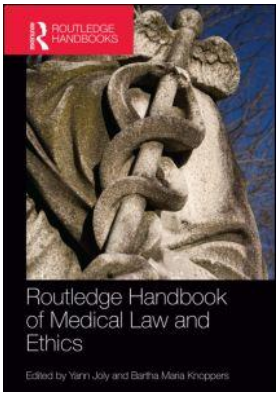

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Towards precision medicine

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Towards precision medicine

The legal and ethical challenges of pharmacogenomics

Gratien Dalpé and Yann Joly

19.1 Introduction

19.1.1 Personalized medicine: from the laboratory to the clinic

Physicians have always explored new ways of making more accurate diagnoses and better drug prescriptions. Since the mid-nineteenth century, evidence-based medicine has supported healthcare decisions by combining the physician's expertise and judgment with the best clinical evidence from scientific research pertinent to a patient's health (Sackett 1997). With such an approach, physicians can obtain more precise diagnoses centered on their patients' personal characteristics. This practice is thought to lead to the discovery of more efficient prognosis markers and to the development of safe and efficient therapeutics.

Modern molecular genetics has the potential to substantially impact many aspects of medicine, including the development of pharmacological treatments. Genetic information enables the identification of individuals through their polymorphisms, small variations in genes related to the inter-individual variability in a given population (Hedrick 2011: 104). It has also increased our understanding of the molecular mechanisms of diseases, allowing genes and their products to become the molecular targets of new pharmaceutical therapies aimed at modulating gene activity (Strachan and Read 1999). As such, the study of genetic biomarkers has been used to foster knowledge and facilitate the prediction of human disease, enable more accurate diagnoses and improve the safety and efficacy of medications tailored to the needs of specific patient groups.

An important element in the success of precision medicine, pharmacogenomics (PGx) is the study of how genomic profile variation between individuals' or subgroups' DNA and RNA influences their response to drugs (Maliepaard *et al.* 2013; Hall 2013). Modern PGx goes beyond the study of single gene mutations and their effect on drug response. It takes advantage of a whole-genome view, using a variety of genomic approaches – such as high-throughput whole-genome sequencing (WGS) and the ability to store and access this data with bioinformatics – to establish a patient's profile and maximize treatment efficacy while lowering the risk of adverse drug reactions (ADRs) (Hall 2013). Between the completion of the Human Genome Project in 2003 and recent advances towards fast and reliable WGS using next-generation sequencing,

it is now possible to obtain an individual's WGS profile for a price approaching $3,000 to $4,000 USD (Green 2013; Yu *et al.* 2012; Crews *et al.* 2012). With the constant decrease in DNA sequencing cost, many have suggested that prices will drop below $1,000 per genome in just a few years (Drmanac 2011; Committee on a Framework for Developing a New Taxonomy of Disease (CFDNTD) 2011; Kedes and Campany 2011; Mardis 2011; Holman 2012). At these prices, WGS has the potential to be used in routine healthcare.

However, epigenetic modifications, proteomics, and microRNA variations can also account for inter-individual variability (Crews *et al.* 2012). Even if the falling cost of WGS makes its clinical use foreseeable, problems such as the complexity of genomic interpretation, our limited knowledge of genes responsible for genetic disease, and WGS's failure to meet quality control sequencing norms such as the *Clinical Laboratory Improvement Amendments* (CLIA) 1988 will need to be resolved prior to implementation in the clinic (US Food and Drug Administration (FDA) 2013a). Nevertheless, this technology might presently be useful for the identification of polymorphisms in genes known to be relevant to drug efficiency and ADR. PGx implementation, combined with affordable and reliable modern sequencing technologies, could result in major healthcare advances by facilitating the identification of new drugs that are safer, more effective, and tailored to patients (CFDNTD 2011).

PGx is often conflated with precision medicine because both disciplines have the same outcome in mind – more personalized healthcare based on the patient's individual characteristics (Poon *et al.* 2013; Katsnelson 2013). Advances in PGx have contributed to an idyllic vision of healthcare practitioners able to quickly determine an individual's genomic profile, and choose the right drug at the right dosage for the specific needs of that patient (Ghosh *et al.* 2010). The promise is a novel, more rational 'precision medicine' which leaves the trial-and-error approach for an evidence-based clinical decision that is 'individualized' and patient-centric (Zineh 2012). Although this chapter will focus on PGx, we do not subscribe to genetic essentialism, and remain conscious of the importance of epigenomic and clinical data in achieving precision medicine.

19.1.2 Regulations, policies and guidelines for clinical pharmacogenomics

In section 19.2 of this chapter, a range of topics related to PGx implementation in drug development will be presented from the point of view of different international regulatory agencies. In Sections 19.3 and 19.4 we analyze some of the major ethical issues perceived as obstructing the implementation of PGx. The role of current and proposed laws and regulatory policies in protecting the public while trying to pave the way for implementation of PGx will also be examined throughout the chapter.

The pharmaceutical industry, governments and non-governmental organizations have shown an increased interest in the sustainable development of PGx. However, there is a need to address significant obstacles faced by stakeholders such as patients' concerns about genetic data privacy and confidentiality; the need for a drug approval process that adequately considers the impact of PGx on patient safety and provides economic incentives during the transition to personalized medicine; and the need for harmonization of drug development regulations at the international level.

PGx tends to stratify a common disease into subgroups based on drug response differences observed in patients. By characterizing this patient stratification with biomarkers, drug developers can design clinical trials that require fewer participants, thereby decreasing cost and streamlining the process (see section 19.2) (Nuffield Council on Bioethics 2006).

One of the most significant impacts of PGx implementation during drug development may be a gradual departure from the current blockbuster model towards a 'nichebuster' model that aims at a higher cost-effectiveness ratio (Brownlee 2011; Outsourcing-Pharma.com 2006). Due to the lower prospect of large profits, it has been predicted by some that the pharmaceutical industry may resist the movement toward PGx. For this reason, reimbursement incentives through third-party payers such as public healthcare agencies or private health insurers could help patients maintain access to affordable drugs while securing stable markets for drug developers (see section 19.3) (National Human Genome Research Institute 2012; Tambuyzer 2010).

Disease stratification due to PGx could also contribute to the identification of more rare conditions in the future (*Orphan Drug Act* (*P.L. 97-414*). Rare diseases are infrequent in the general population and constitute a small market for drug sponsors. The definition of rare disease differs according to the regulatory body. The FDA defines rare diseases as those which affect fewer than 200,000 persons in the United States, or which affect more individuals but still do not occur frequently enough for there to be an economic rationale in trying to develop a medication (*21 United States Code*, § 360bb). Likewise, the European Medicines Agency (EMA) considers the rarity of the condition (less than 5 in 10,000 people) but can also accept life-threatening, debilitating, and chronic diseases if there would otherwise be insufficient expectation of returns to justify the necessary investment (*European Parliament and Council Regulation (EC) No. 141/2000 of 16 December 1999 on orphan medicinal products*, article 3).

Regulatory bodies like the FDA and EMA recognize in their definition of rare disease that current business models present a challenge to orphan drug development (Sharma *et al.* 2010). Therefore 'orphan drug' designations have been created to promote and facilitate the development of medicines for these diseases (see section 19.3) (*Orphan Drug Act*).

In a situation analogous to rare/orphan disease, serious or life threatening conditions (e.g. rare cancers) with unmet medical needs can benefit from programs that facilitate and accelerate the development and approval of new drugs. New regulatory measures have been implemented by different agencies worldwide to allow novel drugs through a faster pathway that manages their risk-benefit elements in a case-by-case manner (Ehmann *et al.* 2013). Since such drugs are generally not destined to the whole public, are subject to continuous regulatory review, and require permission to use, access can be quickly overturned if new data suggest a danger to patient safety. This alternative to the traditional binary licensing approval system is called 'adaptive licensing'. Its step-by-step approval process renders license permission less stringent as long as drug sponsors can demonstrate benefit in the form of milestone accomplishments (see section 19.2).

PGx stratification can occur more easily when patients are segregated by ethnic groups rather than by genotypes. Some genetic variants associated with desired drug responses are thought to be more prevalent in certain ethnic groups, which could have an impact on clinical drug design and healthcare decisions (Tomasi 2012; Otlowski *et al.* 2012). Although the rationale for using ethnicity as a substitute for genotyping is founded on the desire to make drug trials less expensive, safer, and more inclusive, this practice carries significant ethical issues. Poor market prospects could lead companies involved in PGx research and development to exclude individuals with poor drug response from participating in clinical trials, which may lessen their access to safe and efficient drugs for the 'orphan genotype.' It has been suggested that policies should include measures to uphold social equality by preventing financial concerns from limiting patients' access to drugs without lucrative markets (see section 19.4.1) (Tomasi 2012).

In order to use PGx efficiently, a healthcare system should provide patients with access to routine genetic testing services as well as some degree of genetic counseling when indicated. As such, a robust framework of norms and guidelines will be required to ensure and optimize the use of genetic testing, DNA collection, access to patient information, and data confidentiality (FDA 2013a; Zhang *et al.* 2012; Ferreira-Gonzalez *et al.* 2008).

19.2 Regulations, policies, and international outlook

19.2.1 Drug development guidelines proposed by major regulatory agencies

Pharmacokinetics (PK) is defined as the way in which the human body affects the absorption, distribution, metabolism, and excretion (ADME) of a drug, whereas pharmacodynamics (PD) is the way in which that drug affects the human body by acting on biochemical or physiological targets. Genetic differences among human populations can have an effect on the effectiveness of drugs and the possible occurrence of ADRs. The observed clinical variability is partly determined by gene products associated with ADME (Maliepaard *et al.* 2013). Some of the genes encoding drug-metabolizing enzymes are highly polymorphic, and can be used as biomarkers to assess the PK profile of individuals and populations. Indeed, genetic polymorphisms are thought to affect the ADME of about 30 per cent of clinical drugs (Eichelbaum *et al.* 2006). A patient with a 'fast metabolizer' phenotype might break down a drug too quickly and experience low drug efficiency. On the other hand, a 'slow metabolizer' might build up high concentrations of toxic metabolites in their body and experience undesirable side effects. For fast metabolizers, a higher drug dose would be prescribed, whereas the dose of the same drug would be significantly decreased for slow metabolizers.

For instance, cytochrome P450 2D6 (CYP2D6) plays a role in metabolizing 25 per cent of current drugs and has been associated with the occurrence of Risperidone ADRs (Jose de Leon *et al.* 2005). Poor metabolizers lack this enzyme (including 7 per cent of the Caucasian population) and high metabolizers bear two copies of the CYP2D6 gene (including 2 per cent of Northern Europeans, 10 per cent of Southern Europeans and 30 per cent of the African population) (Pirmohamed and Hughes 2013; Bradford 2002).

Many regulatory agencies have assembled data concerning genetic variants associated with ADME. This explains why the emerging policies and guidelines from governing bodies focus on the PK parameter. For instance, 10 per cent of prescription drugs in the United States currently use PGx information in drug labeling, primarily with reference to gene variants and PK (Frueh *et al.* 2008). In this section we review the policies and guidelines of the EMA, the FDA, and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA), pointing out the particulars of each agency's approach and the policy elements they have in common.

Drug clinical trials generally proceed through four phases (*21 Code of Federal Regulations,* § 312.21). Phase I involves establishing a safety profile of the chemical compound, including potential safe dosages and PK/PD parameters, in a sample of 200–400 healthy participants (Organization for Economic Cooperation and Development (OECD) 2009: 50). Phase II evaluates efficacy, with a further focus on safety and broad-range doses in a sample of 200–300 individuals. The results from phase II are used to design the parameters of phase III, which focuses on determining a clinically effective dose. This phase generally involves between several hundred and several thousand participants affected by the condition(s) the drug is likely to treat. The risk-benefit ratio of the drug is evaluated in this phase, and is used as the basis for market approval. Phase IV, or post-market pharmacovigilance, occurs after marketing authorization. Since rare but serious ADRs might have remained undetected due to the low numbers of participants in the

previous clinical trials, this phase involves testing the drug on a high number of participants in the general population.

The use of PGx biomarkers can be beneficial to phased clinical trials if molecular genetics is used to identify markers of efficacy and ADR, thereby determining the participants who are likely to respond well to the drug (OECD 2009: 53). Although clinical trials are generally performed on large samples of randomly selected patients, some believe that PGx could modify this paradigm by altering the aim of each phase. Phase I could try to establish proof of concept; phase II could stratify participants into good responders, non-responders, and adverse responders; and phase III trials could use a much smaller sample of patients if limited to selected genotypes that should respond well to the drug. The obvious benefits of PGx in phased clinical trials include reducing the number of ADRs in participants, accelerating and reducing the cost of trials, and increasing the likelihood of receiving market approval. Drugs unlikely to be approved could also be identified earlier in the process, eliminating the need for further testing.

19.2.1.1 EMA guidelines

The EMA is responsible for the scientific evaluation of applications for marketing authorisation of human drugs in the European Union (EU) (European Medicines Agency 2013). No medical product can be marketed in the European Community without the authorization of the EMA (*Regulation (EC) No. 726/2004 of the European Parliament*, article 3). Its scientific committees, made up of experts from all member states, are responsible for evaluating applications for market authorization.

EMA guidelines provide recommendations for the use of PGx in the evaluation of new medications. Although EMA guidelines cover phases I–IV with a focus on the PK parameter, its mandatory *Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products* (2011: 6) emphasizes the early phases of drug development by specifying the effect of *in vitro* and *in vivo* cut-off values on subsequent PGx-related trial designs. Drug metabolism studies of candidate human enzymes are recommended prior to phase 1 in order to identify the involvement of known ADME pathways. In the event that an enzyme has a significant effect upon a pathway both *in vitro* and *in vivo* (with cut-off values of >50 per cent and >25 per cent respectively), mandatory DNA testing of research participants is performed in order to identify individuals predicted to have the poor metabolizer phenotype and prevent their exposure to unsafe doses (EMA 2011, section 4.2.2.2).

The EMA (2011, section 4.3) considers population PK studies to be useful during both clinical development and pharmacovigilance monitoring. In its guidelines, it recognizes the importance of PGx in pharmacovigilance methodologies and proposes retrospective analysis of stored samples to link patients' genomes with their clinical information (Harrison 2012; EMA 2011: section 4.3). To this end, the EMA (2010) highly recommends storing DNA samples from all participants in phases I–III and is currently preparing new guidelines concerning pharmacovigilance.

19.2.1.2 FDA guidelines

The US Food and Drug Administration (FDA 2013b) protects public health by ensuring that drugs, biological products, and medical devices intended for the public are safe and effective. The FDA (2010) is responsible for enforcing its regulations as well as laws enacted by the US Congress to protect consumer health. Section 21 of the *Code of Federal Regulations* provides the

relevant regulations on drugs destined for human use (*21 CFR Chapter 1, Subchapter D – Drugs for Human Use*).

The FDA (2013c) released updated guidelines in January 2013 that focus on PGx use in premarket evaluation during early-phase (I and II) clinical studies. The FDA emphasizes the use of early PGx studies to identify populations that should receive lower and higher doses based on inter-individual genetic differences in parameters such as drug exposure, dose-response, effectiveness, and possible ADRs. If significant inter-individual differences are found, PGx information can be used to select patients for trials and stratify them into groups (FDA 2013c: 13). Hence, the information learned about the variability of PK and PD in phase I and II of a clinical trial could be used to improve the design of phase III (FDA 2013c: 8). The goal of these steps is to 'increase the average effect, decrease toxicity, and improve the chances of overall success of the study' (2013c: 13).

The FDA (2013c: 7–8) also considers DNA sample collection important in both exploratory studies and drug development. It recommends that DNA samples should be collected from all clinical trial participants with their informed consent. Furthermore, the FDA (2013c: 19) states that PGx information should be included in drug labels in cases where a link is found between genotype and phenotype during trials. The labels should reflect whether genetic testing ought to be considered, recommended or is necessary before the use of the drug.

Although the aforementioned guidance documents reflect the FDA's current thinking on this topic (2013c: 4), they are not mandatory like the EMA's guidelines (2011) and do not impose a responsibility on the industry. Despite the fact that the FDA does not require the submission of biomarkers and PGx data for market authorization, it nevertheless recognizes that all stakeholders (e.g. academics, drug manufacturers) should cooperate in developing new biomarkers for PGx and share preclinical and clinical data related to drug safety. To facilitate this process, the FDA created the Voluntary Exploratory Data Submission Program, which organizes workshops and expert inputs, and creates a voluntary submission process (FDA 2011a; Amur *et al.* 2008). This program aims to address emerging scientific challenges by fostering robust regulatory PGx science (Anatol *et al.* 2013).

19.2.1.3 PMDA guidelines

Japan's Pharmaceuticals and Medical Devices Agency (PMDA 2013a) is the Japanese regulatory agency responsible for conducting scientific reviews of marketing applications for pharmaceutical and medical devices as well as monitoring their post-marketing safety. Drug sponsors have to submit an application for designation consultation to the Minister of Health, Labor and Welfare, who approves drugs and medical devices in accordance with the *Pharmaceutical Affairs Law*. Based on the PMDA's opinion after preliminary evaluations, the Minister may grant orphan designation to a drug or medical device (Ministry of Health, Labor and Welfare (MHLW) 2009).

In 2001, the PMDA published two guidelines regarding PGx in drug evaluation: *Clinical Pharmacokinetic Studies of Pharmaceuticals* and *Methods of Drug Interaction Studies* (2001a, 2001b). The PMDA recognizes the use of genetic studies to stratify the population when there is a high variability of PK parameters and/or when a drug is mainly metabolized by polymorphic enzymes (2001a, article 3). Moreover, if PK profiles differing from those of healthy volunteers are observed, they should be investigated thoroughly (PMDA 2001a, article 5). As such, the PMDA recommends incorporating information about ADME into the drug investigation. Unlike the EMA, it does not provide concrete criteria for when and how PGx studies concerning the PK

parameters must be performed. For example, the PMDA does not enforce *in vitro* and *in vivo* cut-off values that impose specific PGx testing during phases of clinical trials. But like the EMA and FDA, the PMDA does encourage the collection of DNA samples in clinical trials for retrospective and prospective PGx studies related to the efficacy and safety of drugs (2001a, article 6.1.1; Maliepaard *et al.* 2013).

19.2.1.4 Pharmacogenomics and the problem of phase II/III clinical trial failure

Published studies from life science consultants have recognized that failure in phases II and III of the drug approval process is attributable in major part to efficacy and safety issues. They note that drug developers tend to enter phase III with marginal statistical and proof-of-concept evidence. One way to increase the cost-efficiency of phase II–IV trials without compromising patient safety would be to emphasize the use of PGx and biomarkers (PGx/BM) in early trials. Both allow better identification of the target population and define categories of safe dosage, resulting in improved average effect and decreased toxicity (Arrowsmith 2011a, 2011b). Improving drug approval success rates should also result in better patient outcomes.

PGx/BM designs can be divided into three categories. In cohort design, patient randomization is independent of PGx screening; in stratified design, randomization is performed within the groups identified by PGx screening; and in enriched design, a given biomarker-negative population is excluded in order to focus on biomarker-positive participants. Each type of PGx/BM trial design has its own benefits and limitations (Ishiguro *et al.* 2013).

Policies and guidelines that encourage DNA banking can have a positive impact on the implementation of PGx/BM clinical trial design. However, PMDA guidelines on DNA sample banking seem less stringent than those of the EMA and FDA. Indeed, a study evaluating clinical trials performed on anti-cancer drugs in Japan found that PGx-randomized and PGx-enriched designs were used, but no stratified trials had been conducted. Furthermore, PGx/BM-guided trials were used much less frequently in Japan than in other countries studied (Ishiguro *et al.* 2013).

19.2.2 International harmonization and ethnobridging

19.2.2.1 Global drug marketing

Drug-developing companies seek to develop global strategies for worldwide approval and marketing of their products. Hence they must consider mandatory national policies and globally harmonized policies (e.g. regulatory standards agreed upon at international and regional conferences and adopted at a national level), and develop bridging strategies between national policies and harmonization efforts (Nakashima *et al.* 2011).

Agencies from the major pharmaceutical regions in the world issue their own regulatory documents establishing dose-response standards for safe drug exposure, including risk/benefit management policies which define the lowest safe dose for effective treatment. Studies have shown that countries adopt drug dosage regimens specific to their populations; for example, Japan generally selects lower doses than those seen in the EU and the US. This may be due to their conservative review process and its considerations for the 'uniqueness of Japanese people' (see following section) (Malinowski *et al.* 2008). Hence part of the challenge for global pharmaceutical companies is to obtain regulatory approval in different regions in a cost-effective

manner. International harmonization of these guidelines based on PGx data could facilitate drug development worldwide by providing standard evidence-based criteria for drug approval in different countries. Pragmatic, unified and transparent policies should aid in the development of a globalized drug program (Maliepaard *et al.* 2013).

In 1998, the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1998) enacted the *E5* agreement on ethical, scientific, and clinical parameters for the standardization of trial designs and the protection of human participants. Its tripartite guidelines on 'Ethnic Factors in the Acceptability of Foreign Clinical Data' address the intrinsic characteristics of drug recipients (e.g. genetics) and extrinsic environmental factors such as culture and environment that could have an impact upon the outcome of clinical studies. The ICH *E5* objectives are:

- To describe the characteristics of foreign clinical data that will facilitate their extrapolation to different populations and support their acceptance as a basis for registration of a medicine in a new region.
- To describe regulatory strategies that minimize duplication of clinical data and facilitate acceptance of foreign clinical data in the new region.
- To describe the use of bridging studies, when necessary, to allow extrapolation of foreign clinical data to a new region.
- To describe development strategies capable of characterizing ethnic factor influences on safety, efficacy, dosage, and dose regimen.

(ICH 1998)

Thus a regional regulatory authority can assess similarities and differences in PK/PD and the dose-clinical response relationship using clinical data from a foreign country. In a bridging approach, the agency conducts full or partial mirror studies for the purpose of extrapolating foreign clinical data to meet local clinical trial standards (ICH 1998; Nakashima *et al.* 2011). When using external data as the primary source of PGx knowledge, special attention should be given to ethnic biomarker-sensitive approaches in clinical trial design. Ethnobridging (EB) techniques allow evaluation of ethnicity-related differences in PK and PD and their effect on drug efficacy, safety, dosage, and dose regimen (Wang and James Hung 2012).

19.2.2.2 Japanese ethnobridging practices and drug lag

Japan is the second largest pharmaceutical market in the world after the US, with 11 per cent of global sales and a 2.5 per cent growth rate in 2009 despite having less than 2 per cent of the world population (Paek *et al.* 2011; World Population Review 2013). Yet for the period 1999–2007, Japan's approval rate of drugs from the EU and US was fairly low (56.1 per cent and 43.6 per cent respectively) (Tsuji and Tsutani 2010). Approval of Western drugs in Japan requires larger phase II and III studies which take into account the 'intrinsic' PK characteristics of Japanese participants (MHLW 2009; Kelly and Nichter 2012; PMDA 2001a). They may consider data from ethnic Japanese individuals living overseas, but stringent PMDA guidelines (2001a) state that Japanese participants who have spent more than five years abroad are not eligible for EB studies because they do not share 'extrinsic' factors such as diet and exercise. Foreign companies that wish to obtain drug approval in Japan almost always need to repeat the entire clinical drug development process, despite the delay and the enormous cost (Kelly and Nichter 2012).

Although the regulation of EB studies in Japan is meant to protect Japanese patients from inappropriate drugs, it has been suggested that it is also a protectionist measure for the local biopharmaceutical industry (Kelly and Nichter 2012). These regulations created a 'drug lag,' preventing seriously ill Japanese patients from accessing novel foreign drugs that had adequate PGx data but did not make it through the cumbersome Japanese regulatory approval process soon enough (Sinha 2010; Nakashima *et al.* 2011). The drug lag between the US and Japan from 1999 through 2005 was estimated at 40 months (Tsuji and Tsutani 2010). Consequently, some Japanese patients and doctors bought direct-to-consumer (DTC) medications from foreign countries, placing them in a vulnerable position with regard to safety, adequate information and consent to risk (Kelly and Nichter 2012).

The EB approach may also have been used to promote the notion of a pure Japanese bloodline. In attributing special characteristics to the Japanese genome, policy-makers promoted the opinion that the Japanese genome is unique (Kelly and Nichter 2012). This rhetoric may have played a role in justifying and maintaining a separate clinical trial pathway for foreign drugs for many years. However, biological anthropologists and geneticists agree that our established perception of 'race' has no scientific basis (see section 19.4).

The 1998 ICH *E5* agreement and global clinical trial (GCT) guidelines proposed to facilitate foreign drug approval by providing a more compatible framework with international multiethnic PGx studies. GCTs synchronize early-stage drug development by performing simultaneous clinical trials with participants from different ethnic backgrounds in Japan, the EU, and the US (MHLW 2009). These policies helped minimize EB studies and costly reiterations of phase II/III trials. Since 2007, the Japanese Ministry of Health, Labor and Welfare has tried to reduce drug lag by focusing on GCTs. Despite a significant increase in GCT-approved drugs in Japan (13.4 per cent in 2012), most drugs still require some level of EB studies and much more progress is needed in this area (Asano *et al.* 2013; Kelly and Nichter 2012).

The 2013 document *PMDA International Vision* sets Japan's goals for 2020 including the reform of international drug approval regulations (2011, 2013b). The PMDA recognizes that the life cycle of a medical product cannot be achieved only domestically, and states the need to build close international partnerships with foreign regulatory agencies like the EMA and FDA. Therefore the agency affirms its commitment to international harmonization initiatives such as the *ICH* and the International Medical Device Regulators Forum (ICH 2013; International Medical Device Regulators Forum 2013). In order to use resources more effectively, the PMDA also commits itself to accepting foreign clinical data, including PGx studies, and implementing joint GCP (Good Clinical Practice) and GMP (Good Manufacturing Practice) inspections (PMDA 2013b). By removing the dichotomy between national and international standards, the PMDA hopes to enhance its international status and improve domestic healthcare. Faster drug approval should reduce Japan's drug lag by speeding up the delivery of medical products to patients.

19.2.3 Accelerated drug licensing

The traditional drug licensing process generally adopts a binary mode of decision in which the single step of market approval designates a drug as a safe and efficient compound therapy. After long and costly preclinical and clinical trials, an experimental drug either receives marketing approval or fails due to concerns about safety and effectiveness. Problems such as high cost of development, length of time from conception to market, drug lag, and the lack of treatment for orphan diseases are exacerbated by the current binary approval system (Eichler *et al.* 2012). It has also been argued that late-phase drug failures stifle novel pharmacological

development, since each represents a delayed opportunity to develop the next successful drug (Reynolds 2013).

Regulators are looking at novel approaches and opportunities to remove these obstacles. For instance, regulatory agencies around the world are trying to accelerate the approval process by using PGx studies as an early indicator of novel drugs' efficacy and toxicity according to a genetically stratified population (Ehmann *et al.* 2013; Lesko and Woodcock 2002).

19.2.3.1 Expedited drug development programs by the FDA

The *Food and Drug Administration Safety and Innovation Act* was signed into US law on 9 July 2012. It allows drugs to enter an accelerated development and approval pathway if 'preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints' (Reynolds 2013). As such, the development of new drugs targeting serious and life-threatening diseases has seen their development accelerated by approaches based on PGx.

In June 2013, the FDA issued the *Guidance for Industry – Expedited Programs for Serious Conditions – Drugs and Biologics* that describes all expedited programs for drug development in the US, including a novel category, 'Breakthrough Therapies' (*21 USC*, § 356). This document represents the agency's vision for streamlining drug development and should be considered an optional recommendation. When finalized, it will replace the current guidance for industry entitled *Fast Track Drug Development Programs – Designation, Development, and Application Review* and *Available Therapy* (FDA 2006, 2004).

Drug sponsors may only access these programs if the new product addresses 'unmet medical need in the treatment of a serious condition' (FDA 2013d). A serious condition is defined as one that is associated with morbidity and has an impact on day-to-day functioning. The streamlined drug should either constitute a novel treatment or demonstrate improvement over the available therapies (FDA 2013d). Proponents suggest that combining a more flexible regulatory framework with the predicted advantages of PGx approaches could make more new drugs available without compromising their safety and efficacy (Reynolds 2013).

19.2.3.2 Early market entry programs by the EMA

The European Union community code related to medicinal products for human use functions as a single instrument, gathering all provisions for granting authorizations regarding market, production, labeling, classification, distribution, and advertising of medical products. As such, no medicinal product can be put on the market without the authorization of the EMA. If a product sponsor wants to obtain market authorization in more than one member state, the applicant must submit an application based on the same dossier in a process called the decentralized procedure. Likewise, if a product has already been accepted in one member state, an application based on the pre-existing dossier can be submitted to the others. In a second procedure called mutual recognition, the applicant must inform the member state that granted the initial authorization as well as the EMA (*Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*).

In 2004 and 2006, the EMA introduced two new instruments regulating early drug market entry under exceptional circumstances and through conditional market authorization (*Directive 2001/83/EC of the European Parliament*; *Commission Regulation (EC) No. 507/2006 of 29 March*

2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No. 726/2004 of the European Parliament and of the Council). The former is used when sponsors are unable to provide PGx data showing efficacy and safety. Faster market access can be granted based on ethical reasons if the drug is needed to treat a rare disease or a life-threatening condition and there is no other efficient treatment (*Directive 2001/83/EC of the European Parliament*, article 4). As with the FDA's expedited programs, failure to provide the required post-market approval studies can result in the withdrawal of an exceptional circumstance market license (*Directive 2001/83/EC of the European Parliament*, article 5). Although the conditional approval license is also intended for products treating unmet medical needs, drug sponsors are expected to provide the relevant clinical data in the immediate future, proving their product has a positive benefit-risk balance for quality, safety, and efficacy (*Commission Regulation (EC) No. 507/2006*, articles 22–23).

Although the EMA's regulations aim at accelerating access to novel drugs, a 2010 study by Boon *et al.* shows that neither of the two regulatory documents helped achieve this objective. For the 1995–2005 and 2006–9 periods, the mean total approval times for drugs submitted under the two early entry regulations were found to be comparable respectively to those of all drugs submitted during those periods regardless of method (Boon *et al.* 2010).

19.2.3.3 The shift to an adaptive licensing paradigm

The accelerated drug approval programs of the FDA, EMA, and other regulatory agencies attempt to depart from the binary approval paradigm through adaptive licensing, a step-by-step process which begins with early marketing authorization and ends with enhanced post-authorization control of a medicine (Eichler *et al.* 2012; EMA 2010; Ehmann *et al.* 2013). Adaptive licensing necessitates many conceptual changes in the critical elements of drug regulations: (1) evaluation over multiple stages rather than the simple dichotomy of pre- and post-licensing; (2) continuous evaluation of the trade-off between the early access risk and enhanced benefits of the novel therapeutics; (3) conversion of uncertain into acceptable risks by educating the public and providing informed consent; and (4) initial licensing to a small group, selected by PGx approaches, with subsequent increases in the group size based on better-defined evidence and risk assessment (Ehmann *et al.* 2013; Eichler *et al.* 2012).

The transition to adaptive licensing raises challenging legal and ethical issues: (1) mandatory drug labeling and prohibition of off-label use for safety reasons; (2) consumer awareness of dangers related to off-label use; (3) waivers for product liability suits during the initial learning period, except in cases of obvious negligence; and (4) longer post-approval studies (Ehmann *et al.* 2013; Eichler *et al.* 2012).

Earlier approval for restricted usage does not necessarily mean a shorter drug development process overall. Since regulatory bodies want to give earlier drug approval without compromising safety, increased pharmacovigilance in the form of longer post-market studies becomes an implicit term of the contract. For instance, newly approved drugs can be prescribed for off-label use under current FDA regulations (Dresser and Frader 2009). However, the acceptance of higher risks under the adaptive licensing paradigm could make these drugs less safe for patients not stratified by early PGx studies. For this reason, there is also a need to convey the information about the drug to patients and physicians, including any prohibition of off-label use. Some medicines approved under adaptive licensing would need to be restricted to certain patient groups until authorization is granted for a wider use.

Evaluation of benefits and risks becomes a complex process involving large amounts of data. Through the use of PGx early on during adaptive licensing drug development, quantification

of benefit-risk and better methods of clinical trial design and analysis can be envisioned. Early stratification of drug efficacy and toxicity could help design and analyze novel drugs and determine if they are suitable for streamlined approval for unmet clinical needs (e.g. life-threatening diseases).

19.3 Implementation of pharmacogenomics

19.3.1 Handling safety and quality

To ensure its proper development, PGx depends on the availability and reliability of genetic test kits to detect specific biomarkers that facilitate the prescription of the right drug at the right dosage while diminishing risks for ADRs.

Under the FDA's regulatory oversight, genetic test kits that are developed and sold to laboratories or direct-to-consumer are considered medical devices named *in vitro diagnostic tests* (IVDs). However, several genetic tests offered directly by clinical laboratories are considered 'home brew' rather than commercial products and fall in the category of laboratory diagnostic tests (LDTs) (Joly *et al.* 2011). Historically, LDTs were not under FDA authority and lacked the oversight given to IVDs. This influenced many companies to commercialise their tests as LDTs. Hence, it has been proposed that LDTs should be reviewed more stringently in order to evaluate their methods, accuracy, and appropriate labeling. Monitoring their safety will be important because LDTs are frequently used to inform critical treatment decisions for high-risk diseases; furthermore, they may be performed outside the supervision of a patient's physician at distant commercial laboratories and may be marketed directly to patients as DTC tests (Gibbs *et al.* 2013).

The Centers for Medicare and Medicaid Services (2013) and the Centers for Disease Control and Prevention (2013) oversee the quality of laboratory testing through the *Clinical Laboratory Improvement Amendments* (CLIA) of 1988, which introduced standards for quality assurance, certification, recordkeeping, and proficiency for laboratory tests (FDA 2013a; Zhang *et al.* 2012). CLIA does not currently enforce proficiency for genetic testing although most labs perform such tests voluntarily at varying levels (Tucker 2008).

Health Canada is the federal regulatory entity responsible for evaluating the safety and efficacy of health products for human use in Canada (Health Canada 2013). For this purpose, Health Canada can grant market authorization under the *Food and Drugs Act*, the *Food and Drug Regulations*, and the *Medical Devices Regulations* which set up criteria for the safety and effectiveness of PGx tests. In Canada, medical devices are graded from class I to IV according to the potential risk they represent to humans, with class IV being the highest risk. IVDs are considered class III medical devices, which represent a moderate potential risk to public health but a high potential risk to individuals (Joly *et al.* 2011). As such, diagnostic manufacturers are required to provide Health Canada with data on drug safety, PD, efficacy, and dose responses. In 2007, Health Canada released a *Guidance Document on Submission of Pharmacogenomic Information* that encourages the submission of PGx data when filing for market authorization in order to support claims about the safety and efficacy of a drug (Health Canada 2008).

19.3.2 Direct-to-consumer testing and medication

One of the most influential developments in personalized medicine has been the sale of drugs and genetic tests over the Internet. $4.3 billion USD was invested in direct-to-consumer advertisement (DTCA) in 2009, representing a quarter of US pharmaceutical expenditure for the period 1996–2005 (Mackey and Liang 2012). Proponents emphasize that 'consumers have been

empowered with additional information to "level the field" with the health care community, contributing to more efficient doctor–patient exchanges' (Paek *et al.* 2011), or that DTC represents 'the patient power revolution' (Kelly 2004). In contrast, opponents are concerned by emerging issues such as safety risks, increased cost, interference in the doctor–patient relationship, lack of analytical validity and clinical utility, false advertising, challenges in interpreting the results, and the psychosocial impact of the results on various communities (Howard *et al.* 2010; Paek *et al.* 2011).

As mentioned previously, some Japanese patients have opted to obtain foreign DTC medicine as a way to compensate for a prevailing drug lag (Kelly and Nichter 2012). These drugs and genetic tests are often associated with insufficient, inaccurate, and/or misleading information and need expert knowledge to be properly understood and used (US Government Accountability Office (GAO) 2010; Mackey and Liang 2012). Furthermore, DTCA is frequently used to market drugs early in their life cycle when there is a lack of pharmacovigilance data with which to determine health risks. Vioxx and Avandia are examples of blockbuster drug recalls following heavy DTCA (Paek *et al.* 2011; Mackey and Liang 2012).

A 2012 study by Borry *et al.* shows that France, Germany, the Netherlands, Portugal, and Switzerland have national laws that can partially or fully regulate DTC genetic testing. However, they are derived from interpretation of legislation that does not specifically address how those tests are advertised (Borry *et al.* 2012). Regulating DTCA for drugs and genetic tests is difficult because their providers can easily bypass national boundaries through the Internet. The *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine*: *Convention on Human Rights and Biomedicine* 1997 is a binding European treaty, ratified by 29 member states of the European Community, which states that predictive genetic tests should be subject to appropriate genetic counseling (article 12). It also requires that parties provide judicial protection against unlawful infringement of rights and principles, a compensation for undue damage, and appropriate sanctions (*Convention on Human Rights and Biomedicine,* articles 23–35). Moreover, the *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes* 2008, which was originally drafted by the EMA, states that genetic testing should always be performed under individualized medical supervision, and that appropriate genetic counseling should always be available for the person tested (articles 7–8).

One proposed solution is the establishment of an international certificate that would force DTC test providers to comply with ethical standards by demonstrating the scientific reliability of their products and meeting the requirements of genetic counseling (Hauskeller 2011). By analogy with the International Organization for Standardization (2013) certification, the rules of this certificate would be voluntary, but would provide a marketing advantage to compliant DTC providers while ensuring consumers a certain degree of protection against exaggerated claims.

19.3.3 Drug labeling and off-label use

The FDA does not prohibit physicians from prescribing off-label drugs to patients who do not have adequate treatment for their conditions (2011b; American Association of Orthopaedic Surgeons 2013). Unless PGx is used to stratify patients with certain predisposing genotypes, off-label use can result in toxicity and ADRs (e.g. increased metabolite overexposure) (Yamashiro *et al.* 2012; Mello *et al.* 2009). Due to these safety concerns, several bodies have called for more stringent risk-benefit assessments. The United States' *Food and Drug Administration Amendments Act* of 2007 imposes 'Risk Evaluation and Mitigation Strategies' on applicants if the FDA considers them necessary to ensure the benefits of a drug outweigh its risks (FDA 2013b, 2013e).

In 2009, French regulators withdrew Mediator (benfluorex), a drug licensed for diabetes but used off-label for weight loss, which caused between 500 and 2,000 deaths over a period of 33 years (Mullard 2011). The recent French law, *Loi n° 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé* (*Loi n° 2011-2012 du 29 décembre 2011*), aims to improve risk-benefit management and provide a better regulatory process for off-label prescriptions. Applicants under this law can apply only for diseases with severe prognosis and must follow strict criteria concerning the quality of scientific evidence and drug safety, but they may claim reimbursement from France's public health insurance system if the drug is approved (*Loi n° 2011-2012 du 29 décembre 2011*, articles 15 and 18.2.4). Off-label marketing authorization is granted for a period of three years (*Loi n° 2011-2012 du 29 décembre 2011*, article 18.1).

19.3.4 Orphan drugs

19.3.4.1 Regulations and incentives

Stratification through PGx raises some concerns about the creation of new minority groups. One scenario predicts that for a given drug, PGx research will identity 80 per cent of tested patients who would respond well, 10 per cent who would not show any benefit, and 10 per cent who would likely suffer from toxic effects. The principle of equal access to medicine and medication suggests that all patients should benefit from PGx. However, the market reality dictates that pharmaceutical companies focus on the 80 per cent of good responders and ignore the remaining 20 per cent of so-called 'orphan genotypes' (Rothstein 2003).

The European Organization for Rare Diseases (2013) estimates there are between 6,000 and 8,000 known rare diseases which may affect 30 million European citizens. Most are chronic and life-threatening, and 80 per cent are of genetic origin. Although they affect 6–8 per cent of the world population, orphan diseases have traditionally been neglected by the pharmaceutical industry due to the lack of profit incentive (Sharma *et al.* 2010). This situation calls for economic incentives that aim at promoting research and marketing of orphan drugs (Rothstein 2003). Accordingly, many countries have updated their drug regulatory policies by creating orphan drug designations. These have succeeded in shifting some of the pharmaceutical industry's focus towards orphan drug development.

Orphan drug designation is typically given to products intended to be the first treatment for a rare and/or serious disease. It is estimated that there are between 4,000 and 5,000 rare diseases worldwide for which no treatment is currently available (Sharma *et al.* 2010). In the *Orphan Drug Act* of 1983, the US defines an orphan disease as one affecting less than 200,000 people (approximately 0.06 per cent of the American population). The EU defines a rare disease as affecting 5 per 10,000 citizens (0.05 per cent), while Japan's definition of rarity involves fewer than 50,000 patients (approximately 0.03 per cent) (*Regulation (EC) No. 141/2000*; Japan Pharmaceutical Manufacturers Association (JPMA) 2013). Other conditions also affect the granting of orphan drug status. In the EU, a drug must provide diagnosis, prevention or treatment of life-threatening, seriously debilitating, or serious and chronic conditions such that without incentive-driven policies, the drug would be unlikely to generate sufficient returns to justify the necessary investment and there would be no satisfactory medication for the condition. In Japan, the drug must either treat a disease condition for which there are no other treatments available or be clinically superior to a previously accepted drug (EMA 2011; Sharma *et al.* 2010; JPMA 2013).

Canada currently has no orphan drug designation. However, a draft proposal from December 2012 delineates Health Canada's current position on the development of an orphan drug regulatory framework. The new regulatory framework will probably operate similarly to the US and EU laws for drug designation, which could allow drug sponsors in Canada to collaborate with those jurisdictions and file using a common application process. The objective is also to enhance access to orphan drugs without compromising patient safety (Office of Regulatory and Legislative Modernization 2012: 8; *Food and Drug Regulations*).

Regulatory agencies from the EU, US, and Japan grant a similar package of economic incentives to sponsors with an orphan drug designation, such as 7–10 years of market exclusivity, tax credits for development costs and application fee waivers (*Orphan Drug Act*; JPMA 2013; *Regulation (EC) No. 141/2000*; Thorat *et al.* 2012; Melnikova 2012; Meekings *et al.* 2012; Tambuyzer 2010). These incentives are thought to have a positive impact on drug approval rates. Only ten orphan drugs were approved in the decade before the United States' *Orphan Drug Act*, but 350 were accepted between then and 2010. Likewise, in the EU, the implementation of orphan drug regulations increased approval rates from eight before 2000, to 60 in 2010 alone. Third-party payers such as private insurers and public healthcare agencies have also helped to cover orphan drug costs, making it a very profitable business. With an annual growth of 6 per cent, orphan drug sales have been predicted to reach $112.1 billion in 2014 (Tambuyzer 2010).

19.3.4.2 Access to orphan drugs and reimbursement

Market exclusivity tends to increase medication price and hinder drug accessibility for patients (Murphy *et al.* 2012). This has created tension between different stakeholders. Since orphan drugs constitute a small market for pharmaceutical companies, they claim their drug development efforts should be compensated with some profit margin (Tambuyzer 2010; Sharma *et al.* 2010). Although 7–10 years of market exclusivity are granted to orphan drugs as an economic incentive, pharmaceutical companies claim that a market has to exist in the first place. Even if PGx lowers the cost of drug development, the disease stratification paradigm could also reduce market size so much that: (1) there is no chance of returns at all; and (2) market laws drive drug prices so high that patients are unable to afford them. Moreover, companies tend to maintain high drug prices despite public pressure (Arnst 2006). This economic paradox suggests that public healthcare planners should consider being more supportive of orphan drug development programs.

Member states of the European Community have little power in negotiating orphan drug prices since they are determined by market rarity (de Varax *et al.* 2004). This scenario is familiar in medicine. However, national drug coverage programs for orphan drug testing and reimbursement could help provide patients with access to unaffordable orphan drugs while securing markets for their developers with the promise of long-term profitability (Tambuyzer 2010). A study mandated by the European Commission showed that many EU countries, including France, Germany, Spain, Holland, and Sweden, systematically cover the costs of orphan drugs whose prices are higher than those of regular medicines (de Varax *et al.* 2004).

It has been suggested that a surge of high-priced orphan drugs could overwhelm current reimbursement programs, forcing policy-makers to make difficult ethical choices between allowing high expenditure on a few individuals or using the same amount of money to treat a greater number of patients in other disease categories (de Varax *et al.* 2004; Sharma *et al.* 2010). However, the narrow orphan drug market accounts for relatively little of the total national budget for medicine in most countries, and competition would eventually put downward pressure on drug price (Tambuyzer 2010). Thus, in the context of subsidized orphan drug reimbursement costs, disease stratification could indeed play out in favor of 'orphan patients.'

19.3.4.3 Outlook for adequate orphan drug incentives

There are both proponents and critics of the current incentive system for orphan drug marketing. A 2013 study by Matthews and Glass analysed the adoption process of 13 drugs in five European countries. Their results indicate that countries with stronger social welfare programs tend to pay for orphan drugs, unlike those with more of a free market economy. This suggests that economic incentives and national reimbursement programs could effectively encourage pharmaceutical companies to develop drugs for rare diseases (Matthews and Glass 2013). Another study proposes that economic incentives compensate for the reduced market size, resulting in an orphan drug market as profitable as the regular drug market (Meekings *et al.* 2012). However, concerns about whether PGx stratification could reduce the orphan disease market and its profitability persist (Tambuyzer 2010).

Critics of the current orphan drug programs suggest that economic incentives combined with a period of market exclusivity could create lucrative monopolies that do not necessarily serve all stakeholders. They propose that patients, the industry, and regulatory agencies should be able to better communicate their opinions with respect to the risks and advantages of orphan drug regulation. These critics further recommend public genetic screenings for orphan diseases in young children as a non-economic incentive. They argue that this would allow diagnosis to be linked to an assigned and reimbursed treatment, thus significantly improving children's health and lowering the risk of ADRs while securing orphan drug markets (Tambuyzer 2010).

The industry has also called for a clear and internationally harmonized definition of rare disease that would be accompanied by conditional reimbursement as a way of securing markets (Tambuyzer 2010). It is currently difficult to diagnose a rare disease because the available information is inadequate and healthcare professionals lack training and awareness. Although there are no diagnostic methods available for some orphan drugs, PGx and WGS approaches could contribute to the development of new ones since most orphan diseases have a genetic origin (Sharma *et al.* 2010; Li and Jones 2012). Greater coherence between international regulations would also favor the creation of a globalized market with additional economic incentives for these pharmaceuticals (Tambuyzer 2010).

According to a 2006 study by Ridley *et al.*, '[i]nfectious and parasitic diseases accounted for more than half of healthy years lost in Africa in 2002, but only 3 per cent of healthy years lost in developed countries.' Most people affected by these diseases are from low-income countries, so there is a lack of financial incentives for drug development (Ridley *et al.* 2006). They are called 'neglected diseases' not because there is a lack of scientific knowledge, but because the lack of a lucrative market dissuades pharmaceutical companies from investments and research (Ridley *et al.* 2006; Trouiller *et al.* 2002). Equitable access to innovations in pharmacogenomics and personalized medicine in developing countries appears very unlikely based on their lack of research and development infrastructures, financial resources, economical incentives, and well funded public healthcare plans (Kamal *et al.* 2011). Existing public healthcare systems in these countries simply cannot allocate most of their budget to a few patients with orphan genotypes while leaving aside millions in need of more essential care.

19.4 Ethics of personalized medicine

In addition to those introduced earlier in the chapter, there are a number of core ethical issues which stakeholders need to address in order to facilitate the transition to a more personalized healthcare environment. The advent of PGx could force stakeholders to revisit established bioethics principles such as autonomy, beneficence and justice or even formulate new ones that will

facilitate a more comprehensive ethical assessment of this emerging healthcare model (Ozdemir 2010; Breckenridge *et al.* 2004; Beauchamp and Childress 2001).

Genetically stratifying patients permits the identification of good responders who are also unlikely to experience toxic ADRs. On the other hand, patients that do not share the PK parameters set during drug development could be excluded from clinical trials, meaning little or no data related to drug toxicity would be available for their genotype (Nuffield Council on Bioethics 2006). If clinical trial design for subsequent phases were to include racial or ethnic categories as a proxy for known biomarkers, there is a possibility that a particular ethnic group would be selected as good drug responders whereas another would be excluded as poor responders (Peterson-Iyer 2008; Nuffield Council on Bioethics 2006).

According to its proponents, personalized medicine empowers patients to take their healthcare into their own hands (Paek *et al.* 2011). This rhetoric tends to transfer the responsibility of healthcare from the state and the physicians towards individual citizens. This is particularly troubling in a context where publications from the media, government agencies, and direct-to-consumer advertising companies may not provide access to a clear and balanced representation of emerging health products (Howard *et al.* 2010; GAO 2010). Hence, it is of prime importance that doctors receive the training necessary to advise patients about genetic testing and personalized treatments in an unbiased professional manner.

Although patients are rarely offered genetic testing in the current situation, the introduction of PGx in routine healthcare will mean more frequent genetic testing, possibly including WGS. Healthcare professionals will need to consider important ethical issues such as the type of genetic information that warrants disclosure to patients and its psycho-social impact upon them, including cases involving incidental findings (Nuffield Council on Bioethics 2006: 7). As PGx drugs become part of the medical standard of care for some diseases, patients could be required to undergo genetic testing before the prescription of certain medicines in order to avoid ADRs (Nuffield Council on Bioethics 2006: 3). Reimbursement of PGx treatments by public healthcare or private insurers could become dependent on whether or not the genetic test results indicate a particular drug (van Nooten *et al.* 2012). This is likely to create significant distress for patients suffering from life threatening diseases whose genetic profile does not warrant access to any of the available treatments.

19.4.1 Genetic discrimination

Genetic discrimination has been defined as 'the differential treatment of asymptomatic individuals or their relatives on the basis of their actual or presumed genetic characteristics' (Otlowski *et al.* 2012). If a disease predisposition is disclosed to a third party, the patient risks stigmatization and discrimination in his or her social life, in the workplace, and in obtaining health or life insurance (Rothstein 2003: 330–1). The consequences of genetic testing for disease susceptibility risks were first thought to be different to those of PGx tests for recommended drug types and safe dosages (Roses 2000). A genetic test for PGx purposes could have much narrower effects because it applies mainly to predict drug response (i.e. someone already affected by a medical condition). Yet PGx stratification can provide valuable genetic data about how different subgroups within a population react to drugs. This implies that PGx could promote genetic discrimination if a particular subgroup were to be excluded from phased clinical trials or, later in the process, from access to drugs. For instance, poor responders could experience discrimination by being 'more expensive to treat,' a designation which could affect drug reimbursement by third-party payers (Breckenridge *et al.* 2004). As with disease genetics, discriminatory use of PGx data in the aforementioned scenario could contribute to public fear of PGx testing (Joly *et al.* 2013).

Some PGx studies claim to have identified intrinsically determined drug response differences among racial or ethnic groups (FDA 2005). For example, the Caucasian population in the US has been found more likely to have abnormally low levels of the drug-metabolizing enzyme CYP2D6 that affects antidepressants, antipsychotics, and beta-blockers (Xie *et al.* 2001). Other studies indicate that African-Americans have a poor response to antihypertensive agents (Exner *et al.* 2001; Yancy *et al.* 2001). Moreover, a study of 173 publications in nutrigenetics from 1998 to 2007 shows that a vast majority focused on 'white' participants (Hurlimann *et al.* 2011).

In these types of studies, it is extremely important for reviewers to critically assess the criteria used to place individuals in one group or another, and how the research team actually implemented their stratification protocols. The authors of these studies should also be sensitive to the fact that conclusions formulated too broadly can easily be misinterpreted and used as propaganda by racist organizations (National Alliance News 2008). Detailed information by the authors describing the basis of the stratification and the limitations of their findings could also go a long way in preventing unfortunate incidents associated with the misappropriation of scientific findings.

Admixture between ethnic groups is increasingly common in modern society, and there are more genetic differences between individuals of the same ethnic group than between ethnic groups. As such, it is well argued that race is a social construct and cannot be defined scientifically (Lewontin 1995). Hence it is difficult to justify using the concept of race as a genetic biomarker in PGx drug development. Racial classification reflects an imperfect socio-cultural construct that should not be considered equivalent to scientifically validated genetic biomarkers (FDA 2005). The drug response differences that have been recognized between countries (Malinowski *et al.* 2008) may be caused by extrinsic rather than intrinsic factors, suggesting the use of more transparent and science-based stratification criteria based on socio-cultural and/or geographical ancestry (Ozdemir *et al.* 2008). Furthermore, successful PGx implementation should help identify accurate genetic biomarkers capable of supplanting the use of racial or ethnic stratification altogether (Tucker 2008; Nuffield Council on Bioethics 2006). Scientists and drug sponsors should adopt a PGx approach that includes multiple population groups during research and drug design, and should consult representatives from racial or ethnic minorities regarding their protocol design and participant selection process (Peterson-Iyer 2008). Finally, the development of robust, harmonized guidelines outlining acceptable proxies for PGx stratification would provide more transparency, equity, and accuracy in PGx research and implementation.

Genetic discrimination has also been discussed in the context of personal insurance, where insurers might use this information to determine applicants' eligibility for private life or health insurance coverage. Some employers, primarily in the US, have shown an interest in requiring the disclosure of genetic information as a condition for initial employment or promotion. This could allow them to identify individuals who are more susceptible to developing certain illnesses that would lead to greater absenteeism or pose risks to other workers. In some cases, there may be an argument in favor of testing for public health reasons or to fulfill a legal duty of protecting the health of the workers (Otlowski *et al.* 2012; Roberts *et al.* 2012). Genetic discrimination in insurance and employment is particularly concerning given our limited knowledge of the genomics behind complex disorders. Genetic information, including research data, can be easily misinterpreted or given undue weight by third parties lacking proper expertise. Yet the known instances of genetic discrimination have so far remained mostly limited to a few monogenic dominant disorders (Joly *et al.* 2013).

19.4.2 Instruments protecting against genetic discrimination

PGx implementation relies on the voluntary participation of all segments of the population. Yet multiple surveys have shown that although the public is interested in genetic testing, they fear data misappropriation, discrimination, and breaches of patients' privacy and confidentiality (Haga *et al*. 2012; Armstrong *et al*. 2012; Kobayashi *et al*. 2011). Fear of participating in genetic studies, especially for more vulnerable participants or those belonging to easily identifiable minority groups, could be addressed through education campaigns and best practices explaining the limits of genetic information and the importance of preventing misuse and discrimination outside of the clinical and health research spheres. Legislators around the world have also recognized this problem, resulting in a number of international, regional, and national policies which make explicit requirements to protect individuals from genetic discrimination.

The 1993 *Declaration of Bilbao* was the first to denounce the use of genetic information for discrimination in contexts such as work and insurance (Fundación BBV 1993). The United Nations Educational, Scientific, and Cultural Organization's (UNESCO) 1997 *Universal Declaration of the Human Genome and Human Rights* and 2003 *International Declaration on Human Genetic Data* affirm that no one should be subjected to discrimination based on human genetic or proteomic data, as this would infringe on human rights, fundamental freedoms, and human dignity. The United Nations Economic and Social Council's *Resolution 2004/09 on Genetic Privacy and Non-Discrimination* (2004, article 6) also proposed the development and implementation of standards for protection against misuse of genetic information that might lead to discrimination and stigmatization.

The *Charter of Fundamental Rights of the European Union* (2000, article 1) and the *Convention on Human Rights and Biomedicine* (article 11) prohibit discrimination based on genetic data in Europe. In the US, the *Genetic Information Nondiscrimination Act of 2008* provides some protection against genetic discrimination in health insurance and employment.

No national-level legal documents explicitly prohibit genetic discrimination in Canada (Joly 2006). However, the Canadian Life and Health Association Inc. has adopted a *Position Statement on Genetic Testing* (last revised in 2010), which states that members will not impose genetic testing on insurance applicants but will require access to the results of genetic tests. An individual with a genetic predisposition could be protected through generic dispositions protecting the right to privacy or right to equality in existing human rights laws, although there is currently insufficient case law in Canada to be confident in this type of protection (*Canadian Human Rights Act* 1985, article 3; *Canadian Charter of Rights and Freedoms* 1982, article 4; Otlowski *et al*. 2012). The Canadian *Tri-Council Policy Statement*, a prominent research ethics guideline which is national in scope, considers the risk of genetic discrimination against individuals participating in genetic research and recognizes that equal treatment is fundamental (Interagency Advisory Panel on Research 2010).

In March 2011, *Bill C-508 (Historical), an Act to Amend the Canadian Human Rights Act (genetic characteristics)* was introduced in Parliament 'to protect Canadians from discrimination on the basis of their genetic characteristics.' During the same session, *Bill C-536* was introduced to add the term 'genetic characteristics' to the list of prohibited grounds for discrimination in the *Canadian Human Rights Act*. These are both private members' bills and are unlikely to pass through both houses of Parliament. More recently *Bill S-218*, *an Act to prohibit and prevent genetic discrimination*, was proposed to prohibit the act of forcing a person to undergo a genetic test or communicate its results in order to enter or maintain a contract. If adopted, S-218 would modify the *Canada Labor Code* 1985 and the *Canadian Human Rights Act*.

Although laws have been introduced to offer considerable protection against discrimination in many countries, in others genetic data is not impervious to breaches of confidentiality and data misuse. Indeed, the Internet and data-intensive sciences like PGx have raised considerable privacy threats. Progress in bioinformatics has made it possible, in specific instances, to re-identify individuals through their genetic data, biological samples, or associated clinical data (Lin *et al.* 2004; Homer *et al.* 2008; Gymrek *et al.* 2013). Moreover, privacy laws are often riddled with exceptions that greatly limit their effectiveness (Rozovsky and Inions 2002). Examples include the right to communicate or access personal information with the consent of the individual to whom it belongs, such as for reasons relating to public safety. Given these limitations, PGx researchers and clinicians would be well advised to proceed carefully. This requires adopting robust, up-to-date privacy practices and security mechanisms, and describing the potential limitations of these measures clearly to patients and participants.

19.5 Discussion

Along with the completion of the human genome and the subsequent availability of WGS, progress in pharmacology has led to the discovery of many polymorphic genes that confer individual specificity in ADME. According to proponents of this approach, a healthcare professional could use patient biomarkers to prescribe the right drug for the right condition and at the correct dosage to optimize therapeutic outcomes. Genetic testing for polymorphic biomarkers of drug response should contribute to a more personalized healthcare system, providing a better framework to optimize phased-trial designs, expedite the drug approval process, reduce pipeline costs, and improve safety and efficacy (Tucker 2008). Hence, PGx tests and drugs are likely to improve the success of healthcare systems in addressing many forms of illness, including several life threatening diseases and rare disorders. Yet there are still many obstacles in the transition to personalized medicine. At the scientific level, researchers must still find the most appropriate biomarkers and determine when to use them during drug development.

Current initiatives by various national and regional regulatory agencies aim to harmonize regulatory policy to provide broader and easier access to foreign drug markets. For instance, the FDA and EMA are working towards more coherent regulations and policies for PGx approval within their respective jurisdictions as well as at the international level. In this chapter, we discussed the progressive alignment of drug approval guidelines by the FDA, EMA, and PMDA, suggesting an international harmonizing trend which was not so obvious a decade ago. Global harmonization of regulatory drug policies may be the best way of optimizing resources and fulfilling the needs of most stakeholders. International initiatives such as ICH, voluntary submission of biomarkers, orphan drug incentives, and accelerated drug approval appear to be necessary steps in the establishment of a global PGx regulatory framework. With the proper regulatory incentives and safeguards in place, PGx could contribute significantly to the improvement of global health.

However, well-balanced policy frameworks are needed to address the multiple obstacles on the personalized medicine pathway (Hamburg and Collins 2010). For example, national policymakers must reconcile national research priorities and international human rights norms to promote the application of fundamental bioethical principles such as autonomy, benefice, and justice. The paradigm change towards personalized medicine in healthcare does not warrant setting them aside, but could require new interpretation of these principles, as well as the development of new ones, to fill any existing gap in the international bioethical framework for PGx (Knoppers and Chadwick 2005).

Since personalized medicine relies on accurate and reliable genetic diagnostics, healthcare professionals should be trained adequately to perform PGx-related tasks such as interpreting diagnostics, genetic counseling, and drug prescription. In order to protect patients from overly optimistic claims by vested stakeholders, education policies should also provide the public with impartial, up-to-date and accessible information regarding genetic testing and treatments.

Stratification into smaller markets will likely make PGx treatments more expensive than other blockbuster drugs, at least in the short term. Widespread clinical implementation of personalized medicine will not occur if patients cannot obtain reimbursement for PGx drugs by third party payers, such as private insurers or through public healthcare systems. In the transitional period, improved models will need to be developed to assess the cost, benefit and clinical utility of PGx tools for reimbursement purposes. Policies promoting the development of drugs for rare disease will also need to be revisited to better account for the PGx development model.

19.6 Conclusion

Provided that efficient and safe ethical and legal frameworks are in place, personalized medicine will offer substantial benefits to patients in the future. Hamburg and Collins compared personalized medicine to creating a highway system, writing that '[w]e are now building a national highway system for personalized medicine, with substantial investments in infrastructure and standards. We look forward to doctors and patients navigating these roads to better outcomes and better health' (Hamburg and Collins 2010). We contend that law and ethics will play the important role of traffic signs on the personalized medicine highway system. The right policy balance must be attained so that researchers and clinicians can drive through this exciting new infrastructure at the optimal speed, while accounting for all of the necessary public safety requirements.

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