Moral Imperative in the Age of Genetic Medicine

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Modern science demonstrates that if one is not a monozygotic twin, his genome is unique. Today, physicians learn the concept of genetic variability, its interactions with the environment, and its implications for care. Since now we can sequence human genome in the early stage, the practice of medicine enters an era in which the individual genome serves to determine the optimal care, which could be preventive, diagnostic, or therapeutic. Genomics is considered to be a basic science of biomedical research and takes a central place also in clinical medicine. As Guttmacher and Collins show, while genetics is the study of single genes and their effects, "genomics," a term coined only 15 years ago, studies the functions and interactions of all genes in the genome[1]. Genomics has a broader and more ambitious sphere compared to genetics. The study of genomics is based on direct empirical entrance to the entire genome and applies to common conditions such as breast cancer, colorectal cancer, human immunodeficiency virus (HIV) infection, tuberculosis, Parkinson's disease, and Alzheimer's disease. These prevalent conditions are called multifactorial since they are based on the interactions of multiple genes and environmental factors. Genetic variations can have a protective or a pathologic role in the onset of these diseases.

The present-day edical care is influenced also by the occurrence of pharmacogenetics which arised together with the current advances in genomic science, especially by the conception, introduction and ending of the Human Genome Project. In the late 90-s, the interaction of the two areas of biomedical research leads to turn of

1 Guttmacher, A. et F. Collins. Genomic Medicine -A Primer. N Engl J Med, Vol. 347, No. 19

pharmacogenetics into pharmacogenomics. Despite sometimes the terms "pharmacogenetics" and "pharmacogenomics" are used interchangeably, it has to be considered that pharmacogenomics emerged from the coupling of the advances in pharmacogenetics during the last century and the changes in genomic science such as the completion of the Human Genome Project, the development of expression profiling, and high-throughput DNA sequencing and genotyping[1]. Pharmacogenomics can identify the patients who are likely to receive benefit from some drug which resolves the common practice of broad, random prescribing of a medication to all the patients with the same condition. In this way, pharmacogenomics will lead to fragmentation of the markets for pharmaceuticals. Evans maintains that under the actual balkanized system of health care financing, this situation will burden patients, insurers and pharmaceutical industry with problems that increase in direct proportion to the scientific success[2]. Since insurance plans do not have the complete formularies required to obtain the practical benefits of pharmacogenomics, patients are insured by plans that do not provide reimbursement for a drug that could result in optimal care. As a result, the changes in pharmacogenomics lead to problems which could be solved through new practical and ethical approaches such as the described by Evans broadly pooled insurance risk that is a manifestation of the new ethical principles in the form of solidarity, mutuality and universality.

In regard to ethics, genetic interventions must respect the dignity of the human person and must promote the well being of the patient. This is the most fundamental moral principle related to the genetic intervention and it takes various forms. Science and technology require for their own intrinsic meanings an unconditional respect for this principle (James Walter, Thomas Shannon "The new genetic medicine"). Pythagoras, Plato and Aristotle spoke of suicide and mercy killing. Unlike Judaism, Christianity and Islam, the Stoics allowed killing of terminal cases. In the period of Renaissance killing of these was regarded as a trivial issue. In the 17th century the Church permitted killing of those who were incurable. The time provides the needs to respect the right to life under any conditions and imply that the holy books can provide applicable ideas concerning temporal virtues and vices and to try to solve this problem. Respect must be present even from the very moment of individual conception. Scientific interventions into the human

1 Weinshilboum, R. et L. Wang. Pharmacogenomics: Bench to Bedside. Nature Reviews: Drug Discovery, September 2004; 3:739–748.
2 Evans, J. Health care in the age of genetic medicine. Genetics In Medicine, January 2008, Vol. 10, No. 1.

genome must respect the integrity of the person when the focus is put on the benefits for the patient. Experiments that are not strictly directed toward therapy but are aimed at improving the human biological condition can be justified at least partly on the grounds that the experiments respect the human person as one in body and soul. Genetic experiments that are directed toward the creation of different groups of people are morally forbidden because they violate the dignity of the person. The risks and benefits must be calculated in terms of their potential impact upon the patient's well-being and not in terms of their impact on existing others or future humanity.

Since the time when religion was gradually put aside from the social sphere and its presence in culture, politics, management and other fields of social activities was no more tolerated there is more emphasis on secular morals that are free of religion. Development of commerce and industry, social reforms, revolutions in science as well as the birth of secular governments required new principles for individual conduct and social organizations to be enacted. Galileo's naturalism attacked the traditional concepts of the goal of design and value in the corporeal world, which was defended by the Church authorities. The new standards of moral commandments are based instead of the universal design of nature or the Revelation, which suggests God's will on the man himself and it, is founded either on his biological structure or on an agreement between him and his peers or on the socio-political organizations which are founded by him.

When God was replaced by science and religion has been relegated to the background, the question is: was the progress of the sciences and industries of influence in the purification of morals or detrimental to them? The answer which won was the one given by Rousseau in which the second alternative had been emphasized. William Key had no doubt about the contribution of science in solving moral problems. Changes in the political, sexual, economical and environmental texture of human environment introduce new concepts and referents of ethics and anti-ethics to the thought of contemporary man. The attention paid by scientists, physicians to the particular problems with which they are faced can be mentioned as an example. Issues such as the transplantation of organs, the relation between the physician and patient in various cases, awareness or unawareness of patient of his/her disease, euthanasia or saving lives are examples for this.

Concerning moral vices also, taking into account the influence of particular temporal and environmental conditions on human understanding new concepts and referents will originate. The problem of homosexuality which is seriously condemned in the Divine religions can be mentioned as an example. In modern developed societies according to their ways of approach towards issues and in particular based on their special political and governmental system such issues are not so condemned and in these societies all issues are viewed through a social approach; that is what is accepted by society is regarded as good and what is not accepted by society should be ignored. The issue of the temporality of ethics is in turn a function of the temporality of other things, even religion. According to such a view point there are no absolute and eternal things and all of what is related in a way to the context of man's life should be accounted for, because of its temporality in every particular period and society in accordance with that particular temporal, environmental and social condition.

Guttmacher and Collins note that soon it will be possible to sequence anyone's entire genome for a laboratory cost of less than $1,000[1]. This situation will change dramatically research and clinical care but, at the same time, there will be new ethical, legal and social issues. In the 90-s, ethical debates examined influence of the Human Genome Diversity Project on clinical genetics in the forms of counseling, testing, screening or genetic discrimination. Later, ethical questions included genetic enhancement or essentialism and cloning. In the early 21st century, bioethicists discuss preimplantation genetic diagnosis, commercialization, patenting, DNA banking and pharmacogenetics. Knoppers and Chadwick note that there appeared changes in the way that "ethics" is understood. Public concerns about genetically modified food increase the importance of ethical decisions and the concerns that human genetic research suffer from a loss of trust in science[2]. There are proposed new models of health care due to introduction of predictive medicine and targeted therapies, which are result of pharmacogenetic profiling and genetically informed prescribing. These new models call in question the content of actual ethical guidelines. In this way, ethics takes the central place in public policy.

1 Guttmacher, A. et F. Collins. Welcome to the Genomic Era. N Engl J Med, September 4, 2003; 349;10.

2 Knoppers, B. et R. Chadwick. Human Genetic Research: Emerging Trends in Ethics. Nature Reviews: Genetics, January 2005; 6:75–79.

In the 90-s, human genetic research is guided through the moral principles of autonomy, privacy, justice, quality and equity. Current medical ethics has to include the complexity of genetic factors in common diseases and that one of the familial and socio-economic impact of genetic information and genetic tests, together with the concomitant expansion of public participation in policy making. Knoppers and Chadwick identify the new trends in ethics as reciprocity, mutuality, solidarity, citizenry and universality[1]. These moral principle are not completely new – they are well known for moral thinkers but they show possible replacement of the principle of autonomy as the ultimate arbiter in bioethics with the principle of universality which is seen in the so-called participatory approach. We claim that the above-mentioned insurance approach of Evans is an expression of this approach. In this way, genetic research and pharmagogenomics initiate ethical study of personal and social values and their expression in the issues of medical practice.

According to Knoppers and Chadwick, the principle of universality or the claim that the moral point of view has universal coverage, which is very old, receives a new sense in the settings of genomics. In the new ethics, universality is represented by the genome itself as a shared resource. The human genome is shared by all. The conception for the human genome at the degree of the species leads to the specific emergence of the principle of universality in relation to the genome. Universality is expressed also as the common heritage of humanity and grounds obligations to future generations, reinforces the approach of benefit-sharing (also grounded in equity) and of genomic knowledge as beneficial to the public[2]. We think that the principle of universality shows best the main trend of the moral imperative in the age of genetic medicine.

There are many similar features of the principle of universality and the principle of interdependence that is described by Thomas and colleagues[3]. As they show, since the genomics is the study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors, the ethical problems in genomics have their own acronym, ELSI, which represents possible ethical, legal, and social implications. It can be seen that sometimes medicine and public health approach ethical

1 Ibid.

2 Ibid.

3 Thomas, J. et al. Genomics and the Public Health Code of Ethics. American Journal of Public Health, December 2005, Vol 95, No. 12.

questions in different way. Autonomy is a fundamental principle in medical ethics and public health. Thomas and colleagues underline that because physicians have authority and access to protected resources that may cure or harm, it is important to protect the patient's autonomy. Public health concerns not only the sum of individuals but also the relationships between the individuals in society and the relationship between the people and health agencies. In public settings, individual activity can affect other people and one's infection can be another person's exposure. That is way, occasionally personal autonomy has to be restricted to preserve the social good (in utilitarian sense). In this regard, Thomas and colleagues propose another principle that is fundamental in public health ethics – the principle of interdependence. This principle has important ethical reflections on the usage of genomic tools. We attempt to demonstrate the new trends in ethical studies through the case of the fragile X syndrome (FXS).

The American College of Medical Genetics analyzed the state of newborn screening (NBS) in the USA showing the results of expert ratings of 78 candidate conditions. FXS is the most common hereditary intellectual disability. It is not recommended for screening by the ACMG due to absence of appropriate, cost-effective screening test and data about possible benefits from screening. FXS is more prevalent in males causing moderate-to-severe intellectual disability. X inactivation and cellular mosaicism lead to decreased prevalence in females. Both the males and females suffer from social and behavioral difficulties although the females show more intact neurocognitive functioning. Because of its nature FXS interferes equally the patients and their families. The parents of suffered children prefer screening for newborns because it prevents unnecessary tests and allows timely intervention during the critical brain development, providing information about reproductive risk. Along with the benefits, examination of ethical implications of FXS shows also the existence of additional negative aspects of performing NBS. Bailey described a survey of families with children with FXS where the respondents determined whether learning the diagnosis would change their attachment to the child. Most of the respondents (60.2%) answered that the diagnosis cannot change their attitude since this is still their child and they will love him as any other child[1]. A smaller proportion (9.3%) of the respondents answered that the diagnosis will increase their attachment helping them to understand the child better or making them to

1 Bailey, D. et al. Ethical, Legal, and Social Concerns About Expanded Newborn Screening: Fragile X Syndrome as a Prototype for Emerging Issues. Pediatrics, 2008; 121; e693-e704.

spend more time with the child. Only 10% answered that the attachment will be more difficult since there are difficulties to take care for the child with FXS and the diagnosis leads to negative emotions.

Genes influence all human characteristics and diseases. These influences are identified in patients through examination of the family history, physical investigation and diagnostics. The specific molecular mechanisms of some conditions such as cystic fibrosis and sickle cell disease are clear unlike other chronic diseases as diabetes mellitus and hypertension, which responsible genes are still unknown. In this regard, the term “genetic information” is used in different meanings. In most of the cases, genetic information leads to the apprehension that it could be used for denying access to health insurance, job, education or some privileges. Despite popularisation of the principle of confidentiality common people see that their health information is not completely private. Genetic information is considered more definitive and predictive than other types of data because it seems that we cannot change our genes, which may be foretell our tomorrow. Genetic determinism or the belief in it leads to the sense of inevitability but, in fact, biologic systems develop in different manner. As Clayton notes, the DNA sequence is not the Book of Life[1]. Human characteristics are result of continuous interactions between the individual and exterior genes and the environment.

Most part of the males with the full mutation and slight/borderline degree of intellectual functioning and most part of the females with the full mutation and borderline/normal intellectual function are not diagnosed with FXS. Keeping this in mind, NBS identifies a considerable proportion of the males and females with the full mutation who will not be detected otherwise and some of them may not have the symptoms (with the FXS genotype but without the classic phenotype). Identifying these children can have negative impact on parenting or this can increase parental anxiety or lead to a state of hypervigilance without actual symptoms. When the parents know the diagnosis at an early stage they will be very careful about possible signs of mental retardation or severe behavioral and learning disabilities. However, the child can never show such symptoms. Any genetic testing will identify genetic or chromosomal anomalies that can be different from the condition that was assessed. In general, there are many ethical arguments

1 Clayton, E. Ethical, Legal, and Social Implications of Genomic Medicine. N Engl J Med, 2003; 349:562-9.

against screening for carrier status and late-onset disorders. This information can lead to psychosocial impairment of the child, including anxiety, negative self-concept, and impact on important decisions about his/her future life. Initial identification can provoke stigmatization and legal discrimination of individuals who are asymptomatic but are detected as having the genetic disorder. Bailey maintains that screening leads to the conflict between children's (future) autonomy and parents' right to know information about their child[1]. Genomic medicine brings information about health risks which are faced not only by patients but also by their relatives. We already know that the duty to keep confidentiality is not absolute as in the case of some infectious diseases that have to be reported by the physicians not to allow impairment of bystanders. However, we are not sure that genetic risks are very similar to these existing exceptions from the obligation of confidentiality. Physicians have to be permitted to breach confidentiality to warn third parties of genetic risks only as an ultimate means. Clayton claims that the overall question is whether the public's health is actually improved by the knowledge derived[2]. Not everyone will benefit from this knowledge.

The families whose newborns are diagnosed with diseases such FXS are involved in "genealogical ethics" – the process of taking moral decisions of whom in the extended family to tell, what genetic information to reveal, when to disclose, and who should do the telling[3]. In this way, the disclosure or nondisclosure have ethical consequences for relatives' identities and important decisions. Genetic information has the capacity to influence relationships in the family. In this case, the identified family and not medical professionals have the "duty to inform". The parents are responsible for the information that FXS appears in the family lineage. Disclosure of this information can provoke or increase existing conflicts in the family.

The problem about non-paternity is the primary moral challenge related with genetic research and testing. Later, this question spreads to the sphere in which the patients or their representatives have the right to share genetic information with other family members as in the case with the fragile X syndrome. In 1982, the US President's Commission popularizes the idea about the ethical (not legal) duty to admonish increased-risk family members. This violation of confidentiality is circumscribed by the

1 Bailey, D. et al., Op. cit.
2 Clayton, E., Op. cit.
3 Bailey, D. et al., Op. cit.

following factors: the family member has to be identified with high risk for a serious condition that is preventable or treatable[1]. Interestingly, the family can be considered a distinct social unit which possibly means that DNA and the information it contains is familial ownership. Some guidelines allow access to family members to the DNA or genetic information of their relative (even deceased) due to some purpose or necessity. Thus, genetic information has a familial character and has to be discussed through the principle of mutuality, to be shared within families, but it is no longer a question of discretionary medical control.

Ethical issues of genetic research are complex since molecular genetics is a new subject, with constant flow of evolving information, and its complete implications are still unclear. As Vahakangas demonstrates, genetic information differs from any other health care information because it is predictive, although the degree of its certainty varies, and it always involves at least family members, but in some genetically very homogeneous populations even a wider group[2]. Not only the populations but also the world itself is culturally xenogenic and the significance and meaning of genetic information varies between the cultures. Knoppers and Chadwick note that solidarity represents an ethical problem in the discussions about the right to know or not to know, the insurance and human genetic databases. In the discussions about the right to know, the issue is whether individuals have the responsibility to learn about their genetic make-up in order to make important decisions (to perform predictive tests, to take reproductive decisions)[3]. Considering the principle of autonomy, the patient has the right to know since he has to decide about his life by himself. On the other side, the principle of solidarity claims that genetic information has to be shared for the benefit of others. As we can see in the case of FXS, it is not so obvious who the relevant others (all the relatives or part of them) are.

FXS shows gendered characteristics of the response through different presentations in males and females. Bailey notes that affected men can feel guilty for transferring the gene in its carrier state to their daughters and consecutive grandchildren[4].

1 Knoppers, B. et R. Chadwick. Human Genetic Research: Emerging Trends in Ethics Nature Reviews: Genetics, January 2005; 6:75–79.
2 Vahakangas, K. Ethical aspects of molecular epidemiology of cancer. Carcinogenesis, Vol.25, 2004, No.4 pp.465-471.
3 Knoppers, B. et R. Chadwick., Op. cit.
4 Bailey, D. et al. Ethical, Legal, and Social Concerns About Expanded Newborn Screening: Fragile X Syndrome as a Prototype for Emerging Issues. Pediatrics, 2008; 121; e693-e704.

Since the women deliver the full mutation directly mothers can blame themselves for carrying the gene that resulted in their child's problems. NBS can become a primary reason for these feelings. The women can have more complicated reproductive choices compared to the male carriers since right the women risk having an affected child. The gender difference of the disease influences the children who are carriers and their future vital decisions. However, genomics calls into question the definition of disability since it can be considered a functional limitation as an essential feature or it is rather a question of social justice if the disability depends on the concrete social arrangements. According to the new ethical principle of citizenry, disability includes a complex of functional and social factors[1]. Disability represents only disadvantage when functional limitations or social structures are the main factors producing the disadvantage. There is an expressivist objection to genetic interventions that they express intolerance of disability, facilitating social factors (social model of disability). Other authors propose individual-choice model of disability. The example with disability shows that ethical solutions are not static but they constantly change showing a shift from the principles of individuals' ethics to ethics of interdependence and universality.

Conclusion

Most aspects of the usage of genetic research are different manifestations of the principle of universality proposed by Knoppers and Chadwick. In the case of screening for FXS, the obtained information concerns even the relatives beyond the patient's family provoking moral dilemmas that can be solved through the priciples of mutuality and solidarity. Health information is no longer completely private and its implications require moral decisions with increased coverage. Genetic information has to be shared for the benefit of others. We all have genomic risks for some disease, all are genetically impaired, and these risks increase with the capacities of genetic medicine. The future of each individual is strongly associated with the common lot[2] which demonstrates the necessity of accepting the principle of universality as moral imperative in the age of genetic medicine.

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1 Knoppers, B. et R. Chadwick., Op. cit.

2 Evans, J. Health care in the age of genetic medicine. Genetics In Medicine, January 2008, Vol. 10, No. 1.

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