

BIOETHICAL DIMENSION OF THE PHARMACOGENETIC RESEARCH

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Abstract

Pharmacogenetics aims to elucidate the interindividual variability in clinical response to a particular therapeutic regime based on patient's genetic profile, thus improving clinical-decision making process and facilitating the personalized medicine. Pharmacogenetics opens the era of more effective and safer drugs administered as individualized therapies, but, at the same time, it also raises new ethical challenges regarding confidentiality and privacy, the informed consent, the availability of drugs to the patients identified as non-responders, the anti-discriminatory legislation, as well as laws for intellectual properties and exploitation of pharmacogenetics data.

Key words: bioethics of pharmacogenetics, informational risk, patients' stratification, ethical guidelines.

*There are more things in heaven and
in earth, Horatio,
Than are dreamt of in your
philosophy...*

W. Shakespeare, Hamlet act I scene 5

Pharmacogenetics and personalized medicine

The pioneering and interdisciplinary field of pharmacogenetics aims to elucidate the interindividual variability in clinical response to a particular

therapeutic regime based on patient's genetic profile. The main goal of pharmacogenetics is to develop new strategies to predict and optimise the individual's response to therapy based on specific genotype of each patient. Stratification of patients according to their genetic susceptibility to benefit from an efficacious treatment or, on the contrary, to develop adverse reactions, could guide the choice of the best available drug therapy, thus improving

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clinical-decision making process and facilitating the personalized medicine. [8]

Pharmacogenetics focuses on the relationship between “one drug – different patients (many genomes)” and it opens the perspective of individualized therapy by prescribing the right medicine to the right patient. Today it is possible to determine patterns of response before treatment’s prescription due to increasing molecular information concerning the enzymes which play a role in drug metabolism. Therefore, pharmacogenetics has had a great contribution in the reconsideration of medicine as an art according to the prediction of Sir William Osler since 1892: “If it were not for the great variability among individuals medicine might as well be a science and not an art”. [9]

There are “patient-tailored medicines” already approved by Food and Drug Administration (FDA): *trastuzumab* (*Hercept*) and *imatinib mesilate* (*Gleevec*). *Trastuzumab* (*Hercept*) is indicated for metastatic breast cancer overexpressing HER2 protein (1998) and it was released on the pharmaceutical market together with one prognostic pharmacogenetic test and two pharmacogenomic immunohistochemical assays to measure HER2 neu protein expression level in order to select breast cancer patient before *trastuzumab* prescription. The approval of *imatinib mesilate* (*Gleevec*) for late phase chronic myelogenous leukemia in May 2001 is another example of individualization of therapy by molecular targeting to abnormal proteins. [7]

Pharmacogenomics, more comprehensible than pharmacogenetics, represents the study of differences among a number of drugs with regard to gene expression response in a single (normative) genome/expressome: “many drugs – one genome/expressome”

relationship. Accordingly, pharmacogenetics is more useful in clinic for individualized medicine, while pharmacogenomics becomes precious guide in pharmaceutical research and drug design by selecting the best drug candidate from a given series of screening compounds. [10]

The pharmacogenomic research assists drug discovery and design by identifying new targets for traditional drugs, helps to understand why the same drug is efficient for some people but not for others, explains drug side-effects and allows the introduction of new classes of drugs. [9] It significantly increases the chances to interfere with or to diagnose diseases, to discover pre-symptomatically genes for monogenic disorders, to detect genetic predisposition to common diseases as cancer and psychiatric disorders, and, in the near future, to predict behavioural peculiarities, such as imaginativeness, creativity or violent and antisocial behaviour. [14]

Ethical aspects and guidelines in pharmacogenetic testing

Food and Drug Administration (FDA) defines pharmacogenetic testing as “an assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics)”, and makes a distinction from pharmacogenomic testing that involves “an assay intended to study interindividual variations in whole-genome or candidate gene single nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivations that may be correlated with pharmacological function and therapeutic response”. [5]

European Medical Evaluation Agency (EMA) points out that: “it is important to distinguish between genetic testing for

the diagnosis or prognosis of disease and the form of genetic testing performed for pharmacogenetics...generally carries a different magnitude of social, legal and ethical considerations for the patient". [7] Therefore, a clear distinction needs to be made between genetic testing for rare mutations diagnosis in monogenic diseases (Huntington's disease, phenylketonuria, cystic fibrosis, thalassaemias, BRCA1 for familial breast cancer), and pharmacogenetic profiles by identification of common SNPs in different ethnic groups which are predictable for individual drug response. Careful assessment of pharmacogenetic research procedures and management of patients' genetic data must be ensured in order to avoid discriminative attitudes by health care providers which might regard some patients who are detected as non-responders or with high risk of adverse events to certain drugs as difficult or expensive to treat. [12]

All authorities agree that pharmacogenetics opens the era of more effective and safer drugs administered as individualized therapies, but it also raises new ethical challenges in both fields of research and therapy. However, these new pharmacogenetic technologies have generated a multitude of controversies in scientific and medical communities that are attempting to define the ethical connotations of pharmacogenomics spectacular development in the last decade.

According to Buchanan, the ethical problems associated to pharmacogenetic research would be "the regulatory oversight, the confidentiality and privacy, the informed consent, the accessibility of drugs, and the changing of clinicians responsibilities". [2]

In 2001, the Italian Society of Hospital Pharmacy published the ethical guidelines of clinical trials in

pharmacogenetics focused on data collection and storage, confidentiality, consent, anonymity and subject protection [8]. In 2002 the Nuffield Council on Bioethics (UK) began to study the ethical, legal and social issues raised by the development of pharmacogenetics. [12]

Guidelines for the pharmacogenetic research during clinical drug development comprise those issued by FDA in 2004, International Conference on Harmonisation (ICH) Consensus in 2006 upon pharmacogenetic terminology (E15) - the latter defining pharmacogenetics as "the study of variations in DNA sequence as related to drug response", as well as the Industry Pharmacogenomics Working Group (2009) general guidelines relevant to the design and analysis of pharmacogenetic studies and its application to drug development in order to achieve the final goal of personalized medicine. [1]

Informational risk in pharmacogenetic research

If the ethical, social and legal challenges of pharmacogenetics are regarded as less prevalent than genetic testing for disease susceptibility and also the physical risk associated with most pharmacogenetic research is low, on the contrary, the informational risk related to confidentiality is perceived to be important. This informational risk derives from personal, familial and social nature of genetic information, as well as its potential to discriminate and stigmatize from insurance and employment point of view, especially in countries lacking a universal health care system. [5]

Apart from the obvious risk of genetic information dissemination, knowledge of variations of genotype may radically change a person's self-image,

potentially leading to a personal loss of sense of well-being and functionality in society, as well as undermining the career or reproductive choice. [13]

Pharmacogenetics Working Group in the United States and the European Agency for the Evaluation of Medicinal Products in Europe have established different levels of confidentiality within the framework of pharmacogenetic research, from which the most appropriate level of data protection and privacy must be decided according to each research protocol in order to maximize the individual and societal benefit of pharmacogenetic research while safeguarding ethical principles and privacy protection and reducing informational risks. The greatest degree of privacy protection compatible with the objectives of pharmacogenetics research integrated into clinical trials and also with the ultimate goal of supporting label claims, is represented by single-coded or double-coded samples. The Nuffield Council on Bioethics considers that it is possible to request broad consent with regard to the uses of samples and specifies that the participants must be informed of the degree of protection applicable to the research protocol before signing the informed consent. [5]

Anti-discriminatory and privacy legislation are needed to safeguard confidentiality and equality of access to the benefits of pharmacogenetic research, thus preventing insurance companies to exclude or charge higher premiums for people who are revealed by pharmacogenetic testing as “non-responders” to a particular drug and to wrongly assigned them as being “less profitable to treat” / “difficult or expensive to treat”. [14]

Undoubtedly, premedication pharmacogenetic testing will become a main part of regular medical care and the ethical

considerations surrounding the privacy of genetic data should neither require a special informed consent or privacy protection beyond that of usual medical tests, nor impose major constraints on the potential benefits of pharmacogenomics in terms of patients’ well-being and cost-effective healthcare. [13, 14]

Ethical issues of patients’ stratification

Since the pharmacogenetic research is targeted on human being, its most important ethical principle is to minimize the risks for subjects enrolled in clinical trials. The 16th article of European Convention on Human Rights and Biomedicine points out that a person may be recruited for research only if the risks which might appear are not disproportionate to the estimated benefits of the research. The pharmacogenetic analysis will refine the selection criteria and the people at risk of developing adverse reactions could be excluded from phase I and II studies. Consequently, the groups of people enrolled in phase III clinical trials will be less numerous, but more homogenous. The identification of the nonresponsive people on the basis of genetic variations will allow researchers to design smaller, but more effective trials by testing drugs only on people who would have great predictability to respond. Therefore, the increased effectiveness - the main scientific requirement and ethical imperative of any clinical trial, as well as the targeting to specific genetic population groups will facilitate and accelerate the complicate process of drug approval. [11]

In consequence, one of the most important ethical problems involved in pharmacogenomic research is the patient stratification. The positive aspect of this issue is that according to their genetic susceptibility some patients are chosen

for the best available drug therapy and can be detected the people susceptible to develop adverse reactions. The negative aspect resides on the danger of gliding along ethnic or racial lines and it is well known that in 2006 the U.S. Food and Drug Administration approved BiDil® (isosorbide dinitrate/hydralazine hydrochloride) as the first ever race-specific drug in the treatment of heart failure in African-origin Americans. [6]

The social and economical issues connected to disease and patient stratification enabled the creation of so-called “orphan populations.” These are people with very rare disease whose genotype has proven either more difficult to develop drugs for, or too small to be economically attractive for pharmaceutical companies to develop particular treatments. For example, the human gene NAT2 (hepatic arylamine N-acetyltransferase-2) has polymorphic alleles encoding fast acetylation and slow acetylation phenotype. As many drugs are metabolized by acetylation, the group which has the slow acetylation allele may be excluded from many clinical trials and become orphan population, without an access to a wide variety of drugs. [11] In this way, the orphan groups might be ignored both in the clinical trial process and in the terms of drug development, consequently the principle of equality is eluded and may contribute to social stigmatism.

Pharmacogenetics’ challenges to the practice of future medicine

It must be underlined that pharmacogenomics is revolutionary for drug discovery and development and for patient benefit but could (and will?) become challenging not only for economy of drug industry, but also for the actual clinical medicine whose physicians are not yet prepared to

understand and to apply the new individualized therapeutic strategy based on pharmacogenetics. Moreover, there is great concern that the actual doctors’ clinical skills could become inoperative and the technical aspects would dominate the doctor–patient relationship, when the drugs tailored to individual’s genotype will enter the routine health care system. [3]

Pharmacogenetics will change the practice and economics of medicine from various points of view: target validation and selection through functional genomic and proteomic technology (differential gene expression, transgenic animal models, *in situ* hybridization and immunohistochemistry); accurate diagnosis by classification of genetic heterogeneity of diseases; individualized dosing and prediction of efficacy while avoiding adverse effects by using abbreviated SNP linkage disequilibrium profile of each patient; more efficient clinical trials and enhanced post-approval drug surveillance; long-term health-care delivery improvement due to the increase in cost-effectiveness of medicines, limited side effects, lower complications, reduced hospitalization, reduced market withdrawal of drugs. [10]

For instance, in the near future, whole genome SNP linkage disequilibrium mapping applied to patients during phase II clinical trials of a medicine will enable the selection of smaller regions of SNP linkage disequilibrium defined as abbreviated SNP linkage disequilibrium profile. This will allow a more rapid and inexpensive screening of patients, because the groups of patients with high likelihood of adverse reactions and poor efficacy prediction according to their genotype will be excluded from phase III studies based on ethical reasons. Chip technology containing panels of abbreviated SNP linkage disequilibrium

profile will guide the selection of the most efficient and well – tolerated drug for each patient from several medicines having the same clinical indication. In post-marketing surveillance, as rare and serious adverse events are reported, the pattern of abbreviated SNP linkage disequilibrium profile could be compared between groups of patients and could predict those non-responsive or with high probability to develop adverse reactions, instead of the current approach of prolonged and expensive prescribing by trial and error current strategy. [9, 10]

In addition, a newly emerging ethical issue of pharmacogenomics research is that of intellectual property and commercial exploitation of pharmacogenetics databanks. In 1998 the European Parliament passed a law that recognizes isolated genes and nucleotide sequences as patentable inventions under the European Patent Convention. Furthermore, recent laws of the European Patent Office Board of Appeal also stated that the genetic testing methods can be

patented. These rules will considerably restrict the access to innovation and will increase the price of testing proportionally with market maturation [4].

Conclusion

The success of personalized medicine will largely depend on societal acceptance of the benefit/risk ratio implied by pharmacogenetic testing. The ethical implementation of pharmacogenetics will require a broad and ongoing dialogue among academics, industry, community representatives and regulatory agencies. Education of the public, health care providers, employers and policy makers is pre-requisites to prevent reticence, misunderstanding and discriminatory exploitation of pharmacogenetics testing, in order to achieve the goal of individualized therapy without social stigmatism and privacy violation.

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