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Pharmacogenomics and Global Precision Medicine in the Context of Adverse Drug Reactions: Top 10 Opportunities and Challenges for the Next Decade

Marco Alessandrini, Mamoonah Chaudhry, Tyren M. Dodgen, and Michael S. Pepper

Abstract

In a move indicative of the enthusiastic support of precision medicine, the U.S. President Barack Obama announced the Precision Medicine Initiative in January 2015. The global precision medicine ecosystem is, thus, receiving generous support from the United States ($215 million), and numerous other governments have followed suit. In the context of precision medicine, drug treatment and prediction of its outcomes have been important for nearly six decades in the field of pharmacogenomics. The field offers an elegant solution for minimizing the effects and occurrence of adverse drug reactions (ADRs). The Clinical Pharmacogenetics Implementation Consortium (CPIC) plays an important role in this context, and it aims at specifically guiding the translation of clinically relevant and evidence-based pharmacogenomics research. In this forward-looking analysis, we make particular reference to several of the CPIC guidelines and their role in guiding the treatment of highly relevant diseases, namely cardiovascular disease, major depressive disorder, cancer, and human immunodeficiency virus, with a view to predicting and managing ADRs. In addition, we provide a list of the top 10 crosscutting opportunities and challenges facing the fields of precision medicine and pharmacogenomics, which have broad applicability independent of the drug class involved. Many of these opportunities and challenges pertain to infrastructure, study design, policy, and science culture in the early 21st century. Ultimately, rational pharmacogenomics study design and the acquisition of comprehensive phenotypic data that proportionately match the genomics data should be an imperative as we move forward toward global precision medicine.

Introduction

Precision medicine requires a multicomponent strategy targeting both the human host and her/his environment. The environment can play a decisive role in the extent to which individuals are differentially susceptible to disease as well as to the toxicity associated with therapeutic interventions. Environmental factors include technology and innovation policy but do not always receive the same degree of enthusiastic interest from the scientific community, compared with, for example, host-related variables such as genomic and proteomic variation among people and populations (Dandara et al., 2014; Ozdemir and Hekim, 2016).

In a move toward the enthusiastic support of precision medicine, the U.S. President Barack Obama announced the Precision Medicine Initiative (PMI) in January 2015. This is a US$215-million program that is focused largely on genomic variation information, health records, and data from electronic health-monitoring devices (Reardon, 2015). The PMI has a strong mandate to address biological variation and will boost the global precision medicine innovation ecosystem, as the United States has a large share in biomarker and omics research, which are central to the PMI.

In a context of global precision medicine, drug treatment and prediction of its outcomes has been important for nearly six decades since the inception of the field of pharmacogenomics in the mid-20th century (Kalow, 1961). But what should we anticipate from pharmacogenomics, and adverse drug reactions (ADRs) in particular, in the current era of global precision medicine and support from PMI and similar initiatives worldwide?

It has been reported that only 25–60% of patients respond favorably to prescribed medications (Squassina et al., 2010). An unfavorable response can be classified as a complete lack

Department of Immunology, Faculty of Health Sciences, and Institute for Cellular and Molecular Medicine, South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy, University of Pretoria, Pretoria, South Africa.

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of efficacy on one side of the spectrum, to the occurrence of side effects and ADRs on the other. Side effects are expected and predictable in the context of the prescribed drug and seldom require clinical intervention. Examples of side effects include nausea, drowsiness, dry mouth, and constipation—all of which are generally tolerable by the patient or can be managed with relative ease. In contrast, an ADR is defined as an excessive response to a drug, which is unexpected, unintended, and undesired, and results in significant harm, disability, or even death (American Society of Health-System Pharmacists, 1995). It goes without saying that intervention is required in these instances, which could be in the form of significant alterations in drug dosages, treatment discontinuation, changing medications, or even changing the diagnosis and prognosis of the patient (Ray et al., 2015).

Although poorly reported in most regions, ADRs result in considerable morbidity and mortality, which exacerbate the problems faced by already over-burdened healthcare systems. In the United States, fatal ADRs occur in 0.32% of patients and result in more than 100,000 deaths per annum, ranking them among the six leading causes of death (Lazarou et al., 1998). In a Swedish study, it was reported that up to 3% of all deaths in three of its counties could be accounted for by fatal ADRs (Wester et al., 2008). Similarly, based on data derived from four hospitals in South Africa (Western Cape), 2.9% of deaths in admissions were due to ADRs (Mouton et al., 2015). In a prospective study in the United Kingdom, which included nearly 19,000 patients, it was reported that 6.5% of hospital admissions were related to ADRs, and that ~80% of these admissions were a direct result of the ADR itself (Pirmohamed et al., 2004). The authors were further able to project the cost of ADR-related hospital admissions to be in the order of £466 million annually, an amount similar to that reported in the United States (Bates et al., 1997).

Pharmacogenomics, and more broadly precision medicine, comprises technologies to stratify the patient population and to alleviate the burden of ADRs (hypothetically portrayed in Fig. 1). It is said that up to 95% of responses to medication are accounted for by one's genetic make-up (Kalow et al., 1998). With this in mind, there has been a great deal of interest vested in establishing concrete pharmacogenomic associations and the development of pharmacogenomics-based predictive tools. In this context, the Clinical Pharmacogenetics Implementation Consortium (CPIC) was established to specifically assist and guide the translation of clinically relevant and evidence-based pharmacogenomic testing (Relling and Klein, 2011). At present, the CPIC provides pharmacogenetic testing guidelines for 33 drugs, which can be related to genetic variation in 13 genes (Table 1).

In this article, we will make particular reference to several of the CPIC guidelines in the context of cardiovascular disease (CVD), major depressive disorders, cancer, and human immunodeficiency virus (HIV) treatment, and their role in alleviating ADRs. The scope will, therefore, be limited to selected and well-described pharmacogenomic associations (Table 1), and it is not intended to be fully comprehensive. We also provide an outlook highlighting opportunities and some of the important challenges to be overcome in the field.

CVD and Anticlotting Agents

According to the World Health Organization (WHO), CVDs are the number one cause of death globally. Examples

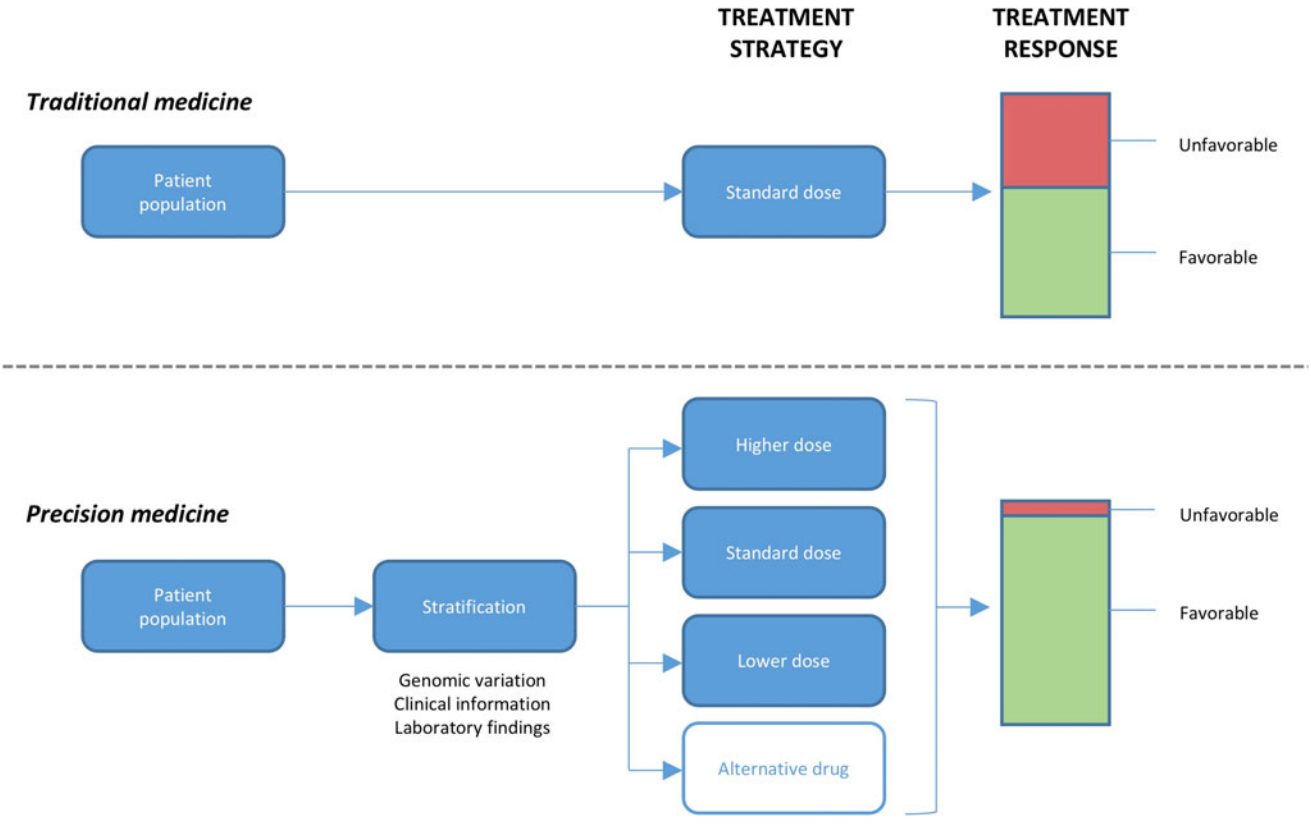

FIG. 1. Hypothetical schematic of traditional versus precision medicine approaches.

Table 1. Overview and Grouping of Dosing Guidelines Provided by the Clinical Pharmacogenetics Implementation Consortium

Pharmacogene(s)	*Drug*	*Drug class*	*Indication*
CYP2D6+CYP2C19	Amitriptyline Clomipramine Doxepin Imipramine Trimipramine	TCAs	Major depressive disorder and anxiety disorders
CYP2D6	Codeine	Analgesic	Pain/coughing
	Desipramine Nortriptyline	TCAs	Major depressive disorder and anxiety disorders
	Fluvoxamine Paroxetine	SSRIs	
CYP2C19	Clopidogrel	Anticlotting agent	Acute coronary syndrome
	Citalopram Escitalopram Sertraline	SSRIs	Major depressive disorder and anxiety disorders
DPYD	Capecitabine 5-Fluorouracil Tegafur	Chemotherapeutics	Cancer
HLA-B	Abacavir	Antiretroviral	HIV infection
	Allopurinol	Gout suppressant	Hyperuricemia (gout)
	Carbamazepine	Anticonvulsant	Seizures
IFNL3	Peginterferon alfa-2a Peginterferon alfa-2b Ribavirin	Antivirals	Hepatitis C
TPMT	Azathioprine Mercaptopurine Thioguanine	Immunosuppressants	Autoimmune disease and for transplantation purposes
CFTR	Ivacaftor	CFTR potentiator	Cystic fibrosis
CYP2C9+HLA-B	Phenytoin	Anticonvulsant	Seizures
CYP2C9+VKORC1	Warfarin	Anticlotting agent	Acute coronary syndrome
CYP3A5	Tacrolimus	Immunosuppressant	Transplantation
G6PD	Rasburicase	Gout suppressant	Hyperuricemia (due to chemotherapy)
SLCO1B1	Simvastatin	Lipid-lowering agent	Hypercholesterolemia
UGT1A1	Atazanavir	Antiretroviral	HIV infection

Adapted from CPIC Dosing Guidelines (www.pharmgkb.org/view/dosing-guidelines.do?source=CPIC#), and delineated according to the pharmacogenes that feature the most prominently.

CPIC, Clinical Pharmacogenetics Implementation Consortium; HIV, human immunodeficiency virus; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

include ischemic heart disease, cerebrovascular disease, deep vein thrombosis, and pulmonary embolism. Anticlotting agents, in the form of anticoagulant and antiplatelet therapy, are widely used for the management of thrombotic disorders, and warfarin and clopidogrel feature prominently. Both have narrow therapeutic indices and also have well-described pharmacogenomic associations (Wang et al., 2011).

Warfarin is the most widely prescribed oral anticoagulant. More than 2 million people start warfarin therapy annually in the United States alone; whereas in the United Kingdom, it is said that more than 1% of the total population is on warfarin medication (Pirmohamed, 2006). However, up to 20% of patients are hospitalized during the first 6 months of therapy due to warfarin-associated ADRs (Kitzmiller et al., 2011). In fact, together with low-dose aspirin (another blood thinner), warfarin is the leading cause of ADR-related hospitalizations in the United Kingdom (Pirmohamed et al., 2004)—a trend that can be extrapolated to many other regions globally.

Warfarin is used as a racemic mixture of both S-warfarin and R-warfarin, with the former being three to five times more potent as an anticoagulant (Johnson et al., 2011). S-warfarin is metabolized by CYP2C9, whereas R-warfarin is metabolized by a number of enzymes, mainly CYP1A2, CYP2C19, and CYP3A (Kaminsky et al., 1993). Warfarin acts by inhibiting the vitamin K epoxide reductase complex subunit 1 (VKORC1) enzyme, which, in turn, limits the availability of reduced vitamin K, an essential blood clotting factor. CYP4F2 acts to remove vitamin K from the vitamin K cycle by converting reduced vitamin K to hydroxyvitamin K1 (Johnson et al., 2011). To maintain an optimal dose within a narrow therapeutic range, the international normalized ratio (INR) and prothrombin time are monitored. An INR of <2 is associated with an increased risk of thromboembolism, whereas an INR >4 is associated with an increased risk of bleeding (Schwarz et al., 2008).

Several pharmacogenes are involved in determining responses to warfarin. The most relevant are *CYP2C9*, *VKORC1*, and *CYP4F2*, which together can explain up to 35% of the variation in response observed in patients (Johnson et al., 2011). Important loss-of-function alleles of *CYP2C9* include

*CYP2C9*2*, **3*, **5*, and **6*. However, these should be evaluated in the context of the patients' *VKORC1* (−1639G>A) and *CYP4F2* (V433M) status, which is responsible for the control of vitamin K metabolism.

A meta-analysis has revealed that *CYP2C9* and *VKORC1* variants account for 12% and 25% of inter-individual variability in warfarin dose, respectively (Au and Rettie, 2008). In addition, individuals with the loss-of-function allele *CYP2C9*2* have a 30% reduced warfarin clearance, whereas this may increase to up to 90% in those harboring *CYP2C9*3* (Gage et al., 2004). The authors also report that a 19% and 33% reduction in dose would be optimal for **2* and **3* allele carriers, respectively (Gage et al., 2004). Likewise, individuals with a −1639G>A mutation in the *VKORC1* gene require a 30% warfarin dose reduction (International Warfarin Pharmacogenetics Consortium, 2009; Wang et al., 2008). Finally, it has been shown that individuals carrying the V433M loss-of-function variant of *CYP4F2* would benefit from a 1 mg/day dose escalation due to increased levels of hepatic vitamin K (Voora and Ginsburg, 2012).

Given the global significance of warfarin and the critical need to maintain a stable INR, several groups have developed tailored dosing algorithms and guidelines. Each takes into account various genetic and nongenetic factors, and each reports varying degrees of efficacy. This has culminated in the establishment of the International Warfarin Pharmacogenetics Consortium (IWPC), which aims at developing a globally accepted consensus dosing algorithm. The current IWPC dosing algorithm takes into account variants in *CYP2C9* and *VKORC1*, age, weight, height, race, and concomitant medications. The algorithm was developed from data from 4043 patients and was subsequently validated in 1009 individuals (International Warfarin Pharmacogenetics Consortium, 2009).

Another algorithm that is accessible at WarfarinDosing.org, also known as the Gage et al. (2004) algorithm, is more extensive in that it also accounts for genetic variants in *CYP4F2* and *GGCX* (gamma-glutamyl carboxylase, responsible for the carboxylation of vitamin K-dependent proteins), as well as additional clinical information. When comparing these algorithms and others (Sconce equation, Anderson Equation; UCHC), it was found that the IWPC algorithm performed best when it came to predicting optimal doses for warfarin (Roper et al., 2010). Finally, when investigating pharmacogenomics-based dosing in a randomized clinical trial using an IWPC-based algorithm (Pirmohamed et al., 2013), it was shown that genotype-guided dosing resulted in significantly fewer cases of excessive anticoagulation (INR ≥4.0).

Clopidogrel is an antiplatelet agent that is used by up to 40 million patients worldwide (Kitzmiller et al., 2011). It is indicated for use in patients who had previously experienced a cardiovascular event, and it decreases the risk of recurrent stroke and myocardial infarction (Helton et al., 2007; The Active Investigators et al., 2009). This prodrug is first converted to its active metabolite by CYP2C19, which then inhibits adenosine diphosphate (ADP)–stimulated platelet activation through irreversible binding to a specific platelet ADP receptor (P2RY12) (Savi et al., 2000). Platelet aggregation is prevented as a result.

The CPIC has suggested the genotype-guided use of clopidogrel in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (Scott et al., 2013). According to these guidelines, knowledge of the *CYP2C19* genotype reduces the risk of recurrent cardiovascular events and ADRs such as bleeding while on clopidogrel. In the case of CYP2C19 poor metabolizers (PMs: *2/*2, *2/*3, *3/*3) or intermediate metabolizers (IMs: *1/*2, *1/*3, *2/*17), an alternative antiplatelet therapy is recommended, provided there are no contraindications. The alternative therapies that may be used are prasugrel and ticagrelor, neither of which are substrates of CYP2C19 (Franchi and Angiolillo, 2015).

Standard dosing is recommended for extensive metabolizers (EMs: *1/*1) and ultra-rapid metabolizers (UMs: *1/*17, *17/*17). Individuals with loss-of-function alleles of *CYP2C19* have an increased risk of myocardial infarction, stroke, and death (Simon et al., 2009) due to the fact that the prodrug is not activated. Similarly, *CYP2C19*2* carriers have been shown to have an almost threefold increased risk of stent thrombosis compared with homozygous *CYP2C19*1* individuals (Sibbing et al., 2009). In a meta-analysis that included 9685 patients with ACS from nine different studies, it was found that patients undergoing percutaneous coronary intervention were at a significantly increased risk of experiencing cardiovascular events in the presence of even one reduced function allele (Mega et al., 2010). Allelic variations in other genes, such as *ABCB1*, *CES1*, *CYP2B6*, *CYP2C9*, *P2RY12*, and *PON1*, have also been associated with clopidogrel response, but they still require further research to establish a definitive association (Scott et al., 2013).

Major Depressive Disorder and Antidepressants

Mental illness is a term generally used to refer to a variety of mental and behavioral disorders. Of these disorders, depression contributes significantly to the global burden of disease affecting people from all walks of life. Often referred to as the ''common cold of psychiatry'' (Goodwin, 2008), major depressive disorder has been estimated to affect 350 million people globally (WHO). Symptoms tend to present from a very young age and continue chronically throughout life (Kovacs et al., 2016). This debilitating disorder has a profound impact on day-to-day activities, including work and social interactions, with suicide being common in sufferers of severe depression.

Effective treatment outcome has proved to be challenging, and treatment often results in unfavorable responses and high remission rates (Serretti and Chiesa, 2009). Treatment is, therefore, largely ''trial-and-error'' and difficult at best (Miller and O'Callaghan, 2013). Chemical classes of pharmaceuticals used to treat major depressive disorders include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and recently, drugs that target melatonin and nicotine receptors (Howland, 2011; Ledford, 2011). TCAs and SSRIs are used extensively and make up the bulk of antidepressant prescriptions.

There are several TCAs on the market, all of which are similar in chemical structure and act by inhibiting reuptake of norepinephrine and serotonin. Many ADRs have been associated with TCAs, which lead to poor treatment outcome and discontinuation thereof. ADR symptoms result from multi-receptor binding of TCAs and their metabolites to cholinergic, α-adrinergic, serotonin, histamine, and muscarinic receptors (Hicks et al., 2013). Broadly, the most prominently experienced ADRs are anticholinergic in nature, and they involve the central nervous and cardiovascular systems (Table 2).

Table 2. Common Adverse Drug Reactions Reported for Selected Disease Areas

Disease	*Drug*	*ADME genes*	*Adverse drug reactions*
Cardiovascular disease	Warfarin and clopidogrel	*CYP2C9, VKORC1, CYP2C19*	Severe bleeding, skin necrosis, systemic atheroemboli and cholesterol microemboli, hypersensitivity/allergic reactions, vasculitis, elevated liver enzymes, hepatitis, nausea, vomiting, diarrhea, abdominal pain, skin rash, dermatitis, pruritis, alopecia, and tracheobronchial calcification.[ab]
Major depressive disorders	TCAs (amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline, trimipramine)	*CYP2D6, CYP2C19 (ABCB1, BDNF, FKBP5, GRIK4, HTR1B, HTR2A, PPM1A, SLC6A4, SLC39A14, TGFBR3)*	Anticholinergic symptoms (blurred vision, constipation, dizziness, urinary retention, and xerostomia—tertiary amines > secondary amines (desmethyl-metabolites) > hydroxy-metabolites[c]), central nervous system (delirium, seizures, and dementia), cardiac symptoms (arrhythmias, heart block, orthostatic hypotension, and tachycardia), headache, and sedation.[de]
	SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)	*CYP2D6, CYP2C19 (ABCB1, BDNF, FKBP5, GRIA1, GRIA3, GRIK2, GRIK4, HTR1B, HTR2A, PLCB1, SLC6A4)*	Neurological symptoms (paresthesias, headache, dizziness, and tremor), psychiatric symptoms (anxiety, confusion, hallucinations, and sleep disturbances), gastrointestinal symptoms (nausea and diarrhea), dermatological symptoms (rash, urticarial, and pruritus), fatigue, hyperhidrosis, and edema.[f] In addition, SSRIs have been found to increase depression and promote suicidal tendencies.[g]
Cancer	Fluorouracil, tegafur, capecitabine	*DPYP*	Diarrhea, nausea, vomiting, dehydration, neutropenia, pyrexia, febrile neutropenia, abdominal pain, pulmonary embolism, cardiotoxicity, mucosal inflammation, asthenia, hypotension, anemia, leukopenia, neutropenia, thrombocytopenia, sepsis, decreased appetite, pneumonia, Palmar-plantar erythrodysesthesia syndrome, and osteonecrosis.[h]
HIV/AIDS	Efavirenz[a]	*CYP2B6 (CYP2A6, ABCB1, NR1I3, UGT2B7 CYP3A5, CYP3A4)*	CNS toxicity, drug hypersensitivity rash, elevated ALT and AST levels,[b] Stevens–Johnson syndrome, drug-induced hepatitis, neuropsychiatric effects (depression, delusions), abnormal dreams, dizziness, drowsiness, nausea, headache, fatigue, neural tube defects, and gynecomastia.[i,j,k]

[a]Coumadin package insert (http://packageinserts.bms.com/pi/pi_coumadin.pdf).
[b]Plavix package insert (http://packageinserts.bms.com/pi/pi_plavix.pdf).
[c]Rudorfer et al. (1999).
[d]Teter et al. (2008).
[e]Preskorn et al. (1988).
[f]Spigset (1999).
[g]Gunnell et al. (2005).
[h]Kadoyama et al. (2012).
[i]Whirl-Carrillo et al. (2012).
[j]Max and Sherer (2000).
[k]Orrell (2011).
ADME, absorption, distribution, metabolism, and excretion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system.

The CIPC guidelines for TCAs focus predominantly on *CYP2C19* and *CYP2D6*. The former metabolizes the tertiary amines (e.g., amitriptyline and imipramine) to desmethyl metabolites or secondary amines (e.g., nortriptyline and desipramine), which present with differing clinical features (Hicks et al., 2013). Both secondary and tertiary amines are metabolized by CYP2D6 to hydroxyl-metabolites, which are less active metabolites. The CIPC guidelines, using amitriptyline and nortriptyline as prototypes for all TCAs, recommend that CYP2D6 UMs (*CYP2D6*1/*1xN or *1/*2xN*—activity

score >2) avoid treatment with TCAs, as they are at risk of poor therapeutic efficacy. EMs (*CYP2D6*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5* or **10/*10*—activity score 1.0–2.0) should initiate therapy as recommended. IMs (*CYP2D6*4/*10* or **5/*41*—activity score 0.5) should consider a 25% reduction in the recommended TCA dose and use therapeutic drug monitoring. PMs (*CYP2D6*4/*4, *4/*5, *5/*5* or **4/*6*—activity score 0.0) should avoid TCAs, as they are at risk of ADRs (Hicks et al., 2013). The CIPC guidelines for CYP2C19 with regard to amitriptyline recommend that UMs (*CYP2C19*17/*17* or **1/*17*) should consider alternative therapy, as they are at risk of lack of efficacy. EMs and IMs (*CYP2C19*1/*1* and **1/*2* or **1/*3*, respectively) should initiate treatment as recommended. Poor metabolizers (*CYP2C19*2/*2, *2/*3* or **3/*3*) should consider a 50% reduction in treatment and institute therapeutic drug monitoring. Clinical data regarding the additive effects of *CYP2D6* and *CYP2C19* alleles are still lacking, and although recommendations are provided in the 2013 supplement of the CPIC guidelines for TCAs, these are classified as optional at present.

Similar to TCAs, the SSRIs act by inhibiting serotonin uptake, but differ in that they do not interfere with uptake of norepinephrine and dopamine activity. The end result is that these drugs are better tolerated and have improved safety margins compared with TCAs. Commonly prescribed SSRIs are citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline. The ADRs experienced with SSRI therapy (Table 2) include central nervous system and gastrointestinal symptoms, and sexual dysfunction, with the frequency of symptoms varying with each drug.

Citalopram, escitalopram, and sertraline are extensively metabolized by CYP2C19 to form metabolites with less SSRI activity. Fluoxetine and paroxetine are largely metabolized by CYP2D6, and their metabolites also have SSRI activity. Fluoxetine metabolism is, however, further complicated by the fact that it is also a CYP2C19 substrate, producing active norfluoxetine enantiomers (Whirl-Carrillo et al., 2012).

For treatment with citalopram, escitalopram, and sertraline, the CPIC recommends that ultra-rapid CYP2C19 metabolizers consider alternate treatment, as they are at risk of poor efficacy. EMs and IMs should continue with treatment as recommended, and PMs should reduce dosage with titration by 50% given that they are at risk of experiencing ADRs. With respect to paroxetine and fluoxetine, ultra-rapid CYP2D6 metabolizers should not be prescribed paroxetine and fluvoxamine, as efficacy is likely to be low. EMs and IMs should continue with treatment as recommended, and PMs should be prescribed an alternative treatment as they are at risk of experiencing ADRs (Hicks et al., 2015).

Cancer and Chemotherapeutic Agents

The fluoropyrimidines (5-fluorauracil, capecitabine, tegafur) are some of the oldest and most widely used chemotherapeutic agents. They are indicated for the treatment of solid tumors such as colorectal, breast, and pancreatic cancers (Caudle et al., 2013). It has been reported that up to 40% of patients on treatment with 5-fluorouracil (5-FU) develop life-threatening toxicities (Meta-Analysis Group in Cancer et al., 1998). The most frequently observed toxicities are hematological (e.g., leukopenia and thrombocytopenia) and gastrointestinal (e.g., mucositis, diarrhea, nausea, and vomiting) (Amstutz et al., 2009). Although less common (<55), cardiovascular-related ADRs are also well described, including myocardial ischemia and atrial thrombosis, cardiomyopathy, and malignant arrhythmias (Malet-Martino, 2002; Virani et al., 2016).

Capecitabine and tegafur are prodrugs of 5-FU, and once converted, they are metabolized in a similar manner. 5-FU is first converted to dihydrofluorouracil by the dihydropyrimidine dehydrogenase (DPD) enzyme, which is encoded by the *DYPD* gene (Thorn et al., 2011). Dihydrofluorouracil is then converted to other metabolites (β-ureidopropionate, fluoro-β-alanine) that are excreted in the urine (Thorn et al., 2011).

Since DPD is responsible for more than 80% of the metabolism of 5-FU (Diasio and Harris, 1989), genetic variation in *DPYD* plays a central role in determining efficacy and the extent of ADRs induced by this drug. Loss-of-function alleles of *DPYD*, which include the **2A*, **13*, and rs67376798 variants, are reported in up to 5% of the population (Morel et al., 2006), and they render patients at risk for over exposure to 5-FU and, therefore, toxicity. Homozygous carriers are considered to be at high risk of toxicity, whereas heterozygous carriers present with intermediate DPD activity and a decreased risk of ADRs.

Dosing guidelines for 5-FU and its prodrugs are provided by the CPIC (Caudle et al., 2013) and the Dutch Pharmacogenetics Working Group (DPWG) (Swen et al., 2011). Both groups recommend the use of alternative drugs in patients who are homozygous for inactive alleles. In patients who are heterozygous for inactive alleles, the CPIC suggests that clinicians consider a 50% reduction in the fluorouracil starting dose. The DPWG recommends the use of alternative drugs or a 50% reduction in dose in individuals carrying one inactive or decreased activity allele. It further suggests that the dose can be increased to achieve efficacy in patients who do not develop toxicity (Caudle et al., 2013). However, some patients may develop toxicity in the absence of risk alleles due to other genetic and environmental factors.

Although the FDA has added the pharmacogenomics testing label to these anticancer drugs, the positive predictive value and sensitivity of the *DPYD**2A genetic test for predicting toxicity are only around 50% and 31%, respectively. However, if the *DPYD**13 and rs67376798 variants are included, the predictive value increases to 62% (Morel et al., 2006; Schwab et al., 2008).

HIV Infection and Antiretroviral Therapy

HIV infection remains a major global health concern. Nearly 37 million people live with HIV, and despite the fact that remarkable strides have been made in combating the disease, more than 1 million people still succumb to this disease annually (UNAIDS). Combination antiretroviral therapy (cART) has proved to be very effective, but it comes with several disadvantages, particularly the need for life-long adherence and the associated side effects and ADRs. Of the more than 30 antiretroviral drugs utilized in clinical practice, efavirenz and abacavir are widely used and have well-described pharmacogenomic associations.

Efavirenz-based regimens are first-line cART, and hence the majority of HIV patients are currently on such regimens. The drug is a non-nucleoside reverse transcriptase inhibitor (NRTI), and it hence prevents conversion of the single-stranded viral RNA into DNA. Although central to

cART, efavirenz is associated with a high frequency of side effects and ADRs, including rash, hepatotoxicity, lipodystrophy, and several neuropsychiatric symptoms (Table 2). The latter symptoms manifest as anxiety, confusion, irritability, abnormal dreams, and suicide (Abah et al., 2015; Mollan et al., 2014). Therapeutic concentrations are recommended to be between 1000 and 4000 ng/mL, and with concentrations on either end of this spectrum, failure to respond to therapy and ADRs can be expected. From an economic perspective, not only is it costly to manage these ADRs, but also it is considerably more expensive to make use of second-line cART regimens, which are required in up to 20% of patients (Scourfield et al., 2012).

The metabolism and variability in efavirenz drug exposure has previously been reported by many groups to be associated with genetic variation in *CYP2B6* and *CYP2A6* (Čolić et al., 2015). CYP2B6 is the most active enzyme in metabolizing efavirenz (Ward et al., 2003), and it is associated with considerable variation at a genetic level. The *c.516G>T* and *c.983T>C* variants have been shown to be predictive of reduced enzyme activity and higher plasma concentrations (Swart et al., 2015).

Although no CIPC guideline exists as yet for efavirenz, it has been shown that *CYP2B6* genotyping, together with gender and age, explains up to 55% of inter-individual variability in efavirenz clearance (Dhoro et al., 2015). The standard daily dose prescribed for efavirenz is 600 mg/day, and with a well-designed multivariate modeling approach the authors calculated that a decrease in daily dose to 200 mg/day in patients who are homozygous for the *CYP2B6*6* minor allele would be adequate to maintain therapeutic levels and to reduce the risk of ADRs (Dhoro et al., 2015; Nemaura et al., 2012).

Abacavir is an NRTI that has been successfully employed in cART or on its own for nearly two decades. Numerous cases of hypersensitivity reactions to abacavir have been reported (Sousa-Pinto et al., 2015), often resulting in severe and potentially fatal reactions. The reactions often include at least two of the following symptoms: fever, rash, fatigue, cough, dyspnea, and gastrointestinal symptoms such as nausea, vomiting, and abdominal pain. Up to 8% of patients experience abacavir hypersensitivity within the first 6 weeks of treatment (Martin et al., 2014).

The *HLA-B* gene belongs to the major histocompatibility complex (MHC) gene family, which consists of class I, II, and III subgroups. The *HLA-B* gene encodes HLA class I molecules that present peptides to immune cells. In infected cells, a foreign protein is presented to immune cells, which, in turn, triggers the immune response. In cases of hypersensitivity, abacavir is responsible for triggering a similar immune reaction through interaction with MHC molecules.

HLA genes are highly polymorphic, and more than 1500 *HLA-B* alleles have been reported. In the context of abacavir, the *HLA-B**57:01 variant allele is the most relevant, and carriers are at higher risk of hypersensitivity. The variant shows co-dominant expression, and individuals are either positive or negative with no intermediate phenotype. The CPIC has published guidelines, and a recent update thereof, for use of abacavir in HIV patients (Martin et al., 2012, 2014). It is recommended to screen HIV patients for *HLA-B**57:01 to reduce the risk of hypersensitivity. Patients positive for one or two HLA-B*57:01 alleles should not be treated with abacavir, and an alternative antiretroviral drug should be prescribed.

Outlook for the Next Decade

Numerous reports have provided promising data and support for the implementation of pharmacogenomics-guided drug therapy. This has resulted in the establishment of more than 30 CPIC guidelines where definitive associations have been demonstrated. The most apparent benefits to be derived from implementing these guidelines into routine clinical practice are improved patient care and compliance. These benefits can also be interpreted as being opportunities, and similarly, we present what we consider to be the top 10 crosscutting opportunities and challenges in the next decade for the field of pharmacogenomics (Table 3). These opportunities and challenges have broad applicability, are independent of the drug class, and mostly pertain to infrastructure, study design, policy, and science culture in the early 21st century. Furthermore, they are not listed in any specific order and are grouped for discussion purposes.

The opportunity to improve patient care naturally implies a reduction in side effects and ADRs (elements of safety), as well as achieving the desired drug efficacy. An improvement in patient compliance is likely to accompany this. From an economic point of view, these improvements would result in decreased healthcare expenditure for patients, medical insurers, and governments alike. Moreover, improved recovery

Table 3. Top 10 Opportunities and Challenges of Precision Medicine and Pharmacogenomics in the Context of Adverse Drug Reactions

Opportunities
1. Improvement in patient care with respect to both safety and efficacy
2. Improved patient compliance
3. Decreased healthcare costs (mostly due to the reduced occurrence of ADRs)
4. Relieving pressure on healthcare facilities
5. Improvement in economic productivity
6. Improved risk stratification of patients
7. Development of novel dosing algorithms (and continuous improvement of existing ones)
8. Improved healthcare guidelines and policies
9. Development of innovative applications and online tools to engage, inform, and educate the public
10. Establishment of well-curated and easily accessible data resources for healthcare professionals
Challenges
1. Establishment of necessary laboratory infrastructure and expertise
2. Turn-around time on testing and interpretation of genomic data
3. Buy-in from clinicians and integration of precision medicine testing into routine clinical practice
4. Cost of testing and willingness of medical insurers to reimburse
5. Training of genetic counselors
6. Management of big data (storage and processing power)
7. Development of bioinformatics and clinical informatics expertise
8. Protection of personal information
9. Development of reliable *in silico* prediction tools
10. Design of definitive randomized clinical trials to demonstrate efficacy of pharmacogenomics testing

ADRs, adverse drug reactions.

rates and decreased hospitalization means relieving pressure on healthcare facilities, decreased time off work, and an increase in economic productivity.

Access to precision medicine and pharmacogenomics tools will enable clinicians to improve the risk stratification of patients and accordingly prescribe medications that have a better chance of showing benefit. For this to come into effect and to be reliable, the most effective means would be via the provision of dosing algorithms, and there is, hence, great scope and opportunity for researchers to develop novel dosing algorithms and to continuously improve on those that exist. As previously described here, the warfarin model is an excellent example of this paradigm. In the medium to longer term, precision medicine offers the opportunity for health authorities to improve on their current treatment guidelines and policies, thereby establishing a framework for improving the local healthcare service offering.

Great opportunities lie within the field of information and communication technology, where the main focus is on making genomic data easily accessible and meaningful for both patients and healthcare providers alike. In today's environment, where software applications are readily available via mobile devices, there will certainly be a wealth of opportunities for software developers to introduce novel applications for the public to access their genomic data online, and to be informed and educated on concepts related to precision medicine. In addition, by integrating genomic data with electronic health records and patient medical histories, clinicians and healthcare providers could have immediate access to comprehensive data resources to improve treatment decision making.

Although the opportunities for precision medicine are certainly very promising, these are matched by several challenges. For precision medicine to be realized on a global scale, it is essential that the requirements for implementation receive careful consideration. In low- to middle-income countries, healthcare infrastructure is one of the greatest challenges. Paradoxically, as these countries become more economically active, access to basic healthcare improves, but so does the incidence of noncommunicable disease. Management of this double burden of disease poses significant challenges in resource-poor environments. Implementation of pharmacogenomic practices in this setting will be challenging and may not feature high on the list of priorities for local health authorities.

The situation in developed countries is, however, very different, where precision medicine is starting to gain noticeable traction. Implementation is certainly feasible and the benefits are far more likely to have a measurable impact on healthcare systems as a whole. The challenges to be faced here include quick turn-around times on testing, the need for adequate training of laboratory staff, and the provision of easy-to-interpret test results. These challenges are by no means trivial, and success will be dependent on how easy and robust the technology will be for early adopters. This will go a long way in convincing clinicians to integrate and apply precision medicine tools into their routine clinical practice.

Other elements to bear in mind from an implementation point of view are the costs associated with testing and the dissemination of genomic data to patients. In the first instance, although the costs for generating sequence data have decreased noticeably, they are still too high for most health authorities and medical insurers to include into their treatment plans. Also to bear in mind are the costs for genetic counselors, who will play a critical role in ensuring that genomic information is transmitted to patients in an accurate and sensitive manner. Notably, there is a great shortage of genetic counselors worldwide, and if precision medicine is to be rolled out to the extent anticipated, a big drive to train and qualify such a workforce is required.

With the advancement of genomic technologies in recent years, the field has evolved to accumulate astronomical amounts of sequence data over short periods of time. For the first time, it is possible to simultaneously analyze genomic data for any of the more than 300 genes encoding proteins involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. Notably, and with the exception of the drug-metabolizing enzymes, we know very little about the genomic architecture of ADME genes and how variation may influence drug response. As an example, in a recent study by Mizzi et al. (2014), more than 16,000 novel variants in 231 ADME genes were identified by using a whole-genome sequencing approach. Although there is tremendous enthusiasm and a rush to generate similar datasets, the complexity of its analysis and the sheer mass of data to be managed are proving to be challenging. However, given that this is the ''engine'' of precision medicine, so to speak, it is central to its success.

From a hardware point of view, the storage and backup of data, as well as the computing power to process/analyze such data require considerable financial investment. Even though off-site or cloud-based solutions are available to store and analyze genomic data, these are still too costly for many research groups. Another significant challenge is the level of bioinformatics expertise required, which is not simply a logical extension of the role of a biologist or clinician. This is a highly specialized skills set, and the ability to extrapolate meaningful findings from raw genomic data requires a considerable level of expertise. Furthermore, the genomic data need to be integrated with clinical and laboratory findings, which requires a cross-platform and often institutional integration of information. The protection of personal information is also very important here, and a high level of security is required to ensure that sensitive patient information remains private.

The reliability of genomic *in silico* prediction tools is tantamount to the success of pharmacogenomics and precision medicine, and in order to train up these programs, a substantial amount of well-curated genomic and phenotypic data is required. Furthermore, these data should be generated locally and in the environments where the precision medicine testing is to be implemented so that the genomic variation of local communities can be accounted for.

The role of ethnicity and genetic background has been shown to be very relevant. As examples, and in the context of the associations discussed in this article, *CYP2C9*2* and *3 alleles are the most frequent in Caucasian (8–20%) and Afro-Asiatic populations of northern Africa; whereas these same alleles are mostly absent or present at frequencies of less than 3% in Asians and populations of African descent (Alessandrini et al., 2013). A *CYP2D6* gene deletion (*CYP2D6*5*) is generally present at frequencies of less than 10% in most populations, but it is as high as 19% in certain African populations (Alessandrini et al., 2013). In contrast, the *CYP2D6*4* loss-of-function allele is present in $\sim$20% of Caucasians; whereas it is less frequent in African (up to 8%) and Asian populations (0–2.7%). Furthermore, *CYP2D6* gene duplications are more pronounced in Ethiopians (16%) and Algerians (28%) when

compared with other populations globally (Alessandrini et al., 2013). Finally, the *CYP2B6*6* allele seems to be more frequent and relevant in African populations, where it was reported at frequencies of 32.8% and 46.9% in African-Americans and a Ghanaian population, respectively. This same allele was found to be present in 25.6% of Caucasians and in 15.9–18.0% of Asians (Klein et al., 2005). Accounting for these inter-ethnic differences will be important if one is to refine and implement precision medicine globally. In line with this and from an African perspective, the recently established ''African Pharmacogenomics Consortium'' is a very positive initiative that plans to coordinate and to be the main driver in establishing local pharmacogenomics guidelines on the continent.

Finally, to ensure the translation of pharmacogenomics-guided treatment regimens into routine clinical practice, the efficacy (or benefits) should be demonstrated in the context of a randomized clinical trial. The design of these studies is, in itself, a challenge, which requires careful attention and foresight if the test in question is to ever reach the clinic and be reimbursed by health insurers.

It is safe to say that the next decade will be a period of massive genomics data generation and advances in our capabilities to analyze these data. Those studies with comprehensive phenotypic data collection and thoughtful study design will prove to be the most useful. With cautious implementation, precision medicine should start delivering on its promise and make a meaningful contribution to patient management.

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Address correspondence to:
Michael S. Pepper, MBChB, PhD, MD
Department of Immunology
Faculty of Health Sciences
Institute for Cellular and Molecular Medicine
South African Medical Research Council Extramural Unit for Stem Cell Research and Therapy
University of Pretoria
P.O. Box 2034
Pretoria 0001
South Africa

E-mail: michael.pepper@up.ac.za

Abbreviations Used

5-FU = 5-fluorouracil
ACS = acute coronary syndrome
ADME = absorption, distribution, metabolism, and excretion
ADP = adenosine diphosphate
ADRs = adverse drug reactions
cART = combination antiretroviral therapy
CPIC = Clinical Pharmacogenetics Implementation Consortium
CVDs = cardiovascular diseases
DPD = dihydropyrimidine dehydrogenase
DPWG = Dutch Pharmacogenetics Working Group
EMs = extensive metabolizers
FDA = Food and Drug Administration
GGCX = gamma-glutamyl carboxylase
HIV = human immunodeficiency virus
IMs = intermediate metabolizers
INR = international normalized ratio
IWPC = International Warfarin Pharmacogenetics Consortium
MHC = major histocompatibility complex
NRTI = nucleoside reverse transcriptase inhibitor
PMI = precision medicine initiative
PMs = poor metabolizers
SSRIs = selective serotonin reuptake inhibitors
TCAs = tricyclic antidepressants
UCHC = University of Connecticut Health Center
UMs = ultra-rapid metabolizers
VKORCI = vitamin K epoxide reductase complex subunit 1
WHO = World Health Organization