The Place of Pharmacogenetics in Person-centered Medicine: A Bioethical Reflection

Eduardo Rodriguez-Yunta and Fernando Lolas-Stepke*

Interdisciplinary Center for Studies on Bioethics, University of Chile, Chile

Correspondence: rodriguezchi@gmail.com Tel: +5622-6031-223

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ABSTRACT

This article reviews social, legal and ethical considerations of personalized medicine in research and development and service provision, with emphasis on Latin America by searching in Medline. The following social, legal and ethical issues involved in integrating pharmacogenetics into health care practice have been identified: it is not clear how to translate the knowledge of using right concentrations of drugs for individuals into public health practice; the possibility of stigmatization and discrimination of individuals and groups; the pharmaceutical industry may be reluctant to develop medicines for small stratified groups of patients; inequalities may be exacerbated; health care providers will need to be well educated on genomics; debates about the right way of using informed consent; respect of privacy and safeguarding confidentiality; commercial use of genetic information; application of pharmacogenetic data in health care according to ethnic differences; regulatory measures may be necessary to encourage the development of medicines for small stratified groups according to genetic tests. Conclusion: however relevant pharmacogenetic studies may be for the development and use of pharmaceuticals in the prevention and treatment of disease, their widespread use and acceptance are limited by social, legal and ethical considerations. These are particularly acute and urgent in those areas of the world where people may not have easy access to medical technologies.

Keywords: Pharmacogenetics; Social, Legal and ethical issues; Person-centered medicine

INTRODUCTION

The notion of a person-centered medicine is intimately linked to the practice of healthcare based on values. It has been for centuries an old aspiration of the healing professions to approach individual sufferers in their own context and to respond in a personal and dedicated form to their needs. The old dictum “there are no diseases, only diseased persons” reminds clinicians that every case is unique and needs personalized attention.

In the context of this person-centredness claimed for the healing practices at all times many aspects must be considered. Among them: rapport, empathy, technical skill, and pertinent knowledge. In particular, prescription
of medication or interventions is a field particularly relevant for the analysis of a value-based practice of healthcare.

Personalized or precision medicine refers to treating persons with the right drug for the right patient with the right dosage based on genetic data; this idea includes also prevention of disease [1]. The Center for Drug Evaluation and Research of the U.S. Food and Drugs Administration defines pharmacogenomics as the study of DNA and RNA variations related to responses to drugs. Pharmacogenetics is a subcategory defined as the influence of DNA variations in the response to drugs [2].

The genome of individuals contains information about reactions to specific drugs, effects of diets on the body, and conditions of life. Personalized medicine based on pharmacogenomic data is being considered a new approach to medicine in which genetic differences of individuals help in the diagnosis, prevention, and treatment of health-related conditions [3]. The genetic variability among individuals is responsible for most of the different pharmacological effects of drugs. There are genetic polymorphisms which can be studied to correlate with the effects, most of them of single nucleotide in ADN sequence [4]. These genetic polymorphisms can modify the expression and function of proteins and enzymes involved in drug metabolism, such as: absorption, biotransformation, distribution in the body and excretion, and also the interactions with drug receptors. The allelic variants can be used to classify people as low, rapid or ultra-rapid metabolizers, which affect the efficacy and safety of drugs.

Pharmacogenomics helps to predict the effective dose of drugs for patients and to identify individuals with risk of toxicity or lack of therapeutic response to specific drugs. The genome information may be translated into public health efforts and the practice of medicine looking for less adverse effects of medications.

The genes associated with safety or therapeutic efficacy of drugs may be classified in five categories [5]:

1. **Pharmacokinetics**: Related to absorption, distribution and metabolism or excretion of drugs.
2. **Pharmacodynamics**: Implicated in the mechanisms of drug action and effects. Genes that codify for drug receptors and functional proteins involved in post-receptor events are also included.
3. **Modifiers of disease**: Genes that affect both a disease and the response to drugs (example: some polymorphisms of ionic channels may produce both cardiac arrhythmias and toxicity with drug use).
4. **Genes that modify cancer processes** such as those that function as respond markers for drugs, such as oncogen her-2 of breast cancer [6]
5. **Genes with biological function** similar to drugs which protect or have a therapeutic effect.

However, the safety and efficacy of drug response depend not only of genetic differences, but also of environmental and epigenetic effects [7,8].

Pharmacogenomics may be used in drug development to improve speed and efficiency. The practice consists in studying drug safety and efficiency with exploratory genomic tests to identify biomarkers predictors of drug response. The Boston Consulting Group considers that the cost of developing a new medicine maybe reduced to about 60% with the help of pharmacogenomics [9]. Fewer participants may be needed to complete the trials required to bring medicines to markets, thus reducing costs and time. Biomarkers may allow stratifying populations of sick people in subgroups according to therapeutic response with the goal to exclude in advance patients who respond inadequately to experimental drug, reducing therapeutic failures, adverse reactions and research costs. In this way it may be possible that some drugs which may have been abandoned due to problems with safety and efficacy may be approved for a subgroup of patients, benefiting patients, regulatory agencies
and the pharmaceutical industry [10]. Furthermore, the probability of withdrawing drugs post-market due to undesired effects may be reduced by finding on time patients with high risk of unwanted effects [11].

In order to justify the application of genotyping technology, the cost-efficacy must be evaluated with specific criteria such as [12]:

- Strong association between polymorphisms and clinically relevant effect
- Prevalence of genomic variant sufficiently high to justify testing
- Genotyping with relevant impact in quality of life, mortality or diminishing treatment costs
- Using genetic tests (versus standard procedures) provides a significant reduction in adverse events
- Sensibility, specificity and associated costs have been previously identified
- Additional costs such as genetic counseling

The Food and Drug Administration (FDA) of the United States, among other agencies, validates and approves pharmacogenetic biomarkers for clinical practice including information for adjusting drug concentrations and for diminishing undesired effects [13].

This article reviews social, legal and ethical considerations of personalized medicine in research and development and service provision, with emphasis on Latin America.

**Pharmacogenomics in Latin America**

In Latin American countries there are practical problems in the application of information gathered in pharmacogenomic studies. Several issues hamper application, such as [14]:

- Lack of enough clinical laboratories to carry out tests in rapid and cost-effective way
- Few health care professionals able to interpret results of tests and associated clinical pharmacology
- Doubts whether insurance or health care systems may subsidize the tests
- Lack of information about relevant pharmacogenomic genes in the population of Latin America, especially considering the variety of ethnic groups in the region
- Lack of governmental support

**Ethical, Legal and Social Issues Related to the Practice of Personalized Medicine**

Many have criticized the concept of personalized medicine on different grounds. The Nuffield Council of Bioethics Report considers that the promise of personalized medicine by pharmacogenetics is misleading since so far the genetic tests are only able to generate probabilistic medicine of varying degrees and rather than being directed person by person it might only be able to suggest a particular drug to genetically defined subgroups [15]. Furthermore, there are many social, legal and ethical issues involved in integrating pharmacogenetics into health care practice. The following issues have been identified:

*The relation between individual benefits with public health interests need attention:* While some individuals may be benefited by using the right concentration of drugs for therapy, it is not clear how to translate this knowledge to public health practice. Another problem is the availability of genetic tests, whether over the counter, through internet or only through the request of a physician. Individual benefits may be in opposition to social needs. An additional problem is that people in disadvantage in less developed countries do not have access to genetic tests [16]. The costs of gene-based therapies and genetic testing are very high and constitute a significant obstacle [17].
The possibility of stigmatization and discrimination of individuals and groups: Genetic discrimination and stigmatization is one of the concerning issues with genetic research since the publication of the human genome. Personalized medicine may amplify the problem by considering slight genetic differences with biological and economic impact. The publication of genetic tests associated to diseases or behaviors linked to specific groups, races or ethnic background may cause stigmatization followed by discrimination. For example, the publication of a genetic study with the Maori of New Zealand gave the wrong impression that Maori people was characterized as violent prompt to criminal behavior. Later, the study was shown to be misleading, but stigmatized the Maori [18]. Discrimination has also been reported by employers, insurers or government [19]. Stigmatization or discrimination may be higher for persons or groups with low probability to respond to treatment, especially for chronic diseases of high cost which may affect insurance fees and the possibility of employment [20].

Stratification of patients groups based on genetic information: Identifying subgroups of patients with low probability to respond to treatment places the dilemma of what to do with them [21]. Genotyping as criteria for inclusion and exclusion may lead to losing benefits for those excluded and less participation of populations with genotype of low respond. This selection may establish categories of persons or groups which may be subjected to stigmatization or discrimination. The pharmaceutical industry may be reluctant to develop medicines for small groups of patients. Already, treatments of rare diseases are grouped into “orphan medicines” due to the small revenue it generates and lack of interest for investment. Pharmacogenetics may extend the number of orphan medicines by stratifying the patient population into genetic base subgroups.

Personalized medicine may exacerbate inequalities: In order to incorporate personalized medicine into health care with equity, genetic information must be gathered from all ethnic and racial groups, but in practice underrepresented poor populations have little chance for recruitment in genetic studies, so that most probably they will not receive benefits [22]. The proponents of personalized medicine content that costs will be reduced in clinical trials using genomic information to select those less susceptible to adverse effects, but including minorities may increase the expenses in drug development [23]. The high cost of new drugs and of genetic tests associated to personalized medicine limits the number of patients that can benefit. In order to design research protocols and resource allocation, optimal availability of individualized treatments in all eligible racial/ethnic groups should be ascertained [24-26].

Currently, genotyping technology may be too costly for many developing countries. The low health care budget determines other priorities in expenses. The high costs limit application to selected population groups who can afford which may highlight inequalities inside countries and among countries. Furthermore, the pharmaceutical companies will have little incentive to develop drugs for diseases with low prevalence in poor countries and the orphan medicines will be more concentrated in these countries.

Changes in physician-patient relationships: The individualization of therapeutic decisions is a joint responsibility of physician and patient requiring greater level of literacy by patients and enough time by physicians to go over with patients considering all possibilities [27,28]. Some scientists define personalized medicine as patient-centric medicine raising the quality of healthcare services and improving outcome [29]. One of the great challenges for physicians is to explain patients the complexity of genomic tests in relation to improving therapeutic effect. The patient may be reduced to his/her genetic characteristics by the physician and may need genetic counseling in order to understand the genetic tests results and the social implications [30].
some countries there are few professionals trained in genetic counseling. Furthermore, decisions must be taken in spite of possible uncertainty of genetic findings [31]. Health care providers will need to be well educated on genomics in order to be able to guide decisions.

Problems with informed consent: When performing pharmacogenetic studies patients are asked to consent not only to the clinical trial they are participating, but also to research involving specific genetic tests related to the effects of a drug and additional pharmacogenetic studies. As a result, patients must give authorization to pharmaceutical companies to link personal and family information to genetic research, which may risk the respect for privacy, often without fully understanding all the implications [32,33]. Additionally, often samples may be stored in biobanks with informed consent issues which are under debate, such as requiring information about: benefits, sample storage, primary and secondary usage, safety procedures, data and biological samples transfer and disposal, anonymity or coding, death or incapacity of participant, safeguarding of confidentiality, having the option for withdrawing the samples from the study, waiver of consent, returning research results including incidental findings [34-36]. The type of consent whether broad, restricted or tiered is highly discussed since the degree of donors’ autonomy diminishes by opening to any kind of research. Furthermore, there are also problems for informed consent when transferring data or biological samples overseas with different legislations among countries [37,38].

Respect of privacy and confidentiality: Genetic data is subjected to privacy protection since it has predictive value for future diseases and quality of life, expandable to family members and the following generations [39]. Pharmacogenetic tests may carry the possibility of revealing additional sensitive information about the patient who may wish not to be shared. In this regard, family members may want to get informed about the risk of a disease which may influence their life, but this should be balanced against patient’s privacy [40]. Complete protection of privacy is difficult when considering the practice of direct-to-consumer genetic tests proposed on the internet [41]. Genomic information may be stored in computerized databases which must be safeguarded since employers and insurance companies may wish to have access to this information for their own interests.

Sharing, storage and use of genetic information: There is risk in some projects that data obtained from patients and derived from research may be used for commercialization or by pharmaceutical companies. Some sequences isolated from patients may be useful for performing genetic tests and file a patent for commercial use. This fact must be informed in informed consent process.

Application of pharmacogenetic data in health care according to ethnic differences: Although the pharmaceutical companies may be prompt to market drugs for specific ethnic or race groups with resources, it may be more reluctant to do it for poor ethnic or race groups due to financial constrains. Linking race to genetics may provoke racial disease stereotyping and simplistic conceptualizations of pharmacogenomics interactions [42-44]. Furthermore, although ethnic differences may be encounter in the respond to treatment by drugs, generalizations must be avoided since there are considerable variations among members of ethnic groups. The real predictor is found through genotyping of individuals not ethnicity [45].

Regulatory issues: The transition of current healthcare system to personalized medicine needs strategy planning and establishing policies to take into account economic, social and ethical issues in order to create a positive impact on quality of health. Regulatory measures may be necessary to encourage the development of medicines for small stratified groups according to genetic tests.
Additionally, there are increased risks of liability since the responsibility of physicians is higher with the greater complexity of medical practice and the chance of increasing medical errors, while the essence of their responsibility remains unclear [19]. In well-defined cases it is possible that in the future a physician may be subject to liability for exposing a patient with an ineffective treatment or excessive doses when there are pharmacogenetics tests that predict response.

Post-marketing surveillance: Clearly, there will be a problem if clinical trials are performed in smaller more targeted patient populations in order to market drugs more quickly, since there will be less available data about potential adverse drug reactions in the general population and it the drug is made available, post-marketing surveillance of drug response must be essential, furthermore, affecting the non-maleficence principle for those in which no genetic tests are available [46].

Challenges and Promises: The Future of Person-centered Medicine

However relevant pharmacogenomic studies may be for the development and use of pharmaceuticals in the prevention and treatment of disease, their widespread use and acceptance are limited by the considerations previously outlined. The idea of the best drug for the appropriate person at the right dosage and the optimal time is a long expectation of medicine since antiquity. It presided over the development of successful therapies in the area of antimicrobial medications and is a target for many interventions in the field of cancer research. As we have observed, developments in this area, however important and promising, are fraught with ethical dilemmas and challenges. These are particularly acute and urgent in those areas of the world where people may not have easy access to medical technologies. The following problems must be addressed for widespread use, considering vulnerable populations: availability of genetic tests for public health use in low income settings; avoiding the stratification of patients groups based on ethnic categories; poor populations must enter into the benefits of pharmacogenomics for equity access; safeguarding of privacy and confidentiality; availability of genetic counseling; policies to take into account economic, social and ethical issues for the stratification of patients groups based on genetic information. Furthermore, a great bioethical concern will exist for post-marketing surveillance if there is little available data about potential adverse drug reactions in the general population in clinical trials data generated with the use of pharmacogenomics in idealized populations, affecting the non-maleficence principle for those in which no genetic tests are available.

Irrefutably, these observations, progress is undoubtedly of value. It should be considered in light of a value-based practice of health care where pharmacogenomics and its associated advantages do certainly have a place which will become more meaningful integrated into a wide notion of person-centered care. The true meaning of a personalized medicine does not rest solely on technical progress but on an adequate integration of this progress to the humanistic conception and the valoric foundation of the healing professions.

Conflict of Interest

The authors of the article declare that there is no potential conflict with the content presented in the article.

References
