

Ethical Issues Surrounding Personalized Medicine: A Literature Review

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Abstract- More than a decade ago, personalized medicine was presented in modern medicine. Personalized medicine means that the right drug should be prescribed for the right patient based on genetic data. No doubt is developing medical sciences, and its shift into personalized medicine complicates ethical challenges more than before. In this review, we categorized all probable ethical considerations of personalized medicine in research and development and service provision. Based on our review, extensive changes in healthcare system including ethical changes are needed to overcome the ethical obstacles including knowledge gap and informed consent, privacy and confidentiality and availability of healthcare services. Furthermore social benefit versus science development and individual benefit should be balanced. Therefore guidelines and regulations should be compiled to represent the ethical framework; also ethical decision making should be day-to-day and individualized.

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Introduction

Since over a decade ago personalized medicine (precision medicine) entered in the academic as a new term and showed a fast growth. It refers to a new approach to prevention and treatment modalities based on each individual genetic and lifestyle variability (1). This term is used interchangeably with precision medicine and genomic medicine while not completely the same. Its rapid implication is in line with new achievements in genetic science and finalization of Human Genome Project. Personalized medicine means that “one size fits all” is replaced with the “right drug” for the right patient and at the right time (2). Based on personalized medicine each individual’s genome specifies the individual’s reactions to specific drugs, diets, and lifestyle. Personalized medicine is a new approach to medicine in which inter-individual genetic differences help diagnosis, prevention, and treatment of a health-related condition (3).

Based on the United States Food and Drug Administration (FDA) personalized medicine is relying on pharmacogenomics (4). These advancements opened a new horizon in front of medicine to specify

the diseases at the molecular level. In this new definition of medicine, the genome information is translated into public health practice and practice of medicine. At first glance its benefits can be summarized in the identification of genetic predisposition and using preventive measures, better diagnostic assessment followed by sooner and ameliorated therapeutic interventions, improved efficacy and lesser adverse effects of medications (5). There are different controversial points of views about personalized medicine. Some consider it as a hopeful transition from modern medicine to personalized medicine which may improve human health (6) and is practical in clinics (7), while others consider it as unrealistic and far from scientific evidence (8,9).

Modern bioethics in the 21st century is facing with challenges mostly focused on analysis, theory, and individualism (10). Like the other new advancements in medical sciences, personalized medicine which is based on genome information and translation created new ethical challenges. Bunnik *et al.*, present four specifications of genome testing which raise ethical, legal, and societal issues (ELSI) including the non-targeted type of testing, analytical validity, clinical

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validity and clinical utility (11).

Hansson believes that not only scientists and industry but also bioethicists, anthropologists, social scientists, and lawyers may be equally faulty in developing hype instead of evidence-based hope about personalized medicine (12). He indicates the possibility of the negative impact of hypists on the public sphere which may cause premature termination of personalized medicine (12). Joly *et al.*, describe the dynamism of the ethical issues of personalized medicine (13). Juengst *et al.*, indicate the possible benefits of personalized medicine as individualized diagnosis and risk prediction, more effective prevention and health promotion, and patient empowerment and recommend outreaching scientific and technological obstacles to realizing ethical and social implications (14).

Obviously, it seems that personalized medicine is facing several challenges including ethical problems in its initial way to implication. Therefore development and enhancement of personalized medicine could not take place while ethical problems stay undiagnosed and unresolved. In this regard, we aimed at reviewing all anticipated ethical challenges of personalized medicine in two fields of research and development and service provision to propose and design some solutions.

Materials and Methods

To have a structured approach to the ethical challenges of personalized medicine we have done a thorough search using keywords and MeSH terms including personalized medicine and precision medicine, pharmacogenetics, ethics, ethical issues, and synonyms. Those keywords were searched by several search engines including Medline, Scopus, and ProQuest. Our search was not limited to a time frame, but it was limited to English papers which considered ethical issues in personalized medicine. Our search resulted in approximately 8300 articles. Although the challenges of personalized medicine are considered as ethical, legal, and social issues (ELSI), we only focused on the ethical issues. Finally, we reviewed 60 papers.

Results

Our review shows the ethical considerations of personalized medicine from different aspects including research and development, and the physician-patient relationship. All positive and negative effects of the

personalized medicine and ethical considerations are summarized in table 1.

Table 1. Positive and negative effects and ethical considerations of personalized medicine

Negative effects	Positive effects	Ethical considerations
High cost	Improving quality of healthcare (accessibility, effectiveness, affordability, public trust)	Increase personal responsibility Individual vs. societal rights in access to information
Inequality in health care		
Violation of privacy		
Discrimination	Fair subject selection	Informed consent Incidental findings Genetic counseling
Negative effect on physician-patient relationship		
Stigmatization		
Exploitation		

Research and development

Pharmacogenetics studies

Research and development in personalized medicine have a strong junction with research in pharmacogenetics because genetic science is considered as a basis for the transition from modern medicine to personalized medicine. Development in pharmacogenetics was a human hope to decrease the incidence of serious adverse drug effects, but the issue is questionable (15). One of the major advantages of pharmacogenetics is providing more effective and much safer drugs. Greater efficacy may anticipate greater cost-efficacy, but drugs are responsible for a small portion of health care costs. Nuffield Council on Bioethics Report considers pharmacogenetics as a promising mechanism for reducing adverse drug effects, but the possibility of a substantial effect is debatable because genetic is one of the several factors influencing adverse drug reactions (15).

Risk/benefit assessment in pharmacogenetics studies

Developing personalized medicine needs increasing number of researches especially genetic studies. In considering the benefits of genetic tests, the individuals benefit versus societal benefit should be balanced. Genetic test results are the main evidence used for the implication of personalized medicine. Research ethics makes a balance between individuals benefit versus societal benefit. The individuals benefit from genetic testing versus public health interests is questionable, and only the public health ethics can justify the violation of the individual rights by genetic tests. About pharmacogenomics, Daar and Singer argue against

introducing benefits of personalized medicine in an individualistic “boutique-style” type of healthcare to the disadvantage of less developed countries (16).

Appropriate genetic testing helps us selecting the patients who are more likely to benefit from a certain drug or suffer from a side effect (10). Selecting cohorts of patients by pharmacogenetics for clinical trials helps in performing smaller clinical trials, quicker and with lower costs. Pharmacogenetics assists in assessing the safety profile of medicines in the market. Although all those above indications are considered as benefits and implications of pharmacogenetics (10); this issue is controversial, and Petersen *et al.*, reported the costs of gene-based therapies and genetic testing as the most significant obstacles (17).

From the other point of view, most of phase three clinical trials are performing in the developing countries while their benefits are limited because of high costs of new drugs. Supporters of personalized medicine argue that the routine phase I-III of clinical trials may not be needed to prove some specified personalized medicine modalities. Their assumption is that personalized medicine modalities are working based on known mechanisms of action (18). So, different types of studies may need at the hope of lower costs and in a shorter duration. Corrigan *et al.*, indicate that the pharmacogenetics studies have no direct benefit to study participants in comparison with regular clinical drug trials (19).

The risks of genetic testing are possible but not certain, and the clinical validity and utility of the risks of genetic testing are questionable. Conducting genetic studies to assess genetic traits across groups is carried out in personalized medicine while it may have a devastating effect on some races such as stigmatizing followed by discrimination. A study in Maori (a group of native people in New Zealand) explained overrepresentation of a genetic characteristic of violent crime in Maori. Afterward, it was shown that the study was scientifically wrong and misleading. However, the study had catastrophic effects on this group of people (20). This example shows the knowledge gap-the risks and benefits of genetic researches are not well known.

Subject selection

Selecting study participants using pharmacogenetics information can be considered as one of the best methods for decreasing the risks and increasing the benefits of a trial. Also, it provides a guide for fair subject selection; in the other word by using pharmacogenetics knowledge we can impose the limited amount of the research risks to a

limited number of patients who may receive the greater amount of benefit, and this means fairness. But financial profits make the larger groups of patients more attractive than smaller groups or orphan patients for study participation (21,22). The utilization of race with genetic characteristics and superficial understanding of pharmacogenomics may lead to inappropriate health care (23-25). Further, this type of healthcare services is complicating and perhaps worsens inequalities and variations in healthcare delivery. Also, the pharmaceutical industry might be unconcerned with drug development which has a limited impact on a small population.

Personalized medicine to be practicable as a routine, needs gathering genetic information from all ethnic and racial groups while underrepresented poor populations have little chance for recruitment in genetic studies. So these groups may receive suboptimal benefits from personalized medicine (26). It is suggested that the health problems which lead to morbidity and mortality in developing countries are less likely to occur in developed countries. So the personalized medicine to be effective in developing countries, the medical researches should be conducted in developing countries on the populations who have been under-represented in medical research until now (16).

Biobank

Emerging personalized medicine using the genomic information necessitates the establishment of biobanks throughout the world and accordingly the number and types of specimens stored in biobanks are increasing. Ethical concerns about biobanks have increased including sample collection, storage, use, informed consent, identifiability of the samples, sharing samples throughout the world, re-identification, and privacy and confidentiality (10,27).

Informed consent

In personalized medicine full voluntary participation of patients in decision making is critical and needs better physician-patient relationship and comprehensive patient's awareness (28).

In fact, individualization of therapeutic decisions and taking joint responsibilities by physician and patient are the main challenges created by personalized medicine. Making individualized therapeutic decisions need a greater level of literacy and is influenced by patient's preferences and values (29). Accordingly, the traditional informed consent should be restructured possibly to a dynamic model to save the participants autonomy on their genetic information (30) or choose a public health

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approach (31). Establishing informed consent necessities is negatively affected by informational problems of personal genome testing (11). Misapprehension of complicated genetic science and ambiguity in the test results and their meaning may diminish the importance of informed consent (32). So it seems that when there is no individual benefit, no genetic testing should be performed except for the tests which have at least public health benefits.

The specific consent form for pharmacogenetics studies should contain patients consent to the main clinical drug trial, genetic research including specific genetic testing pertinent to a drug effect, and nonspecific genetic testing needed for subsequent pharmacogenetics studies (15). This means that patients should give authorization to the pharmaceutical company to link their personal and family information to genetic research; therefore they may not be comprehensively informed about the potential risks and benefits of the studies which put them at the risk of exploitation (15,33). Furthermore, sample gathering for pharmacogenetics studies is named as non-therapeutic so financial compensation is another issue (15).

Regarding the Maori story, the knowledge gap in genetic research should be fully explained to the patients. In addition, the informed consent in genetic researches should include the way of using the human samples (20).

Generally the issue of informed consent is the most challenging issue in biobanks because as it should be comprehensive it should contain critical information about sample storage, usage, and destruction, sample anonymity, and coding, an option for withdrawing the samples from the study as well as returning research results including incidental findings which are under discussion (34-36). Further, because biobanks operate in relation to national and international networks, the informed consent should obey of universal models or should be easily amenable (37,38).

Different legal systems in addition to the little difference in scientific aims may differentiate informed consent mechanism; an opt-in or opt-out mechanism for studying on biorepositories (39).

Data availability

The Iranian National Ethical Guideline for Genetic Researches states that "The results of research on human genome should be accessible for the society".

In genetic researches for the development of personalized medicine, the data ownership is questionable. The risks of genetic studies may affect non-participants who identified affiliated to a particular group

or their relatives (40,41). Furthermore, for personalized medicine to be implemented, all data on genotype-phenotype and their correlations should be accessible for interpretation, but some laboratories and hospitals save their data in private databases, limiting its accessibility. In addition, gene patenting is permitted in some countries, but the broad accessibility of sequence data and their correlations affect clinical practice in personalized medicine. Because of the importance of genetic data sharing and availability, belonging the data to the patients and public funding for genetic findings, maintaining proprietary databases is unethical. But from the other point of view data sharing raises the debate over patients' privacy and confidentiality (42).

Confidentiality

Genetic data are unique because these types of data are expandable to families and next generations and influence quality of life. According to the importance of genetic data, the raw genetic data is not usable, and interpretation of genetic data affects individual's personhood and global position. Each individual has the right to privacy and confidentiality which should be respected by health care professionals. Brothers *et al.*, considers three reasons for respecting confidentiality. As the first one, they mention embarrassment, stigma, and discrimination to patient's dignity because of disclosure of sensitive data. Compromised quality of health care due to fear of improper disclosure of sensitive information is the second reason. Finally public health harms of mental illnesses, infectious diseases, etc. due to delayed treatment results from fear of loss of privacy (26).

No doubt when we are talking about the genetic information, the issue is more critical. Furthermore, the development of electronic health records jeopardized the risk of privacy violation. Personalized medicine and providing health care services beyond the spectrum of health services based on genomic information means that individual privacy and confidentiality could be at risk. At the first glance confidentiality is absolute, but when the immediate and serious risk to the health of the third party emerges, confidentiality may breach. When an individual's health depends upon the genetic makeup of the other family members, the concerns about confidentiality emerges; but fortunately, genetic predisposition is not always definitely certain, and the most genetic conditions develop with delay. Therefore all health professionals should consider patient's confidentiality against informing family members about a hereditary disease risk (43). In addition to the interest of family members, insurance companies and employers are

interested in genomic data. So genetic data protection is completely indispensable.

Hansson *et al.*, indicate that personalized medicine may cause a crisis of confidence (12) therefore the social context should be considered for implementing personalized medicine. Hodge also recommends balancing individual interests in protecting genetic information versus society's interests in the limited use of such data for public health benefit (32).

Because genetic data is unique, has a predictive rule, shows the risk of future diseases in individuals or their offsprings, and remains stable during life, genetic exceptionalism considers genetic data far different from others (32). In this regard, interfamilial privacy issues or the right of the family member to get informed about the risk of a disease which may influence his life should be balanced against patient's privacy (44). Conversely, Knopper believes that complete protection of privacy is not realistic when the direct-to-consumer genetic tests are proposed on the internet (45). However, it should not be ignored that the risk of violation of confidentiality exists in non-genetic-based testing (10).

Discrimination

Genetic discrimination is one of the concerning issues since Human Genome Project. Personalized medicine could amplify the problem by considering even slight genetic differences which may have great biological and economic impact. Some examples of discrimination are as selecting a subset of population based on racial or ethnic differences, the willing of employers, insurers or government by biobanks, and genetic intervention as gene therapy (46). However, there is good evidence which shows that race and ethnicity are good proxies for pharmacogenetics science in increasing effectiveness and decreasing side effects. Joly *et al.* presented that the available genetic information which discriminates individuals did not cause a systemic problem (34,47). Further cultural and environmental differences should be taken into consideration (12).

Incidental findings

When more than one family member are taken genetic testing there is the risk of incidental findings beyond the primary aims of the test such as non-paternity or finding a gene variant which may have serious health implication for family members. The possibility of such findings is not easily predictable, and sometimes the importance of those data may not fully understand before facing (48); nevertheless, it is recommended the incidental findings to be anticipated as much as possible before testing.

Recently the American College of Medical Genetics and Genomics (ACMG) recommended for disclosure of incidental findings originated from the whole-genome analysis which took the four bioethical principles autonomy, justice, beneficence and non-maleficence under debate in personalized medicine (49). While ethicists consider the autonomy as the first priority of those principles, ACMG gives priority to beneficence and recommends that the study participants should not be proposed to choose to inform about incidental findings or no (50). Ormond and Cho assume that returning incidental findings is critical and should be considered based on patients preferences and evidence-based approaches (43). Therefore the necessity of compilation of guideline regarding the return of the genetic results and incidental findings is highly felt (51).

Service provision

Physician-patient relationship

Brothers *et al.*, mentioned the major impact of personalized medicine on the physician-patient relationship because of the possibility of lack of enough training by healthcare providers, time pressure, and greater patient's role in healthcare (26). Some scientists name the personalized medicine as patient-centric medicine by defining an integrated approach for healthcare delivery based on each individual's condition to raise the quality of healthcare services and improve outcome (52). In modern medicine, the physician-patient relationship and healthcare provision are based on the patient's interest as the main goal and the first priority. One of the challenging issues in personalized medicine is to reduce the individuals to their genetic characteristics. Human dignity necessitates respect for each individual as an entire human dignity regardless of his/her characteristics including genetic, race, age, religion, etc. Ignoring this fact in personalized medicine may harm the physician-patient relationship and reduce their level of relation because the patient will be considered as a genetic material by the physician (53).

Personalized medicine and performing genetic testing for diagnosis and treatment needs genetic counseling before testing to ensure the patient's realization of the indication of the test and social implication of the test results. For all of these stages, the physician has to spend enough time with the patient but today's trend in health care system is not accompanying (26), and this hurts the physician-patient relationship. What is important in personalized medicine is how medical professionals must operate in spite of uncertainty in genetic findings (54).

Responsibility

Science development and emerging new medical technologies such as personalized medicine make medicine more complex. By increasing the complexity, the chance of medical error is increased, physicians' responsibility will rise, and the essence of their responsibility will remain unclear (26).

Justice

Dorothy Wertz debated about the cost of drug development based on pharmacogenetics science in the minority. According to him increasing the expenses of drug development in the minority is controversial among governments, industry, and insurance companies (55). Holm argues about global justice and resource allocation and the possibility of the benefit of low and middle-income countries if not. But Hansson believes that this is the responsibility of policymakers such as governments and parliaments to justify personalized medicine (12). One study showed that mostly the European descent participated in the National Human Genome Research Institute (NHGRI) and less than 10% of participants were from China, Japan, and other Asian countries (56). Continuing these disparities in basic researches which create information and knowledge into personalized medicine causes uneven distribution and contribution of study participants or unfair subject selection. Access to healthy food and lifestyle affects the quality of health especially in poor populations and creates an asymmetrical distribution of health support. So there is the possibility that personalized medicine exacerbates the existing health variations (26).

Some researchers believe that the personalized medicine to be implemented, enough attention should be paid to optimal individualization of treatment and optimal availability of individualized treatments in all eligible racial/ethnic groups. So in designing the research protocols and resource allocation, those issues should be regarded (57,58).

Service availability

In addition, Universal Declaration on Human Genome and Human Rights (1997) insists on the "availability of benefits from advances in biology, genetic and medicine to all". Therefore the healthcare services based on new genetic knowledge should be provided to all, not just to patients whom it is affordable while most of those services are expensive and not covered by insurance. For example, gene modification for cancer treatment is highly expensive and not covered by insurance nor is accessible for all. Another example is Herceptin which is an FDA

approved the drug for early and advanced HER2-positive breast cancer. It is an expensive drug but recently is covered by insurance in Iran. DeVries *et al.*, believe that insurance and regulation are necessary for fair and justifiable resource allocation to prevent inequality and protect vulnerable populations (low-income and low-literacy) (59). The high cost of new drugs and laboratory tests which inform personalization limits the number of patients who benefit.

Discussion

Individual care and global health are two sides of a coin, and the ethical principles should be considered in personalized from both two sides; individuals versus public health benefits. In other words, personalized medicine in research and development and service provision should be evaluated from individual and social aspects. The study shows that each novel study result takes place in practice after about 17 years (60) and because of our limited pharmacogenetics knowledge, genomic studies are required for knowledge development in personalized medicine, and implementation of personalized medicine even takes longer. Furthermore, the above-mentioned obstacles are barriers to implementing personalized medicine; so without substantial alterations, its use cannot be supported especially from the ethical point of view. Free after all, it seems that personalized medicine is finding its way into routine practice and there is no doubt that genomic information will be widely used in the medicine in the future and genetic testing is becoming more available as a part of health care services.

So a critical need for providing the more accurate and sensitive genetic testing and its availability are completely sensed, and an accurate tool for evaluating trials during and post-approval surveillance and controlling off-label drug indications should be designed.

Also, the transition of the healthcare system to personalized medicine needs strategy planning and policy making by considering wide and extensive alterations in the healthcare system including economic and ethical modifications to create a positive impact on quality of health.

In this regard and as the first step, the three most challenging ethical issues in the pharmacogenetics-the scientific baseline of personalized medicine- are considered as equity in drug development and access to genetic testing, confidentiality in storing bodily samples and genetic information, and the individual's autonomy on taking a genetic testing (10). In addition, some findings

become clinically important and valid during the time; so valid informed consent, clarity in defining goals and patient's expectations, open argumentation and the scientific relationship may solve ethical challenges of personalized medicine.

Pointing out the ethical considerations, Schleidgen and Marckmann proposed constructive ethical monitoring of all of the ethical concerns regarding personalized medicine and counterbalancing them with benefits of personalized medicine (5).

Frankly, nevertheless, pharmacogenetics science is following its rapid growth in the world regardless of its ethical challenges. Because of rapid knowledge development, without recognition and solution, the ethical challenges of personalized medicine will get more complicated and remain unresolved. As an example, genomic knowledge is shared, and pharmacogenetics is implemented in medicine to help in new discoveries. Likewise in our country, the Iranian National Ethical Guideline for Genetic Researches did not restrict genomic data sharing. However, there are religious considerations; also the balance between societal and individual benefit versus science development is determinant. Ignoring the balance leads to discrimination and ethical bias and exacerbates the cultural and religious differences. Regulations should protect all human beings from discrimination, stigmatization, and violence of privacy and confidentiality. So the question raises to whether bioethics principles should be evaluated and implicated fundamentally in the base of personalized medicine. Therefore the need for proper guidelines and regulations is serious, and in the meantime, those frameworks should provide the condition at which genetic information can be used.

Finally, the ethical decisions in personalized medicine should be day-to-day and individualized. Accordingly, a framework addressing ethical and social challenges of personalized medicine is recommended. This framework may support solving ethical challenges by considering values, and their implications for decision making and study design. At the end and after final confirmation the framework should be integrated into personalized medicine in research and development and service provision.

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