involved in pharmacokinetics and –dynamics of the respective compounds and their metabolites, the overall functional relevance of rare genetic variants differed substantially across evaluated drugs. Rare genetic variants are expected to only explain a minor part in explaining the inter-individual differences in olanzapine serum levels or simvastatin-induced myopathies. By contrast, rare genetic variations are expected to account for 18.4% of the genetically encoded functional variability in *CYP2C9*, which is of central importance for warfarin response. Furthermore, >40% of the variability in irinotecan transport was found to be allotted to rare variants (Ingelman-Sundberg et al., 2018). Thus, these analyses can be used to flag medications for which comprehensive NGS-based genotyping instead of candidate SNP interrogations can likely reveal significant additional information for the personalization of pharmacological therapy.

In an elegant study by Hauser et al., the authors characterized the genetic variability in the human GPCR gene family and, by utilizing available crystallographic data and literature information, found >2000 variants in known functional sites (Hauser et al., 2018). Moreover, they experimentally evaluated the effects of selected variants in *OPRM1*, encoding the μ-opioid receptor, on the response to different ligands. One variant resulted in generally reduced responses to different agonists, whereas other variants had ligand specific effects, exhibiting normal response to endomorphin and morphine but increased response to buprenorphine, a medication used in the treatment of opioid addiction. Most surprisingly, some variants conferred resistance to the opioid receptor antagonist naloxone, resulting in potentially life-threatening lack of efficacy in variant carriers when treated for opioid overdose. Combined, the presented studies indicate that rare genetic variants can have substantial clinically relevant impact on drug disposition and treatment efficacy and underscore the importance of comprehensive pharmacogenetic characterization for personalized medicine.

Notably, genetic variants that are rare globally might be common in specific geographical regions. One example is the functionally defective *CYP3A4*20* allele which is found exclusively in parts of Spain, in which the frequency can be as high as 4% (Apellaniz-Ruiz et al., 2015). *CYP3A4*20* affects paclitaxel metabolism and thus consideration of this polymorphism is clinically relevant in these specific regions (Apellaniz-Ruiz et al., 2015).

4.2.3. Missing pharmacogenomic heritability

Missing heritability refers to the difference between the estimated heritability of a complex phenotype and the contributions of common genetic variants associated with the trait of interest using a simplistic additive model. One simple explanation could be an overestimation of the phenotype's heritability in twin studies due to a violation of the equal-environment assumption, i.e. monozygotic twins tend to shape an environment for themselves that is more similar than that for dizygotic twins. However, elegant twin studies of antipyrine and theophylline pharmacokinetics showed no differences between twins living in the same household and twins living in different households, regardless of zygosity (Miller, Slusher, & Vesell, 1985; Penno, Dvorchik, & Vesell, 1981).

As discussed above, available data suggest that rare genetic variations indeed explain a considerable fraction of the missing heritability in drug response phenotypes; yet, multiple other effects have been proposed that likely contribute as well. Particularly epistatic phenomena, i.e. the interaction between genetic variations, play important roles for pharmacogenomics. Specifically, we refer here to its classical physiological notion in which a combination of genetic variants gives rise to phenotypic consequences that are different from the additive of the individual variant effects (Cheverud & Routman, 1995). For a comprehensive review of the different notions of epistasis, we refer to a recent comprehensive review by Sackton and Hartl (Sackton & Hartl, 2016). To identify and quantify epistatic interactions in pharmacogenomic data a multitude of machine learning tools are available, including regression trees, random forests, deep neural networks and combinatorial partitioning (Motsinger, Ritchie, & Reif, 2007).

Importantly, epistatic mechanisms are already harnessed in clinical therapy, particularly in the area of oncology. Cancers accumulate genetic variants that drive cancer growth and these mutations can result in unexpected sensitivities to pharmacological interventions. For instance, breast cancers with mutations in *BRCA1* or *BRCA2* become reliant on the cellular PARP excision repair system and treatment of *BRCA*-mutation positive breast cancer patients with the PARP inhibitor olaparib resulted in high toxicity specifically in tumors (Fong et al., 2009). We expect that consideration of the genomic context can substantially improve drug response predictions, particularly for medications with complex pharmacology. Thus, systematic epistatic analyses represent an important frontier in contemporary pharmacogenomics.

In addition, missing heritability in complex phenotypes has been postulated to be due to insufficient power of the conducted studies to identify variants with limited effects. When the effects of all genetic variants, including those that do not reach statistical significance, are aggregated, the authors report that for Crohn's disease, bipolar disorder and type I diabetes common genetic variants explained substantially more (25–50%) of the estimated heritability compared to more conservative models (Lee, Wray, Goddard, & Visscher, 2011). Furthermore, based on findings from genetic model organisms, including plants (Undurraga et al., 2012) and flies (Sawyer et al., 1997), as well as human diseases, such as Huntington disease (OMIM identifier 143100), dentatorubro-pallidoluysian atrophy (OMIM 125370), spinal and bulbar muscular atrophy (OMIM 313200) and spinocerebellar ataxias, tandem repeat variations have been suggested as major modulators of gene activity and additional sources of missing heritability of complex human phenotypes (Press, Carlson, & Queitsch, 2014; Quilez et al., 2016). However, further studies are needed to quantify the importance of these postulated factors.

Table 10
Importance of rare genetic variants in important pharmacokinetic genes. The frequency of functional genetic variants were calculated based on data from 130,000 individuals in the GnomAD database using a computational prediction framework specific for ADME genes (Yitian Zhou, et al., 2018).

Class	Gene name (Gene product)	Important substrates	Estimated number of individuals that need to be screened to find one rare deleterious variant	Fraction of functional variability allotted to rare variants
Transporter	*ABCB1 (MDR1, P-gp)*	Anthracyclines, vinca alkaloids, methotrexate, etoposide, clozapine, tricyclic antidepressants, selective serotonin reuptake inhibitors, aliskiren, irinotecan, proton pump inhibitors, verapamil, zidovudine, olanzapine	36 individuals	28%
	ABCC1 (MRP1)	Anthracyclines, vinca alkaloids, epipodophyllotoxins	20 individuals	39%
	ABCC3 (MRP3)	Etoposide, methotrexate	24 individuals	37%
	ABCG2 (BCRP)	Irinotecan, rosuvastatin, nitrofurantoin, leflunomide, cimetidine, glyburide, sulfasalazine	50 individuals	100%
	SLC22A1 (OCT1)	Metformin, oxaliplatin, furaminidine, acyclovir, lamivudine	24 individuals	3%
	SLCO1B1 (OATP1B1)	Statins, meglitinides, rifampicin, angiotensin II receptor antagonists	36 individuals	9%
Phase I	*CYP1A2*	Olanzapine, theophylline, clozapine, tizanidine, caffeine, flutamide, tacrine	49 individuals	2%
	CYP2C9	Warfarin, acenocoumarol, phenytoin, sulfonylureas, torasemide, fluoxetine, terbinagine, sildenafil, celecoxib, piroxicam, lesinurad, dronabinol, tolbutamide	23 individuals	19%
	CYP2C19	Clopidogrel, tricyclic antidepressants, selective serotonin reuptake inhibitors, proton pump inhibitors, voriconazole, moclobemide.	18 individuals	12%
	CYP2D6	Tricyclic antidepressants, selective serotonin reuptake inhibitors, codeine, tramadol, clozapine, risperidone, aripiprazole, venlafaxine, flupentixol, haloperidol, 5-HT3 receptor antagonists, tamoxifen, carvedilol, metoprolol,	12 individuals	7%
	CYP3A4	Aripiprazole, gefitinib, erlotinib, sirolimus, cabazitaxel, dronedarone, ivabradine, ranolazine, tlithromycin, posaconazole, simvastatin, enzalutamide, protease inhibitors, ivacaftor, maraviroc, fesoterodine, phosphodiesterase type V inhibitors	44 individuals	27%
	DPYD	Fluoropyrimidines	18 individuals	22%
Phase II	*UGT1A1*	Irinotecan, lamotrigine, etoposide, belinostat, carvedilol	22 individuals	5%
	TPMT	Thiopurines	119 individuals	6%

4.3. Opportunities of national biobanks

National biobanks in which clinical, phenotypic and lifestyle data are integrated with longitudinal health registries and extensive omics profiles (primarily genomics but also metabolomic, transcriptomic and epigenomic data sets) provide powerful resources for biomarker discovery and personalized medicine. By now multiple countries have established such biobanks, including Estonia (Leitsalu et al., 2015), Iceland (Gulcher & Stefansson, 1999), Japan (Nagai et al., 2017) and the UK (Bycroft et al., 2018). While these platforms have demonstrated their utility for epidemiological research, implementation of available personalized omics information into primary care still faces multiple important challenges. The most significant obstacles include the sensitivity, privacy and highly distinguishable nature of the data, as well as issues pertaining to insufficient acceptance or lack of knowledge on the part of clinicians (Dankar, Ptitsyn, & Dankar, 2018; Hess, Fonseca, Scott, & Fagerness, 2015; Lauschke & Ingelman-Sundberg, 2016c).

Estonia is among the countries that are spearheading the implementation efforts of NGS-guided therapy. Genome-scale genotype data are available for >44,000 individuals, corresponding to 3.5% of the entire population (Reisberg et al., 2018). Importantly, >99% of these participants were found to harbor at least one pharmacogenetically actionable allele and implementation of genotype-guided prescribing is expected to affect drug choice or dosing for 55 daily drug doses per 1000 individuals in the general population. Furthermore, integrating genomic data with longitudinal health records of the respective individuals provides a powerful tool for the discovery of novel pharmacogenomic associations. In a first proof-of-concept study, Tasa et al. identified associations between *CTNNA3* variations and myopathies in biobank participants taking oxicams and were able to replicate this finding in an independent validation cohort (meta-analysis $p = 2.4^{*}10^{-7}$) (Tasa et al., 2018).

Multiple other countries have launched initiatives intended to facilitate the implementation of NGS-based genotyping into the health care system to utilize genomic information for personalized therapy and diagnostics. Qatar aspires to expand its biobank program (Al Kuwari et al., 2015) that already contains longitudinal clinical data with sequencing data from about one fifth of all Qatari citizens within the next years. Furthermore, Korea promotes a precision medicine initiative focusing mainly on pharmacogenomics (Cho et al., 2010). These efforts include reimbursement of pharmacogenetic tests and the development of clinical decision support (CDS) systems to facilitate the implementation of genotype information into clinical care.

The US has presented strategies for the nationwide implementation of personalized medicine, termed Precision Medicine Initiative. The framework encompasses the All of US program in which >1 million volunteers will be sequenced and followed-up with periodic clinical evaluations. A current status report of the clinical implementation of pharmacogenomic testing in the US has been published recently (Volpi et al., 2018). In addition a large number of national biobanks centered on cancer samples have been established and we refer the interested reader to recent overviews for further information (Krieger & Jahn, 2018; Vaught, Kelly, & Hewitt, 2009).

5. Pharmacoepigenomics

The term “epigenetics” can be interpreted as a cellular or molecular phenomenon (Deans & Maggert, 2015). The former follows the classical Waddingtonian concept of cell state or fate determination, primarily in the context of embryonic development and stem cell biology, whereas the latter can describe any mechanism of gene regulation that can be passed on through cell divisions or, in its widest definition commonly applied particularly in the field of pharmacoepigenetics, alludes to any additional layer transcriptional regulation apart from transcription factors, thus also including non-coding RNA species. In the context of this review, we follow the restricted molecular definition of epigenetics, in

which we consider a phenomenon as "epigenetic" if it pertains to chromosome-bound changes of gene expression that can be transmitted through mitosis and that are not caused by alterations in the primary DNA sequence, thus explicitly excluding regulatory RNAs.

5.1. Epigenetic regulation of gene expression

Epigenetic regulation plays an essential role in the modulation of gene expression across eukaryotes. Epigenetic signals can be encoded as modifications of the DNA itself or of associated histones. At the level of DNA, the predominant epigenetic mark is methylation of cytosine–guanine dinucleotides (5mC) affecting 3–5% of all cytosines. In recent years however multiple additional CpG modifications were discovered, including hydroxymethylcytosine (5hmC), formylcytosine (5fC) and carboxylcytosine (5caC) (Ito et al., 2011; Tahiliani et al., 2009). Of these "additional bases" 5hmC is most common, accounting for up to 1% of all cytosines in hmC-rich tissues, such as liver and central nervous system, compared to <0.02% for 5fC and 5caC (Bachman et al., 2015; Globisch et al., 2010; Ivanov et al., 2013).

While these DNA modifications form during the oxidative removal of 5mC marks, they seem to be more than mere demethylation intermediates (Wu & Zhang, 2017); they appear to be temporally stable for multiple weeks in certain contexts and elicit distinct biological responses by changing DNA conformation and selectively binding to specific reader proteins (Iurlaro et al., 2013; Kitsera et al., 2017; Pfaffeneder et al., 2014; Raiber et al., 2015; Spruijt et al., 2013). Generally, 5mC, 5fC and 5caC inhibit transcription factor binding and promote condensation to heterochromatin, whereas 5hmC is commonly associated with actively transcribed genes. Thus, given their antagonistic functional roles and significant abundance in human liver, 5mC and 5hmC have received particular attention in pharmacoepigenetic research.

Compared to DNA marks, epigenetic modifications at the level of histones are more diverse and >35 chemically distinct modifications have been described to date, including acetylation, methylation, phosphorylation, ubiquitinylation, sumoylation, ADP-ribosylation, propionylation, butyrylation and deamination (Lawrence, Daujat, & Schneider, 2016; Zhang, Cooper, & Brockdorff, 2015). Depending on nature and position within the histone tail, histone modifications can associate with transcriptional activation or transcriptional silencing. Arguably the most extensively studied modifications are trimethylation of lysines 4 and 27 in histone 3 (H3K4me3 and H3K27me3, respectively) and acetylation marks in the tails of histones 3 and 4. Actively transcribed genes are generally marked by H3K4me3 and H3 and H4 acetylation in their promoters and gene bodies (Barrera et al., 2007; Guillemette et al., 2011; Liang et al., 2004). H3K4me3 promotes the recruitment of histone acetyltransferases, which entails coordination of different activating histone marks, jointly supporting the formation of a transcriptionally permissive chromatin state (Bian et al., 2011; Hung et al., 2009). In turn, acetylated lysines promote transcription due to specific recognition by proteins containing bromodomains, which are part of many transcriptional regulators (Fujisawa & Filippakopoulos, 2017). Importantly, recruitment of the DNA methyltransferase DNMT3 that catalyzed 5mC formation is blocked by H3K4me3, thus interlocking epigenetic signatures at the level of DNA and histones and resulting in mutual exclusivity of repressive 5mC and activating H3K4me3 marks (Balasubramanian et al., 2012; Ooi et al., 2007; Otani et al., 2009).

In contrast, repressive histone gene signatures feature H3K27me3 and H2AK119ub (ubiquitinylation of lysine 119 in histone H2A). Methylation of H3K27 is catalyzed by the Polycomb repressive complex 2 (PRC2), whereas the PRC1 catalyzes H2AK119ub (Czermin et al., 2002; Endoh et al., 2012). PRC1 components of the *CBX* gene family recognize PRC2-catalyzed H3K27me3, resulting in largely overlapping maps of H3K27me3 and H2AK119ub modifications (Bernstein et al., 2006; Cao et al., 2002; Kuzmichev et al., 2002). Furthermore, binding of the PRC2 to H3K27me3 provides a positive feedback that reinforces transcriptionally repressive domains (Margueron et al., 2009). For a more detailed overview of the mechanistic underpinnings of the various levels of epigenetic regulation, we refer the interested reader to recent reviews (Allis & Jenuwein, 2016; Chen, Li, Subramaniam, Shyy, & Chien, 2017).

Importantly, many epigenetic alterations appear to be the consequence rather than the cause of the observed phenotype they correlate with. By analyzing epigenetic signatures in whole blood of 3296 individuals phenotyped for fasting blood lipid levels using a Mendelian randomization framework, Dekkers and colleagues found strong evidence that triglycerides and cholesterol cause alterations in DNA methylation patterns and not vice versa (Dekkers et al., 2016). Similar observations were obtained for associations between DNA methylation patterns and adiposity (Li et al., 2018; Mendelson et al., 2017; Richmond et al., 2016; Wahl et al., 2017) or lung cancer risk (Battram et al., 2018). Thus, while more data about the functional role of epigenetic patterns are warranted, these data incentivize analyses of forward and reverse causality in epidemiological studies of epigenetic phenomena.

5.2. Analytical methods

A plethora of protocols has been presented to decode epigenomic profiles. These methods differ by their input requirements, feature resolution, scalability and costs (Clark, Lee, Smallwood, Kelsey, & Reik, 2016; Kurdyukov & Bullock, 2016; Yong, Hsu, & Chen, 2016). For analyses of DNA modifications, approaches are based on bisulfite conversion, enzymatic digestion or affinity enrichment. Bisulfite conversion exploits differences in chemical reactivity of modified and unmodified cytosine variants and constitutes the most widely used method. Bisulfite deaminates unmodified cytosine, as well as 5fC and 5caC to uracil, whereas 5mC and 5hmC are protected. Thus, these conventional bisulfite-based methods cannot distinguish between "repressive" 5mC and "activating" 5hmC marks, which can confound biological conclusions and limits the usefulness of these protocols, particularly for epigenetic studies of liver biology or hepatic metabolism in which 5hmC levels are high.

To overcome these limitations multiple techniques have been presented that change bisulfite sensitivity between 5mC and 5hmC. Oxidative bisulfite sequencing (oxBS-seq) employs chemical oxidation of 5hmC to 5fC before bisulfite conversion (Booth et al., 2012). As a result, 5mC remains protected from bisulfite conversion (thus appearing as cytosine during sequencing), whereas 5hmC is deaminated to uracil during the bisulfite conversion step. In a second method, termed TET-assisted bisulfite sequencing (TAB-Seq), 5hmC is first glycosylated enzymatically by β-glucosyltransferase to 5gmC (Yu et al., 2012). Subsequently, 5mC is oxidized to 5caC by recombinant TET enzymes and deaminated in the bisulfite conversion step. In contrast, 5gmC is protected from TET-mediated oxidation and subsequent bisulfite-mediated deamination. Thus, comparison of results from conventional bisulfite sequencing (5mC and 5hmC are not deaminated and appear as cytosine after bisulfite treatment) with TAB-Seq (5mC appear as uracil, whereas 5hmC appears as cytosine, as it is protected from bisulfite treatment), allows to identify 5hmC positions with base-pair resolution. In a conceptually similar approach, Schutsky and colleagues presented a bilsufite-free enzymatic approach that utilizes cytidine deaminases of the APOBEC gene family, termed APOBEC-coupled epigenetic sequencing (ACE-seq) (Schutsky et al., 2018). In a first step 5hmC is glucosylated to 5gmC as in TAB-Seq. Subsequently, 5mC is deaminated enzymatically by AID/APOBEC enzymes, whereas 5gmC is protected. Notably, as deamination is achieved by enzymes rather than harsh chemical conditions, ACE-Seq requires >1000-fold less input material, thus allowing epigenetic analyses of samples with limited availability.

In addition, single molecule sequencing methods can be used to decode cytosine modifications independent of bisulfite conversion. In SMRT-Seq a single DNA molecule of interest is sequenced by measuring the polymerase-mediated integration of fluorescently labeled nucleotides into the complementary strand (Eid et al., 2009). Importantly, differences in polymerase kinetics as evident from sequencing

fluorescence traces allow to directly distinguish cytosine, 5mC and 5hmC (Flusberg et al., 2010). Furthermore, all five different cytosine species (C, 5mC, 5hmC, 5fC and 5caC) can be identified by changes in ionic current signal using nanopore sequencing (Laszlo et al., 2013; Rand et al., 2017; Wescoe, Schreiber, & Akeson, 2014).

In contrast to the analyses of covalent DNA modifications discussed above, methods for studies of posttranslational modifications (PTMs) on histones are primarily antibody based, such as such as Western blot and chromatin immunoprecipitation (ChIP). However, generation of antibodies that specifically recognize a histone modification of interest with suitable sensitivity is difficult and time-consuming (Kidder, Hu, & Zhao, 2011; Wardle & Tan, 2015). Furthermore, these approaches are poorly scalable and can only analyze one or few modifications per experiment. Besides antibody-based detections of histone PTMs, proteomic approaches constitute a quantitative and high-throughput compatible approach to obtain overall histone modification profiles on global chromatin (El Kennani, Crespo, Govin, & Pflieger, 2018; Huang, Lin, Garcia, & Zhao, 2015; Soldi, Bremang, & Bonaldi, 2014).

5.3. Effect of epigenetic gene regulation on pharmacokinetics and drug response

In the past decade a multitude of studies have revealed correlation between epigenetic modifications and expression levels or activity of genes involved in drug ADME and pharmacodynamics and we refer to comprehensive recent reviews for further details (Fisel, Schaeffeler, & Schwab, 2016; Tang & Chen, 2015). Prominent examples for such associations are the correlations between DNA methylation in the promoters of *CYP3A4*, *CYP1A2*, *CYP2C19* and *UGT1A1* with the respective expression levels (Gagnon et al., 2006; Habano et al., 2015; Kacevska et al., 2012; Miyajima, Furihata, & Chiba, 2009). In hepatic cell lines (HepG2) transcriptional activation of *CYP3A4* has been shown to require the histone methyltransferase PRMT1, as knock-down of PRMT1 resulted in 20-fold reduced activation of *CYP3A4* by rifampicin (Xie et al., 2009). Furthermore, PXR-mediated induction of CYP3A4 by rifampicin results in changes of the histone profile with increased levels of H3K4me3 and H3ac, as well as decreased levels of the repressive histone mark H3K27me3 (Yan et al., 2017). Notably, these changes are the consequence of transcriptional activation as knock-down of PXR prevents both transcriptional activation and epigenetic alterations. In addition, histone modification patterns have been found to correlate with expression levels of multiple drug transporters, such as *ABCB1* (MDR1) and *ABCG2* (BCRP) (Henrique et al., 2013; To et al., 2008); in light of above-mentioned data, a similar cause-consequence relationship is likely.

The promoters of various *CYP* genes, including *CYP1A1*, *CYP1B1*, *CYP2D6* and *CYP2E1*, are hypermethylated in hepatocyte-like cells derived from embryonic stem cells, correlating with drastically reduced expression (multiple orders of magnitude) of these genes compared to primary human hepatocyte cultures (Park et al., 2015). Notably, pharmacological inhibition of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) resulted in 10-fold increased expression of *CYP1A1* and *CYP1B1*, whereas changes of *CYP2D6* and *CYP2E1* were negligible (Park et al., 2015). Combined, these findings provide evidence that epigenetic remodeling and ADME gene expression levels can be directly linked.

Epigenetic changes in ADME genes particularly correlate with expression patterns during embryonic development. While *CYP3A7* constitutes the predominant *CYP3A* isoform in embryonic liver, expression switches to *CYP3A4* in postnatal stages and this switching is paralleled by changes in methylation levels of transcription factor binding sites within the *CYP3A* promoters in mice and humans (Kacevska et al., 2012; Li et al., 2009). A further example is the regulation of *CYP2W1* expression. Whereas the gene is expressed in fetal gut, neonatal methylation inhibits further expression in healthy adult tissues (Guo, Johansson, Mkrtchian, & Ingelman-Sundberg, 2016). However, in transformed colon cancer cells and metastases, a critical CpG island in the exon 1 - intron 1 junction is hypomethylated and expression of *CYP2W1* is reactivated (Choong et al., 2015). Since the enzyme can bioactivate anticancer prodrugs its specific expression in cancer cells makes it as an interesting target for future anticancer drug development (Travica et al., 2013).

Notably, global hmC content varies by a factor of four between human livers and we could show that hydroxymethylation in coding regions positively correlates with the expression levels of the corresponding human ADME genes (Ivanov et al., 2016). These data suggest that hmC variability contributes to the epigenetic control of hepatic gene expression, possibly by causing chromatin alterations that facilitate gene transcription.

Importantly, epigenomic profiles are highly tissue-specific with each cell type having its unique signature and correlations between the epigenomes of different tissues, particularly blood, are generally poor (Bonder et al., 2014; Hannon, Lunnon, Schalkwyk, & Mill, 2015; Lowe, Slodkowicz, Goldman, & Rakyan, 2015; Lunnon et al., 2016). Yet, most epigenetic association studies are performed using peripheral blood as surrogate tissue. Thus, we emphasize our previously raised concerns (Lauschke, Ivanov, & Ingelman-Sundberg, 2017) that conclusions about epigenetic regulation critically require the analysis of carefully isolated biopsy material from the given tissue of interest to account for this tissue-specificity.

Mutations in epigenetic modifiers, such as DNMT, HDAC, and TET enzymes are found in up to 50% of all cancers, resulting in profound changes of their epigenetic landscape (Ceccacci & Minucci, 2016; Scourzic, Mouly, & Bernard, 2015; Zhang & Xu, 2017). Thus, exploiting these epigenetic changes provides an appealing therapeutic avenue and six small molecule inhibitors of epigenetic modifiers (azacitidine, decitabine, belinostat, panobinostat, romidepsin, and vorinostat), termed epidrugs, have already received regulatory approval for the treatment of various cancers and hundreds of additional clinical trials are currently ongoing. Furthermore, epidrugs are in various stages of development for the treatment of autoimmune disorders, neurodegenerative diseases and type 2 diabetes. For a status update of the clinical implementation of epigenetic therapy and the utilization of epigenetic biomarkers we refer to our recent comprehensive review (Lauschke, Barragan, & Ingelman-Sundberg, 2018).

6. Clinical implementation efforts

Our understanding of the complexity of pharmcogenomic loci has made tremendous advances. As discussed above, only during the last years has it become evident that genes involved in pharmacokinetics and -dynamics harbor a plethora of rare genetic variants and copy number variations that can have important consequences for human drug response. However, today's array-based pharmacogenomic analyses only interrogate common genetic variants. We advocate for a methodological paradigm shift that allows to embrace the entire pharmacogenomic complexity, including rare variants and copy number variations, by comprehensively interrogating loci of interest using NGS-based technologies (Fig. 3). Only then will it be possible to take into account the entire repertoire of genetic variability of a given patient to inform and enhance treatment decisions.

At present, we recommend to focus pharmacogenetic analyses on loci with importance for drug ADME, adverse reactions or response. Restricting analyses to those genes as well as their surrounding regions with potential regulatory importance (e.g. 50 kb) allows to drastically reduce sequencing costs and analytical complexity with minimal loss of information. Targeted sequencing libraries supporting such focused analyses have already been developed and, when applied to 5000 individuals, revealed >40,000 variants across 82 pharmacogenes (Bush et al., 2016; Gordon et al., 2016). However, little is known about the impact of variants on interindividual variability in drug response that reside in genomic areas beyond well-characterized pharmacogenes and thus library designs might have to be expanded in the future.

Advances in machine learning and artificial intelligence have resulted in a rapid improvement of the methodological toolbox for the

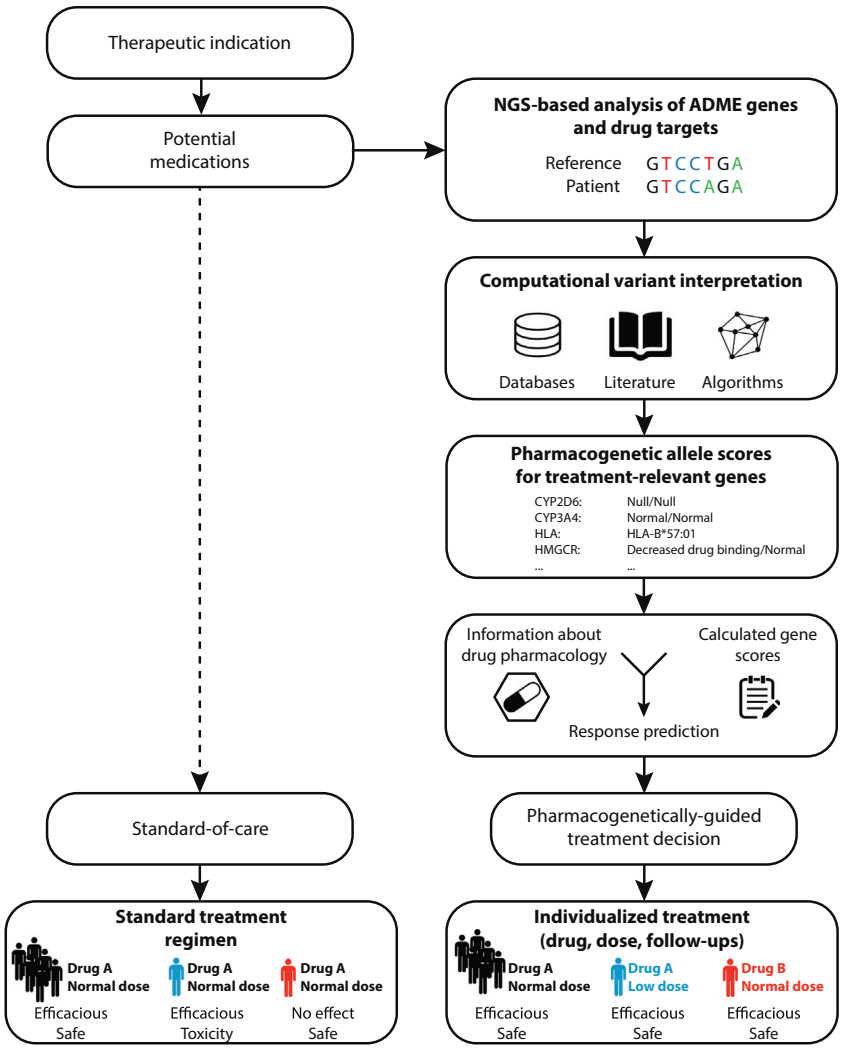

Fig. 3. Individualization of treatment based on comprehensive NGS-based genotyping data. In conventional care for most indications, treatment is based on clinical parameters without consideration of the patient's genotype (left track in the figure). While these regimens are efficacious and safe in most individuals, some patients do not respond to the prescribed medication or might experience adverse reactions. The utilization of Next Generation Sequencing (NGS) aims to leverage genomic data to predict those outlier patients and pre-emptively provide advice regarding alternative treatments or to flag patients for follow-up monitoring (right track in the figure). To achieve this goal, variations in genes encoding proteins involved in drug absorption, distribution, metabolism and excretion (ADME) and drug targets, as well as their regulatory regions are identified in the NGS data of the given patient. The effects of these variants are interpreted based on available characterization data collected in dedicated databases or the scientific literature. For novel variants, functional effects will be predicted using quantitative computational algorithms specifically developed for pharmacogenomic predictions. Effects of target variations on drug binding are predicted using available structural information. Subsequently, effects of all identified variants are collated and translated into activity scores for all pharmacogenes. Integration of gene activity scores with information about the pharmacology of medications available for the given therapeutic indication, allows to predict their efficacies and risks to cause adverse reactions. These results can provide guidance to the responsible physician regarding choice of drug and its dose, as well as incentivize the scheduling of more frequent follow-ups in at-risk patients, resulting in increased treatment efficacy and safety also for outlier patients. Figure modified with permission from the publisher and authors (Lauschke & Ingelman-Sundberg, 2018).

functional interpretation of genetic variations identified by NGS-based sequencing. Novel algorithms can predict loss-of-function and functionally neutral missense mutations with reasonable accuracy of >90%. Moreover, tools have been presented that can not only dichotomously distinguish between deleterious and functionally neutral variations but rather provide with quantitative estimates about the extent of functional impact for a given variant. This opens up possibilities to rapidly translate NGS-based sequences into gene activity scores, which can be used in conjunction with existing pharmacogenetic guidelines to advise treatment decisions.

7. Conclusions and future outlook

The translation of pharmacogenomic findings into patient or societal benefits in the past has been relatively slow. However, in light of the rapid methodological developments in the areas of genomics, statistical genetics and machine learning, as well as the multitude of ongoing efforts to quantify the added value of preemptive pharmacogenomic tests, we anticipate that their clinical implementation will accelerate in the near future. With decreasing costs of genetic testing, concerns will shift away from monetary considerations and the main hurdle in the future process will be the accuracy of phenotypic interpretation of a given genotype, particularly pertaining to the rare mutations which are often specific for a given individual. Importantly, computational methods are not (and likely will never be) able to predict alterations of gene function with complete accuracy. However, we believe that they are useful to flag patients with genotypes that indicate an increased likelihood of an outlier response. This information can be of value for the physician who in such cases can adjust follow-up schedules and initiate therapeutic drug monitoring and dose titrations.

Our knowledge of pharmacogenomic variation is rapidly increasing; however, there is still much to learn. Important frontiers include the

understanding and functional interpretation of regulatory parts of the genome. Furthermore, non-coding RNAs might be important, currently underappreciated modulators of drug response, as suggested for the response to lithium treatment in bipolar disorder (Hou et al., 2016). Most importantly, there is an urgent need for prospective, randomized clinical trials that evaluate patient benefits and cost effectiveness of preemptive NGS-based genotyping coupled to state-of-the-art computational prediction tools across diseases, medicines and health care systems, as a more wide-spread clinical implementation of personalized medicine can only be achieved by providing a solid base of evidence. Overall, we envision that ongoing development, optimization and validation efforts in the area of pharmacogenomics will pave the way for an increased personalization of drug therapy, resulting in more cost-efficient health care, increased drug development efficiency and improved public health.

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