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The value of free and informed consent in personalising medicine (review)

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Background. Personalised medicine is an approach towards more efficacious and safe treatment on the basis of understanding the molecular mechanisms and pathways of disease and unique genetic characteristics of the individuals. Biomedical research involving humans is essential for its development and clinical application, but raises a number of ethically sensitive issues. Free and informed consent to participate in such investigation is central in ensuring the principles of respect for persons, beneficence, non-maleficence and justice.

Materials and methods. This review is based on the analysis of the recent publications on personalised medicine, bioethics of research on humans as well as international laws and regulations and laws of the Republic of Lithuania.

Results. Discovery of a number of polymorphic human genes affecting response to drug leads to the development of pharmacogenetic tests aimed to individual drug selection and optimal dosing. At the same time, the genetic nature of such testing and the probabilistic character of its results raise considerable ethically sensitive problems, which are being solved on the basis of a number of international and national regulations related to the bioethics of research on humans. Contemporary international rules establish free and informed consent as an essential precondition for the research on humans allowing some ethically sound flexibility to enable testing individuals with the absent / limited capacity to consent, while some national regulations such as Lithuanian appear to be over-stringent.

Conclusions. The constantly increasing development and application of personalised medicine, both globally and in each country, needs a harmonious and risks-*versus*-benefit balanced ethically sound compromise between the respect of human rights and the necessity of biomedical research and clinical practice, particularly when the disease affects minors and / or leads to mental disability. Overstringent straightforward adherence to the principle of free and informed consent, even in a single country, ultimately leads to forgoing expected benefits of personalised medicine for the particularly vulnerable patients. To ensure an efficient compliance with all essential elements of informed consent in the development and application of personalised medicine, adequate public knowledge and perception of potential benefits and risks in the field are necessary, pointing to the importance of education of the society on (pharmaco)genetics, (pharmaco)genomics and bioethics. Physicians' education is even more crucial.

Key words: pharmacogenetics, pharmacogenomics, biomedical ethics, informed consent, national and international regulations in biomedical research

INTRODUCTION

Medication is currently the most extensively applied means of treatment. Until recently, the main trend in the development of pharmaceutical research and industry has mostly been aimed towards "one size fits all" treatment routinely targeted average individuals for therapy and production of blockbuster drugs focusing on large groups of patients with precisely defined diseases. Nevertheless, a medicine effective for one patient may not work for another or cause serious adverse events, even though both suffer from the same condition, thus making individual variations in response to drugs a substantial problem (1, 2). Considerable resources are wasted by prescribing many current mainstream drugs showing only a limited ef-

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ficacy: even the most effective therapies do not work in 20% or more of the treated patients, while in the case of cancer effective treatments may be as low as 25% (1). Besides that, almost all drugs that produce a favourable response may also produce adverse drug reactions (ADRs), which at present are a great burden for health care, being a significant cause of morbidity and mortality as well as having a significant impact on healthcare costs (3).

Recent breakthroughs in understanding both the individual and the disease at the genetic level and especially success in sequencing the human genome, as well as the development of molecular genetic techniques gave an impulse to moving from "one size fits all" treatment towards its personalising by increasingly developing an alternative approach named personalised medicine, which promises a "right medicine, for the right patient, at the right dose" (1, 4). Biomedical investigation is related to personalised medicine on all levels – from scientific research of the biological (especially genetic) basis of normal and impaired functions of the body and the ways to influence them, to clinical trials of the developed treatments and, finally, to clinical application of testing and treatment – and besides benefits inevitably raises a number of societal, economical, educational, political, legal and ethical considerations, which often act in opposite directions and are to be adequately addressed to achieve optimal results both on the global scale and with respect to concrete conditions in each country. Most of these considerations are related to risks and burdens for participants of research and / or patients, their families, social groups and, ultimately, society as a whole.

Biomedical ethics is aimed at finding a maximally efficient compromise between the scientific interests of a researcher / professional interests of a physician and the interests of a participant of the research / patient together with the necessity to respect his / her human rights, autonomy and dignity. The ethical and legal responsibilities, which the investigator has towards the person being investigated, reflect the basic ethical values of respect for persons, beneficence, non-maleficence and justice (5). Various aspects of a wide social background of performing biomedical research and implementing its results into clinical practice act by increasing or reducing these risks, while regulations and oversight practices on all levels (international, national, regional, institutional) and various types and scope (from international conventions, declarations, guidelines to national laws and administrative provisions) are necessary to ensure the adequate application of the principles of biomedical ethics in the context of concrete societal, cultural, economical, political and other conditions in each country.

This overview is focused on the principle of the voluntary informed consent, which predominates in the ethics of biomedical research in humans, with special regard to the development of personalised medicine. It is aimed to point to the main problems in the field to be dealt with by the countries, such as Lithuania, which currently are at the doorway of introducing the principles and developments of personalised medicine into their health care systems.

PERSONALISED MEDICINE

Most essential criteria of the treatment of pathology, namely its efficacy and safety, are highly dependent on large inter-individual variations in response to medications applied. In most cases individual response to treatment is a very complex phenotype resulting from the interaction of numerous factors such as patient's age, gender, body mass (obese or cachetic), timing of dose, environmental exposures (including workplace chemical exposures, food, alcohol, etc.), co-medications (inhibition or induction of a drug metabolising enzyme or competing for it), individual's state of health (especially the function of liver, kidney, endocrine and immune systems), etc. (6, 7). Genetic factors, which are more or less directly related to virtually all conditions of a living organism, play an important role in the individual response to treatment (1, 4, 8). In a broad sense, personalised medicine is an approach aimed to such individual response based on a deep understanding of the mechanisms and pathways of the disease together with a person's genetic makeup to tailor strategies for the detection, treatment, or prevention of disease. Nevertheless, the term "personalised medicine" is often understood more specifically as another term for pharmacogenetics and / or pharmacogenomics. Research, particularly investigation involving humans, is an essential part in the development of personalised medicine and its clinical application (Figure). It is currently developing in two main directions: (1) identifying specific genes and gene products associated with various diseases, which may act as **targets for new drugs**, and (2) identifying genes and allelic variants of genes that affect individual **response to current drugs** (2, 4, 9, 10).

Pharmacogenetics and pharmacogenomics

A. Garrod's work on alcaptonuria at the turn of the 19th and 20th centuries led him to the hypothesis that genetically determined differences in biochemical processes could be the reason for ADRs to some drugs (11). Clinical observations and investigations of inherited differences in drug effects gave rise to pharmacogenetics in the early 1950s, and recent advances in human genome research have spawned pharmacogenomics, a spin-off from the Human Genome Project. **Pharmacogenetics** is the study how an individual's genetic inheritance affects the body's response to drugs, thus it is an intersection of phar-

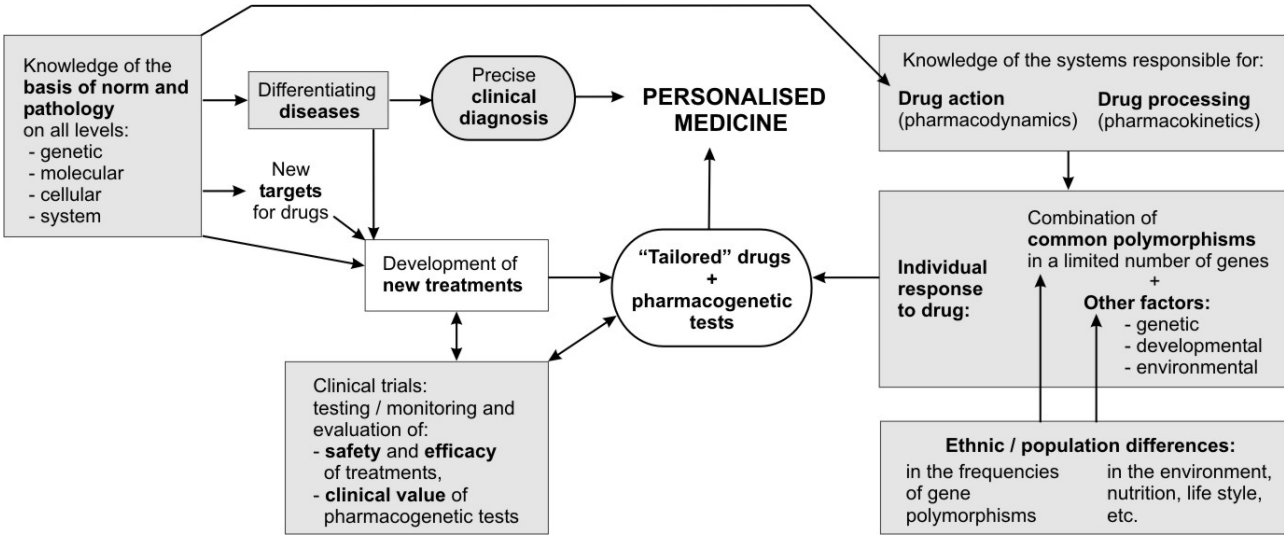

Figure. Development and application of personalised medicine. Shaded areas: biomedical investigation on humans is essential

macology and genetics (2, 10, 12). **Pharmacogenomics**, being an intersection of pharmacology and genomics, is a more wide-ranging discipline encompassing a novel gene expression profiling, proteomics, and bioinformatics tools, which implies examination of the whole genome or a substantial number of genes, aimed towards the improvement of the treatment with existing medicines and identification of targets for new ones (4, 12).

Human genetic factors may influence individual response to a medication in several different ways (2, 4, 13). Processes of drug absorption, distribution to the site of action, metabolism (de-activation of drugs and activation of prodrugs) and excretion (ADME), which are studied by pharmacokinetics, involve numerous proteins (metabolising enzymes in the first place) encoded by a large but finite number of genes and gene families. Individual variations in these proteins, leading to increased or decreased ADME processes, can substantially alter a person's response to that drug (often to a class of drugs). The same degree of common variation is being found in drug targets, which are components of the biochemical pathways (receptors, enzymes, carrier molecules and other proteins and / or molecular complexes). A genetically determined variation of the structure and expression level of these molecules, on the one hand, may influence their interaction with an administered drug by extending or narrowing their pharmacological effect and, on the other hand, lie in the basis of inherited diseases and / or susceptibility to a great variety of complex disorders. In numerous cases of major diseases, patients given the same clinical label of a single disorder may actually have a number of separate diseases with a common set of phenotypic features but a diverse genetically based biochemistry. Genetically determined variability in the targets of palliatively acting drugs provides another explanation for different response to such drugs. Certain diseases, notably cancers, develop in cells which have an altered genetic constitution, so that the genetic make-up of the affected tissue differs from that inherited by the person, in which it is present. These different ways in which genetic variation can influence response to medicines are related and may overlap.

Pharmacogenetics and pharmacogenomics are aimed to exploit the knowledge of the genetic component of the individual response to treatment to increase the **safety** and **efficacy** of medicines applied (or to be applied in future) in clinical practice (2, 10, 12). Adverse drug reactions may have numerous causes such as side effects, overdosage toxicity, allergies, idiosyncrasy, and at least part of them have been associated with genetic factors. Most ADRs are related to the dose and, therefore, could be influenced by polymorphisms in ADME genes. About 60% of the main drugs causing ADRs have been shown to be metabolised by one or more cytochrome P450 enzymes with a high frequency of inactive alleles (14), suggesting that the current genetic information, if properly applied in therapy, might be able to reduce the incidence of ADRs. The genetic basis of drug efficacy is related to the genetic variations that affect pharmacodynamics and involve genes that either interact directly with the drug or contribute to the disease process *per se* (1, 4).

Investigation in the field of pharmacogenetics is analogous to that of disease genetics. Early studies were focused to Mendelian effects on drug response, in the first place those related to drug metabolism and, similarly to monogenic diseases, a number of polymorphisms in the ADME genes (in the first place genes coding for the members of hepatic microsomal monoxygenases of the cytochrome P450 superfamily) affecting drug metabolism in a monogenic

way were identified, such as the failure of CYP2D6 null alleles to demethylate codeine to morphine (9, 15). Nevertheless, the majority of drug effects are similar to multifactorial disorders: they are determined by a complex interplay of the products of several genes that govern the pharmacokinetics and pharmacodynamics of medications, each with a mild effect on the phenotype, are confounded by the abundance of DNA sequence polymorphisms in these genes (16), and are influenced by numerous internal and external factors and thus are very problematic to investigate.

Summarised data of pharmacogenetics research are now available online in the knowledge base, PharmGKB (17). On October 16, 2005 it contained entries* on 21764 (1847) genes, 3803 (382) drugs, and 4075 (269) diseases.

Pharmacogenetic testing

The fields of pharmacogenetics and pharmacogenomics have emerged as potential new testing platforms for the individualised management of patients. Pharmacogenetic test can be defined as a test to detect the presence or absence of a particular change (causative mutation or its marker) in genetic information, which has been shown to be related to pharmacokinetics or pharmacodynamics of a drug or a class of drugs, aimed to improve drug selection, identify optimal dosing, maximize drug efficacy and / or minimize the risk of toxicity (2, 10). A considerable and rapidly expanding list of allelic variants in the genes coding for drug metabolising enzymes and targets often showing high variant allele frequencies in the populations (13) is already known (16, 17). What is not yet known is the clinical significance of these DNA polymorphisms for the majority of currently marketed medicines as well as for those under development. Therefore, there are still only a few examples of commercially available genotyping tests with an adequate validity and clinical significance of the results to be incorporated into clinical drug therapy. GENDIA, an international network consisting of more than 50 laboratories from leading genetic diagnostics laboratories over the world, currently (October 2005) offers 20 pharmacogenetics tests (18). The first chip-based test, AmpliChip CYP450, entered the EU and US diagnostic market in 2004 (19). A number of diagnostic molecular genetic laboratories in several countries also offer pharmacogenetic tests for different panels of drugs metabolised by best investigated enzymes.

Pharmacogenetic testing offers several advantages over the traditional therapeutic monitoring of drug effects (2, 10): it can be undertaken pre-and post-prescription, can be predictive for multiple drug substrates rather than a single drug, the relevant genetic markers are constant over an individual's lifetime (somatic mutations are not to be of importance, except those leading to malignant neoplasias), while the results of traditional phenotype-based tests are significantly influenced by a number of external factors. On the other hand, even monogenic diseases may have significant individual differences in phenotypic expressivity (20), while the majority of drug responses are complex traits. Thus pharmacogenetic tests generate probabilistic information of varying degree of clinical utility: no single test or even a set of tests will enable to detect all DNA sequence polymorphisms influencing the pharmacokinetics and pharmacodynamics of Drug X and to enable foreseeing all possible correlations of the identified genotype and complex phenotype of the individual response to that drug. Thus, among the group of "non-responders" predicted on the basis of their genotyping data, a small to considerable fraction of "responders" will inevitably emerge, and *vice versa* (21).

In summary, current achievements and disappointments in the actively evolving field of pharmacogenetics and pharmacogenomics have made evident that the initial bold promise of "the right drug, for the right patient, at the right dose" is a hardly (if ever) attainable aim and that the term "personalised medicine" should not be interpreted to mean that drugs are developed for individual patients, but rather implies redefining diseases on the molecular level so that diagnostics and therapeutics can be targeted to specific patient populations based upon genetic factors thus reducing trial-and-error prescribing and dose adjustment (12). Also, it is to be pointed out that the genetic basis is only one – although important – aspect of individual response to treatment, thus personalised medicine and its applications (including pharmacogenetic testing) are supposed not to replace but to supplement and further develop the phenotype-based fields of medicine.

INFORMED CONSENT

The basic principle of bioethics is that no biomedical interventions into person (either for research, for clinical trials or treatment purposes, whereas personalised medicine is attendant with all of them) may be carried out without his / her free and informed consent, which must be expressed, specific and documented (5, 22–27). "Informed consent is a decision to participate, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation" (5). This definition comprises four essential

* The total number of displayed entries (number of entries with phenotype data and/or genotype data and / or literature annotations)

elements of individual informed consent: information, understanding, voluntariness, and decision-making capacity (26).

If an individual is **incapable to give informed consent** or is restricted in complying with all its elements due to cognitive, situational, institutional, deferential, medical, economic, and social factors, he / she is being considered as vulnerable (28).

Therefore, the doctrine of individual informed consent rests on the primary principle of biomedical ethics – the respect for persons, which has two fundamental aspects: 1) respect for the autonomy of those individuals who are capable of making informed choices and respect for their capacity for self-determination, and 2) protection of persons with impaired or diminished autonomy, that is, those individuals who are incompetent or whose voluntariness is compromised (5, 22–28).

Implementing voluntary informed consent in practice, its impact and extent of flexibility depends on:

– internal and external factors influencing the person's willingness to consent,

– various external factors compromising the person's free and informed consent,

– readiness of researchers and health professionals to comply with all essential elements of informed consent,

– various aspects of informed consent itself, such as scope (narrow or broad consent), content, form, process, level of formality / documentation, in general and on the case-to-case base,

– international, national and institutional regulations, guidelines and administrative provisions (discussed below) directly ensuring application of informed consent in compliance to its essential elements as well as the main bioethical principles of respect for persons, beneficence, non-maleficence and justice (7), which are related to the informed consent by reducing the risks and burdens of investigation and ensuring the protection of personal genetic and health data.

On the other hand, adherence of research and clinical practice to informed consent as well as to other ethical principles has considerable costs – not only financial (*i.e.* related to additional procedures, documents, services), but also in terms of foregone potential benefits (7). Policies aimed to reduce risks to zero sacrifice other ethically important values. An example is the straightforward and rigid prohibition of research involving persons not able to give free and informed consent (discussed below). Thus, a sensitive balancing of risks and benefits is necessary in the development and implementing all-level regulations and oversight practices ensuring adherence to the principles of ethics in biomedical research in general and guaranteeing the central principle of free informed consent in particular. The lower is the risks / benefits ratio the greater flexibility in the regulations is ethically sound.

The international regulation concerning informed consent

It was the shock of violent experiments performed by Nazi doctors on the prisoners in the concentration camps that initiated a particularly vigorous debate on the doctrine of informed consent in the context of therapy and biomedical research, which resulted in the demand for the protection of human rights and ethical principles of research involving humans on the legal level. The Nuremberg Trial, which started in 1946, produced the Code of Ethics on Medical Research (Nuremberg Code) (29). The Nuremberg Code was the first international document to enunciate some fundamental principles aimed at the protection of the human subjects in general and in biomedical trials in particular. It stated that "the voluntary consent of the human subject is absolutely essential"; it should be free choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him / her to make an understanding and enlightened decision. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature. Strictly construed, these demands prohibit medical experiments (*i.e.* biomedical research) with minors (especially infants) and other subjects incapable to consent.

Although at the time of its writing the Nuremberg Code had little impact on therapeutic clinical research (which has the potential to benefit the health of the participant directly) and a number of sensitive aspects of non-therapeutic research (*i.e.* study elements performed to seek a generalisable knowledge and not intended as a therapy to benefit the participating individual directly), its moral, ethical and legal value is unquestionable, and the basic principles of the Code continue to influence the contemporary policy of biomedical research on humans.

Nevertheless, it was subsequently recognised that excluding individuals not able to give an informed consent from biomedical research would lead to significant problems (up to eliminating most research) in the field of the investigation of a number of diseases and conditions. Biomedical research on the health conditions specific to definite groups of vulnerable persons is essential in developing new means aimed to improve the care of those who suffer from diseases or conditions that impair their capacity to consent (such as psychiatric illness, behavioural disorder, mental retardation, or dementia / coma / vegetative state or emergency cases – due to shock, pain, fear), and / or particularly affect certain groups of individuals with no or limited capacity or voluntariness to consent (such as children, elderly,

people in underdeveloped countries, especially in the regions with an increased risk of certain diseases, etc.). Prohibiting biomedical research involving such classes of persons might harm these classes as a whole by depriving them of benefits they could have received if the research had proceeded. Therefore, the principles of ethics on medical research were further developed in a number of international documents aimed towards a harmonious compromise between the rigorous respect of human rights and the urgent need for biomedical research on the health conditions specific to definite groups of vulnerable persons, and resulted in defining a number of ethically acceptable conditions, which enable biomedical investigation in vulnerable groups by ensuring significant limitations on risk for those who cannot consent and reducing the contrast between therapeutic and non-therapeutic research. An example of such conditions related to the protection of persons not able to consent to research is Articles 6 and 17 of the Convention on Human Rights and Biomedicine (25). They include "the authorisation of his or her representative or an authority or a person or body provided for by law" in the case of research on a minor or adult who "does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons" (Article 6), restrict allowable research to the cases when "research of comparable effectiveness cannot be carried out on individuals capable of giving consent" (Article 17), and exceptionally allow the research which "has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition" and "entails only minimal risk and minimal burden for the individual concerned" in the cases "where the research has not the potential to produce results of direct benefit to the health of the person concerned" (Article 17).

Creation and continuous amendment of the international documents relevant to the ethical principles of biomedical research and the development of personalised medicine were influenced by the development of national and international law, of the concept of informed consent, of means to ensure protection of vulnerable persons, as well as by the changing situation in the world (*e.g.*, outbreak of HIV/AIDS pandemic), achievements of biomedical research, development of new (especially non-invasive) methods of testing, emerging new possibilities in the development of new means of treatment. The most important documents are as follows:

– Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects (WMA, 1964; last revised in 2004) (22);

– Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997) (30);

– International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS, 1982, 1993, 2002) (5);

– Guideline for Good Clinical Practice. ICH Harmonised Tripartite Guideline, adopted by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, 1996) (24);

– 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 (EU Council, 1997) (25);

– Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (EU Council, 2005) (26);

– Directive 2001/20/EC: approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (European Parliament, EU Council, 2001) (27).

The majority of such international documents (except the Convention on Human Rights and Biomedicine and EC Directives) cannot be considered as a treaty in public international law according to Vienna Convention on the Law of Treaties (31) and are adopted by each regulatory authority as one of their own guidelines. Their legal force is therefore limited. These documents agree to a very large extent on the basic principles of the biomedical research ethics and provide the philosophical underpinning and guidelines for countries in defining national policies on biomedical research involving human subjects. Thus, informed consent as the central principle of biomedical ethics is entrenched in the legislation of virtually all civilised / democratic countries. Nevertheless, there are local differences in the national legislation, caused by local variation in economical, political, social and cultural conditions (*e.g.*, different cultural background leading to differences in what is considered as ethical, different interpretation of the concept of person's vulnerability, different level of the religious and philosophical background of western culture emphasising the "mind" aspects of psychopathology rather than its "body" side). Conceptions and principles presented by these documents are efficient to the extent the State acknowledges them and implements into national legal norms.

INFORMED CONSENT IN THE DEVELOPMENT AND APPLICATION OF PERSONALISED MEDICINE

Voluntary informed consent is an essential prerequisite for all investigations on humans in the constantly

increasing development and clinical application of personalised medicine, but its implementation into practice and impact on the protection of the persons under investigation encounters a number of ethically sensitive aspects, which are closely interrelated with general and local legal, social, economical, etc. implications in the field (7, 10, 21, 32–36). The majority of such implications are related to (1) additional burdens and risks of harm for participants of research, patients and their families, social groups and society as a whole, which emerge alongside with suggested significant benefits, and to (2) the necessity to develop personalised medicine for patients not able to give consent.

The most important and ethically sensitive **risks** in the field are related to the **genetic nature of pharmacogenetic testing**. Information obtained from such testing and the way in which it could be used may lead to psychosocial harms of knowing one's genetic assessment. Being highly predictive or diagnostic about the patient's and / or his / her relatives' future health, genetic information may affect the patient's self-estimation, increased anxiety, reproductive decisions. Family-based DNA testing may reveal non-paternity. Disclosure of genetic information to third parties (from family members to insurers and employers) may lead to stigmatisation and(or) discrimination of individuals, families and groups (7, 10, 37). In addition, the volume of information that can be extracted from one sample of DNA which can be kept indefinitely, the speed of DNA testing, the link between genetics and computer technology, combined with collecting and banking large numbers of DNA samples and potential use of biomaterials and genetic information for purposes other than initially specified also contribute to the risks (7, 10, 35, 37).

Pharmacogenetic tests are considered less ethically sensitive than molecular genetic testing for diagnostic purposes, because their intent is not specifically to determine or predict the risk of monogenic diseases or susceptibility to complex disorders (38). Nevertheless, their results can reveal a sort of personal information (secondary information), which may cause psychological problems and / or lead to unfavourable implications under disclosure (either on the legal basis or unintended, or illegal) to third parties (reviewed elsewhere (7, 10, 28)).

1. Identifying some genotypes in the loci of drug metabolising enzymes may disclose the individual's increased risk of environmentally caused toxicity or susceptibility to cancer as well as pointing to the diagnosis of several inborn errors of metabolism (reviewed by Nebert and Dieter (13)). Genotyping the loci related to the pharmacodynamic properties of Drug X is even more sensitive in this respect as DNA sequence changes found in the drug target gene(s) may be related to the disease being treated or in question, but also may reveal initially unintended information implying increased risk of other inherited disease(s) or common complex disorder(s) such as cancer, cardiovascular, nutritional, allergic, auto-immune, degenerative diseases, etc. This is an especially sensitive issue when such condition cannot be effectively treated. On the other hand, recent studies have shown that it may be virtually impossible with current knowledge and technologies to predict an environmental disease on the basis of DNA testing alone (39).

2. A genotype-based label of "non-responder" or "unsafe-responder", which often implies that the patient cannot be treated effectively (at least at present), may lead to stigmatisation. Such patients could be at risk being denied future coverage, especially bearing in mind that such genotype might imply unsafety of or non-responsiveness to a group of drugs (2, 10).

3. Psychological aspects related to patient's self-estimation, anxiety, reproductive decisions, etc. in the case of revealing a "non-responder" genotype and / or identified genetic markers of an inherited or complex disease also decrease the public and individual acceptance of pharmacogenetic testing (10).

Thus, as the development and application of personalised medicine is highly dependent on obtaining, using and storing samples of biomaterials (DNA in the first place) and personal genetic and health information, the dominating bioethical issue is respect for persons, *i.e.* protection of individual's autonomy and dignity, especially by ensuring privacy and confidentiality of his / her personal information. Free and informed consent is a procedure of particular importance and must be obtained on all stages of research in the development of personalised medicine:

– in **scientific research** aimed to generate a generalisable knowledge and not intended as therapy to benefit the participating individual directly;

– in **clinical trials** of developed pharmacogenetics-based medicines and pharmacogenetic tests, which are less related to a direct benefit to the patient's health if compared to conventional clinical trials;

– in **clinical application** of the pharmacogenetic / pharmacogenomic developments (new treatments and tests to predict their safety and / or efficacy for the patient), which have the greatest potential to produce a real and direct benefit to the patient and pose a particularly wide variety of problems related to the importance of informed consent and possibilities of compliance to all its elements.

Each of the above-stated stages deals with a large set of general and specific aspects related to informed consent and thus needs separate discussion, which is not within the scope of this paper. The majority of such issues have been extensively reviewed elsewhere (7, 10).

Nevertheless, voluntariness of consent for the participation in a pharmacogenetic investigation needs consideration as it is most often being discussed just as free agreement or refusal to participate in research made in the absence of coercion, but without more detailed attention to the aspects influencing the person's free will. The person's willingness to consent to the participation in a pharmacogenetic investigation or reluctance to participate is strongly influenced by individual as well as public perception or misperception of genetic testing and ranges from rejecting anything regarded as a genetic test as a possible source of stigmatisation and / or discrimination irrespective of the type of the test and potential information obtained (especially in non-clinical research not aimed to an immediate and direct benefit to an individual under investigation), to insisting on pharmacogenetic testing and / or treatment due to over-expectations of particular benefits of new pharmacogenetic medications based on marketing information and media hypes, notably when the patient's condition is difficult and existing treatments are inefficient or unavailable or absent. The positive and adequate personal and public attitude towards scientific and clinical (pharmaco)genetic investigations may be significantly increased by educating patients and society in the field of (pharmaco)genetics and (pharmaco)genomics and biomedical ethics and by improving knowledge of international and local regulations reducing their risks.

Development of personalised medicine for individuals not capable to consent: a case of Lithuania

The above-stated aspects of informed consent in personalised medicine are related to individuals capable of genuine informed consent and are in principle general for all countries which recognise this principle as a predominating one in the ethics of biomedical research in humans. The situation is more complicated when individuals with diminished or no capacity to consent are considered (cases of voluntariness to consent compromised by socio-economical factors are not within the scope of this article). Lithuania represents the situation of a country at the doorway of personalised medicine, which adheres to the particularly stringent legal protection of vulnerable persons.

The legal basis of biomedical research in Lithuania is as follows: 1) the Constitution of the Republic of Lithuania, which states that "no person may be subjected to scientific research or medical tests without his free and informed consent" (Article 21, pt 4) (40); 2) laws of the Republic of Lithuania; in the first place the Law on Ethics of Biomedical Research (41) and a number of related documents; 3) international laws and regulations, which have entered into force after their ratification (Convention on Human Rights and Biomedicine (25): signature on 4/4/1997; ratification on 17/10/2002; entry into force on 1/2/2003), when Lithuania became a EU member (Directive 2001/20/EC (27)) or were implemented into national legal acts (*e.g.*, Guidelines for Good Clinical Practice (24) were implemented into national law by 12/06/1998 Decree No. 320 of the Health Care Minister of the Republic of Lithuania, while implementation order of the Guidelines was approved by 11/05/2004 Decree No. 357; Directive 2001/20/EC (31) was implemented into the Law on Ethics of Biomedical Research of the Republic of Lithuania (11/05/2000 No. VIII-1679).

The Law on Ethics of Biomedical Research (41) defines a particularly stringent protection of vulnerable persons (Article 7) by stating that biomedical research involving vulnerable persons shall be permitted if 1) this kind of biomedical research may be *carried out only on vulnerable persons**; 2) the results of biomedical research have the potential to produce *real and direct benefit to the health of research subjects;* 3) a biomedical research *shall not pose a risk to the health or life of a research subject.* Accordingly, biomedical research involving vulnerable persons (defined by Article 5) is restricted at most to clinical trials, while basic investigation of a condition specific to these groups of patients aimed towards a generalisable knowledge and not intended as therapy is not possible in Lithuania. Moreover, strict adherence to the formulation of the 3rd condition implies prohibition of any biomedical research in these groups, because any investigation involving intervention (either physical or psychological) into a human cannot be absolutely risk-free. Such over-protection is applicable to persons with mental disorders but able to give their consent to take part in biomedical research (Articles 5 and 7), but there is a considerable inconsistency regarding a particularly vulnerable (and recognised by international documents) group of patients not able to give informed consent because of mental disability, a disease or for similar reasons. The latter group appears to be *excluded from biomedical research in Lithuania by default.* Alternatively, the Law lets them to be recognised as attributed to other groups of vulnerable persons by a reasoned decision of the Lithuanian Bioethics Committee (Article 5), but in this case such patients appear to be *deprived of protection ensured by Article 7.*

It should be pointed out that Lithuanian legislation has already introduced a possibility of research and clinical trials with minors by recognising the proxy consent of a minor's parents or legal guardians, and regional Services for Protection of Child's Rights as an additional step in the protection of minors' rights and well-being (Law on Ethics of Biomedical Research (41), Articles 5 and 7, pt 3).

*Italicised by the authors of the paper.

It should be concluded that, on the one hand, the Republic of Lithuania has used the possibility provided by Article 27 of the Convention on Human Rights and Biomedicine (25) "to grant a wider measure of protection with regard to the application of biology and medicine than is stipulated in this Convention". On the other hand, it does not make use of the potential advantages of the precisely defined flexibility in the application of the principle of informed consent defined by the Convention, which enables ethically sound research involving particularly vulnerable groups of patients not able to give genuine informed consent (Article 6 and Article 17).

What are the potential consequences of such stringent regulations of biomedical research in a limited number of countries (and even in a single one) such as Lithuania in the context of more flexible international regulations?

The starting point for the development and efficient application of personalised medicine is the profound knowledge of the basis of the pathology on all levels and the systems responsible for the effects of medicines. Current basic research in the field is mainly focused on complex conditions and therefore needs very large numbers of patients (as well as their families) to achieve statistically significant results. Numerous disorders of such category lead to severe mental and / or physical disabilities, and the patients who lack legal competency to consent are the only subjects suitable for a large part of the research in the field. Excluding the whole populations (such as patients from Lithuania) from the studies reduce the overall chance of success, especially when the condition is rare, thus, the possibility of a precise clinical diagnosis, which enables more specific and efficient currently available treatment, as well as finding new targets for the development of target-directed treatments is at least shifted to a more or less distant future. As a result, potential benefits of personalised medicine are not yet available for the patients who particularly need better individualised treatment.

There is considerable evidence of unequal inter-population or inter-ethnic prevalence rates of drug metabolism phenotypes (see Table for some examples) and definite nucleotide sequence polymorphisms (8, 16) in the genes responsible for pharmacokinetic / pharmacodynamic effects of medicines. Besides that, some pharmacogenetic tests under development are based on linkage disequilibrium between functionally neutral SNPs and the genetic variation that is responsible for the effect of a drug. Such SNPs may not co-occur with the functional genetic variation in the population group with different genetic history. Thus, the statement about the safety and / or efficacy of a drug as well as the predictive value of a pharmacogenetic test based on data of a clinical trial in one population may not be valid for another population (2, 43). Bridging trials are suggested to solve this problem when marketing new pharmaceuticals to "foreign" populations (2). Although clinical trials are being extensively performed in Lithuania, within the current legal order such trials are not possible for persons unable to give their informed consent due to mental and / or physical disability. Thus, groups of patients with particularly difficult conditions are deprived of the best available pharmacogenetics-based treatments, which either cannot be obtained in Lithuania (*i.e.* not yet registered by the State Medicines Control Agency of Lithuania (44)) or might appear to be less efficacious and / or less safe for at least some of patients

Table. **Some examples of pharmacogenetic polymorphisms in drug metabolising enzymes in different ethnic groups***

Drug metabolising enzyme	Variant poor metabolism phenotype	
	Population	Frequency
Cytochrome P450 2D6 (CYP2D6)	Swedish Chinese	6.8% 1%
Cytochrome P450 2C19 (CYP2C19)	White Americans Swedish Chinese Japanese	2.7% 3.3% 14.6% 18%
N-Acethyltransferase 2	White Americans Japanese	52% 17%
Uridine diphosphate-glucuronosyltransferase 1A1 (TATA box polymorphism)	Whites Chinese Japanese	10.9% 4% 1%
Thiopurine S-methyltransferase	Whites Asians	Approx. 1 in 300 Approx. 1 in 2500

* Source: (42).

in Lithuania if such treatments were introduced just on the basis of the results of clinical trials performed in other populations.

Over-strict protection of persons unable to consent, even in a limited number of countries, has wider ethical implications, especially concerning the principle of justice, which implies an equitable distribution of burdens and benefits of biomedical research (5). First, although the primacy of the interests and well-being of the research subject over any benefits to science or society is stressed in all major international legal acts regulating research on humans (26–30), this does not mean that interests of science and society, and especially the interests of patients with the same condition or in the same age group – both on the national and global levels – are not to be taken into account (of course, carefully considering the risks / benefits ratio). Maximally protecting each single individual incapable for free and informed consent from potential suffering and inconveniences in fact means that the burdens of investigation not offering immediate and direct benefit for the patient under investigation are just shifted from the individual to the population group with the same condition or of the same age: the elucidation of the basis of their pathology is slowed down thus leaving particularly vulnerable patients – and ultimately the very patients aimed to be protected – in the era of "one size fits all" medicines. Waiting for the progress in the diagnosis and treatment based on the biomedical research in other countries with more flexible regulations is even more unethical.

Second, to be coherent and escape "dual moral", the national legislation, which over-protects patients incapable to give informed consent from risks and inconveniences of biomedical research, ought to be supplemented by prohibition to benefit from using medications tested in other countries under "unacceptable conditions", and this ethical incoherence has not yet been solved in Lithuania.

CONCLUDING REMARKS

Development of personalised medicine and constantly increasing its introduction into clinical practice – although at a slower and evolutionary pace if compared to initial expectations – suggests appealing benefits of safer and more efficacious treatments and at the same time poses new risks, especially those related to collecting, storage and analysis of DNA samples banks, and knowing, storage and using personal genetic information. The role of the principles of biomedical ethics ensuring the respect and protection of human rights is of prime importance in this context, while free and informed consent to participate or not to participate in a biomedical research takes the central place. The cost of concentrating attention just on reducing risks inevitably sacrifices other values ultimately leading to the loss of or at least considerable forgoing potential benefits. Thus, exceptionally straightforward and rigid adherence to the principle of free and informed consent, even in a single country, just replaces the individual burden related to testing the vulnerable patient by the collective burden of receiving insufficiently efficacious and / or safe treatment for all patients with the same disease or the same age group.

Therefore, active development of ways towards a harmonious compromise between a rigorous respect of human rights and considerations of the need for biomedical research, particularly in the field of the diseases affecting minors and / or leading to mental disability, is essential. It should be based on a very sensitive balancing of risks and benefits in biomedical research in general as well as in the development and application of personalised medicine. In the long run, it will benefit a very large number of patients. In this context, it is crucial for the international and national regulations of research involving humans, in particular those related to the principle of informed consent, to be rigorous but not rigid.

Globalisation of biomedical research, together with the development and markets of new medicines, need harmonisation in the development of appropriate guidelines and protections, both at the national and international levels. At the same time, national regulations should maximally correspond to the constantly changing economical, political, social background in each country.

Another important aspect in the development and clinical application of personalised medicine, exploiting its benefits and overcoming problems is public perception / misperception regarding the benefits and risks. On the one hand, it affects the person's free will to consent to pharmacogenetic investigation and / or treatment. On the other hand, the developers of such regulations, science and health policy makers, as well as potential participants of investigations are also significantly influenced. Thus, education of the society is essential to achieve the positive attitude towards and adequate knowledge of (pharmaco)genetics, (pharmaco)genomics and bioethics. Education of physicians is even more crucial, as their current knowledge in the field of personalised medicine is far from adequate. Contemporary courses on pharmacogenetics and pharmacogenomics are to be included in the curricula of the basic and post-graduate medical studies as well as life-long education.

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INFORMUOTO ASMENS SUTIKIMO REIKÐMË PERSONALIZUOJANT MEDICINÀ

Santrauka

Ávadas. Personalizuota medicina yra ðiuolaikinë veiksmingesnio ir saugesnio gydymo kryptis, pagrásta þiniomis apie ligos mechanizmus ir individualius paciento genetinius ypatumus. Biomedicininiai þmoniø tyrimai bûtini plëtojant ir á klinikinæ praktikà diegiant personalizuotos medicinos pasiekimus. Kita vertus, tokie tyrimai kelia etiniø problemø. Laisvas informuoto asmens sutikimas dalyvauti juose yra esminis siekiant uþtikrinti pagarbos asmeniui, naudingumo, nekenksmingumo ir teisingumo principus.

Medþiaga ir metodai. Ðiame straipsnyje apþvelgiamos pastarøjø metø publikacijos farmakogenetikos, farmakogenomikos ir þmoniø tyrimø bioetikos klausimais, taip pat tarptautiniai bei Lietuvos teisës aktai ir nuostatos.

Rezultatai ir jø aptarimas. Daugelio þmogaus genø ir jø polimorfizmø, susijusiø su vaisto poveikiu, atskleidimas leidþia kurti farmakogenetinius testus, padedanèius individualiai parinkti vaistà ir optimalià jo dozæ. Kita vertus, genetinë tokiø tyrimø prigimtis ir jø rezultatø tikimybiðkumas kelia etines problemas, kurias sprendþia daugelis tarptautiniø biomedicininës etikos nuostatø ir teisës aktø, reglamentuojanèiø biomedicininius þmoniø tyrimus. Ðiuolaikiniai tarptautiniai dokumentai ir taisyklës átvirtina informuoto asmens sutikimà kaip bûtinà þmoniø tyrimø sàlygà, taèiau kartu yra ir pagrástai lankstûs, leidþiantys tirti asmenis, negalinèius duoti sàmoningo sutikimo tyrimams, ir kartu uþtikrinantys jø apsaugà. Lietuvos ástatymai reglamentuoja daug grieþtesná informuoto asmens sutikimo principà.

Išvados. Personalizuotos medicinos mokslo tyrimø ir jø taikymo plëtrai globaliu mastu ir atskirose ðalyse bûtinas harmoningas rizikos ir naudos pusiausvyra pagrástas kompromisas tarp þmogaus teisiø apsaugos ir biomedicinos mokslo tyrimø bei praktiniø reikmiø, ypaè vaikø ligø ir protinæ negalià sukelianèiø ligø atveju. Pernelyg grieþtai traktuojant laisvo informuoto asmens sutikimà net ir atskiroje ðalyje, ypaè paþeidþiamus asmenis galiausiai daug vëliau tepasiekia potencialûs personalizuotos medicinos privalumai. Siekiant uþtikrinti adekvatø informuoto asmens sutikimo taikymà ágyvendinant ir taikant personalizuotà medicinà, visuomenë turi pakankamai gerai þinoti ir suprasti potencialius jos privalumus ir pavojus. Tam bûtina þmones ðviesti (farmako)genetikos, (farmako)genomikos ir bioetikos klausimais. Gydytojø þinios ðioje srityje ypaè svarbios.

Raktaþodþiai: farmakogenetika, farmakogenomika, biomedicininë etika, informuoto asmens sutikimas, biomedicininius þmoniø tyrimus reglamentuojantys nacionaliniai ir tarptautiniai dokumentai