Realities and expectations of pharmacogenomics and personalized medicine: impact of translating genetic knowledge into clinical practice

The implementation of genetic data for a better prediction of response to medications and adverse drug reactions is becoming a reality in some clinical fields. However, to be successful, personalized medicine should take advantage of an informational structured framework of genetic, phenotypic and environmental factors in order to provide the healthcare system with useful tools that can optimize the effectiveness of specific treatment. The impact of personalized medicine is potentially enormous, but the results that have so far been gathered are often difficult to translate into clinical practice. In this article we have summarized the most relevant applications of pharmacogenomics on diseases to which they have already been applied and fields in which they are currently emerging. The article provides an overview of the opportunities and shortcomings of the implementation of genetic information into personalized medicine and its full adoption in the clinic. In the second instance, it provides readers from different fields of expertise with an accessible interpretation to the barriers and opportunities in the use/adoption of pharmacogenomic testing between the different clinical areas.

KEYWORDS: adverse drug reaction ■ cancer ■ cardiovascular disease ■ genetic test ■ infectious disease ■ personalized medicine ■ pharmacogenomics ■ psychiatry

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Clinicians have known for decades that substantial interindividual variability can occur in the clinical response to drug treatments for acute and chronic diseases. The proportion of patients who respond positively to their medications is, on average, only approximately 50% (ranging from 25 to 60%), implying that the rest of the patient population is not receiving the proper medication or is suffering from significant therapeutic delays by switching from one medication to another until appreciable clinical benefit is attained [1]. Furthermore, the onset of side effects can manifest itself in drastically different patterns within the same therapeutic regime. Adverse drug reactions (ADRs) represent a frequent event estimated to be between the fourth and sixth leading cause of death in the USA, with fatal ADRs occurring in 0.32% of patients [2]. Data from the UK [201] show that ADRs also have a cumbersome economic burden on national healthcare systems, leading to costs equivalent to GB£380 million a year. ADRs can be unpredictable, and broader knowledge of predisposing factors would be of great help in increasing prevention capabilities.

It has been shown that the great heterogeneity in the phenotypic expression of the drug treatment response trait and ADRs is determined by a complex interplay of multiple genetic variants and environmental factors [3,4]. The complex nature of treatment response traits greatly increases the need for the design of personalized prescriptions that should take advantage of the creation of a structured informational framework of phenotypic, environmental and genetic data, ultimately leading to the reduction of the very high incidence of ADRs and therapeutic failure [5].

Over the years, research on the genetic predictors of drug response has involved an ever wider array of molecular targets, so that the original definition evolved from pharmacogenetics, which assumes investigation of a specific or limited number of candidate genetic markers, to pharmacogenomics, reflecting the broader perspective of analyzing molecular determinants at the genome-, transcriptome- and proteome-wide level. Currently, pharmacogenomics is being adopted as a unique tool for achieving different goals. On one hand, pharmacogenomic approaches are used to identify biomarkers and targets of currently prescribed medications as a source of new molecules suitable for the drug-development process. On the other hand, pharmacogenomic-based techniques are used as diagnostics tools to select and/or dose currently available therapeutics. However, these discoveries do not lead to personalized therapeutics unless predictive tests are proactively codeveloped, together with new drug candidates [6,7].

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Personalized medicine has been cleverly defined as 'the delivery of the right drug to the right patient at the right dose' and is consequent to the full implementation of pharmacogenomics into the clinic [8]. More specifically, personalized medicine refers to the development of treatment regimes decisions based on a wide set of data comprising patients' personal and family history of disease and treatment response, exposure to environmental factors as well as their interaction with individuals' genomic profile in determining the drug response and disease phenotype. In this context, pharmacogenomics paves the path to personalized medicine, consisting of the application of genetic information in order to develop targeted therapies by means of the identification of those individuals unlikely to respond to a drug or likely to respond adversely to that same drug.

A detailed review of pharmacogenomic applications to different disorders and medical disciplines lies outside the scope of this article. For this purpose, the reader is referred to numerous review articles for each area. Instead, we selectively review the issues pertaining to the applications of pharmacogenomics and personalized medicine in clinical and research settings. Specifically, we address the magnitude of their impact on diseases to which they have already been applied, such as cancer and cardiovascular diseases, or fields where the application of pharmacogenomics into the clinical practice is currently emerging, such as psychiatry or hemoglobinopathies. Finally, we review the educational, economic and ethical issues related to the inclusion of pharmacogenomics and personalized medicine into the public healthcare system. The article contributes to the current literature by offering an overview of the opportunities and shortcomings of the implementation of genetic information in personalized medicine and its full adoption in the clinic. In the second instance, it provides readers from different fields of expertise with an accessible interpretation of the barriers and opportunities in the use/adoption of pharmacogenomics between the different clinical areas.

Reality & expectations of pharmacogenomics in the clinic

For the past five decades, the goal of clinical pharmacology has been to individualize the dosage of many drugs with low therapeutic indices. The identification of correlations between gene mutations and drug levels were derived from clinical empirical observations, especially in patients affected by monogenic Mendelian diseases. After the establishment of the Human Genome Project, the exploration of genomic variability has been providing a plethora of new targets suitable for drug development in different fields, including cancer, cardiovascular diseases, infectious diseases and neuropsychiatric disorders [9]. However, despite the availability of the huge amount of genomic data, much remains to be discovered in regards to the function encoded by the gene and how this affects the phenotype of disease and treatment response. In this context, pharmacogenomics is instrumental in facilitating the mediation between basic research and the establishment of clinical usefulness, as well as in the creation of more effective and cost-saving paths for the development of new drugs [10,11].

Aware of this aspect, the pharmaceutical industry has recently started to implement pharmacogenomics into the drug-development pipeline by correlating quantitative measures derived from treatment-specific diagnostic testing and the associated therapeutic outcome. Specifically, rather than defining diagnostic markers to select or predict individual patients who will respond to therapies, prospective application of pharmacogenomics in the pharmaceutical pipeline has been introduced in Phase IIA/IIB of clinical trials with the aim of accelerating and facilitating the development of new molecules, while reducing the associated risks and costs [12]. In this respect, pharmacogenomic tests based on the genotype of an individual can be considered as a type of biomarker test. The term biomarker can be referred to any useful characteristic that can be measured and used as an indicator of a normal biologic process, a pathogenic process or a pharmacologic response to a therapeutic agent [13]. Biomarkers have been proposed as powerful tools, given their capability of bridging animal and human data, guiding drug dose and adjustments, guarding safety in animal models and in early clinical development, and establishing initial proof of efficacy in proof-of-concept studies [11]. However, to be successful tools in clinical practice, biomarkers should present high-positive and negative-predictive values, be simple, easy to repeat, sourced from easily accessible body fluids and tissues, and cost effective [11]. These criteria can be easily translated in the field of pharmacogenomics, whereas, even if testing in human patients can reach a high level of accuracy and precision, cost–effectiveness, accessibility and management of data are still areas of concerns for its full implementation into clinical practice.

However, the current barriers for the adoption of pharmacogenomics into the healthcare system and the opportunities that might be originated present different concerns and operate differently among the diverse clinical areas. For instance, pharmacogenetic tests are currently used for defining the response profile or the dose of drugs, such as warfarin, with known mechanisms of action and targets. However, while a validated genetic algorithm has been created, there are still some concerns regarding its validity and reliability, and there appear to be major barriers to the uptake of the tests despite the US FDA relabeling warfarin, indicating that the genotyping of specific genes (discussed in another section of this article) can assist in optimizing warfarin dosing. On the other hand, opportunities and barriers to the application of pharmacogenomics to the treatment of other complex diseases, such as psychiatric disorders, is more intended for the identification, development and validation of meaningful biomarkers, and their clinical application to the existing treatment and the development of novel therapies.

In the next sections, we highlight the most promising applications of pharmacogenomics by providing some examples of diseases in which it has been implemented in the clinic for defining risk for ADRs, dosages and response to medications, and in fields which it is currently emerging or in which it is used more as a discovering tool.

Pharmacogenomics for cancer therapeutics

The past decade has seen significant movement beyond traditional techniques in tissue analysis and cancer patient stratification. Cancer is very heterogeneous, varying both genetically and phenotypically among patients who have identical types and stages of the disease. Furthermore, a significant proportion of breast cancer patients are not responding to chemotherapy uniformly, something that is likely to be genetically determined [14]. Individualized therapies for various types of solid tumors are now a reality. The first steps have involved the evolution of tumor classification, disease prognosis, molecularly targeted treatment and response to therapy based on molecular features. In this regard, diagnostic tests have been developed and are now readily available for several treatment procedures in cancer patients.

Trastuzumab, a monoclonal antibody (MAb) blocking HER2 (also known as ERBB2) receptors, is indicated for breast cancer. Pharmacogenetic testing has become an integral part of the treatment of breast cancer with trastuzumab. In this case, however, variable expression of the *HER2* receptor gene determines whether or not a patient will respond to trastuzumab. HER2, a receptor for hormones stimulate tumor growth, is overexpressed in approximately a quarter of breast cancer patients. Overexpression of the *HER2* oncogene is correlated with a poor prognosis, increased tumor formation and metastasis, as well as resistance to chemotherapeutic agents. HER2 testing predetermines patients who overexpress HER2 and who will respond to trastuzumab.

Erlotinib (Tarceva®) and gefitinib (Iressa®) are tyrosine kinase inhibitors that have been on the market for several years and are designed to target the EGF receptor (EGFR), which has been shown to play a role in predisposing to lung cancer. A recent study from east Asia has pointed out the role of an *EGFR* mutation as a predictor of the improved progression-free survival (PFS) with gefitinib in comparison with carboplatin–paclitaxel therapy [15]. Response to gefitinib was almost entirely limited to the mutation-positive group, whereas mutation-negative patients benefited from the chemotherapy. Another study from Europe has shown the feasibility of large-scale screening for *EGFR* mutations in patients with advanced non-small-cell lung cancer (NSCLC) for selection to be treated with erlotinib therapy [16]. Taken together, these reports suggest that first-line tyrosine kinase inhibitor agents should be considered for carefully selected subgroups of patients of east Asian and non-east Asian origin affected by NSCLC. Other MAbs that are used for colorectal cancer treatment are cetuximab and panitumumab, both directed against EGFR. Cetuximab is a chimeric MAb indicated for the treatment of patients with metastatic colorectal cancer (mCRC). Panitumumab is a fully humanized MAb utilized in the treatment of patients with EGFR-expressing mCRC. Mutations in *K-ras* are thought to cause acquired activation of the Ras/Raf/MAPK pathway, independent of EGF binding. This in turn leads to a lack of activity of EGFR inhibitors [17]. The relationship between *K-ras* mutations and survival investigated in mCRC patients treated with cetuximab showed that the presence of a *K-ras* mutation was an independent predictor for shorter PFS and overall survival [18,19]. A similar relationship between the presence of a *K-ras* mutation and a lack of response was also demonstrated with single-agent panitumumab [20]. In addition to *K-ras* status, other molecular markers of cetuximab

and panitumumab efficacy are being investigated. Increases in *EGFR* gene copy number have also been correlated with tumor response rate [21]. Although conflicting evidence does not yet allow us to translate these findings into clinical practice, ongoing investigations will clarify the importance of these differences in the *EGFR* gene sequence and copy number.

Irinotecan has been approved for the treatment of advanced colorectal cancer, both as first-line therapy in combination with 5-fluorouracil (5-FU) or oxaliplatin, and as salvage treatment in 5-FU-refractory disease. The drug has limiting toxicities, comprising diarrhea and severe neutropenia. The *UGT1A1*28* polymorphism is associated with reduced *UGT1A1* gene expression and decreased glucuronidation of the active metabolite SN38. This results in increased toxicity owing to increased blood levels of the active metabolite. The *UGT1A1*28* polymorphism is characterized by the presence of an additional TA repeat in the TATA sequence of the *UGT1A1* gene promoter, ($[TA]_7$, instead of $[TA]_6$) [22]. Patients with the 7/7 genotype are at higher risk of developing irinotecan-associated neutropenia and diarrhea. In July 2005, the FDA recommended an addition to the irinotecan package insert to include *UGT1A1*28* genotype as a risk factor for severe neutropenia. This decision was based on the findings of four pharmacogenetic trials assessing the relationship between irinotecan toxicity and *UGT1A1*28* genotype. *XRCC1* genotype polymorphisms were more likely to predict overall survival and objective response in mCRC patients treated with irinotecan-based chemotherapy [23,24].

The antileukemics 6-mercaptopurine and 6-thioguanine, along with the immune suppressant azathioprine, are metabolized by the thiopurine methyltransferase (TPMT) enzyme. Patients with inherited TPMT deficiency suffer severe, potentially fatal hematopoietic toxicity when exposed to standard doses of thiopurine drugs. A pharmacogenomic test enables physicians to predetermine patients' TPMT activity levels based on whether or not they have inherited the alleles associated with TPMT deficiency. The test classifies patients according to normal, intermediate and deficient levels of TPMT activity. Concordance between genotype and phenotype approaches 100%. Patients classified as having normal activity, namely approximately 90% of patients of African and Caucasian descent, are treated with conventional doses. Lower doses are tailored to avoid toxicity in deficient and intermediate patients, who represent approximately 10% of each of these populations and who are liable to suffer exaggerated, potentially life-threatening toxic responses to normal doses of azathioprine and thiopurine drugs [25]. The *TPMT* genetic test has been well documented in the effective clinical management of patients with acute lymphoblastic leukemia (ALL).

Pharmacogenomics for cardiovascular disease

The field of cardiology lagged behind in pharmacogenomics in the 1990s, although in recent years it is growing quickly, thanks to discoveries that appear to hold great promise for the improvement of clinical applications of two antithrombotic drugs, the anticoagulant drug warfarin and its analogs, and the antiplatelet agent clopidogrel.

Coumarinic oral anticoagulants (COAs), namely warfarin, acenocoumarol and phenprocoumon, constituted the standard worldwide oral anticoagulant treatment for thromboembolic disorders for more than 60 years. Despite their indisputable effectiveness, COAs have a narrow therapeutic window and are associated with high risk of major bleeding, especially during the initial phase of treatment. COAs are one of the leading causes of emergency hospitalizations worldwide, and there is substantial individual variation in response to COAs, necessitating frequent monitoring and dosage adjustment [26]. Several factors are known to contribute to interindividual COA dose variability, including age, sex, BMI, smoking, vitamin K intake and concomitant drug therapy [27].

Evidence accumulated during the last decade suggests that interindividual COA dose variability is also significantly influenced by genetic variations in two enzymes, namely *CYP2C9*, the enzyme that metabolizes COA, and vitamin K epoxide reductase (VKORC1), the pharmacologic target enzyme of these drugs [28–30]. The variant alleles *CYP2C9*2* and **3* result in decreased CYP2C9 enzymatic activity, affecting coumarin pharmacokinetics, while the *VKORC1* -1639G>A polymorphism influences pharmacodynamic response to coumarins [31]. These polymorphisms, are the major genetic determinants of COAs response variability [28,29].

Several pharmacogenetic-based dosing algorithms incorporating *CYP2C9* and *VKORC1* genotype information have been proposed for warfarin, including those by Sconce and coworkers in 2005, and Gage and coworkers in 2008 [32,33]. The latter algorithm has

been made available online and can be freely used [202]. Recently, the International Warfarin Pharmacogenetics Consortium used clinical and genetic data from 4043 patients to create a dosing algorithm that was then validated in a cohort of over 1000 patients [34]. However, to the best of our knowledge, information on validated pharmacogenetic-based clinical algorithms for acenocoumarol and phenprocoumon is still lacking.

Results from four small-scale prospective trials of genotype-guided warfarin dosing showed a tendency towards improvement during warfarin therapy initiation, but have not convincingly demonstrated the potential benefit of pharmacogenetic-guided dosing on treatment outcome [35–38]. Additional randomized trials have already started. The clinical trial registry site of the NIH lists three small clinical trials currently recruiting patients, to assess the clinical benefits of pharmacogenetic-guided dosing of warfarin in Singapore, Turkey and the USA [203]. Moreover, one large randomized trial in the USA (Clarification of Optimal Anticoagulant through Genetics [COAG]) is about to start recruiting patients [204]. These studies are expected to further elucidate the clinical utility of pharmacogenetic-guided dosing of warfarin. For acenocoumarol and phenprocoumon, the other two COAs prescribed in Europe in addition to warfarin, no data from prospective pharmacogenetic clinical trials are available. To fill this gap, a trial is about to start in Europe, supported by the European Commission Framework Programme 7. The European Pharmacogenetics of Anticoagulant Therapy (EU-PACT) trial will involve seven European countries and will start recruiting patients in early 2010 [39] to assess the safety, clinical utility and cost–effectiveness of a newly developed pharmacogenetic-guided dosing algorithms for warfarin, acenocoumarol and phenprocoumon in 3000 patients, with a follow-up period of 3 months.

In 2005, the Clinical Pharmacology Subcommittee of the FDA Advisory Committee for Pharmaceutical Science in the USA recommended that the FDA relabel warfarin, indicating that *CYP2C9* and *VKORC1* genotyping can assist in optimizing warfarin dosing. The FDA relabeled warfarin with genomic information, in August 2007. The revised label for warfarin states that lower doses may be best for patients with variations in one or both of these genes [205]. However, this has yet to lead to a change in guidelines by specialist societies such as the American College of Chest Physicians (IL, USA), owing to the lack of sufficient randomized data from prospective studies [40].

Clopidogrel is the standard of care for acute coronary syndromes and is the second best selling drug in the world. It is indicated in patients undergoing percutaneous coronary interventions with or without stenting, and is also used for the reduction of atherothrombotic events in patients with recent myocardial infarction, recent stroke or diagnosed peripheral arterial disease [41,42].

Nonresponsiveness to clopidogrel is widely recognized and is related to recurrent ischemic events; approximately 25% of patients receiving clopidogrel experience a subtherapeutic antiplatelet response associated with increased risk of recurrent ischemic events [43–45]. There is growing evidence that the response to clopidogrel may be determined by the *CYP2C19* genotype [46–48]. Specifically, it was shown that the *CYP2C19*2* allele, which leads to impaired CYP2C19 function, is associated with a marked decrease in platelet responsiveness to clopidogrel [49]. This finding was confirmed by two *post hoc* clinical trial analyses in the substudies of Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 (465 participants) and Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON)-TIMI 38 (1477 participants) [50,51] and in cohort studies (6489 participants) [52–55]. Consequently, in May 2009, the FDA relabeled the drug information for clopidogrel to highlight the impact of *CYP2C19* genotype on the drug's pharmacokinetics, pharmacodynamics and clinical response [56,206]. Recently, a novel allelic variant, *CYP2C19*17*, resulting in increased transcriptional activity of *CYP2C19* and increased enzymatic activity of the enzyme, was discovered [57] and appears to be quite common in Caucasian populations (prevalence: ≤30%) [58].

Pharmacogenomics for psychiatric diseases

Since the response to psychotropic medication is a complex trait, the identification of key phenotypic measures for its definition is still a major issue in psychiatry. As a consequence, pharmacogenomics has as yet been only partially implemented in the clinical setting, and personalized medicine is still far from being achieved in this field. In this section, we briefly summarize the most promising data from pharmacogenomics of response to psychotropic medications that have the potential for the development of personalized treatment.

To date, a large number of pharmacogenetic studies in psychiatry have provided intriguing results, mostly for genes encoding phase I metabolic enzymes. Most psychiatric drugs are metabolized by the cytochrome P450 isoenzymes. Specifically, antidepressants and antipsychotics are mainly oxidized by CYP2D6, CYP1A1, CYP3A4, CYP2C9 and CYP2C19. A number of studies reported that *CYP2D6* polymorphisms predict side effects and metabolic ratios of the antipsychotic risperidone but do not predict response to it or to clozapine [59–62]. It has also been shown that the metabolism of haloperidol is significantly reduced in poor metabolizer (PM) patients [63]. While variants in CYP1A2 are responsible for decreased enzyme activity [64], the response to clozapine, one of the CYP1A2 substrates, does not seem to be influenced by these polymorphisms [65].

In addition to predicting metabolic capacity to a certain extent, the genotyping of *CYP2D6* gene can also assist health professionals in the decisional process of identifying patients who need to be monitored for serum levels or for the potential onset of ADRs. A number of findings have also demonstrated that *CYP2D6* genetic variants correlate with serum levels of risperidone and the antidepressants venlafaxine, nortriptyline and paroxetine [66–71]. It has been reported that depressed patients with a duplication of CYP2D6 are ultrametabolizers for nortriptyline and fail to respond to treatment [72]. Nevertheless, subjects with two nonfunctional copies of *CYP2D6* have increased plasma concentrations of tricyclic antidepressants and are PMs for them [73].

In contrast to pharmacokinetic processes that rely on CYP450 isoenzymes, pharmacodynamics is characterized by a more intricate genetic background. Pharmacogenetic studies of pharmacokinetic elements have been mostly intended for the identification of biomarkers and new molecular targets in order to provide information that might be potentially implemented in the drug-development process.

Typical antipsychotics act on the dopamine pathway, exerting a number of effects at different levels [74]. A number of papers reported significant association between polymorphisms of the dopamine receptor genes *DRD2* and *DRD3* and response outcome [75–78].

With regard to atypical antipsychotics, pharmacogenetic studies have, for the most part, focused on the serotonin system reporting association for the serotonin receptor genes, *HTR2A* and *HTR2C* [79]. The integration of data from serotonergic genes' variants in pharmacogenetic testing is discussed in another section of this article.

As a result of the use of selective serotonin reuptake inhibitors as the current standard treatment for depression, the majority of pharmacogenetic studies have focused on serotonin system genes, reporting significant association for the *5-HTTLPR* polymorphism of the serotonin transporter (*SLC6A4*) gene [80–87], as well as for polymorphisms in *HTR2A* and *HTR1A* genes [86,88–92]. Recently, several genome-wide association studies of antidepressant treatment responses have identified genetic variants that provide new insights on molecular targets suitable for possible implementation in personalized treatment frameworks. Interestingly, these papers have highlighted associations for genes of the serotonergic and noradrenergic systems as well as for genetic markers other than traditional candidates [93–95].

Lithium chloride is a unique drug in medicine: it is an ion with mood-stabilizing and antisuicidal effects, and it currently represents the mainstay of the therapeutic management of acute mania and depression in bipolar disorder [96]. However, owing to the complexity of the phenotype of response and to the not yet clear mechanism of action of this ion, pharmacogenetic studies on lithium response have so far produced little evidence. The majority of papers have dealt with genes encoding for elements that seem to be directly or indirectly implicated in the mechanism of action of lithium, specifically genes coding for elements involved in the inositol pathway [97]. Various papers have also shown association between the *5-HTTLPR* polymorphism and response to lithium [98–100]. Genome-wide association studiesof lithium treatment response have been already performed [101] or are currently ongoing [102, Squassina et al., Unpublished Data] with the aim of identifying genetic determinants of lithium response using narrow criteria for the phenotypic characterization of treatment response.

Pharmacogenomics for infectious diseases

The therapeutic management of infectious diseases has been challenged by the soaring phenomenon of antibiotic resistance, the high rate of which is mainly due to improper and/or aspecific prescription and use of antimicrobials.

The inappropriate use of antimicrobials is well-illustrated by a study showing that the number of antimicrobial prescriptions was three-times

higher than the number of patients diagnosed with a bacterial infection [103]. Microbial identification and antimicrobial susceptibility testing methods currently used in clinical microbiology laboratories require at least 2 days. This long delay has enormous consequences on antimicrobial usage. It frequently forces physicians to treat patients empirically with broad-spectrum antimicrobials, which are often toxic and expensive [104]. Personalized medicine for infectious diseases is an emerging concept in which molecular biology tools are used to provide rapid, accurate and more informative diagnostic microbiology assays, thus enabling more effective therapeutic intervention [105]. Over the past decade, several companies have developed various nucleic acid testing assays for the direct detection of viral pathogens and some resistant bacteria from clinical samples [105]. Comparative genomics exploits available genome sequences to perform either inter- or intra-species comparisons of bacterial genome content, or compares the human genome with those of other model organisms [106]. Based on powerful tools of bioinformatics and microarray technology, comparative genomics has been used to identify virulence determinants, antimicrobial drug targets, vaccine targets and new markers for diagnostics. One of the first attempts was to use microarray-based comparative genomics to study the genome content of various Bacillus Calmette-Guérin strains using *Mycobacterium tuberculosis* [107].

In addition, pharmacogenomics gradually assumes an important role in predicting adverse effects caused by antiretroviral drug therapies. Nowadays, highly active antiretroviral therapy enhanced the battery of HIV treatment modalities. However, antiretroviral drugs display certain ADRs, usually characterized by short- and long-term toxicities, depending on the class of antiretroviral agent used [108]. For instance, Mallal and coworkers showed that the allele *HLA-B5701* is indicative of hypersensitivity reaction to abacavir [109]. Moreover, Young and coworkers have shown that screening for the *HLA-B5701* allele resulted in a reduction to hypersensitivity related to abacavir treatment to less than 1%, compared with 4–8% when HLA testing was not performed [110]. Futhermore, the c.516G/T variant in the *CYP2B6* gene is a potential pharmacogenetic marker for ADRs in patients treated with efavirenz [111].

Interestingly, certain polymorphisms, such as the c.3435C/T variation in the *MDR1* gene, can be also employed to predict antiretroviral therapy response [112]. Furthermore, nucleotide substitutions in the genes encoding for the organic anion transporter 1 or multidrug resistant protein 2 or 4 are associated with increased risk of kidney tubulopathy in patients treated with tenofovir disoproxil fumarate, a nucleotide analog used as part of HIV therapy [113].

Overall, these new technologies will offer multiple rapid diagnostic opportunities that will slowly replace classical phenotypic methods for identifying microbes and determining their antimicrobial susceptibility pattern, while they can assist towards predicting and avoiding ADRs often seen in a significant proportion of HIV patients treated with antiretroviral drugs. Thus, novel, rapid molecular diagnostic tools will provide clinicians with real-time, crucial clinical information that should greatly improve the management of microbial and viral infections and, ultimately, save lives, improve the quality of life of infected patients and reduce healthcare costs [105].

Currently available pharmacogenetic tests

Several pharmacogenetic tests have been developed, representing tangible deliverables of the numerous genomic studies to correlate genetic variation with variable drug response. A handful of these tests, both protein- and DNA-based, have subsequently been approved for *in vitro* diagnostic testing (Table 1). In this section, we outline some of the pharmacogenetic tests present in the market or currently used in some selected laboratories.

The test kit Herceptest™, developed by Dako (CA, USA), was one of the first to be developed and approved by the Center for Devices and Radiological Health (CDRH; MD, USA) in 2001. Diagnosis is performed using immunohistochemistry, which measures the overexpression of HER2 protein. Herceptin treatment is considered only when the patient suffers from a very aggressive form of cancer (HER positive 3, defined by very high levels of HER2 protein in the tumor, assessed by immunohistochemistry). Similar tests measuring HER2 copy number using FISH are also available.

In 2005, the FDA approved the first pharmacogenetic test (AmpliChip™ CYP450 Test; Roche Molecular Systems, Inc., NJ, USA) based on Affymetrix (CA, USA) microarray technology for genotyping 27 alleles in *CYP2D6* and three alleles in *CYP2C19* genes associated with different metabolizing phenotypes. The test is recommended for the assessment of the metabolizing rate for each drug that is a substrate for

Table 1. Selected pharmacogenetic tests in the context of US FDA-approved drug labels.

Drug	Target test	Comments	Notes
Trastuzumab	*HER2* overexpression using FISH or IHC	Recommended for breast cancer	Test required
Lapatinib	*HER2* overexpression using FISH or IHC	Recommended for breast cancer	Test required
Cetuximab	*EGFR* expression and *KRAS* mutation	Recommended for colon cancer	Information only
Erlotinib, gefitinib	*EGFR* mutation	Response to EGFR tyrosine kinase inhibitors	Information only
Irinotecan	*UGT1A1* variants	Recommended against toxicity	Recommended
Imatinib	Philadelphia chromosome, c-KIT, PDGF receptor	Recommended for CML and GIST	Information only
Capecitabine	Dihydropyrimidine dehydrogenase deficiency	Related severe toxicity	Information only
Warfarin	*CYP2C9* and *VKORC1* (-1639G>A)	Recommended for optimizing warfarin dosing	Recommended
Clopidogrel	*CYP2C19*	Response to clopidogrel and side effects	Recommended
Maraviroc	Trofile (CCR5 tropism)	Amplification of patient HIV genome	Required
Abacavir	*HLA-B 5701b*	Predictive for hypersensitivity	Recommended
Voriconazole	*CYP2C19*	Affects drug metabolism	Information only
Atomoxetine	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Venlafaxine	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Risperidone	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Tamoxifen	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Fluoxetine	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Olanzapine	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Tramadol	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Clozapine	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Aripiprazole	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Timodol	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Propanolol	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Carvedilol	*CYP2D6*	Recommended for evaluating patients' metabolizing rates	Information only
Carbamazepine	*HLA-B*1502*	Risk for carbamazepine-induced Steven–Johnson syndrome	Recommended for patients of Asian origin

CCR5: Chemokine (C-C motif) receptor 5; c-KIT: Receptor tyrosine kinase; CML: Chronic myeloid leukemia; EGFR: EGF receptor; GIST: Gastrointestinal stromal tumor; IHC: Immunohistochemistry.

CYP isoenzymes 2D6 and 2C19. Other genetic tests, such as the *HLA-B*1502* allele test for carbamazepine-induced Stevens–Johnson syndrome, are currently being performed in some laboratories. Based on findings from pharmacogenetic studies on Asian and Caucasian populations, the test is recommended by the FDA, but only for patients of Asian descent [114–116]. The DMET™ Plus Panel (Affymetrix) covers a wide range of genetic variations, including common and rare SNPs, insertions, deletions, trialleles and copy number variants, many of which are not assayed by conventional SNP methods [117]. Unlike other SNP detection methods interrogating markers with an average minor allele frequency of approximately 20%, the absorption, distribution, metabolism and excretion (ADME) core markers in the DMET Plus Panel have allelic frequencies below 9%, although more common genetic variants are also present. This DMET Plus Panel interrogates some 1936 drug metabolism markers in 225 genes, including markers for all FDA-validated genes, namely markers that have been included in the corresponding drug labels.

Other pharmacogenetic tests are commercially available for the identification of predictors for susceptibility to ADRs in antipsychotic pharmacotherapies. The PhyzioType™ (Genomas, Inc., CT, USA) system employs an ensemble of DNA markers from several genes, along with a biostatistical algorithm, to predict an individual's risk of developing ADRs, including antipsychotic-induced metabolic syndrome [118,119]. The current prototype DNA microarray includes 384 SNPs from 222 genes. Genomas, Inc. has a patent pending and is waiting for FDA approval.

The PGxPredict:CLOZAPINE® (PGxHealth, Division of Clinica Data, Inc.) test is based on a nucleotide change in the *HLA-DQB1* gene. The test ascertains the risk of clozapine-induced agranulocytosis and the risk–benefit ratio of clozapine treatment [207]. Other tests based on genetic variants in genes coding for pharmacodynamic factors are currently being performed in some laboratories, such as tests that include variants in *HTR2A*, *HT2RC* and the *5-HTT* genes for predicting clozapine response [120].

Future applications of pharmacogenomics: the paradigm of hemoglobinopathies

The application of pharmacogenomics to β-type hemoglobinopathies therapeutics is particularly attractive owing to the limited therapeutic capabilities and narrow therapeutic index of presently available drugs, namely iron chelation and fetal hemoglobin (Hb-F)-inducing agents. Hemoglobinopathies, particularly β-thalassemia and sickle cell disease (SCD), are major health problems, as approximately 4.5% of the worldwide population is a carrier of a thalassemia-causing genetic defect. Iron chelation and pharmacological reactivation of fetal γ-globin genes in the adult are among the few therapeutic procedures presently available, aiming to alleviate patients from iron overload and compensate for absent or defective β-globin chains, respectively. In the latter case, decitabine (5-aza-2′-deoxycytidine), butyrate and hydroxyurea (HU) are commonly used, with decitabine and butyrate being essentially experimental drugs. HU is the drug most frequently administrated to symptomatic SCD patients and, to a lesser extent, to β-thalassemia patients. HU-driven Hb-F stimulation occurs by erythroid regeneration, leading to the appearance of more 'fetal-like' cells in peripheral blood. Such cytostatic effects are presumably related to its ability to inhibit cellular ribonucleotide reductase [121]. Hb-F response of β-hemoglobinopathy patients to HU treatment varies, particularly in β-thalassemia, with approximately 25% of patients being poor or nonresponders [122–124]. Genetic variation correlated with Hb-F expression, HU metabolism and erythroid progenitor proliferation might modulate patient response to Hb-F-inducing pharmacological agents. Presently, correlation of SNPs with Hb-F induction owing to HU treatment is a controversial issue, and very few studies are currently available [4]. Association studies on a cohort of 137 SCD patients revealed seemingly useful pharmacogenetic markers for HU treatment with possible roles in HU metabolism and effects and Hb-F regulation [124], while candidate genes involved in response to HU treatment have been also determined using a whole-genome transcription profiling approach [Phylactides et al., Unpublished Data]. On the contrary, there is considerable controversy regarding the association of SNPs in the human β-globin gene cluster as modulating factors involved in good and moderate response to HU. Clearly, more pharmacogenetic studies on larger and ethnically diverse β-thalassemia and SCD patient groups are required to enable clinicians to identify patients who are likely to benefit from the various therapies. Similar studies may also be conducted not only on additional pharmacological agents and different treatment methods, presently only at the experimental stage, but may also be extended to other therapeutic procedures for β-thalassemia, that is, iron chelation therapy.

Facing the current challenges of pharmacogenomics & personalized medicine

Education of health professionals

Following the introduction of pharmacogenetic testing in some clinical areas, the provision of an adequate level of knowledge for healthcare professionals is becoming an increasingly cumbersome issue, especially in view of the application of these diagnostic tools to an ever-greater number of patients.

Specifically, even if it is true that tailored drug treatments provide more efficacious pharmacotherapy based on individual genetic profiling, a gap still exists between the application of pharmacogenetic testing and how its results are interpreted and utilized in the clinical and therapeutic management of patients. A recent systematic review revealed a gap regarding how the health system can ensure appropriate, effective clinical integration of genomic information and technologies for common chronic diseases [125]. Moreover, the study clearly identified one of the weaknesses in the health system: the lack of preparation of the primary care workforce in facilitating the integration of common disease genomics into clinical practice.

In this context, the International Society of Pharmacogenomics Education Forum has called for the enhanced implementation of pharmacogenomics and personalized medicine into core medical education and practice [126]. A request to Deans of Education to incorporate pharmacogenomics into the core teaching curricula was presented, to prevent medical education from

becoming a bottleneck along the road to implementing personalized medicine. Moreover, the urgent need to incorporate pharmacogenomics teaching into medical schools has been motivated by the challenging ethical implications implied by personalized medicine [127,128]. Finally, in order to successfully bring pharmacogenetic testing to the prescription pad, it is imperative for scientists and teachers in the field to accept the challenge of disseminating pharmacogenomics insights to a broader audience [128]. Although still far from reaching fulfilling results, the appeals made by the scientific community and the intervention at the educational level seem to have set the correct route for the complete achievement of these educational aims [129,130].

Researchers in the field of pharmacogenomics have started focusing on assessing the attitudes of healthcare professionals and patients regarding genetic testing, since these opinions may be used to shape the development of emerging pharmacogenetic services [131]. This study clearly showed that patients expect to receive pharmacogenetic services from healthcare professionals who can confidently explain the test and interpret its implications for prescriptions, but a gap still exists between patients' high expectations and healthcare professionals' knowledge. Interestingly, an awareness survey of parties (healthcare professionals, industry, academia and the government) involved in pharmacogenetics in Japan evidenced the same pattern of expectations, although concerns regarding issues such as lack of genetic knowledge on the part of the public and the possibility of genetic privacy violations were raised [132]. Attitudes toward pharmacogenetic testing were reported as positive among psychiatrists [133] and university students [Lanktree M, Pers. Comm.]. Although the level of pharmacogenetic knowledge among healthcare providers is still not optimal, intervention at the educational level has had the overall effect of increasing understanding, consequently facilitating the incorporation of genetics into patient care. Moreover, the parties involved in pharmacogenetics appear to have a generally positive attitude, despite concerns regarding privacy issues.

Healthcare costs

The more cost effective a pharmacogenetic test is, the more likely it is to be adopted in a clinical setting. Thus, in order to demonstrate its economic benefits, pharmacogenetic testing needs to show evidence of clinical effectiveness, with increasing need for greater participation of experts in comparative effectiveness research [134]. However, economic barriers to the adoption of genetic data for personalized medicine do exist and, for instance in the USA, operate differentially by clinical area, by payer and the nature of the technology employed. Furthermore, policy making agencies in the USA and the EU, namely the FDA and the European Medicine Agency (EMA), respectively, have some fundamental differences in their structure and operation principles, which are reflected in some of the directives and guidelines that they produce. In an attempt to operate in concert, these agencies, in conjunction with the Japanese authorities, are gradually attempting to coordinate to minimize overlap and avoid unnecessary delay by duplicating efforts.

In regard to their impact on different clinical areas, recent reports have presented cost–effectiveness analyses on drug treatments for psychiatry, cancer and chronic inflammatory diseases [135–137]. Estimating the costs and benefits of a putative pharmacogenetic test for antidepressant response in the treatment of a major depressive disorder, Perlis and coworkers showed that the presence of circumstances such as the availability of alternative treatment strategies and effect-size tests for differential antidepressant response could lead to cost–effectiveness [135]. In cancer therapy, *EGFR* pharmacogenomic testing had the potential to improve quality-adjusted life expectancy in the treatment of refractory NSCLC by a clinically meaningful value commensurate with the approved therapies available in this setting [136]. Finally, in pharmacoeconomic models estimated from data deriving from New Zealand drug and service costs, Priest and coworkers suggested that testing for PMs of azathiophrine, a first-line immunosuppressant used for inflammatory bowel disease, may be cost effective, although phenotype testing appears to be even more so than genotype testing [137].

In the second instance, in the US healthcare system payers and their different reimbursement policies can act as obstacle to the rapid dissemination of innovative therapies and technologies such as pharmacogenomics. In an exhaustive review, Ginsburg and Willard point out that if the Centers for Medicare and Medicaid Services (CMS; MD, USA) start paying for genetic tests to guide the prescription of companion drugs or for the prevention or management of chronic diseases, then personalized medicine will have reached a turning point [138]. However, as demonstrated by the example of warfarin, this

perspective seems far from becoming reality. In 2007, the FDA added information to the warfarin label based on the influence of the *CYP2C9* and *VKORC1* genes on anticoagulation-related outcomes, but the CMS decided to reimburse the genetic test for warfarin dosing covered only when provided to Medicare beneficiaries in the context of a prospective randomized, controlled clinical study when that study meets certain criteria [208]. This decision was based on the CMS policy according to which 'tests for screening purposes that are performed in the absence of signs, symptoms, complaints, or personal history of disease or injury are not covered except as explicitly authorized by statute. These include exams required by insurance companies, business establishments, government agencies, or other third parties' [209]. In this regard, Williams states that there is increasing recognition that the enabling legislation for Medicare that prohibits coverage for preventive services is an anachronism [139].

Overall, these findings seem to indicate that pharmacogenetic testing may represent a resource for healthcare decision-makers, leading to increased quality of clinical care, along with increased economic benefits, both for pharmaceutical companies and public health [134], although pharmacogenetic tests will probably prove to be more cost effective than cost saving [140] or eventually cost effective for only certain combinations of disease, treatment, test and gene characteristics [141]. Moreover, in the US healthcare system, payers exert a great influence on the diffusion of pharmacogenetic tests since they can refuse to cover and reimburse their cost.

Insurance & privacy issues

The complete implementation of pharmacogenomics and personalized medicine will take place only by overcoming the obstacles represented for the most part by the lack of adequate application of current regulations, as the co-development of diagnostics and therapeutics is not yet effectively encouraged [142].

Indeed, as pharmacogenomics is a research field that, by definition, investigates differences in genetic patterns among subjects, it has to deal with a number of issues related to genetic discrimination (GD), privacy and possible implications for access to life and health insurance. A 1998 survey of the membership of the National Society of Genetic Counselors (NSGC) Special Interest Group (SIG) on cancer showed that more than half of respondents would not bill their insurance companies for genetic testing, largely due to fear of GD [143]. In 2007, Huizenga and coworkers [144], comparing the results of a new survey provided with NSGC SIG using the Matloff and coworkers data [143], pointed out a notable change in perceptions and behavioral intent among cancer genetics professionals over time, fear having become less common since 1998.

Although the data presented earlier concern the broad concept of genetic testing, pharmacogenomics has to deal with the same issues of stigmatization and discrimination [142,145–147]. In detail, the social consequences arising from new disease labels, such as being defined as either a 'responder' or a 'nonresponder' to a given therapy, would involve interpersonal stigmatization or identity issues [146]. Moreover, pharmaceutical companies could voluntarily ignore, for economic reasons, patients with rare or complex genetic conditions or those who are not responding to any known treatment, leading to consequent deprivation of effective treatments [148,149].

Genomic data present specific properties of magnitude, stability, implications to kin and ease of dissemination that render their management a qualitatively different challenge as compared with traditional, self-limited and often temporally transient medical information [150]. Specifically, an important element of concern is raised by the storage of a large amount of information in databases with the potential for a loss of confidentiality or privacy, since they link an enormous quantity of genotypic, phenotypic and demographic data regarding individuals [150]. In this regard, as stated by Buchanan and coworkers [151], appropriate protection for privacy and confidentiality is crucial because a pharmacogenetic test can carry several types of secondary information that represent a risk of psychosocial harm. Among these, one of the most problematic is given by the possibility that information on an individual's response or nonresponse to a particular drug or class of drugs might itself have adverse insurance and/or employment implications [151]. Moreover, discrimination in access to healthcare or health insurance may face particular genetic subgroups, according to Smart and coworkers [152]. However, the fears of GD and specifically the implications for life and health insurance appear to be overemphasized, and the risk related to pharmacogenomics is likely to be even further attenuated [142].

In the attempt to regulate these questions by means of legislation, national authorities and governments have enacted specific measures in the USA, such as the Genetic Information Nondiscrimination Act (GINA), the Health

Insurance Portability and Accountability Act Privacy Rule, and the Genomics and Personalized Medicine Act (GPMA) [153–155]. However, regulatory tools such as GINA are only part of the answer to a larger problem, and all stakeholders must be educated regarding the law, in a manner tailored to their needs [156]. Moreover, the GPMA also seems to lack in clarity and leadership on critical issues of translation of human genetic variation from bench to bedside [157].

Conclusion

In the last decade, the implementation of pharmacogenomics into clinical practice as a fundamental tool for the achievement of personalized medicine has shown a different degree of diffusion in the various clinical fields. In some areas, such as in cardiovascular diseases or in cancer, pharmacogenomic testing is already applied for selecting and/or dosing a specific medication, while in other fields, such as in psychiatry, the pharmacogenomic approach has been mostly used for the identification, validation and development of new meaningful biomarkers. To this regard, the pharmacogenomic approach presents different potentiality and limitations depending on the clinical field to which it is applied. For instance in cancer, pharmacogenomics has already provided physicians with valuable information given the opportunity to easily collect tissues directly affected by the disease. On the other hand, in psychiatric disorders, the question of whether the use of peripheral tissues for the identification of biomarkers for a 'brain disease' might represent a feasible approach is still to be answered.

In conclusion, the adoption of pharmacogenomic testing for the design of personalized prescriptions still has to face a number of barriers in order to be integrated into clinical practice, but the increasing knowledge on the molecular basis of response to medications, ADRs and disease susceptibility and the growing attention of pharmaceutical industry and national healthcare policy makers will probably accelerate the pace towards the achievement of personalized medicine.

Future perspective

The application of pharmacogenomics to complex diseases characterized by a great phenotypic and genetic variability might constitute an almost unconquerable challenge. The phenotype of response is a complex and heterogeneous trait by itself, and it is definable as a continuous more than a dichotomous (response/nonresponse) trait. It has been stated that, given the weak effects of susceptibility genotypes, it is theoretically improbable that genetic screening will be used for the assessment of risk or prognosis in complex diseases [158].

Although this evidence may lead us to conclude that translating pharmacogenomic findings to personalized medicine in complex diseases will be difficult, some strategies can be employed to overcome the challenges and lay the foundation for pharmacogenomic implementation in clinics. For instance, in complex diseases, missing heritability might be ascribed to the presence of rare variants and structural variations [159]. It has been stated that DNA sequencing might allow the identification of rare SNPs either in target regions or in the whole genome. The use of subjects at the extreme of a quantitative trait, such as complete nonresponse versus response to specific treatment, has been suggested as a useful mechanism for the identification of associated variants, both rare and common, by sequencing [159]. Moreover, some analytical approaches, such as case-only genome-wide interaction, can provide a straightforward method for detecting genetic interactions related to treatment response in complex diseases [160]. On the whole, this evidence might provide a framework of operational and decisional criteria for setting the course leading to widespread use of pharmacogenomics in public health.

In addition, novel concepts emerge in the burgeoning field of pharmacogenomics, for example, in the area of antibiotic therapy, where sequence variations in the mitochondrial DNA (mtDNA) can constitute putatively useful pharmacogenetic markers [161]. Cell systems, known as transmitochondrial cell lines or cybrids, where the mtDNA of a parental cell line is depleted and the resulting cell is fused to enucleated cells, have been employed to analyze the interaction between antibiotics and mtDNA genetic variants. These cell lines have the same nuclear genetic composition and grow in the same environment, while only differing in their mtDNA, which would yield distinct phenotypic differences as a result of drug treatment [162,163]. Such cell lines have been used to correlate human chloramphenicol resistance with two mtDNA variations, namely m.2939C>A and m.2991T>C in the *MT-RNR2* gene [162,163]. This experimental system has been also used to explore susceptibility to erythromycin [164]. Such approaches would give us a new perspective of the pharmacogenomics of

antibiotic therapy, and could possibly assist towards optimizing or increasing the number of available antibiotics on the basis of the patient's genetic background.

Furthermore, pharmacogenomics can be associated with variable response to drug therapy in organ transplantation. For example, tacrolimus is perhaps the best established example of the *CYP3A5* gene effect on drug disposition and dosage, with the *CYP3A5*3* allele correlating with lower dose of tacrolimus to achieve therapeutic blood concentrations. This same observation has been made for every type of solid organ transplant, but unfortunately this effect is not uniform among patients, especially in those bearing the *CYP3A5*3/*3* genotype. The effectiveness of other drugs used in organ transplantation have been correlated *vis à vis* to a number of gene alleles, such as azathioprine with *TPMT* alleles, ciclosporin with *ABCB1* alleles, sirolimus, like tacrolimus, with *CYP3A5* alleles, corticosteroids with *ABCB1* and *IL-10* polymorphisms (reviewed in [165]).

Besides the promising evidence towards a wider adoption of pharmacogenomics in the clinical settings, a number of obstacles on its full implementation for the achievement of personalized therapy must be taken into account (Figure 1). In a broad perspective, personalized medicine will require changes in healthcare infrastructure, diagnostic business models and a reimbursement policy on the part of government and private payers. To address this need, the Personalized Medicine Coalition (PMC; Washington, DC, USA) was founded as a nonprofit organization of pharmaceutical biotechnology, diagnostic and information technology companies, healthcare providers and payers, patient advocacy groups, industry policy organizations, academic institutions and government agencies [166]. PMC attempts to facilitate the use of molecular diagnostics and personalized medicine approaches, providing opinion leadership, help in training the public, and conveying information to the media, government officials and healthcare leaders. Other initiatives by nonprofit foundations were undertaken in the last few years to facilitate the implementation of personalized medicine in everyday healthcare. In October 2009, leaders from the field of research, medicine, industry, government and philanthropy founded the Mayflower Action Group Initiative, an idea instigated by Brain Research And Integrative Neuroscience Network (BRAINNet), a new nonprofit foundation that provides a database on the human brain using standardized methods [167]. The foundation aims to address the need for combining genetic information, electrical measurements of brain and body function, structural and functional MRI, and cognitive and medical history data within a single framework. These data are from both healthy people and those experiencing a range of brain-related illnesses, and are freely provided for research and scientific publication, thereby maximizing and sharing benefits. Furthermore, the Pharmacogenetics for Every Nation Initiative (PGENI [210]) is a worldwide initiative with the stated goal of developing "…innovative strategies for Health Bodies to integrate pharmacogenetics into public health decision-making without placing an extra burden on sparse healthcare funds". Such efforts would be particularly useful for developing nations to defray healthcare costs and improve quality of life by minimizing ADRs.

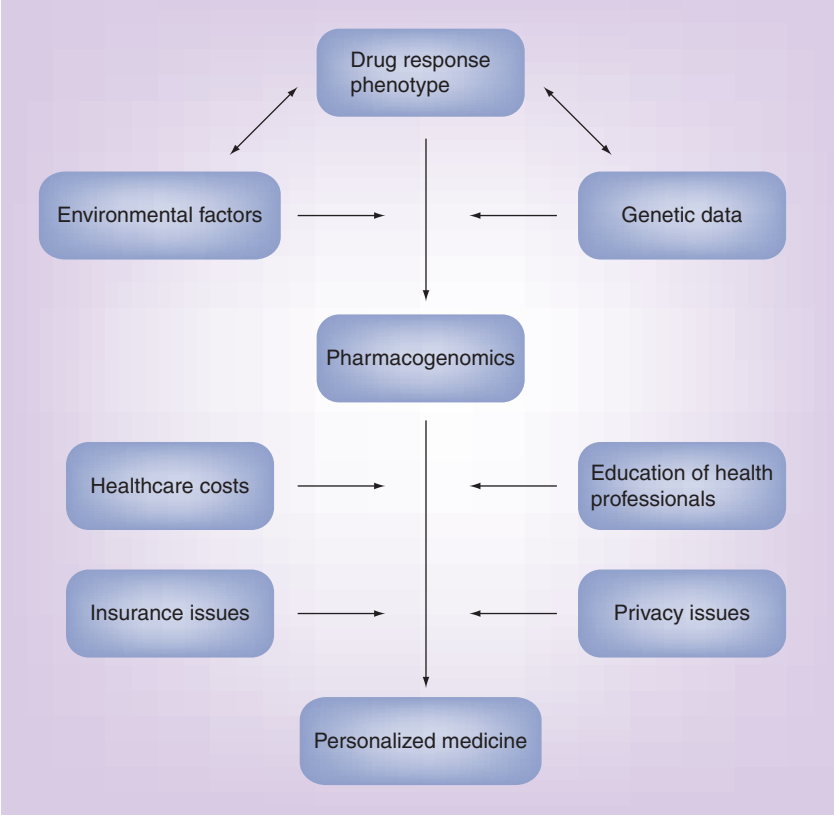

Figure 1. The discovery of pharmacogenomic determinants able to predict treatment outcome in specific populations of patients can be represented as a heuristic process that takes into account different empirical factors acting at a phenotypic, genetic and environmental level. Specifically, a refined phenotype of treatment response is needed in order to empower the pharmacogenomic approach. The drug-response phenotype can result from the complex interplay with environmental and genomic factors. Once identified, pharmacogenomic predictors can enter a clinical implementation pipeline leading to their practical application into personalized therapy. This path might present different degrees of efficacy, depending on the influence of factors such as privacy and insurance issues, healthcare costs and the educational level of healthcare providers. Actions undertaken at these levels can facilitate the process of clinical implementation, consequently leading to empowered personalized medicine tools.

The era of personalized medicine has already begun, and even though it is not yet a widespread practice, ongoing international efforts confirm that the concept of personalized prescription is close to becoming a reality.

While pharmacogenomics in psychiatry is a rapidly emerging field, it has to face difficulties related to the complexity of the phenotype and the polygenic features of response to psychotropic medication. Nevertheless, promising results from genome-wide studies on response to lithium and antidepressants currently underway might provide validation of the candidate genes mentioned earlier, as well as identification of novel genes. Application of sophisticated 'machine-learning' algorithms to data from genome-wide studies of treatment response will allow researchers to develop personalized treatments based on genetic data.

In light of these assumptions, it is reasonable to presume that the implementation of genetic data for the design of a personalized prescription will be achieved more quickly in other fields such as oncology, where healthcare professionals have access to tissues permitting various types of testing. However, increasing pharmacological information on the genetic bases of response to medications, drug–drug interactions and variability due to clinical and environmental factors will lead to more widespread use of pharmacogenomics in psychiatry in the near future.

Personalized medicine has always been a component of good medical practice. Genetic tests may provide new tools, but do not change the fundamental goal of clinicians: to adapt available medical tests and technologies to the individual circumstances of their patients. As genetic tests become widely available, personalized medicine will make wise use of genetic information in analyzing the complex picture regarding variability in response to medication.

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Executive summary

- Pharmacogenomic approaches to cancer are already implemented in clinical practice. Diagnostic tests have been developed and are now available for several molecules employed in cancer treatment.
- Pharmacogenomics is also enhancing the clinical applications of two antithrombotic drugs, the anticoagulant drug warfarin and its analogs, and the antiplatelet agent clopidogrel, used in the treatment of cardiovascular diseases.
- Knowledge of the genetic bases of the response to psychotropic medications and the onset of their side effects has greatly increased in the last decade. Genetic variants in genes encoding for pharmacokinetic factors involved in the metabolizing processes of psychotropic drugs have been shown to predict, to some extent, response to antidepressants and antipsychotics.
- Educational, economic and ethical challenges need to be faced in the implementation process of pharmacogenomics and personalized medicine in healthcare systems.
- Personalized medicine is an essential component of modern medical practice. Genetic tests may provide new tools, but do not change the fundamental goal of clinicians: to adapt available medical tests and technologies to the individual circumstances of their patients.
- As pharmacogenetic tests become widely available, personalized medicine will make use of genetic information in order to dissect the complex picture of variability in response to medication and manifestation of adverse drug reactions.

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